Rectal gonorrhoea and chlamydia among men who have sex with men in coastal Kenya [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: Men who have sex with men (MSM) experience a high burden of Chlamydia trachomatis (CT) and Neisseria gonorrhoea (NG) infections. These remain largely undiagnosed in the context of syndromic treatment. In Kenya, prevalence of rectal CT and NG infection and NG antimicrobial sensitivity are poorly described.

Methods: MSM who reported receptive anal intercourse (RAI) were recruited from an ongoing human immunodeficiency virus acquisition and treatment study in coastal Kenya in 2016-2017. Rectal swabs were collected at two time points 6 months apart to estimate prevalence of CT/NG using a molecular point-of-care assay. Participants positive for CT or NG were treated according to national guidelines. NG culture and antimicrobial susceptibility testing was performed. Participant and risk behaviour characteristics were collected and association with baseline CT/NG prevalence was assessed by multivariable regression analysis.

Results: Prevalence of CT/NG in 104 MSM was 21.2% (CT 13.5%, NG 9.6%, dual infection 1.9%) at baseline and 25% in 84 MSM at follow-up (CT 14.3%, NG 14.3%, dual infection 3.6%). Most CT/NG positive participants were asymptomatic: 95.5% at baseline and 100% at follow-up. CT/NG infection was associated with being paid for sex (aOR=6.2, 95%CI...
Six NG isolates were obtained at follow-up; all isolates were susceptible to ceftriaxone and cefixime (1st line treatment for NG) and all were resistant to penicillin, tetracycline and ciprofloxacin.

**Conclusions:** The high prevalence of asymptomatic rectal CT and NG in MSM reporting RAI demonstrates the need for frequent screening or presumptive treatment. MSM who were paid for sex or had formal employment were more likely to be infected with CT/NG, suggesting increased risk behaviour during transactional sex. Antimicrobial susceptibility results suggest that current antibiotic choices in Kenya are appropriate for NG treatment.

**Keywords**
Chlamydia, Gonorrhoea, Men Who Have Sex With Men, Kenya, Cefixime, Azithromycin, Antimicrobial Susceptibility
Introduction

*Chlamydia trachomatis (CT)* and *Neisseria gonorrhoea (NG)* infections are curable, high-burden sexually transmitted infections (STIs) that result in considerable morbidity and mortality\(^1\). Global estimates of prevalence of genitourinary CT and NG infections from 2005 to 2012 were 2.7% and 0.6%, respectively, amongst men aged 15–49 years old\(^2\). Men who have sex with men (MSM) are a key population with regards to transmission of STIs. Worldwide, prevalence of rectal CT and NG infections in MSM has ranged as high as 21.7%-27.2% and 13.8%-25.4%, respectively\(^3,4\). As a traditionally highly stigmatized population, the true burden of STI infection in MSM in sub-Saharan Africa has only been studied since 2005\(^5,6\). Prevalence of rectal CT and NG has been estimated at 8% and 8% respectively in South African MSM above the age 18\(^7\), and 13.5% and 23.3%, respectively, in adult Nigerian MSM\(^8\). In Kenya, prevalence of rectal CT and/or NG was estimated to be 11.6% in a small sample of 43 human immunodeficiency virus (HIV)-negative adult MSM in the coastal region\(^9\) and 5.2% in HIV-positive and HIV-negative MSM over the age of 18 in the west of the country\(^10\). In MSM, younger age, sex with men only (as opposed to sex with both men and women), transactional sexual intercourse, unprotected anal intercourse, and being HIV positive have been found to be associated with rectal CT/NG\(^11-13\).

Over the years, the diagnosis and treatment of CT and NG infection has changed as a result of evolving technology and the development of antimicrobial resistance (AMR). Diagnosis is based on a combination of clinical suspicion, such as symptoms and signs suggestive of urethritis or proctitis, and laboratory investigations\(^14,15\). Nucleic acid amplification testing (NAAT), both highly sensitive and specific in detecting CT and NG, has superseded the use of cultures for the detection of infection\(^16-17\). In addition, with the advent of commercial point-of-care (POC) NAAT tests such as the GeneXpert® CT/NG assay (Cepheid), results can be obtained much more rapidly (90 minutes with the GeneXpert®)\(^18-19\). The provision of same-day results is of particular importance in treating the MSM population, who are less likely to attend healthcare services\(^20\). In the context of NG infection, however, bacterial culture is still recommended to enable detection of AMR\(^21\).

Globally, AMR is a major threat to public health and resistance to the key antibiotic classes has been detected\(^22\). In Kenya, plasmid-mediated resistance of NG to penicillin and tetracycline has been shown to be more prevalent in other countries and is likely related to extensive use of doxycycline\(^23\). The World Health Organization (WHO) currently recommends treating CT with either azithromycin or doxycycline\(^24\). Where sensitivity is unknown, the WHO recommends treating NG with ceftriaxone or cefixime combined with azithromycin. In cases where sensitivity is known, a single agent can be used\(^25\).

The WHO has recommended syndromic treatment of STIs as an answer to the low health-seeking behaviour and continuity of care typically seen in developing countries\(^26,27\). In Kenya, first-line recommended treatment for proctitis is cefixime or ceftriaxone and azithromycin\(^28\). Given higher prevalence amongst MSM, the WHO recommends presumptive treatment of MSM reporting unprotected receptive anal intercourse (RAI) in the previous six months and either a partner with an STI or multiple partners\(^29,30\). Sensitivity of this approach has been estimated at 74.1% with a specificity of 45.8% in MSM in coastal Kenya\(^31\). This study was performed to estimate the prevalence of asymptomatic CT and NG infections in MSM reporting RAI and to assess the susceptibility of NG to commonly used antimicrobials.

