

An evaluation of the performance characteristics of World Health Organization syndromic management for *C. trachomatis* and *N. gonorrhoeae* infections among female sex workers in Mombasa, Kenya

Gregory Zane

A thesis
submitted in partial fulfillment of the
requirements for the degree of

Master of Public Health

University of Washington

2020

Committee:

Jennifer Balkus

R. Scott McClelland

Christine Khosropour

Program Authorized to Offer Degree:

Epidemiology

©Copyright 2020

Gregory Zane

University of Washington

Abstract

An evaluation of the performance characteristics of World Health Organization syndromic management for *C. trachomatis* and *N. gonorrhoeae* infections among female sex workers in

Mombasa, Kenya

Gregory Zane

Chair of the Supervisory Committee:

Dr. Jennifer Balkus

Department of Epidemiology

Objectives: To assess the performance characteristics of the World Health Organization's (WHO) syndromic surveillance algorithms for the management of *C. trachomatis* (CT) and *N. gonorrhoeae* (GC) compared to nucleic acid amplification testing (NAAT) in a cohort of cisgender women at high risk of sexually transmitted infections (STIs) in Mombasa, Kenya.

Methods: Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were calculated for syndromic criteria (self-reported vaginal discharge, vaginal discharge plus lower abdominal/adnexal pain, and vaginal discharge and/or lower abdominal/adnexal pain) versus CT/GC results from Aptima Combo II Assays for the study population overall and stratified by age (<25 years versus ≥ 25 years). We estimated the proportion of CT/GC infections that would be missed if only syndromic surveillance were implemented for routine screening (1 minus sensitivity). In addition, we assessed factors associated with self-reported vaginal discharge and lower abdominal/adnexal pain.

Results: Between 2004-2017, 1,860 participants contributed 20,550 visits to this analysis. At first NAAT, median age was 31.7 years (interquartile range 26.9, 37.5). There were 353 (1.7%) cases of CT, 470 (2.3%) cases of GC, and 795 (3.9%) cases of CT and/or GC. Vaginal discharge, abdominal pain, and vaginal discharge and/or abdominal pain were reported at 1,247 (6.1%), 249 (1.5%) and 1,484 (7.3%) visits, respectively. Sensitivity, specificity, NPV, and PPV for self-reported vaginal discharge and/or abdominal pain versus NAAT for CT/GC were 15.3% 93.0%, 96.5%, and 8.1%, respectively. Limiting STI screening to syndromic management would result in 84.7% of CT/GC infections being missed due to asymptomatic presentation (95% confidence interval (CI) 82.0, 87.2). Results were similar when CT and GC were assessed as separate outcomes for all three syndromic algorithms. When stratified by age, sensitivity and PPV were higher for younger women (<25 years) than older women when CT or CT/GC NAAT results were used as a gold standard. Correlates analyses showed factors associated with reduced odds of self-reported vaginal discharge included age, parameterized as a continuous variable, (OR = 0.94 (95% CI 0.93, 0.95)) and use of highly effective, modern contraception (oral contraceptive pills (OCP), depot medroxyprogesterone acetate (DMPA), intrauterine device (IUD), and hormonal implant) compared to coitally-dependent (i.e. condoms) or no family planning method (OR = 0.75; 95% CI = 0.62, 0.89). Factors associated with an increased odds of self-reported vaginal discharge included any vaginal washing (OR = 1.28; 95% CI 1.01, 1.64) and reporting of any sexual partners in the last working week (OR = 1.03; 95% CI 1.01, 1.04), after adjustment for respective covariates. Factors associated with reduced odds of self-reported abdominal/adnexal pain were older age (OR = 0.97; 95% CI 0.95, 0.99) and any vaginal washing during the last working week (OR = 0.56; 95% CI 0.41, 0.76). Any contraception use (OR = 1.68; 95% CI 1.04, 2.71) was the only factor associated with increased odds of self-reported abdominal/adnexal pain, after adjustment for respective covariates.

Conclusions: Among cisgender women with CT or GC diagnosed by NAAT, the prevalence of asymptomatic infections was extremely high, limiting the utility of syndromic approaches for routine STI screening. The development of low-cost, point-of-care STI diagnostics remains a public health priority, both to inform clinical decision making and improve STI surveillance in resource-limited settings

Table of Contents:

Introduction 7

Methods 8

Results 11

Discussion 14

Acknowledgements19

References 20

Appendix 24

Introduction

The global burden of sexually transmitted infections (STIs) has consistently increased over the past several decades.^{1,2} In 2016 alone, an estimated 127.2 million incident cases of *Chlamydia trachomatis* and 86.9 million incident cases of *Neisseria gonorrhoeae* occurred globally, with a higher burden in resource-limited settings.² Addressing the rise in STIs has been impeded by limited availability of diagnostic testing in many resource-limited settings. To mitigate issues with testing access, the World Health Organization (WHO) established syndromic surveillance guidelines for the management of STIs in settings where diagnostic testing is not available or highly limited.³ These guidelines focus on the identification of symptom groups and easily recognized syndromes in order to guide subsequent treatment plans that will eradicate the majority of organisms responsible for producing the syndrome(s). The WHO guidelines have led to the development of national, standardized treatment protocols for STI management in resource-limited settings that serve as the basis for presumptive diagnosis and treatment.³

Although the guidelines provide a framework for global implementation, there are several limitations for the effective management of chlamydial and gonococcal infections. Individuals with asymptomatic infections are not treated, as the current algorithms require the presence of at least one clinically-identifiable symptom.^{3,4} Recent studies have shown the proportion of asymptomatic cases of *C. trachomatis* and *N. gonorrhoeae* infections among women globally may be greater than 50%.⁵ Undertreatment of infections can lead to the development of short- and long-term complications in women, such as pelvic inflammatory disease and infertility, and may increase transmission through populations.^{6,7} Conversely, women presenting with symptoms, including vaginal discharge and abdominal pain, may be overtreated with antibiotics regardless of their true disease status. The current WHO guidelines recommend the use of several antibiotics, including doxycycline, metronidazole, and ceftriaxone, to treat conditions that produce these symptoms.³ Antibiotic resistance is becoming a major barrier to care for the treatment of *N. gonorrhoeae* as

an increased number of infections are reported to be highly-resistant to commonly used antibiotics.⁸⁻¹⁰

Several studies have assessed the performance characteristics of the WHO's syndromic surveillance algorithms in a variety of settings and have been valuable in characterizing the performance of syndromic management of STIs compared to diagnostic testing.^{4,11-14} Most women enrolled in these studies were evaluated because they were seeking care for symptoms. There is limited understanding of the performance of the WHO's syndromic surveillance guidelines among female sex workers (FSW) who are at high risk for STIs, including *C. trachomatis* and *N. gonorrhoeae*, and could benefit from active syndromic screening in settings where diagnostic STI testing is not readily available. To add to the current body of research, we assessed the performance characteristics of WHO syndromic surveillance compared to diagnostic testing for *C. trachomatis* and *N. gonorrhoeae*, including estimating the proportion of infections that would be missed if only syndromic surveillance algorithms were implemented among cisgender women participating in a longitudinal open cohort study in Kenya. Correlates analyses were also used to assess if associations exist between behavioral and clinical factors and self-reporting symptoms of either vaginal discharge or lower abdominal/adnexal pain.

Methods

Study population and procedures

This study utilized a cross-sectional analysis of longitudinal data nested within the Mombasa Cohort, an ongoing prospective, open cohort study assessing risk factors for HIV-1 acquisition among cisgender women who report transactional sex in Mombasa, Kenya. Women are eligible to participate in the cohort if they are 16 – 60 years old, identify as a cisgender woman, reside within a 1-day commuting distance from the study clinic, self-identify as exchanging sex for payment in cash or in kind, and are able to provide informed consent. Regardless of symptoms, participants complete a standardized interviewer-administered

questionnaire that asks about clinical symptoms including vaginal discharge and lower abdominal/adnexal pain. Questions pertaining to interim health history regarding sexual behavior, personal hygiene practices, and contraceptive use are also asked in the questionnaire. A physical examination, including a pelvic examination, and clinical and laboratory evaluation for vaginal infections are performed monthly. *Chlamydia trachomatis* and *N. gonorrhoeae* infections are assessed quarterly using the Aptima Combo II Assay, a nucleic acid amplification test (NAAT) designed to detect rRNA, first implemented in the Cohort in 2004.¹⁵

Statistical Analysis

This analysis included data from visits occurring between November 2004 and June 2017. Visits were included if complete data were available for NAAT results for *C. trachomatis* and *N. gonorrhoeae* and a completed evaluation of symptoms including vaginal discharge and/or abdominal pain, or no clinical symptoms reported at the time of follow-up. This analysis was restricted to study participants who were 16 – 49 years old at the time of visit. Syndromic surveillance algorithms were used as the exposures to assess performance characteristics when compared to NAAT (Figure 1). First, the WHO's "vaginal discharge only" algorithm included individuals who only report vaginal discharge. The second WHO algorithm used in this analysis is the "vaginal discharge and lower abdominal/adnexal pain" algorithm. When self-reported values for vaginal discharge and lower abdominal/adnexal pain were recorded, only individuals who reported experiencing both symptoms were considered as having the exposure. If an individual experienced vaginal discharge but no lower abdominal/adnexal pain or they experienced no symptoms, they were classified as not having the exposure. A third, pragmatic algorithm was implemented to assess a combination of the two WHO algorithms: vaginal discharge and/or lower abdominal pain. In this algorithm, all individuals who had a positive self-report of either vaginal discharge and/or lower abdominal pain were classified as having the exposure. This exposure

was the primary focus of this analysis as it best represents the approach implemented in settings where diagnostic testing is not available.

