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

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Summary

Background Guidelines recommend screening for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* at three anatomical sites (urethra, anus, and pharynx) every 3 months (3×3) in men who have sex with men (MSM) and transgender women taking HIV pre-exposure prophylaxis (PrEP). We present the first randomised controlled trial to compare the effect of screening versus non-screening for *N gonorrhoeae* and *C trachomatis* on the incidence of these infections in MSM and transgender women taking PrEP.

Methods A multicentre, randomised, controlled trial of 3×3 screening for *N gonorrhoeae* and *C trachomatis* versus non-screening was done among MSM and transgender women taking PrEP in five HIV reference centers in Belgium. Participants attended the PrEP clinics quarterly for 12 months. *N gonorrhoeae* and *C trachomatis* was tested at each visit in both arms, but results were not provided to the non-screening arm, if asymptomatic. The primary outcome was incidence rate of *N gonorrhoeae* and *C trachomatis* infections in each arm, assessed in the per-protocol population. Non-inferiority of the non-screening arm was proven if the upper limit of the 95% CI of the incidence rate ratio (IRR) was lower than 1·25. This trial is registered with ClinicalTrials.gov, NCT04269434, and is completed.

Findings Between Sept 21, 2020, and June 4, 2021, 506 participants were randomly assigned to the 3×3 screening arm and 508 to the non-screening arm. The overall incidence rate of *N gonorrhoeae* and *C trachomatis* was 0·155 cases per 100 person-days (95% CI 0·128–0·186) in the 3×3 screening arm and 0·205 (95% CI 0·171–0·246) in the non-screening arm. The incidence rate was significantly higher in the non-screening arm (IRR 1·318, 95% CI 1·068–1·627). Participants in the non-screening arm had a higher incidence of *C trachomatis* infections and symptomatic *C trachomatis* infections. There were no significant differences in *N gonorrhoeae* infections. Participants in the non-screening arm consumed significantly fewer antimicrobial drugs. No serious adverse events were reported.

Interpretation We failed to show that non-screening for *N gonorrhoeae* and *C trachomatis* is non-inferior to 3×3 screening in MSM and transgender women taking PrEP in Belgium. However, screening was associated with higher antibiotic consumption and had no effect on the incidence of *N gonorrhoeae*. Further research is needed to assess the benefits and harms of *N gonorrhoeae* and *C trachomatis* screening in this population.

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Introduction

International guidelines stipulate that screening programmes should only be introduced once they have met a set of criteria: the benefits should outweigh the harms, screening should be cost-effective, and there should be scientific evidence of screening programme effectiveness.[1] No randomised controlled trial (RCT) has evaluated the efficacy of screening for *Neisseria gonorrhoeae* or *Chlamydia trachomatis* in men who have sex with men (MSM) and transgender women.[2] Two large cluster RCTs have evaluated the effect of screening for *C trachomatis* in general populations.[3,4] Both found no significant effect of screening on the prevalence of *C trachomatis*. No RCTs have evaluated the efficacy of screening for *N gonorrhoeae*.[5]

Ecological analyses have found that countries where MSM are more intensively screened for *N gonorrhoeae* and *C trachomatis* do not have lower incidence and prevalence of asymptomatic or symptomatic *N gonorrhoeae* and *C trachomatis* infection than countries that screen less.[6] One study that used self-reported data from two surveys in 2010 and 2017

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Research in context

Evidence before this study

We searched PubMed until April 6, 2023, for reports of randomised controlled trials (RCTs) reporting the effect of screening for *Neisseria gonorrhoeae* or *Chlamydia trachomatis* on the prevalence or incidence of these infections. We used the search terms "chlamydia" OR "gonorrh*" AND "screening" OR "testing" AND "trial". We found no reports of such trials for *N gonorrhoeae*. We found two RCTs assessing the effect of screening for *C trachomatis* in the general population. A step-wedge RCT explored the effect of yearly screening for *C trachomatis* among more than 300 000 men and women aged 16–29 years in the Netherlands and did not show a reduction in positivity rates (odds ratio 0·96, 95% CI 0·83–1·10; p=0·52) nor estimated population prevalence (3·0% in the control arm *vs* 2·6% in the intervention arm). An Australian cluster RCT assessed the effect of yearly screening for *C trachomatis* in about 4000 men and women aged 16–29 years and did not show a significant reduction in the prevalence of this infection (adjusted relative difference 0·9, 95% CI 0·5–1·6; p=0·67).

Added value of this study

We describe the results of the first RCT to compare screening for *N gonorrhoeae* and *C trachomatis* versus non-screening among men who have sex with men (MSM) and transgender women taking HIV pre-exposure prophylaxis. In the primary analysis, we found that non-screening was associated with an overall higher incidence of *N gonorrhoeae* and *C trachomatis* infections, but this difference was driven by non-lymphogranuloma venereum *C trachomatis* infections alone as no difference in *N gonorrhoeae* infections was found. Given that asymptomatic participants in the non-screening arm were not aware of a positive *N gonorrhoeae* and *C trachomatis* result and thus not treated, two consecutive *N gonorrhoeae* and *C trachomatis* diagnoses in this arm might represent the same, untreated infection. Therefore, we did a sensitivity analysis, controlling for this untreated-infections bias in the non-screening arm. In this sensitivity analysis, we found no difference in terms of *N gonorrhoeae* or *C trachomatis* incidence, or incidence of both infections, between both arms. Screening and subsequent treatment for *N gonorrhoeae* and *C trachomatis* was associated with a 21–45% increase in antimicrobial consumption.

