Analysis of the sex ratio of reported gonorrhoea incidence in Shenzhen, China

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ABSTRACT
Objective: To assess the clinical process of gonorrhoea diagnosis and report in China, and to determine the difference of sex ratio between reported incidence based on reporting data and true diagnosis rate based on reference tests of gonorrhoea.

Setting: A total of 26 dermatology and sexually transmitted disease (STD) departments, 34 obstetrics-gynaecology clinics and 28 urology outpatient clinics selected from 34 hospitals of Shenzhen regarded as our study sites.

Participants: A total of 2754 participants were recruited in this study, and 2534 participants completed the questionnaire survey and provided genital tract secretion specimens. There were 1106 male and 1428 female participants. Eligible participants were patients who presented for outpatient STD care at the selected clinics for the first time in October 2012 were at least 18 years old, and were able to give informed consent.

Outcome measures: Untested rate, true-positive rate, false-negative rate and unreported rate of gonorrhoea, as well as reported gonorrhoea incidence sex ratio and true diagnosis sex ratio were calculated and used to describe the results.

Results: 2534 participants were enrolled in the study. The untested rate of gonorrhoea among females was significantly higher than that among males (female 88.1%, male 68.3%, p=0.001). The male-to-female sex ratios of untested rate, true-positive rate, false-negative rate and unreported rate were 1:1.3, 1:2.1, 1:1.6 and 1:1.4, respectively. The reported gonorrhoea incidence sex ratio of new diagnosed gonorrhoea was 19.8:1 (male vs female: 87/1106 vs 5/1420), while the true diagnosis sex ratio was 2.5:1 (male vs female: 161/1106 vs 84/1420). These data indicate that the sex ratio of reported gonorrhoea incidence has been overestimated by a factor of 7.9 (19.8/2.5).

Conclusions: We found the current reported gonorrhoea incidence and sex ratios to be inaccurate due to underestimations of gonorrhoea incidence, especially among women.

INTRODUCTION
Gonorrhoea is a pyogenic infection of the urogenital system caused by Neisseria gonorrhoeae (NG) that can cause epididymitis and prostatitis in men, and endometritis and pelvic inflammatory disease in women, and can ultimately lead to infertility in men and women. Females are more susceptible to NG infection than males due to differences in the structure of the respective reproductive systems, and nearly half of the female infections are asymptomatic. According to the WHO estimates in 2008, gonorrhoea is the most frequently sexually transmitted bacterial infection in the world, with approximately 106.1 million new cases diagnosed every year. In 2012, China reported 95,263 new gonorrhoea cases, resulting in an reported incidence of 7.07/100,000. The gonorrhoea epidemic was especially prominent in Guangdong, which reported 18,014 new cases with a reported incidence of 17.15/100,000. Over the past several decades, newly reported cases of gonorrhoea within Guangdong province consistently ranked within the top five provinces in China. Shenzhen, a part of the Guangdong province located in south coastal China and adjacent to Hong Kong, has witnessed an alarmingly rapid spread of sexually transmitted diseases (STDs) in recent years. The reported gonorrhoea incidence in Shenzhen was 51.5/
100,000 in 2011,8 which was the highest reported incidence in the entire province.

Interestingly, the reported gonorrhoea incidence among males was much higher than that among females. In 2011, the male-to-female gonorrhoea incidence sex ratio in Shenzhen, Guangdong province and China were 9.9:1, 6.4:1 and 4.3:1,5,8,9 respectively.

Gonorrhoea is one of the second-class infectious diseases, according to the Infectious Disease Prevention Act of China.10 After the severe acute respiratory syndrome (SARS) epidemic in 2003, the Chinese government built the China Information System for Diseases Control and Prevention (CISDCP) in 2004, and issued “The measures for the management of public health emergencies and infectious disease epidemic surveillance information report” in 2005.11 According to this document, gonorrhoea should report to CISDCP mandatorily within 6 h in urban areas or 12 h in rural areas. The reported gonorrhoea incidence can be calculated on the basis of reported data. Reported incidence is a very important measure for evaluating the urgency of an epidemic situation, and for establishing prevention and control efforts to combat the disease. However, a number of factors influence the accuracy of reported incidence, including community characteristics and social determinants of health (SDH),12,13 as well as potential variability due to biological aspects such as gender.