The three algorithms were compared to the gold standard results of the NAAT. The primary comparisons of interest were the results for *C. trachomatis* and/or *N. gonorrhoeae*. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) with corresponding 95% confidence intervals (CIs) were calculated. Separate sensitivity analyses were calculated using NAAT results for *C. trachomatis* and *N. gonorrhoeae* as separate outcomes. Given that the prevalence of *C. trachomatis* tends to be higher in women < 25 years, performance characteristics for all three syndromic algorithms were also assessed when stratified by age (<25 versus ≥25 years) to determine if differences existed comparing younger and older study participants.¹⁶ We then estimated the proportion of *C. trachomatis*, *N. gonorrhoeae*, and *C. trachomatis/N. gonorrhoeae* infections that would be missed if only syndromic surveillance were implemented for routine screening within this study population (1-sensitivity).

To better understand factors associated with report of symptoms, the relationship between demographic, behavioral and clinical factors and report of vaginal discharge or report of lower abdominal/adnexal pain was assessed. Univariate logistic regression with generalized estimating equations (GEE) and an independent correlation structure, which accounts for multiple visits per woman, was implemented. Factors assessed included age, contraception use, vaginal washing, and number of sexual partners in the prior working week with vaginal discharge or lower abdominal/adnexal pain as separate outcomes. Contraception use was categorized as either highly effective modern method, permanent method, or coitally-dependent (i.e. condoms) or no family planning method. Use of oral contraceptive pills (OCP), depot medroxyprogesterone acetate (DMPA), intrauterine device (IUD), or hormonal implant were considered as highly effective modern methods. Tubal ligation and hysterectomy were considered as permanent methods. Visits missing data for any of the covariates of interest were excluded from this analysis. Step-wise regression was performed to build multivariable models by adding covariates

sequentially based on statistical significance (p -value < 0.10). After the addition of each covariate, variables that did not improve the model fit were removed. This process ended once there were no statistically significant covariates remaining. R software, version 3.6.0, was utilized for all data cleaning and analyses (R Foundation for Statistical Computing, Vienna, Austria).

Results

Descriptive Summary

Between 2004 and 2017, 1,860 study participants from the Mombasa Cohort were eligible to be included in this analysis. The median number of visits contributed per woman was 5.0 (interquartile range (IQR) 2.0, 15.0). Characteristics at enrollment into the cohort are presented in Table 1. Median age at enrollment and median age at first NAAT was 29.5 years (IQR 25.5, 34.5) and 31.7 years (IQR 26.9, 37.5), respectively. At enrollment, 98.8% of study participants reported having one or more sexual partners during the last working week. Of women reporting one or more sexual partners, the median number of sex acts and the median number of sex acts with condoms during the last working week was 3.0 (IQR 2.0, 4.0) and 2.0 (1.0, 4.0), respectively. At first NAAT, 74.6% of study participants reported having 1 or more sexual partners during the last working week. Of women reporting one or more sexual partners, the median number of sex acts and the median number of sex acts with condoms during the last working week was 2.0 (IQR 1.0, 3.0) and 1.0 (0.0, 2.0), respectively. Within the same time period, study participants contributed 20,550 study visits (Table 2). The median age across all study visits was 37.7 years (IQR 32.3, 42.4) with 950 (4.6%) visits contributed by study participants under the age of 25. At first NAAT, one or more sexual partners during the last working week was reported at 62.2% of study visits. Among study visits where one or more sexual partners was reported, the median number of sex acts and the median number of sex acts with condoms during the last working week was 2.0 (IQR 1.0, 3.0) and 1.0 (1.0, 2.0), respectively.

Self-report of only vaginal discharge, only lower abdominal pain, or vaginal discharge and lower abdominal pain was low across all study visits (Table 3). Self-reported vaginal discharge was reported at 1,247 (6.1%) visits. Among study visits with a reported value for abdominal pain (n = 20,379), 249 (1.5%) reported lower abdominal pain and 58 (0.3%) reported lower abdominal pain and vaginal discharge. The number of *C. trachomatis* and *N. gonorrhoeae* infections detected by NAAT was also low. Across all study visits, there were 353 (1.7%) cases of *C. trachomatis* and 470 (2.3%) cases of *N. gonorrhoeae*; in aggregate, there were 795 (3.9%) study visits that recorded a diagnosis of *C. trachomatis* and/or *N. gonorrhoeae* (Table 4).

Performance Characteristics

Performance characteristics for the three syndromic surveillance algorithms, self-reported vaginal discharge, vaginal discharge plus lower abdominal/adnexal pain, and vaginal discharge and/or lower abdominal/adnexal pain, for *C. trachomatis* and/or *N. gonorrhoeae* are summarized in Tables 5 – 7. When vaginal discharge and/or lower abdominal/adnexal pain was compared to NAAT as the gold standard, sensitivity and PPV estimates were low at 15.3% (95% CI 12.8, 18.0) and 8.1% (95% CI 6.8, 9.6), respectively. Specificity and NPV estimates were higher at 93.0% (95% CI 92.7, 93.4) and 96.5% (95% CI 96.2, 96.7), respectively. Results for vaginal discharge or vaginal discharge plus lower abdominal/adnexal pain compared to NAAT as the gold standard were comparable (Tables 6, 7). Additionally, high sensitivity and PPV with low specificity and NPV were seen when performance characteristics for all three algorithms were evaluated using *C. trachomatis* or *N. gonorrhoeae* as separate outcomes (Tables 8 - 13).

The proportion of *C. trachomatis* and/or *N. gonorrhoeae* infections that would be missed if only syndromic surveillance algorithms based on self-reported vaginal discharge and/or lower abdominal pain were implemented in the study population was estimated to be 84.7% (95% CI 82.0, 87.2). Additionally, syndromic management based on self-reported vaginal discharge and/or lower abdominal pain would have also led to 82.8% (95% CI 79.1, 86.1) and 87.4% (95% CI 83.4,

90.7) of *N. gonorrhoeae* infections alone and *C. trachomatis* infections alone being missed, respectively (Table 14).

Sensitivity analyses assessing performance characteristics of vaginal discharge and/or lower abdominal/adnexal pain when compared to *C. trachomatis* and/or *N. gonorrhoeae* results produced observable difference after stratification by age (Table 15). Women aged < 25 years had higher sensitivity (17.5%; 95% CI 10.6, 26.6) and PPV (12.4%; 95% CI 7.4, 19.1) compared to the sensitivity (14.9%; 95% CI 12.4, 17.8) and PPV (7.7%; 95% CI 6.3, 9.2) of women aged ≥ 25 years. Specificity (85.8% (95% CI 83.3, 88.1) versus 93.4% (95% CI 93.0, 93.7)) and NPV (90.1% (95% CI 87.8, 92.1) versus 96.8% (95% CI 96.5, 97.0)) remained comparable or lower among women aged < 25 years versus women aged ≥ 25 years, respectively. Similar results, stratified by age, were observed when vaginal discharge or vaginal discharge plus lower abdominal/adnexal pain were compared to *C. trachomatis* and/or *N. gonorrhoeae* results (Tables 16, 17).

Sensitivity analyses, stratified by age, comparing vaginal discharge and/or lower abdominal/adnexal pain with *C. trachomatis* or *N. gonorrhoeae* alone produced varying results (Tables 18, 19). When *C. trachomatis* alone was used, women aged < 25 years had higher sensitivity (20.9%; 95% CI 11.9, 32.6) and PPV (10.2%; 95% CI 5.7, 16.6) compared to the sensitivity (10.6%; 95% CI 7.3, 14.8) and PPV (2.2%; 95% CI 1.5, 3.2) of women aged ≥ 25 years. When *N. gonorrhoeae* alone was used, women aged < 25 years had lower sensitivity (12.5%; 95% CI 3.5, 29.0) and PPV (2.9%; 95% CI 0.1, 7.3) compared to the sensitivity (17.5%; 95% CI 14.1, 21.4) and PPV (5.6%; 95% CI 4.5, 7.0) of women aged ≥ 25 years. Specificity and NPV remained comparable or lower among women aged < 25 years versus women aged ≥ 25 years for *C. trachomatis* or *N. gonorrhoeae* alone. Similar results, stratified by age, were observed when vaginal discharge or vaginal discharge plus lower abdominal/adnexal pain were compared to *C. trachomatis* or *N. gonorrhoeae* alone (Tables 20 - 23).

Correlates Analyses

In univariate analysis assessing factors associated with self-reported vaginal discharge, age, contraception use, number of sexual partners in the last week, and any vaginal washing during the last week were associated with self-reported vaginal discharge and were retained in the multivariable model (Tables 24, 25). Every increasing year in age was associated with a lower odds of reporting vaginal discharge (OR = 0.94; 95% CI 0.93, 0.95). Compared to coitally-dependent or no contraceptive use, use of modern contraception was also associated with decreased odds of reporting vaginal discharge (OR = 0.75; 95% CI = 0.62, 0.89). Inversely, with every additional sexual partner in the last working week, there was an increased odds of reporting vaginal discharge (OR = 1.03; 95% CI 1.01, 1.04). Finally, any vaginal washing in the last working week was also associated with increased odds of reporting vaginal discharge (OR = 1.28; 95% CI 1.01, 1.64).

For self-reported lower abdominal/adnexal pain, the same factors were associated with the outcome in univariate models; however, only age, any contraception use, and any vaginal washing during the last week were retained in the final multivariate model (Tables 26, 27). Multivariate analyses showed that every increasing year in age was associated with lower odds of reporting lower abdominal/adnexal pain (OR = 0.97; 95% CI 0.95, 0.99). Any vaginal washing in the last working week was also associated with decreased odds of reporting lower abdominal/adnexal pain (OR = 0.56; 95% CI 0.41, 0.76). Finally, any contraception use was the only factor associated with increased odds of reporting lower abdominal/adnexal pain in this study (OR = 1.68; 95% CI 1.04, 2.71).

