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Correlations of chlamydia and gonorrhea between pharyngeal, rectal, and urethral sites among Thai men who have sex with men: how much can we missed by single site anatomical screening?

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TITLE PAGE

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Running head: Anatomical site correlations of CT/NG infections among MSM

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ABSTRACT (299/300)

Objective: Routine screening for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) infections in sexually-exposed anatomical sites may be challenging due to high cost, especially in resource-limited settings. The objective of this study was to evaluate concurrent CT/NG infections in pharyngeal, rectal, and urethral sites to determine the potential proportion of missed CT/NG infections if single anatomical site screening was performed among men who have sex with men (MSM).

Methods: Thai MSM were enrolled to the Community-led Test and Treat cohort. Screening for CT/NG infections was performed from pharyngeal swab, rectal swab, and urine using nucleic acid amplification testing. The correlations of CT/NG among the three anatomical sites were analyzed.

Results: Of 1610 MSM, with a median (IQR) age of 24.2 (20.8-30.0) years, enrolled, the prevalence of CT/NG infections was 29.9%. HIV-positive participants had significantly higher prevalence of CT/NG infections in all anatomical sites, except for pharyngeal NG. In a correlation analysis, 22.7% of those tested negative at pharyngeal site had either rectal or urethral infections (41.3% in HIV-positive vs 18.6% in HIV-negative MSM, p<0.001), 12.8% of those tested negative at rectal site had either pharyngeal or urethral infections (18.8% vs 11.8%, p=0.007), and 22.4% of those tested negative from urine had either pharyngeal or rectal infections (40.0% vs 18.6%, p<0.001). HIV-positive status was associated with urethral CT/NG infections among MSM who tested negative at the rectal site (adjusted odd ratio [aOR] 1.9; 95%CI 1.1-3.5, p=0.04). Among 481 MSM with CT/NG infections, 34.5-68.8% can be missed if the screening test was done in single anatomical site.

Conclusions: High proportions of CT/NG infections would be missed if single anatomical site screening was performed, especially rectal CT/NG infections among HIV-positive MSM. Studies on new technologies which allow CT/NG screening in pooled samples from different anatomical sites at affordable price are urgently needed.

Strengths and limitations of this study

- The study includes a large number of sexually active MSM who completed CT/GC screening in all 3 anatomical sites.
- Correlations of CT/NG infections between pharyngeal, rectal, and urethral sites among sexually active MSM were identified, and showed the percentage of possible missed diagnosis if single anatomical site screening was performed.
- Because CT/NG screening in our study were based on self-reported site of exposure, we were unable to compare the performance between a history-based and universal approach.
- Extra-genitalia samples from a modest number of participants may have been missed due to social desirability bias regarding questions about the site(s) of sexual contact.

MAIN TEXT

Introduction

Chlamydia trachomatis (CT) and *Neisseria gonorrhoeae* (NG) infections are among the most common bacterial sexually transmitted infections (STIs) and disproportionately affect men who have sex with men (MSM) worldwide.[1] Two large studies conducted in Thailand between 2006 and 2010 showed that, compared to men who have sex exclusively with women, MSM had approximately 30% higher prevalence of CT infection and up to 5 times higher prevalence of NG infection.[2 3]

CT/NG infections are associated with acquiring and transmitting HIV infection.[4] In particular, rectal CT/NG infection is strongly associated with an increased risk of HIV acquisition among MSM.[5 6] In contrast, the role of pharyngeal CT/NG infections towards HIV acquisition is less understood. One large cross-sectional study showed an association between pharyngeal infection and MSM diagnosed with HIV,[7] but this can be an indirect effect of oral sex increasing the risk of STIs at other anatomical sites.[8] As CT/NG infections often occur without symptoms,[1] the lack of routine asymptomatic screening has resulted in the missed opportunity to diagnosis these easily treated STIs.

The diagnosis of CT/NG infections, both at genital and extra-genital sites, can be made using nucleic acid amplification tests (NAATs). Many studies have shown superior sensitivity and specificity of NAATs in detecting extra-genital CT/NG infection compared to culture.[9-12] The findings prompted the US Center for Disease Control and Prevention (CDC) to recommend the use of NAATs for pharyngeal and rectal CT/NG screening,[13] although they have not been cleared by the US Food and Drug Administration.

Frequency of testing and anatomical sites to be tested are the two factors to consider in asymptomatic CT/NG screening. Most recommendations for CT/NG screening, including the one by the US CDC, recommend all sexually active MSM to be screened at least annually at sites of contact regardless of condom use.[13] More frequent screening is advised if the individuals are at increased risk. Conversely, the Australian STI management guidelines recommend screening at all sites regardless of reported sites of contact.[14] However, many barriers prevent the implementation of these recommendations in clinical practice. For the clients, these barriers may include the cost of tests, underestimating the risk of asymptomatic infections, and concern of being stigmatized.[15 16] Healthcare providers also often lack knowledge on the importance of STI screening at appropriate anatomical sites,[15] which may also be the case in Thailand where there are no consensus recommendations for CT/NG screening.

Our primary objective was to study the correlations between pharyngeal, rectal, and urethral CT/NG infections to determine the proportions and associated factors of potential CT/NG infections missed if single anatomical site screening was performed. Other objectives were to determine the prevalence of CT/NG infections among MSM enrolled in the Community-led Test and Treat cohort and to determine the pattern of single and multiple anatomic sites of CT/NG infections. The findings from our study will be crucial to guide recommendations for CT/NG screening among MSM, both in HIV treatment and prevention programs, in resource-limited settings.

Methods

Enrollment of participants

The present study used data from MSM participants enrolled in the Community-led Test and Treat cohort between October 2015 and October 2016. The Community-led Test and Treat cohort aims to evaluate the feasibility of empowering lay providers who are members of MSM and transgender women (TGW) communities to provide HIV-related services, increasing uptake of HIV testing and treatment services among MSM and TGW in Thailand.

Eligible criteria and study procedures for the Community-led Test and Treat cohort have been reported in detail previously.[17] Adults Thai MSM and TGW with a history of at least one unprotected anal sexual intercourse with a man in the past 6 months were enrolled from Service Workers IN Group (SWING) drop-in centers (DICs) in Bangkok and Pattaya city, Rainbow Sky Association of Thailand (RSAT) DICs in Bangkok and Songkhla, Caremat DIC in Chiang Mai, and Sisters DIC in Pattaya city, Thailand for an 18-month follow-up period for an 18-month follow-up period. Only participants of unknown HIV-status were enrolled, volunteers with known HIV infection were excluded from enrollment. Screening for CT and NG was performed at enrollment using nucleic acid amplification testing (NAAT, Abbott Real Time CT/NG, Abbott Molecular Inc., Illinois, USA) with pharyngeal swab, rectal swab, and/or urine collection depending of participants' self-report of site(s) of sexual contact. Participants who completed both CT and NG screening in all 3 anatomical sites were included in this analysis.

The study (NCT03580512) was approved by the institutional review boards of the Faculty of Medicine, Chulalongkorn University (IRB No. 181/57), the Department of Disease Control, Thai Ministry of Public Health (IRB No. 9/57-678), the Provincial Health Offices of Chonburi (IRB No. 0032.003/658), Songkhla (IRB No. 075/2014), and Chiang Mai (IRB No. 0032.002/35859). All participants gave informed consent.

Statistical Analysis

Statistical analysis was performed using Stata 13 (StataCorp LP, College Station, TX, USA). Demographic, CT/NG and HIV testing results, and sexual risk behaviors were summarized as median (interquartile range [IQR]) and number (percentage) for continuous and categorical variables, respectively. Characteristics between HIV-positive and HIV-negative participants were compared using a chi-square or Fisher's exact test, or Mann-Whitney test as appropriate. The baseline prevalence of CT/NG infections was calculated.

Multivariate logistic regression with 95% confidence intervals (CI), based on covariates associated with outcomes in univariate regression with p-value of <0.2, was used to identify associated factors for the prevalence of CT/NG in the remaining 2 sites. The proportion of potential CT/NG infections missed to the overall prevalence of CT/NG infections at baseline in the study was also analyzed to determine the case for CT/NG infections missed in the community. The correlation of CT/NG infections between each positive anatomical site were also analyzed to determine infection at multiple sites. Statistical significance was defined as $p<0.05$.

Results

Participant characteristics

Of 1858 MSM enrolled in the Community-led Test and Treat cohort, a total of 1610 (86.7%) participants completed both CT and NG testing in all 3 anatomical sites and were included in the analysis. Compared to MSM who did not complete CT/NG testing in all 3 anatomical sites, MSM who completed CT/NG testing in all 3 anatomical sites had higher

prevalence of CT/NG infections at any anatomical sites (29.9% vs 16.4%, p<0.001) and reported higher sexual risk behaviors **(Supplementary Files 1)**.