According to “The measures for the prevention and treatment of sexually transmitted diseases” of China,14 each new gonorrhoea case should be reported through CISDCP in hospitals with qualification of STD diagnosis and treatment. The “2007 diagnostic criteria for gonorrhoea in China” indicated,15 people who were tested positive for gonorrhoea with or without symptoms could be diagnosed with gonorrhoea. This document recommended Gram stain and isolate culture to test NG. Before sampling the urethral swab of a male patient, urination was not allowed at least 2 h. For male patient with symptoms, secretes can be collected using swabs. For an asymptomatic male patient, samples can be collected by placing swabs in urethra for 10–15 seconds. For a female patient, samples can be collected by placing swabs in cervix for 20–30 s. Samples can also be obtained by massaging perineum and dip in secretes using swabs. Male patients without complications can be diagnosed conclusively with gonorrhoea with a positive Gram stain microscopy result; the diagnosis of male patients with complications and female patients should be based on the confirmation of NG-isolated culture. NG is a very fastidious organism and will perish if not kept in ideal circumstances. The laboratory conditions and the ability of workers would affect the sensitivity and specificity of the test. Nucleic acid amplification tests (NAATs) for gonorrhoea has enabled significant implementation since 2002, creating opportunities for more rapid and accurate gonorrhoea diagnosis.16 It has been demonstrated NAATs has a higher sensitivity and specificity than culture and microscopy for gonorrhoea test.17 However, this method has recently limited use in some of the big cities in China, due to its high cost and technical requirements. The Guideline for Diagnosis, Treatment and Prevention of Sexually Transmitted Diseases of China,18 which was published in 2014, has regarded this method as one of the recommendatory methods to test NG, which has been adopted by the US Food and Drug Administration (FDA).

As the American Centers for Disease Control and Prevention (CDC) estimated, only half of the gonorrhoea cases in America are reported.4 Actually, the same problem was also presented or even worse in China. The problem occurred in the process of seeking healthcare in clinics, diagnosis, and case report to CISDCP. First, the physician should believe that the patient has a risk of infection and suggest to the patient to get an NG test done. Second, the patient should accept the physician’s suggestion and get the NG test done. Third, the patient got a true positive result. Finally, the physician confirmed that the patient had NG infection, and reported this case to CISDCP. It is possible that the physician did not give the test suggestion, or that the patient was unwilling to get the NG test done, and the false-positive results may also be got by patients. The physician may also have forgotten to report the diagnosed gonorrhoea cases to CISDCP on time. In these instances, the information of these patients with gonorrhoea cannot be obtained from CISDCP. Moreover, some of the individuals may get a false-positive test result and be reported to CISDCP even though they do not have NG infection. The widespread use of CISDCP has underscored the importance of ensuring its accuracy. The discrepancies in symptoms and test methods between males and females may even lead to a different degree of accuracy of male and female reported gonorrhoea incidence.

An inaccurate reported gonorrhoea incidence sex ratio, generated by an inaccurate reported gonorrhoea incidence, may mislead the gonorrhoea prevention policy to target the wrong population for NG screening. To the best of our knowledge, the impact of influence factors in the clinical diagnosis and the reporting process on the reported gonorrhoea incidence sex ratio has not as yet been quantified. It is helpful to find the weakness of disease surveillance system by identifying the influence factors of sex ratio. Thus, we designed and applied a patient survey questionnaire to collect information for gender and sociodemographic characteristics, and collected reporting data of gonorrhoea cases. Furthermore, we performed NG testing on all participants to ascertain gonorrhoea diagnosis. We used rates of untested patients, true-positive rate, false-negative rate and unreported rate to quantify the accuracy of the reported gonorrhoea incidence during diagnosis and the reporting process. Finally, we calculated and compared the reported gonorrhoea incidence sex ratio with the true diagnosis sex ratio, and devised strategies to resolve these discrepancies.
METHODS

