The Journal of Infectious Diseases

MAJOR ARTICLE

Asymptomatic screening for *Neisseria gonorrhoeae* among gay and bisexual men attending public sexual health services in Australia and associations with patterns of ceftriaxone consumption: a retrospective observational study

Arthur Wong[1,2], Htein Linn Aung[2], Rick Varma[1,2], David J Templeton[2], Alison Nikitas[5], Sarah Martin[6], Louise Owen[7], Arun Menon[8], Christopher K. Fairley[9], Catriona S. Bradshaw[9], Eric P.F. Chow[9,10,11], Jason J. Ong[9,10], Mark Stoove[3,12], Rebecca Guy[2*] & Michael W Traeger[3,12*]

[1]Sydney Sexual Health Centre, Sexual Health & Bloodborne Viruses Services, South Eastern Sydney Local Health District, Sydney, Australia; [2]The Kirby Institute, University of New South Wales, Sydney, Australia; [3]Burnet Institute, Melbourne, Australia; [4]Department of Sexual Health Medicine, Sydney Local Health District, Sydney, Australia and Discipline of Medicine, Central Clinical School, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW 2050, Australia; [5]Murrumbidgee Local Health District, Australia; [6]Canberra Health Service, Canberra, Australia; [7]Statewide Sexual Health Service Tasmania, Australia; [8]Townsville Sexual Health Service, Australia; [9]Melbourne Sexual Health Centre, Alfred Health, Melbourne, Australia; [10]School of Translational Medicine, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Australia; [11]Centre for Epidemiology and Biostatistics, Melbourne School

*These authors contributed equally

Corresponding author: Dr Arthur Wong, The Kirby Institute, Wallace Wurth Building, University of New South Wales, Kensington NSW 2033, Australia, Sexual Health Service, South Eastern Sydney Local Health District, Macquarie Street, Sydney NSW 2000, Australia, Arthur.wong@health.nsw.gov.au

DOI: 10.1093/infdis/jiag192

of Population and Global Health, The University of Melbourne, Melbourne, Australia; [12]School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

Background: Neisseria gonorrhoeae is a significant public health concern due to rising antimicrobial resistance (AMR). Current strategies for *N.gonorrhoeae* among GBM include frequent (3-monthly) screening however, high-frequency screening may increase ceftriaxone consumption, potentially contributing to AMR. We investigated trends in ceftriaxone prescribing among GBM attending public sexual health services (PSHS) in Australia and the association between screening frequency and ceftriaxone consumption.

Methods: We conducted a retrospective cohort study of GBM screened for *N.gonorrhoeae* at 16 Australian PSHS between 2016-2023. We classified *N.gonorrhoeae* tests and ceftriaxone prescriptions as screening-related (asymptomatic screening) or non-screening-related (testing/treatment of contacts, symptomatic testing or empirical treatment). We explored trends in annual ceftriaxone prescription rates and used multivariable Poisson regression to examine the association between individuals' annual asymptomatic screening frequency and ceftriaxone consumption, adjusted for age, year, PrEP, HIV status, injecting drug use, and syphilis and chlamydia diagnoses.

Results: In total, 65,261 GBM contributed 133,846 person-years. Total ceftriaxone prescription rate increased from 2.92 to 5.25 defined daily dose (DDD)/100 person-year at-risk (PYAR) from 2016-2023: screening-related ceftriaxone increased from 0.91 to 2.96 DDD/100 PYAR (p<0·001) whilst non-screening-related ceftriaxone remained stable (p=0.570). Compared to having one screening test per year, having ≥4 tests was associated with a higher rate of screening-related ceftriaxone prescriptions (aIRR=5·47, 95%CI=5·16-5·79).

Conclusion: Ceftriaxone consumption increased among GBM from 2016 to 2023, largely driven by increased *N.gonorrhoeae* screening rather than non-screening-related treatment. Our findings highlight the association between high-frequency screening and antibiotic consumption, providing real-world data to guide discussions on the benefits and risks of screening.

Keywords: *Neisseria gonorrhoeae*, Gay and bisexual men, Asymptomatic screening, Antibiotic, Antimicrobial resistance

INTRODUCTION

Neisseria gonorrhoeae, causing gonorrhoea, is a common sexually transmissible infection (STI), with more than 80 million new cases per year globally and leads to sequalae such as bothersome symptoms, infertility and other reproductive complications (1, 2). *N.gonorrhoeae* is included on the World Health Organization's priority pathogen list due to its propensity to develop antimicrobial resistance (AMR) to every major antibiotic (3). The World Health Organization

(WHO) has set a target to reduce new STIs by 50% between 2020 and 2030 via its global STI strategy; a key action is frequent screening to diagnose and treat asymptomatic infections and reduce onward transmission (1). In parallel, the WHO Global Action Plan on Antimicrobial Stewardship highlights optimising antimicrobial use through evidence-based prescribing as essential to preserving antimicrobial effectiveness (4).

Evidence-based prescribing is based on guidelines. Given rising STI rates, many countries have adopted guidelines which recommend three-monthly screening for *N.gonorrhoeae* at all three anatomical sites (pharynx, anorectum, genitals) in populations at increased STI risk, such as gay and bisexual men (GBM) (also called "3x3 screening") (5, 6). Other strategies recommended in guidelines to diagnosed and treat people with gonorrhoea include: (i) testing people who report contact with someone with *N.gonorrhoeae* (contact testing), (ii) testing people with symptoms that may be due to *N.gonorrhoeae* (symptomatic testing) and (ii) presumptive treatment among symptomatic people and/or contacts of *N.gonorrhoeae* (empirical treatment) – in some settings antibiotics are administered before test results are available given the high likelihood of infection and in others antibiotics are withheld until test results are known (7). Collectively, these screening and non-screening strategies result in a high proportion of antibiotics consumed by GBM (8-10). Increasing rates of treatment for gonorrhoea is concerning as the infection is predominantly treated with ceftriaxone - a broad-spectrum antibiotic - with ecological evidence showing a significant association between population-level consumption of cephalosporins and rates of gonorrhoea AMR (11).

Some propose that more evidenced-based, judicious and limited use of antibiotics is a key strategy to combat *N.gonorrhoeae* AMR (12, 13). However, more data on the patterns of antibiotic prescribing are required to inform clinical guidelines and public health responses that strike a balance between reducing the burden of gonorrhoea sequelae and antibiotic overuse. Some have argued that empirical treatment leads to unnecessary ceftriaxone prescribing in resource-rich settings (10, 14). On the other hand, gaps in access to appropriate testing, treatment and contact tracing are identified as factors for the development of *N.gonorrhoeae* AMR globally (15).