Methods

Study design

The study was conducted between April 2016 and January 2017 at the Kenya Medical Research Institute (KEMRI) Mtwapa Clinic, located in a town popular for its beach tourism and nightlife. A total of 104 MSM were recruited from an ongoing cohort study of high-risk MSM; methods of recruitment into that study have been previously described\(^32\). Men reporting RAI in the previous 6 months and aged between 18–49 years old were included for analysis. MSM were tested for CT/NG at baseline and at a follow-up visit 6 months later. Participants who tested positive were treated accordingly; CT infection was treated with azithromycin (2 g stat dose) and doxycycline (100 mg twice a day for 7 days), NG infection with cefixime (400 mg stat dose) and azithromycin (2 g stat dose) and dual infection treated with triple therapy (cefixime, azithromycin and doxycycline). A clinician observed the participant taking cefixime, azithromycin and the first dose of doxycycline.

Collection of participant characteristics

At baseline, counsellors conducted personal interviews with the participants. Men were considered to have sex with men exclusively (MSME) as opposed to both men and women (MSMW) based on answers they had given in previous clinic visits; if they had never reported having sex with women, they were considered MSME. Participants were asked if they had received money for or paid for sex in the 3 months prior to CT/NG sample collection. Condom use and number of sexual partners was also assessed. Clinicians recorded participant complaints at the visit, and a participant was considered symptomatic of proctitis if he complained of rectal discharge, pain or an ulcer in the perianal region.

Sample collection and antimicrobial susceptibility testing for NG

At baseline and follow-up, a trained clinician collected rectal swabs according to a standardized methodology: the first swap was used to detect CT and NG infection by NAAT with the GeneXpert® CT/NG Assay (Cepheid AB, Sweden), and the second was inoculated on Thayer Martin Modified agar. Inoculated plates were transported to a reference laboratory 40 km away at the end of each day for culture and antimicrobial susceptibility testing of NG\(^33\). A case of NG or CT infection was defined as a positive result on the GeneXpert® CT/NG assay.

The disc diffusion test was used to assess antimicrobial susceptibility of NG to ceftriaxone, penicillin and tetracycline\(^34\).
The Etest was performed to obtain minimum inhibitory concentrations (MIC) for cefixime and ciprofloxacin; cut-off values, as follows, were obtained from the Clinical and Laboratory Standards Institute (CLSI)\textsuperscript{23}. For cefixime, a MIC $\leq 0.5$ µg/ml indicated susceptibility. For ciprofloxacin, a MIC of $\leq 0.06$ µg/ml indicated susceptibility, 0.12-0.5 µg/ml intermediate susceptibility, and $\geq 1$ µg/ml resistance.

Data analysis
Data were analysed using Stata 13.0 (StataCorp LP, College Station, TX). Baseline participant characteristics were described. Prevalence of NG and CT at baseline and follow-up was estimated. Bivariable logistic regression was used to estimate association between participant characteristics and prevalence of CT / NG infection at baseline. Any variable with a p-value of $p<0.2$ was used in a multivariable regression analysis to determine adjusted odds ratios (aOR). Age was used a priori in the multivariable regression, given that the population at the clinic is principally under 25 years of age and that STIs are more prevalent in younger age groups\textsuperscript{15,30}. During analysis, a cut-off p-value of $p<0.05$ was used to indicate statistical significance.

Ethical approval
Ethical approval (protocol numbers 894 and 1224) was obtained from the KEMRI/Scientific and Ethics Review Unit (KEMRI/ SERU). Written informed consent was obtained from every participant.

Results
Participant backgrounds
Between April and July 2016, 104 participants were recruited and tested. Participant characteristics are described in full in Table 1. Approximately half (55.8%) of those recruited were between the ages of 25–34, almost nine out of ten (87%) were never married, and approximately half (49%) received secondary education only. Half the participants (51%) were Christian, and one quarter were Muslim (26%). One in four (25%) were unemployed, with the rest either self-employed (58%) or in formal employment (17%). One in four (25%) of the participants reported unprotected sex in the week preceding testing; with a similar number indicating they had sex with men exclusively (26.9%). Half the participants had been paid for sex in the 3 months prior to the study. Just over one in three (34.6%) MSM were HIV positive.

Prevalence of CT/NG
At baseline, 22 of the 104 MSM who took part in the study (21.2%) tested positive for CT and/or NG; 10 had NG (9.6%), 14 had CT (13.5%) and 2 (1.9%) had dual infection. Only one participant reported symptoms whilst the rest (95.5%) were asymptomatic (Table 2). The symptomatic participant was one of the two participants co-infected with both CT and NG. At baseline, none of the 104 swabs taken for culture, including those from the ten GeneXpert® NG positive participants, grew NG.

The prevalence of CT and/or NG infection was associated with receiving payment for sex (aOR=6.2, 95%CI (1.7-22.9)) and being in formal employment (aOR=7.5, 95%CI (1.14-49.2)) on multivariable logistic regression (Table 1), in a model controlling for age, having sex with men only or both men and women (MSME or MSMW, respectively), employment status and receiving payment for sex in the previous three months. MSME was also associated with greater odds of prevalent CT/NG, though this did not reach statistical significance (aOR=2.5, 95%CI (0.8-7.4)).