Patient selection

Participants were recruited from the dermatology and STD department (STD clinic), obstetrics-gynaecology (OBGYN clinic) and urology outpatient clinic (GUM clinic). A total of 88 clinics, including 26 STD clinics, 34 OBGYN and 28 GUM clinics, were selected from 34 hospitals in Shenzhen City. A probability sampling strategy was generated on the basis of patient flow (measured by the average number of STD cases reported to CISDCP in 2009–2011) and administrative level set (municipal level, street level and privately operated). Participants were sampled conveniently and sequentially among those who presented to these clinics for care. Eligible participants were patients who presented for outpatient STD care at the selected clinics for the first time in October, 2012, were at least 18 years old, and were able to give informed consent.

Patient information and sample collection

Participants were given a questionnaire to collect information on gender and sociodemographic characteristics. Next, a genital tract secretion specimen (urethral swabs from men, vaginal or cervical swabs from women) was collected from each participant and sent to the Shenzhen Center for Chronic Disease Control (SCCDC) to detect NG by nucleic acid testing. The sample collections were performed according to the Guidelines for Laboratory Diagnosis of Sexually Transmitted Diseases of China. This test result was regarded as the reference test to evaluate the accuracy of NG tests in clinics. After finishing the above procedures, the participant would continue their normal medical service. The clinic physicians then decided on whether or not to collect a second specimen and test for NG in clinics according to their typical diagnostic practices and experiences. Patients with a positive diagnosis of gonorrhoea (according to the second gonorrhoea test result) from the clinics were reported to CISDCP online within 6 or 12 h. The staff at SCCDC compared the original clinical records and reported case information in CISDCP to calculate the unreported rate at the end of the survey.

Laboratory testing

Clinic laboratories used the methods recommended by ‘Diagnostic criteria for gonorrhoea’ to test the second specimens. Male patients were tested using a Gram stain microscopic smear examination and/or NG-isolated culture. Female patients were tested by the NG-isolated culture. The clinical laboratory technicians had not been informed that the results of these specimens would be confirmed by SCCDC, in order to exclude the impact of our research work on them. SCCDC used the Roche Cobas Amplicor automated nucleic acid testing system (Roche Diagnostic Systems, Indianapolis, Indiana, USA) to test for the presence of NG of the first collected specimens.

Outcome measurement

Figure 1 represents the whole process of identifying gonorrhoea cases, from infection to reporting. Among patients who are infected with NG, a proportion of them would not to seek medical service because of asymptomatic infections or other reasons. These patients would like to choose private clinics or some irregular private hospitals where gonorrhoea cases are not mandatory reported to CISDCP, and the others would go to general hospital which mandatory reporting STD cases to CISDCP. Next, on the basis of the suggestion of physicians and the decision of patients, some of the patients would get the NG test done, and the others would not. Among gonorrhoea patients who were tested for NG, some of them would receive a true-positive result and be diagnosed with gonorrhoea, and the others’ results would be false negative. Except them, some of the other people who did not have NG infection but got NG test done and got false-positive results would be wrongly diagnosed with gonorrhoea. Among the diagnosed gonorrhoea cases (including the true positive and false positive), most of them would be reported to CISDCP as required, and some of them would not because of the negligence of physicians. Our study focused on the clinical diagnosis of gonorrhoea and subsequent reporting as presented within the dashed frame.

Stratified analysis was used to analyse patient demographics, which were separated by gender. Untested rate, true-positive rate, false-negative rate and unreported rate of gonorrhoea, as well as reported gonorrhoea incidence sex ratio and true diagnosis sex ratio, were calculated for all participants. The definitions of the various outcomes are listed below:
1. Untested: Participants who were infected with NG and confirmed by reference test, but were not given the NG test in clinics.
2. True positive: The true-positive participants who were diagnosed with gonorrhoea in clinics.
3. False negative: Participants who were infected with NG according to the reference test, but had a negative result in clinics.
4. Unreported: Participants who were diagnosed with gonorrhoea in clinics but not reported to CISDCP on time.
5. Reported gonorrhoea incidence sex ratio: The sex ratio (male vs female) of participants who have been diagnosed with gonorrhoea and reported to CISDCP by physicians.
6. True diagnosis sex ratio: The sex ratio (male:female) of patients with positive NG results on reference test. This excludes the influences of untested rate, true-positive rate, false-negative rate and unreported rate.