Australia has national guidelines on the screening and treatment of bacterial STI which all public sexual health services (PSHS) adhere to (7). The national recommendation for 3x3 *N.gonorrhoeae* screening among all GBM, regardless of HIV or pre-exposure prophylaxis (PrEP) status, was introduced in 2019 (16). This occurred following widespread implementation of HIV PrEP between 2016-2019 (17). PrEP implementation was accompanied by dedicated STI/HIV screening recommendations for GBM and a longitudinal model of STI/HIV care which saw much higher adherence to the 3-monthly screening recommendation among GBM (18). Importantly, following the rollout of these recommendations, the proportion of gonorrhoea isolates with decreased susceptibility to ceftriaxone (minimum inhibitory concentration $\geq$0·125 mg/L) increased from 0·05% in 2016 to 0·22% in 2023 (19).

We aimed to examine trends in ceftriaxone prescription rates in a cohort of Australian GBM attending PSHS for *N.gonorrhoeae* screening, stratified by whether ceftriaxone was prescribed for infections diagnosed through asymptomatic screening or for non-screening indications (contact testing, symptomatic testing or empirical treatment). We also aimed to examine, among this screening-engaged cohort of GBM, the association between individual-level asymptomatic screening frequency and ceftriaxone consumption as well as identify patient characteristics that are associated with higher likelihood of receiving screening-related ceftriaxone.

METHODS

Study setting and population

We conducted a retrospective cohort study using data from a network of 16 PSHS participating in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmissible Infections and Bloodborne Viruses (ACCESS; www.accessproject.org.au) (20). The ACCESS protocol, which has previously been described, allows patient data to be de-identified and extracted from the electronic medical records of participating clinics using a specialised data extraction software (GHRANITE™). This software enables linkage within and across services using a probabilistic algorithm and non-identifiable linkage keys generated prior to extraction (21).

Data collection

Data extracted from electronic medical records included age, clinical consultations, presence of symptoms at time of consultation (recorded in the reason for presentation field or reason for testing recorded as potential contact with a bacterial STI (via coding and free text)), electronic prescriptions for HIV pre-exposure prophylaxis (PrEP), HIV status, history of injecting drug use (IDU), chlamydia, gonorrhoea and syphilis pathology, and ceftriaxone prescriptions. New cases of gonorrhoea or chlamydia were defined as positive NAAT. Individuals were classified as ever PrEP users if they had any electronic prescription for PrEP during the study period. New cases of infectious syphilis were coded by the diagnosing clinician.

Outcomes

We classified all *N.gonorrhoeae* tests as either: (i) screening-related, (ii) contact testing-related, (iii) symptomatic testing-related or (iv) empirical treatment-related (the last three indications were collectively defined as non-screening-related). We defined *N.gonorrhoeae* screening-related tests as a nucleic acid amplification test (NAAT) for the organism from any anatomical site during a visit where the individual did not report any symptoms or recent contact with a bacterial STI. Contact testing was defined as tests where an asymptomatic individual reported recent contact with an STI, symptomatic testing was defined as tests where the individual reported any symptoms, and empirical treatment was defined as testing and antibiotic treatment undertaken during the same

consultation. All *N.gonorrhoeae* tests within 14 days of each other were considered part of the same episode.

Ceftriaxone prescriptions were also stratified. Ceftriaxone prescribed within 14 days of (but not on the day of) screening-related testing, contact testing and symptomatic testing was presumed to be for the treatment of gonorrhoea diagnosed through those tests respectively. Ceftriaxone prescribed on the same day as gonorrhoea testing was presumed to be empirical treatment, regardless of reason for testing. Ceftriaxone prescriptions that do not fit into any aforementioned indications were categorised as unknown indication and grouped into non-screening-related prescriptions. Ceftriaxone was quantified as defined daily dose (DDD) according to the WHO method (22) and prescription rate calculated by DDD per 100 person-years at risk (100 PYAR). The DDD is a widely recognised unit with a predetermined conversion factor to calculate the maintenance dose per day for a medication.

Our analysis included GBM aged 16 years and above who had at least one *N.gonorrhoeae* asymptomatic screening-related test at an included clinic during the study period (2016-2023). Included GBM each contributed one person-year of observation for each year they had at least one screening-related test. We excluded GBM who did not attend any asymptomatic screening visits in a calendar year to reduce mixing of our cohort with patients who attended screening in other settings (for example, in general practice) but attended a sexual health clinic for treatment of positive results. GBM status was determined via patient-reported sexuality, gender of sexual partners or previous history of rectal STI swab (23).

Statistical analyses

We defined the unit of analysis as a person-year at risk (PYAR) of receiving screening-related ceftriaxone, with individuals contributing one year of observation for each calendar year in which they had at least one screening-related test. These PYARs represent periods of engagement in routine screening care and therefore reflect service utilisation time rather than continuous biological time. We categorised each PYAR based on the number of screening-related tests the individual had in the calendar year (1, 2, 3 or $\geq$4) as a measure of individual screening frequency. We also measured the annual rate of ceftriaxone prescription per person-year at risk (defined as the total number of ceftriaxone prescriptions in each year divided by the total number of PYARs), stratified by prescription type (screening-related, contact testing-related, symptomatic testing-related, empirical treatment-related and indication unknown).

We used multivariable Poisson regression models to examine the relationship between annual *N.gonorrhoeae* screening frequency and ceftriaxone prescription. In these models, the outcome was annual number of ceftriaxone prescriptions and the exposure was annual number of *N.gonorrhoeae* screening tests (categorised as 1, 2, 3 or $\geq$4 per year). We performed separate models with the outcome as screening-related prescriptions and non-screening-related prescriptions. As each individual could potentially contribute multiple person-years of observation

during the study period, we used robust standard errors to account for non-independent clustering of observations within individual.

We explored the associations between ceftriaxone prescription and the following covariates in bivariable Poisson models; age group (16-29, 30-39, 40-49 and ≥50 years), current HIV status, PrEP use during the study, history of injecting drug use, and diagnosis of infectious syphilis or incident chlamydia within the respective year. Covariates found to be associated with increased ceftriaxone prescription (P<0·20) in bivariable analyses were included in a multivariable model. Unadjusted and adjusted incident rate ratios (IRRs) for ceftriaxone prescriptions were computed from each multivariable model. In addition, to explore whether more frequent screening was associated with differences in symptomatic or contact-related infections, we examined the relationship between annual *N.gonorrhoeae* screening frequency and the number of positive *N.gonorrhoeae* tests performed for non-screening-related indications also using a bivariable Poisson model.