Implications of all the available evidence

Our study found that screening for *N gonorrhoeae* and *C trachomatis* at three anatomical sites every 3 months in MSM and transgender women taking HIV pre-exposure prophylaxis could lead to a reduction in the incidence of *C trachomatis* infections but not *N gonorrhoeae* infections and comes at the cost of higher antimicrobial consumption. More studies are needed to assess the benefits and harms of *N gonorrhoeae* and *C trachomatis* screening in this population.

of over 100 000 MSM from 46 European countries found that the intensity of screening increased over time, but intensity was positively associated with the number of symptomatic *N gonorrhoeae* and *C trachomatis* cases.[6] The authors concluded that intensive screening might abrogate the development of an immune response to these infections, which paradoxically increases the risk of subsequent re-infection. In the case of *C trachomatis*, there are experimental data from animal models, an observational clinical study, and some epidemiological evidence to support this arrested immunity hypothesis.[7] Several authors have argued for more frequent *N gonorrhoeae* and *C trachomatis* screening in MSM.[8] They have largely based this call on modelling studies, some of which have found that screening every 2–3 months reduces incidence, and that more frequent screening detects more infections which, if treated, will reduce the population prevalence.[8] Partly as a response to these arguments and evidence of increasing incidence of infections in many countries, numerous guidelines have recommended increasing intensity of screening for *N gonorrhoeae* and *C trachomatis* in MSM taking pre-exposure prophylaxis (PrEP) to testing at three sites (urethra, anus, and pharynx) once every 3 months (3×3 screening).[9]

Screening of MSM for *N gonorrhoeae* and *C trachomatis* results in high consumption of macrolide, cephalosporin, and tetracycline.[10] For instance, 3×3 screening results in up to 12 defined daily doses of macrolides per 1000 inhabitants per year.[11] This high antimicrobial consumption exceeds the approximate thresholds for the induction of antimicrobial resistance in *Streptococcus pneumoniae*, *Mycoplasma genitalium*, and *Treponema pallidum* by five-fold to nine-fold.[12] Screening MSM for *N gonorrhoeae* and *C trachomatis* might therefore select for antimicrobial resistance in these and other bacteria such as *Helicobacter pylori* and *N gonorrhoeae*. In a previous study, for example, we found a positive ecological association between the intensity of screening MSM for *N gonorrhoeae* and *C trachomatis* and reduced gonococcal susceptibilities to cephalosporins.[13] However, this study was prone to the ecological-inference fallacy. Increased antimicrobial consumption is of particular concern in PrEP users as gonococcal antimicrobial resistance has frequently emerged in such core groups heavily exposed to antimicrobials.[14] For instance, the proportion of *N gonorrhoeae* isolates with azithromycin resistance in Belgium has increased from 2% to 33% in less than a decade, and this increase is more pronounced among MSM.[15] A similar but larger increase in resistance to macrolide and multidrug resistance has occurred in *M genitalium* in Belgium, meaning that some individuals have untreatable infections.[16] Interestingly, we showed that changing

N gonorrhoeae and *C trachomatis* screening intensity in a PrEP cohort from testing three sites once every 3 months to testing one site every 6 months reduced consumption of macrolides from 12·05 to 3·27 daily doses without any noticeable adverse clinical consequences.[11] Such insights are important given evidence that a decline in macrolide consumption can lead to a decline in the prevalence of antimicrobial resistance in bacteria such as group A streptococci.[17]

Given the unclear benefits and the potential harms of screening MSM taking PrEP for *N gonorrhoeae* and *C trachomatis*, authors have underlined the urgent need for RCTs on this topic.[5] Here we present the results of an RCT comparing the effect of screening on the incidence of *N gonorrhoeae* and *C trachomatis* infections in MSM and transgender women taking PrEP. We also assessed the effect of screening on the incidence of symptomatic *N gonorrhoeae* and *C trachomatis* infections, syphilis infections, and antibiotic consumption as well as PrEP users' perceptions of screening for sexually transmitted infections (STIs).

Methods

Study design

We did a multicentre RCT of 3×3 screening for *N gonorrhoeae* and *C trachomatis* versus non-screening among MSM and transgender women taking HIV PrEP in Belgium. The study took place in five HIV reference centres in Belgium (Institute of Tropical Medicine in Antwerp, Saint-Pierre University Hospital and Erasme University Hospital in Brussels, Ghent University Hospital in Ghent, and Liège University Hospital in Liège). A qualitative substudy was embedded within the trial at the Institute of Tropical Medicine to explore PrEP users' perceptions of STI screening. This study was approved by the Institutional Review Board of the Institute of Tropical Medicine, Antwerp, and by the Ethics Committees of the University Hospital of Antwerp, Saint-Pierre University Hospital, Ghent University Hospital, Erasme University Hospital, and Liège University Hospital. Written informed consent was obtained from all participants in Dutch, French, or English. The study protocol is available in the appendix (p 6).

Participants

All men followed up for PrEP in these five centres were approached for study inclusion. Inclusion criteria were being able and willing to provide informed consent, being born as male, being at least 18 years old, having had oral sex or anal sex, or both, with another man in the past 12 months, being enrolled in a Belgian PrEP centre, and willingness to comply with the study procedures. Exclusion criteria were being enrolled in another interventional trial, testing positive for HIV at screening, and having symptoms of proctitis or urethritis.

Randomisation and masking

Participants who met all inclusion criteria were randomly assigned (1:1) into the non-screening (intervention) or 3×3 screening (control) arms. The randomisation list was prepared by an independent statistician using SAS (version 9.4). To ensure (approximate) treatment balance within study sites, the randomisation list was blocked by site using variable block sizes (block size four or six). The overview of the randomisation list was not shared with the investigators until trial database lock. Study participants, doctors, and nurses were not blinded. The study statistician was blinded until approval of the statistical analysis plan.

Procedures

As in routine PrEP care, participants were asked to attend quarterly visits at the PrEP clinic. The study duration was 12 months, hence five study visits were planned. One baseline visit took place at day 0 and four subsequent visits at months 3, 6, 9, and 12, each within a window of 1 week earlier and 6 weeks later.