Discussion

Overall, the three syndromic algorithms assessed in the study had poor sensitivity and PPV, but high specificity and NPV for detection of *C. trachomatis* and/or *N. gonorrhoeae*. This finding was not surprising given study participants in the cohort attend monthly follow-up visits at

the study clinic, regardless of symptom presentation. Of all eligible study visits, abnormal vaginal discharge was reported at 6.1% of visits and lower abdominal/adnexal pain was reported at only 1.5% of visits. Among visits with NAAT-confirmed *C. trachomatis* and/or *N. gonorrhoeae* infections, roughly 667 (84.7%) cases would be missed if self-reporting of vaginal discharge and/or lower abdominal pain were utilized solely to detect presumptive infections. The low prevalence of symptoms, combined with the low frequency of *C. trachomatis* and *N. gonorrhoeae* infections reporting symptoms overall, led to a large proportion of false negatives, resulting in poor sensitivity. A low prevalence of infection also resulted in a low PPV. The NPV remained high across all three syndromic algorithms as a result of the low prevalence of infection and high specificity.

Previous studies utilizing diagnostic testing as the gold standard for comparison to syndromic surveillance algorithms have also reported similar results.^{4,17-20} Low sensitivity and PPV appear to be a universal drawback of syndromic surveillance algorithms. However, the magnitude of estimated performance characteristics largely relies on the prevalence of self-reported symptoms within the study population. A 2012 study of HIV-uninfected women in South Africa conducted similar analyses using bi-annual follow-up visits over the course of 24 months to record the prevalence of several laboratory-diagnosed STIs and clinical symptoms.⁴ As women attended clinic visits regardless of symptom presentation, the prevalence of vaginal discharge was low at 1.5% and 4.8% during the 6- and 12-month study visits, respectively. Sensitivity, specificity, PPV, and NPV for syndromic management of *N. gonorrhoeae* using vaginal discharge were estimated to be 17.9%, 92.8%, 6.9%, and 97.5%, respectively. Sensitivity, specificity, PPV, and NPV for syndromic management of *C. trachomatis* using vaginal discharge were comparable at 13.9%, 92.8%, 6.9%, and 96.6%, respectively. Although syndromic management using lower abdominal/adnexal pain was not assessed, these results mirror the findings found in the present study.

In studies with a high prevalence of self-reporting symptoms, stronger estimates for sensitivity and PPV were observed. A 2003 study of FSW, conducted in India, recruited women using a health camp approach at a local clinic.¹⁷ While researchers recruited women with or without symptoms, the use of an established clinic that performed diagnostic and therapeutic services for FSW may have led to the higher prevalence of symptom presentation in their study population. Roughly 19.5% and 12.7% of study participants reported lower abdominal pain and vaginal discharge, respectively. Additionally, the prevalence of *C. trachomatis* (8.5%) and *N. gonorrhoeae* (16.9%) was much higher than the prevalences recorded in this study. Using syndromic management guidelines for vaginal discharge, sensitivity and PPV for *C. trachomatis* was estimated to be 70.0% and 11.5%, respectively. Sensitivity and PPV for *N. gonorrhoeae*, when Pace2 tests were utilized, was estimated to be 58.3% and 11.5%, respectively.

The number of women reporting no symptoms is likely much higher in our study population than in most standard clinical settings, including the one used in the 2003 FSW study in India. If this were true, we would expect the values of sensitivity and PPV calculated in this study to underestimate the true performance characteristics of the three syndromic algorithms in clinical settings.^{18,19} However, the values calculated in this study provide a unique perspective into the potential impacts of using syndromic surveillance algorithms as an unintended proactive screening tool to identify cases of *C. trachomatis* and *N. gonorrhoeae*. The results also highlight the need to fulfill the WHO's 2019 call-to-action to develop low-cost, point-of-care STI diagnostics as a public health priority.²¹

Slight differences in the performance characteristics of the syndromic algorithms were observed when comparing women aged < 25 years to women aged ≥ 25 years. When *C. trachomatis* and/or *N. gonorrhoeae* results were used as a gold standard, women aged < 25 years had higher sensitivity and PPV compared to women aged ≥ 25 years. Given the higher risk of STI acquisition among FSW, it was uncertain if we would see a higher burden of *C. trachomatis* among younger women as we do in the general population. However, these findings were consistent

with global *C. trachomatis* epidemiologic studies.^{22,23} Additionally, specificity and NPV were comparable between younger and older women. Results from *C. trachomatis* alone were similar to *C. trachomatis* and/or *N. gonorrhoeae* results, when stratified by age, because of the higher proportion of *C. trachomatis* cases among women <25 years of age compared to *N. gonorrhoeae*. There were no meaningful differences in performance characteristics between younger and older women for *N. gonorrhoeae* results alone.

Correlates analyses found that self-reporting vaginal discharge was associated with age, contraception use, number of sexual partners and vaginal washing. When age was parameterized as a continuous variable, every increasing year in age was associated with a lower odds of reporting vaginal discharge. Modern contraception use was also found to be associated with decreased odds of reporting vaginal discharge when compared to coitally-dependent or no contraception use. Every additional sexual partner in the last working week was associated with an increased odds of reporting vaginal discharge. Additionally, any vaginal washing in the last working week was also found to be associated with increased odds of vaginal discharge reporting within this study.

Age, parametrized as a continuous variable, was associated with a lower odds of reporting lower abdominal/adnexal pain with every increasing year. Any contraception use was also found to be associated with a lower odds of reporting lower abdominal/adnexal pain. The only factor to be associated with increased odds of reporting lower abdominal adnexal pain was the use of any contraception. These results match prior research studying factors associated with vaginal discharge and lower abdominal pain.²⁴⁻²⁷ Increased sexual activity among younger age groups and vaginal washing can contribute to a higher prevalence of symptom-causing infections, including *C. trachomatis*. Prior studies have also reported associations between highly effective, modern methods of contraception and onset of lower abdominal/adnexal pain and vaginal discharge.

The use of data from the Mombasa Cohort did provide several strengths, including a large study population followed for multiple years. The median number of eligible study visits contributed by each study participant was 5.0 (IQR 2.0, 15.0). Routine screening for STIs using highly sensitive NAAT testing at these visits provided data on the frequency of both symptomatic and asymptomatic cases of *C. trachomatis* and *N. gonorrhoeae* and allowed for the calculation of precise performance characteristics with comparably narrow confidence intervals. The extensive time period of data collection from 2004 to 2017 also provided a more representative sample of women participating in transactional sex in Mombasa. The use of monthly study visits and questions pertaining to the previous working week also limited the impacts of recall bias on the study results.

The results of this study should be interpreted in the context of several limitations. It is unclear how generalizable these findings are to other populations. The data used in the analyses was taken from a specific study population of cisgender women aged 16 – 49 years participating in transactional sex work in Mombasa, Kenya. It is possible that the estimates produced in this study are only valid for other cisgender women with similar, underlying characteristics as our study participants. Different study populations, including samples taken from standard clinical settings, may provide a greater proportion of individuals with *C. trachomatis* and/or *N. gonorrhoeae* infections than what was observed in this study. Additionally, the use of correlates analyses to assess if an association exists between selected covariates and self-reporting symptoms of either vaginal discharge or lower abdominal/adnexal pain does not provide causative evidence. Interpretation of these results should be made cautiously and serve as a foundation for future research assessing if biological and behavioral characteristics might inform case-by-case screening practices in settings without point-of-care diagnostics.

Overall, poor sensitivity in detecting *C. trachomatis* and *N. gonorrhoeae* infections exists when using syndromic surveillance algorithms – a finding comparable to previous research studies.^{4,12,13,17-20} It is also clear that the use of syndromic surveillance algorithms is not functional,

nor recommended, for use as an effective screening tool in resource-limited settings. An estimated 84.7% of *C. trachomatis* and/or *N. gonorrhoeae* infections would be missed if self-reporting of vaginal discharge and/or lower abdominal pain were utilized to detect infections. The high prevalence of asymptomatic infections creates barriers to the effective use of syndromic algorithms which require self-reported symptoms that may go unnoticed by patients and health care providers, leading to undertreatment and serious sequelae. The results of this study provide further evidence in support of the WHO's push to develop low-cost, point-of-care STI diagnostics in order to inform clinical decision making and improve STI surveillance in resource-limited settings.²¹

Acknowledgements:

I would like to express my appreciation and gratitude for Dr. Jennifer Balkus, my committee chair and mentor, as well as Dr. Scott McClelland and Dr. Christine Khosropour, my committee members, for their unmatched guidance, encouragement, and commitment to empowering my development as a researcher and global citizen. I would also like to thank all of the faculty, staff, and participants associated with the Mombasa Cohort who have provided a unique opportunity to explore my passions and contribute to the expanding body of scientific knowledge. Finally, I would like to thank my family and friends for their continued love and support as I navigate the end of graduate school and the beginning of my next stage in life.