All analyses were performed using STATA version 17.0 (Stata Statistical Software, Stata Corp., College Station, USA).

Ethics

Ethical approval for ACCESS was granted by the human research ethics committees of the Alfred Hospital (248/17), Northern Territory Department of Health and Menzies School of Health (08/47), University of Tasmania (H0016971) and St. Vincent's Hospital (08/051).

RESULTS

Study population

Overall, there were 237,507 person-years of GBM attending included services during the study period, including 213,708 (90.0%) with any *N.gonorrhoeae* testing in a calendar year. Among these, 133,846 (62.6%) person-years from 65,261 GBM included at least one asymptomatic screening test and were therefore considered at-risk of screening-related ceftriaxone and included in the analysis. Of these, 21,641 GBM (33.2%) contributed one PYAR, 14,420 (22.1%) contributed two PYARs, 9,473 (14.5%) contributed three PYARs and 19,727 (30.23%) contributed four or more PYARs. Characteristics of GBM at their first test during the study period are reported in Table 1. The median age at first test was 32 years (IQR 27-40), 13,661 (10·2%) were living with HIV at the end of the study period and 44,173 (33·0%) were prescribed PrEP at least once during the study period. There were 6,215 (4.6%) PYARs with at least one gonorrhoea diagnosis, 6,577 (4·9%) with at least one chlamydia diagnosis and 4,680 (3·5%) with at least one infectious syphilis diagnosis (Table 2).

Asymptomatic gonorrhoea screening tests

For all PYARs, the number categorised as having 1, 2, 3 and ≥4 screening-related tests within the year was 84,192 (62·9%), 28,738 (21·5%), 12,474 (9·3%) and 8,442 (6·3%) respectively (Table 2). The number of PYAR who had at least one *N.gonorrhoeae* screening-related test increased from 15,378 in 2016 to 19,320 in 2019. This was followed by a decrease during the period of COVID-19 restriction – down to 15,841 in 2020 and 14,678 in 2021. Among those tested, the proportion who had two or more screening test per year increased from 33·6% to 38·2% (Figure 1).

Ceftriaxone prescriptions

Ceftriaxone prescription for any indication per person-year at risk consistently increased during the study period – from 2.92 DDD/100 PYAR in 2016 to 5.25 DDD/100 PYAR in 2023 (Figure 2). The rate of screening-related ceftriaxone prescribing increased steadily over the study period, from 0.91 DDD/100 PYAR in 2016 to 2.96 DDD/100 PYAR in 2023 (IRR 1·14, 95%CI 1·13-1·15, p<0·001). In contrast, the rate of non-screening-related ceftriaxone prescribing remained stable over this period (IRR 1·00, 95%CI 0·99-1·01, p=0·570). In 2016, there were 0.08 DDD/100 PYAR of contact testing-related, 0.53 DDD/100 PYAR of symptomatic testing-related and 1.27 DDD/100 PYAR of empirical treatment-related ceftriaxone. These figures were at 0.27 DDD/100 PYAR, 0.56 DDD/100 PYAR and 1.19 DDD/100 PYAR respectively in 2023 (Figure 2).

Factors associated with prescription

We observed a dose-response relationship between the number of screening-related tests within a year and the rate of screening-related ceftriaxone prescribed, with the rate of prescription highest for GBM who had four or more asymptomatic screening tests per year (7.09 DDD/100 PYAR) followed by those with three tests (4.50 DDD/100 PYAR), two tests (2.67 DDD/100 PYAR) and one test (1.07 DDD/100 PYAR) (Table 3). The rate of non-screening-related ceftriaxone was highest among GBM who had three screening tests per year (3.04 DDD/100 PYAR) (Table 3).

Screening-related prescriptions

Unadjusted and adjusted incident rate ratios (IRR) for screening-related and non-screening-related ceftriaxone are presented in Table 4.

In bivariable analysis, the number of screening-related tests per year was significantly associated with the number of screening-related ceftriaxone prescriptions per year (p<0·001 for all categories compared to 1 test per year). Compared to GBM who had only one screening-related test, the uIRR was 2·50 (95%CI 2·37-2·61) for those who had two, 4·19 (95%CI 3·35-3·74) for those who had three and 6·60 (95%CI 6·23-6·99) for those who had four or more screening tests.

In the multivariable analysis, after adjusting for age, calendar year, PrEP use, HIV status, history of IDU, infectious syphilis and new chlamydia diagnoses in the same year, the number of screening tests remain associated with ceftriaxone prescriptions (p<0·001 for all categories). Older age was

associated with reduced ceftriaxone prescription in the multivariable model – compared to those aged 16-29 years, the aIRR was 0·86 (95%CI 0·82-0·90) for those aged 30-39 years, 0·69 (95%CI 0·65-0·73) for those aged 40-49 years and 0·452 (95%CI 0·42-0·49) for those aged 50 years and above (Table 4).

Non-screening-related prescriptions

In bivariable analysis, the number of *N.gonorrhoeae* screening tests was significantly associated with the number of non-screening-related ceftriaxone prescriptions. Compared to those who had 1 screening test, the uIRR was 1·39 (95%CI 1·32-1·46) for those who had 2, 1·56 (95%CI 1·46-1·66) for those who had 3 and 1·39 (95%CI 1·27-1·52) for those who had ≥4 tests per year. However, after adjusting for the co-variates in the multivariable model, only those who had two screening tests were more likely to receive more non-screening-related ceftriaxone (aIRR 1·11, 95%CI 1·05-1·16) (Table 4).

Association with positive N.gonorrhoeae tests for non-screening-related indications

In bivariable analysis, the number of *N.gonorrhoeae* screening tests per year was positively associated with the number of positive *N.gonorrhoeae* tests performed for non-screening indications (ie. for symptom-related and contact-related testing). See Supplementary Table 1 for regression outputs.