At the baseline visit, after eligibility assessment, informed consent procedure, and randomisation, sociodemographic characteristics, sexual behaviour, STI history in the past 12 months, and antibiotic use in the past 6 months were collected. First-void urine samples, pharyngeal swabs, and anorectal swabs were collected. Pharyngeal swabs were collected by physicians, whereas both other samples were self-collected. Samples per participant were pooled and tested for *N gonorrhoeae* and *C trachomatis* by nucleic acid amplification tests. Those who tested positive were recalled for treatment according to current guidelines.[18] This generally entailed ceftriaxone 500 mg or 1 g intramuscularly with or without azithromycin 2 g orally for *N gonorrhoeae* and doxycycline 200 mg per day orally for 7 days for *C trachomatis* and 21 days for lymphogranuloma venereum. Syphilis and HIV testing was done on blood samples.

At the month 3, 6, and 9 visits, symptoms compatible with an STI, STIs diagnosed, antibiotic use, and sexual behaviour since the previous visit were recorded. First-void urine samples, pharyngeal swabs, and anorectal swabs were collected from all participants. For asymptomatic participants in the 3×3 screening arm, these samples were analysed and, if positive, participants were recalled for treatment according to current guidelines. In the non-screening arm, results were only provided when symptoms were present. Asymptomatic participants in the non-screening arms were thus not informed of the result of these samples, nor were physicians who did study visits. All participants who reported symptoms either during study visits, or between study visits, were tested and treated as per current guidelines.

See Online for appendix

At month 12, data were collected as for the previous visits. First-void urine samples, pharyngeal swabs, and

anorectal swabs were collected and analysed for *N gonorrhoeae* and *C trachomatis* for all participants. If positive, participants from both arms were treated as per current guidelines. HIV and syphilis testing was done on blood samples every 3 months.

Study participants were able to attend PrEP or STI clinics at any point in between the scheduled visits for any health problems. Participants were encouraged to attend clinic for any symptoms compatible with an STI. Participants who received a partner notification for an STI were tested and treated according to the current guidelines. Test-of-cure visits were done according to local protocols.

For the qualitative substudy, social scientists trained in qualitative research held three focus group discussions, among randomly selected study participants from the Institute of Tropical Medicine centre. Each focus group consisted of three to five participants. To maximise variation in perceptions, two in-depth interviews with PrEP users who declined participation to the main study were done. The interviewers obtained verbal informed consent from each participant before the start of each discussion and in-depth interview. Audio-recording took place upon agreement. Focus group discussions and in-depth interviews were done in Dutch and online via a secured platform, respecting General Data Protection Regulation.

N gonorrhoeae and *C trachomatis* testing was done at each site's laboratory. The three samples were pooled per patient and visit according to a validated pooling strategy. Positive samples for *C trachomatis* were sent to the National Reference Center for STIs (Institute of Tropical Medicine, Antwerp) for genotyping to detect lymphogranuloma venereum serovars. HIV and syphilis testing was done according to local protocols.

Outcomes

The primary outcome was the overall incidence of *N gonorrhoeae* and *C trachomatis* infections in each arm. Each participant could contribute one diagnosis of *C trachomatis* and one diagnosis of *N gonorrhoeae* per scheduled or unscheduled visit. Only laboratory-confirmed diagnoses made between scheduled visits, done inside or outside of the study clinic, were included.

Secondary outcomes were ceftriaxone, azithromycin, and doxycycline exposure in the two study arms (expressed in daily defined doses per 1000 person-years according to WHO methodology), incidence rate of symptomatic *N gonorrhoeae* and *C trachomatis*, and incidence rates of syphilis and HIV.

All *N gonorrhoeae* and *C trachomatis* diagnoses were included in the primary outcome. Hence, it was implicitly assumed that every diagnosis was a new infection. Median durations of untreated infections are 16 weeks for pharyngeal *N gonorrhoeae*, 9 weeks for anorectal *N gonorrhoeae*, 6 weeks for pharyngeal *C trachomatis*, and 13 weeks for anorectal *C trachomatis*.[19,20] Therefore, it is possible that *N gonorrhoeae* and *C trachomatis* infections detected at visits from 3 months to 12 months in the non-screening arm were non-resolved infections already present at a preceding visit. This could spuriously increase the measured incidence in the non-screening arm as the same infection would be counted twice. Therefore, a sensitivity analysis was done to deal with this untreated-infection bias. In this analysis, consecutive diagnoses of the same type (eg, *C trachomatis* at two consecutive visits) in the non-screening arm were counted as one infection unless the preceding diagnosis was a symptomatic one (and therefore treated), or if the participants reported having used antibiotics efficacious against the relevant STI between both diagnoses.

In addition, a prespecified subgroup analysis was performed by stratifying the participants according to STI risk behaviour. We hypothesised that the effects of screening for *N gonorrhoeae* and *C trachomatis* could be different in individuals with a lower number of sexual partners given the lower sexual network connectivity in these individuals. For that purpose, participants that consistently reported four or fewer partners in all five study visits were categorised as being at lower risk and all other participants were categorised as being at higher risk. Finally, a separate, non-prespecified analysis was added with gonorrhoea and chlamydia separately as outcomes.

All focus group discussions and in-depth interviews were transcribed verbatim and pseudonymised. Data were collected and analysed iteratively with a thematic analysis approach and Nvivo. We inductively developed an initial coding scheme. Subsequently, we re-read all transcripts with the focus on describing the variation in perceptions towards testing for asymptomatic and symptomatic *N gonorrhoeae* and *C trachomatis* infections and how the emergence of antibiotic resistance influences these perceptions.

The largest safety concern for this study was that the participants in the non-screening arm could have higher incidence of symptomatic *N gonorrhoeae* and *C trachomatis*. Rather than reporting each symptomatic episode of *N gonorrhoeae* and *C trachomatis* as an adverse event, an independent data and safety monitoring board evaluated if the non-screening arm had an unacceptably high incidence of symptomatic *N gonorrhoeae* and *C trachomatis*. For this purpose, the board included two independent STI experts (infectious disease physicians and epidemiologists) and the study statistician to evaluate the incidence of symptomatic *N gonorrhoeae* and *C trachomatis* in both arms at two interim timepoints: once 50% and 100% of all study participants had completed their month 6 visit. It was decided that serious consideration would be given to stopping the study if the incidence of symptomatic *N gonorrhoeae* and *C trachomatis* infections in the non-screening arm was double that of the screening arm.