At enrollment, the prevalence of CT/NG infections at any anatomical sites was 29.9% (95%CI 27.6-32.2). The most prevalent CT/NG infections by anatomical sites were rectal CT (15.0%), rectal NG (9.3%), and urethral CT (7.0%). HIV-positive participants had significantly higher prevalence of both CT and NG infections in all anatomical sites, except for pharyngeal NG, and were more likely than HIV-negative participants to be enrolled from the Bangkok sites, self-perceived high risk of HIV transmission in the past month, had unprotected sex in the past month, and self-reported or unsure of having STIs in the past month **(Table 1)**.

Correlation between anatomical sites: the proportion of potential CT/NG missed if single anatomical site screening was performed

We analyzed the prevalence of CT/NG infections in the remaining 2 sites to that of negative result site to determine the potential CT/NG infections that would be missed and left untreated if they were tested at single anatomical site. Among 1460 participants who tested negative for pharyngeal CT/NG infections, 16.9% had rectal infection and 8.8% had urethral infection (22.7% had either rectal or urethral infection). HIV-positive MSM had significantly higher prevalence of both rectal infection (34.1% vs 13.0%, p<0.001) and urethral infection (13.6% vs 7.8%, p=0.002) compared to MSM who were HIV-negative **(Table 2)**. Among 1295 participants who tested negative for rectal CT/NG infections, 6.3% had pharyngeal infection and 7.4% had urethral infection (12.8% had either pharyngeal or urethral infection). HIV-positive MSM had significantly higher prevalence of either pharyngeal or urethral infection compared to HIV-negative MSM (18.8% vs 11.8%, p=0.01). Among 1455 participants who tested negative for urethral CT/NG infections, 8.5% had pharyngeal infection and 17.6% had rectal infection

(22.4% had either pharyngeal or rectal infection). HIV-positive MSM had significantly higher prevalence of both pharyngeal infection (11.6% vs 7.7%, p=0.049) and rectal infection (33.7% vs 14.1%, p<0.001) compared to HIV-negative MSM.

In multivariate analysis, among those who tested negative at pharyngeal site, HIV-positive status (adjusted odd ratio [aOR] 2.9; 95%CI 2.1-4.1, p<0.001), age ≤25 years old (aOR 1.7; 95% CI 1.2-2.3, p=0.003), refusal to identify the number of sexual partners (aOR 1.8; 95% CI 1.1-2.9, p=0.02), and had group sex in the past 6 months (aOR 1.9; 95% CI 1.3-3.0, p=0.002) were associated with CT/NG infections at rectal site; and HIV-positive status (aOR 1.9; 95% CI 1.2-3.1, p=0.01), enrolment in Bangkok (aOR 1.7; 95% CI 1.1-2.7, p=0.01), had unprotected sex (aOR 2.0; 95% CI 1.1-3.9, p=0.04), and had any STIs in the past 6 months (aOR 2.3; 95% CI 1.2-4.4, p=0.01) were associated with CT/NG infections at urethral site **(Table 3)**. Among those who tested negative for rectal CT/NG infections, HIV-positive status (aOR 1.9; 95%CI 1.1-3.5, p=0.04) and enrolment in Bangkok (aOR 1.8; 95%CI 1.1-3.0, p=0.02) were associated with urethral CT/NG infections. Among participants who tested negative for urethral CT/NG infections, had group sex in the past 6 months was associated with pharyngeal CT/NG infections (aOR 2.0; 95% CI 1.2-3.4, p=0.01); and HIV-positive status (aOR 3.0; 95%CI 2.1-4.1, p<0.001), age ≤25 years (aOR 1.5; 95%CI 1.1-2.1, p=0.01), single status (aOR 1.7; 95% CI 1.2-2.5, p=0.003), refusal to identify the number of sexual partners (aOR 1.6; 95% CI 1.1-2. 6, p=0.01), and had group sex in the past 6 months (aOR 1.9; 95%CI 1.3-2.8, p=0.002) were associated with rectal CT/NG infections.

Figure 1 details the distribution of all 481 participants with CT/NG infections by anatomical site. If only pharyngeal, rectal, or urethral screening had been conducted, 331

(68.8%), 166 (34.5%), 326 (67.8%) of 481 total CT/NG infections in the study would have been missed, respectively.

Relationship between anatomical sites: the pattern of single and multiple anatomic sites of CT/NG infections.

Of 150 participants who had pharyngeal CT/NG, 46.7% were isolated to pharyngeal site, while 53.3% had additional infection in rectal and/or urethral sites. Among 315 participants who had rectal CT/NG, 64.1% were isolated to rectal site, while 35.9% had additional infection in pharyngeal and/or urethral site. And among 155 participants who tested positive for urethral CT/NG, 54.8% were isolated to urethral site, while 45.2% had additional infection in pharyngeal and/or rectal sites **(Figure 1)**.

Discussion

We demonstrated correlations between CT/NG infections identified in different anatomical sites and showed that 13-23% of Thai MSM would miss having CT/NG infections diagnosed if the test was done in single anatomical site. Among MSM who were newly diagnosed with HIV infection, the proportion who would miss CT/NG diagnoses increased to 19-41% **(Table 2)**. HIV-positive status was associated with non-rectal CT/NG infections among MSM who tested negative at the rectal site **(Table 3)**. Up to 35-69% of overall CT/NG infection in the study can be missed if the screening test was done in single anatomical site **(Figure 1)**.

CT and NG infections are common among sexually active Thai MSM. The overall prevalence in our cohort was 20.6% for CT infection and 14.5% for NG infection at any sites, both are comparable to the historical Thai Facility-based Test and Treat cohort (21.4% and

12.4%, respectively) as well as the report from the CDC among US MSM.[18 19] The prevalence of both rectal CT and NG infections in our study were considerably higher than previously reported in the US and the Netherlands,[1 20] possibly due to our protocol's specific criteria of enrolling sexually active MSM and analyzing the subset of MSM who self-reported sexual contact in all 3 anatomical sites, and the fact that we do not have routine screening which could cause higher prevalence than other settings with more routine screening.

In contrast to calculating the proportion of individuals in a population with missed CT/NG infections, prior studies calculated the proportion of potential missed diagnoses to the overall number of infections. Among the first large study to report the proportion of infections missed if only single anatomical site screening was performed was the 2003 study among MSM in San Francisco, which showed that 90% of rectal CT and 78% of rectal NG would be missed if only urethral screening was performed.[1] A review of more recent studies reported a range of 68-84% of extra-genital NG infections and 64-76% of extra-genital CT infections among MSM would have been missed by urethral screening.[20-23] Our findings that 69%, 35%, 68% of CT/NG infections would have been missed, respectively, if only pharyngeal, rectal, or urethral screening was performed is in line with comparable to a large study among asymptomatic MSM in the U.S.[22]

Among participants tested negative, we found a range of 13-23% of MSM with "false negative" result if the screening test was done at one anatomical site, with an increase up to 19-41% among HIV-positive participants. Ideally, screening in all 3 anatomical sites should be done among MSM. Our findings suggest that if only single anatomical site screening for CT/NG infections is available, rectal site screening results in the least percentage of MSM with missed CT/NG infections. If rectal was to be the only site for CT/NG screening, it would miss 35% of

all CT/NG infections compared to approximately 70% by screening only pharyngeal or urethral sites. Multiple logistic regression showed that HIV-positive status was associated with non-rectal CT/NG infections among those tested negative at the rectal sites. Therefore, if resources only allow screening for all anatomical sites in selected sub-populations, HIV-positive MSM should be prioritized.

Although there are some differences in characteristics of CT/NG infections in each anatomical site,[24] once diagnosed, the site of infection may not be of great concern because the recommended treatment for CT/NG at either site is similar.[25-27] Therefore, what is most important is the ability to detect CT and/or NG infections regardless of the anatomical site. Due to their asymptomatic nature,[1] many patients may not be aware of the importance of the infections and do not seek medical advice.[16] Healthcare provider can take the lead in encouraging sexually active MSM to screen for CT/NG infections in all sites regardless of their self-reported contact routs as the first step towards detecting and providing timely screening and treatment to prevent transmission in the community.

Certain limitations of this study need to be considered. First, we assessed sexual behaviors using a self-administered paper questionnaire and risk behaviors were captured within the past 6 months. While self-administered questionnaires help minimize participants' shyness and reluctance to provide information, actual risk behaviors may be underreported. Because CT and NG infections have a long duration of infection, capturing risk behaviors within the past 6 months was beneficial in assessing risk behaviors since the potential contact date of the infections. However, the relatively long recall period may lead to recall bias. Second, because CT/NG screening in our study were based on self-reported site of exposure rather than universal screening at all sites, we were unable to compare the performance between a history-based and

universal approach. Furthermore, by limiting our analysis to MSM who self-reported sexual contact in all 3 anatomical sites, the findings may biased towards those with higher risks which may have led to an over-estimation of prevalence of CT/NG infections in our sample. Finally, we may have missed extra-genitalia samples from a modest number of participants (248 MSM [13.4% of total MSM enrolled]) due to social desirability bias regarding questions about the site(s) of sexual contact.