Of the 104 participants included in the baseline analysis, 20 (19.2%) participants were lost to follow-up at 6 months (Table 2). Baseline CT/NG prevalence in these 20 participants was 31.8% (31.8%) compared to 18.3% in those who attended follow-up, although this difference was not statistically significant ($p=0.217$). In total, 21 (25%) of 84 participants at follow-up tested positive for CT and/or NG infection; 12 (14.3%) participants had CT, 12 (14.3%) had NG, and 3 (3.6%) had dual infection. In total, 5 of the 21 (23.8%) cases of CT or NG that tested positive for CT or NG at follow-up were also positive at baseline; 5 had CT and 1 NG (1 CT and NG co-infection). All 21 follow-up participants were asymptomatic (Table 2). NG was isolated from six of twelve GeneXpert® NG positive follow-up participants (50%).

Antimicrobial susceptibility of N. gonorrhoea
Out of the 188 cultures performed (104 at baseline, 84 at follow-up), only 6 (3.2%) isolated NG; all six had been detected by the GeneXpert® NAAT and were isolated from follow-up samples. The NG isolates were found to be 100% resistant to tetracycline and ciprofloxacin, partially resistant to penicillin (33% resistant, 67% intermediate susceptibility), and 100% sensitive to ceftriaxone and cefixime (Figure 1).

Discussion
This study assessed the prevalence of rectal CT and NG in 104 MSM, identifying one in five participants at baseline and one in four participants at follow-up who were infected with either or both infections. A similarly high prevalence of CT/NG infections were reported from other parts of sub-Saharan Africa\textsuperscript{31-33}. Prevalence at baseline was statistically associated with receiving money for sexual intercourse—a four-fold increase in odds—which is consistent with the findings from previous studies\textsuperscript{31,33}. Men who engage in transactional sex may have increased vulnerability to STIs, which is compounded by an increased burden of psychosocial morbidities, such as stigmatization and discrimination\textsuperscript{34}. Being in formal employment was also associated with prevalent infection with CT/NG. This may possibly indicate that formal employment leads to greater financial means and thus a greater likelihood of paying for sex, although paying for sex was not found to be statistically associated with rectal CT/NG in this study.

The WHO recommends that CT/NG infections should be detected and treated in a timely manner, by either presumptive treatment or syndromic treatment\textsuperscript{31,22,24}. This is particularly important as these infections can remain undiagnosed for a long time unless routinely screened for, and thus be easily transmitted to other sexual partners. In this study, 95.5% of infections at baseline and 100% of infections at follow-up were asymptomatic. There are more asymptomatic cases of anorectal...
Table 1. Risk factors associated with *Chlamydia trachomatis* (CT) and/or *Neisseria gonorrhoea* (NG) infection in 104 men who have sex with men (MSM) at baseline.

| Variable (years)*       | All, n (% of total) | CT/NG, n (%) | OR, (95% CI) | p value | AOR (95% CI) | p value |
|-------------------------|---------------------|--------------|--------------|---------|--------------|---------|
| Age (years)             |                     |              |              |         |              |         |
| 18–24                   | 36 (34.6)           | 10 (27.8)    | 0.9 (0.2-4.2) | 0.890   | 1.2 (0.2 – 8.5) | 0.883   |
| 25–34                   | 58 (55.8)           | 9 (15.5)     | 0.4 (0.1-2.0) | 0.277   | 0.8 (0.1 – 5.7) | 0.853   |
| 35+                     | 10 (9.6)            | 3 (33.3%)    | Reference    |         | Reference    | -       |
| Education (years)       |                     |              |              |         |              |         |
| Primary/none            | 43 (41.3)           | 9 (20.9)     | Reference    | -       |              |         |
| Secondary               | 51 (49.0)           | 13 (25.5)    | 1.3 (0.5-3.4) | 0.603   |              |         |
| Higher/tertiary         | 10 (9.6)            | 0 (0.0)      | n/a          | n/a     | n/a          | δ       |
| Marital status          |                     |              |              |         |              |         |
| Never married           | 90 (86.5)           | 19 (21.1)    | Reference    | -       |              |         |
| Ever married            | 14 (13.5)           | 3 (21.4)     | 1.0 (0.3-4.0) | 0.978   |              |         |
| Religion                |                     |              |              |         |              |         |
| Christian               | 53 (51.0)           | 13 (24.5)    | Reference    | -       |              |         |
| Muslim                  | 27 (26.0)           | 6 (22.2)     | 0.9 (0.3-2.6) | 0.819   |              |         |
| Other/None              | 24 (23.1)           | 3 (12.5)     | 0.4 (0.1-1.7) | 0.237   |              |         |
| Employment‡             |                     |              |              |         |              |         |
| None                    | 26 (25.0)           | 3 (11.5)     | Reference    | -       | Reference    | -       |
| Self                    | 60 (57.7)           | 13 (21.7)    | 2.1 (0.8-7.1) | 0.275   | 1.8 (0.4-7.8) | 0.416   |
| Formal                  | 18 (17.3)           | 6 (33.3)     | 3.8 (0.8-18.1) | 0.090   | 7.5 (1.1-49.2) | 0.036   |
| Sex with‡               |                     |              |              |         |              |         |
| MSMW                    | 76 (73.1)           | 13 (17.1)    | Reference    | -       | Reference    | -       |
| MSME                    | 28 (26.9)           | 9 (32.1)     | 2.3 (0.9-6.2) | 0.101   | 2.3 (0.7-7.1) | 0.159   |
| Received payment for sex in past 3 months†| | | | | | |
| No                      | 52 (50)             | 5 (9.6)      | Reference    | -       | Reference    | -       |
| Yes                     | 52 (50)             | 17 (32.7)    | 4.6 (1.5-13.6) | 0.006   | 6.2 (1.7-22.9) | 0.006   |
| Paid for sex in past 3 months| | | | | | |
| No                      | 97 (99.3)           | 21 (21.6)    | Reference    | -       |              |         |
| Yes                     | 7 (6.7)             | 1 (14.3)     | 0.6 (0.1-5-3) | 0.648   |              |         |
| Alcohol use in past month|                    |              |              |         |              |         |
| No                      | 62 (59.6)           | 12 (20)      | Reference    | -       |              |         |
| Yes                     | 42 (40.4)           | 10 (22.7)    | 1.3 (0.5-3.4) | 0.586   |              |         |
| Sexual exposure and condom use in past week| | | | | | |
| No activity             | 34 (32.7)           | 6 (13.6)     | Reference    | -       |              |         |
| All protected           | 44 (42.3)           | 8 (21.1)     | 1.0 (0.3-3.3) | 0.951   |              |         |
| Any unprotected         | 26 (25)             | 8 (36.4)     | 2.1 (0.6-7.0) | 0.238   |              |         |
| Condom use for anal sex in past 3 months‡| | | | | | |
| No                      | 75 (72.1)           | 18 (23.7)    | Reference    | -       |              |         |
| Yes                     | 26 (25)             | 4 (14.3)     | 0.6 (0.2-1.9) | 0.363   |              |         |
| Total sex partners in past month| | | | | | |
| None                    | 15 (14.4)           | 3 (6.8)      | Reference    | -       |              |         |
| One                     | 21 (20.2)           | 2 (7.1)      | 0.4 (0.1-2.9) | 0.380   |              |         |
| Two or more             | 68 (65.4)           | 17 (53.1)    | 1.3 (0.3-5.3) | 0.683   |              |         |
| HIV status              |                     |              |              |         |              |         |
| Negative                | 68 (65.4)           | 15 (22.1)    | Reference    | -       |              |         |
| Positive                | 36 (34.6)           | 7 (19.4)     | 0.9 (0.3-2.3) | 0.756   |              |         |