References:

1. Hussen, S., Wachamo, D., Yohannes, Z. *et al.* Prevalence of chlamydia trachomatis infection among reproductive age women in sub Saharan Africa: a systematic review and meta-analysis. *BMC Infect Dis* 18, 596 (2018). <https://doi.org/10.1186/s12879-018-3477-y>
2. Rowley J, Vander Hoorn S, Korenromp E, et al. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. *Bull World Health Organ.* 2019;97(8):548–562P. doi:10.2471/BLT.18.228486
3. WHO. Guidelines for the Management of Sexually Transmitted Infections. Geneva: World Health Organization, 2003.
4. Mlisana K, Naicker N, Werner L, et al. Symptomatic vaginal discharge is a poor predictor of sexually transmitted infections and genital tract inflammation in high-risk women in South Africa. *J Infect Dis* 2012; 206: 6–14.
5. 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):503–509.
6. Aral SO, Over M, Manhart L, et al. Sexually Transmitted Infections. Disease Control Priorities in Developing Countries. 2nd edition. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2006. Chapter 17.
7. Krupp K, Madhivanan P. Antibiotic resistance in prevalent bacterial and protozoan sexually transmitted infections. *Indian J Sex Transm Dis AIDS.* 2015;36(1):3–8. doi:10.4103/0253-7184.156680
8. WHO. Report of the expert consultation and review of the latest evidence to update guidelines for the management of sexually transmitted infections. Geneva: World Health Organization, 2011.
9. Unemo M, Del Rio C, Shafer WM. Antimicrobial Resistance Expressed by Neisseria gonorrhoeae: A Major Global Public Health Problem in the 21st Century. *Microbiol Spectr.*

2016;4(3):10.1128/microbiolspec.EI10-0009-2015.doi:10.1128/microbiolspec.EI10-0009-2015

10. WHO. WHO guidelines for the treatment of Chlamydia trachomatis. Geneva: World Health Organization, 2016.
11. Otieno FO, Ndivo R, Oswago S, et al. Evaluation of syndromic management of sexually transmitted infections within the Kisumu incidence cohort study. *Int J STD AIDS* 2014; 25: 851–59.
12. Chirenje ZM, Dhibi N, Handsfield HH, et al. The etiology of vaginal discharge syndrome in Zimbabwe: results from the Zimbabwe STI etiology study. *Sex Transm Dis* 2018; 45: 422–28.
13. 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: e0163365.
14. Kettler H, White K, Hawkes S. Mapping the landscape of diagnostics for sexually transmitted infections: key findings and recommendations. Geneva: World Health Organization on behalf of the Special Programme for Research and Training in Tropical Disease, 2004.
15. Hologic. Aptima Combo 2 for CT/NG Assay. Marlborough, MA: Hologic Inc.
16. CDC. Sexually Transmitted Disease Surveillance 2018 – Chlamydia. Atlanta: Centers for Disease Control and Prevention, 2018.
17. Desai VK, Kosambiya JK, Thakor HG, et al. Prevalence of sexually transmitted infections and performance of STI syndromes against aetiological diagnosis, in female sex workers of red light area in Surat, India. *Sexually Transmitted Infections* 2003;79:111-115.
18. Djomand G, Gao H, Singa B, et al. Genital infections and syndromic diagnosis among HIV-infected women in HIV care programmes in Kenya. *Int J STD AIDS*. 2016;27(1):19-24. doi:10.1177/0956462415568982

19. Mayaud P, Grosskurth H, Changalucha J, et al. Risk assessment and other screening options for gonorrhoea and chlamydial infections in women attending rural Tanzanian antenatal clinics. *Bull World Health Organ.* 1995;73(5):621-630.
20. Verwijs MC, Agaba SK, Sumanyi J-C, et al. Targeted point-of-care testing compared with syndromic management of urogenital infections in women (WISH): a cross-sectional screening and diagnostic accuracy study. *Lancet Infect Dis.* 2019;19(6):658-669. doi:10.1016/S1473-3099(18)30724-2
21. WHO. *The Point-of-Care Diagnostic Landscape for Sexually Transmitted Infections (STIs)*. Geneva: World Health Organization, 2019.
22. 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):503-509.
23. Tao X, Ghanem KG, Page KR, Gilliams E, Tuddenham S. Risk factors predictive of sexually transmitted infection diagnosis in young compared to older patients attending sexually transmitted diseases clinics. *Int J STD AIDS.* 2020;31(2):142-149. doi:10.1177/0956462419886772
24. Abasiattai AM, Basse EA, Udoma EJ. Profile of intrauterine contraceptive device acceptors at the University of Uyo Teaching Hospital, Uyo, Nigeria. *Ann Afr Med.* 2008;7(1):1-5. doi:10.4103/1596-3519.55692
25. Martino JL, Vermund SH. Vaginal douching: evidence for risks or benefits to women's health. *Epidemiol Rev.* 2002;24(2):109-124. doi:10.1093/epirev/mxf004
26. La Ruche G, Messou N, Ali-Napo L, et al. Vaginal douching: association with lower genital tract infections in African pregnant women. *Sex Transm Dis.* 1999;26(4):191-196. doi:10.1097/00007435-199904000-00001

27. Venugopal S, Gopalan K, Devi A, Kavitha A. Epidemiology and clinico-investigative study of organisms causing vaginal discharge. *Indian J Sex Transm Dis AIDS*. 2017;38(1):69-75. doi:10.4103/0253-7184.203433

Appendix:

Figure 1: Syndromic Surveillance Algorithms for Management of *C. trachomatis* and/or *N. gonorrhoeae* in Mombasa Cohort