This study found a high proportion of CT/NG infections are missed in sexually active MSM if single anatomical site screening is performed, especially among HIV-positive MSM. We recommend that all anatomical sites should be screened for all MSM. However, if this is not feasible, rectal-only screening would ensure the greatest proportion of CT/NG would be diagnosed. Our results also suggest that HIV-positive MSM should be prioritized for all-site screening. Studies on new technologies that allow pooled samples from different anatomical sites and at an affordable price are urgently needed for routine asymptomatic CT/NG screening among MSM in resource-limited settings.

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Conflict of interest

The authors declared no conflict of interest relevant to this work.

Authors' contributions

AH interpreted the data, drafted the manuscript, and performed statistical analysis. TS and JJ coordinated the study and oversaw data management. DT gave advised on statistical analysis and performed statistical analysis. TS, JJ, SM, RV, and NP designed and conducted the study. NP advised on the analysis plan. NP and PP led the study. All authors critically reviewed and approved the final draft of manuscript.

Data sharing statement

Data are available. Please contact corresponding author.

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Table 1. Demographic of 1610 men who have sex with men included in the analysis

Characteristics	Overall (n=1610)		HIV-positive (n=303)		HIV-negative (n=1307)		p-value
	n	%	n	%	n	%	
Median age (IQR) years	24.1 (20.8-30.0)		24.1 (21.0-28.7)		24.1 (20.8-30.5)		0.48
Site							<0.001
Bangkok	676	42.0	164	54.1	512	39.2	
Chiang Mai	541	33.6	61	20.1	480	36.7	
Hat Yai	152	9.4	17	5.6	135	10.3	
Pattaya city	241	15.0	61	20.1	180	13.8	
Marital status							0.19
Single	1158/1598	72.5	218/301	72.4	940/1297	72.5	
Living together with male partner	381/1598	23.8	77/301	25.6	304/1297	23.4	
Married to a woman	59/1598	3.7	6/301	2.0	53/1297	4.1	
Highest education							0.46
Lower than high school	325/1594	20.4	68/299	22.7	257/1295	19.9	
High school	638/1594	40.0	120/299	40.1	518/1295	40.0	
Higher than high school	631/1594	39.6	111/299	27.1	520/1295	40.2	
Main occupation							0.06
Unemployed	97/1598	6.1	25/300	8.3	72/1298	5.6	
Student	486/1598	30.4	76/300	25.3	410/1298	31.6	
Sex worker	707/1598	44.2	133/300	44.3	574/1298	44.2	
Employed, other than sex worker	308/1598	19.3	66/300	22.0	242/1298	18.6	
Income >10,000 THB ($320) per month	672/1383	48.6	124/264	47.0	548/1119	49.0	0.56
Median age (IQR) of first sexual intercourse	17 (15-19)		17 (15-19)		17 (15-19)		0.22
Male circumcision	186/1391	13.4	25/240	10.4	161/1151	14.0	0.14
Number of sexual partners in the past 6 months							0.34
No sexual partner	30/1603	1.9	7/300	2.3	23/1303	1.8	
Single partner	308/1603	19.2	59/300	19.7	249/1303	19.1	
Multiple partners	870/1603	54.3	150/300	50.0	720/1303	55.3	
Refuse to answer	395/1603	24.6	84/300	28.0	311/1303	23.9	
Self-perceived risk for HIV transmission in the past 6 months							<0.001
No risk	161/1589	10.1	16/296	5.4	145/1293	11.2	
Mild	590/1589	37.1	85/296	28.7	505/1293	39.1	
Moderate	550/1589	34.6	114/296	38.5	436/1293	33.7	
High	288/1589	18.1	81/296	27.4	207/1293	16.0	
Unprotected sex in the past 6 months	1261/1586	79.5	252/298	84.6	1009/1288	78.3	0.02
Illicit drug used in the past 6 months	599/1530	39.2	100/278	36.0	499/1252	39.9	0.23
Self-reported STIs in the past 6 months							<0.001
No	977/1546	63.2	146/291	50.2	831/1255	66.2	
Yes	106/1546	6.9	21/291	7.2	85/1255	6.8	
Not sure	463/1546	29.9	124/291	42.6	339/1255	27.0	
Group sex in the past 6 months	207/1520	13.6	47/286	16.4	160/1234	13.0	0.12
Overall CT infections	349	21.7	111	36.6	238	18.2	<0.001
Pharyngeal CT	48	3.0	17	5.6	31	2.4	0.003
Rectal CT	242	15.0	88	29.0	154	11.8	<0.001
Urethral CT	112	7.0	29	9.6	83	6.4	0.04
Overall NG infections	249	15.5	91	30.0	158	12.1	<0.001
Pharyngeal NG	110	6.8	25	8.3	85	6.5	0.28
Rectal NG	150	9.3	68	22.4	82	6.3	<0.001
Urethral NG	56	3.5	22	7.3	34	2.6	<0.001

Abbreviations: CT, *Chlamydia trachomatis*; NG, *Neisseria gonorrhoeae*; STIs, Sexually transmitted infections

Table 2. Prevalence of CT/NG infections at the remaining 2 sites among men who have sex with men who had negative result at pharyngeal, rectal, and urethral site, respectively.

Negative site	Positive site	Prevalence (95%CI)			p-value
		Overall	HIV-positive	HIV-negative	
Pharyngeal (n=1460)	Rectal (n=246)	16.9 (15.0-18.9)	34.1 (28.4-40.2)	13.0 (11.2-15.1)	<0.001
	Urethral (n=129)	8.8 (7.4-10.4)	13.6 (9.7-18.4)	7.8 (6.3-9.4)	0.002
	Rectal or urethral (n=331)	22.7 (20.6-24.9)	41.3 (35.3-47.5)	18.6 (16.4-20.9)	<0.001
Rectal (n=1295)	Pharyngeal (n=81)	6.3 (5.0-7.7)	8.9 (5.3-13.9)	5.8 (4.5-7.3)	0.10
	Urethral (n=96)	7.4 (6.1-9.0)	10.5 (6.5-15.7)	6.9 (5.5-8.5)	0.08
	Pharyngeal or urethral (n=166)	12.8 (11.1-14.8)	18.8 (13.6-25.1)	11.8 (9.9-13.8)	0.01
Urethral (n=1455)	Pharyngeal (n=124)	8.5 (7.1-10.2)	11.6 (8.0-16.2)	7.7 (6.4-9.5)	0.049
	Rectal (n=256)	17.6 (15.7-19.7)	33.7 (28.0-39.8)	14.1 (12.2-16.2)	<0.001
	Pharyngeal or rectal (n=326)	22.4 (20.3-24.6)	40.0 (33.9-46.2)	18.6 (16.5-21.0)	<0.001

Abbreviations: CT, *Chlamydia trachomatis*; NG, *Neisseria gonorrhoeae*

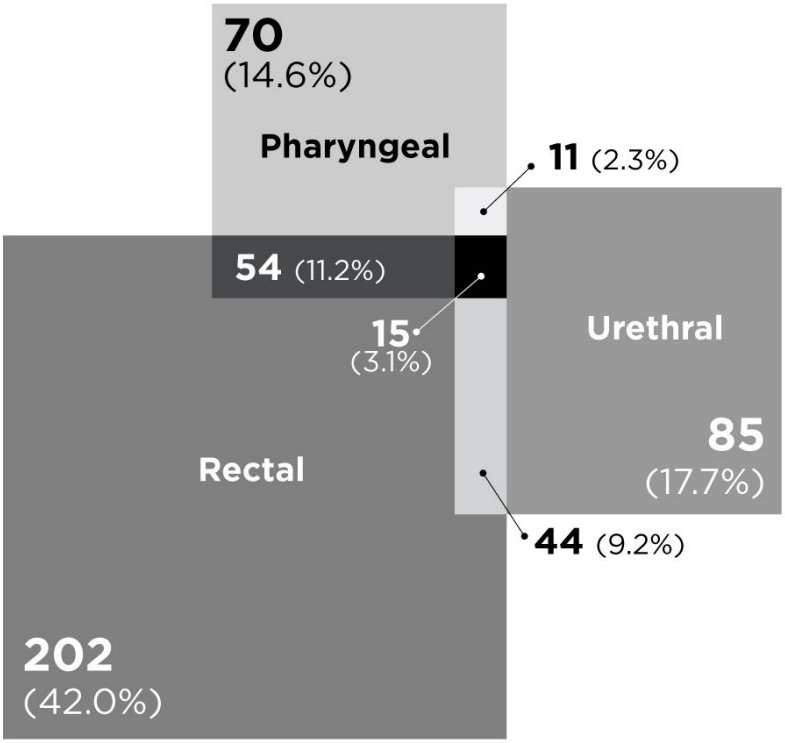
Table 3. Factors associated with CT/NG infections at the remaining 2 sites among men who have sex with men who tested negative at pharyngeal, rectal, and urethral sites, respectively