* Included in the multivariable analysis priori. ‡ Only factors significant at ps≤0.2 in the bivariable analysis were included in the multivariable model. †3 participants did not report anal sex in the last 3 months but reported within the past 6 months. MSME, MSM exclusively; MSMW, MSM and women. OR - odds ratio; aOR - adjusted odds ratio.
CT/NG reported in this study compared to other studies on MSM from the USA (58% asymptomatic CT, and 69% asymptomatic NG)\(^{32}\) and Kenya (58.3% asymptomatic CT/NG infection)\(^{30}\). This may be a true picture of the burden of infection in coastal Kenya, but larger research studies are needed to confirm these findings. Nevertheless, this finding does support the need for more etiologic diagnosis when and where possible programmes to detect asymptomatic infections in developing countries, particularly in high-risk populations such as MSM\(^{33,34}\).

No NG was isolated from baseline rectal swabs in GeneXpert® NG-positive participants. At follow-up, six NG isolates were successfully cultured from 12 GeneXpert® NG positive participants. The only methodological difference at follow-up was prior notification of the laboratory at the reference centre 40 km away that a participant was positive on the GeneXpert® assay, one extra day of incubation was added to give more time to the scanty colonies to grow. It is well recognized that test methodology and technical expertise have an impact on the positivity rates of samples. Hence, antimicrobial susceptibility testing may be more reliably evaluated using rapid molecular POC tests in the future\(^{35}\). The low yield in this case may also be due to the practicalities of having to transport the culture plates to the reference laboratory and the order of swab collections. As the culture swab was taken last, the bacterial yield may have been insufficient to result in a positive culture.

Regardless of yield, antimicrobial susceptibility testing revealed that all cultured NG isolates were sensitive to cefixime (first line treatment for NG) and ceftriaxone, and that all isolates were resistant to tetracycline and ciprofloxacin (Figure 1). Though azithromycin sensitivity was not assessed and baseline cultures were negative, the susceptibility of NG to cefixime at follow-up suggests that all treated participants were cured. Previous susceptibility studies of NG have shown that AMR is rising globally, and is a very real threat to healthcare systems, particularly for those caring for high-risk populations\(^{19,20,36,37}\). Genomic studies have demonstrated that resistant NG strains are transmitted between MSM partners\(^{36}\). This information calls for careful treatment of NG, and for routine antimicrobial susceptibility testing to be performed where possible. It is crucial that global guidelines on STI treatment in MSM and other key populations be updated to take into account AMR and POC testing\(^{21,22}\).