Quality control

Investigators and quality control staff in our study were trained to ensure that their work complied with standards and methods of this survey. Coding labels,
supplies, specimen preservation and transportation strictly abided by the ISO17025 laboratory accreditation standards. The operating procedures were performed in strict accordance with the COBAS AMPLICOR CT/NG Test instructions.

Data analysis
Epidata 3.0 was used to create the database of patient information. The data were double entered and checked for consistency. Data analysis was performed using SPSS V.17.0. Proportion, rate and ratio were the main statistical indices in our study. The \( \chi^2 \) test and Fisher probabilities in a 2×2 table data were used to determine statistically significant differences, and the significance level was set at \( p=0.05 \).

All participants met with a researcher to discuss the study, and gave written informed consent regarding their inclusion in all parts of the study.

RESULTS
Patient demographics
A total of 2754 participants were recruited in this study, and 2534 participants (92.0%) completed the questionnaire survey and provided genital tract secretion specimens. There were 1106 male and 1428 female participants. Most of the participants were 20–39 years old (84.7%). More female patients were aged 20–39 years and had a residence permit outside of Shenzhen (88.2% and 80.0%, respectively) than males (80.2% and 70.6%, respectively). Most of the participants completed a middle school degree (67.1%), but more male participants had a bachelor’s degree or higher education (32.8%). Thirty per cent of men (n=332) and 56.2% of women (n=803) earned less than ¥2000 RMB (approximately US$300) a month. Most of the participants were married (male 68.3%; female 69.3%) (table 1).

Untested rate
A total of 161 male patients with gonorrhoea (male: A+B+F, table 2) were detected by reference test among 1106 male participants (male: E+H). Among them, 51 accepted NG test in clinics (male: A+B), and 110 cases were missed. The resulting untested rate was 68.3% (95% CI 61.9% to 74.7%). Among 84 female patients with gonorrhoea (female: A+B+F) who were diagnosed by reference test among 1420 female participants (female: E+H), 10 accepted the NG test (female: A+B) and 74 cases were missed in clinics. The untested rate among females was 88.1% (95% CI 83.2% to 93.0%). The gender difference of untested patients was statistically significant (\( p=0.001 \)). The sex ratio of untested rate was 1:1.3 (table 2).

True-positive and false-negative rates
A total of 92 male participants received positive results for the NG test in clinics (male: A+C), and 22 were confirmed by reference test, resulting in a true-positive rate of 23.9% (95% CI 17.7% to 30.0%). Among the five female participants who tested positive in clinical settings, only one was confirmed by reference test with a true-positive rate of 20.0% (95% CI 0.0% to 44.8%). The gender difference for the true-positive rate was not statistically significant (\( p=0.661 \)). The male-to-female sex ratio of the true-positive rate was 1.2:1. For false-negative cases, 29 of 51 male participants with positive reference test results had negative results at the clinics (56.9%, 95% CI 47.3% to 66.5%). Among the 10 (A+B) female patients with gonorrhoea confirmed by reference testing, 9 got false-negative results in clinics (90.0%, 95% CI 76.9% to 100.0%). The gender difference of the false-negative rate was not statistically significant.
The false-negative rate sex ratio was 1:1.6 (table 2). Unreported rate
Among 92 male participants with positive NG results in clinics, five cases were unreported to CISDCP (5.4%, 95% CI 2.2% to 8.6%). One case was unreported among five NG positive female participants (20.0%, 95% CI 0.0% to 44.8%). The gender difference of unreported rate was not statistically significant (p=0.278). The sex ratio of unreported rate was 1:3.7 (table 3).