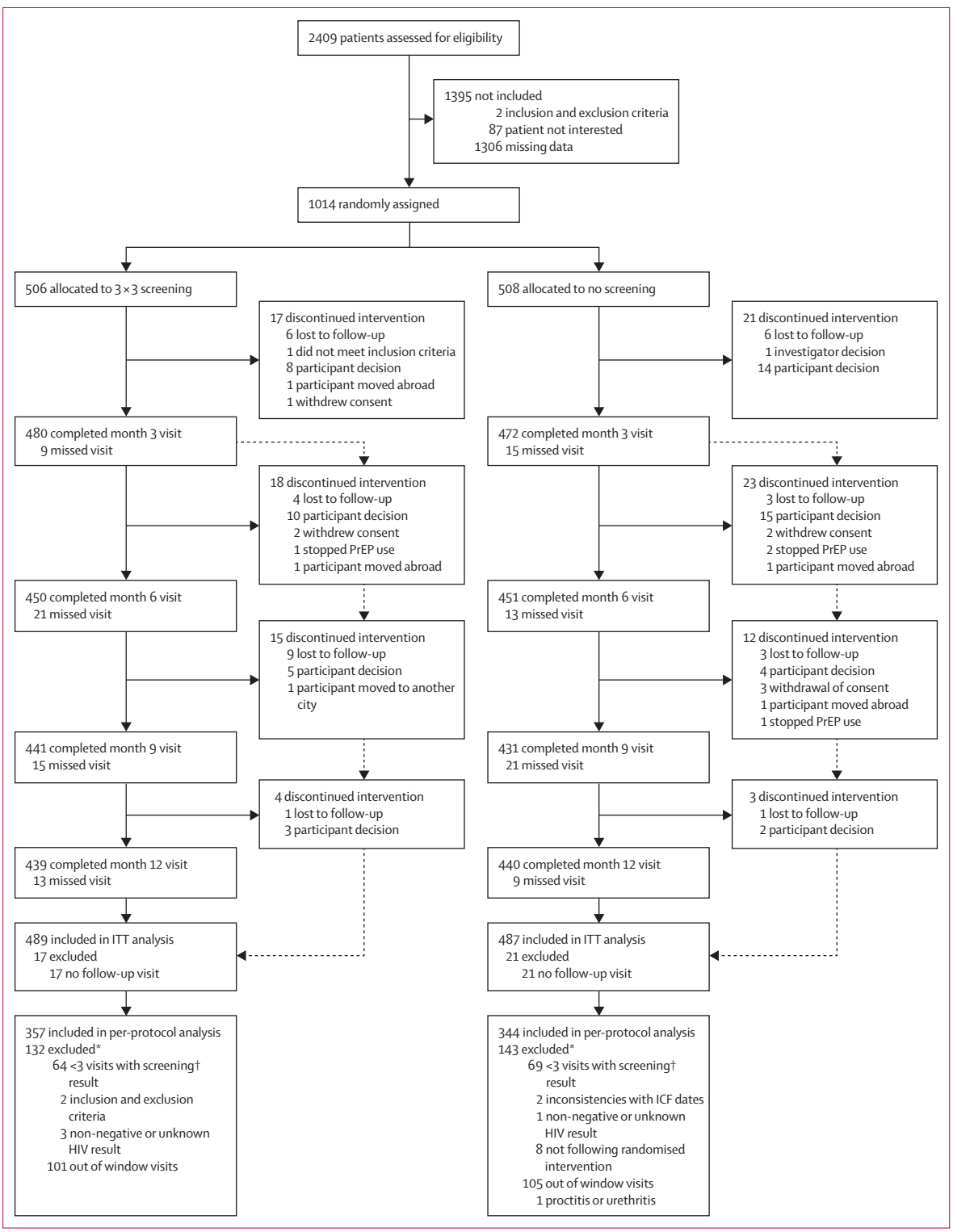

Figure 1: **Trial profile**
3×3 screening=screening of three anatomical sites (urethra, anus, and pharynx) every 3 months. ICF=informed consent form. ITT=intention-to-treat. PrEP=pre-exposure prophylaxis. *Data are not mutually exclusive. †Screening for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.

Statistical analysis

For the primary outcome, estimates were based on a negative-binomial regression model with number of diagnoses as dependent variable, study arm and study site as independent variable, and log(visit number) as offset. This model also provided an estimate of the log incidence rate ratio (IRR, no screening *vs* screening), together with 95% CI. The predicted values and SEs estimated from the regression models were used to calculate the 95% CI for the incidence rate. The standard formula for Wald CIs was then used in the log scale and exponentiated. Non-inferiority of the no screening arm was concluded if the upper limit of the 95% CI was lower than 1·25. The same methodology was applied for the secondary outcomes except for antimicrobial consumption, for which a rate ratio was calculated, with number of daily defined doses as dependent variable. The number needed to screen was calculated by dividing 1 by the absolute risk reduction between both arms.

The primary analysis was done with the per-protocol approach. Participants who had fewer than three visits with *N gonorrhoeae* and *C trachomatis* results or did not follow the randomly assigned intervention were excluded from the per-protocol analysis. Participants were excluded from the intention-to-treat (ITT) analysis if they did not attend any of the follow-up visits.

Participants in each intervention arm were described with respect to baseline characteristics. The description was done in terms of median (IQR) and mean (SD) for continuous characteristics and using counts and percentages for categorical characteristics.

