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# Performance of syndromic management for the detection and treatment of genital Chlamydia trachomatis, Neisseria gonorrhoeae and Trichomonas vaginalis among women attending antenatal, well woman and sexual health clinics in Papua New Guinea: a cross-sectional study.



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## ABSTRACT

**Objective:** Papua New Guinea has among the highest estimated prevalences of genital *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG) and *Trichomonas vaginalis* (TV) of any country in the Asia-Pacific region. Diagnosis and treatment of these infections has relied on the WHO-endorsed syndromic management strategy that uses clinical presentation without laboratory confirmation to make treatment decisions. We evaluated the performance of this strategy in clinical settings in PNG.

**Design:** Women attending antenatal (ANC), well woman (WWC) and sexual health (SHC) clinics in four provinces were invited to participate, completed a face-to-face interview and clinical examination, and provided genital and venepuncture specimens for laboratory testing. We estimated the performance characteristics of syndromic diagnoses against combined laboratory diagnoses.

**Results:** 1764 women were enrolled (ANC=765; WWC=614; SHC=385). The prevalences of CT, NG and TV were 17.0%, 12.5% and 18.0% respectively, and highest among women attending ANC and SHC. Among antenatal women, syndromic STI diagnosis had low sensitivity (9%-21%) and positive predictive value (7%-37%); but high specificity (76%-89%) and moderate negative predictive value (55%-86%) for the combined endpoint of laboratory-confirmed CT, NG or TV. Among women attending WWC and SHC, 'vaginal discharge syndrome' had moderate to high sensitivity (72%-78%) and NPV (62%-94%), but low specificity (26%-33%) and PPV (8%-38%). 'Lower abdominal pain syndrome' had low sensitivity (26%-41%) and PPV (8%-23%) but moderate specificity (66%-68%) and high NPV (74%-93%) among women attending WWC; and moderate-high sensitivity (67%-79%) and NPV (62%-86%), but low specificity (26%-28%) and PPV (14%-33%), among SHC attendees.

**Conclusion:** The performance of syndromic management for the detection and treatment of genital chlamydia, gonorrhoea and trichomonas was poor among women in different clinical settings in PNG. New diagnostic strategies are needed to control these infections and to prevent their adverse health outcomes in PNG and other high-burden countries.

**Article summary:**

***Strengths and limitations of this study***

- We identified high prevalences of CT, NG and TV among antenatal, well woman and sexual health clinic attenders (42.7%; 25.1%; 37.2%, respectively) in PNG.
- Our findings reflect the high proportion of asymptomatic infections among women in these clinical populations, and the limited association between clinical findings and laboratory-confirmed genital STIs.

- Our findings are consistent with earlier studies, which demonstrated inadequate performance of syndromic management for STI detection and treatment in pregnancy, based either on symptoms alone, or on symptoms plus clinical examination.
- We did not investigate bacterial vaginosis or *Mycoplasma genitalium*, both of which are sexually transmitted, and may therefore have underestimated the performance of syndromic management for the detection of STIs and genital infections.

## INTRODUCTION

Sexually transmissible infections (STIs) are a major global public health concern.[3] Every year there are an estimated 500 million new cases of curable STIs, the majority of which occur in low-income settings.[4] Adverse outcomes of curable STIs include pelvic inflammatory disease, infertility, ectopic pregnancy, miscarriage, stillbirth, premature labour and low birth weight; and increased risk of HIV acquisition and transmission.[5] The three most common curable genital STIs, *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG) and *Trichomonas vaginalis* (TV) are frequently asymptomatic, particularly in women[6]. Inability to diagnose curable STIs has been a major barrier to their control, because many cases remain undetected and therefore untreated, with the potential for onward transmission. Accurate, nucleic acid-based diagnostic tests are now widely used in high-income countries but are largely unavailable in low- and middle-income countries (LMICs) where the highest prevalences of these STIs and their associated adverse health outcomes occur.[4] Even more traditional methods, such as microscopy, culture and serology are not widely available in LMICs, and in any case have low sensitivity for detecting current infection.

In the absence of access to diagnostic STI testing, the World Health Organization (WHO) in the 1990s developed a syndromic management strategy for diagnosing genital infections based on groups of genital symptoms to guide treatment decisions without laboratory tests.[4] The main syndromic diagnoses in women have been 'vaginal discharge syndrome' (VDS); 'lower abdominal pain syndrome' (LAPS); and 'genital ulcer syndrome' (GUS), each of which are treated using a combination of antibiotics to cover the most likely underlying infection(s). Syndromic management strategies lead to overtreatment, because there are other, non-sexually transmitted causes of the syndromes; or underdiagnosis,[7] because they do not address asymptomatic infections that account for the majority of STIs globally.[6] Consequently, despite the wide-scale implementation of syndromic management, this has not been an effective strategy in reducing population-level prevalences, particularly in high-burden settings such as Papua New Guinea (PNG),[8 9] which has among the highest estimated prevalences of genital chlamydia, gonorrhoea and trichomonas of any country in the Asia-Pacific region.[4 9 10]

In this paper, we present findings on the performance of syndromic STI management for the detection and treatment of curable genital STIs among women attending antenatal, well woman and sexual health clinics in PNG.

## METHODS

### Study design and procedures

We undertook a cross-sectional bio-behavioural survey to investigate STI prevalences and risk factors for infection among women attending routine antenatal, well woman and sexual health clinics in four provinces in PNG (Eastern Highlands, Hela, Western Highlands and Central provinces). A key objective of the study was to evaluate the performance of syndromic STI diagnosis as a guide to treatment of curable genital STIs in the PNG setting.

All women attending their first clinic visit during the study period (which varied across clinics, between December 2011 and January 2015) were invited to join and were consecutively enrolled into the study following informed consent procedures. Age eligibility criteria varied by clinic type: women aged 18 years or older were recruited at antenatal and sexual health clinics; women aged 30 – 59 years (the target age group for cervical cancer screening in PNG) were recruited at well woman clinics.

Women took part in a face-to-face interview, conducted by a trained health care worker using study-specific case record forms (CRFs) in which socio-demographic, behavioural and clinical information were collected. Participants in all clinical settings were asked about current genital symptoms, and past history of STIs. Genital examination was conducted as part of routine clinical assessment among women attending well woman and sexual health clinics only, in accordance with PNG standard guidelines (genital examination is not routinely offered in antenatal clinics).[11] Women attending antenatal clinics provided a self-collected mid-cavity vaginal swab for laboratory-based STI testing (CT, NG, TV); women attending well woman and sexual health clinics provided clinician-collected high vaginal (for TV) and cervical (for CT, NG) swabs. All women provided a venepuncture specimen for laboratory testing. Women with clinical features (symptoms and/or clinical examination findings) consistent with one or more STI syndromes were managed according to national syndromic management guidelines.[11] Point-of-care syphilis screening and HIV counselling and testing were offered to all women as per PNG national guidelines.[11] Clinical findings and treatment provided were recorded in individual client-held health record books and in study-specific CRFs.

### Laboratory Methods

Genital swabs were tested for CT, NG and TV by real-time polymerase chain reaction (PCR) at the PNG Institute of Medical Research (PNGIMR) Sexual and Reproductive Health unit laboratory in Goroka, using procedures and methods as previously described.[12] Sexual and Reproductive Health unit laboratory was enrolled in an external quality assurance program through the Royal College of Pathologists of Australia for CT and NG PCR.

**Data management and statistical methods**

Participant study folders (containing completed case record forms and laboratory results slips) were subject to quarterly clinical audits by the study lead investigator (AV) throughout. Data were entered at each clinical site into a study-specific MS Access database. Database entries were validated against participant study folders for accuracy. Laboratory test results entered into the clinical database were checked for accuracy against source documents (laboratory results slips) for all participants at the end of the study. The performance characteristics (sensitivity, specificity, negative predictive value and positive predictive value) of vaginal discharge syndrome' (VDS) and 'lower abdominal pain syndrome' (LAPS) were estimated against laboratory diagnoses of CT, NG and TV, and combinations of two or more STIs were calculated for the three population groups (antenatal clinic, well woman and sexual health clinic). Fisher's Exact Test was used to compare statistical differences in outcomes of interest between groups. There were no modifications for multiple comparisons. All statistical analyses were performed with Stata ver. 12.1 (StataCorp LP, College Station, TX, USA).

**Ethical considerations**

Ethical approval was obtained from the Institutional Review Board of the PNGIMR (1124; 1111) and the Medical Research Advisory Committee of the PNG National Department of Health in Papua New Guinea (11.34;11.18; 10.17) ; and from Human Research Ethics Committees of the Alfred Hospital Melbourne (390/11), and the UNSW Sydney (HC12155; HC11250; HC 12120), in Australia. Written informed consent (signature or witnessed thumbprint) was obtained from all participants prior to study enrolment. Women were each assigned a unique alphanumeric study identification number from a pre-printed study register to ensure anonymity and confidentiality.

## RESULTS

During the study period, a total of 1764 women were enrolled at 10 participating clinics (six antenatal clinics, n=765; two well woman clinics, n=614; and two sexual health clinics, n=385; Table 1).

**Table 1: Sociodemographic characteristics by clinic type**

| | Total | Clinic attended | | | |
|---|---|---|---|---|---|
| | N (%) 1764 | Antenatal N=765 | Well woman N= 614 | Sexual health N= 385 | P-value |
| **Age groups** | | | | | <0.001 |
| <20 years | 99 (5.6) | 85 (11.1) | 0 | 14 (3.6) | |
| 20-24 years | 300 (17.0) | 246 (31.2) | 0 | 54 (14.1) | |
| 25-29 years | 295 (16.7) | 224 (29.3) | 0 | 71 (18.4) | |
| 30+ years | 1070 (60.7) | 210 (27.5) | 614 (100) | 246 (63.1) | |
| **Median age (IQR)** | 32 (25-37) | 25 (22-30) | 37 (34-41) | 32 (26-37) | <0.001 |
| **Marital status** | | | | | <0.001 |
| Married | 1573 (89.2) | 719 (94.0) | 544 (88.6) | 310 (80.8) | |
| Single | 37 (2.1) | 22 (2.9) | 1 (0.2) | 14 (3.6) | |
| Other | 154 (8.7) | 24 (3.1) | 69 (11.2) | 61 (15.8) | |
| **Employment status** | | | | | |
| No current paid work | 920 (57.2) | 591 (77.3) | 311 (50.7) | 18 (4.7) | <0.001 |
| Gardening/farmer | 996 (56.5) | 482 (63.0) | 382 (62.2) | 132 (34.3) | <0.001 |
| House hold duties | 1464 (83.0) | 666 (87.1) | 491 (80.0) | 307 (79.7) | <0.001 |
| **Education** | | | | | <0.001 |
| No formal education | 427 (24.2) | 145 (14.6) | 172 (28.0) | 110 (28.6) | |
| Attended only Primary School (Grades 1-8) | 904 (51.3) | 386 (50.5) | 313 (51.0) | 205 (53.3) | |
| Attended Secondary School (Grades 9-12) | 331 (18.8) | 207 (27.1) | 73 (11.9) | 51 (13.3) | |
| Other (Tertiary, tech, voc.) | 102 (5.8) | 27 (3.5) | 56 (9.1) | 19 (4.9) | |
| **When did you last have sex** | | | | | <0.001 |
| Today/yesterday | 168 (9.5) | 73 (9.5) | 54 (8.8) | 41 (10.7) | |
| 2 days ago | 187 (10.6) | 74 (9.7) | 49 (8.0) | 64 (16.6) | |
| 3 days ago | 117 (6.6) | 59 (7.7) | 33 (5.4) | 25 (6.5) | |
| 4 or more days ago | 1292 (73.2) | 559 (73.1) | 478 (77.9) | 255 (66.2) | |
| **Vaginal sex in the last week** | | | | | <0.001 |
| None | 702 (39.8) | 372 (48.6) | 233 (38.0) | 97 (25.2) | |
| Once | 623 (35.3) | 196 (25.6) | 271 (44.1) | 156 (40.5) | |
| Twice | 212 (12.0) | 100 (13.1) | 51 (8.3) | 61 (15.8) | |
| Three times | 114 (6.5) | 55 (7.2) | 28 (4.6) | 31 (8.1) | |
| Four or more times | 113 (6.4) | 42 (5.5) | 31 (5.1) | 40 (10.4) | |
| **Condom used last vaginal sex** | | | | | <0.001 |
| No | 1621 (91.9) | 718 (93.9) | 578 (94.1) | 325 (84.4) | |
| Yes | 143 (8.1) | 47 (6.1) | 36 (5.9) | 60 (15.6) | |
| **Number of people had vaginal sex with in the last week** | | | | | <0.001 |
| None | 655 (37.1) | 308 (40.3) | 229 (37.3) | 118 (30.7) | |
| 1-person | 1069 (60.6) | 447 (58.4) | 373 (60.8) | 249 (64.7) | |
| 2 or more people | 40 (2.3) | 10 (1.3) | 12 (2.0) | 18 (4.7) | |
| **Condom use in the past month** | | | | | <0.001 |
| Always | 24 (1.4) | 3 (0.4) | 8 (1.3) | 13 (3.4) | |
| Sometimes | 298 (16.9) | 128 (16.7) | 105 (17.1) | 65 (16.9) | |
| Most of the time | 32 (1.8) | 5 (0.7) | 6 (1.0) | 21 (5.5) | |
| Never | 1410 (79.9) | 629 (82.2) | 495 (80.6) | 286 (74.3) | |
| **Ever had sex for money/gifts** | | | | | <0.001 |
| No | 1475 (83.6) | 723 (94.5) | 542 (88.3) | 210 (54.6) | |
| Yes | 289 (16.9) | 42 (5.5) | 72 (11.7) | 175 (45.5) | |
| **Age at sexual debut** | | | | | <0.001 |
| ≤18 | 692 (39.2) | 260 (34.0) | 214 (34.9) | 218 (56.6) | |
| >18 years | 1072 (60.8) | 505 (66.0) | 400 (65.2) | 167 (43.4) | |
| **Lifetime number of sexual partners** | | | | | <0.001 |
| 1-person | 805 (45.6) | 357 (46.7) | 338 (55.1) | 110 (28.6) | |
| 2-people | 349 (19.8) | 165 (21.6) | 127 (20.7) | 57 (14.8) | |
| 3-people | 178 (10.1) | 87 (11.4) | 49 (8.0) | 42 (10.9) | |
| 4 or more people | 432 (24.5) | 156 (20.4) | 100 (16.3) | 176 (45.7) | |
| **Ever had anal sex** | | | | | <0.001 |
| No | 1538 (87.2) | 685 (89.5) | 570 (92.8) | 283 (73.5) | |
| Yes | 226 (12.8) | 80 (10.5) | 44 (7.2) | 102 (26.5) | |

**Socio-demographic characteristics**

Women attending antenatal clinics were significantly younger than those attending well woman or sexual health clinics (Table 1). Overall, 89% (1573/1764) of women were married; around half reported attending primary school only (904/1764); and 57% were not in paid employment (920/1764). Women attending sexual health clinics were less likely to be married, or to be in paid employment and had lower educational attainment, compared to women enrolled in antenatal and well woman clinics.

**Sexual behavioural characteristics**

Overall, around 40% of women (692/1764) reported sexual debut before 18 years of age. Sexual health clinic attendees were more likely to have had a younger age of sexual debut than women attending antenatal or well woman clinics (56.6% vs. 34.0 and 34.9%, respectively, p<0.001; Table 1). Women attending sexual health clinics were also significantly more likely to report having more than four lifetime sexual partners; more than two sexual partners in the past week; vaginal sex more than four times in the past week; and ever having had sex in exchange for gifts or money compared with women attending antenatal or well woman clinics. Sexual health clinic attendees were more likely to report condom use at last vaginal sex, compared with women in other clinical settings.

**Clinical and laboratory findings**

The prevalence of CT, NG and TV were 17.0%, 12.5% and 18.0% respectively, with highest prevalences observed among women attending antenatal and sexual health clinics (Table 2). Overall, around one third of women (626/1764; 35.5%) had one or more STI, among whom 71.6% (448/626) had one STI; 23.1% (145/626) had two STIs; and 5.3% (33/626) had three STIs (Table 2). Almost half of all women (47.6%; 840/1764) reported at least one current symptom suggestive of an STI (Table 3). Abdominal pain was the most frequently reported symptom (36.7%, 648/1764), followed by vaginal discharge (25.8%, 455/ 1764) and dysuria (14.4%, 254/1764).