Reported incidence sex ratio versus true diagnosis sex ratio
Of the 1106 male participants, 7.9% (n=87) of cases diagnosed in clinics were reported to CISDCP. Of the 1420 female participants, 4 were reported to the system by physicians, resulting in a reported gonorrhoea incidence of 0.4%. According to the clinic results, the reported gonorrhoea incidence sex ratio was 19.8:1, while the reference test found 161 cases in 1106 male patients and 84 cases in 1420 female patients. However, on the basis of the number of cases detected by the reference laboratory, the true diagnosis rates for male and female participants were 14.6% and 5.9%, respectively. The true diagnosis sex ratio was 2.5:1. Compared to the true diagnosis sex ratio, the reported incidence sex ratio has been overestimated by a factor of 7.9.

**DISCUSSION**
Understanding how the reported incidence of disease is measured and documented is critical to devising strategies for treating diseased populations. Gonorrhoea, while treatable, is a communicable disease that poses a continuing problem in certain locations, which could be attributed, at least in part, to inaccurate diagnosis and reporting. In this paper, we provided new insight into the issue of the gender difference of reported gonorrhoea incidence due to the inaccurate diagnostic and reporting process. We found that females were more likely to be untested, get false-negative results in the clinical process, and have a higher proportion of being unreported to CISDCP. The sex ratio of reported newly diagnosed gonorrhoea in Shenzhen has been overestimated by a factor of 7.9 times as compared with the true diagnosis sex ratio.

The gonorrhoea incidence among males and females is underestimated in China. These inaccurate estimates may impede gonorrhoea treatment and control. First, health policymakers may not be aware of the true prevalence and severity of the NG epidemic leading to an inadequate allocation of resources. Second, the inaccurately reported data may lead physicians and public health doctors to put more efforts into screening male patients versus female patients. Third, untreated NG infection can cause pelvic inflammatory disease, or even infertility and ectopic pregnancy in females. This

Table 1 The demographic characteristics distribution of the study participants

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male n (%)</th>
<th>Female n (%)</th>
<th>Total n (%)</th>
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<tbody>
<tr>
<td>Age (year)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤19</td>
<td>12 (1.1)</td>
<td>43 (3.0)</td>
<td>55 (2.2)</td>
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<tr>
<td>20–39</td>
<td>887 (80.2)</td>
<td>1259 (88.2)</td>
<td>2146 (84.7)</td>
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<td>≥40</td>
<td>163 (14.7)</td>
<td>102 (7.1)</td>
<td>265 (10.5)</td>
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<td>44 (4.0)</td>
<td>24 (1.7)</td>
<td>68 (2.6)</td>
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<td>Census register*</td>
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<td></td>
<td></td>
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<tr>
<td>Shenzhen</td>
<td>308 (27.9)</td>
<td>270 (18.9)</td>
<td>578 (22.8)</td>
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<tr>
<td>Outside Shenzhen</td>
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<td>1142 (80.0)</td>
<td>1923 (75.9)</td>
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<tr>
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<td>Education*</td>
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<td></td>
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<td>Primary school and below</td>
<td>37 (3.3)</td>
<td>99 (7.0)</td>
<td>136 (5.4)</td>
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<tr>
<td>Middle school</td>
<td>666 (60.2)</td>
<td>1035 (72.4)</td>
<td>1701 (67.1)</td>
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<td>Bachelor degree or above</td>
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<td>270 (18.9)</td>
<td>632 (24.9)</td>
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<td>&lt;2000</td>
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<td>803 (56.2)</td>
<td>1135 (44.8)</td>
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<td>776 (30.7)</td>
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<td>Married</td>
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<td>987 (69.2)</td>
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<td>13 (0.5)</td>
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<td>3 (0.2)</td>
<td>3 (0.1)</td>
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*The difference was statistically significant (p<0.05).
contributes a large part to the disease burden across the world, especially in developing countries. Moreover, these undiagnosed cases could become a hidden reservoir of gonorrhoea infection and lead to a much more serious spread of the disease. In recent years, drug-resistant NG has been increasingly common due to the irregular use and abuse of antibiotics. ‘Superbugs’, which are resistant to ceftriaxone, have been found in several countries since being identified in Japan in 2011. Timely and standardised treatment is needed to prevent the transmission of superbugs.