On the basis of a previous study, we estimated an average number of diagnoses per participant of 0·72 over four visits.[21] The no screening arm was considered to be non-inferior if there was an increase of maximal 25% in number of diagnoses (ie, increase of an average of 0·72 to 0·90 per four visits). Assuming that 95% of the participants would have data on all four follow-up visits, and 5% would have data on only three visits, the required sample size to obtain 80% power at a significance level of 5% was 912. Assuming an additional 10% drop out rate, the final sample size was estimated to be 1014 participants.

We estimated the duration of *N gonorrhoeae* and *C trachomatis* infections in the non-screening arm by calculating the time difference in days between the estimated infection date and the estimated clearance date. The infection date was defined as the midpoint between the diagnosis date and the date of the previous negative test. The clearance date was either the date where a treatment was provided, or the midpoint between the last positive test result and the first subsequent negative test.

All statistical analyses were done with R (version 4.2).

The trial protocol was registered at ClinicalTrials.gov, NCT04269434, and is completed.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

2409 individuals were approached for the study between Sept 21, 2020, and June 4, 2021, of whom 1014 were randomly assigned (506 to the 3×3 screening arm and 508 to the non-screening arm figure 1). 38 participants who did not attend any follow-up visit were excluded from the analysis. 275 participants were excluded from the per-protocol analysis: 206 had out of window visits, 133 had fewer than three visits with *N gonorrhoeae* and *C trachomatis* results, and eight in the non-screening arm did not follow the assigned intervention. The study ended on Aug 26, 2022. The baseline characteristics as well as number of sex partners were well balanced between the two arms (table 1). The number of sex partners and unprotected sex partners remained stable across all study visits in both arms (appendix p 1).

196 *N gonorrhoeae* cases and 224 *C trachomatis* cases were diagnosed in the non-screening arm after the baseline visit, and 164 *N gonorrhoeae* cases and 157 *C trachomatis* cases were found in the 3×3 screening arm (table 2). In the primary analysis, the incidence of *N gonorrhoeae* and *C trachomatis* was 0·205 cases per 100 person-days (95% CI 0·171–0·246) in the non-screening arm and 0·155 cases per 100 person-days (95% CI 0·128–0·186) in the 3×3 screening arm (table 3). The incidence rate of *N gonorrhoeae* and *C trachomatis* was higher in the non-screening arm compared with the 3×3 screening arm (IRR 1·318, 95% CI 1·068–1·627; table 3; figure 2) and the upper limit of the 95% CI included the non-inferiority cutoff of 1·25, indicating we cannot conclude non-inferiority of non-screening compared with 3×3 screening. The IRR of symptomatic *N gonorrhoeae* and *C trachomatis* was 1·373 (95% CI 0·963–1·956; table 3). Participants in the non-screening arm consumed less azithromycin, ceftriaxone, and doxycycline (table 4) compared with the 3×3 screening arm. The incidence of syphilis was not significantly higher in the non-screening arm compared with the 3×3 screening arm: incidence rate for non-screening 0·026 (95% CI 0·016–0·042) and for 3×3 screening 0·018 (0·011–0·029); non-screening versus 3×3 screening IRR 1·471 (95% CI 0·943–2·299; p=0·089).

In the per-protocol sensitivity analysis accounting for the untreated-infection bias, there was no difference between arms in terms of the incidence rate of *N gonorrhoeae* and *C trachomatis* (IRR 1·093, 95% CI 0·895–1·334; figure 2, table 3), but the 95% CI of the IRR included the non-inferiority cutoff of 1·25.

Results were similar between the per-protocol and ITT analysis, except for the incidence of syphilis, which was higher in the non-screening arm than in the 3×3 screening arm in the ITT analysis (appendix p 2).

Differences in *N gonorrhoeae* and *C trachomatis* incidence were driven by differences in *C trachomatis* incidence. We could not establish a difference in *N gonorrhoeae* incidence in the per-protocol analysis (table 3, figure 2) or in symptomatic *N gonorrhoeae* incidence. The incidence of *C trachomatis* and symptomatic *C trachomatis* was higher in the non-screening arm. However, there was no difference in *C trachomatis* incidence in the sensitivity analysis. On the basis of these results, the estimated number needed to screen for symptomatic and asymptomatic *C trachomatis* infections was 25·55 and 10·92, respectively (appendix p 3).

A total of 231 participants reported less than five sex partners at all study visits and were thus considered as being at lower risk of STIs and the remaining 783 participants were considered to be at higher risk. Participants at higher risk had a higher incidence of *N gonorrhoeae* and *C trachomatis* in the non-screening arm compared with the 3×3 screening arm in the primary analysis (table 3) but this difference disappeared in the sensitivity analysis, when accounting for the untreated-infection bias. Similar results were obtained for the incidence rates of *C trachomatis* cases and symptomatic *C trachomatis* cases. However, no difference was found in terms of the incidence of *N gonorrhoeae* cases or symptomatic *N gonorrhoeae* cases in these participants. The IRRs in participants categorised as being at lower risk were not different.

The median estimated duration of *N gonorrhoeae* infections in the non-screening arm was 72·5 days (IQR 52·5–98·0), and of *C trachomatis* infections 90·5 days (53·0–132·4).

Symptomatic participants typically presented with mild symptoms and no participant reported severe outcomes or adverse events (appendix p 4). The number of unscheduled visits and visits for partner notification can be found in the appendix (p 5).

Participants of the qualitative substudy reported mixed reactions towards non-screening for asymptomatic *N gonorrhoeae* and *C trachomatis*. The fact that these STIs are mostly asymptomatic and self-limiting, without causing serious complications or harm to the individual, were mentioned as arguments against screening.

> "Why would you try to detect something if you have no symptoms? And that is actually not very dangerous either? Even if you pass it on."
>
> *(Focus group discussion 3, ID 32)*

The main reported disadvantage of non-screening was the possibility of ongoing transmission to sexual partners. For some participants, not testing and treating was accompanied with feelings of guilt, risk, and irresponsibility. Some participants suggested adjusting the testing strategy according to the number of sexual contacts a person has, and whether or not condoms are used.