DISCUSSION

In this cohort of 65,261 GBM engaging in asymptomatic *N.gonorrhoeae* screening (133,846 person-years of data), we examined both cohort-level and individual-level ceftriaxone prescribing within a large national network of PSHS during the period of widespread PrEP implementation and associated increases in 3x3 *N.gonorrhoeae* screening. To our knowledge, this is the first large national study to demonstrate the association between screening and ceftriaxone consumption on an individual and cohort level. Over the 8-year study period, the increase in *N.gonorrhoeae* screening among GBM was followed by a sustained increase in ceftriaxone use, mostly driven by an increase in screening-related prescribing. On the other hand, the rate of ceftriaxone prescribed for non-screening indications combined (i.e. contact testing-related, symptomatic testing-related and empirical treatment-related) have remained stable, and in the second half of the study period was lower than screening-related prescribing. At the individual level, we found that an increase in the number of annual asymptomatic screening tests had a dose-response relationship with ceftriaxone prescribing for screening-related indications.

It has been proposed that asymptomatic screening for *N.gonorrhoeae* in GBM should be significantly reduced due to the ecological association between population-level ceftriaxone use and the likelihood of emergent gonococcal resistance (11, 13, 24). Coinciding with the introduction

of 3x3 *N.gonorrhoeae* screening, the proportion of isolates from the Australian Gonococcal Surveillance Program with reduced susceptibility to ceftriaxone increased from 0.05% in 2016 to 0.51% in 2024 (25). Based on our 2023 estimates, cessation of asymptomatic screening could result in a reduction of up to 510 DDD in cohort-level ceftriaxone prescribing among screening-engaged GBM. However, it is unclear to what extent a reduction in screening may translate into the slowing of gonorrhoea AMR given other contributing factors. For instance, high rates of gonococcal AMR are also seen in settings where regular gonorrhoea screening is unavailable and are instead due to the lack of access to testing and appropriate treatment (15, 26).

Proponents for 3x3 *N.gonorrhoeae* screening among GBM argue that early diagnosis interrupts onward transmission. However, in our analysis, intensification of screening was not associated with a commensurate decrease in the use of ceftriaxone or decrease in positive *N.gonorrhoea* tests detected through non-screening-related indications (such as symptomatic presentation or contact testing). Nevertheless, there are other potential benefits to frequent *N.gonorrhoeae* screening beyond avoidance of antibiotic use that require careful consideration. For example, 3x3 *N.gonorrhoeae* screening may prevent bridging transmission into sexual networks with cisgender women and transgender men who are at higher risk of serious sequalae from gonorrhoea (18, 27). Our analysis also showed that up to a third of ceftriaxone prescriptions were for non-screening indications, which would still contribute to a significant amount of cohort-level ceftriaxone use even without regular asymptomatic screening (28, 29). Our analysis provides real-world data on antibiotic exposure associated with intensive screening strategies, and may help inform ongoing discussions about the value of frequent asymptomatic screening and its potential impact on *N.gonorrhoeae* transmission, community prevalence and antimicrobial resistance.

Notification rates of *N.gonorrhoeae* in Australia increased over the study period and were disproportionately concentrated among GBM on PrEP and GBM living with HIV (29). One possible explanation for the increase in ceftriaxone prescription rate is the increase in adherence to 3x3 screening recommendations (17). This is further supported by our observation that the increase in ceftriaxone prescribing is driven by screening-related indications whilst non-screening-related ceftriaxone prescribing has remained stable. Furthermore, in 2019 Australian guidelines changed from recommending empirical antibiotics for all gonorrhoea contacts to recommending testing in asymptomatic contacts and treatment only if gonorrhoea is detected (30), potentially confounding the amount of contact testing-related ceftriaxone prescribed in the subsequent period.

Our finding that higher rates of asymptomatic screening are associated with more antibiotic consumption is consistent with recent data from a randomised control trial on the impact of 3x3 screening on the incidence of STI diagnoses (31). In this study, the difference in antibiotic consumption was driven by lower consumption among those randomised to less frequent screening not being told of their gonorrhoea diagnoses (18). Similarly, our findings are likely explained by the fact that those who are attending PSHS for more screening tests are more likely to have asymptomatic gonorrhoea infections diagnosed and therefore be prescribed ceftriaxone – rather than any true difference in incidence between GBM being screened at different frequencies.

The finding that the likelihood of receiving screening-related ceftriaxone is highest among the youngest GBM (16-29 years), even after adjustment for other factors associated with STI risk is notable. Previous epidemiological evidence among Australian GBM attending PSHS highlights that *N.gonorrhoeae* incidence remains high until the fourth decade of life (32). Therefore, younger GBM who commence asymptomatic *N.gonorrhoeae* screening early in adulthood and continue screening over subsequent decades may experience high cumulative exposure to broad-spectrum antibiotics such as ceftriaxone. Emerging evidence also suggests that exposure to cephalosporins during early adulthood may be associated with enduring alterations to the human microbiome (33, 34), and long-term metabolic outcomes such as diabetes mellitus (35) and obesity (36). These considerations highlight the importance of carefully evaluating the long-term risk-benefit profile of intensive 3x3 screening strategies in this population.

There are several important limitations. Our cohort included only PYARs in which an individual had undergone asymptomatic screening in a calendar year – therefore our finding of increased ceftriaxone consumption applies specifically to GBM engaged in routine screening. As we relied on data from electronic medical records from PSHS, screening tests which occurred outside of these services were not captured. Sexual health care in Australia is provided by both PSHS and general practitioners (GP) in the community, meaning we may have missed tests which occurred outside of the PSHS network. We excluded GBM who did not attend *any* asymptomatic screening at PSHS in a calendar year to avoid misclassification of those who were undergoing regular asymptomatic screening via GP but attended a sexual health service for treatment of positive results or symptoms. This may have led to under-estimation of the prescription rate of both screening and non-screening-related ceftriaxone. Also, we were not able to extract patient notes and therefore there may be some missing data on patient symptoms or STI contact if there was incomplete coding. However, we have endeavoured to address this by conducting free text search in the reason for presentation field. Ceftriaxone prescriptions with unknown indication only represented 5.3% of total prescriptions.

CONCLUSIONS

Our large cohort study using surveillance data from GBM undergoing *N.gonorrhoeae* screening in Australian PSHS showed a significant and sustained increase in ceftriaxone prescribing since widespread rollout of HIV PrEP and 3x3 screening recommendations. We observed a dose-response relationship between frequent screening and increases in ceftriaxone consumption, and that ceftriaxone prescribing due to screening-related testing increased while prescribing due to other indications remained stable. Our findings contribute to current global discussions to understand the benefits and harms of intensive *N.gonorrhoeae* screening in GBM and to reduce antibiotic consumption.