**Table 2: Prevalence of *C. trachomatis, N. gonorrhoeae, T. vaginalis* by clinic type**

| | Antenatal clinic N=765 (%) | Well woman clinic N=614 (%) | Sexual health clinic N=385 (%) | Totals N=1764 (%) |
|---|---|---|---|---|
| *C. trachomatis* (CT) | 175 (22.9) | 46 (7.5) | 78 (21.4) | 299 (17.0) |
| *N. gonorrhoeae* (NG) | 109 (14.2) | 49 (8.0) | 63 (16.4) | 221 (12.5) |
| *T. vaginalis* (TV) | 171 (22.4) | 92 (15.0) | 54 (14.0) | 317 (18.0) |
| More than 1 of CT, NG, TV | 109 (14.25) | 29 (4.72) | 40 (10.39) | 178 (10.1) |
| No STI | 438 (57.25) | 460 (74.92) | 240 (62.34) | 1138 (64.51) |
| Any STI | 327 (42.7) | 154 (25.1) | 145 (37.7) | 626 (35.5) |
| One STI | 218 (28.50) | 125 (20.36) | 105 (27.27) | 448/626 (71.6) |
| Two STIs | 90 (11.76) | 25 (4.07) | 30 (7.79) | 145/626 (23.1) |
| Three STIs | 19 (2.48) | 4 (0.65) | 10 (2.60) | 33/626 (5.3) |

**Table 3: Symptoms associated with *C. trachomatis, N. gonorrhoeae, T. vaginalis***

| | Overall | CT N=299 | | | NG N=221 | | | TV N=317 | | | More than 1 of CT,NG,TV N=178 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N (%) | N (%) | OR (95% CI) | P Value | N (%) | OR (95% CI) | P Value | N (%) | OR (95% CI) | P Value | N (%) | OR (95% CI) | P Value |
| Current symptoms (any) | 840 (47.6) | 158 (52.8) | 1.29 (1.00, 1.65) | 0.048 | 102 (46.2) | 0.93 (0.70, 1.24) | 0.641 | 129 (40.7) | 0.71 (0.56, 0.91) | 0.007 | 79 (44.4) | 0.87 (0.63, 1.18) | 0.362 |
| Abdominal pain | 648 (36.7) | 111 (37.1) | 1.02 (0.79, 1.32) | 0.878 | 76 (34.4) | 0.89 (0.66, 1.20) | 0.439 | 93 (29.3) | 0.67 (0.51, 0.87) | 0.003 | 52 (29.2) | 0.69 (0.49,0.96) | 0.029 |
| Lumps in groin | 34 (1.9) | 4 (1.3) | 0.65 (0.23, 1.85) | 0.419 | 2 (0.9) | 0.43 (0.10, 1.81) | 0.251 | 4 (1.3) | 0.60 (0.21, 1.73) | 0.346 | 2 (1.1) | 0.55 (0.13,2.32) | 0.417 |
| Pain passing urine | 254 (14.4) | 60 (20.1) | 1.64 (1.19, 2.27) | 0.002 | 42 (19.0) | 1.47 (1.02, 2.12) | 0.038 | 32 (13.3) | 0.89 (0.62, 1.27) | 0.520 | 37 (20.8) | 1.66 (1.12, 2.44) | 0.011 |
| Vaginal discharge | 455 (25.8) | 105 (35.1) | 1.72 (1.32, 2.25) | <0.001 | 71 (32.1) | 1.43 (1.05, 1.94) | 0.022 | 75 (23.7) | 0.87 (0.65, 1.16) | 0.338 | 58 (32.6) | 1.45 (1.04,2.02) | 0.030 |
| Vulval irritations | 128 (7.3) | 33 (11.1) | 1.79 (1.18, 2.72) | 0.006 | 27 (12.2) | 2.00 (1.27, 3.12) | 0.003 | 24 (7.6) | 1.06 (0.67, 1.68) | 0.812 | 20 (11.2) | 1.73 (1.95, 2.87) | 0.033 |
| Anal itching/irritations | 147 (8.3) | 28 (9.4) | 1.17 (0.76, 1.80) | 0.479 | 14 (6.3) | 0.72 (0.41, 1.27) | 0.252 | 30 (9.5) | 1.19 (0.78, 1.81) | 0.422 | 15 (8.4) | 1.01 (0.58, 1.77) | 0.962 |

Women with CT were significantly more likely to report any current symptoms compared with women with NG or TV (52.8% *vs.* 46.2% and 40.7% respectively; p=0.048). Women with TV were significantly less likely to report abdominal pain compared with women with CT or NG (29.3% *vs.* 37.1% and 34.4% respectively; p=0.003). Women with CT and NG were significantly more likely to report dysuria, vaginal discharge, and vulval irritation, compared with women who had TV. Women with multiple infections were also more likely to report these symptoms.

Genital symptoms were more prevalent among women attending sexual health and well woman clinics than among antenatal women (Table 4). For example, the prevalence of vaginal discharge syndrome was 73.0%, 68.7% and 20.4% respectively in these clinic populations.

**Table 4: Clinical diagnosis and laboratory-confirmed STI diagnosis, all clinics**

| Syndromic diagnosis | | Any STI N (%)* | | | *C. trachomatis* N (%)* | | | *N. gonorrhoeae* N (%)* | | | *T. vaginalis* N (%)* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Yes | No | Performance (95% CI) | Yes | No | Performance (95% CI) | Yes | No | Performance (95% CI) | Yes | No | Performance (95% CI) |
| **Antenatal clinics (n=765)** | | | | | | | | | | | | | |
| LAPS** (166/765; 21.7%) | Yes | 60 (18.4) | 106 (14.2) | SENS: 18% (14%, 23%) SPEC: 76% (72%, 80%) PPV: 36% (29%, 44%) NPV: 55% (51%, 59%) | 30 (17.1) | 136 (23.0) | SENS:17% (12%, 24%) SPEC:77% (73%,80%) PPV: 18% (13%, 25%) NPV: 76% (72%, 79%) | 15 (13.8) | 151 (23.0) | SENS: 14% (8%, 22%) SPEC: 77% (74%, 80%) PPV: 9% (5%, 14%) NPV: 84% (81%, 87%) | 29 (83.0) | 457 (77.0) | SENS:17% (12%,23%) SPEC: 77% (73%, 80%) PPV: 17% (12%, 24%) NPV: 76% (73%, 80%) |
| | No | 267 (81.7) | 332 (75.8) | | 145 (82.9) | 454 (77.0) | | 94 (86.2) | 505 (77.0) | | 142 (83.0) | 457 (77.0) | |
| VDS *** (156/765; 20.4%) | Yes | 60 (18.4) | 96 (22.0) | SENS: 18% (14%, 23%) SPEC: 78% (74%, 82%) PPV: 38% (40%, 47%) NPV: 56% (52%, 60%) | 37 (21.1) | 119 (20.2) | SENS: 21%(15%, 28%) SPEC: 80% (76%,83%) PPV: 24% (17%, 31%) NPV: 77% (74%, 81%) | 16 (14.7) | 140 (21.3) | SENS: 15% (9%,23%) SPEC: 79% (75%,82%) PPV: 10% (96%,16%) NPV: 85% (82%,87%) | 33 (19.3) | 123 (20.7) | SENS: 19% (14%,26%) SPEC: 79% (76%, 82%) PPV: 21% (15%, 28%) NPV: 77% (74%,81%) |
| | No | 267 (81.7) | 342 (78.1) | | 138 (78.9) | 471 (79.8) | | 93 (85.3) | 516 (78.7) | | 138 (80.7) | 471 (79.3) | |
| **Well woman clinics (n=614)** | | | | | | | | | | | | | |
| LAPS** (200/614; 32.6%) | Yes | 46 (29.9) | 154 (33.5) | SENS: 30% (23%, 38%) SPEC: 67% (62%, 71%) PPV: 23% (17%, 29%) NPV: 74% (69%, 78%) | 19 (41.3) | 181 (31.9) | SENS: 41%(27%, 57%) SPEC: 68% (64%,72%) PPV: 10% (6%, 14%) NPV: 93% (91%, 96%) | 15 (30.6) | 185 (32.7) | SENS: 31% (18%, 45%) SPEC: 67% (63%, 71%) PPV: 8% (4%, 12%) NPV: 92% (89%, 94%) | 24 (26.1) | 176 (33.7) | SENS: 26% (17%, 36%) SPEC: 66% (62%, 70%) PPV: 12% (8%, 17%) NPV: 84% (80, 87%) |
| | No | 108 (70.1) | 306 (66.5) | | 27 (58.8) | 387 (68.1) | | 34 (69.4) | 380 (67.3) | | 68 (73.9) | 346 (66.3) | |
| VDS *** (422/614; 68.7%) | Yes | 114 (74.0) | 308 (67.0) | SENS: 74% (66%, 81%) SPEC: 33% (29%, 38%) PPV: 25% (22%, 29%) NPV: 79% (74%, 84%) | 33 (71.7) | 389 (68.5) | SENS: 72% (57%,84%) SPEC: 32% (28%,36%) PPV: 8% (6%, 9%) NPV: 93% (90%, 96%) | 37 (75.5) | 385 (68.1) | SENS: 75% (61%, 87%) SPEC: 32% (28%, 36%) PPV: 9% (7%, 10%) NPV: 94% (90%, 96%) | 70 (76.1) | 352 (67.4) | SENS: 76% (66%, 84%) SPEC: 33% (28%, 37%) PPV: 17% (15%, 18%) NPV: 89% (84%, 92%) |
| | No | 40 (26.0) | 152 (33.0) | | 13 (28.3) | 179 (31.5) | | 12 (24.5) | 180 (31.9) | | 22 (23.9) | 170 (32.6) | |
| **Sexual health clinics (n=385)** | | | | | | | | | | | | | |
| LAPS ** (282/385; 73.2%) | Yes | 109 (75.1) | 173 (72.1) | SENS: 75% (67%, 82%) SPEC: 28% (22%, 34%) PPV: 39% (33%, 45%) NPV: 65% (55%, 74%) | 62 (79.5) | 220 (71.7) | SENS:79% (69%, 88%) SPEC:28% (23%, 34%) PPV: 22% (20%, 24%) NPV: 84% (77%, 90%) | 46 (27.0) | 236 (73.3) | SENS: 73% (60%, 83%) SPEC: 27% (22%, 32%) PPV: 16% (12%, 21%) NPV: 84% (75%, 90%) | 40 (74.1) | 242 (73.1) | SENS: 74% (60%,85%) SPEC: 27% (22%,32%) PPV: 14% (11%, 18%) NPV: 86% (78%, 92%) |
| | No | 36 (24.8) | 67 (27.9) | | 16 (20.5) | 87 (28.3) | | 17 (27.0) | 86 (26.7) | | 14 (25.9) | 89 (26.9) | |
| VDS *** (281/385; 73.0%) | Yes | 106 (73.1) | 175 (72.9) | SENS: 73% (65%,80%) SPEC: 27% (22%, 33%) PPV: 38% (35%, 41%) NPV: 62% (54%, 70%) | 61 (78.2) | 220 (71.7) | SENS: 78% (67%,87%) SPEC: 28% (23%,34%) PPV: 22% (19%, 24%) NPV: 84% (76%, 89%) | 42 (66.7) | 239 (74.2) | SENS: 67% (54%, 78%) SPEC: 26% (21%, 31%) PPV: 15% (13%, 17%) NPV: 80% (73%, 85%) | 40 (74.1) | 241 (72.8) | SENS: 74% (60%,85%) SPEC: 27% (22%, 32%) PPV: 14% (12%, 16%) NPV: 86% (80%, 91%) |
| | No | 39 (26.9) | 65 (27.1) | | 17 (21.8) | 87 (28.3) | | 21 (33.3) | 83 (25.8) | | 14 (25.9) | 90 (27.2) | |

* = prevalence of any and individual STIs in this population ** Lower Abdominal Pain Syndrome *** Vaginal Discharge Syndrome

Among antenatal women, syndromic diagnosis (based on clinical symptoms alone) had low sensitivity (9%-21%) and positive predictive value (7%-37%); but high specificity (76%-89%) and moderate negative predictive value (55%-86%) for correctly classifying women as having infection with CT, NG or TV (Table 4). Syndromic management alone would have led to considerable overtreatment and under-diagnosis in this population. For example, 38% (60/156) of antenatal women with VDS had any of CT, NG or TV and would have been appropriately treated; 62% (96/156) of women with symptoms but without detectable CT, NG or TV would have been treated unnecessarily; and 82% (267/327) of those with any of CT, NG or TV infection would not have been treated because they did not have vaginal discharge (Table 4).

Among women attending well woman clinics, LAPS had low sensitivity (26%-41%) and positive predictive value (8%-23%) but moderate to high specificity (66%-68%) and negative predictive value (74%-93%) for the detection of any laboratory-confirmed STI, or CT, NG, TV individually (Table 4). VDS had high sensitivity (72%-75%) and negative predictive value (79%-94%) but low specificity (32%-33%) and positive predictive value (8%-25%). Around 1 in 4 women with LAPS (46/200; 23%) had any of CT, NG or TV, and would have been correctly treated based on syndromic management alone; 77% (154/200) of women with LAPS did not have a laboratory-confirmed infection, and therefore would have been treated unnecessarily; and 70% (108/154) of those with any of CT, NG or TV would not have been detected and treated based on a diagnosis of LAPS alone, because they did not have appropriate clinical features. Correspondingly, around 27% (114/422) of women with VDS would have been correctly treated; 73% (308/422) of those with VDS would have been unnecessarily treated; and 26% (40/154) of those with any of CT, NG or TV would not have been diagnosed and treated (Table 4).

Among women attending sexual health clinics, LAPS and VDS had a moderate to high sensitivity (67%-79%) and negative predictive value (62%- 86%), but low specificity (26%-28%) and positive predictive value (14%-33%) for the detection of any laboratory confirmed STI, or CT, NG, TV individually (Table 4). Around 39% (109/282) of women with LAPS would have been correctly treated; 61% (173/282) with LAPS would have been unnecessarily treated; and 25% (36/145) of women with any of CT, NG or TV would not have been diagnosed and treated. Among women with VDS, around 38% (106/281) would have been correctly treated; 62% (175/281) would have been unnecessarily treated; and 27% (39/145) of those with any of CT, NG or TV would not have been diagnosed and treated (Table 4).

## DISCUSSION

High prevalences of genital *C. trachomatis, N. gonorrhoeae* and *T. vaginalis* were observed among women attending antenatal, well woman and sexual health clinics in Papua New Guinea. The performance of syndromic management for the detection and treatment of these infections was poor, particularly among antenatal women where more than 80% of those with laboratory-confirmed CT, NG or TV would not have been diagnosed and treated. These findings reflect the high proportion of asymptomatic infections among women in these clinical populations, and the limited association between clinical findings and laboratory-confirmed genital STIs. Around 43% of women attending their first antenatal clinic visit had genital CT, NG or TV; 1 in 5 reported symptoms of abdominal pain or vaginal discharge, and around 1 in 8 reported dysuria or vulval irritation. Despite high prevalences of both genital infections and genital symptoms, syndromic management had extremely low sensitivity and positive predictive value for the detection of CT, NG or TV, and would have resulted in significant overtreatment and missed diagnoses in this population. These findings are consistent with earlier studies, which demonstrated inadequate performance of syndromic management for STI detection and treatment in pregnancy, based either on symptoms alone, or on symptoms plus clinical examination.[7 10 13-15] Among women attending well woman clinics and sexual health clinics, VDS had moderate to high sensitivity (up to 79%) and NPV (up to 94%) but low specificity and PPV (both around 30%) for the detection of CT, NG or TV. Around 62-73% of women with symptoms did not have a laboratory-confirmed infection and would have been unnecessarily treated. Lower abdominal pain syndrome performed less well than VDS, particularly among well woman clinic attendees. Similar results have been reported from studies conducted in other high-burden settings, among women attending sexual health and family planning clinics,[15-17] and among women at increased risk of infection, such as commercial or transactional sex workers.[18 19]

In the current study, we did not investigate bacterial vaginosis or *Mycoplasma genitalium*, both of which are sexually transmitted, and may therefore have underestimated the performance of syndromic management for the detection of STIs and genital infections. High prevalences of bacterial vaginosis (18-23%) have previously been reported among pregnant women,[8 14] the majority of whom were asymptomatic in this setting.[14] It is possible that women with symptoms of vaginal discharge but without laboratory-confirmed CT, NG or TV in the current study may have had bacterial vaginosis (BV). Earlier studies in other settings suggest however, that the inclusion of BV appears to have little impact on the performance of syndromic management among antenatal women [13 20] or among women attending sexual health or family planning clinics.[21-23] *M. genitalium* (MG) has been associated with vaginal discharge among women in a variety of settings[21 24] but its presence and clinical correlates have not been investigated among women in PNG. It is therefore difficult to estimate the impact of undiagnosed MG on the performance of syndromic management in the current study. Research from elsewhere indicates that inclusion of MG has little impact on performance[19 25] and that the majority of

MG infections in women are asymptomatic,[26] and therefore not amenable to syndromic management strategies.