	3×3 screening (n=506)	Non-screening (n=508)	Total population (n=1014)
Age, years	39 (33·0–47·0)	39 (32·5–48·0)	39 (33·0–47·0)
Gender			
Man	506 (100%)	505 (99·4%)	1011 (99·7%)
Transgender woman	0	3 (0·6%)	3 (0·3%)
Number of sex partners (past 3 months)	4 (2–8)	4 (2–8)	4 (2–8)
Number of unprotected sex partners (past 3 months)	2 (1–5)	2 (1–5)	2 (1–5)
Any antibiotic use (past 6 months)	192 (37·9%)	173 (34·1%)	365 (36·0%)
Cephalosporins	67 (13·2%)	77 (15·2%)	144 (14·2%)
Macrolides	81 (16·0%)	94 (18·5%)	175 (17·3%)
Penicillin	63 (12·5%)	47 (9·3%)	110 (10·8%)
Quinolones	11 (2·2%)	5 (1·0%)	16 (1·6%)
Tetracyclines	57 (11·3%)	54 (10·6%)	111 (10·9%)

Data are n (%) or median (IQR). 3×3 screening=screening of three anatomical sites (urethra, anus, and pharynx) every 3 months.

Table 1: **Baseline characteristics in both arms**

	N gonorrhoeae	*C trachomatis* (non-LGV)	*C trachomatis* (LGV)
Total number of cases	360	381	24
Non-screening	196 (54·4%)	224 (58·8%)	10 (41·6%)
3×3 screening	164 (45·5%)	157 (41·2%)	14 (58·3%)
Symptomatic cases			
Total	104 (28·8%)	66 (18·4%)	10 (41·7%)
Non-screening*	56 (53·8%)	43 (65·2%)	3 (0·3%)
3×3 screening*	48 (46·2%)	23 (34·8%)	7 (0·7%)

Data are n (%). LGV=lymphogranuloma venereum *C trachomatis*. 3×3 screening=screening of three anatomical sites (urethra, anus, and pharynx) every 3 months. *% among symptomatic infections.

Table 2: **Number of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* cases diagnosed during the study (baseline visit excluded)**

> "Assuming that a condom is almost never used because there is PrEP. And that there are about five to six or so changing contacts per month. With that in mind, I feel safer being fully tested all the time. If I had a steady partner, and if someone were to come once a month, I would think: okay, let me get tested once every 6 months."
>
> *(Focus group discussion 2, ID 26)*

The qualitative data showed that perceptions towards antimicrobial resistance varied. Some participants were concerned about the emergence of antimicrobial resistance or stated they preferred to avoid using antibiotics when possible. Others reported a lack of knowledge on the subject.

> "I compare it to a scale and I find it difficult to see where that carries the most weight: is the weight in the sense of antibiotic resistance, or is the weight in the sense of I'm walking with an asymptomatic gonorrhoea infection that I could spread to many others. I, personally, find that a difficult balancing act."
>
> *(Focus group discussion 2, ID 26)*

	Total population						Stratified analysis, ≥5 partners						Stratified analysis, <5 partners					
	Primary analysis			Sensitivity analysis			Primary analysis			Sensitivity analysis			Primary analysis			Sensitivity analysis		
	IR estimate (95% CI)	IRR (95% CI)	p value	IR estimate (95% CI)	IRR (95% CI)	p value	IR estimate (95% CI)	IRR (95% CI)	p value	IR estimate (95% CI)	IRR (95% CI)	p value	IR estimate (95% CI)	IRR (95% CI)	p value	IR estimate (95% CI)	IRR (95% CI)	p value
***N gonorrhoeae* and *C trachomatis* cases**																		
Non-screening*	0·205 (0·171–0·246)	1·318 (1·068–1·627)	0·0102	0·169 (0·141–0·200)	1·093 (0·895–1·334)	0·385	0·236 (0·196–0·284)	1·290 (1·040–1·599)	0·021	0·194 (0·162–0·233)	1·071 (0·874–1·312)	0·511	0·0009 (0·0004–0·002)	1·430 (0·694–2·944)	0·332	0·0007 (0·0003–0·0016)	1·178 (0·594–2·334)	0·640
3×3 screening*	0·155 (0·128–0·186)	1 (ref)	..	0·154 (0·128–0·184)	1 (ref)	..	0·182 (0·150–0·220)	1 (ref)	..	0·181 (0·151–0·217)	1 (ref)	..	0·0006 (0·00003–0·0015)	1 (ref)	..	0·0006 (0·0003–0·0014)	1 (ref)	..
***N gonorrhoeae* and *C trachomatis*, symptomatic**																		
Non-screening*	0·046 (0·032–0·066)	1·373 (0·963–1·956)	0·0801	..	..	..	0·055 (0·038–0·079)	1·352 (0·940–1·945)	0·104	..	..	..	0·000 (0·000–0·000)†	1·473 (0·353–6·155)	0·595	..	..	..
3×3 screening*	0·034 (0·023–0·049)	1 (ref)	..	..	..	..	0·040 (0·027–0·059)	1 (ref)	..	..	..	..	0·000 (0·000–0·000)†	1 (ref)	..	..	..	..
***N gonorrhoeae* cases**																		
Non-screening*	0·099 (0·078–0·125)	1·212 (0·940–1·564)	0·138	0·089 (0·055–0·112)	1·073 (0·837–1·376)	0·579	0·116 (0·091–0·147)	1·213 (0·826–1·367)	0·637	0·103 (0·081–0·130)	1·062 (0·685–1·256)	0·626	0·000 (0·000–0·000)†	1·041 (0·389–2·787)	0·936	0·000 (0·000–0·000)†	1·041 (0·389–2·787)	0·936
3×3 screening*	0·081 (0·064–0·103)	1 (ref)	..	0·082 (0·065–0·104)	1 (ref)	..	0·095 (0·074–0·122)	1 (ref)	..	0·096 (0·076–0·122)	1 (ref)	..	0·000 (0·000–0·000)†	1 (ref)	..	0·000 (0·000–0·000)†	1 (ref)	..
***N gonorrhoeae*, symptomatic**																		
Non-screening*	0·024 (0·015–0·040)	1·162 (0·757–1·783)	0·492	..	..	..	0·029 (0·018–0·048)	1·155 (0·742–1·801)	0·522	..	..	..	0·000 (0·000–0·000)†	1·117 (0·225–5·533)	0·893	..	..	..
3×3 screening*	0·021 (0·013–0·035)	1 (ref)	..	..		..	0·025 (0·015–0·042)	1 (ref)	..	..		..	0·000 (0·000–0·000)†	1 (ref)	..	..	..	..
***C trachomatis* cases**																		
Non-screening*	0·104 (0·083–0·130)	1·435 (1·098–1·875)	0·008	0·079 (0·063–0·099)	1·114 (0·865–1·434)	0·404	0·117 (0·093–0·148)	1·375 (1·041–1·815)	0·025	0·090 (0·071–0·114)	1·077 (0·826–1·403)	0·586	0·0006 (0·0002–0·002)	1·902 (0·783–4·620)	0·156	0·0004 (0·0002–0·001)	1·351 (0·584–3·128)	0·482
3×3 screening*	0·072 (0·056–0·092)	1 (ref)	..	0·071 (0·056–0·089)	1 (ref)	..	0·085 (0·066–0·109)	1 (ref)	..	0·083 (0·0465–0·106)	1 (ref)	..	0·0003 (0·0001–0·001)	1 (ref)	..	0·0003 (0·0001–0·001)	1 (ref)	..
***C trachomatis*, symptomatic**																		
Non-screening*	0·021 (0·012–0·034)	1·798 (1·038–3·117)	0·037	..	..	..	0·024 (0·014–0·041)	1·743 (0·990–3·067)	0·054	..	..	..	0·000 (0·000–0·000)†	2·301 (0·209–25·400)	0·496	..	..	..
3×3 screening*	0·011 (0·006–0·020)	1 (ref)	..	..	..	..	0·014 (0·008–0·025)	1 (ref)	..	..	..	..	0·000 (0·000–0·000)†	1 (ref)	..	..	..	..