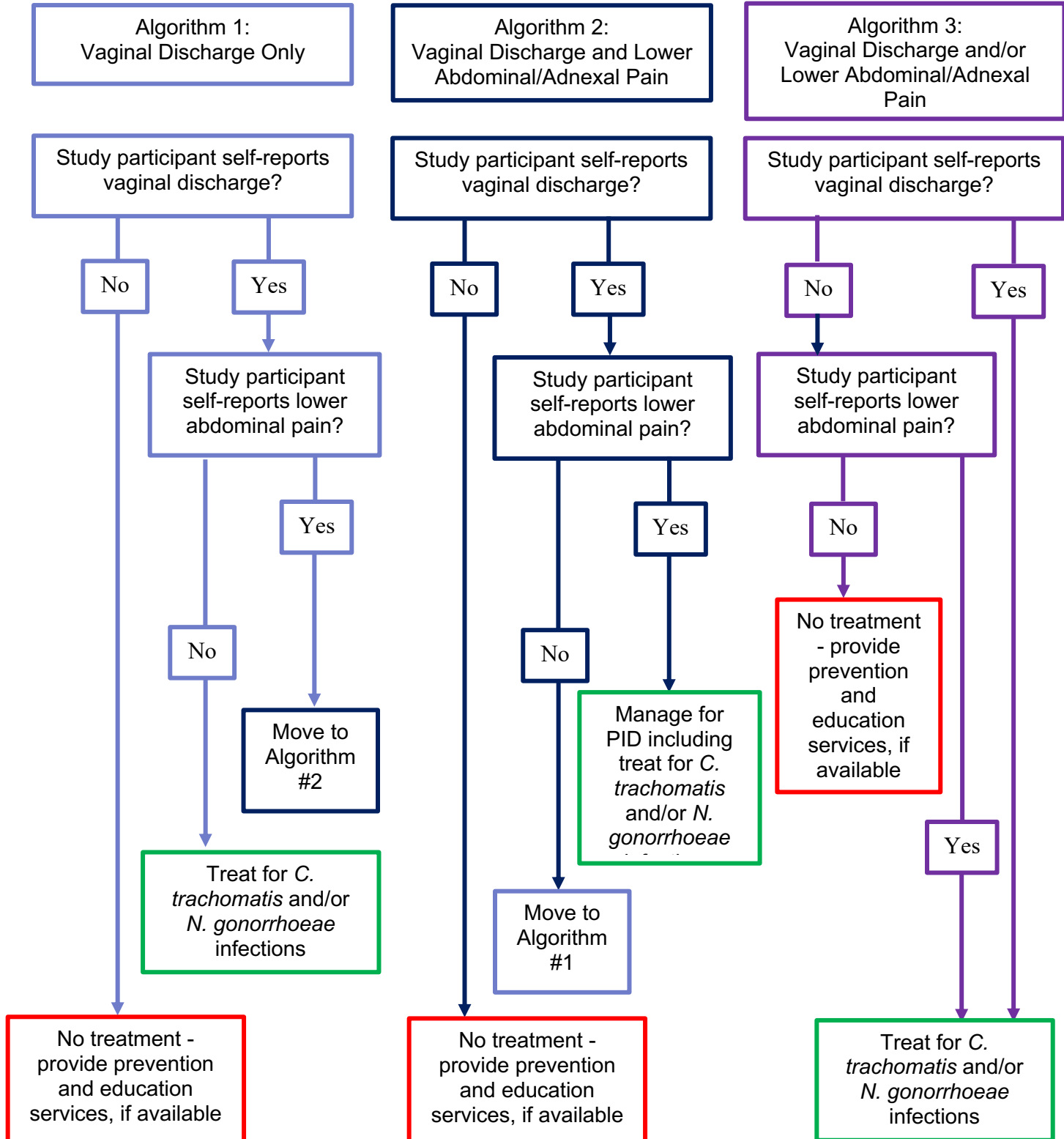


Figure 2: Study Participant/Study Visit Inclusion Flowchart

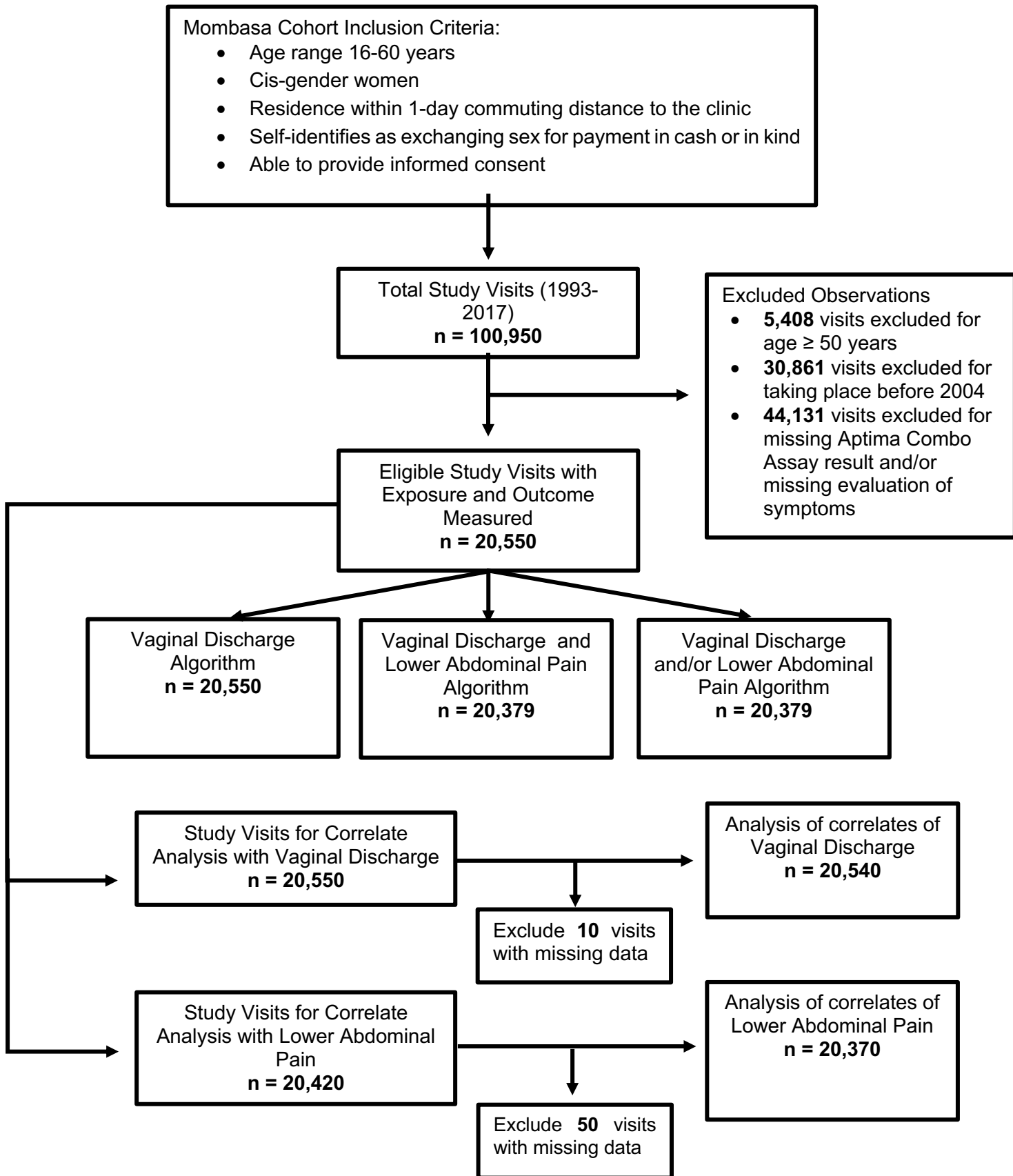


Table 1: Characteristics of eligible study participants in the Mombasa Cohort (N=1,860)

Study Participants (N=1,860)	
Age at enrollment**	
Under 25 years	436 (23.4%)
25 – 29 years	534 (28.7%)
30 – 34 years	465 (25.0%)
35 – 40 years	271 (14.6%)
40 + years	154 (8.3%)
Age at enrollment (median (IQR))	29.5 (25.5, 34.5)
Age at first Aptima Combo II Assay test***	
Under 25 years	295 (15.9%)
25 – 29 years	458 (24.6%)
30 – 34 years	452 (24.3%)
35 – 40 years	365 (19.6%)
40 + years	290 (15.6%)
Age at first Aptima (median (IQR))	31.7 (26.9, 37.5)
Marital Status**	
Never Married	735 (39.5%)
Currently Married	28 (1.5%)
Widowed/Divorced	1,059 (56.9%)
Other	1 (0.05%)
Missing/No Response	37 (2.0%)
Nationality**	
Kenyan	1,686 (90.6%)
Tanzanian	58 (3.1%)
Ugandan	69 (3.7%)
Somali	3 (0.2%)
Other	8 (0.4%)
Missing/No Response	36 (1.9%)
Religion**	
Protestant	906 (48.7%)
Catholic	633 (34.0%)
Muslim	220 (11.8%)
Other	33 (1.8%)
Missing/No Response	68 (3.7%)
Workplace**	
Bar/Restaurant/Guesthouse	1,028 (55.3%)
Nightclub	569 (30.6%)
Home-based	57 (3.1%)
Other	206 (11.1%)
At cohort enrollment**	
Proportion of women reporting 1 or more sexual partners during the last working week	
1+ sexual partners	1,838 (98.8%)
0 sexual partners	22 (1.2%)

Table 1: Characteristics of eligible study participants in the Mombasa Cohort (N=1,860) continued

Study Participants (N=1,860)	
Of women reporting 1 or more sexual partners during the last working week	
No. sex acts during the last working week (median (IQR))	3.0 (2.0, 4.0)
No. sex acts w/condoms during the last working week (median (IQR))	2.0 (1.0, 4.0)
At first NAAT for <i>C. trachomatis</i> and <i>N. gonorrhoeae</i>***	
Proportion of women reporting 1 or more sexual partners during the last working week	
1+ sexual partners	1,387 (74.6%)
0 sexual partners	473 (25.4%)
Of women reporting 1 or more sexual partners during the last working week	
No. sex acts during the last working week (median (IQR))	2.0 (1.0, 3.0)
No. sex acts w/condoms during the last working week (median (IQR))	1.0 (0.0, 2.0)
Vaginal washing during the last working week	
None	52 (2.8%)
Water alone	774 (41.6%)
Omo	9 (0.5%)
Soap/water	845 (45.4%)
Dettol	59 (3.2%)
Other	21 (1.1%)
Current contraception use	
No contraception	845 (45.4%)
Condoms only	353 (19.0%)
Oral contraceptive pills (OCP)	91 (4.9%)
Spermicides	1 (0.1%)
Depot medroxyprogesterone acetate (DMPA)	367 (19.7%)
Intrauterine device (IUD)	35 (1.9%)
Tubal ligation	29 (1.6%)
Hysterectomy	6 (0.3%)
Hormonal implant	124 (6.7%)
Other	6 (0.3%)
Missing/No Response	3 (0.2%)

* Proportions may not add to 100% due to rounding of values;

** Measured at enrollment into Mombasa Cohort study;

*** Measured at first Aptima Combo II Assay test; IQR = Interquartile range

Table 2: Characteristics of study participants in the Mombasa Cohort at all visits to Ganjoni Clinic meeting inclusion criteria between 2004 – 2017 (N = 20,550)*

		Study Visits (N=20,550)	
Age at visit			
	Under 25 years	950	(4.6%)
	25 – 29 years	2,504	(12.2%)
	30 – 34 years	4,019	(19.6%)
	35 – 40 years	5,438	(26.5%)
	40 + years	7,639	(37.2%)
	Age at visit (median (IQR))	37.7	(32.3, 42.4)
Pregnancy status			
	Not pregnant	20,276	(98.8%)
Current contraception use			
	No contraception	10,261	(49.9%)
	Condoms only	3,461	(16.8%)
	Oral contraceptive pills (OCP)	797	(3.9%)
	Spermicides	3	(0.01%)
	Depot medroxyprogesterone acetate (DMPA)	3,865	(18.8%)
	Intrauterine device (IUD)	356	(1.7%)
	Tubal ligation	703	(3.4%)
	Hysterectomy	156	(0.8%)
	Hormonal implant	914	(4.5%)
	Other	24	(0.1%)
	Missing/No Response	10	(0.05%)
Vaginal washing during the last working week			
	None	2,551	(12.4%)
	Water alone	10,982	(53.4%)
	Omo	33	(0.2%)
	Soap/water	6,618	(32.2%)
	Dettol	310	(1.5%)
	Other	56	(0.3%)
Sexual Behaviors			
	Proportion of women reporting 1 or more sexual partners during the last working week		
	1+ sexual partners	12,784	(62.2%)
	0 sexual partners	7,766	(37.8%)
	Of women reporting 1 or more sexual partners during the last working week		
	No. sex acts during the last working week (median (IQR))	2.0	(1.0, 3.0)
	No. sex acts w/condoms during the last working week (median (IQR))	1.0	(1.0, 2.0)

* Proportions may not add to 100% due to rounding of values.
IQR = Interquartile range

Table 3: Count and proportion of study visits with participants self-reporting only vaginal discharge, only lower abdominal pain, or vaginal discharge and lower abdominal pain in the Mombasa Cohort (2004-2017)

	Vaginal Discharge (N=20,550)	Abdominal Pain (N= 20,379)	Abdominal Pain and Vaginal Discharge (N= 20,379)
Self-Reporting Result	n (%)	n (%)	n (%)
Positive	1,247 (6.1%)	249 (1.5%)	58 (0.3%)
Negative/Missing	19,303 (93.9%)	20,344 (98.5%)	20,321 (99.7%)

Table 4: Count and proportion of positive *N. gonorrhoeae*, *C. trachomatis*, and *C. trachomatis* and/or *N. gonorrhoeae* test results among study visits with self-reported vaginal discharge or lower abdominal pain in the Mombasa Cohort (2004-2017)

	Vaginal Discharge (N=20,540)	Lower Abdominal Pain (N=20,370)
	n (%)	n (%)
<i>N. gonorrhoeae</i>		
Positive	469 (2.3%)	465 (2.3%)
Negative	20,071 (97.7%)	19,905 (97.7%)
<i>C. trachomatis</i>		
Positive	353 (1.7%)	349 (1.7%)
Negative	20,187 (98.3%)	20,021 (98.3%)
<i>C. trachomatis</i> and/or <i>N. gonorrhoeae</i>		
Positive	794 (3.9%)	786 (3.9%)
Negative	19,746 (96.1%)	19,584 (96.1%)

*Proportions may not add to 100% due to rounding of values.

Table 5: Performance of the pragmatic syndromic surveillance algorithm of vaginal discharge and/or lower abdominal pain for *C. trachomatis* and/or *N. gonorrhoeae* compared with gold standard Aptima Combo II Assay testing in the Mombasa Cohort (2004-2017)*

<i>C. trachomatis</i> and/or <i>N. gonorrhoeae</i> (N=20,379)			
Aptima Combo II Assay¹	<i>n</i> (%)		
Positive	787	(3.9%)	
Negative	19,592	(96.1%)	
Presumptive Diagnosis by Pragmatic Algorithm			
	Aptima +	Aptima -	Total
Pragmatic Algorithm +	120	1,364	1,484
Pragmatic Algorithm -	667	18,228	18,895
Total	787	19,592	20,379
Pragmatic Algorithm Performance Characteristics	<i>Estimate</i> (95% <i>CI</i>**)		
Sensitivity	15.3%	(12.8, 18.0)	
Specificity	93.0%	(92.7, 93.4)	
Positive Predictive Value	8.1%	(6.8, 9.6)	
Negative Predictive Value	96.5%	(96.2, 96.7)	

*Proportions may not add to 100% due to rounding of values.