In accordance with current PNG national STI guidelines, genital examination was not routinely conducted among women attending their first antenatal clinic visit, and even had we elected to do so, would not have been feasible due to a lack of suitable examination rooms and equipment at participating antenatal clinics as well as limited and over-stretched human resources. This may have led to underestimation of the performance of syndromic management in this population, but we consider this unlikely given earlier evidence on the impact on performance if speculum examination is included as part of syndromic assessment.[15]

The performance of syndromic management contrasts markedly with that of newly-available, highly-accurate molecular STI diagnostic tests that can be implemented at point-of-care, such as the GeneXpert platform (Cepheid, Sunnyvale CA), which has been shown to be as accurate as laboratory-based polymerase chain reaction tests for the detection of chlamydia, gonorrhoea and trichomonas infection using genital or urine specimens.[27 28] For example, Xpert had 98.7% sensitivity and 99.4% specificity for the detection of CT using vaginal specimens.[27] Test results are available in approximately 90 minutes for Xpert CT/NG (which simultaneously tests for both chlamydia and gonorrhoea) and 60 minutes for the Xpert TV test. The platform has been shown to be robust and portable and has already revolutionised the diagnosis and management of tuberculosis in many LMICs, including PNG.[29] We have previously demonstrated the operational feasibility of Xpert point-of-care testing and treatment for CT, NG and TV in antenatal clinics in PNG;[14] and for the detection of high-risk human papillomavirus infection (hrHPV) for cervical cancer screening in well woman clinics in this same setting.[30]

The limitations of syndromic management as an effective strategy for the diagnosis, treatment and control of STIs in LMICs have been recognized for over two decades.[1 2] Newly-available STI diagnostic tests that can be provided at point of clinical care offer a possible solution to these public health priorities for the first time. A major research effort is warranted to evaluate the effectiveness, acceptability, health system implementation requirements and cost-effectiveness of these newly-available technologies in order to tackle the continuing epidemics of STIs and their associated adverse health outcomes in high-burden, low-resource settings.

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**Conflicts of interest**

None declared

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**Data sharing statement**

"No additional data is available".

**Contributors:**

LMV Supported data collection in antenatal clinics; wrote first draft of manuscript. She is guarantor.

PT Supported laboratory testing.

CR Led and supervised laboratory testing.

GR Supported laboratory testing.

JW Supported laboratory testing.

JG Supported data collection in well woman clinics.

JA Supported data collection in sexual health and well woman clinics.

CO Supported data collection in sexual health clinics.

GM Supported data collection in antenatal clinics.

PK Supported data collection in sexual health clinics.

BK Provided support and oversight in data collection at sites in Western Highlands

AK Provided support and oversight in data collection at sites in Eastern Highlands

ZK Provided laboratory support and testing in Western Highlands

GL Provided guidance and support in the design of the study in sexual health and well woman clinics

AK-H Provided guidance and oversight in the design and data collection at each clinic type

HW Cleaned and analysed the data.

PS Provided guidance and oversight in the design of each study

GDLM Provided guidance and support in the design of the study in each of the clinic settings.

JMK Provided guidance and support in the design of the study in each of the clinic settings.

ALV designed the studies and data collection tools and monitored data collection for each of the three studies and revised the first draft of the paper.

All authors have read and approve the final manuscript.

## References

1. Adler MW. Sexually transmitted diseases control in developing countries. *Genitourin Med* 1996;72(2):83-8. [published Online First: 1996/04/01]

2. van Dam CJ, Becker KM, Ndowa F, et al. Syndromic approach to STD case management: where do we go from here? *Sex Transm Infect* 1998;74 Suppl 1:S175-8. [published Online First: 1999/02/19]

3. Newman L, Rowley J, Vander Hoorn S, et al. Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting. *PLoS One* 2015;10(12):e0143304. doi: 10.1371/journal.pone.0143304 [published Online First: 2015/12/10]

4. WHO. Sexually transmitted infections (STIs): The importance of a renewed commitment to STI prevention and control in achieving global sexual and reproductive health. Geneva: WHO, 2012.

5. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;386(9995):743-800. doi: 10.1016/s0140-6736(15)60692-4 [published Online First: 2015/06/13]

6. Detels R, Green AM, Klausner JD, et al. The incidence and correlates of symptomatic and asymptomatic Chlamydia trachomatis and Neisseria gonorrhoeae infections in selected populations in five countries. *Sex Transm Dis* 2011;38(6):503-9. [published Online First: 2012/01/19]

7. Shah M, Deshmukh S, Patel SV, et al. Validation of vaginal discharge syndrome among pregnant women attending obstetrics clinic, in the tertiary hospital of Western India. *Indian J Sex Transm Dis* 2014;35(2):118-23. doi: 10.4103/0253-7184.142406 [published Online First: 2014/07/01]

8. Vallely A, Page A, Dias S, et al. The prevalence of sexually transmitted infections in Papua New Guinea: A systematic review and meta-analysis. *PLoS ONE* 2010;5(12):e15586.

9. Vallely LM, Toliman P, Ryan C, et al. Prevalence and risk factors of Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis and other sexually transmissible infections among

women attending antenatal clinics in three provinces in Papua New Guinea: a cross-sectional survey. *Sex Health* 2016 doi: 10.1071/sh15227 [published Online First: 2016/06/02]

10. Wangnapi RA, Soso S, Unger HW, et al. Prevalence and risk factors for Chlamydia trachomatis, Neisseria gonorrhoeae and Trichomonas vaginalis infection in pregnant women in Papua New Guinea. *Sex Transm Infect* 2014 doi: 10.1136/sextrans-2014-051670 [published Online First: 2014/10/15]
11. Mola GDL. Manual of Standard Managements in Obstetrics and Gynaecology for Doctors, HEOs and Nurses in Papua New Guinea. Seventh Edition ed2016.
12. Vallely A, Ryan CE, Allen J, et al. High prevalence and incidence of HIV, sexually transmissible infections and penile foreskin cutting among sexual health clinic attendees in Papua New Guinea. *Sex Health* 2014;11(1):58-66. doi: 10.1071/sh13197 [published Online First: 2014/03/13]
13. Msuya SE, Uriyo J, Stray-Pedersen B, et al. The effectiveness of a syndromic approach in managing vaginal infections among pregnant women in northern Tanzania. *East Afr J Public Health* 2009;6(3):263-7. [published Online First: 2010/09/02]
14. Badman SG, Vallely LM, Toliman P, et al. A novel point-of-care testing strategy for sexually transmitted infections among pregnant women in high-burden settings: results of a feasibility study in Papua New Guinea. *BMC Infect Dis* 2016;16:250. doi: 10.1186/s12879-016-1573-4 [published Online First: 2016/06/09]
15. Pettifor A, Walsh J, Wilkins V, et al. How effective is syndromic management of STDs?: A review of current studies. *Sex Transm Dis* 2000;27(7):371-85. [published Online First: 2000/08/19]
16. White RG, Moodley P, McGrath N, et al. Low effectiveness of syndromic treatment services for curable sexually transmitted infections in rural South Africa. *Sex Transm Infect* 2008;84(7):528-34. doi: 10.1136/sti.2008.032011 [published Online First: 2008/08/19]
17. Maina AN, Kimani J, Anzala O. Prevalence and risk factors of three curable sexually transmitted infections among women in Nairobi, Kenya. *BMC Res Notes* 2016;9:193. doi: 10.1186/s13104-016-1990-x [published Online First: 2016/03/31]

18. Francis SC, Ao TT, Vanobberghen FM, et al. Epidemiology of curable sexually transmitted infections among women at increased risk for HIV in northwestern Tanzania: inadequacy of syndromic management. *PLoS One* 2014;9(7):e101221. doi: 10.1371/journal.pone.0101221 [published Online First: 2014/07/16]

19. Shah NS, Kim E, de Maria Hernandez Ayala F, et al. Performance and comparison of self-reported STI symptoms among high-risk populations - MSM, sex workers, persons living with HIV/AIDS - in El Salvador. *Int J STD AIDS* 2014;25(14):984-91. doi: 10.1177/0956462414526860 [published Online First: 2014/03/13]

20. Tann CJ, Mpairwe H, Morison L, et al. Lack of effectiveness of syndromic management in targeting vaginal infections in pregnancy in Entebbe, Uganda. *Sex Transm Infect* 2006;82(4):285-9. doi: 10.1136/sti.2005.014845 [published Online First: 2006/08/01]

21. Lusk MJ, Garden FL, Rawlinson WD, et al. Cervicitis aetiology and case definition: a study in Australian women attending sexually transmitted infection clinics. *Sex Transm Infect* 2016;92(3):175-81. doi: 10.1136/sextrans-2015-052332 [published Online First: 2015/11/21]

22. Ryan CA, Courtois BN, Hawes SE, et al. Risk assessment, symptoms, and signs as predictors of vulvovaginal and cervical infections in an urban US STD clinic: implications for use of STD algorithms. *Sex Transm Infect* 1998;74 Suppl 1:S59-76. [published Online First: 1999/02/19]

23. Zemouri C, Wi TE, Kiarie J, et al. The Performance of the Vaginal Discharge Syndromic Management in Treating Vaginal and Cervical Infection: A Systematic Review and Meta-Analysis. *PLoS One* 2016;11(10):e0163365. doi: 10.1371/journal.pone.0163365 [published Online First: 2016/10/06]

24. Vandepitte J, Bukenya J, Hughes P, et al. Clinical characteristics associated with Mycoplasma genitalium infection among women at high risk of HIV and other STI in Uganda. *Sex Transm Dis* 2012;39(6):487-91. doi: 10.1097/OLQ.0b013e31824b1cf3 [published Online First: 2012/05/18]

25. van der Eem L, Dubbink JH, Struthers HE, et al. Evaluation of syndromic management guidelines for treatment of sexually transmitted infections in South African women. *Trop Med Int Health* 2016;21(9):1138-46. doi: 10.1111/tmi.12742 [published Online First: 2016/06/29]

26. Pereyre S, Laurier Nadalie C, Bebear C. Mycoplasma genitalium and Trichomonas vaginalis in France: a point prevalence study in people screened for sexually transmitted diseases. *Clin Microbiol Infect* 2017;23(2):122.e1-22.e7. doi: 10.1016/j.cmi.2016.10.028 [published Online First: 2016/11/12]

27. Gaydos CA, Van Der Pol B, Jett-Goheen M, et al. Performance of the Cepheid CT/NG Xpert Rapid PCR Test for Detection of Chlamydia trachomatis and Neisseria gonorrhoeae. *J Clin Microbiol* 2013;51(6):1666-72. doi: 10.1128/jcm.03461-12 [published Online First: 2013/03/08]

28. Tabrizi SN, Unemo M, Golparian D, et al. Analytical evaluation of GeneXpert CT/NG, the first genetic point-of-care assay for simultaneous detection of Neisseria gonorrhoeae and Chlamydia trachomatis. *J Clin Microbiol* 2013;51(6):1945-7. doi: 10.1128/jcm.00806-13 [published Online First: 2013/04/05]

29. Aia P, Kal M, Lavu E, et al. The Burden of Drug-Resistant Tuberculosis in Papua New Guinea: Results of a Large Population-Based Survey. *PLoS One* 2016;11(3):e0149806. doi: 10.1371/journal.pone.0149806 [published Online First: 2016/03/24]

30. Toliman P, Badman SG, Gabuzzi J, et al. Field Evaluation of Xpert HPV Point-of-Care Test for Detection of Human Papillomavirus Infection by Use of Self-Collected Vaginal and Clinician-Collected Cervical Specimens. *J Clin Microbiol* 2016;54(7):1734-7. doi: 10.1128/jcm.00529-16 [published Online First: 2016/04/15]

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

**I confirm that all the items listed below have been considered and included as applicable in the submitted manuscript.**

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4-5 |
| Objectives | 3 | State specific objectives, including any pre-specified hypotheses | 5 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 6 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 6 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 7 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 6 |
| Study size | 10 | Explain how the study size was arrived at | 6 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6,7 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 7 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 7 |
| | | (*c*) Explain how missing data were addressed | N/A |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | 7 |
| | | (*e*) Describe any sensitivity analyses | 7 |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 8 |
| | | (b) Give reasons for non-participation at each stage | N/A |
| | | (c) Consider use of a flow diagram | N/A |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 10 |
| | | (b) Indicate number of participants with missing data for each variable of | N/A |

| | | | |
|---|---|---|---|
| | | interest | |
| Outcome data | 15* | Report numbers of outcome events or summary measures | 10,11 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 11-14 |
| | | (*b*) Report category boundaries when continuous variables were categorized | N/A |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | N/A |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 11-14 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 15 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 15-16 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 16 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 16 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 17 |
| Data sharing statement | | "No additional data is available". | 17 |
| Contributors | | Lists all contributors to research and manuscript | 17 |

*Give information separately for exposed and unexposed groups.

**Lisa Vallely**
**12 July 2017**

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Performance of syndromic management for the detection and treatment of genital Chlamydia trachomatis, Neisseria gonorrhoeae and Trichomonas vaginalis among women attending antenatal, well woman and sexual health clinics in Papua New Guinea: a cross-sectional study.



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|---|---|
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Title: **Performance of syndromic management for the detection and treatment of genital *Chlamydia trachomatis, Neisseria gonorrhoeae* and *Trichomonas vaginalis* among women attending antenatal, well woman and sexual health clinics in Papua New Guinea: a cross-sectional study.**

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**ABSTRACT**

**Objective:** Papua New Guinea (PNG) has among the highest estimated prevalences of genital *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG) and *Trichomonas vaginalis* (TV) of any country in the Asia-Pacific region. Diagnosis and treatment of these infections has relied on the WHO-endorsed syndromic management strategy that uses clinical presentation without laboratory confirmation to make treatment decisions. We evaluated the performance of this strategy in clinical settings in PNG.

**Design:** Women attending antenatal (ANC), well woman (WWC) and sexual health (SHC) clinics in four provinces were invited to participate, completed a face-to-face interview and clinical examination, and provided genital specimens for laboratory testing. We estimated the performance characteristics of syndromic diagnoses against combined laboratory diagnoses.

**Results:** 1764 women were enrolled (ANC=765; WWC=614; SHC=385). The prevalences of CT, NG and TV were highest among women attending ANC and SHC. Among antenatal women, syndromic STI diagnosis had low sensitivity (9%-21%) and positive predictive value (7%-37%); but high specificity (76%-89%) and moderate negative predictive value (55%-86%) for the combined endpoint of laboratory-confirmed CT, NG or TV. Among women attending WWC and SHC, 'vaginal discharge syndrome' had moderate to high sensitivity (72%-78%) and NPV (62%-94%), but low specificity (26%-33%) and PPV (8%-38%). 'Lower abdominal pain syndrome' had low sensitivity (26%-41%) and PPV (8%-23%) but moderate specificity (66%-68%) and high NPV (74%-93%) among women attending WWC; and moderate-high sensitivity (67%-79%) and NPV (62%- 86%), but low specificity (26%-28%) and PPV (14%-33%), among SHC attendees.

**Conclusion:** The performance of syndromic management for the detection and treatment of genital chlamydia, gonorrhoea and trichomonas was poor among women in different clinical settings in PNG. New diagnostic strategies are needed to control these infections and to prevent their adverse health outcomes in PNG and other high-burden countries.

**Article summary:**

***Strengths and limitations of this study***

- We present data highlighting high prevalences of *C. trachomatis, N. gonorrhoeae* and *T. vaginalis* infection among women from three different clinical populations in Papua New Guinea .
- Our findings reflect the high proportion of asymptomatic infections among women in these clinical populations, and the limited association between clinical findings and laboratory-confirmed genital STIs.
- Our findings are consistent with earlier studies, which demonstrated inadequate performance of syndromic management for STI detection and treatment in pregnancy, based either on symptoms alone, or on symptoms plus clinical examination.
- We did not investigate bacterial vaginosis or *Mycoplasma genitalium*, and may therefore have underestimated the performance of syndromic management for the detection of STIs and genital infections.

## INTRODUCTION

Sexually transmissible infections (STIs) are a major global public health concern.[1] Every year there are an estimated 500 million new cases of curable STIs, the majority of which occur in low-income settings.[2] Adverse outcomes of curable STIs include pelvic inflammatory disease, infertility, ectopic pregnancy, miscarriage, stillbirth, premature labour and low birth weight; and increased risk of HIV acquisition and transmission.[3] The three most common curable genital STIs, *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG) and *Trichomonas vaginalis* (TV) are frequently asymptomatic, particularly in women[4]. Inability to diagnose curable STIs has been a major barrier to their control, because many cases remain undetected and therefore untreated, with the potential for onward transmission. Accurate, nucleic acid-based diagnostic tests are now widely used in high-income countries but are largely unavailable in low- and middle-income countries (LMICs) where the highest prevalences of these STIs and their associated adverse health outcomes occur.[2] Even more traditional methods, such as microscopy, culture and serology are not widely available in LMICs, and in any case have low sensitivity for detecting current infection.