IR=incidence rate. IRR=incidence rate ratio. 3×3 screening=screening of three anatomical sites (urethra, anus, and pharynx) every 3 months. *IR in cases per 100 person-days.†The incidences in these instances were in the magnitude of 1×10^{-7}, thus both the point estimate and the CIs appear as 0 in the table

Table 3: **IR and IRR of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* and symptomatic *N gonorrhoeae* and *C trachomatis* (per-protocol analysis)**

Lastly, not all participants were familiar with the natural course of *N gonorrhoeae* and *C trachomatis* infections and the mechanisms of antimicrobial resistance. As knowledge increased during the sessions, participants' attitudes sometimes shifted towards non-screening for asymptomatic *N gonorrhoeae* and *C trachomatis*.

Discussion

This RCT did not establish that non-screening for *N gonorrhoeae* and *C trachomatis* in MSM and transgender women on PrEP is non-inferior to 3×3 screening with respect to *N gonorrhoeae* and *C trachomatis* incidence. The overall incidence of *N gonorrhoeae* and *C trachomatis* was significantly higher in the non-screening arm than in the screening arm in the primary analysis. However, in the sensitivity analysis, controlling for the untreated-infections bias, we could not show a statistically significant difference in the incidence of *N gonorrhoeae* and *C trachomatis* between both arms. Differences in *N gonorrhoeae* and *C trachomatis* incidence were driven by a higher incidence of *C trachomatis* in the non-screening arm, as the incidence of *N gonorrhoeae* did not differ. The incidence of symptomatic *C trachomatis* was also higher in the non-screening arm. Participants in the screening arm consumed considerably more antimicrobials compared with the non-screening arm. Among participants categorised as being at higher risk for STIs, the incidences of *N gonorrhoeae* and *C trachomatis*, *C trachomatis*, and symptomatic *C trachomatis* were higher as well. These results provide the first RCT-based evidence of the benefits and harms of screening for *N gonorrhoeae* and *C trachomatis* in MSM taking PrEP.

Our finding that screening was associated with a lower incidence of *C trachomatis* but not *N gonorrhoeae* is commensurate with the presumed longer duration of infection for *C trachomatis* and possible higher proportion of *C trachomatis* infections that are asymptomatic in MSM.[20,22] For instance, a systematic review found that, compared with gonorrhoea, chlamydia had a longer duration of infection in both the oropharynx and anorectum in MSM.[20] Hence, periodic screening for *N gonorrhoeae* and *C trachomatis* might detect more *C trachomatis* infections as *N gonorrhoeae* infections might have cleared spontaneously between screening timepoints. Although the findings of our study do not provide strong support to continue screening for *N gonorrhoeae* in MSM in PrEP cohorts, they do provide some evidence to support screening for *C trachomatis*.[22] Nonetheless, screening might exert its effect at both individual and population levels. Therefore, benefits and harms of screening for *N gonorrhoeae* and *C trachomatis* must be assessed at both levels.

Besides the population-level effect, other elements should be taken into account when assessing the effect of screening for *N gonorrhoeae* and *C trachomatis*. An increase in the incidence of *N gonorrhoeae* and *C trachomatis* infections in PrEP users resulting from a non-screening strategy might result in an increased transmission and subsequent morbidity in other populations. For instance, there is evidence of bridging transmission of *N gonorrhoeae* between MSM and women.[23] The additional *N gonorrhoeae* infections in women could result in increased adverse events such as infertility. Moreover, a modelling study has suggested that screening for *N gonorrhoeae* might allow for early detection and treatment of already resistant strains, and therefore limit their spread.[24] Lastly, other aspects such as the effect of screening on the costs for both patients and health insurance are also important.