** 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 6: Performance of the WHO Syndromic Surveillance algorithm of vaginal discharge for *C. trachomatis* and/or *N. gonorrhoeae* compared with gold standard Aptima Combo II Assay testing in the Mombasa Cohort (2004-2017)*

<i>C. trachomatis</i> and/or <i>N. gonorrhoeae</i> (N=20,550)			
Aptima Combo II Assay¹	<i>n</i> (%)		
Positive	795	(3.9%)	
Negative	19,755	(96.1%)	
Presumptive Diagnosis by WHO Algorithm			
	Aptima +	Aptima -	Total
WHO Algorithm +	104	1,143	1,247
WHO Algorithm -	691	18,612	19,303
Total	795	19,755	20,550
WHO Algorithm Performance Characteristics	<i>Estimate</i> (95% <i>CI</i>**)		
Sensitivity	13.1%	(10.8, 15.6)	
Specificity	94.2%	(93.9, 94.5)	
Positive Predictive Value	8.3%	(6.9, 10.0)	
Negative Predictive Value	96.4%	(96.2, 96.7)	

*Proportions may not add to 100% due to rounding of values.

** 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 7: Performance of the WHO Syndromic Surveillance algorithm of vaginal discharge and lower abdominal pain for *C. trachomatis* and/or *N. gonorrhoeae* compared with gold standard Aptima Combo II Assay testing in the Mombasa Cohort (2004-2017)*

<i>C. trachomatis</i> and/or <i>N. gonorrhoeae</i> (N=20,379)			
Aptima Combo II Assay¹		n (%)	
Positive		787	(3.9%)
Negative		19,592	(96.1%)
Presumptive Diagnosis by WHO Algorithm			
	Aptima +	Aptima -	Total
WHO Algorithm +	5	53	58
WHO Algorithm -	782	19,539	20,321
Total	787	19,592	20,379
WHO Algorithm Performance Characteristics		Estimate (95% CI**)	
Sensitivity		0.6%	(0.2, 1.5)
Specificity		99.7%	(99.6, 99.8)
Positive Predictive Value		8.6%	(2.9, 19.0)
Negative Predictive Value		96.2%	(95.9, 96.4)

*Proportions may not add to 100% due to rounding of values.

** 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 8: Performance of the WHO Syndromic Surveillance algorithm of vaginal discharge for *N. gonorrhoeae* compared with gold standard Aptima Combo II Assay testing in the Mombasa Cohort (2004 - 2017)*

<i>N. gonorrhoeae</i> (N=20,550)			
Aptima Combo II Assay¹		n (%)	
Positive		470	(2.3%)
Negative		20,080	(97.7%)
Presumptive Diagnosis by WHO Algorithm			
	Aptima +	Aptima -	Total
WHO Algorithm +	68	1,179	1,247
WHO Algorithm -	402	18,901	19,303
Total	470	20,080	20,550
WHO Algorithm Performance Characteristics		Estimate (95% CI**)	
Sensitivity		14.5%	(11.4, 18.0)
Specificity		94.1%	(93.8, 94.5)
Positive Predictive Value		5.5%	(4.3, 6.9)
Negative Predictive Value		97.9%	(97.7, 98.1)

*Proportions may not add to 100% due to rounding of values.

** 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 9: Performance of the WHO Syndromic Surveillance algorithm of vaginal discharge or *C. trachomatis* compared with gold standard Aptima Combo II Assay testing in the Mombasa Cohort (2004-2017)*

<i>C. trachomatis</i> (N=20,550)			
Aptima Combo II Assay¹	<i>n</i> (%)		
Positive	353	(1.7%)	
Negative	20,197	(98.3%)	
Presumptive Diagnosis by WHO Algorithm			
	Aptima +	Aptima -	Total
WHO Algorithm +	40	1,207	1,247
WHO Algorithm -	313	18,990	19,303
Total	353	20,197	20,550
WHO Algorithm Performance Characteristics	Estimate	(95% CI**)	
Sensitivity	11.3%	(8.2, 15.1)	
Specificity	94.0%	(93.7, 94.4)	
Positive Predictive Value	3.2%	(2.3, 4.3)	
Negative Predictive Value	98.4%	(98.2, 98.6)	

*Proportions may not add to 100% due to rounding of values.

** 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 10: Performance of the WHO Syndromic Surveillance algorithm of vaginal discharge and lower abdominal pain for *N. gonorrhoeae* compared with gold standard Aptima Combo II Assay testing in the Mombasa Cohort (2004-2017)*

<i>N. gonorrhoeae</i> (N=20,379)			
Aptima Combo II Assay¹	<i>n</i> (%)		
Positive	466	(2.3%)	
Negative	19,913	(97.7%)	
Presumptive Diagnosis by WHO Algorithm			
	Aptima +	Aptima -	Total
WHO Algorithm +	4	54	58
WHO Algorithm -	462	19,859	20,321
Total	466	19,913	20,379
WHO Algorithm Performance Characteristics	Estimate	(95% CI**)	
Sensitivity	0.9%	(0.2, 2.2)	
Specificity	99.7%	(99.6, 99.8)	
Positive Predictive Value	6.9%	(1.9, 16.7)	
Negative Predictive Value	97.7%	(97.5, 97.9)	

*Proportions may not add to 100% due to rounding of values.

** 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 11: Performance of the WHO Syndromic Surveillance algorithm of vaginal discharge and lower abdominal pain for *C. trachomatis* compared with gold standard Aptima Combo II Assay testing in the Mombasa Cohort (2004-2017)*

<i>C. trachomatis</i> (N=20,379)			
Aptima Combo II Assay¹	<i>n</i> (%)		
Positive	349	(1.7%)	
Negative	20,030	(98.3%)	
Presumptive Diagnosis by WHO Algorithm			
	Aptima +	Aptima -	Total
WHO Algorithm +	1	57	58
WHO Algorithm -	348	19,973	20,321
Total	349	20,030	20,379
WHO Algorithm Performance Characteristics	Estimate (95% CI**)		
Sensitivity	0.3%	(0.007, 1.6)	
Specificity	99.7%	(99.6, 99.8)	
Positive Predictive Value	1.7%	(0.04, 9.2)	
Negative Predictive Value	98.3%	(98.1, 98.5)	

*Proportions may not add to 100% due to rounding of values.

** 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 12: Performance of the pragmatic syndromic surveillance algorithm of vaginal discharge and/or lower abdominal pain for *N. gonorrhoeae* compared with gold standard Aptima Combo II Assay testing in the Mombasa Cohort (2004-2017)*

<i>N. gonorrhoeae</i> (N=20,379)			
Aptima Combo II Assay¹	<i>n</i> (%)		
Positive	466	(2.3%)	
Negative	19,913	(97.7%)	
Presumptive Diagnosis by Pragmatic Algorithm			
	Aptima +	Aptima -	Total
Pragmatic Algorithm +	80	1,404	1,484
Pragmatic Algorithm -	386	18,509	18,895
Total	466	19,913	20,379
Pragmatic Algorithm Performance Characteristics	Estimate (95% CI**)		
Sensitivity	17.2%	(13.9, 20.9)	
Specificity	93.0%	(92.6, 93.3)	
Positive Predictive Value	5.4%	(4.3, 6.7)	
Negative Predictive Value	98.0%	(97.8, 98.2)	

*Proportions may not add to 100% due to rounding of values.

** 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 13: Performance of the pragmatic syndromic surveillance algorithm of vaginal discharge and/or lower abdominal pain for *C. trachomatis* compared with gold standard Aptima Combo II Assay testing in the Mombasa Cohort (2004-2017)*

<i>C. trachomatis</i> (N=20,379)			
Aptima Combo II Assay¹	<i>n</i> (%)		
Positive	349	(1.7%)	
Negative	20,030	(98.3%)	
Presumptive Diagnosis by Pragmatic Algorithm			
	Aptima +	Aptima -	Total
Pragmatic Algorithm +	44	1,440	1,484
Pragmatic Algorithm -	305	18,590	18,895
Total	349	20,030	20,379
Pragmatic Algorithm Performance Characteristics	<i>Estimate</i> (95% <i>CI</i>**)		
Sensitivity	12.6%	(9.3, 16.6)	
Specificity	92.8%	(92.4, 93.2)	
Positive Predictive Value	3.0%	(2.2, 4.0)	
Negative Predictive Value	98.4%	(98.2, 98.6)	

*Proportions may not add to 100% due to rounding of values.