Variable	Negative at the pharyngeal site (n=1460)			Negative at the rectal site (n=1295)			Negative at the urethral site (n=1455)		
Site of infection		Rectal	Urethral		Pharyngeal	Urethral		Pharyngeal	Rectal
Number (%) of infected participants		246 (16.9%)	129 (8.8%)		81 (6.3%)	96 (7.4%)		124 (8.5%)	256 (17.6%)
Covariates	n (%)	aOR (95%CI)	aOR (95%CI)	n (%)	aOR (95%CI)	aOR (95%CI)	n (%)	aOR (95%CI)	aOR (95%CI)
HIV-positive	264 (18.1)	2.9 (2.1-4.1)*	1.9 (1.2-3.1)*	191 (14.8)	1.6 (0.9-2.8)	1.9 (1.1-3.5)*	258 (17.7)	1.4 (0.9-2.2)	3.0 (2.1-4.1)*
Age ≤25 years	801 (54.9)	1.7 (1.2-2.3)*		686 (53.0)			801 (55.1)		1.5 (1.1-2.1)*
Site: Bangkok	610 (41.8)		1.7 (1.1-2.7)*	538 (41.5)		1.8 (1.1-3.0)*	597 (41.0)		
Marital status: Single	1048 (72.3)	1.2 (0.9-1.8)		910 (70.8)		1.5 (0.9-2.7)	1047 (72.5)		1.7 (1.2-2.5)*
Education: High school or lower	870 (60.3)	1.2 (0.8-1.6)		756 (58.8)			862 (59.8)		1.3 (0.0-1.7)
Self-perceived risk for HIV transmission in the past 6 months									
No risk/Mild	690 (48.0)	Ref		619 (48.4)	Ref		688 (47.8)	Ref	
Moderate	493 (34.3)	0.9 (0.7-1.4)		447 (35.0)	1.6 (0.9-2.7)		496 (34.5)	1.2 (0.7-2.1)	0.9 (0.7-1.3)
High	256 (17.8)	1.4 (0.9-2.2)		213 (16.7)	1.5 (0.8-2.9)		254 (17.7)	1.7 (0.9-3.0)	1.2 (0.8-1.8)
Number of sexual partners in the past 6 months									
No or single partner	314 (21.6)	Ref		127 (21.9)	Ref		316 (21.8)	Ref	
Multiple partners	792 (54.5)	1.4 (0.9-2.2)	1.2 (0.7-2.3)	700 (54.3)	0.9 (0.5-1.8)	1.2 (0.6-2.4)	781 (53.9)		1.3 (0.9-2.0)
Refuse to answer	347 (23.9)	1.8 (1.1-2.9)*	1.5 (0.8-3.0)	301 (23.4)	1.8 (0.9-3.5)	1.4 (0.6-3.0)	352 (24.3)		1.6 (1.1-2.6)*
Male circumcision	170 (13.5)		0.7 (0.3-1.4)	156 (13.7)		0.7 (0.3-1.5)	173 (13.8)		
Unprotected sex in the past 6 months	1138 (79.1)	1.3 (0.8-1.9)	2.0 (1.1-3.9)*	1003 (78.7)		1.6 (0.8-3.2)	1125 (78.5)	1.4 (0.8-2.4)	
Illicit drug used in the past 6 months	552 (39.7)		1.4 (0.9-2.1)	483 (39.0)		1.4 (0.8-2.3)	524 (37.8)	0.6 (0.4-1.0)	
Had any symptoms or being diagnosed with any STIs in the past 6 months									
No	893 (63.7)	Ref		806 (64.6)	Ref		904 (64.4)	Ref	
Yes	94 (6.7)	1.1 (0.6-2.0)	2.3 (1.2-4.4)*	81 (6.5)		1.6 (0.7-3.5)	85 (6.1)		
Not sure	414 (29.6)	0.9 (0.7-1.3)	1.1 (0.6-1.7)	360 (28.9)		0.9 (0.5-1.6)	415 (29.6)		
Had group sex in the past 6 months	178 (12.9)	1.9 (1.3-3.0)*	1.3 (0.7-2.2)	146 (12.0)	1.6 (0.8-3.1)	0.9 (0.5-1.9)	177 (12.9)	2.0 (1.2-3.4)*	1.9 (1.3-2.8)*

Abbreviations: CT, *Chlamydia trachomatis*; NG, *Neisseria gonorrhoeae*; STIs, Sexually transmitted infections

Multivariate logistic regression is based on covariates associated with outcomes in univariate regression with p-value of <0.2

* indicates p-value < 0.05



Type(s) of infection	No. of participants (%) with CT/NG infections		
	Pharyngeal (n = 150)	Rectal (n = 315)	Urethral (n = 155)
Isolated site	70 (46.7)	202 (64.1)	85 (54.8)
Multiple sites			
Pharyngeal and rectal	54 (36)	54 (17.1)	-
Pharyngeal and urethral	11 (7.3)	-	11 (7.1)
Rectal and urethral	-	44 (14.0)	44 (28.4)
All 3 sites	15 (10)	15 (4.8)	15 (9.7)

Abbreviations: CT, *Chlamydia trachomatis*; NG, *Neisseria gonorrhoeae*

Figure 1. Distribution of CT/NG infections by anatomical site.

Supplementary File 1. Demographic of all men who have sex with men enrolled in the Community-based Test and Treat Cohort

Characteristics	Overall (n=1858)		MSM who were included in the analysis (completed 3 sites CT/NG screening) (n=1610)		MSM who were excluded from the analysis (did not complete 3 sites CT/NG screening) (n=248)		p-value
	n	%	n	%	n	%	
Median age (IQR) years	24.2 (20.9-30.2)		24.1 (20.8-30.0)		24.4 (21.4-31.9)		0.09
Site							<0.001
Bangkok	824	44.4	676	42.0	148	59.7	
Chiang Mai	564	30.4	541	33.6	23	9.3	
Hat Yai	216	11.6	152	9.4	64	25.8	
Pattaya city	254	13.7	241	15.0	13	5.2	
Marital status							<0.001
Single	1319/1845	71.5	1158/1598	72.5	161/247	65.2	
Living together with male partner	434/1845	23.5	381/1598	23.8	53/247	21.5	
Married to a woman	92/1845	5.0	59/1598	3.7	33/247	13.4	
Highest education							0.003
Lower than high school	392/1838	21.3	325/1594	20.4	67/244	27.5	
High school	710/1838	38.6	638/1594	40.0	72/244	29.5	
Higher than high school	736/1838	40.1	631/1594	39.6	105/244	43.0	
Main occupation							0.13
Unemployed	116/1843	6,3	97/1598	6.1	19/245	7.8	
Student	547/1843	29.7	486/1598	30.4	61/245	24.9	
Sex worker	367/1843	19.9	707/1598	44.2	106/245	43.3	
Employed, other than sex worker	813/1843	44.1	308/1598	19.3	59/245	24.1	
Income >10,000 THB ($320) per month	792/1594	49.7	672/1383	48.6	120/211	56.9	0.03
Median age (IQR) of first sexual intercourse	17 (15-19)		17 (15-19)		17 (15-19)		0.46
Male circumcision	213/1603	13.3	186/1391	13.4	27/212	12.7	0.80
Number of sexual partners in the past 6 months							0.27
No sexual partner	39/1851	2.1	30/1603	1.9	9	3.6	
Single partner	353/1851	19.1	308/1603	19.2	45	18.2	
Multiple partners	1009/1851	54.5	870/1603	54.3	139	56.1	
Refuse to answer	450/1851	24.3	395/1603	24.6	55	22.2	
Self-perceived risk for HIV transmission in the past 6 months							0.02
No risk	197/1835	10.7	161/1589	10.1	36/246	14.6	
Mild	693/1835	37.8	590/1589	37.1	103/246	41.9	
Moderate	614/1835	33.5	550/1589	34.6	64/246	26.0	
High	331/1835	18.0	288/1589	18.1	43/246	17.5	
Unprotected sex in the past 6 months	1432/1831	78.2	1261/1586	79.5	171/245	69.8	0.001
Illicit drug used in the past 6 months	685/1765	38.8	599/1530	39.2	86/235	36.6	0.45
Self-reported STIs in the past 6 months							0.007
No	1157/1788	64.7	977/1546	63.2	180/242	74.4	
Yes	119/1788	6.7	106/1546	6.9	13/242	5.4	
Not sure	512/1788	28.6	463/1546	29.9	49/242	20.2	
Group sex in the past 6 months	217/1747	12.4	207/1520	13.6	10/227	4.4	<0.001
Overall CT infections	379/1842	20.6	349	21.7	30/232	12.9	0.002
Pharyngeal CT	54/1840	2.9	48	3.0	6/230	2.6	0.75
Rectal CT	245/1617	15.2	242	15.0	3/7	42.9	0.04
Urethral CT	133/1833	7.3	112	7.0	21/223	9.4	0.18
Overall NG infections	267/1842	14.5	249	15.5	18/232	7.8	0.002
Pharyngeal NG	120/1840	6.5	110	6.8	10/230	4.4	0.15
Rectal NG	151/1617	9.3	150	9.3	1/7	14.3	0.65
Urethral NG	64/1833	3.5	56	3.5	8/223	3.6	0.93

Abbreviations: CT, *Chlamydia trachomatis*; NG, *Neisseria gonorrhoeae*; STIs, sexually transmitted infections

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
		Other information	
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

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

BMJ Open

Correlations of chlamydia and gonorrhea between pharyngeal, rectal, and urethral sites among Thai men who have sex with men: a multicentre community-led test and treat cohort in Thailand

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TITLE PAGE

Title: Correlations of chlamydia and gonorrhea between pharyngeal, rectal, and urethral sites among Thai men who have sex with men: a multicentre community-led test and treat cohort in Thailand

Running head: Anatomical site correlations of CT/NG infections among MSM

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ABSTRACT (298/300)

Objective: Routine screening for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) infections in sexually exposed anatomical sites may be challenging in resource-limited settings. The objective of this study was to determine the proportion of missed CT/NG diagnoses if a single anatomical site screening was performed among men who have sex with men (MSM) by examining the pattern of anatomical sites of CT/NG infections.