Approximately one-third of participants in this study (34.6%) were HIV positive, though this was not statistically associated with CT/NG prevalence. HIV infection has been found to be

### Table 2. Prevalence of *Chlamydia trachomatis* (CT) and/or *Neisseria gonorrhoea* (NG) infections at baseline and follow-up, and proportion of asymptomatic cases.

| Variable                  | Baseline, n (asymptomatic %) | Follow-up, n (asymptomatic %) | Baseline and follow-up, n |
|---------------------------|------------------------------|-------------------------------|---------------------------|
| All participants          | 104                          | 84                            | -                         |
| Total CT or NG            | 22 (95.5%)                   | 21 (100%)                     | 5                         |
| CT only                   | 12 (100%)                    | 9 (100%)                      | 4                         |
| NG only                   | 8 (100%)                     | 9 (100%)                      | 0                         |
| CT/NG co-infection        | 2 (50%)                      | 3 (100%)                      | 1                         |
higher in participants with an underlying STI, presumably facilitated by inflammation of mucosal epithelium. It is therefore critical to rapidly detect and treat STIs in order to minimize future HIV-related epidemics in the MSM populations. Several studies have looked at the association between pre-exposure prophylaxis (PrEP) and the incidence of STIs: these studies demonstrated increased rates of CT/NG infections with PrEP use, potentially related to increased screening for STIs, increased condomless sexual intercourse and decreased seroconversion between sexual contacts. Several months after this study concluded, HIV-negative MSM in the same larger cohort started receiving PrEP; it will be interesting to assess the impact this has on CT/NG infection rates in this population.

This study has several limitations. The sample size was small, rendering statistical analysis and interpretation of results for subgroups difficult. Furthermore, the small yield of NG cultures highlights the difficulty of generalizing resistance data, azithromycin resistance had not been assessed and this calls for larger studies of antimicrobial resistance in Kenya.

**Conclusion**

The prevalence of rectal CT/NG infections in MSM who report RAI in coastal Kenya is estimated to be between 21.2% and 25%, and is associated with transactional sex and formal employment. All but one of the participants who tested positive for CT/NG infection were asymptomatic, supporting the use of a presumptive treatment approach. All positive NG infections were treated with cefixime and azithromycin; all NG isolates were sensitive to cefixime and azithromycin; all NG isolates were sensitive to cefixime/ceftriaxone. The study findings suggest a need for continued surveillance of NG antimicrobial susceptibility and for sharing of data between research groups studying NG in Kenya.

**Data availability**

Figshare. Data Sharing Excel.xlsx. [https://doi.org/10.6084/m9.figshare.7735001.v1](https://doi.org/10.6084/m9.figshare.7735001.v1). This file contains infection status for each participant, alongside details of risk factors and de-identified demographic information.

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

**Grant information**

This work was partially funded by the International AIDS Vaccine Initiative (IAVI) with the generous support of USAID and other donors; a full list of IAVI donors is available at www.iavi.org. KWTRP is supported by core funding from the Wellcome Trust (203077). SMG was supported by NIH grant R01AI24968 and the Robert W. Anderson Endowed Professorship in Medicine. EJS receives research funding from IAVI, NIH (grant R01AI124968), and the Wellcome Trust. This work was also supported through the Sub-Saharan African Network for TB/HIV Research Excellence (SANTHE), a DELTAS Africa Initiative [grant # DEL-15-006]. The contents are the responsibility of the study authors and do not necessarily reflect the views of USAID, the NIH, the United States Government or the Wellcome Trust. This report was published with permission from KEMRI.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Acknowledgements**

The authors would like to acknowledge study clients/patients for participating in the research, and counsellors at the KEMRI-Wellcome Trust Research Programme Mtwapa clinic and the microbiology team in Kilifi for supporting this study. This study formed part of a MSc thesis by C. Ngetsa at Kenyatta University. Dr Rohini Manuel, consultant clinical microbiologist, in the UK, is thanked for her expert review of the final version of this manuscript.

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Wellcome Open Research 2019, 4:79 Last updated: 17 JUN 2020
Open Peer Review

Current Peer Review Status: ✔️ ?

Version 1

Reviewer Report 13 August 2019

https://doi.org/10.21956/wellcomeopenres.16606.r36001

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Nicola Low
Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

Thank you for giving me the opportunity to review this manuscript, which addresses the important issue of extra-genital sexually transmitted infections (STI) in men who have sex with men (MSM) in Kenya. I have no concerns about the relevance and validity of the data. The study is small but, on the other hand, has detailed behavioural information, antimicrobial susceptibility data and a follow-up visit. The findings lack statistical precision, so the authors are restricted in the certainty of the conclusions that they can draw. In this situation, data from such studies are very important for future syntheses of evidence in systematic reviews.

In Wellcome Open Research, I think the authors have more flexibility about what to report, meaning that there is an opportunity for useful contextual information about the study and for full reporting that will make the findings reproducible and able to be used in a future systematic review. I have some suggestions that I hope the authors will find useful in revising their manuscript.

Major comments

1. Study design: this is a report of a cohort study, nested within a larger cohort study. Please make sure that all the items proposed in the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) checklist for cohort studies (https://www.strobe-statement.org/index.php?id=available-checklists) are reported. In particular, I would like to see: a) the proportion enrolled and whether or not they differed from the men in the larger cohort study. The authors only report (p4, Results, Participant backgrounds, line 1), “104 participants were recruited and tested”; b) the follow-up time reported as a total number of months and average for each participant; 95% confidence intervals (CI) for the main percentages.

2. Study design: Can the authors say whether this study was pre-planned? If so, was there a target sample size with a power calculation? Was enrolment less than expected?

3. Data analysis: can the authors please calculate and report the incidence rate of Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (NG) detection in anorectal samples? The availability of data from a follow-up visit is a strength of the study. Prevalence at follow-up (p4, Methods, Data
analysis, line 3, and Table 2) isn’t very useful. It would be great to change the columns in Table 2 to report: numbers with positive results at baseline; the numbers of incident cases and follow-up time; incidence rate (with 95% CI) in those with a negative test result at baseline; repeat detection rate (with 95% CI) in those with a positive test at baseline who received treatment.