In the absence of access to diagnostic STI testing, the World Health Organization (WHO) in the 1990s developed a syndromic management strategy for diagnosing genital infections based on groups of genital symptoms to guide treatment decisions without laboratory tests.[2] The main syndromic diagnoses in women have been 'vaginal discharge syndrome' (VDS); 'lower abdominal pain syndrome' (LAPS); and 'genital ulcer syndrome' (GUS), each of which are treated using a combination of antibiotics to cover the most likely underlying infection(s). Syndromic management strategies lead to overtreatment, because there are other, non-sexually transmitted causes of the syndromes; or undertreatment ,[5] because they do not address asymptomatic infections that account for the majority of STIs globally.[4] Consequently, despite the wide-scale implementation of syndromic management, this has not been an effective strategy in reducing population-level prevalences, particularly in high-burden settings such as Papua New Guinea (PNG),[6 7] which has among the highest estimated prevalences of genital chlamydia, gonorrhoea and trichomonas of any country in the Asia-Pacific region.[2 7 8]

In this paper, we present findings on the performance of syndromic STI management for the treatment of curable genital STIs among women attending antenatal, well woman and sexual health clinics in PNG.

## METHODS

### Study design and procedures

We undertook a cross-sectional bio-behavioural survey to investigate STI prevalences and risk factors for infection among women attending routine clinical services in four provinces (Eastern Highlands, Hela, Western Highlands and Central provinces): (a) pregnant women attending routine antenatal clinics; (b) women attending cervical cancer screening services at dedicated well woman clinics; and (c) women attending sexual health clinics. A key objective of the study was to evaluate the clinical performance of syndromic STI diagnosis for the treatment of curable genital STIs among three different clinical populations in this setting. An *a priori* assumption, based on our earlier systematic review and meta-analysis,[6] was that the prevalence of STIs would vary between women in these different populations and lead to differences in the performance of syndromic management.

All women attending their first clinic visit during the study period (which varied across clinics, between December 2011 and January 2015) were invited to join and were consecutively enrolled into the study following informed consent procedures. Age eligibility criteria varied by clinic type: women aged 18 years or older were recruited at antenatal and sexual health clinics; women aged 30 – 59 years (the target age group for cervical cancer screening in PNG) were recruited at well woman clinics.

Women took part in a face-to-face interview, conducted by a trained health care worker using study-specific case record forms (CRFs) in which socio-demographic, behavioural and clinical information were collected. Locator information and mobile phone contact details were also collected to facilitate subsequent follow-up. Participants in all clinical settings were asked about current genital symptoms, and past history of STIs. Genital examination was conducted as part of routine clinical assessment among women attending well woman and sexual health clinics only, in accordance with PNG standard guidelines (genital examination is not routinely offered in antenatal clinics).[9] Women attending antenatal clinics provided a self-collected mid-cavity vaginal swab for laboratory-based STI testing (CT, NG, TV); women attending well woman and sexual health clinics provided clinician-collected high vaginal (for TV) and cervical (for CT, NG) swabs. All women provided a venepuncture specimen for point-of-care syphilis screening and HIV counselling and testing.[9] In all clinic settings, women were provided with a date to return for follow-up, when they were given their STI test results, and additional treatment if indicated.[9] Women with clinical features (symptoms and/or clinical examination findings) consistent with one or more STI syndromes were managed according to national guidelines.[9] Clinical findings and treatment provided were recorded in individual client-held health record books and in study-specific CRFs. All participants were advised to return for clinical review to receive their laboratory STI test results, and additional treatment if required. Women with

positive STI test results who did not return for scheduled visits were contacted by mobile phone or by clinical research staff in the community, and were advised to re-attend for review. All diagnostic tests and antibiotic treatment were provided free-of-charge.

**Laboratory Methods**

Genital swabs were tested for CT, NG and TV by real-time polymerase chain reaction (PCR) at the PNG Institute of Medical Research (PNGIMR) Sexual and Reproductive Health unit laboratory in Goroka, using procedures and methods as previously described.[10] Sexual and Reproductive Health unit laboratory was enrolled in an external quality assurance program through the Royal College of Pathologists of Australia for CT and NG PCR.

**Data management and statistical methods**

Participant study folders (containing completed case record forms and laboratory results slips) were subject to quarterly clinical audits by the study lead investigator (AV) throughout. Data were entered at each clinical site into a study-specific MS Access database. Database entries were validated against participant study folders for accuracy. Laboratory test results entered into the clinical database were checked for accuracy against source documents (laboratory results slips) for all participants at the end of the study. The performance characteristics (sensitivity, specificity, positive and negative predictive value) of vaginal discharge syndrome' (VDS) and 'lower abdominal pain syndrome' (LAPS) were estimated against laboratory diagnoses of CT, NG and TV, and combinations of two or more STIs were calculated for the three population groups (antenatal clinic, well woman and sexual health clinic). Fisher's Exact Test was used to compare statistical differences in outcomes of interest between groups. There were no modifications for multiple comparisons. All statistical analyses were performed with Stata ver. 12.1 (StataCorp LP, College Station, TX, USA).

**Ethical considerations**

Ethical approval was obtained from the Institutional Review Board of the PNGIMR (1124; 1111) and the Medical Research Advisory Committee of the PNG National Department of Health in Papua New Guinea (11.34;11.18; 10.17) ; and from Human Research Ethics Committees of the Alfred Hospital Melbourne (390/11), and the UNSW Sydney (HC12155; HC11250; HC 12120), in Australia. Written informed consent (signature or witnessed thumbprint) was obtained from all participants prior to study enrolment. Women were each assigned a unique alphanumeric study identification number from a pre-printed study register to ensure anonymity and confidentiality.

## RESULTS

During the study period, a total of 1764 women were enrolled at 10 participating clinics (six antenatal clinics, n=765; two well woman clinics, n=614; and two sexual health clinics, n=385; Table 1).

### Socio-demographic characteristics

Women attending antenatal clinics were significantly younger than those attending well woman or sexual health clinics (Table 1). Overall, 89% (1573/1764) of women were married; around half reported attending primary school only (904/1764); and 57% were not in paid employment (920/1764). Women attending sexual health clinics were less likely to be married, or to be in paid employment and had lower educational attainment, compared to women enrolled in antenatal and well woman clinics.

### Sexual behavioural characteristics

Overall, around 40% of women (692/1764) reported sexual debut before 18 years of age. Sexual health clinic attendees were more likely to have had a younger age of sexual debut than women attending antenatal or well woman clinics (56.6% vs. 34.0 and 34.9%, respectively, $p<0.001$; Table 1). Women attending sexual health clinics were also significantly more likely to report having more than four lifetime sexual partners; more than two sexual partners in the past week; vaginal sex more than four times in the past week; and ever having had sex in exchange for gifts or money compared with women attending antenatal or well woman clinics. Sexual health clinic attendees were more likely to report condom use at last vaginal sex, compared with women in other clinical settings.

358 **Table 1: Sociodemographic characteristics by clinic type**

| | Total | Clinic attended | | | |
|---|---|---|---|---|---|
| | N (%) 1764 | Antenatal N=765 | Well woman N= 614 | Sexual health N= 385 | P-value |
| **Age groups** | | | | | <0.001 |
| <20 years | 99 (5.6) | 85 (11.1) | 0 | 14 (3.6) | |
| 20-24 years | 300 (17.0) | 246 (31.2) | 0 | 54 (14.1) | |
| 25-29 years | 295 (16.7) | 224 (29.3) | 0 | 71 (18.4) | |
| 30+ years | 1070 (60.7) | 210 (27.5) | 614 (100) | 246 (63.1) | |
| **Median age (IQR)** | 32 (25-37) | 25 (22-30) | 37 (34-41) | 32 (26-37) | <0.001 |
| **Marital status** | | | | | <0.001 |
| Married | 1573 (89.2) | 719 (94.0) | 544 (88.6) | 310 (80.8) | |
| Single | 37 (2.1) | 22 (2.9) | 1 (0.2) | 14 (3.6) | |
| Other | 154 (8.7) | 24 (3.1) | 69 (11.2) | 61 (15.8) | |
| **Employment status** | | | | | |
| No current paid work | 920 (57.2) | 591 (77.3) | 311 (50.7) | 18 (4.7) | <0.001 |
| Gardening/farmer | 996 (56.5) | 482 (63.0) | 382 (62.2) | 132 (34.3) | <0.001 |
| House hold duties | 1464 (83.0) | 666 (87.1) | 491 (80.0) | 307 (79.7) | <0.001 |
| **Education** | | | | | <0.001 |
| No formal education | 427 (24.2) | 145 (14.6) | 172 (28.0) | 110 (28.6) | |
| Attended only Primary School (Grades 1-8) | 904 (51.3) | 386 (50.5) | 313 (51.0) | 205 (53.3) | |
| Attended Secondary School (Grades 9-12) | 331 (18.8) | 207 (27.1) | 73 (11.9) | 51 (13.3) | |
| Other (Tertiary, tech, voc.) | 102 (5.8) | 27 (3.5) | 56 (9.1) | 19 (4.9) | |
| **When did you last have sex** | | | | | <0.001 |
| Today/yesterday | 168 (9.5) | 73 (9.5) | 54 (8.8) | 41 (10.7) | |
| 2 days ago | 187 (10.6) | 74 (9.7) | 49 (8.0) | 64 (16.6) | |
| 3 days ago | 117 (6.6) | 59 (7.7) | 33 (5.4) | 25 (6.5) | |
| 4 or more days ago | 1292 (73.2) | 559 (73.1) | 478 (77.9) | 255 (66.2) | |
| **Vaginal sex in the last week** | | | | | <0.001 |
| None | 702 (39.8) | 372 (48.6) | 233 (38.0) | 97 (25.2) | |
| Once | 623 (35.3) | 196 (25.6) | 271 (44.1) | 156 (40.5) | |
| Twice | 212 (12.0) | 100 (13.1) | 51 (8.3) | 61 (15.8) | |
| Three times | 114 (6.5) | 55 (7.2) | 28 (4.6) | 31 (8.1) | |
| Four or more times | 113 (6.4) | 42 (5.5) | 31 (5.1) | 40 (10.4) | |
| **Condom used last vaginal sex** | | | | | <0.001 |
| No | 1621 (91.9) | 718 (93.9) | 578 (94.1) | 325 (84.4) | |
| Yes | 143 (8.1) | 47 (6.1) | 36 (5.9) | 60 (15.6) | |
| **Number of people had vaginal sex with in the last week** | | | | | <0.001 |
| None | 655 (37.1) | 308 (40.3) | 229 (37.3) | 118 (30.7) | |
| 1-person | 1069 (60.6) | 447 (58.4) | 373 (60.8) | 249 (64.7) | |
| 2 or more people | 40 (2.3) | 10 (1.3) | 12 (2.0) | 18 (4.7) | |
| **Condom use in the past month** | | | | | <0.001 |
| Always | 24 (1.4) | 3 (0.4) | 8 (1.3) | 13 (3.4) | |
| Sometimes | 298 (16.9) | 128 (16.7) | 105 (17.1) | 65 (16.9) | |
| Most of the time | 32 (1.8) | 5 (0.7) | 6 (1.0) | 21 (5.5) | |
| Never | 1410 (79.9) | 629 (82.2) | 495 (80.6) | 286 (74.3) | |
| **Ever had sex for money/gifts** | | | | | <0.001 |
| No | 1475 (83.6) | 723 (94.5) | 542 (88.3) | 210 (54.6) | |
| Yes | 289 (16.9) | 42 (5.5) | 72 (11.7) | 175 (45.5) | |
| **Age at sexual debut** | | | | | <0.001 |
| ≤18 | 692 (39.2) | 260 (34.0) | 214 (34.9) | 218 (56.6) | |
| >18 years | 1072 (60.8) | 505 (66.0) | 400 (65.2) | 167 (43.4) | |
| **Lifetime number of sexual partners** | | | | | <0.001 |
| 1-person | 805 (45.6) | 357 (46.7) | 338 (55.1) | 110 (28.6) | |
| 2-people | 349 (19.8) | 165 (21.6) | 127 (20.7) | 57 (14.8) | |
| 3-people | 178 (10.1) | 87 (11.4) | 49 (8.0) | 42 (10.9) | |
| 4 or more people | 432 (24.5) | 156 (20.4) | 100 (16.3) | 176 (45.7) | |
| **Ever had anal sex** | | | | | <0.001 |
| No | 1538 (87.2) | 685 (89.5) | 570 (92.8) | 283 (73.5) | |
| Yes | 226 (12.8) | 80 (10.5) | 44 (7.2) | 102 (26.5) | |

359

360

**Clinical and laboratory findings**

Prevalences of CT, NG and TV were highest among women attending antenatal and sexual health clinics, compared with those attending well woman clinics e.g. the prevalence of chlamydia was 22.9%, 21.4% and 7.5%, respectively in these populations (Table 2). Antenatal women and those attending sexual health clinics were also more likely to have two or more STIs compared with well woman clinic attendees (14.2%, 10.6% and 4.8%, respectively; Table 2).

**Table 2: Syndromic STI diagnosis and prevalence of *C. trachomatis, N. gonorrhoeae, T. vaginalis***

| | **Antenatal clinic** N=765 (%) | **Well woman clinic** N=614 (%) | **Sexual health clinic** N=385 (%) |
|---|---|---|---|
| Lower abdominal pain syndrome (LAPS) | 166 (21.7) | 200 (32.6) | 282 (73.2) |
| Vaginal discharge syndrome (VDS) | 156 (20.4) | 422 (67.8) | 281 (73.0) |
| *C. trachomatis* (CT) | 175 (22.9) | 46 (7.5) | 78 (21.4) |
| *N. gonorrhoeae* (NG) | 109 (14.2) | 49 (8.0) | 63 (16.4) |
| *T. vaginalis* (TV) | 171 (22.4) | 92 (15.0) | 54 (14.0) |
| More than 1 of CT, NG, TV | 109 (14.3) | 29 (4.7) | 40 (10.4) |
| No STI | 438 (57.3) | 460 (74.9) | 240 (62.3) |
| Any STI | 327 (42.7) | 154 (25.1) | 145 (37.7) |
| One STI | 218 (28.5) | 125 (20.4) | 105 (27.3) |
| Two STIs | 90 (11.7) | 25 (4.1) | 30 (8.0) |
| Three STIs | 19 (2.5) | 4 (0.7) | 10 (2.6) |

The prevalence of vaginal discharge syndrome was highest among women attending sexual health clinics (73.0%) and well woman clinics (68.7%), compared with antenatal women (20.4%; Table 2). Lower abdominal pain syndrome was also less frequently diagnosed among antenatal women (Table 2).

**Performance of syndromic management**

Among antenatal women, syndromic diagnosis (based on clinical symptoms alone) had low sensitivity (9%-21%) and positive predictive value (7%-37%); but high specificity (76%-89%) and moderate negative predictive value (55%-86%) for correctly classifying women as having infection with CT, NG or TV (Table 3). Syndromic management alone would have led to considerable overtreatment and under-diagnosis in this population. For example, 38% (60/156) of antenatal women with VDS had any of CT, NG or TV and would have been appropriately treated; 62% (96/156) of women with symptoms but without detectable CT, NG or TV would have been treated unnecessarily; and 82% (267/327) of those with any of CT, NG or TV infection would not have been treated because they did not have vaginal discharge (Table 3).

Among women attending well woman clinics, LAPS had low sensitivity (26%-41%) and positive predictive value (8%-23%) but moderate to high specificity (66%-68%) and negative predictive value (74%-93%) for the detection of any laboratory-confirmed STI, or CT, NG, TV individually (Table 3). VDS had high sensitivity (72%-75%) and negative predictive value (79%-94%) but low specificity (32%-

33%) and positive predictive value (8%-25%). Around 1 in 4 women with LAPS (46/200; 23%) had any of CT, NG or TV, and would have been correctly treated based on syndromic management alone; 77% (154/200) of women with LAPS did not have a laboratory-confirmed infection, and therefore would have been treated unnecessarily; and 70% (108/154) of those with any of CT, NG or TV would not have been detected and treated based on a diagnosis of LAPS alone, because they did not have appropriate clinical features. Correspondingly, around 27% (114/422) of women with VDS would have been correctly treated; 73% (308/422) of those with VDS would have been unnecessarily treated; and 26% (40/154) of those with any of CT, NG or TV would not have been diagnosed and treated (Table 3).

Among women attending sexual health clinics, LAPS and VDS had a moderate to high sensitivity (67%-79%) and negative predictive value (62%- 86%), but low specificity (26%-28%) and positive predictive value (14%-33%) for the detection of any laboratory confirmed STI, or CT, NG, TV individually (Table 4). Around 39% (109/282) of women with LAPS would have been correctly treated; 61% (173/282) with LAPS would have been unnecessarily treated; and 25% (36/145) of women with any of CT, NG or TV would not have been diagnosed and treated. Among women with VDS, around 38% (106/281) would have been correctly treated; 62% (175/281) would have been unnecessarily treated; and 27% (39/145) of those with any of CT, NG or TV would not have been diagnosed and treated (Table 3).