** 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 14: Proportion of *C. trachomatis* and *N. gonorrhoeae* infections that would be missed if only syndromic surveillance algorithms were implemented in the Mombasa Cohort (2004-2017)*

WHO Syndromic Surveillance Algorithm	<i>N. gonorrhoeae</i>		<i>C. trachomatis</i>		<i>C. trachomatis</i> and/or <i>N. gonorrhoeae</i>	
	<i>Estimate</i>	(95% <i>CI</i>*)	<i>Estimate</i>	(95% <i>CI</i>*)	<i>Estimate</i>	(95% <i>CI</i>*)
Vaginal Discharge	85.5%	(82.0, 88.6)	88.7%	(84.9, 91.8)	86.9%	(84.4, 89.2)
Vaginal Discharge and Lower Abdominal Pain	99.1%	(97.8, 99.8)	99.7%	(98.4, 99.9)	99.4%	(98.5, 99.8)
Vaginal Discharge and/or Lower Abdominal Pain	82.8%	(79.1, 86.1)	87.4%	(83.4, 90.7)	84.7%	(82.0, 87.2)

* 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 15: Performance of the pragmatic syndromic surveillance algorithm of vaginal discharge and/or lower abdominal pain for *C. trachomatis* and/or *N. gonorrhoeae* compared with gold standard Aptima Combo II Assay testing, stratified by age (<25 vs. ≥25), in the Mombasa Cohort (2004-2017)*

<i>C. trachomatis</i> and/or <i>N. gonorrhoeae</i> (N=20,379)			
Age < 25			
Aptima Combo II Assay¹		<i>n</i> (%)	
Positive		97	(10.3%)
Negative		847	(89.7%)
Presumptive Diagnosis by Pragmatic Algorithm			
	Aptima +	Aptima -	Total
Pragmatic Algorithm +	17	120	137
Pragmatic Algorithm -	80	727	807
Total	97	847	944
Pragmatic Algorithm Performance Characteristics		Estimate (95% CI^{**})	
Sensitivity		17.5%	(10.6, 26.6)
Specificity		85.8%	(83.3, 88.1)
Positive Predictive Value		12.4%	(7.4, 19.1)
Negative Predictive Value		90.1%	(87.8, 92.1)
Age ≥ 25			
Aptima Combo II Assay¹		<i>n</i> (%)	
Positive		690	(3.6%)
Negative		18,745	(96.4%)
Presumptive Diagnosis by Pragmatic Algorithm			
	Aptima +	Aptima -	Total
Pragmatic Algorithm +	103	1,244	1,347
Pragmatic Algorithm -	587	17,501	18,088
Total	690	18,745	19,435
Pragmatic Algorithm Performance Characteristics		Estimate (95% CI^{**})	
Sensitivity		14.9%	(12.4, 17.8)
Specificity		93.4%	(93.0, 93.7)
Positive Predictive Value		7.7%	(6.3, 9.2)
Negative Predictive Value		96.8%	(96.5, 97.0)

*Proportions may not add to 100% due to rounding of values.

** 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 16: Performance of the WHO Syndromic Surveillance algorithm of vaginal discharge for *C. trachomatis* and/or *N. gonorrhoeae* compared with gold standard Aptima Combo II Assay testing, stratified by age (<25 vs. ≥25), in the Mombasa Cohort(2004-2017)*

<i>C. trachomatis</i> and/or <i>N. gonorrhoeae</i> (N=20,550)			
Age < 25			
Aptima Combo II Assay¹	n (%)		
Positive	98	(10.3%)	
Negative	852	(89.7%)	
Presumptive Diagnosis by WHO Algorithm			
	Aptima +	Aptima -	Total
WHO Algorithm +	15	108	123
WHO Algorithm -	83	744	827
Total	98	852	950
WHO Algorithm Performance Characteristics	Estimate (95% CI**)		
Sensitivity	15.3%	(8.8, 24.0)	
Specificity	87.3%	(84.9, 89.5)	
Positive Predictive Value	12.2%	(7.0, 19.3)	
Negative Predictive Value	90.0%	(87.7, 91.9)	
Age w 25			
Aptima Combo II Assay¹	n (%)		
Positive	697	(3.6%)	
Negative	18,903	(96.4%)	
Presumptive Diagnosis by WHO Algorithm			
	Aptima +	Aptima -	Total
WHO Algorithm +	89	1,035	1,124
WHO Algorithm -	608	17,868	18,476
Total	697	18,903	19,600
WHO Algorithm Performance Characteristics	Estimate (95% CI**)		
Sensitivity	12.8%	(10.4, 15.5)	
Specificity	94.5%	(94.2, 94.8)	
Positive Predictive Value	7.9%	(6.4, 9.7)	
Negative Predictive Value	96.7%	(96.4, 97.0)	

*Proportions may not add to 100% due to rounding of values.

** 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 17: Performance of the WHO Syndromic Surveillance algorithm of vaginal discharge and lower abdominal pain for *C. trachomatis* and/or *N. gonorrhoeae* compared with gold standard Aptima Combo II Assay testing, stratified by age (<25 vs. ≥25), in the Mombasa Cohort (2004-2017)*

<i>C. trachomatis</i> and/or <i>N. gonorrhoeae</i> (N=20,379)			
Age < 25			
Aptima Combo II Assay¹		<i>n</i> (%)	
Positive		97	(10.3%)
Negative		847	(89.7%)
Presumptive Diagnosis by WHO Algorithm			
	Aptima +	Aptima -	Total
WHO Algorithm +	1	1	2
WHO Algorithm -	96	846	942
Total	97	847	944
WHO Algorithm Performance Characteristics		Estimate (95% CI^{**})	
Sensitivity		1.0%	(0.03, 5.6)
Specificity		99.9%	(99.3, 99.9)
Positive Predictive Value		50%	(1.3, 98.7)
Negative Predictive Value		89.8%	(87.7, 91.7)
Age ≥ 25			
Aptima Combo II Assay¹		<i>n</i> (%)	
Positive		690	(3.6%)
Negative		18,745	(96.4%)
Presumptive Diagnosis by WHO Algorithm			
	Aptima +	Aptima -	Total
WHO Algorithm +	4	52	56
WHO Algorithm -	686	18,693	19,379
Total	690	18,745	19,435
WHO Algorithm Performance Characteristics		Estimate (95% CI^{**})	
Sensitivity		0.6%	(0.2, 1.5)
Specificity		99.7%	(99.6, 99.8)
Positive Predictive Value		7.1%	(2.0, 17.3)
Negative Predictive Value		96.5%	(96.2, 96.7)

*Proportions may not add to 100% due to rounding of values.

** 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 18: Performance of the pragmatic syndromic surveillance algorithm of vaginal discharge and/or lower abdominal pain for *N. gonorrhoeae* compared with gold standard Aptima Combo II Assay testing, stratified by age (<25 vs. ≥25), in the Mombasa Cohort (2004-2017)*

<i>N. gonorrhoeae</i> (N=20,379)			
Age < 25			
Aptima Combo II Assay¹	<i>n</i> (%)		
Positive	32	(3.4%)	
Negative	912	(96.6%)	
Presumptive Diagnosis by Pragmatic Algorithm			
	Aptima +	Aptima -	Total
Pragmatic Algorithm +	4	133	137
Pragmatic Algorithm -	28	779	807
Total	32	912	944
Pragmatic Algorithm Performance Characteristics	Estimate (95% CI^{**})		
Sensitivity	12.5%	(3.5, 29.0)	
Specificity	85.4%	(83.0, 87.6)	
Positive Predictive Value	2.9%	(0.1, 7.3)	
Negative Predictive Value	96.5%	(95.0, 97.7)	
Age ≥ 25			
Aptima Combo II Assay¹	<i>n</i> (%)		
Positive	434	(2.2%)	
Negative	19,001	(97.8%)	
Presumptive Diagnosis by Pragmatic Algorithm			
	Aptima +	Aptima -	Total
Pragmatic Algorithm +	76	1,271	1,347
Pragmatic Algorithm -	358	17,730	18,088
Total	434	19,001	19,435
Pragmatic Algorithm Performance Characteristics	Estimate (95% CI^{**})		
Sensitivity	17.5%	(14.1, 21.4)	
Specificity	93.3%	(93.0, 93.7)	
Positive Predictive Value	5.6%	(4.5, 7.0)	
Negative Predictive Value	98.0%	(97.8, 98.2)	

*Proportions may not add to 100% due to rounding of values.

** 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 19: Performance of the pragmatic syndromic surveillance algorithm of vaginal discharge and/or lower abdominal pain for *C. trachomatis* compared with gold standard Aptima Combo II Assay testing, stratified by age (<25 vs. ≥25), in the Mombasa Cohort (2004-2017)*

<i>C. trachomatis</i> (N=20,379)			
Age < 25			
Aptima Combo II Assay¹	<i>n</i> (%)		
Positive	67	(7.1%)	
Negative	877	(92.9%)	
Presumptive Diagnosis by Pragmatic Algorithm			
	Aptima +	Aptima -	Total
Pragmatic Algorithm +	14	123	137
Pragmatic Algorithm -	53	754	807
Total	67	877	944
Pragmatic Algorithm Performance Characteristics	Estimate (95% CI^{**})		
Sensitivity	20.9%	(11.9, 32.6)	
Specificity	86.0%	(83.5, 88.2)	
Positive Predictive Value	10.2%	(5.7, 16.6)	
Negative Predictive Value	93.4%	(91.5, 95.0)	
Age ≥ 25			
Aptima Combo II Assay¹	<i>n</i> (%)		
Positive	282	(1.5%)	
Negative	19,153	(98.5%)	
Presumptive Diagnosis by Pragmatic Algorithm			
	Aptima +	Aptima -	Total
Pragmatic Algorithm +	30	1,317	1,347
Pragmatic Algorithm -	252	17,836	18,088
Total	282	19,153	19,435
Pragmatic Algorithm Performance Characteristics	Estimate (95% CI^{**})		
Sensitivity	10.6%	(7.3, 14.8)	
Specificity	93.1%	(92.8, 93.5)	
Positive Predictive Value	2.2%	(1.5, 3.2)	
Negative Predictive Value	98.6%	(98.4, 98.8)	

*Proportions may not add to 100% due to rounding of values.

** 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 20: Performance of the WHO Syndromic Surveillance algorithm of vaginal discharge for *N. gonorrhoeae* compared with gold standard Aptima Combo II Assay testing, stratified by age (< 25 vs. ≥ 25), in the Mombasa Cohort (2004 - 2017)*

<i>N. gonorrhoeae</i> (N=20,550)			
Age < 25			
Aptima Combo II Assay¹		<i>n</i> (%)	
Positive		33	(3.5%)
Negative		917	(96.5%)
Presumptive Diagnosis by WHO Algorithm			
	Aptima +	Aptima -	Total
WHO Algorithm +	2	121	123
WHO Algorithm -	31	796	827
Total	33	917	950
WHO Algorithm Performance Characteristics		Estimate (95% CI^{**})	
Sensitivity		6.1%	(0.7, 20.2)
Specificity		86.8%	(84.4, 88.9)
Positive Predictive Value		1.6%	(0.2, 5.8)
Negative Predictive Value		96.3%	(94.7, 97.4)
Age ≥ 25			
Aptima Combo II Assay¹		<i>n</i> (%)	
Positive		437	(2.2%)
Negative		19,163	(97.8%)
Presumptive Diagnosis by WHO Algorithm			
	Aptima +	Aptima -	Total
WHO Algorithm +	66	1,058	1,124
WHO Algorithm -	371	18,105	18,476
Total	437	19,163	19,600
WHO Algorithm Performance Characteristics		Estimate (95% CI^{**})	
Sensitivity		15.1%	(11.9, 18.8)
Specificity		94.5%	(94.2, 94.8)
Positive Predictive Value		5.9%	(4.6, 7.4)
Negative Predictive Value		98.0%	(97.8, 98.2)

*Proportions may not add to 100% due to rounding of values.