4. Data analysis (p4, Methods, Data analysis, line 11-13): Please delete the sentence with “...a cut-off p-value of p<0.05...” The p-value will be driven by the sample size and not clinical relevance. There are no pre-specified hypotheses, so null hypothesis significance testing does not make sense.

5. Antimicrobial resistance: thank you for reporting results of antimicrobial susceptibility testing even though culture at baseline was unsuccessful. The recovery rate at follow-up (6 of 12 GeneXpert positive results is as expected for rectal swabs). I didn't find the presentation of the data in Figure 3 or percentages in the text very useful. A table of the results for each isolate would take up the same amount of space as Figure 3 and, for each antimicrobial tested, the MIC for each isolate could be shown. In the text, the absolute numbers are more useful than the percentages.

Minor comments
1. The causative agent of gonorrhoea is *Neisseria gonorrhoeae* (not *gonorrhoea*). Please check the spelling throughout.

2. “Burden” – this term is used several times to refer to the frequency of infection. “Burden of disease” usually includes a measurement of the consequences of the condition, e.g. a disability-adjusted life year. With asymptomatic infections for which the clinical complications are unknown or rare, burden is not really an appropriate term.

3. Introduction (p3, Para 1): Literature review. It would be useful to be a bit more precise in the reporting of the chosen studies:
   - Of interest, you may wish to update ref 2. WHO has just published its newest estimates for 2016 ([https://www.who.int/bulletin/volumes/97/8/18-228486.pdf](https://www.who.int/bulletin/volumes/97/8/18-228486.pdf)). The estimates of global prevalence for CT and NG for men are very similar to 2012. For men in the African region, 2016 estimates for urogenital infection in men are: CT 4.0% (95% CI 2.4–6.1), NG 1.6% (95% CI 0.9–2.6).
   - Line 8, “Worldwide” is not really accurate – these are two studies, one in Italy and one in Thailand is particularly high risk populations. Please rephrase.
   - Differences in reports of prevalence will differ depending on whether the study population is unselected or all report recent receptive anal intercourse. Your description should take these factors into account.
   - Is there a systematic review? If so, please cite. If not, maybe worth pointing out in Discussion as a research need.

4. Introduction (p3, ref 10): you could acknowledge that this estimate comes from your own group.

5. Introduction (p3, para 2): “…(NAAT)… has superseded the use of cultures…” NAAT are not available everywhere so you may want to qualify this statement with “where available”.

6. Methods, Sample collection (p4): Could you give more detail about the “standardized methodology” for collection of the swabs? Was a proctoscope used? How far inside the anal canal was the swab inserted? Was it moistened? These are important details for reproducibility. Technically, the swab is a rectal swab only if inserted past the dentate line, so swabs collected
without proctoscopy, which sample mainly from the anal canal might be more accurately termed as "anorectal".

7. Data analysis (p4, Methods, line 4): “bivariable” is ambiguous. When the model examines an association between an outcome and one other variable, it is usual to call this a univariable analysis.

8. Data analysis and Table 1: the p-values are given for each stratum (e.g. age, religion). In the multivariable statistical model, it is the contribution of the variable as a whole that is important. These ‘global’ p values should be derived from a likelihood ratio test that compares the model fit with the variable to the model that includes all variables other than the one of interest. For a binary variable the results are the same.

9. Table 1: is the ethnic origin of MSM in Kenya associated with their risk of rectal STIs? If so, ethnic group might be a useful descriptive variable to report.

10. Discussion: This could be better structured. It is important that you collected data about infections, behaviours and antimicrobial susceptibility. Both presumptive treatment and frequent screening and treatment impose selection pressure for the emergence of antimicrobial resistance. The discussion is an opportunity to bring together these lines of thought in thinking about how to address rectal STIs in MSM.

11. Discussion, Limitations (p7): It’s worth mentioning the limitation of having combined the data for CT and NG owing to the small sample size.

12. Conclusion (p7): “…between 21.2% and 25%.” These point estimates suggest spurious precision and lower 95% CI is much lower. I expect each estimate lies within the confidence interval of the other, given the sample size. Please rephrase in context of confidence intervals.

13. Conclusions: in Abstract (p1, and main text (p7) don’t match. In the Abstract, there is no support from the results that “The high prevalence of asymptomatic rectal CT and NG in MSM reporting RAI demonstrates the need for frequent screening”. The more cautious statements in the main text are more appropriate.

14. Dataset: could you add a worksheet with a key to the abbreviations for the variables?

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Epidemiology, bacterial sexually transmitted infections, antimicrobial resistance.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 17 Dec 2019

**Caroline Ngetsa,** KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya

Dear Reviewers,

Many thanks for your comments on our manuscript. We have responded to each individually and reflect the changes in the amended manuscript.

**Major comments**

Study design: this is a report of a cohort study, nested within a larger cohort study. Please make sure that all the items proposed in the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) checklist for cohort studies ([https://www.strobe-statement.org/index.php?id=available-checklists](https://www.strobe-statement.org/index.php?id=available-checklists)) are reported.

Thank you for your review. We have ensured that all elements of the STROBE checklist are included, and have responded to each of your comments individually. We will make sure this is visible in the revised paper.