**Table 3: Syndromic diagnosis and laboratory-confirmed STIs**

| Syndromic diagnosis | | Any STI N (%)* | | | *C. trachomatis* N (%)* | | | *N. gonorrhoeae* N (%)* | | | *T. vaginalis* N (%)* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Yes | No | Performance (95% CI) | Yes | No | Performance (95%CI) | Yes | No | Performance (95% CI) | Yes | No | Performance (95% CI) |
| **Antenatal clinics (n=765)** | | | | | | | | | | | | | |
| LAPS** (166/765; 21.7%) | Yes | 60 (18.4) | 106 (14.2) | SENS: 18% (14%, 23%) SPEC: 76% (72%, 80%) PPV: 36% (29%, 44%) NPV: 55% (51%, 59%) | 30 (17.1) | 136 (23.0) | SENS:17% (12%, 24%) SPEC:77% (73%,80%) PPV: 18% (13%, 25%) NPV: 76% (72%, 79%) | 15 (13.8) | 151 (23.0) | SENS: 14% (8%, 22%) SPEC: 77% (74%, 80%) PPV: 9% (5%, 14%) NPV: 84% (81%, 87%) | 29 (83.0) | 457 (77.0) | SENS:17% (12%,23%) SPEC: 77% (73%, 80%) PPV: 17% (12%, 24%) NPV: 76% (73%, 80%) |
| | No | 267 (81.7) | 332 (75.8) | | 145 (82.9) | 454 (77.0) | | 94 (86.2) | 505 (77.0) | | 142 (83.0) | 457 (77.0) | |
| VDS *** (156/765; 20.4%) | Yes | 60 (18.4) | 96 (22.0) | SENS: 18% (14%, 23%) SPEC: 78% (74%, 82%) PPV: 38% (40%, 47%) NPV: 56% (52%, 60%) | 37 (21.1) | 119 (20.2) | SENS: 21%(15%, 28%) SPEC: 80% (76%,83%) PPV: 24% (17%, 31%) NPV: 77% (74%, 81%) | 16 (14.7) | 140 (21.3) | SENS: 15% (9%,23%) SPEC: 79% (75%,82%) PPV: 10% (96%,16%) NPV: 85% (82%,87%) | 33 (19.3) | 123 (20.7) | SENS: 19% (14%,26%) SPEC: 79% (76%, 82%) PPV: 21% (15%, 28%) NPV: 77% (74%,81%) |
| | No | 267 (81.7) | 342 (78.1) | | 138 (78.9) | 471 (79.8) | | 93 (85.3) | 516 (78.7) | | 138 (80.7) | 471 (79.3) | |
| **Well woman clinics (n=614)** | | | | | | | | | | | | | |
| LAPS** (200/614; 32.6%) | Yes | 46 (29.9) | 154 (33.5) | SENS: 30% (23%, 38%) SPEC: 67% (62%, 71%) PPV: 23% (17%, 29%) NPV: 74% (69%, 78%) | 19 (41.3) | 181 (31.9) | SENS: 41%(27%, 57%) SPEC: 68% (64%,72%) PPV: 10% (6%, 14%) NPV: 93% (91%, 96%) | 15 (30.6) | 185 (32.7) | SENS: 31% (18%, 45%) SPEC: 67% (63%, 71%) PPV: 8% (4%, 12%) NPV: 92% (89%, 94%) | 24 (26.1) | 176 (33.7) | SENS: 26% (17%, 36%) SPEC: 66% (62%, 70%) PPV: 12% (8%, 17%) NPV: 84% (80, 87%) |
| | No | 108 (70.1) | 306 (66.5) | | 27 (58.8) | 387 (68.1) | | 34 (69.4) | 380 (67.3) | | 68 (73.9) | 346 (66.3) | |
| VDS *** (422/614; 68.7%) | Yes | 114 (74.0) | 308 (67.0) | SENS: 74% (66%, 81%) SPEC: 33% (29%, 38%) PPV: 25% (22%, 29%) NPV: 79% (74%, 84%) | 33 (71.7) | 389 (68.5) | SENS: 72% (57%,84%) SPEC: 32% (28%,36%) PPV: 8% (6%, 9%) NPV: 93% (90%, 96%) | 37 (75.5) | 385 (68.1) | SENS: 75% (61%, 87%) SPEC: 32% (28%, 36%) PPV: 9% (7%, 10%) NPV: 94% (90%, 96%) | 70 (76.1) | 352 (67.4) | SENS: 76% (66%, 84%) SPEC: 33% (28%, 37%) PPV: 17% (15%, 18%) NPV: 89% (84%, 92%) |
| | No | 40 (26.0) | 152 (33.0) | | 13 (28.3) | 179 (31.5) | | 12 (24.5) | 180 (31.9) | | 22 (23.9) | 170 (32.6) | |
| **Sexual health clinics (n=385)** | | | | | | | | | | | | | |
| LAPS ** (282/385; 73.2%) | Yes | 109 (75.1) | 173 (72.1) | SENS: 75% (67%, 82%) SPEC: 28% (22%, 34%) PPV: 39% (33%, 45%) NPV: 65% (55%, 74%) | 62 (79.5) | 220 (71.7) | SENS:79% (69%, 88%) SPEC:28% (23%, 34%) PPV: 22% (20%, 24%) NPV: 84% (77%, 90%) | 46 (27.0) | 236 (73.3) | SENS: 73% (60%, 83%) SPEC: 27% (22%, 32%) PPV: 16% (12%, 21%) NPV: 84% (75%, 90%) | 40 (74.1) | 242 (73.1) | SENS: 74% (60%,85%) SPEC: 27% (22%,32%) PPV: 14% (11%, 18%) NPV: 86% (78%, 92%) |
| | No | 36 (24.8) | 67 (27.9) | | 16 (20.5) | 87 (28.3) | | 17 (27.0) | 86 (26.7) | | 14 (25.9) | 89 (26.9) | |
| VDS *** (281/385; 73.0%) | Yes | 106 (73.1) | 175 (72.9) | SENS: 73% (65%,80%) SPEC: 27% (22%, 33%) PPV: 38% (35%, 41%) NPV: 62% (54%, 70%) | 61 (78.2) | 220 (71.7) | SENS: 78% (67%,87%) SPEC: 28% (23%,34%) PPV: 22% (19%, 24%) NPV: 84% (76%, 89%) | 42 (66.7) | 239 (74.2) | SENS: 67% (54%, 78%) SPEC: 26% (21%, 31%) PPV: 15% (13%, 17%) NPV: 80% (73%, 85%) | 40 (74.1) | 241 (72.8) | SENS: 74% (60%,85%) SPEC: 27% (22%, 32%) PPV: 14% (12%, 16%) NPV: 86% (80%, 91%) |
| | No | 39 (26.9) | 65 (27.1) | | 17 (21.8) | 87 (28.3) | | 21 (33.3) | 83 (25.8) | | 14 (25.9) | 90 (27.2) | |

* = prevalence of any and individual STIs in this population ** Lower Abdominal Pain Syndrome *** Vaginal Discharge Syndrome

## DISCUSSION

High prevalences of genital *C. trachomatis, N. gonorrhoeae* and *T. vaginalis* were observed among women attending antenatal, well woman and sexual health clinics in Papua New Guinea. The performance of syndromic management for the detection and treatment of these infections was poor, particularly among antenatal women where more than 80% of those with laboratory-confirmed CT, NG or TV would not have been diagnosed and treated. These findings reflect the high proportion of asymptomatic infections among women in these clinical populations, and the limited association between clinical findings and laboratory-confirmed genital STIs. Around 43% of women attending their first antenatal clinic visit had genital CT, NG or TV; 1 in 5 reported symptoms of abdominal pain or vaginal discharge, and around 1 in 8 reported dysuria or vulval irritation. Despite high prevalences of both genital infections and genital symptoms, syndromic management had extremely low sensitivity and positive predictive value for the detection of CT, NG or TV, and would have resulted in significant overtreatment and missed diagnoses in this population. These STIs have been associated with increased risk of adverse maternal and neonatal health outcomes, including stillbirth, prematurity and low birthweight, if they are not detected and treated during pregnancy.[11-14] The findings presented in this paper are consistent with earlier studies, which demonstrated inadequate performance of syndromic management for STI detection and treatment in pregnancy, based either on symptoms alone, or on symptoms plus clinical examination.[5 8 15-17]

Among women attending well woman clinics and sexual health clinics, VDS had moderate to high sensitivity (up to 79%) and NPV (up to 94%) but low specificity and PPV (both around 30%) for the detection of CT, NG or TV. Around 62-73% of women with symptoms did not have a laboratory-confirmed infection and would have been unnecessarily treated. Lower abdominal pain syndrome performed less well than VDS, particularly among well woman clinic attendees. Similar results have been reported from studies conducted in other high-burden settings, among women attending sexual health and family planning clinics,[17-19] and among women at increased risk of infection, such as commercial or transactional sex workers.[20-22]

In the current study, we did not investigate bacterial vaginosis (BV), *Candida albicans,* or *Mycoplasma genitalium*, and may therefore have underestimated the performance of syndromic management for the detection of STIs and genital infections. High prevalences of bacterial vaginosis (18-23%) have previously been reported among pregnant women,[6 16] the majority of whom were asymptomatic in this setting.[16] It is possible that women with symptoms of vaginal discharge but without laboratory-confirmed CT, NG or TV in the current study may have had BV. Earlier studies in other settings suggest however, that the inclusion of BV appears to have little impact on the performance of syndromic management among antenatal women [15 23] or among women attending

sexual health or family planning clinics.[22 24 25] *M. genitalium* (MG) has been associated with vaginal discharge among women in a variety of settings[24 26] but its presence and clinical correlates have not been investigated among women in PNG. It is therefore difficult to estimate the impact of undiagnosed MG on the performance of syndromic management in the current study. Research from elsewhere indicates that inclusion of MG has little impact on performance[21 27] and that the majority of MG infections in women are asymptomatic,[28] and therefore not amenable to syndromic management strategies.

In accordance with current PNG national STI guidelines, genital examination was not routinely conducted among women attending their first antenatal clinic visit, and even had we elected to do so, would not have been feasible due to a lack of suitable examination rooms and equipment at participating antenatal clinics as well as limited and over-stretched human resources. This may have led to underestimation of the performance of syndromic management in this population, but we consider this unlikely given earlier evidence on the impact on performance if speculum examination is included as part of syndromic assessment.[17]

The performance of syndromic management contrasts markedly with that of newly-available, highly-accurate molecular STI diagnostic tests that can be implemented at point-of-care, such as the GeneXpert platform (Cepheid, Sunnyvale CA), which has been shown to be as accurate as laboratory-based polymerase chain reaction tests for the detection of chlamydia, gonorrhoea and trichomonas infection using genital or urine specimens.[29 30] For example, Xpert had 98.7% sensitivity and 99.4% specificity for the detection of CT using vaginal specimens.[29] Test results are available in approximately 90 minutes for Xpert CT/NG (which simultaneously tests for both chlamydia and gonorrhoea) and 60 minutes for the Xpert TV test. The platform has been shown to be robust and portable and has already revolutionised the diagnosis and management of tuberculosis in many LMICs, including PNG.[31] We have previously demonstrated the operational feasibility of Xpert point-of-care testing and treatment for CT, NG and TV in antenatal clinics in PNG;[16] and for the detection of high-risk human papillomavirus infection (hrHPV) for cervical cancer screening in well woman clinics in this same setting.[16]

The limitations of syndromic management as an effective strategy for the diagnosis, treatment and control of STIs in LMICs have been known for over two decades.[32 33] Recognizing these limitations, the WHO recently advocated a transition from syndromic to etiological STI diagnosis as part of a new and ambitious strategy to eliminate STIs as a public health threat globally by 2030.[34] A major research effort is warranted to evaluate the effectiveness, acceptability, health system implementation requirements and cost-effectiveness of newly-available STI diagnostic tests that can be provided at

point of clinical care in order to tackle the continuing epidemics of STIs and their associated adverse health outcomes in low-resource settings, and to progress down a pathway towards elimination.

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**Conflicts of interest**

None declared

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**Data sharing statement**

"No additional data is available".

**Contributors:**

LMV Supported data collection in antenatal clinics; wrote first draft of manuscript. She is guarantor.

PT Supported laboratory testing.

CR Led and supervised laboratory testing.

GR Supported laboratory testing.

JW Supported laboratory testing.

JG Supported data collection in well woman clinics.

JA Supported data collection in sexual health and well woman clinics.

CO Supported data collection in sexual health clinics.

GM Supported data collection in antenatal clinics.

PK Supported data collection in sexual health clinics.

BK Provided support and oversight in data collection at sites in Western Highlands

AK Provided support and oversight in data collection at sites in Eastern Highlands

ZK Provided laboratory support and testing in Western Highlands

GL Provided guidance and support in the design of the study in sexual health and well woman clinics

AK-H Provided guidance and oversight in the design and data collection at each clinic type

HW Cleaned and analysed the data.

PS Provided guidance and oversight in the design of each study

GDLM Provided guidance and support in the design of the study in each of the clinic settings.

JMK Provided guidance and support in the design of the study in each of the clinic settings.

ALV designed the studies and data collection tools and monitored data collection for each of the three studies and revised the first draft of the paper.

All authors have read and approve the final manuscript.

**References**

1. Newman L, Rowley J, Vander Hoorn S, et al. Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting. *PloS one* 2015;10(12):e0143304. doi: 10.1371/journal.pone.0143304 [published Online First: 2015/12/10]

2. WHO. SEXUALLY TRANSMITTED INFECTIONS (STIs): The importance of a renewed commitment to STI prevention and control in achieving global sexual and reproductive health. Geneva, Switzerland: World Health Organization, 2012.

3. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet (London, England)* 2015;386(9995):743-800. doi: 10.1016/s0140-6736(15)60692-4 [published Online First: 2015/06/13]

4. Detels R, Green AM, Klausner JD, et al. The incidence and correlates of symptomatic and asymptomatic Chlamydia trachomatis and Neisseria gonorrhoeae infections in selected populations in five countries. *Sexually transmitted diseases* 2011;38(6):503-9. [published Online First: 2012/01/19]

5. Shah M, Deshmukh S, Patel SV, et al. Validation of vaginal discharge syndrome among pregnant women attending obstetrics clinic, in the tertiary hospital of Western India. *Indian journal of sexually transmitted diseases* 2014;35(2):118-23. doi: 10.4103/0253-7184.142406 [published Online First: 2014/07/01]

6. Vallely A, Page A, Dias S, et al. The prevalence of sexually transmitted infections in Papua New Guinea: A systematic review and meta-analysis. *PloS one* 2010;5(12):e15586.