References

1. World Health Organization. Progress Report on HIV, Viral Hepatitis and Sexually Transmitted Infections 2021. World Health Organization; 2021.
2. World Health Organization. Global and regional sexually transmitted infection estimates for 2020. In: World Health Organization, editor. 2020.
3. World Health Organization. WHO Bacterial Priority Pathogens List, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. World Health Organisation; 2024.
4. World Health Organization. Global action plan on antimicrobial resistance. In: World Health Organization, editor. 2016.
5. Clutterbuck D, Asboe D, Barber T, Emerson C, Field N, Gibson S, et al. 2016 United Kingdom national guideline on the sexual health care of men who have sex with men. Int J STD AIDS. 2018:956462417746897.
6. US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States -- 2021 update : a clinical practice guideline. 2021.
7. Australasian Society for HIV VHaSHM. Australian STI Management Guidelines for use in primary care 2021 [Available from: https://sti.guidelines.org.au/sexually-transmissible-infections/gonorrhoea/.
8. Kenyon C, Baetselier ID, Wouters K. Screening for STIs in PrEP cohorts results in high levels of antimicrobial consumption. International Journal of STD & AIDS. 2020;31(12):1215-8.
9. Wong A, Applegate T, Boettiger DC, Varma R, Guy R, Medland N. Unnecessary antibiotic use in men who have sex with men (MSM) with anogenital symptoms attending a sexual health clinic: a retrospective analysis. Sex Transm Infect. 2024;(no pagination).
10. Rasul R, McIver R, Patel P, Foster R, McNulty A. Non-empirical management of asymptomatic chlamydia and gonorrhoea reduces unnecessary antibiotic use fivefold: a before and after study. Sex Transm Infect. 2023;99(1):30-4.
11. Kenyon C, Buyze J, Spiteri G, Cole MJ, Unemo M. Population-Level Antimicrobial Consumption Is Associated With Decreased Antimicrobial Susceptibility in Neisseria gonorrhoeae in 24 European Countries: An Ecological Analysis. J Infect Dis. 2020;221(7):1107-16.
12. Kenyon C. We need to consider collateral damage to resistomes when we decide how frequently to screen for chlamydia/gonorrhoea in preexposure prophylaxis cohorts. AIDS. 2019;33(1).
13. Williams E, Williamson DA, Hocking JS. Frequent screening for asymptomatic chlamydia and gonorrhoea infections in men who have sex with men: time to re-evaluate? The Lancet Infectious Diseases. 2023.
14. Wong A, Applegate T, Boettiger DC, Varma R, Guy R, Medland N. Unnecessary antibiotic use in men who have sex with men (MSM) with anogenital symptoms attending a sexual health clinic: a retrospective analysis. Sex Transm Infect. 2024;100(7):435-41.
15. Zhu X, Xi Y, Gong X, Chen S. Ceftriaxone-Resistant Gonorrhea - China, 2022. MMWR Morb Mortal Wkly Rep. 2024;73(12):255-9.
16. STIs in Gay Men Action Group. Australian Sexually Transmitted Infection & HIV Testing Guidelines 2019. New South Wales, Australia: STI Programs Unit (STIPU); 2019.

17. McManus H, Grulich AE, Amin J, Selvey C, Vickers T, Bavinton B, et al. Comparison of Trends in Rates of Sexually Transmitted Infections Before vs After Initiation of HIV Preexposure Prophylaxis Among Men Who Have Sex With Men. JAMA Netw Open. 2020;3(12):e2030806.
18. Medland N, Guy R. Who benefits from frequent asymptomatic STI screening? The Lancet HIV. 2024;11(4):e201-e2.
19. Lahra MM, van Hal S, Hogan TR. Australian Gonococcal Surveillance Programme Annual Report, 2023. Commun Dis Intell (2018). 2025;49.
20. Callander D, Moreira C, El-Hayek C, Asselin J, van Gemert C, Watchirs Smith L, et al. Monitoring the Control of Sexually Transmissible Infections and Blood-Borne Viruses: Protocol for the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS). JMIR Res Protoc. 2018;7(11):e11028.
21. Nguyen L, Stoové M, Boyle D, Callander D, McManus H, Asselin J, et al. Privacy-Preserving Record Linkage of Deidentified Records Within a Public Health Surveillance System: Evaluation Study. J Med Internet Res. 2020;22(6):e16757.
22. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment. Oslo, Norway: WHO; 2023.
23. Ampt FH, El Hayek C, Agius PA, Bowring AL, Bartnik N, C VANG, et al. Anorectal swabs as a marker of male-to-male sexual exposure in STI surveillance systems. Epidemiol Infect. 2017;145(12):2530-5.
24. Van Dijck C, Laumen J, Zlotorzynska M, Manoharan-Basil SS, Kenyon C. Association between STI screening intensity in men who have sex with men and gonococcal susceptibility in 21 States in the USA: an ecological study. Sex Transm Infect. 2020;96(7):537-40.
25. Lahra M, Hurley S, van Hal S, Hogan T. Australian Gonococcal Surveillance Program, 1 April to 30 June 2025. Communicable Diseases Intelligence. 2026;50.
26. Unemo M, Lahra MM, Cole M, Galarza P, Ndowa F, Martin I, et al. World Health Organization Global Gonococcal Antimicrobial Surveillance Program (WHO GASP): review of new data and evidence to inform international collaborative actions and research efforts. Sex Health. 2019;16(5):412-25.
27. Williamson DA, Chow EPF, Gorrie CL, Seemann T, Ingle DJ, Higgins N, et al. Bridging of Neisseria gonorrhoeae lineages across sexual networks in the HIV pre-exposure prophylaxis era. Nat Commun. 2019;10(1):3988.
28. Traeger MW, Guy R, Asselin J, Patel P, Carter A, Wright EJ, et al. Real-world trends in incidence of bacterial sexually transmissible infections among gay and bisexual men using HIV pre-exposure prophylaxis (PrEP) in Australia following nationwide PrEP implementation: an analysis of sentinel surveillance data. Lancet Infect Dis. 2022;22(8):1231-41.
29. King JKJM, H.: Gray, R.; McGregor, S. HIV, viral hepatitis and sexually transmissible infections in Australia: Annual surveillance report 2024. Sydney, Australia: The Kirby Institute, UNSW Sydney; 2024.
30. Ong JJ, Bourne C, Dean JA, Ryder N, Cornelisse VJ, Murray S, et al. Australian sexually transmitted infection (STI) management guidelines for use in primary care 2022 update. Sex Health. 2023;20(1):1-8.
31. Vanbaelen T, Tsoumanis A, Florence E, Van Dijck C, Huis in 't Veld D, Sauvage A-S, et al. Effect of screening for Neisseria gonorrhoeae and Chlamydia trachomatis on incidence of these infections in men who have sex with men and transgender women taking HIV pre-exposure prophylaxis (the