Methods: Thai MSM were enrolled to the community-led test and treat cohort. Screening for CT/NG infections was performed from pharyngeal swab, rectal swab, and urine using nucleic acid amplification testing. The correlations of CT/NG among the three anatomical sites were analyzed.

Results: Among 1610 MSM included in the analysis, 21.7% had CT and 15.5% had NG infection at any anatomical site. Among those tested negative for CT or NG infection at either pharyngeal, rectal, or urethral site, 8-19% had CT infection and 7-12% had NG infection at the remaining two sites. Of the total 349 CT infections, 85.9%, 30.6%, and 67.8% would have been missed if only pharyngeal, rectal, or urethral screening was performed, respectively. Of the total 249 NG infection, 55.7%, 39.6%, and 77.4% would have been missed if only pharyngeal, rectal, or urethral screening was performed, respectively. The majority of each anatomical site of CT/NG infection were isolated to their respective site, with rectal site having the highest proportion of isolation: 78.9% of rectal CT and 62.7% of rectal NG infection.

Conclusions: A high proportion of CT/NG infections would be missed if single anatomical site screening was performed among MSM. All-site screening is highly recommended, but if not feasible, rectal screening provides the highest yield of CT/NG diagnoses. Effort in lowering the

cost of the CT/NG screening test or developing affordable molecular technologies for CT/NG detection is needed for MSM in resource-limited settings.

Strengths and limitations of this study

- The study includes a large number of sexually active MSM who completed CT/GC screening in all three anatomical sites based on their self-reported sexually exposed contact routes.
- Correlations of CT/NG infections between pharyngeal, rectal, and urethral sites among sexually active MSM were identified, and showed the proportion of missed diagnoses if single anatomical site screening was performed.
- Because CT/NG screening in our study were based on self-reported sexually exposed contact routes, we were unable to compare the performance between a history-based and universal approach.
- Extra-genitalia samples from a modest number of participants may have been missed due to social desirability bias regarding questions about the site(s) of sexual contact.

MAIN TEXT

Introduction

Chlamydia trachomatis (CT) and *Neisseria gonorrhoeae* (NG) infections are among the most common bacterial sexually transmitted infections (STIs) and disproportionately affect men who have sex with men (MSM) worldwide.[1] Two large studies conducted in Thailand between 2006 and 2010 showed that MSM had approximately 30% higher prevalence of CT infection and up to 5 times higher prevalence of NG infection compared to men who have sex exclusively with women.[2 3]

CT/NG infections are associated with acquiring and transmitting HIV infection.[4] In particular, rectal CT/NG infection is strongly associated with an increased risk of HIV acquisition among MSM.[5 6] And while the impact of pharyngeal infection towards HIV acquisition is less understood, it is highly prevalent and may, therefore, serve as an important for infection at genital sites.[7-9] Since CT/NG infections are often asymptomatic,[10] the lack of routine screening may result in a missed opportunity to diagnosis these curable STIs.

The diagnosis of CT/NG infections, both at genital and extra-genital sites, can be made using nucleic acid amplification tests (NAATs). Many studies have shown superior sensitivity and specificity of NAATs in detecting extra-genital CT/NG infection compared to culture.[11-14] The findings prompted the US Center for Disease Control and Prevention (CDC) to recommend the use of NAATs for pharyngeal and rectal CT/NG screening,[15] although they have not been cleared by the US Food and Drug Administration.

Frequency of testing and anatomical sites to be tested are the two factors to consider in asymptomatic CT/NG screening. The Centers for Disease Control and Prevention STD treatment

guideline recommends that all sexually active MSM should be screened at least annually at sites of contact regardless of condom use.[15] More frequent screening is advised if the individuals are at increased risk. Conversely, the Australian STI management guideline recommends screening at all sites regardless of sexually exposed contact routes.[16] However, many barriers prevent the implementation of these recommendations in clinical practice. For the clients, these barriers may include the cost of tests, underestimating the risk of asymptomatic infections, and concern of being stigmatized.[17 18] Healthcare providers also often lack knowledge on the importance of STI screening at appropriate anatomical sites,[17] which may also be the case in Thailand where there are currently no consensus recommendations for CT/NG screening.

Our primary objective was to determine the proportion of missed CT/NG diagnoses if a single anatomical site screening was performed among men who have sex with men (MSM) by examining the pattern of anatomical sites of CT/NG infections. Other objectives were to determine the prevalence of CT/NG infections among MSM enrolled in the community-led test and treat cohort and to examined the prevalence of CT/NG infections in the remaining two anatomical sites if one site was negative to evaluate the proportion of missed diagnoses per individual. The findings from our study will be crucial in guiding the recommendations for CT/NG screening among MSM, both in HIV treatment and prevention programs, in resource-limited settings.

Methods

Enrollment of participants

The present study used data from MSM participants enrolled in the community-led test and treat cohort between October 2015 and October 2016. The community-led test and treat cohort aimed to evaluate the feasibility of empowering lay providers who are members of MSM and transgender women (TGW) communities to provide HIV-related services, increasing uptake of HIV testing and treatment services among MSM and TGW in Thailand.

Eligible criteria and study procedures for the community-led test and treat cohort have been reported in detail elsewhere.[19] In brief, adults Thai MSM and TGW with a history of at least one unprotected anal sexual intercourse with a man in the past 6 months were enrolled from Service Workers IN Group (SWING) drop-in centers (DICs) in Bangkok and Pattaya city, Rainbow Sky Association of Thailand (RSAT) DICs in Bangkok and Songkhla, Caremat DIC in Chiang Mai, and Sisters DIC in Pattaya city, Thailand for an 18-month follow-up period. Only participants of unknown HIV-status were enrolled, and those with known HIV infection were excluded from enrollment. Screening for CT and NG was performed at enrollment using nucleic acid amplification testing (NAAT, Abbott Real Time CT/NG, Abbott Molecular Inc., Illinois, USA) from pharyngeal swab, rectal swab, and/or urine collection based on the self-report sexually exposed contact routes. Participants who completed both CT and NG screening in all three anatomical sites at baseline were included in this analysis.

The study (NCT03580512) was approved by the institutional review boards of the Faculty of Medicine, Chulalongkorn University (IRB No. 181/57), the Department of Disease Control, Thai Ministry of Public Health (IRB No. 9/57-678), the Provincial Health Offices of

Chonburi (IRB No. 0032.003/658), Songkhla (IRB No. 075/2014), and Chiang Mai (IRB No. 0032.002/35859). All participants gave informed consent.

Statistical Analysis

Statistical analysis was performed using Stata 13 (StataCorp LP, College Station, TX, USA). Demographic, CT/NG and HIV testing results, and sexual risk behaviors were summarized as median (interquartile range [IQR]) and number (percentage) for continuous and categorical variables, respectively. Characteristics between HIV-positive and HIV-negative participants were compared using a chi-square or Fisher's exact test, or Mann-Whitney test as appropriate.

The distribution of anatomical sites of CT/NG infections at baseline was analyzed to determine the proportion (prevalence with 95%CI) of missed CT/NG diagnoses per individual if single anatomical site screening was performed, pattern of anatomical distribution for all CT/NG infections, and pattern of anatomical distribution of CT/NG infections by anatomical site. Statistical significance was defined as p-value of <0.05.

Participant and public involvement

Neither participants nor public were directly involved in the development, design or recruitment of the study.

Results

Participant characteristics

Of 1858 MSM enrolled in the community-led test and treat cohort, a total of 1610 (86.7%) participants completed both CT and NG testing in all three anatomical sites at baseline based on their self-reported sexually exposed contact routes and were included in the analysis. Compared to MSM who did not complete CT/NG testing in all three anatomical sites, MSM who completed CT/NG testing in all three anatomical sites had higher prevalence of CT/NG infections at any anatomical sites (29.9% vs 16.4%, p<0.001) and reported higher sexual risk behaviors **(Supplementary Files 1)**.