7. Vallely LM, Toliman P, Ryan C, et al. Prevalence and risk factors of Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis and other sexually transmissible infections among

women attending antenatal clinics in three provinces in Papua New Guinea: a cross-sectional survey. *Sexual health* 2016 doi: 10.1071/sh15227 [published Online First: 2016/06/02]

8. Wangnapi RA, Soso S, Unger HW, et al. Prevalence and risk factors for Chlamydia trachomatis, Neisseria gonorrhoeae and Trichomonas vaginalis infection in pregnant women in Papua New Guinea. *Sexually transmitted infections* 2014 doi: 10.1136/sextrans-2014-051670 [published Online First: 2014/10/15]
9. Mola GDL. Manual of Standard Managements in Obstetrics and Gynaecology for Doctors, HEOs and Nurses in Papua New Guinea. Seventh Edition ed2016.
10. Vallely A, Ryan CE, Allen J, et al. High prevalence and incidence of HIV, sexually transmissible infections and penile foreskin cutting among sexual health clinic attendees in Papua New Guinea. *Sexual health* 2014;11(1):58-66. doi: 10.1071/sh13197 [published Online First: 2014/03/13]
11. Arol OA, Over M, Manhart L, et al. Sexually Transmitted Infections. In: Dean T, ed. Disease control priorities in developing countries. 2nd edition ed: World Bank 2006:311-30.
12. UNFPA. STIs: Breaking the cycle of transmission. Geneva: Reproductive Health Branch, Technical Support Division, UNFPA 2004.
13. WHO. Global Prevalence and Incidence of Selected Curable Sexually Transmitted Infections: Overview of Estimates Geneva: World Health Organization 2001.
14. WHO. Sexually Transmitted Infections Fact Sheet No. 110. Geneva: World Health Organization 2013.
15. Msuya SE, Uriyo J, Stray-Pedersen B, et al. The effectiveness of a syndromic approach in managing vaginal infections among pregnant women in northern Tanzania. *East African journal of public health* 2009;6(3):263-7. [published Online First: 2010/09/02]
16. Toliman P, Badman SG, Gabuzzi J, et al. Field Evaluation of Xpert HPV Point-of-Care Test for Detection of Human Papillomavirus Infection by Use of Self-Collected Vaginal and Clinician-Collected Cervical Specimens. *Journal of clinical microbiology* 2016;54(7):1734-7. doi: 10.1128/jcm.00529-16 [published Online First: 2016/04/15]

17. Pettifor A, Walsh J, Wilkins V, et al. How effective is syndromic management of STDs?: A review of current studies. *Sexually transmitted diseases* 2000;27(7):371-85. [published Online First: 2000/08/19]

18. White RG, Moodley P, McGrath N, et al. Low effectiveness of syndromic treatment services for curable sexually transmitted infections in rural South Africa. *Sexually transmitted infections* 2008;84(7):528-34. doi: 10.1136/sti.2008.032011 [published Online First: 2008/08/19]

19. Maina AN, Kimani J, Anzala O. Prevalence and risk factors of three curable sexually transmitted infections among women in Nairobi, Kenya. *BMC research notes* 2016;9:193. doi: 10.1186/s13104-016-1990-x [published Online First: 2016/03/31]

20. Francis SC, Ao TT, Vanobberghen FM, et al. Epidemiology of curable sexually transmitted infections among women at increased risk for HIV in northwestern Tanzania: inadequacy of syndromic management. *PloS one* 2014;9(7):e101221. doi: 10.1371/journal.pone.0101221 [published Online First: 2014/07/16]

21. Shah NS, Kim E, de Maria Hernandez Ayala F, et al. Performance and comparison of self-reported STI symptoms among high-risk populations - MSM, sex workers, persons living with HIV/AIDS - in El Salvador. *International journal of STD & AIDS* 2014;25(14):984-91. doi: 10.1177/0956462414526860 [published Online First: 2014/03/13]

22. Zemouri C, Wi TE, Kiarie J, et al. The Performance of the Vaginal Discharge Syndromic Management in Treating Vaginal and Cervical Infection: A Systematic Review and Meta-Analysis. *PloS one* 2016;11(10):e0163365. doi: 10.1371/journal.pone.0163365 [published Online First: 2016/10/06]

23. Tann CJ, Mpairwe H, Morison L, et al. Lack of effectiveness of syndromic management in targeting vaginal infections in pregnancy in Entebbe, Uganda. *Sexually transmitted infections* 2006;82(4):285-9. doi: 10.1136/sti.2005.014845 [published Online First: 2006/08/01]

24. Lusk MJ, Garden FL, Rawlinson WD, et al. Cervicitis aetiology and case definition: a study in Australian women attending sexually transmitted infection clinics. *Sexually transmitted infections* 2016;92(3):175-81. doi: 10.1136/sextrans-2015-052332 [published Online First: 2015/11/21]

25. Ryan CA, Courtois BN, Hawes SE, et al. Risk assessment, symptoms, and signs as predictors of vulvovaginal and cervical infections in an urban US STD clinic: implications for use of STD algorithms. *Sexually transmitted infections* 1998;74 Suppl 1:S59-76. [published Online First: 1999/02/19]

26. Vandepitte J, Bukenya J, Hughes P, et al. Clinical characteristics associated with Mycoplasma genitalium infection among women at high risk of HIV and other STI in Uganda. *Sexually transmitted diseases* 2012;39(6):487-91. doi: 10.1097/OLQ.0b013e31824b1cf3 [published Online First: 2012/05/18]

27. van der Eem L, Dubbink JH, Struthers HE, et al. Evaluation of syndromic management guidelines for treatment of sexually transmitted infections in South African women. *Tropical medicine & international health : TM & IH* 2016;21(9):1138-46. doi: 10.1111/tmi.12742 [published Online First: 2016/06/29]

28. Pereyre S, Laurier Nadalie C, Bebear C. Mycoplasma genitalium and Trichomonas vaginalis in France: a point prevalence study in people screened for sexually transmitted diseases. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2017;23(2):122.e1-22.e7. doi: 10.1016/j.cmi.2016.10.028 [published Online First: 2016/11/12]

29. Gaydos CA, Van Der Pol B, Jett-Goheen M, et al. Performance of the Cepheid CT/NG Xpert Rapid PCR Test for Detection of Chlamydia trachomatis and Neisseria gonorrhoeae. *Journal of clinical microbiology* 2013;51(6):1666-72. doi: 10.1128/jcm.03461-12 [published Online First: 2013/03/08]

30. Tabrizi SN, Unemo M, Golparian D, et al. Analytical evaluation of GeneXpert CT/NG, the first genetic point-of-care assay for simultaneous detection of Neisseria gonorrhoeae and Chlamydia trachomatis. *Journal of clinical microbiology* 2013;51(6):1945-7. doi: 10.1128/jcm.00806-13 [published Online First: 2013/04/05]

31. Aia P, Kal M, Lavu E, et al. The Burden of Drug-Resistant Tuberculosis in Papua New Guinea: Results of a Large Population-Based Survey. *PloS one* 2016;11(3):e0149806. doi: 10.1371/journal.pone.0149806 [published Online First: 2016/03/24]

32. Adler MW. Sexually transmitted diseases control in developing countries. *Genitourinary medicine* 1996;72(2):83-8. [published Online First: 1996/04/01]

33. van Dam CJ, Becker KM, Ndowa F, et al. Syndromic approach to STD case management: where do we go from here? *Sexually transmitted infections* 1998;74 Suppl 1:S175-8. [published Online First: 1999/02/19]

34. WHO. Global Health Sector Strategy on Sexually Transmitted Infections 2016–2021. Towards Ending STIs. Geneva, Switzerland: World Health Organization, 2016.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

**I confirm that all the items listed below have been considered and included as applicable in the submitted manuscript.**

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4-5 |
| Objectives | 3 | State specific objectives, including any pre-specified hypotheses | 5 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 6 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 6 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 7 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 6 |
| Study size | 10 | Explain how the study size was arrived at | 6 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6,7 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 7 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 7 |
| | | (*c*) Explain how missing data were addressed | N/A |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | 7 |
| | | (*e*) Describe any sensitivity analyses | 7 |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 8 |
| | | (b) Give reasons for non-participation at each stage | N/A |
| | | (c) Consider use of a flow diagram | N/A |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 10 |
| | | (b) Indicate number of participants with missing data for each variable of | N/A |

| | | | |
|---|---|---|---|
| | | interest | |
| Outcome data | 15* | Report numbers of outcome events or summary measures | 10,11 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 11-14 |
| | | (*b*) Report category boundaries when continuous variables were categorized | N/A |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | N/A |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 11-14 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 15 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 15-16 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 16 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 16 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 17 |
| Data sharing statement | | "No additional data is available". | 17 |
| Contributors | | Lists all contributors to research and manuscript | 17 |

*Give information separately for exposed and unexposed groups.

**Lisa Vallely**
**12 July 2017**

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Performance of syndromic management for the detection and treatment of genital Chlamydia trachomatis, Neisseria gonorrhoeae and Trichomonas vaginalis among women attending antenatal, well woman and sexual health clinics in Papua New Guinea: a cross-sectional study.



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| Secondary Subject Heading: | Sexual health |

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|---|---|

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**ABSTRACT**

**Objective:** Papua New Guinea (PNG) has among the highest estimated prevalences of genital *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG) and *Trichomonas vaginalis* (TV) of any country in the Asia-Pacific region. Diagnosis and treatment of these infections has relied on the WHO-endorsed syndromic management strategy that uses clinical presentation without laboratory confirmation to make treatment decisions. We evaluated the performance of this strategy in clinical settings in PNG.

**Design:** Women attending antenatal (ANC), well woman (WWC) and sexual health (SHC) clinics in four provinces were invited to participate, completed a face-to-face interview and clinical examination, and provided genital specimens for laboratory testing. We estimated the performance characteristics of syndromic diagnoses against combined laboratory diagnoses.

**Results:** 1764 women were enrolled (ANC=765; WWC=614; SHC=385). The prevalences of CT, NG and TV were highest among women attending ANC and SHC. Among antenatal women, syndromic STI diagnosis had low sensitivity (9%-21%) and positive predictive value (7%-37%); but high specificity (76%-89%) and moderate negative predictive value (55%-86%) for the combined endpoint of laboratory-confirmed CT, NG or TV. Among women attending WWC and SHC, 'vaginal discharge syndrome' had moderate to high sensitivity (72%-78%) and NPV (62%-94%), but low specificity (26%-33%) and PPV (8%-38%). 'Lower abdominal pain syndrome' had low sensitivity (26%-41%) and PPV (8%-23%) but moderate specificity (66%-68%) and high NPV (74%-93%) among women attending WWC; and moderate-high sensitivity (67%-79%) and NPV (62%- 86%), but low specificity (26%-28%) and PPV (14%-33%), among SHC attendees.

**Conclusion:** The performance of syndromic management for the detection and treatment of genital chlamydia, gonorrhoea and trichomonas was poor among women in different clinical settings in PNG. New diagnostic strategies are needed to control these infections and to prevent their adverse health outcomes in PNG and other high-burden countries.

**Article summary:**

***Strengths and limitations of this study***

- This is the first study to evaluate the performance of syndromic management (based on clinical presentation without laboratory confirmation) for the detection and treatment of genital sexually transmitted infections (STIs) among women in Papua New Guinea (PNG).
- Few previous studies have compared the performance of syndromic management among different clinical populations in the same setting.
- The study included the collection of socio-demographic, sexual behavioural and clinical information; and the collection of genital specimens for laboratory-based STI testing.
- We did not investigate bacterial vaginosis (BV), *Candida albicans* or *Mycoplasma genitalium*, and may have underestimated the performance of syndromic management for the detection of STIs and genital infections.

## INTRODUCTION

Sexually transmissible infections (STIs) are a major global public health concern.[1] Every year there are an estimated 500 million new cases of curable STIs, the majority of which occur in low-income settings.[2] Adverse outcomes of curable STIs include pelvic inflammatory disease, infertility, ectopic pregnancy, miscarriage, stillbirth, premature labour and low birth weight; and increased risk of HIV acquisition and transmission.[3] The three most common curable genital STIs, *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG) and *Trichomonas vaginalis* (TV) are frequently asymptomatic, particularly in women[4]. Inability to diagnose curable STIs has been a major barrier to their control, because many cases remain undetected and therefore untreated, with the potential for onward transmission. Accurate, nucleic acid-based diagnostic tests are now widely used in high-income countries but are largely unavailable in low- and middle-income countries (LMICs) where the highest prevalences of these STIs and their associated adverse health outcomes occur.[2] Even more traditional methods, such as microscopy, culture and serology are not widely available in LMICs, and in any case have low sensitivity for detecting current infection.

In the absence of access to diagnostic STI testing, the World Health Organization (WHO) in the 1990s developed a syndromic management strategy for diagnosing genital infections based on groups of genital symptoms to guide treatment decisions without laboratory tests.[2] The main syndromic diagnoses in women have been 'vaginal discharge syndrome' (VDS); 'lower abdominal pain syndrome' (LAPS); and 'genital ulcer syndrome' (GUS), each of which are treated using a combination of antibiotics to cover the most likely underlying infection(s). Syndromic management strategies lead to overtreatment, because there are other, non-sexually transmitted causes of the syndromes; or undertreatment ,[5] because they do not address asymptomatic infections that account for the majority of STIs globally.[4] Consequently, despite the wide-scale implementation of syndromic management, this has not been an effective strategy in reducing population-level prevalence, particularly in high-burden settings such as Papua New Guinea (PNG),[6 7] which has among the highest estimated prevalences of genital chlamydia, gonorrhoea and trichomonas of any country in the Asia-Pacific region.[2 7 8]

In this paper, we present findings on the performance of syndromic STI management for the treatment of curable genital STIs among women attending antenatal, well woman and sexual health clinics in PNG.

## METHODS

### Study design and procedures

We undertook a cross-sectional bio-behavioural survey to investigate the STI prevalence and risk factors for infection among women attending routine clinical services in four provinces (Eastern Highlands, Hela, Western Highlands and Central provinces): (a) pregnant women attending routine antenatal clinics; (b) women attending cervical cancer screening services at dedicated well woman clinics; and (c) women attending sexual health clinics. A key objective of the study was to evaluate the clinical performance of syndromic STI diagnosis for the treatment of curable genital STIs among three different clinical populations in this setting. An *a priori* assumption, based on our earlier systematic review and meta-analysis,[6] was that the prevalence of STIs would vary between women in these different populations and lead to differences in the performance of syndromic management.

All women attending their first clinic visit during the study period (which varied across clinics, between December 2011 and January 2015) were invited to join and were consecutively enrolled into the study following informed consent procedures. Age eligibility criteria varied by clinic type: women aged 18 years or older were recruited at antenatal and sexual health clinics; women aged 30 – 59 years (the target age group for cervical cancer screening in PNG) were recruited at well woman clinics.

Women took part in a face-to-face interview, conducted by a trained health care worker using study-specific case record forms (CRFs) in which socio-demographic, behavioural and clinical information were collected. Locator information and mobile phone contact details were also collected to facilitate subsequent follow-up. Participants in all clinical settings were asked about current genital symptoms, and past history of STIs. Genital examination was conducted as part of routine clinical assessment among women attending well woman and sexual health clinics only, in accordance with PNG standard guidelines (genital examination is not routinely offered in antenatal clinics).[9] Women attending antenatal clinics provided a self-collected mid-cavity vaginal swab for laboratory-based STI testing (CT, NG, TV); women attending well woman and sexual health clinics provided clinician-collected high vaginal (for TV) and cervical (for CT, NG) swabs. All women provided a venepuncture specimen for point-of-care syphilis screening and HIV counselling and testing.[9] In all clinic settings, women were provided with a date to return for follow-up, when they were given their STI test results, and additional treatment if indicated.[9] Women with clinical features (symptoms and/or clinical examination findings) consistent with one or more STI syndromes were managed according to national guidelines.[9] Clinical findings and treatment provided were recorded in individual client-held health record books and in study-specific CRFs. All participants were advised to return for clinical review to receive their laboratory STI test results, and additional treatment if required. Women with

positive STI test results who did not return for scheduled visits were contacted by mobile phone or by clinical research staff in the community, and were advised to re-attend for review. All diagnostic tests and antibiotic treatment were provided free-of-charge.

**Laboratory Methods**

Genital swabs were tested for CT, NG and TV by real-time polymerase chain reaction (PCR) at the PNG Institute of Medical Research (PNGIMR) Sexual and Reproductive Health unit laboratory in Goroka, using procedures and methods as previously described.[10] Sexual and Reproductive Health unit laboratory was enrolled in an external quality assurance program through the Royal College of Pathologists of Australia for CT and NG PCR.

**Data management and statistical methods**

Participant study folders (containing completed case record forms and laboratory results slips) were subject to quarterly clinical audits by the study lead investigator (AV) throughout. Data were entered at each clinical site into a study-specific MS Access database. Database entries were validated against participant study folders for accuracy. Laboratory test results entered into the clinical database were checked for accuracy against source documents (laboratory results slips) for all participants at the end of the study. The performance characteristics (sensitivity, specificity, positive and negative predictive value) of vaginal discharge syndrome' (VDS) and 'lower abdominal pain syndrome' (LAPS) were estimated against laboratory diagnoses of CT, NG and TV, and combinations of two or more STIs were calculated for the three population groups (antenatal clinic, well woman and sexual health clinic). Fisher's Exact Test was used to compare statistical differences in outcomes of interest between groups. There were no modifications for multiple comparisons. All statistical analyses were performed with Stata ver. 12.1 (StataCorp LP, College Station, TX, USA).

**Ethical considerations**

Ethical approval was obtained from the Institutional Review Board of the PNGIMR (1124; 1111) and the Medical Research Advisory Committee of the PNG National Department of Health in Papua New Guinea (11.34;11.18; 10.17) ; and from Human Research Ethics Committees of the Alfred Hospital Melbourne (390/11), and the UNSW Sydney (HC12155; HC11250; HC 12120), in Australia. Written informed consent (signature or witnessed thumbprint) was obtained from all participants prior to study enrolment. Women were each assigned a unique alphanumeric study identification number from a pre-printed study register to ensure anonymity and confidentiality.

## RESULTS

During the study period, a total of 1764 women were enrolled at 10 participating clinics (six antenatal clinics, n=765; two well woman clinics, n=614; and two sexual health clinics, n=385; Table 1).

### Socio-demographic characteristics

Women attending antenatal clinics were significantly younger than those attending well woman or sexual health clinics (Table 1). Overall, 89% (1573/1764) of women were married; around half reported attending primary school only (904/1764); and 57% were not in paid employment (920/1764). Women attending sexual health clinics were less likely to be married, or to be in paid employment and had lower educational attainment, compared to women enrolled in antenatal and well woman clinics.

### Sexual behavioural characteristics

Overall, around 40% of women (692/1764) reported sexual debut before 18 years of age. Sexual health clinic attendees were more likely to have had a younger age of sexual debut than women attending antenatal or well woman clinics (56.6% vs. 34.0 and 34.9%, respectively, $p<0.001$; Table 1). Women attending sexual health clinics were also significantly more likely to report having more than four lifetime sexual partners; more than two sexual partners in the past week; vaginal sex more than four times in the past week; and ever having had sex in exchange for gifts or money compared with women attending antenatal or well woman clinics. Sexual health clinic attendees were more likely to report condom use at last vaginal sex, compared with women in other clinical settings.