In particular, I would like to see: a) the proportion enrolled and whether or not they differed from the men in the larger cohort study. The authors only report (p4, Results, Participant backgrounds, line 1), “104 participants were recruited and tested”;

Between April 2016 and January 2017, eligible participants were identified at follow-up visits in an existing cohort study on HIV acquisition, based on self-report of any receptive anal intercourse (RAI) within the past 6 months. We were able to enrol 70 of 174 eligible men (i.e. 40%). We have added a supplemental table that can be accessed on [figshare](https://figshare.com) to compare characteristics of the 104 cohort participants not included with those of the 70 participants included in this study: “Participants not enrolled were more likely to report sex with men exclusively, transactional sex, RAI, group sex, and any unprotected sex (data in supplemental material).

b) the follow-up time reported as a total number of months and average for each participant; 95% confidence intervals (CI) for the main percentages.

Total follow-up was 5.7 months on average (range 5.4-6.2 months) for each participant, which amounted to a total follow-up time of 39.6 person-years.

**Study design:** Can the authors say whether this study was pre-planned? If so, was there a target sample size with a power calculation? Was enrolment less than expected?

This study was planned and done to estimate prevalence and incidence of CT/NG
infections among MSM participants who reported RAI. We did not have a prespecified hypothesis, therefore a sample size was not calculated. The precision estimate of the confidence interval was based on exact binomial confidence intervals. The study was limited by a small budget to conduct the study.

Data analysis: can the authors please calculate and report the incidence rate of Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (NG) detection in anorectal samples? The availability of data from a follow-up visit is a strength of the study. Prevalence at follow-up (p4, Methods, Data analysis, line 3, and Table 2) isn’t very useful. It would be great to change the columns in Table 2 to report: numbers with positive results at baseline; the numbers of incident cases and follow-up time; incidence rate (with 95% CI) in those with a negative test result at baseline; repeat detection rate (with 95% CI) in those with a positive test at baseline who received treatment.

Thank you for the suggestion. Given that the data is available, we have used it to calculate incidence as well and revised our Table 2 to reflect this.

Data analysis (p4, Methods, Data analysis, line 11-13): Please delete the sentence with “…a cut-off p-value of p<0.05…” The p-value will be driven by the sample size and not clinical relevance. There are no pre-specified hypotheses, so null hypothesis significance testing does not make sense.

Thank you for highlighting this.

Antimicrobial resistance: thank you for reporting results of antimicrobial susceptibility testing even though culture at baseline was unsuccessful. The recovery rate at follow-up (6 of 12 GeneXpert positive results is as expected for rectal swabs). I didn’t find the presentation of the data in Figure 3 or percentages in the text very useful. A table of the results for each isolate would take up the same amount of space as Figure 3 and, for each antimicrobial tested, the MIC for each isolate could be shown. In the text, the absolute numbers are more useful than the percentages.

Many thanks for these comments. We have included a Table 3 instead of Figure 1, which presents the data you have suggested. In addition, we have written down whole numbers instead of percentages when describing the AMR data in the manuscript.

Minor comments
The causative agent of gonorrhoea is Neisseria gonorrhoeae (not gonorrhoea). Please check the spelling throughout.

Thank you for highlighting this.

“Burden” – this term is used several times to refer to the frequency of infection. “Burden of disease” usually includes a measurement of the consequences of the condition, e.g. a disability-adjusted life year. With asymptomatic infections for which the clinical complications are unknown or rare, burden is not really an appropriate term.

We have rethought our use of this word and ensured appropriate terminology is used throughout this manuscript.

Introduction (p3. Para 1): Literature review. It would be useful to be a bit more precise in the reporting of the chosen studies:

Of interest, you may wish to update ref 2. WHO has just published its newest estimates for 2016 (https://www.who.int/bulletin/volumes/97/8/18-228486.pdf). The estimates of global prevalence for CT and NG for men are v similar to 2012. For men in the African region, 2016 estimates for
urogenital infection in men are: CT 4.0% (95% CI 2.4–6.1), NG 1.6% (95% CI 0.9–2.6).

Thank you for pointing us to this updated piece of literature, we have updated our manuscript to reflect the most recent evidence.

Line 8, “Worldwide” is not really accurate – these are two studies, one in Italy and one in Thailand is particularly high risk populations. Please rephrase.

Thank you, we have been more specific in describing the results found.

Differences in reports of prevalence will differ depending on whether the study population is unselected or all report recent receptive anal intercourse. Your description should take these factors into account.

Is there a systematic review? If so, please cite. If not, maybe worth pointing out in Discussion as a research need.

Many thanks for pointing out that it may seem that way. It was not our intention to do a systematic review, but rather just present existing estimates of rectal STIs in MSM in other geographical regions than Kenya. This serves as a prelude to presenting our own data. We have included in our limitations the fact that we did not systematically review all existing literature.

Introduction (p3, ref 10): you could acknowledge that this estimate comes from your own group.

Thank you, we have now acknowledged our own results.

Introduction (p3, para 2): “…(NAAT)… has superseded the use of cultures…” NAAT are not available everywhere so you may want to qualify this statement with “where available”.

This has been amended.

Methods, Sample collection (p4): Could you give more detail about the “standardized methodology” for collection of the swabs? Was a proctoscope used? How far inside the anal canal was the swab inserted? Was it moistened? These are important details for reproducibility.

Technically, the swab is a rectal swab only if inserted past the dentate line, so swabs collected without proctoscopy, which sample mainly from the anal canal might be more accurately termed as “anorectal”.

This has been detailed in the revised manuscript. We used proctoscopy and dry swab kits for sample collection.

Data analysis (p4, Methods, line 4): “bivariable” is ambiguous. When the model examines an association between an outcome and one other variable, it is usual to call this a univariable analysis.