At enrollment, the prevalence of CT/NG infections at any anatomical sites was 29.9%: 21.7% for CT infection and 15.5% for NG infection. The most prevalent CT/NG infections by anatomical sites were rectal CT (15.0%), rectal NG (9.3%), and urethral CT (7.0%). HIV-positive participants had significantly higher prevalence of both CT and NG infections in all anatomical sites, except for pharyngeal NG, and were more likely than HIV-negative participants to be enrolled from the Bangkok sites, self-perceived high risk of HIV transmission in the past month, had unprotected sex in the past month, and self-reported or unsure of having STIs in the past month **(Table 1)**.

The proportion of missed CT/NG diagnoses per individual if single anatomical site screening was performed

Among participants who tested negative for CT infection at pharyngeal, rectal, or urethral sites, 19.3%, 7.8%, or 15.8% had CT infection in any of the remaining two sites, respectively **(Table 2)**. HIV-positive MSM had significantly higher prevalence of CT infection in any of the

remaining two sites among those who tested negative for pharyngeal (32.9% vs 16.2%, p<0.001) or urethral CT (29.9% vs 12.7%, p<0.001) compared to HIV-negative MSM. Among those who tested negative for NG infection at pharyngeal, rectal, or urethral site, 9.3%, 6.8%, or 12.4% had NG infection in any of the remaining two sites, respectively **(Table 3)**. HIV-positive MSM had significantly higher prevalence of NG infection in any of the remaining two sites across all anatomical sites tested negative (23.7% vs 6.0%, p<0.001 among those who tested negative for pharyngeal NG; 9.6% vs 6.2%, p=0.045 among those who tested negative for rectal NG; and 24.6% vs 9.7%, p<0.001 among those who tested negative for urethral NG).

Pattern of anatomical distribution for all CT/NG infections

Of the total 349 CT infections in our study, 8.0% were isolated to pharyngeal site, 54.7% to rectal site, and 22.4% to urethral site **(Figure 1)**. On the basis of our data, 85.9%, 30.6%, and 67.8% of the total CT infections in our study would have been missed if only pharyngeal, rectal, or urethral screening was performed, respectively. Of the total 249 NG infections, 25.3%, 37.8%, and 12.5% were isolated to pharyngeal, rectal, and urethral site, respectively **(Figure 2)**. Collectively, 55.7%, 39.6%, and 77.4% of NG infections would have been missed if only pharyngeal, rectal, or urethral screening was performed, respectively.

Pattern of anatomical distribution of CT/NG infections by anatomical site

Rectal site was the most isolated site of CT/NG infection: 191 out of 242 (78.9%) rectal CT infection and 94 out of 150 rectal NG infection were isolated to rectum **(Figure 1 and 2)**. Importantly, the majority of each anatomical site of CT/NG infection were isolated to their respective site: 58.3% and 57.3% for pharyngeal CT and NG infection, respectively; and 69.6% and 55.4% for urethral CT and NG infection, respectively.

Discussion

We examined the pattern of anatomical sites of CT/NG infections and showed that among MSM who tested negative for CT or NG infection at either pharyngeal, rectal, or urethral site, 8-19% had CT infection and 7-12% had NG infection at the remaining two sites. Of the 349 CT infections, 8.0% were isolated to pharyngeal site, 54.7% to rectal site, and 22.4% to urethral site; and 85.9%, 30.6%, and 67.8% of would have been missed if only pharyngeal, rectal, or urethral screening was performed, respectively. Of the 249 NG infections, 25.3%, 37.8%, and 12.5% were isolated to pharyngeal, rectal, and urethral site, respectively; and 55.7%, 39.6%, and 77.4% of NG infections would have been missed if only pharyngeal, rectal, or urethral screening was performed, respectively. The majority of each anatomical site of CT/NG infection were isolated to their respective site, with rectal site having the highest proportion of isolation: 78.9% of rectal CT and 62.7% of rectal NG infection. These data suggest that screening at all self-report sexually exposed contact routes is highly recommended. However, if this is not feasible, screening at rectal site would provide the highest yield of CT/NG diagnoses.

The overall prevalence CT/NG infections at any anatomical sites in our cohort was comparable to the historical Thai Facility-based Test and Treat cohort which enrolled previously-unknown HIV-status Thai adult MSM and TGW with similar risk behaviors in 2012 (21.4% for CT and 12.4% for NG infection).[20] The prevalence of CT/NG infections per each anatomical site in our study was comparable to one of the largest studies tested for pharyngeal, rectal, and urethral CT/NG infections based on their self-reported exposure conducted in San Francisco between 2010 and 2011. Among 3039 MSM enrolled, the prevalence of pharyngeal, rectal, and urethral CT infections were 2.3%, 11.9, and 4.4%, respectively; and 6.5%, 9.7%, and 5.5% for pharyngeal, rectal, and urethral NG infections, respectively.[21]

To the best of our knowledge, our study was among the first to report the proportion of missed CT/NG diagnoses per individual if single anatomical site screening was performed. Supposing that one anatomical site screening was performed, 8-19% of MSM who tested negative for CT infection and 7-12% of those tested negative for NG infection actually had CT and NG infection at the remaining two anatomical sites, respectively. Importantly, the proportion of these potential missed CT/NG diagnoses increased to 11-33% for CT and 10-25% for NG infection among newly-diagnosed HIV-positive MSM. This may be because a higher proportion of unprotected sex and self-reported STIs in the past 6 months among HIV-positive MSM compared with HIV-negative MSM. These results point out the importance of CT/NG screening at all self-report sexually exposed contact routes. However, if resource limit the number of sites screened, rectal site proves to be the site of choice for screening, with less than 10% showed any infection in the remaining two anatomical sites if tested negative.

A study conducted in San Francisco in 2003, in which NAATs were used to test MSM for chlamydia and gonorrhea at all three anatomical sites, was among the first published studies to show that the majority of CT (53%) and NG (64%) infections were at non-urethral sites, and would have been missed if only urethral screening was performed.[10] More recent published data from multisite in US and the Netherlands showed a range of 43-69% of extra-genital CT infection and 46-76% of extra-genital NG infection would have been missed if only urethral screening was performed, which were in line to our findings.[21-24] Data from the San Francisco's STD clinic between 2008 and 2009 showed that if one anatomical site screening was performed, screening only the pharynx would miss 81% of CT infection and 32% of NG infection; and screening only the rectum would miss 23% of CT infection and 52% of NG infection.[25] Regardless of our similar findings that rectal site screening would miss the fewest infections, the

high proportion of potential missed diagnoses if a single anatomical site screening was performed in any of the three sites support the critical need for all-site, at least depending on self-reported sexually exposed contact routes, among MSM.

Although CT/NG infections at each anatomical site possess distinct characteristics, such as clinical manifestations, different duration of infections, and concerns over drug-resistant pathogens,[26 27] the most important thing is the ability to detect and treat those infections regardless of site. Due to their asymptomatic nature, many patients may not be aware of the importance of the infections and do not seek medical advice.[18] Healthcare provider can take the lead in encouraging sexually active MSM to screen for CT/NG infections, at least depending on their self-reported site of exposure, as the first step towards detecting and providing timely screening and treatment towards preventing transmission in the community.

Nonetheless, the cost of the test could be a major obstacle in implementing this recommendation resource-limited settings. For instance, the current cost of NAAT test for CT/NG infections in Thailand is approximately $30 per anatomical site. This is considered expensive since more than half of our MSM participants have monthly income of less than $320. To reduce the cost of test, a strategy to test pooled specimen has been made with promising results.[28] Effort in lowering the cost of the CT/NG screening test or developing affordable molecular technologies for CT/NG detection is needed for MSM in resource-limited settings.

Certain limitations need to be considered. Firstly, sexual behaviors were assessed using a self-administered paper questionnaire. While self-administered questionnaires may improve disclosure of sensitive behaviors, actual risk behaviors may still be underreported. Secondly, risk behaviors were captured within the past 6 months. Because CT and NG infections have a long duration of infection, capturing risk behaviors within the past 6 months was beneficial in

assessing risk behaviors since the potential contact date of the infections. However, the relatively long recall period may lead to recall bias. Thirdly, because CT/NG screening in our study were based on self-reported sexually exposed contact routes rather than universal screening at all sites, we were unable to compare the performance between a history-based and universal approach. Furthermore, by limiting our analysis to MSM who self-reported sexual contact in all three anatomical sites, the findings may biased towards those with higher risks which may have led to an over-estimation of prevalence of CT/NG infections in our sample. Finally, we may have missed extra-genitalia samples from a modest number of participants (248 MSM [13.4% of total MSM enrolled]) due to social desirability bias regarding questions about the site(s) of sexual contact.

Our study found a high proportion of CT/NG infections would have been missed among MSM if single anatomical site screening is performed, especially among HIV-positive MSM. We recommend that all-site screening should be performed among MSM, at least based on self-reported sexually exposed contact routes. However, if this is not feasible, rectal screening provides the highest yield of CT/NG diagnoses. Effort in lowering the cost of the CT/NG screening test or developing affordable molecular technologies for CT/NG detection is needed for MSM in resource-limited settings.