358 **Table 1: Sociodemographic characteristics by clinic type**

| | Total | Clinic attended | | | |
|---|---|---|---|---|---|
| | N (%) 1764 | Antenatal N=765 | Well woman N= 614 | Sexual health N= 385 | P-value |
| **Age groups** | | | | | <0.001 |
| <20 years | 99 (5.6) | 85 (11.1) | 0 | 14 (3.6) | |
| 20-24 years | 300 (17.0) | 246 (31.2) | 0 | 54 (14.1) | |
| 25-29 years | 295 (16.7) | 224 (29.3) | 0 | 71 (18.4) | |
| 30+ years | 1070 (60.7) | 210 (27.5) | 614 (100) | 246 (63.1) | |
| **Median age (IQR)** | 32 (25-37) | 25 (22-30) | 37 (34-41) | 32 (26-37) | <0.001 |
| **Marital status** | | | | | <0.001 |
| Married | 1573 (89.2) | 719 (94.0) | 544 (88.6) | 310 (80.8) | |
| Single | 37 (2.1) | 22 (2.9) | 1 (0.2) | 14 (3.6) | |
| Other | 154 (8.7) | 24 (3.1) | 69 (11.2) | 61 (15.8) | |
| **Employment status** | | | | | |
| No current paid work | 920 (57.2) | 591 (77.3) | 311 (50.7) | 18 (4.7) | <0.001 |
| Gardening/farmer | 996 (56.5) | 482 (63.0) | 382 (62.2) | 132 (34.3) | <0.001 |
| House hold duties | 1464 (83.0) | 666 (87.1) | 491 (80.0) | 307 (79.7) | <0.001 |
| **Education** | | | | | <0.001 |
| No formal education | 427 (24.2) | 145 (14.6) | 172 (28.0) | 110 (28.6) | |
| Attended only Primary School (Grades 1-8) | 904 (51.3) | 386 (50.5) | 313 (51.0) | 205 (53.3) | |
| Attended Secondary School (Grades 9-12) | 331 (18.8) | 207 (27.1) | 73 (11.9) | 51 (13.3) | |
| Other (Tertiary, tech, voc.) | 102 (5.8) | 27 (3.5) | 56 (9.1) | 19 (4.9) | |
| **When did you last have sex** | | | | | <0.001 |
| Today/yesterday | 168 (9.5) | 73 (9.5) | 54 (8.8) | 41 (10.7) | |
| 2 days ago | 187 (10.6) | 74 (9.7) | 49 (8.0) | 64 (16.6) | |
| 3 days ago | 117 (6.6) | 59 (7.7) | 33 (5.4) | 25 (6.5) | |
| 4 or more days ago | 1292 (73.2) | 559 (73.1) | 478 (77.9) | 255 (66.2) | |
| **Vaginal sex in the last week** | | | | | <0.001 |
| None | 702 (39.8) | 372 (48.6) | 233 (38.0) | 97 (25.2) | |
| Once | 623 (35.3) | 196 (25.6) | 271 (44.1) | 156 (40.5) | |
| Twice | 212 (12.0) | 100 (13.1) | 51 (8.3) | 61 (15.8) | |
| Three times | 114 (6.5) | 55 (7.2) | 28 (4.6) | 31 (8.1) | |
| Four or more times | 113 (6.4) | 42 (5.5) | 31 (5.1) | 40 (10.4) | |
| **Condom used last vaginal sex** | | | | | <0.001 |
| No | 1621 (91.9) | 718 (93.9) | 578 (94.1) | 325 (84.4) | |
| Yes | 143 (8.1) | 47 (6.1) | 36 (5.9) | 60 (15.6) | |
| **Number of people had vaginal sex with in the last week** | | | | | <0.001 |
| None | 655 (37.1) | 308 (40.3) | 229 (37.3) | 118 (30.7) | |
| 1-person | 1069 (60.6) | 447 (58.4) | 373 (60.8) | 249 (64.7) | |
| 2 or more people | 40 (2.3) | 10 (1.3) | 12 (2.0) | 18 (4.7) | |
| **Condom use in the past month** | | | | | <0.001 |
| Always | 24 (1.4) | 3 (0.4) | 8 (1.3) | 13 (3.4) | |
| Sometimes | 298 (16.9) | 128 (16.7) | 105 (17.1) | 65 (16.9) | |
| Most of the time | 32 (1.8) | 5 (0.7) | 6 (1.0) | 21 (5.5) | |
| Never | 1410 (79.9) | 629 (82.2) | 495 (80.6) | 286 (74.3) | |
| **Ever had sex for money/gifts** | | | | | <0.001 |
| No | 1475 (83.6) | 723 (94.5) | 542 (88.3) | 210 (54.6) | |
| Yes | 289 (16.9) | 42 (5.5) | 72 (11.7) | 175 (45.5) | |
| **Age at sexual debut** | | | | | <0.001 |
| ≤18 | 692 (39.2) | 260 (34.0) | 214 (34.9) | 218 (56.6) | |
| >18 years | 1072 (60.8) | 505 (66.0) | 400 (65.2) | 167 (43.4) | |
| **Lifetime number of sexual partners** | | | | | <0.001 |
| 1-person | 805 (45.6) | 357 (46.7) | 338 (55.1) | 110 (28.6) | |
| 2-people | 349 (19.8) | 165 (21.6) | 127 (20.7) | 57 (14.8) | |
| 3-people | 178 (10.1) | 87 (11.4) | 49 (8.0) | 42 (10.9) | |
| 4 or more people | 432 (24.5) | 156 (20.4) | 100 (16.3) | 176 (45.7) | |
| **Ever had anal sex** | | | | | <0.001 |
| No | 1538 (87.2) | 685 (89.5) | 570 (92.8) | 283 (73.5) | |
| Yes | 226 (12.8) | 80 (10.5) | 44 (7.2) | 102 (26.5) | |

359

360

**Clinical and laboratory findings**

The prevalence of CT, NG and TV were highest among women attending antenatal and sexual health clinics, compared with those attending well woman clinics e.g. the prevalence of chlamydia was 22.9%, 21.4% and 7.5%, respectively in these populations (Table 2). Antenatal women and those attending sexual health clinics were also more likely to have two or more STIs compared with well woman clinic attendees (14.2%, 10.6% and 4.8%, respectively; Table 2).

**Table 2: Syndromic STI diagnosis and prevalence of *C. trachomatis, N. gonorrhoeae, T. vaginalis***

| | **Antenatal clinic** N=765 (%) | **Well woman clinic** N=614 (%) | **Sexual health clinic** N=385 (%) |
|---|---|---|---|
| Lower abdominal pain syndrome (LAPS) | 166 (21.7) | 200 (32.6) | 282 (73.2) |
| Vaginal discharge syndrome (VDS) | 156 (20.4) | 422 (67.8) | 281 (73.0) |
| *C. trachomatis* (CT) | 175 (22.9) | 46 (7.5) | 78 (21.4) |
| *N. gonorrhoeae* (NG) | 109 (14.2) | 49 (8.0) | 63 (16.4) |
| *T. vaginalis* (TV) | 171 (22.4) | 92 (15.0) | 54 (14.0) |
| More than 1 of CT, NG, TV | 109 (14.3) | 29 (4.7) | 40 (10.4) |
| No STI | 438 (57.3) | 460 (74.9) | 240 (62.3) |
| Any STI | 327 (42.7) | 154 (25.1) | 145 (37.7) |
| One STI | 218 (28.5) | 125 (20.4) | 105 (27.3) |
| Two STIs | 90 (11.7) | 25 (4.1) | 30 (8.0) |
| Three STIs | 19 (2.5) | 4 (0.7) | 10 (2.6) |

The prevalence of vaginal discharge syndrome was highest among women attending sexual health clinics (73.0%) and well woman clinics (68.7%), compared with antenatal women (20.4%; Table 2). Lower abdominal pain syndrome was also less frequently diagnosed among antenatal women (Table 2).

**Performance of syndromic management**

Among antenatal women, syndromic diagnosis (based on clinical symptoms alone) had low sensitivity (9%-21%) and positive predictive value (7%-37%); but high specificity (76%-89%) and moderate negative predictive value (55%-86%) for correctly classifying women as having infection with CT, NG or TV (Table 3). Syndromic management alone would have led to considerable overtreatment and under-diagnosis in this population. For example, 38% (60/156) of antenatal women with VDS had any of CT, NG or TV and would have been appropriately treated; 62% (96/156) of women with symptoms but without detectable CT, NG or TV would have been treated unnecessarily; and 82% (267/327) of those with any of CT, NG or TV infection would not have been treated because they did not have vaginal discharge (Table 3).

Among women attending well woman clinics, LAPS had low sensitivity (26%-41%) and positive predictive value (8%-23%) but moderate to high specificity (66%-68%) and negative predictive value (74%-93%) for the detection of any laboratory-confirmed STI, or CT, NG, TV individually (Table 3). VDS had high sensitivity (72%-75%) and negative predictive value (79%-94%) but low specificity (32%-

33%) and positive predictive value (8%-25%). Around 1 in 4 women with LAPS (46/200; 23%) had any of CT, NG or TV, and would have been correctly treated based on syndromic management alone; 77% (154/200) of women with LAPS did not have a laboratory-confirmed infection, and therefore would have been treated unnecessarily; and 70% (108/154) of those with any of CT, NG or TV would not have been detected and treated based on a diagnosis of LAPS alone, because they did not have appropriate clinical features. Correspondingly, around 27% (114/422) of women with VDS would have been correctly treated; 73% (308/422) of those with VDS would have been unnecessarily treated; and 26% (40/154) of those with any of CT, NG or TV would not have been diagnosed and treated (Table 3).

Among women attending sexual health clinics, LAPS and VDS had a moderate to high sensitivity (67%-79%) and negative predictive value (62%- 86%), but low specificity (26%-28%) and positive predictive value (14%-33%) for the detection of any laboratory confirmed STI, or CT, NG, TV individually (Table 4). Around 39% (109/282) of women with LAPS would have been correctly treated; 61% (173/282) with LAPS would have been unnecessarily treated; and 25% (36/145) of women with any of CT, NG or TV would not have been diagnosed and treated. Among women with VDS, around 38% (106/281) would have been correctly treated; 62% (175/281) would have been unnecessarily treated; and 27% (39/145) of those with any of CT, NG or TV would not have been diagnosed and treated (Table 3).

**Table 3: Syndromic diagnosis and laboratory-confirmed STIs**

| Syndromic diagnosis | | Any STI N (%)* | | | *C. trachomatis* N (%)* | | | *N. gonorrhoeae* N (%)* | | | *T. vaginalis* N (%)* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Yes | No | Performance (95% CI) | Yes | No | Performance (95%CI) | Yes | No | Performance (95% CI) | Yes | No | Performance (95% CI) |
| **Antenatal clinics (n=765)** | | | | | | | | | | | | | |
| LAPS** (166/765; 21.7%) | Yes | 60 (18.4) | 106 (14.2) | SENS: 18% (14%, 23%) SPEC: 76% (72%, 80%) PPV: 36% (29%, 44%) NPV: 55% (51%, 59%) | 30 (17.1) | 136 (23.0) | SENS:17% (12%, 24%) SPEC:77% (73%,80%) PPV: 18% (13%, 25%) NPV: 76% (72%, 79%) | 15 (13.8) | 151 (23.0) | SENS: 14% (8%, 22%) SPEC: 77% (74%, 80%) PPV: 9% (5%, 14%) NPV: 84% (81%, 87%) | 29 (83.0) | 457 (77.0) | SENS:17% (12%,23%) SPEC: 77% (73%, 80%) PPV: 17% (12%, 24%) NPV: 76% (73%, 80%) |
| | No | 267 (81.7) | 332 (75.8) | | 145 (82.9) | 454 (77.0) | | 94 (86.2) | 505 (77.0) | | 142 (83.0) | 457 (77.0) | |
| VDS *** (156/765; 20.4%) | Yes | 60 (18.4) | 96 (22.0) | SENS: 18% (14%, 23%) SPEC: 78% (74%, 82%) PPV: 38% (40%, 47%) NPV: 56% (52%, 60%) | 37 (21.1) | 119 (20.2) | SENS: 21%(15%, 28%) SPEC: 80% (76%,83%) PPV: 24% (17%, 31%) NPV: 77% (74%, 81%) | 16 (14.7) | 140 (21.3) | SENS: 15% (9%,23%) SPEC: 79% (75%,82%) PPV: 10% (96%,16%) NPV: 85% (82%,87%) | 33 (19.3) | 123 (20.7) | SENS: 19% (14%,26%) SPEC: 79% (76%, 82%) PPV: 21% (15%, 28%) NPV: 77% (74%,81%) |
| | No | 267 (81.7) | 342 (78.1) | | 138 (78.9) | 471 (79.8) | | 93 (85.3) | 516 (78.7) | | 138 (80.7) | 471 (79.3) | |
| **Well woman clinics (n=614)** | | | | | | | | | | | | | |
| LAPS** (200/614; 32.6%) | Yes | 46 (29.9) | 154 (33.5) | SENS: 30% (23%, 38%) SPEC: 67% (62%, 71%) PPV: 23% (17%, 29%) NPV: 74% (69%, 78%) | 19 (41.3) | 181 (31.9) | SENS: 41%(27%, 57%) SPEC: 68% (64%,72%) PPV: 10% (6%, 14%) NPV: 93% (91%, 96%) | 15 (30.6) | 185 (32.7) | SENS: 31% (18%, 45%) SPEC: 67% (63%, 71%) PPV: 8% (4%, 12%) NPV: 92% (89%, 94%) | 24 (26.1) | 176 (33.7) | SENS: 26% (17%, 36%) SPEC: 66% (62%, 70%) PPV: 12% (8%, 17%) NPV: 84% (80, 87%) |
| | No | 108 (70.1) | 306 (66.5) | | 27 (58.8) | 387 (68.1) | | 34 (69.4) | 380 (67.3) | | 68 (73.9) | 346 (66.3) | |
| VDS *** (422/614; 68.7%) | Yes | 114 (74.0) | 308 (67.0) | SENS: 74% (66%, 81%) SPEC: 33% (29%, 38%) PPV: 25% (22%, 29%) NPV: 79% (74%, 84%) | 33 (71.7) | 389 (68.5) | SENS: 72% (57%,84%) SPEC: 32% (28%,36%) PPV: 8% (6%, 9%) NPV: 93% (90%, 96%) | 37 (75.5) | 385 (68.1) | SENS: 75% (61%, 87%) SPEC: 32% (28%, 36%) PPV: 9% (7%, 10%) NPV: 94% (90%, 96%) | 70 (76.1) | 352 (67.4) | SENS: 76% (66%, 84%) SPEC: 33% (28%, 37%) PPV: 17% (15%, 18%) NPV: 89% (84%, 92%) |
| | No | 40 (26.0) | 152 (33.0) | | 13 (28.3) | 179 (31.5) | | 12 (24.5) | 180 (31.9) | | 22 (23.9) | 170 (32.6) | |
| **Sexual health clinics (n=385)** | | | | | | | | | | | | | |
| LAPS ** (282/385; 73.2%) | Yes | 109 (75.1) | 173 (72.1) | SENS: 75% (67%, 82%) SPEC: 28% (22%, 34%) PPV: 39% (33%, 45%) NPV: 65% (55%, 74%) | 62 (79.5) | 220 (71.7) | SENS:79% (69%, 88%) SPEC:28% (23%, 34%) PPV: 22% (20%, 24%) NPV: 84% (77%, 90%) | 46 (27.0) | 236 (73.3) | SENS: 73% (60%, 83%) SPEC: 27% (22%, 32%) PPV: 16% (12%, 21%) NPV: 84% (75%, 90%) | 40 (74.1) | 242 (73.1) | SENS: 74% (60%,85%) SPEC: 27% (22%,32%) PPV: 14% (11%, 18%) NPV: 86% (78%, 92%) |
| | No | 36 (24.8) | 67 (27.9) | | 16 (20.5) | 87 (28.3) | | 17 (27.0) | 86 (26.7) | | 14 (25.9) | 89 (26.9) | |
| VDS *** (281/385; 73.0%) | Yes | 106 (73.1) | 175 (72.9) | SENS: 73% (65%,80%) SPEC: 27% (22%, 33%) PPV: 38% (35%, 41%) NPV: 62% (54%, 70%) | 61 (78.2) | 220 (71.7) | SENS: 78% (67%,87%) SPEC: 28% (23%,34%) PPV: 22% (19%, 24%) NPV: 84% (76%, 89%) | 42 (66.7) | 239 (74.2) | SENS: 67% (54%, 78%) SPEC: 26% (21%, 31%) PPV: 15% (13%, 17%) NPV: 80% (73%, 85%) | 40 (74.1) | 241 (72.8) | SENS: 74% (60%,85%) SPEC: 27% (22%, 32%) PPV: 14% (12%, 16%) NPV: 86% (80%, 91%) |
| | No | 39 (26.9) | 65 (27.1) | | 17 (21.8) | 87 (28.3) | | 21 (33.3) | 83 (25.8) | | 14 (25.9) | 90 (27.2) | |