Gonoscreen study): results from a randomised, multicentre, controlled trial. The Lancet HIV. 2024;11(4):e233-e44.
32. Jin F, Prestage GP, Mao L, Kippax SC, Pell CM, Donovan B, et al. Incidence and risk factors for urethral and anal gonorrhoea and chlamydia in a cohort of HIV-negative homosexual men: the Health in Men Study. Sex Transm Infect. 2006;83(2):113.
33. Zimmermann P, Curtis N. The effect of antibiotics on the composition of the intestinal microbiota - a systematic review. J Infect. 2019;79(6):471-89.
34. Baldanzi G, Larsson A, Sayols-Baixeras S, Dekkers KF, Hammar U, Nguyen D, et al. Antibiotic use and gut microbiome composition links from individual-level prescription data of 14,979 individuals. Nature Medicine. 2026.
35. Boursi B, Mamtani R, Haynes K, Yang YX. The effect of past antibiotic exposure on diabetes risk. Eur J Endocrinol. 2015;172(6):639-48.
36. Furlong M, Deming-Halverson S, Sandler DP. Chronic antibiotic use during adulthood and weight change in the Sister Study. PLoS One. 2019;14(5):e0216959.

Figure 1· Proportion of person-years at risk (PYAR) of screening-related ceftriaxone among gay and bisexual men at each N.gonorrhoeae screening frequency, stratified by calendar year

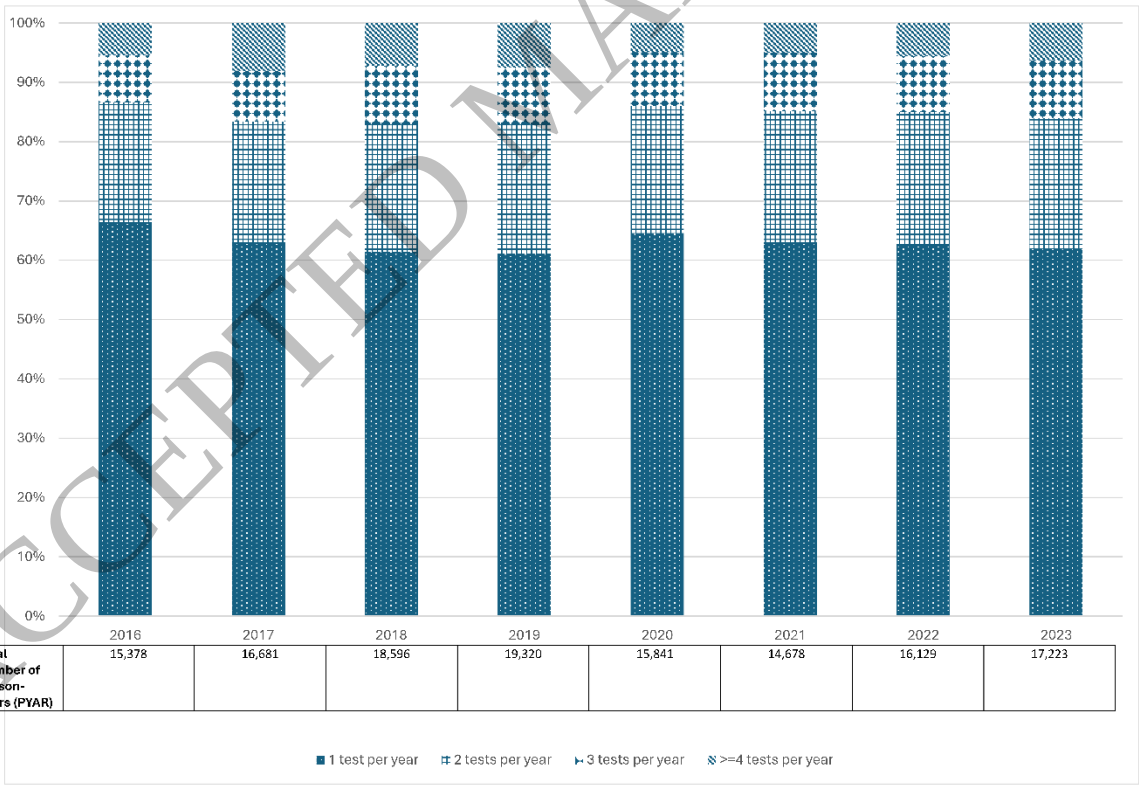
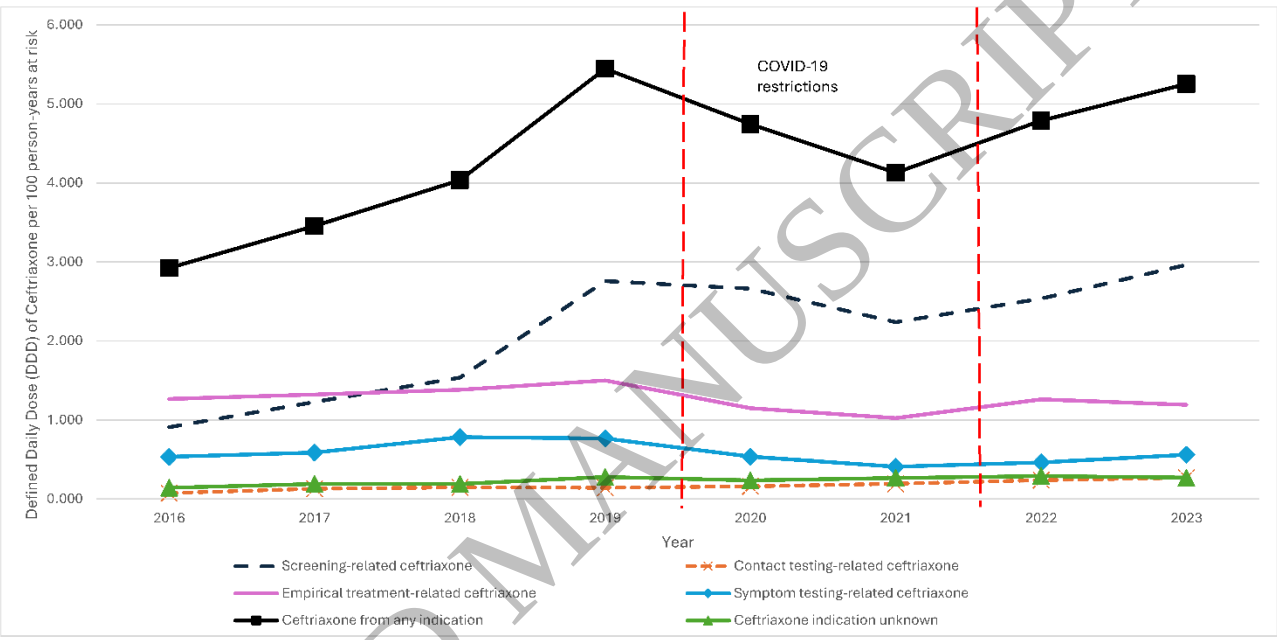