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Conflict of interest

The authors declared no conflict of interest relevant to this work.

Authors' contributions

AH interpreted the data, drafted the manuscript, and performed statistical analysis. TS and JJ coordinated the study and oversaw data management. DT gave advised on statistical analysis and performed statistical analysis. TS, JJ, SM, RV, and NP designed and conducted the study. NP advised on the analysis plan. NP and PP led the study. All authors critically reviewed and approved the final draft of manuscript.

Data sharing statement

Data are available. Please contact corresponding author.

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Table 1. Demographic of 1610 men who have sex with men included in the analysis

Characteristics	Overall (n=1610)		HIV-positive (n=303)		HIV-negative (n=1307)		p-value
	n	%	n	%	n	%	
Median age (IQR) years	24.1 (20.8-30.0)		24.1 (21.0-28.7)		24.1 (20.8-30.5)		0.48
Site							<0.001
Bangkok	676	42.0	164	54.1	512	39.2	
Chiang Mai	541	33.6	61	20.1	480	36.7	
Hat Yai	152	9.4	17	5.6	135	10.3	
Pattaya city	241	15.0	61	20.1	180	13.8	
Marital status							0.19
Single	1158/1598	72.5	218/301	72.4	940/1297	72.5	
Living together with male partner	381/1598	23.8	77/301	25.6	304/1297	23.4	
Married to a woman	59/1598	3.7	6/301	2.0	53/1297	4.1	
Highest education							0.46
Lower than high school	325/1594	20.4	68/299	22.7	257/1295	19.9	
High school	638/1594	40.0	120/299	40.1	518/1295	40.0	
Higher than high school	631/1594	39.6	111/299	27.1	520/1295	40.2	
Main occupation							0.06
Unemployed	97/1598	6.1	25/300	8.3	72/1298	5.6	
Student	486/1598	30.4	76/300	25.3	410/1298	31.6	
Sex worker	707/1598	44.2	133/300	44.3	574/1298	44.2	
Employed, other than sex worker	308/1598	19.3	66/300	22.0	242/1298	18.6	
Income >10,000 THB ($320) per month	672/1383	48.6	124/264	47.0	548/1119	49.0	0.56
Median age (IQR) of first sexual intercourse	17 (15-19)		17 (15-19)		17 (15-19)		0.22
Male circumcision	186/1391	13.4	25/240	10.4	161/1151	14.0	0.14
Number of sexual partners in the past 6 months							0.34
No sexual partner	30/1603	1.9	7/300	2.3	23/1303	1.8	
Single partner	308/1603	19.2	59/300	19.7	249/1303	19.1	
Multiple partners	870/1603	54.3	150/300	50.0	720/1303	55.3	
Refuse to answer	395/1603	24.6	84/300	28.0	311/1303	23.9	
Unprotected sex in the past 6 months	1261/1586	79.5	252/298	84.6	1009/1288	78.3	0.02
Illicit drug used in the past 6 months	599/1530	39.2	100/278	36.0	499/1252	39.9	0.23
Self-reported STIs in the past 6 months							<0.001
No	977/1546	63.2	146/291	50.2	831/1255	66.2	
Yes	106/1546	6.9	21/291	7.2	85/1255	6.8	
Not sure	463/1546	29.9	124/291	42.6	339/1255	27.0	
Group sex in the past 6 months	207/1520	13.6	47/286	16.4	160/1234	13.0	0.12
Overall CT infections	349	21.7	111	36.6	238	18.2	<0.001
Pharyngeal CT	48	3.0	17	5.6	31	2.4	0.003
Rectal CT	242	15.0	88	29.0	154	11.8	<0.001
Urethral CT	112	7.0	29	9.6	83	6.4	0.04
Overall NG infections	249	15.5	91	30.0	158	12.1	<0.001
Pharyngeal NG	110	6.8	25	8.3	85	6.5	0.28
Rectal NG	150	9.3	68	22.4	82	6.3	<0.001
Urethral NG	56	3.5	22	7.3	34	2.6	<0.001

Abbreviations: CT, *Chlamydia trachomatis*; NG, *Neisseria gonorrhoeae*; STIs, Sexually transmitted infections

Table 2. Prevalence of *Chlamydia trachomatis* infections at the remaining two sites among men who have sex with men who had negative result at pharyngeal, rectal, and urethral site, respectively.

Negative site	Positive site	Prevalence (95%CI)			p-value
		Overall	HIV-positive	HIV-negative	
Pharyngeal (n=1562)	Rectal (n=223)	14.3 (12.6-16.1)	27.6 (22.5-33.2)	11.3 (9.6-13.2)	<0.001
	Urethral (n=110)	7.0 (5.8-8.4)	10.1 (6.9-14.2)	6.4 (5.1-7.8)	0.02
	Rectal or urethral (n=301)	19.3 (17.3-21.3)	32.9 (27.5-38.6)	16.2 (14.2-18.4)	<0.001
Rectal (n=1368)	Pharyngeal (n=29)	2.1 (1.4-3.0)	3.7 (1.6-7.2)	1.8 (1.1-2.8)	0.08
	Urethral (n=79)	5.8 (4.6-7.2)	7.0 (4.0-11.2)	5.6 (4.3-7.0)	0.41
	Pharyngeal or urethral (n=107)	7.8 (6.5-9.4)	10.7 (6.9-15.6)	7.3 (5.9-8.9)	0.09
Urethral (n=1498)	Pharyngeal (n=46)	3.1 (2.3-4.1)	6.2 (3.7-9.7)	2.4 (1.6-3.4)	0.001
	Rectal (n=209)	14.0 (12.2-15.8)	27.0 (21.8-32.7)	11.0 (9.3-12.9)	<0.001
	Pharyngeal or rectal (n=237)	15.8 (14.0-17.8)	29.9 (24.6-35.7)	12.7 (10.9-14.7)	<0.001

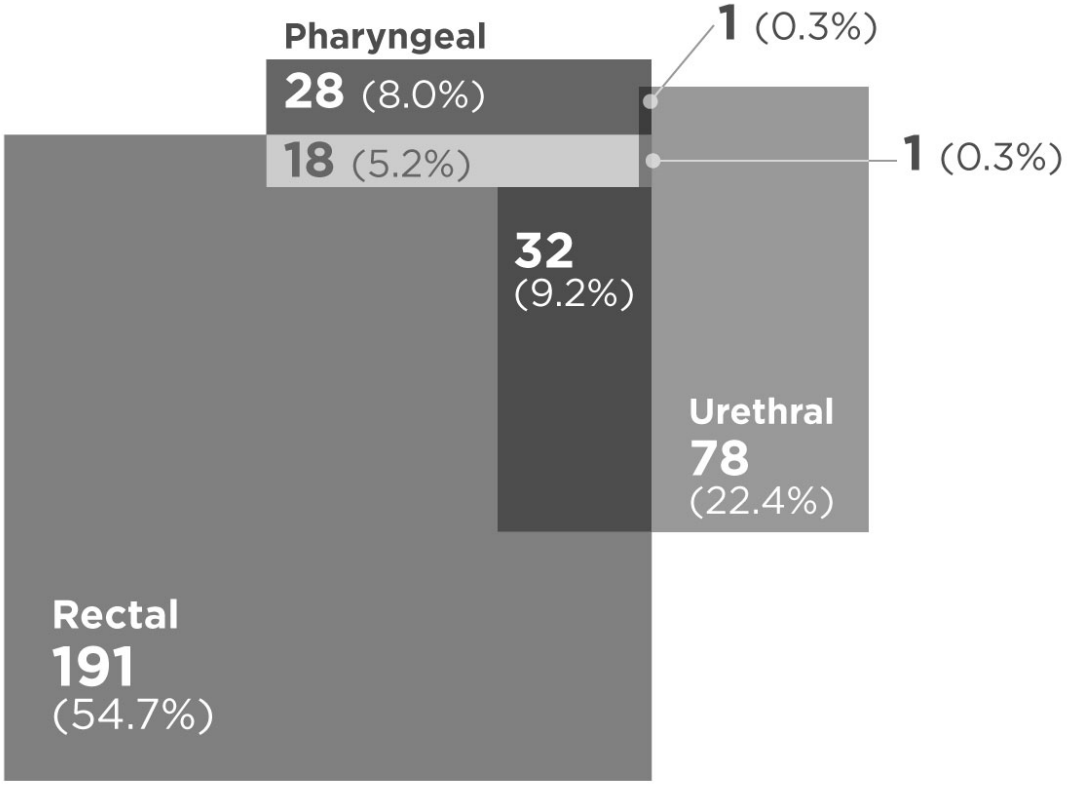
Table 3. Prevalence of *Neisseria gonorrhoeae* infections at the remaining two sites among men who have sex with men who had negative result at pharyngeal, rectal, and urethral site, respectively.