As Liu et al found in Hefei city (the capital of Anhui province, China), 82% of patients with gonorrhoea could be identified by clinical laboratories, which was much higher than that in our research. Maybe the different study site and research design have led to the difference in results. Laboratory testing for NG is the key point to find new gonorrhoea cases, especially for asymptomatic infections. Cases reported to CISDCP should be detected positive for gonorrhoea. NG test should be conducted for asymptomatic patients. The current ‘Diagnostic criteria for gonorrhoea’ of China, which were implemented from 15 October 2007 and recommended microscopy and culture to test NG, have a large impact on the appearance of gender difference. Compared to culture, microscopy is quick and the result can be obtained in minutes. On the other hand, culture methods usually require 2–7 days (depending on the hospital) to obtain results. A large number of female patients are unwilling to take such a long time to get an NG test result. Therefore, when female patients present with mild symptoms or non-specific symptoms and seek medical service in a hospital, physicians may opt for empirical antibiotic treatment instead of an NG test. By then, many female patients lost the opportunity to be detected, which explains why female patients have a higher untested rate in our study. Besides that, Gram stain has a relatively low sensitivity (around 70% in China), while NG culture has a relative high sensitivity (80–95% in China). However, culture methods have a high potential for human error. When collecting the sample, NG specimens are easily contaminated by other bacteria and die after separation from the host leading to many false negatives. These differences in laboratory and clinical diagnosis of gonorrhoea are likely to have contributed to the underestimation of male and female cases and an inflated male-to-female ratio. Moreover, the inadequate responsibility of the physician and ability of laboratory personnel also have a negative impact on the accuracy of gender difference of reported gonorrhoea incidence.

Some changes need to be made to get a more accurate reported gonorrhoea incidence. First, the way of disease surveillance needs to be improved. Active surveillance is significantly superior on data accuracy than passive surveillance. CISDCP is a passive surveillance system with all data reported by hospitals. The gonorrhoea cases might be under-reported by physicians both in the diagnostic and reporting process. Some active surveillance methods, such as sentinel surveillance and special survey, can avoid the bias due to the under-reporting of new cases. Second, it is of great importance to update the diagnostic criteria for gonorrhoea. Gram stain microscopic smear examination and NG-isolated culture methods both have flaws as aforementioned. NAAIs has not become the recommendatory method for

<table>
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<th>Table 3</th>
<th>The gender difference of unreported rate</th>
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<td>Reported</td>
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<tr>
<td>Male</td>
<td>87</td>
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<tr>
<td>Female</td>
<td>4</td>
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<tr>
<td>Total</td>
<td>91</td>
</tr>
<tr>
<td>Ratio</td>
<td>1:1.37</td>
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*Fisher’s exact test p value.
gonorrhea in the current diagnostic criteria. We suggest that the diagnostic criteria should be updated to recommend NAATs as the standard method for gonorrhea diagnosis. Furthermore, physicians should perform regularly NG screening tests for potential patients, particularly for female patients who are often asymptomatic.

**Study limitations**

The reference test method in our study was imperfect, although this device was one of the most accurate NG test systems in China at the time. Thus, false reference results existed. Second, the patient sampling period was only 1 month, leading to a potential selection bias. However, most studies have found no seasonal variation in NG incidence with a single study showing a slight difference throughout the year.

**Conclusions**

We found the current reported gonorrhea incidence and sex ratios to be inaccurate due to underestimations of gonorrhea incidence, especially among women. Physicians’ patient assessments should be monitored by the government and/or hospital to ensure that they are in compliance with diagnostic criteria for gonorrhea and the diagnostic criteria for gonorrhea should be updated soon. Physicians should recommend NG tests for any patient with potential gonorrhea, with particular attention being paid to screening female patients as they are often asymptomatic.

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**Contributors**

TF, FH and LW have designed this research. XW, LL and CZ have implemented this research and collected research data. GZ and FW completed the reference laboratory test. MX and AL have analysed the research data and written this manuscript. JMB and WT contribute to the writing and language editing of the manuscript.

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**Competing interests**

None declared.

**Patient consent**

Obtained.

**Ethics approval**

The ethics Committee of Shenzhen Center for Chronic Disease Control approved this study.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data sharing statement**

Additional data are available by emailing MX (lewnxmlong@163.com).