Figure 2· Defined daily dose (DDD) of Ceftriaxone administered per 100 person-years at risk of screening-related ceftriaxone stratified by indication (screening-related, empirical, contact testing-related, symptomatic testing-related and indication unknown)



Author contributions	AW & MWT conceived the study. MWT, RG, CT, VJC, EPFC, CKF, BD, MEH, MAS contributed substantially to interpretation of the data. AW & MWT undertook the formal data analysis. AW MWT & HA curated the data. RG, HA, MS coordinate the ACCESS study and were responsible for funding acquisition. RV DJ AN SM LO AM CKF CSB EPFC JJO are ACCESS clinic investigators and contributed to data acquisition. AW & MWT had full access to all the data in the study and verified the data. MWT & RG provided academic supervision.

	AW lead the manuscript preparation. All authors read and revised the manuscript critically for important intellectual content and approved the final version of the manuscript for publication.
Data sharing	De-identified individual participant data included in this study cannot be shared publicly because of the sensitive nature of participant data anonymously extracted from participating clinical services. Access to deidentified data is available via the Burnet Institute with approval from the Alfred Hospital Human Research Ethics Committee for researchers who meet the criteria for access to confidential data. The ACCESS study protocol has been published previously.
Financial support	ACCESS receives core funding from the Australian Department of Health and Aged Care with the aim to monitor Australia's progress in the control of blood borne viruses and sexually transmitted infections. In addition, funding has been received from the governments of New South Wales, Victoria, Northern Territory, Western Australia and the Australian Capital Territory for state level outcomes, as well as from the Blood Borne Virus & STI Research, Intervention and Strategic Evaluation Program (BRISE), an NHMRC Project Grant (APP1082336), a NHMRC Partnership Grant (GNT1092852), and the Prevention Research Support Program, funded by the New South Wales Ministry of Health. The Burnet Institute gratefully acknowledges support from the Victorian Operational Infrastructure Support Program. This work was supported by funding from Australian Research Council Industrial Transformation Research Hub to Combat Antimicrobial Resistance (IH190100021). Arthur Wong receives a doctoral scholarship from the University of New South Wales and the AMR Hub. M.W.T. is supported by a fellowship from the National Health and Medical Research Council.
Potential conflicts of interest	M.W.T. reports speakers' honoraria, consultancy fees and investigator initiated research grants from Gilead Sciences. EPFC is supported by an Australian National Health and Medical Research

	Council (NHMRC) Emerging Leadership Investigator Grant (GNT1172873), and has received speakers' honoraria from Gilead Sciences, MSD and CSL Seqirus. CKF is supported by an Australian NHMRC Leadership Investigator Grant (GNT1172900). All other authors declare no conflicts of interest.
Acknowledgement	The authors would like to acknowledge the late Dr Nicholas Medland, who helped conceive the initial study design and analysis plan. His insights were pivotal to the planning of this work. The authors acknowledge the contribution of the ACCESS team members and ACCESS advisory committee members who are not coauthors of this article. The authors also acknowledge all clinical services participating in ACCESS. The list of ACCESS team members, ACCESS advisory committee members, and participating ACCESS services can be found on the ACCESS website (accessproject.org.au). ACCESS is a partnership between the Burnet Institute, Kirby Institute and National Reference Laboratory.

Table 1. Characteristics of gay & bisexual men (GBM) at first test (N=65,261)

	n	%
Age, years, median (IQR)	30 (26-38)	
Age group, years		
16-29	29,680	45·48%
30-39	20,604	31·57%
40-49	7,959	12·20%
≥50	7,018	10·75%
HIV status		
HIV-negative	60,598	92·85%
HIV-positive	4,663	7·15%
On PrEP		
No	50,671	77·64%
Yes	14,590	22·36%
Year at entry into observational period		
2016	15,378	23·56%
2017	9,906	15·18%
2018	9,016	13·82%
2019	8,603	13·18%
2020	5,855	8·97%
2021	4,865	7·45%
2022	5,472	8·38%

	2023	6,166	9·45%

Footnote: N is the total number of person-years in which a gay or bisexual man had at least one screening-related gonorrhoea test

Table 2· Characteristics of gay and bisexual men undergoing asymptomatic *N.gonorrhoeae* screening at sexual health services in Australia (N = 133,846 person-years at risk of screening-related ceftriaxone)

	Characteristics associated with each person-year at risk	%
Age, years, median (IQR)	32 (27-40)	
Age group, years		
16-29	51,329	38·35%
30-39	47,537	35·52%
40-49	18,824	14·06%
≥50	16,156	12·07%
CT/NG screening visits per year		
1	84,192	62·90%
2	28,738	21·47%
3	12,474	9·32%
≥4	8,442	6·31%
Year		
2016	15,378	11·49%
2017	16,681	12·46%
2018	18,596	13·89%
2019	19,320	14·43%
2020	15,841	11·84%
2021	14,678	10·97%
2022	16,129	12·05%
2023	17,223	12·87%
HIV status		
HIV-negative	120,185	89·79%
HIV-positive	13,661	10·21%
Prescribed PrEP during study period		
No	89,673	67·00%
Yes	44,173	33·00%
History of injecting drug use		
No	130,171	97·25%
Yes	3,675	2·75%
Infectious syphilis[a]		

	No	129,166	96·50%
	Yes	4,680	3·50%
Incident chlamydia diagnosis[a]			
	No	127,269	95·09%
	Yes	6,577	4·91%
Incident gonorrhoea diagnosis[a]			
	No	127,631	95·36%
	Yes	6,215	4·64%