** 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 21: Performance of the WHO Syndromic Surveillance algorithm of vaginal discharge for *C. trachomatis* compared with gold standard Aptima Combo II Assay testing, stratified by age (<25 vs. ≥25), in the Mombasa Cohort(2004-2017)*

<i>C. trachomatis</i> (N=20,550)			
Age < 25			
Aptima Combo II Assay¹		<i>n</i> (%)	
Positive		67	(7.1%)
Negative		883	(92.9%)
Presumptive Diagnosis by WHO Algorithm			
	Aptima +	Aptima -	Total
WHO Algorithm +	14	109	123
WHO Algorithm -	53	774	827
Total	67	883	950
WHO Algorithm Performance Characteristics		Estimate (95% CI**)	
Sensitivity		20.9%	(11.9, 32.6)
Specificity		87.7%	(85.3, 89.8)
Positive Predictive Value		11.4%	(6.4, 18.4)
Negative Predictive Value		93.6%	(91.7, 95.2)
Age ≥ 25			
Aptima Combo II Assay¹		<i>n</i> (%)	
Positive		286	(1.5%)
Negative		19,314	(98.5%)
Presumptive Diagnosis by WHO Algorithm			
	Aptima +	Aptima -	Total
WHO Algorithm +	26	1,098	1,124
WHO Algorithm -	260	18,216	18,476
Total	286	19,314	19,600
WHO Algorithm Performance Characteristics		Estimate (95% CI**)	
Sensitivity		9.1%	(6.0, 13.0)
Specificity		94.3%	(94.0, 94.6)
Positive Predictive Value		2.3%	(1.5, 3.4)
Negative Predictive Value		98.6%	(98.4, 98.8)

*Proportions may not add to 100% due to rounding of values.

** 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 22: Performance of the WHO Syndromic Surveillance algorithm of vaginal discharge and lower abdominal pain for *N. gonorrhoeae* compared with gold standard Aptima Combo II Assay testing, stratified by age (<25 vs. ≥25), in the Mombasa Cohort (2004-2017)*

<i>N. gonorrhoeae</i> (N=20,379)			
Age < 25			
Aptima Combo II Assay¹	<i>n</i> (%)		
Positive	32	(3.4%)	
Negative	912	(96.6%)	
Presumptive Diagnosis by WHO Algorithm			
	Aptima +	Aptima -	Total
WHO Algorithm +	0	2	2
WHO Algorithm -	32	910	942
Total	32	912	944
WHO Algorithm Performance Characteristics		Estimate (95% CI^{**})	
Sensitivity		0% (0, 10.9)	
Specificity		99.8% (99.2, 99.9)	
Positive Predictive Value		0% (0, 84.2)	
Negative Predictive Value		96.6% (95.2, 97.7)	
Age ≥ 25			
Aptima Combo II Assay¹	<i>n</i> (%)		
Positive	434	(2.2%)	
Negative	19,001	(97.8%)	
Presumptive Diagnosis by WHO Algorithm			
	Aptima +	Aptima -	Total
WHO Algorithm +	4	52	56
WHO Algorithm -	430	18,949	19,379
Total	434	19,001	19,435
WHO Algorithm Performance Characteristics		Estimate (95% CI^{**})	
Sensitivity		0.9% (0.3, 2.3)	
Specificity		99.7% (99.6, 99.8)	
Positive Predictive Value		7.1% (2.0, 17.3)	
Negative Predictive Value		97.8% (97.6, 98.0)	

*Proportions may not add to 100% due to rounding of values.

** 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 23: Performance of the WHO Syndromic Surveillance algorithm of vaginal discharge and lower abdominal pain for *C. trachomatis* compared with gold standard Aptima Combo II Assay testing, stratified by age (<25 vs. ≥25), in the Mombasa Cohort (2004-2017)*

<i>C. trachomatis</i> (N=20,379)			
Age < 25			
Aptima Combo II Assay¹	<i>n</i> (%)		
Positive	67	(7.1%)	
Negative	877	(92.9%)	
Presumptive Diagnosis by WHO Algorithm			
	Aptima +	Aptima -	Total
WHO Algorithm +	1	1	2
WHO Algorithm -	66	876	942
Total	67	877	944
WHO Algorithm Performance Characteristics		Estimate (95% CI**)	
Sensitivity		1.5% (0.04, 8.0)	
Specificity		99.9% (99.4, 99.9)	
Positive Predictive Value		50% (12.6, 98.7)	
Negative Predictive Value		93.0% (91.2, 94.5)	
Age ≥ 25			
Aptima Combo II Assay¹	<i>n</i> (%)		
Positive	282	(1.5%)	
Negative	19,153	(98.5%)	
Presumptive Diagnosis by WHO Algorithm			
	Aptima +	Aptima -	Total
WHO Algorithm +	0	56	56
WHO Algorithm -	282	19,097	19,379
Total	282	19,153	19,435
WHO Algorithm Performance Characteristics		Estimate (95% CI**)	
Sensitivity		0% (0, 1.3)	
Specificity		99.7% (99.6, 99.8)	
Positive Predictive Value		0% (0, 6.4)	
Negative Predictive Value		98.5% (98.4, 98.7)	

*Proportions may not add to 100% due to rounding of values.

** 95% CI = 95% Confidence Interval ($\alpha = 0.05$)

Table 24: Results of univariate GEE logistic regression for the association between selected covariates and self-reported vaginal discharge (N=20,540)

Covariates	OR	(95% CI*)	p-value*
Age	0.94	(0.93, 0.95)	<0.0001
Contraception use reported at study visit			
Coitally-dependent method or no contraception ¹	1.00	(Reference)	
Highly effective, modern method ²	0.82	(0.68, 0.98)	0.0320
Permanent method ³	0.48	(0.23, 1.00)	0.0490
Any contraception use reported at study visit	0.90	(0.77, 1.06)	0.2200
Number of sexual partners in the last working week	1.04	(1.03, 1.06)	<0.0001
Vaginal washing during the last working week:			
None	1.00	(Reference)	
Water alone	1.46	(1.13, 1.89)	0.0035
Omo	3.09	(1.28, 7.43)	0.0118
Soap/water	1.59	(1.21, 2.09)	0.0009
Dettol	1.22	(0.63, 2.34)	0.5529
Other	2.69	(0.84, 8.60)	0.0958
Any vaginal washing during the last working week:	1.51	(1.18, 1.93)	0.0010

Reference group for nominal data chosen based on coding = 0

*Bolded p-values < 0.10

1 = includes no contraception, condoms only, spermicides, and other

2 = includes oral contraceptive pills (OCP), depot medroxyprogesterone acetate (DMPA), intrauterine device (IUD), and hormonal implant

3 = includes tubal ligation and hysterectomy

Table 25: Results of multivariate GEE logistic regression for the association between selected covariates and self-reported vaginal discharge (N=20,540)

Covariates	OR	(95% CI*)	p-value*
Age	0.94	(0.93, 0.95)	<0.0001
Contraception use reported at study visit**			
Highly effective, modern method ¹	0.75	(0.62, 0.89)	0.0014
Permanent method ²	0.72	(0.35, 1.51)	0.3882
Number of sexual partners in the last working week	1.03	(1.01, 1.04)	0.0027
Any vaginal washing during the last working week:	1.28	(1.01, 1.64)	0.0449

*Bolded p-values < 0.05

** Reference group = single use method or no contraception¹

1 = includes oral contraceptive pills (OCP), depot medroxyprogesterone acetate (DMPA), intrauterine device (IUD), and hormonal implant

2 = includes tubal ligation and hysterectomy

Table 26: Results of GEE Univariate Logistic Regression for the association between selected covariates and self-reported lower abdominal pain (N= 20,370)

Covariates	OR	(95% CI*)	p-value
Age	0.97	(0.95, 1.00)	0.0190
Contraception Use reported at study visit			
Coitally-dependent method or no contraception ¹	1.00	(Reference)	
Highly effective, modern method ²	0.68	(0.48, 0.96)	0.0270
Permanent method ³	1.02	(0.28, 3.69)	0.9770
Any contraception use reported at study visit	0.58	(0.43, 0.79)	0.0006
Number of sexual partners during the last working week	1.02	(1.00, 1.05)	0.0600
Vaginal washing during the last working week			
None	1.0	(Reference)	
Water alone	1.64	(1.02, 2.63)	0.0398
Soap/water	2.14	(1.28, 3.57)	0.0036
Dettol	2.24	(0.79, 6.38)	0.1293
Other	2.09	(0.26, 16.70)	0.4863
Any vaginal washing during the last working week	1.83	(1.15, 2.91)	0.0110

Reference group for nominal data chosen based on coding = 0

*Bolded p-values < 0.10

1 = includes no contraception, condoms only, spermicides, and other

2 = includes oral contraceptive pills (OCP), depot medroxyprogesterone acetate (DMPA), intrauterine device (IUD), and hormonal implant

3 = includes tubal ligation and hysterectomy

Table 27: Results of multivariate GEE logistic regression for the association between selected covariates and self-reported lower abdominal pain (N= 20,370)

Covariates	OR	(95% CI*)	p-value*
Age	0.97	(0.95, 0.99)	0.0142
Any contraception use reported at study visit	1.68	(1.04, 2.71)	0.0335
Any vaginal washing during the last working week	0.56	(0.41, 0.76)	0.0003

*Bolded p-values < 0.05