Negative site	Positive site	Prevalence (95%CI)			p-value
		Overall	HIV-positive	HIV-negative	
Pharyngeal (n=1500)	Rectal (n=108)	7.2 (5.9-8.6)	20.5 (15.9-25.7)	4.2 (3.1-5.5)	<0.001
	Urethral (n=45)	3.0 (2.2-4.0)	6.1 (3.6-9.6)	2.3 (1.5-3.3)	0.001
	Rectal or urethral (n=139)	9.3 (7.8-10.8)	23.7 (18.9-29.2)	6.0 (4.7-7.5)	<0.001
Rectal (n=1460)	Pharyngeal (n=68)	4.7 (3.6-5.9)	6.0 (3.3-9.8)	4.4 (3.3-5.7)	0.30
	Urethral (n=36)	2.5 (1.7-3.4)	4.3 (2.1-7.7)	2.1 (1.4-3.1)	0.05
	Pharyngeal or urethral (n=99)	6.8 (5.5-8.2)	9.8 (6.3-14.3)	6.2 (4.9-7.7)	0.045
Urethral (n=1554)	Pharyngeal (n=99)	6.4 (5.2-7.7)	7.1 (4.4-10.8)	6.2 (4.9-7.7)	0.57
	Rectal (n=130)	8.4 (7.0-9.9)	19.9 (15.4-25.1)	5.8 (4.6-7.2)	<0.001
	Pharyngeal or rectal (n=193)	12.4 (10.8-14.2)	24.6 (19.6-30.0)	9.7 (8.2-11.5)	<0.001

FIGURE LEGENDS

Figure 1. Distribution of CT infections (n=349) by anatomical site.

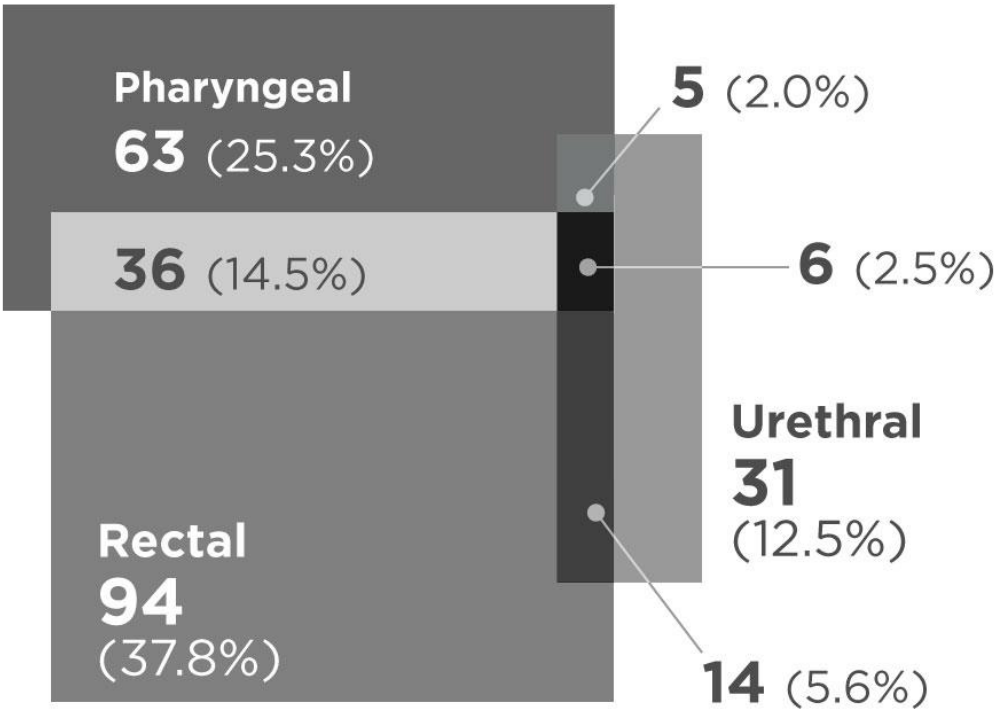
Figure 2. Distribution of NG infections (n=249) by anatomical site.



	No. of participants (%) with CT infections		
Type(s) of infection	Pharyngeal (n = 48)	Rectal (n = 242)	Urethral (n = 112)
Isolated site	28 (58.3)	191 (78.9)	78 (69.6)
Multiple sites			
Pharyngeal and rectal	18 (37.5)	18 (7.4)	-
Pharyngeal and urethral	1 (2.1)	-	1 (0.9)
Rectal and urethral	-	32 (13.2)	32 (28.6)
All 3 sites	1 (2.3)	1 (0.4)	1 (0.9)

Abbreviations: CT, *Chlamydia trachomatis*

Figure 1. Distribution of CT infections (n=349) by anatomical site.



Type(s) of infection	No. of participants (%) with NG infections		
	Pharyngeal (n = 110)	Rectal (n = 150)	Urethral (n = 56)
Isolated site	63 (57.3)	94 (62.7)	31 (55.4)
Multiple sites			
Pharyngeal and rectal	36 (32.7)	36 (24.0)	-
Pharyngeal and urethral	5 (4.6)	-	5 (8.9)
Rectal and urethral	-	14 (9.3)	14 (25.0)
All 3 sites	6 (5.7)	6 (4.2)	6 (11.5)

Abbreviations: NG, *Neisseria gonorrhoeae*

Figure 2. Distribution of NG infections (n=249) by anatomical site.

Supplementary File 1. Demographic of all men who have sex with men enrolled in the community-based test and treat cohort

Characteristics	Overall (n=1858)		MSM who were included in the analysis (completed 3 sites CT/NG screening) (n=1610)		MSM who were excluded from the analysis (did not complete 3 sites CT/NG screening) (n=248)		p-value
	n	%	n	%	n	%	
Median age (IQR) years	24.2 (20.9-30.2)		24.1 (20.8-30.0)		24.4 (21.4-31.9)		0.09
Site							<0.001
Bangkok	824	44.4	676	42.0	148	59.7	
Chiang Mai	564	30.4	541	33.6	23	9.3	
Hat Yai	216	11.6	152	9.4	64	25.8	
Pattaya city	254	13.7	241	15.0	13	5.2	
Marital status							<0.001
Single	1319/1845	71.5	1158/1598	72.5	161/247	65.2	
Living together with male partner	434/1845	23.5	381/1598	23.8	53/247	21.5	
Married to a woman	92/1845	5.0	59/1598	3.7	33/247	13.4	
Highest education							0.003
Lower than high school	392/1838	21.3	325/1594	20.4	67/244	27.5	
High school	710/1838	38.6	638/1594	40.0	72/244	29.5	
Higher than high school	736/1838	40.1	631/1594	39.6	105/244	43.0	
Main occupation							0.13
Unemployed	116/1843	6,3	97/1598	6.1	19/245	7.8	
Student	547/1843	29.7	486/1598	30.4	61/245	24.9	
Sex worker	367/1843	19.9	707/1598	44.2	106/245	43.3	
Employed, other than sex worker	813/1843	44.1	308/1598	19.3	59/245	24.1	
Income >10,000 THB ($320) per month	792/1594	49.7	672/1383	48.6	120/211	56.9	0.03
Median age (IQR) of first sexual intercourse	17 (15-19)		17 (15-19)		17 (15-19)		0.46
Male circumcision	213/1603	13.3	186/1391	13.4	27/212	12.7	0.80
Number of sexual partners in the past 6 months							0.27
No sexual partner	39/1851	2.1	30/1603	1.9	9	3.6	
Single partner	353/1851	19.1	308/1603	19.2	45	18.2	
Multiple partners	1009/1851	54.5	870/1603	54.3	139	56.1	
Refuse to answer	450/1851	24.3	395/1603	24.6	55	22.2	
Unprotected sex in the past 6 months	1432/1831	78.2	1261/1586	79.5	171/245	69.8	0.001
Illicit drug used in the past 6 months	685/1765	38.8	599/1530	39.2	86/235	36.6	0.45
Self-reported STIs in the past 6 months							0.007
No	1157/1788	64.7	977/1546	63.2	180/242	74.4	
Yes	119/1788	6.7	106/1546	6.9	13/242	5.4	
Not sure	512/1788	28.6	463/1546	29.9	49/242	20.2	
Group sex in the past 6 months	217/1747	12.4	207/1520	13.6	10/227	4.4	<0.001
Overall CT infections	379/1842	20.6	349	21.7	30/232	12.9	0.002
Pharyngeal CT	54/1840	2.9	48	3.0	6/230	2.6	0.75
Rectal CT	245/1617	15.2	242	15.0	3/7	42.9	0.04
Urethral CT	133/1833	7.3	112	7.0	21/223	9.4	0.18
Overall NG infections	267/1842	14.5	249	15.5	18/232	7.8	0.002
Pharyngeal NG	120/1840	6.5	110	6.8	10/230	4.4	0.15
Rectal NG	151/1617	9.3	150	9.3	1/7	14.3	0.65
Urethral NG	64/1833	3.5	56	3.5	8/223	3.6	0.93

Abbreviations: CT, *Chlamydia trachomatis*; NG, *Neisseria gonorrhoeae*; STIs, sexually transmitted infections

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
		Other information	
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

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