Footnote: N is the total number of person-years at risk of screening-related ceftriaxone in which a gay or bisexual man had at least one screening-related gonorrhoea test·
a, Incident syphilis, chlamydia or gonorrhoea diagnoses in a year

Table 3· Screening-related vs· non-screening-related ceftriaxone administered per person-year stratified by characteristics of gay and bisexual men
DDD, defined daily dose. PYAR, person-year at risk

	Total person-years at risk (PYAR) of screening-related ceftriaxone	DDD of **screening**-related ceftriaxone	DDD of **screening**-related ceftriaxone per 100 PYAR	DDD of **non-screening**-related ceftriaxone	DDD of **non-screening**-related ceftriaxone per 100 PYAR
Age group, years					
16-29	51,329	1160	2.26	1245	2.43
30-39	47,537	1136	2.39	1149	2.42
40-49	18,824	349	1.85	395	2.10
≥50	16,156	188	1.16	242	1.50
Gonorrhoea screening tests per year					
1	84,192	905	1.07	1644	1.95
2	28,738	768	2.67	778	2.71
3	12,474	561	4.50	379	3.04
≥4	8,442	599	7.09	229	2.71
Year					
2016	15,378	140	0.91	310	2.01
2017	16,681	205	1.23	372	2.23
2018	18,596	286	1.54	465	2.50
2019	19,320	533	2.76	519	2.69
2020	15,841	422	2.66	330	2.08
2021	14,678	329	2.24	278	1.89
2022	16,129	409	2.54	363	2.25

2023	17,223	510	2.96	394	2.29
HIV status					
HIV-negative	120,185	2402	2.00	2576	2.14
HIV-positive	13,661	431	3.15	454	3.32
Prescribed PrEP during study period					
No	89,673	1412	1.57	1369	1.53
Yes	44,173	1421	3.22	1661	3.76
History of injecting drug use					
No	130,171	2671	2.05	2818	2.16
Yes	3,675	161	4.39	212	5.78
Infectious syphilis diagnosis in years					
No	129,166	1170	0.91	2777	2.15
Yes	4,680	244	5.21	253	5.41
New chlamydia diagnosis in year					
No	127,269	2477	1.95	2585	2.03
Yes	6,577	355	5.40	445	6.76

Table 4· Unadjusted and adjusted incident risk ratio (IRR) for factors associated with ceftriaxone consumption among GBM attending ACCESS clinics between 2016 and 2023

		Screening-related ceftriaxone						**Non-screening** related ceftriaxone					
	N	unadjusted IRR	95% CI	p-value	adjusted IRR	95% CI	p-value	unadjusted IRR	95% CI	p-value	adjusted IRR	95% CI	p-value
Total person-years at risk	133,846												
Screening visits per year													
1	84,192	1			1			1			1		
2	28,738	2·488	2·370-2·610	<0·001	2·210	2·104-2·320	<0·001	1·385	1·319-1·455	<0·001	1·107	1·053-1·163	<0·001
3	12,474	4·188	3·969-4·419	<0·001	3·540	3·352-3·736	<0·001	1·556	1·456-1·662	<0·001	1·063	0·994-1·137	0·074
4 or more	8,442	6·602	6·233-6·992	<0·001	5·466	5·158-5·793	<0·001	1·389	1·270-1·519	<0·001	0·790	0·721-0·866	<0·001
Age group, years													

16-29	51,329	1			1			1			1		
30-39	47,537	1·058	1·009-1·109	0·02	0·861	0·824-0·899	<0·001	0·996	0·943-1·052	0·893	0·877	0·832-0·925	<0·001
40-49	18,824	0·819	0·766-0·877	<0·001	0·688	0·645-0·733	<0·001	0·864	0·798-0·936	<0·001	0·732	0·678-0·791	<0·001
≥50	16,156	0·515	0·472-0·562	<0·001	0·452	0·416-0·491	<0·001	0·618	0·562-0·679	<0·001	0·563	0·513-0·617	<0·001
Year													
2016	15,378	1			1			1			1		
2017	16,681	1·351	1·215-1·502	<0·001	1·180	1·061-·1·312	0·002	1·106	1·020-1·199	0·015	0·967	0·892-1·049	0·418
2018	18,596	1·689	1·526-1·871	<0·001	1·453	1·312-1·608	<0·001	1·241	1·145-1·344	<0·001	0·995	0·918-1·079	0·907
2019	19,320	3·056	2·760-3·340	<0·001	2·528	2·300-2·780	<0·001	1·334	1·231-1·444	<0·001	0·994	0·917-1·078	0·881
2020	15,841	2·930	2·657-3·231	<0·001	2·590	2·349-2·856	<0·001	1·033	0·948-1·127	0·456	0·720	0·660-0·786	<0·001
2021	14,678	2·463	2·226-2·725	<0·001	2·084	1·884-2·306	<0·001	0·939	0·857-1·028	0·173	0·614	0·559-0·674	<0·001
2022	16,129	2·790	2·530-3·088	<0·001	2·371	2·149-2·616	<0·001	1·118	1·025-1·220	0·012	0·727	0·664-0·796	<0·001
2023	17,223	3·260	2·962-3·588	<0·001	2·716	2·466-2·991	<0·001	1·136	1·043-1·237	0·003	0·726	0·665-0·793	<0·001
PrEP ever													
No	89,673	1			1			1			1		
Yes	44,173	2·042	1·956-2·132	<0·001	1·368	1·307-1·432	<0·001	2·464	2·346-2·588	<0·001	2·927	2·774-3·089	<0·001
Current HIV													
No	120,185	1			1			1			1		
Yes	13,661	1·577	1·482-1·678	<0·001	1·756	1·650-1·868	<0·001	1·549	1·436-1·671	<0·001	2·342	2·164-2·536	<0·001
History of injecting drug use													
No	130,171	1			1			1			1		

	Yes	3,675	2·138	1·957-2·336	<0·001	1·744	1·607-1·892	<0·001	2·668	2·432-2·927	<0·001	1·941	1·768-2·130	<0·001
Infectious syphilis														
	No	129,166	1			1			1			1		
	Yes	4,680	2·601	2·431-2·784	<0·001	1·652	1·548-1·763	<0·001	2·515	2·330-2·714	<0·001	1·747	1·618-1·887	<0·001
New chlamydia														
	No	127,269	1			1			1			1		
	Yes	6,577	2·775	2·613-2·947	<0·001	1·680	1·586-1·779	<0·001	3·327	3·140-3·525	<0·001	2·51	2·419-2·733	<0·001