* = prevalence of any and individual STIs in this population ** Lower Abdominal Pain Syndrome *** Vaginal Discharge Syndrome

## DISCUSSION

High prevalences of genital *C. trachomatis, N. gonorrhoeae* and *T. vaginalis* were observed among women attending antenatal, well woman and sexual health clinics in Papua New Guinea. The performance of syndromic management for the detection and treatment of these infections was poor, particularly among antenatal women where more than 80% of those with laboratory-confirmed CT, NG or TV would not have been diagnosed and treated. These findings reflect the high proportion of asymptomatic infections among women in these clinical populations, and the limited association between clinical findings and laboratory-confirmed genital STIs. Around 43% of women attending their first antenatal clinic visit had genital CT, NG or TV; 1 in 5 reported symptoms of abdominal pain or vaginal discharge, and around 1 in 8 reported dysuria or vulval irritation. Despite the high prevalence of both genital infections and genital symptoms, syndromic management had extremely low sensitivity and positive predictive value for the detection of CT, NG or TV, and would have resulted in significant overtreatment and missed diagnoses in this population. These STIs have been associated with increased risk of adverse maternal and neonatal health outcomes, including stillbirth, prematurity and low birthweight, if they are not detected and treated during pregnancy.[11-14] The findings presented in this paper are consistent with earlier studies, which demonstrated inadequate performance of syndromic management for STI detection and treatment in pregnancy, based either on symptoms alone, or on symptoms plus clinical examination.[5 8 15-17]

Among women attending well woman clinics and sexual health clinics, VDS had moderate to high sensitivity (up to 79%) and NPV (up to 94%) but low specificity and PPV (both around 30%) for the detection of CT, NG or TV. Around 62-73% of women with symptoms did not have a laboratory-confirmed infection and would have been unnecessarily treated. Lower abdominal pain syndrome performed less well than VDS, particularly among well woman clinic attendees. Similar results have been reported from studies conducted in other high-burden settings, among women attending sexual health and family planning clinics,[17-19] and among women at increased risk of infection, such as commercial or transactional sex workers.[20-22]

In the current study, we did not investigate bacterial vaginosis (BV), *Candida albicans,* or *Mycoplasma genitalium*, and may therefore have underestimated the performance of syndromic management for the detection of STIs and genital infections. A high prevalence of bacterial vaginosis (18-23%) has previously been reported among pregnant women,[6 16] the majority of whom were asymptomatic in this setting.[16] It is possible that women with symptoms of vaginal discharge but without laboratory-confirmed CT, NG or TV in the current study may have had BV. Earlier studies in other settings suggest however, that the inclusion of BV appears to have little impact on the performance of syndromic management among antenatal women [15 23] or among women attending

sexual health or family planning clinics.[22 24 25] *M. genitalium* (MG) has been associated with vaginal discharge among women in a variety of settings[24 26] but its presence and clinical correlates have not been investigated among women in PNG. It is therefore difficult to estimate the impact of undiagnosed MG on the performance of syndromic management in the current study. Research from elsewhere indicates that inclusion of MG has little impact on performance[21 27] and that the majority of MG infections in women are asymptomatic,[28] and therefore not amenable to syndromic management strategies.

In accordance with current PNG national STI guidelines, genital examination was not routinely conducted among women attending their first antenatal clinic visit, and even had we elected to do so, would not have been feasible due to a lack of suitable examination rooms and equipment at participating antenatal clinics as well as limited and over-stretched human resources. This may have led to underestimation of the performance of syndromic management in this population, but we consider this unlikely given earlier evidence on the impact on performance if speculum examination is included as part of syndromic assessment.[17]

The performance of syndromic management contrasts markedly with that of newly-available, highly-accurate molecular STI diagnostic tests that can be implemented at point-of-care, such as the GeneXpert platform (Cepheid, Sunnyvale CA), which has been shown to be as accurate as laboratory-based polymerase chain reaction tests for the detection of chlamydia, gonorrhoea and trichomonas infection using genital or urine specimens.[29 30] For example, Xpert had 98.7% sensitivity and 99.4% specificity for the detection of CT using vaginal specimens.[29] Test results are available in approximately 90 minutes for Xpert CT/NG (which simultaneously tests for both chlamydia and gonorrhoea) and 60 minutes for the Xpert TV test. The platform has been shown to be robust and portable and has already revolutionised the diagnosis and management of tuberculosis in many LMICs, including PNG.[31] We have previously demonstrated the operational feasibility of Xpert point-of-care testing and treatment for CT, NG and TV in antenatal clinics in PNG;[16] and for the detection of high-risk human papillomavirus infection (hrHPV) for cervical cancer screening in well woman clinics in this same setting.[16]

The limitations of syndromic management as an effective strategy for the diagnosis, treatment and control of STIs in LMICs have been known for over two decades.[32 33] Recognizing these limitations, the WHO recently advocated a transition from syndromic to etiological STI diagnosis as part of a new and ambitious strategy to eliminate STIs as a public health threat globally by 2030.[34] A major research effort is warranted to evaluate the effectiveness, acceptability, health system implementation requirements and cost-effectiveness of newly-available STI diagnostic tests that can be provided at

point of clinical care in order to tackle the continuing epidemics of STIs and their associated adverse health outcomes in low-resource settings, and to progress down a pathway towards elimination.

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**Conflicts of interest**

None declared

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**Data sharing statement**

"No additional data is available".

**Contributors:**

LMV Supported data collection in antenatal clinics; wrote first draft of manuscript. She is guarantor.

PT Supported laboratory testing.

CR Led and supervised laboratory testing.

GR Supported laboratory testing.

JW Supported laboratory testing.

JG Supported data collection in well woman clinics.

JA Supported data collection in sexual health and well woman clinics.

CO Supported data collection in sexual health clinics.

GM Supported data collection in antenatal clinics.

PK Supported data collection in sexual health clinics.

BK Provided support and oversight in data collection at sites in Western Highlands

AK Provided support and oversight in data collection at sites in Eastern Highlands

ZK Provided laboratory support and testing in Western Highlands

GL Provided guidance and support in the design of the study in sexual health and well woman clinics

AK-H Provided guidance and oversight in the design and data collection at each clinic type

HW Cleaned and analysed the data.

PS Provided guidance and oversight in the design of each study

GDLM Provided guidance and support in the design of the study in each of the clinic settings.

JMK Provided guidance and support in the design of the study in each of the clinic settings.

AJV designed the studies and data collection tools and monitored data collection for each of the three studies and revised the first draft of the paper.

All authors have read and approve the final manuscript.

**References**

1. Newman L, Rowley J, Vander Hoorn S, et al. Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting. *PloS one* 2015;10(12):e0143304. doi: 10.1371/journal.pone.0143304 [published Online First: 2015/12/10]

2. WHO. SEXUALLY TRANSMITTED INFECTIONS (STIs): The importance of a renewed commitment to STI prevention and control in achieving global sexual and reproductive health. Geneva, Switzerland: World Health Organization, 2012.

3. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet (London, England)* 2015;386(9995):743-800. doi: 10.1016/s0140-6736(15)60692-4 [published Online First: 2015/06/13]

4. Detels R, Green AM, Klausner JD, et al. The incidence and correlates of symptomatic and asymptomatic Chlamydia trachomatis and Neisseria gonorrhoeae infections in selected populations in five countries. *Sexually transmitted diseases* 2011;38(6):503-9. [published Online First: 2012/01/19]

5. Shah M, Deshmukh S, Patel SV, et al. Validation of vaginal discharge syndrome among pregnant women attending obstetrics clinic, in the tertiary hospital of Western India. *Indian journal of sexually transmitted diseases* 2014;35(2):118-23. doi: 10.4103/0253-7184.142406 [published Online First: 2014/07/01]

6. Vallely A, Page A, Dias S, et al. The prevalence of sexually transmitted infections in Papua New Guinea: A systematic review and meta-analysis. *PloS one* 2010;5(12):e15586.

7. Vallely LM, Toliman P, Ryan C, et al. Prevalence and risk factors of Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis and other sexually transmissible infections among

women attending antenatal clinics in three provinces in Papua New Guinea: a cross-sectional survey. *Sexual health* 2016 doi: 10.1071/sh15227 [published Online First: 2016/06/02]

8. Wangnapi RA, Soso S, Unger HW, et al. Prevalence and risk factors for Chlamydia trachomatis, Neisseria gonorrhoeae and Trichomonas vaginalis infection in pregnant women in Papua New Guinea. *Sexually transmitted infections* 2014 doi: 10.1136/sextrans-2014-051670 [published Online First: 2014/10/15]
9. Mola GDL. Manual of Standard Managements in Obstetrics and Gynaecology for Doctors, HEOs and Nurses in Papua New Guinea. Seventh Edition ed2016.
10. Vallely A, Ryan CE, Allen J, et al. High prevalence and incidence of HIV, sexually transmissible infections and penile foreskin cutting among sexual health clinic attendees in Papua New Guinea. *Sexual health* 2014;11(1):58-66. doi: 10.1071/sh13197 [published Online First: 2014/03/13]
11. Arol OA, Over M, Manhart L, et al. Sexually Transmitted Infections. In: Dean T, ed. Disease control priorities in developing countries. 2nd edition ed: World Bank 2006:311-30.
12. UNFPA. STIs: Breaking the cycle of transmission. Geneva: Reproductive Health Branch, Technical Support Division, UNFPA 2004.
13. WHO. Global Prevalence and Incidence of Selected Curable Sexually Transmitted Infections: Overview of Estimates Geneva: World Health Organization 2001.
14. WHO. Sexually Transmitted Infections Fact Sheet No. 110. Geneva: World Health Organization 2013.
15. Msuya SE, Uriyo J, Stray-Pedersen B, et al. The effectiveness of a syndromic approach in managing vaginal infections among pregnant women in northern Tanzania. *East African journal of public health* 2009;6(3):263-7. [published Online First: 2010/09/02]
16. Toliman P, Badman SG, Gabuzzi J, et al. Field Evaluation of Xpert HPV Point-of-Care Test for Detection of Human Papillomavirus Infection by Use of Self-Collected Vaginal and Clinician-Collected Cervical Specimens. *Journal of clinical microbiology* 2016;54(7):1734-7. doi: 10.1128/jcm.00529-16 [published Online First: 2016/04/15]

17. Pettifor A, Walsh J, Wilkins V, et al. How effective is syndromic management of STDs?: A review of current studies. *Sexually transmitted diseases* 2000;27(7):371-85. [published Online First: 2000/08/19]

18. White RG, Moodley P, McGrath N, et al. Low effectiveness of syndromic treatment services for curable sexually transmitted infections in rural South Africa. *Sexually transmitted infections* 2008;84(7):528-34. doi: 10.1136/sti.2008.032011 [published Online First: 2008/08/19]

19. Maina AN, Kimani J, Anzala O. Prevalence and risk factors of three curable sexually transmitted infections among women in Nairobi, Kenya. *BMC research notes* 2016;9:193. doi: 10.1186/s13104-016-1990-x [published Online First: 2016/03/31]

20. Francis SC, Ao TT, Vanobberghen FM, et al. Epidemiology of curable sexually transmitted infections among women at increased risk for HIV in northwestern Tanzania: inadequacy of syndromic management. *PloS one* 2014;9(7):e101221. doi: 10.1371/journal.pone.0101221 [published Online First: 2014/07/16]

21. Shah NS, Kim E, de Maria Hernandez Ayala F, et al. Performance and comparison of self-reported STI symptoms among high-risk populations - MSM, sex workers, persons living with HIV/AIDS - in El Salvador. *International journal of STD & AIDS* 2014;25(14):984-91. doi: 10.1177/0956462414526860 [published Online First: 2014/03/13]

22. Zemouri C, Wi TE, Kiarie J, et al. The Performance of the Vaginal Discharge Syndromic Management in Treating Vaginal and Cervical Infection: A Systematic Review and Meta-Analysis. *PloS one* 2016;11(10):e0163365. doi: 10.1371/journal.pone.0163365 [published Online First: 2016/10/06]

23. Tann CJ, Mpairwe H, Morison L, et al. Lack of effectiveness of syndromic management in targeting vaginal infections in pregnancy in Entebbe, Uganda. *Sex Transm Infect* 2006;82(4):285-9. doi: 10.1136/sti.2005.014845 [published Online First: 2006/08/01]

24. Lusk MJ, Garden FL, Rawlinson WD, et al. Cervicitis aetiology and case definition: a study in Australian women attending sexually transmitted infection clinics. *Sexually transmitted infections* 2016;92(3):175-81. doi: 10.1136/sextrans-2015-052332 [published Online First: 2015/11/21]

25. Ryan CA, Courtois BN, Hawes SE, et al. Risk assessment, symptoms, and signs as predictors of vulvovaginal and cervical infections in an urban US STD clinic: implications for use of STD algorithms. *Sexually transmitted infections* 1998;74 Suppl 1:S59-76. [published Online First: 1999/02/19]

26. Vandepitte J, Bukenya J, Hughes P, et al. Clinical characteristics associated with Mycoplasma genitalium infection among women at high risk of HIV and other STI in Uganda. *Sexually transmitted diseases* 2012;39(6):487-91. doi: 10.1097/OLQ.0b013e31824b1cf3 [published Online First: 2012/05/18]

27. van der Eem L, Dubbink JH, Struthers HE, et al. Evaluation of syndromic management guidelines for treatment of sexually transmitted infections in South African women. *Tropical medicine & international health : TM & IH* 2016;21(9):1138-46. doi: 10.1111/tmi.12742 [published Online First: 2016/06/29]

28. Pereyre S, Laurier Nadalie C, Bebear C. Mycoplasma genitalium and Trichomonas vaginalis in France: a point prevalence study in people screened for sexually transmitted diseases. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2017;23(2):122.e1-22.e7. doi: 10.1016/j.cmi.2016.10.028 [published Online First: 2016/11/12]

29. Gaydos CA, Van Der Pol B, Jett-Goheen M, et al. Performance of the Cepheid CT/NG Xpert Rapid PCR Test for Detection of Chlamydia trachomatis and Neisseria gonorrhoeae. *Journal of clinical microbiology* 2013;51(6):1666-72. doi: 10.1128/jcm.03461-12 [published Online First: 2013/03/08]

30. Tabrizi SN, Unemo M, Golparian D, et al. Analytical evaluation of GeneXpert CT/NG, the first genetic point-of-care assay for simultaneous detection of Neisseria gonorrhoeae and Chlamydia trachomatis. *Journal of clinical microbiology* 2013;51(6):1945-7. doi: 10.1128/jcm.00806-13 [published Online First: 2013/04/05]

31. Aia P, Kal M, Lavu E, et al. The Burden of Drug-Resistant Tuberculosis in Papua New Guinea: Results of a Large Population-Based Survey. *PloS one* 2016;11(3):e0149806. doi: 10.1371/journal.pone.0149806 [published Online First: 2016/03/24]

32. Adler MW. Sexually transmitted diseases control in developing countries. *Genitourinary medicine* 1996;72(2):83-8. [published Online First: 1996/04/01]

33. van Dam CJ, Becker KM, Ndowa F, et al. Syndromic approach to STD case management: where do we go from here? *Sexually transmitted infections* 1998;74 Suppl 1:S175-8. [published Online First: 1999/02/19]

34. WHO. Global Health Sector Strategy on Sexually Transmitted Infections 2016–2021. Towards Ending STIs. Geneva, Switzerland: World Health Organization, 2016.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

**I confirm that all the items listed below have been considered and included as applicable in the submitted manuscript.**

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4-5 |
| Objectives | 3 | State specific objectives, including any pre-specified hypotheses | 5 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 6 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 6 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 7 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 6 |
| Study size | 10 | Explain how the study size was arrived at | 6 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6,7 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 7 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 7 |
| | | (*c*) Explain how missing data were addressed | N/A |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | 7 |
| | | (*e*) Describe any sensitivity analyses | 7 |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 8 |
| | | (b) Give reasons for non-participation at each stage | N/A |
| | | (c) Consider use of a flow diagram | N/A |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 10 |
| | | (b) Indicate number of participants with missing data for each variable of | N/A |

| | | | |
|---|---|---|---|
| | | interest | |
| Outcome data | 15* | Report numbers of outcome events or summary measures | 10,11 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 11-14 |
| | | (*b*) Report category boundaries when continuous variables were categorized | N/A |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | N/A |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 11-14 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 13 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 14-15 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 15 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 15 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 16 |
| Data sharing statement | | "No additional data is available". | 16 |
| Contributors | | Lists all contributors to research and manuscript | 16 |

*Give information separately for exposed and unexposed groups.

**Lisa Vallely**
**12 July 2017**

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