Thank you for pointing this out, we have amended this.

Data analysis and Table 1: the p-values are given for each stratum (e.g. age, religion). In the multivariable statistical model, it is the contribution of the variable as a whole that is important. These ‘global’ p values should be derived from a likelihood ratio test that compares the model fit with the variable to the model that includes all variables other than the one of interest. For a binary variable the results are the same.

Thank you for this suggestion. When we apply the p-values derived from the likelihood ratio test, we lose individual characteristic of the variable with more than 2 strata. For example, formal employment was associated with prevalent infection (borderline) when we apply the Wald p-values. When we apply the likelihood ratio test, this association
becomes concealed despite having an estimate with CI’s above 0. We therefore prefer to present the Wald P values for this analysis.

Table 1: is the ethnic origin of MSM in Kenya associated with their risk of rectal STIs? If so, ethnic group might be a useful descriptive variable to report.

Thank you, we looked at this value as 5 major ethnic categories and there is no significant difference by ethnicity.

Discussion: This could be better structured. It is important that you collected data about infections, behaviours and antimicrobial susceptibility. Both presumptive treatment and frequent screening and treatment impose selection pressure for the emergence of antimicrobial resistance. The discussion is an opportunity to bring together these lines of thought in thinking about how to address rectal STIs in MSM.

Many thanks for pointing this out. We have now better structured our conclusion and highlighted the very important fact that these methods could increase AMR.

Discussion, Limitations (p7): It’s worth mentioning the limitation of having combined the data for CT and NG owing to the small sample size.

Thank you for your suggestion, we have now added this as one of our limitations.

Conclusion (p7): “…between 21.2% and 25%. ” These point estimates suggest spurious precision and lower 95% CI is much lower. I expect each estimate lies within the confidence interval of the other, given the sample size. Please rephrase in context of confidence intervals.

Thank you, we’ve done this now.

Conclusions: in Abstract (p1, and main text (p7) don’t match. In the Abstract, there is no support from the results that “The high prevalence of asymptomatic rectal CT and NG in MSM reporting RAI demonstrates the need for frequent screening”. The more cautious statements in the main text are more appropriate.

We have modified the abstract to reflect this, thank you.

Dataset: could you add a worksheet with a key to the abbreviations for the variables?

We have now included a worksheet with dataset abbreviations (it can be found on figshare, and there is a link to that in the References section of the manuscript).

Competing Interests: None
Michael W. Ross
Program in Human Sexuality, Department of Family Medicine, University of Minnesota Medical School, Minneapolis, MN, USA

This is a useful report of rectal gonorrhea and chlamydia in MSM in coastal Kenya. The Introduction suffers from missing some crucial findings from a similar study of prevalence of rectal NG/CT in MSM in Tanga and Dar es Salaam, a few hundred miles south of where this study was carried out (Ross MW et al., BMJ Open 2014). Some of those interesting findings were replicated, including the lack of association between HIV and STI in MSM, plus similar high rates of rectal STIs. There may be lessons here about access to clinics that will perform rectal examinations/swabs, especially if the MSM are not "out" to health care workers (rectal STIs are a marker for MSM activity and likely to engender discriminatory behavior in many health workers). Religion was given for 77%, but what was the other quarter? Hindi? No religion?

This is an important study, with the gaps noted above. It would also have been helpful to briefly speculate as to what bias might have been associated with recruiting participants from an existing high-risk cohort study.

References
1. Ross MW, Nyoni J, Ahaneku HO, Mbwambo J, et al.: High HIV seroprevalence, rectal STIs and risky sexual behaviour in men who have sex with men in Dar es Salaam and Tanga, Tanzania. BMJ Open. 2014; 4 (8): e006175 PubMed Abstract | Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Behavioral Epidemiology of STIs and HIV in MSM, Africa.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
Dear Reviewers,

Many thanks for your comments on our manuscript. We have responded to each individually and reflect the changes in the amended manuscript.

This is a useful report of rectal gonorrhea and chlamydia in MSM in coastal Kenya. The Introduction suffers from missing some crucial findings from a similar study of prevalence of rectal NG/CT in MSM in Tanga and Dar es Salaam, a few hundred miles south of where this study was carried out (Ross MW et al., BMJ Open 2014)\textsuperscript{1}. Some of those interesting findings were replicated, including the lack of association between HIV and STI in MSM, plus similar high rates of rectal STIs. There may be lessons here about access to clinics that will perform rectal examinations/swabs, especially if the MSM are not “out” to health care workers (rectal STIs are a marker for MSM activity and likely to engender discriminatory behavior in many health workers).

Religion was given for 77%, but what was the other quarter? Hindi? No religion?

Thank you for your review. We have now referred to the study in Dar Es Salaam and Tanga in the background and discussion sections of this manuscript. The point of discussion regarding access to clinics is also very relevant; we feel that we do raise this issue a bit in our introduction and discussion, by raising issues with stigma related to MSM in general; this should encompass healthcare access as well.

We have also written down the religious background of the remaining quarter of participants; this is also visible in Table 1.

This is an important study, with the gaps noted above. It would also have been helpful to briefly speculate as to what bias might have been associated with recruiting participants from an existing high-risk cohort study.

Thank you for noting this. We have included details of eligible patients who were not included in the study (and have included data available on figshare, a link is available in the References of the manuscript): importantly, it was noted that patients not included in the study had higher risk behaviour. This is unlikely to underestimate true infection prevalence and rate within this population.

Competing Interests: None