We have previously established that intense screening for *N gonorrhoeae* and *C trachomatis* is a key driver of high antibiotic consumption in PrEP users.[10] In a similar vein, reducing the intensity of screening for *N gonorrhoeae* and *C trachomatis* in PrEP users has been shown to result in a large reduction in macrolide consumption.[11] However, screening and subsequent treatment for *C trachomatis* might be less likely to induce antimicrobial resistance than screening for *N gonorrhoeae*. This is because treatment guidelines recommend the less resistogenic doxycycline for *C trachomatis* therapy compared with *N gonorrhoeae* therapy where ceftriaxone with or without azithromycin (both WHO reserve antimicrobials) are advised.[25] We calculated that 10·92 men would need to be screened at three anatomical sites every 3 months for a year to prevent one asymptomatic *C trachomatis* infection and 25·55 to prevent one symptomatic *C trachomatis* infection. This would require 2·34 courses of doxycycline therapy for each symptomatic *C trachomatis* infection prevented.

In our study, participants categorised as being at higher risk had a higher incidence of asymptomatic *N gonorrhoeae* and *C trachomatis* infections. Previous

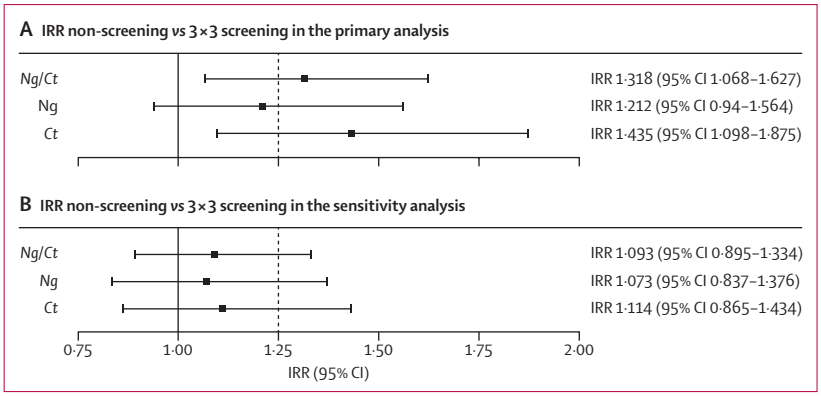

Figure 2: **Forest plots of IRRs of of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections in the primary (A) and sensitivity (B) analyses**
The vertical plain line represents 1 and the vertical dotted line the non-inferiority cutoff. 3×3 screening=screening of three anatomical sites (urethra, anus, and pharynx) every 3 months. IRR=incidence rate ratio. *Ng/Ct=N gonorrhoeae and C trachomatis.*

	Total population			Stratified analysis, ≥5 partners			Stratified analysis, <5 partners		
	Rate estimate (95% CI)	Rate ratio	p value	Rate estimate (95% CI)	Rate ratio	p value	Rate estimate (95% CI)	Rate ratio	p value
Azithromycin									
Non-screening*	0·0046 (0·0043–0·0050)	0·788 (0·719–0·863)	<0·0001	0·512 (0·367–0·713)	0·741 (0·493–1·112)	0·148	0·139 (0·051–0·381)	0·543 (0·124–2·208)	0·393
3×3 screening*	0·0059 (0·0075–0·0063)	1 (ref)	..	0·691 (0·505–0·945)	1 (ref)	..	0·257 (0·096–0·689)	1 (ref)	..
Ceftriaxone									
Non-screening*	0·0004 (0·0004–0·0006)	0·561 (0·426–0·739)	<0·0001	0·053 (0·041–0·068)	0·540 (0·398–0·733)	<0·0001	0·015 (0·006–0·038)	0·913 (0·312 – 2·677)	0·869
3×3 screening*	0·0008 (0·0007–0·0009)	1 (ref)	..	0·099 (0·081–0·121)	1 (ref)	..	0·017 (0·007–0·038)	1 (ref)	..
Doxycycline									
Non-screening*	0·0044 (0·0041–0·0048)	0·55 (0·515–0·588)	<0·0001	0·595 (0·374–0·948)	0·579 (0·319–1·052)	0·073	0·141 (0·031–0·644)	0·369 (0·034–3·991)	0·412
3×3 screening*	0·0081 (0·0075–0·0086)	1 (ref)	..	1·028 (0·636–1·661)	1 (ref)	..	0·381 (0·075–1·924)	1 (ref)	..

3×3 screening=screening of three anatomical sites (urethra, anus, and pharynx) every 3 months. *Rate in defined daily doses per 100 person-days.

Table 4: **Rate and ratio of antibiotic consumption (per-protocol analysis)**

studies have similarly found that the majority of STIs in PrEP cohorts were diagnosed in a small subgroup with a high rate of partner turnover.[26] In such individuals, high numbers of partners results in a dense sexual network that generates a high equilibrium prevalence for STIs such as *N gonorrhoeae* and *C trachomatis*.[27] Intensive screening for these STIs in this group might reduce this prevalence but would place evolutionary pressures on these STIs to acquire mutations that would enable them to regain their equilibrium prevalence. This could be via evading the diagnostic tests used (as has occurred with *C trachomatis*),[28] or via the emergence of antimicrobial resistance as has transpired on multiple occasions with *N gonorrhoeae*.[14] Therefore, although the effect of screening for *C trachomatis* was greatest in those with higher STI risk behaviour (ie, five or more partners reported at any study visit). Important to clarify what is meant by risk, screening in this group could confer the greatest risk for the emergence of antimicrobial resistance. Modelling studies have suggested that intensive screening might reduce the prevalence of *N gonorrhoeae* and *C trachomatis* to such an extent that the consumption of antibiotics could be reduced in this group.[29] These modelling studies are, however, at odds with the results of observational studies, which have found that screening MSM for *N gonorrhoeae* and *C trachomatis* was not associated with reduced prevalence regardless of intensity of screening.[30]

We found an increased incidence of syphilis infections in the non-screening arm compared with the 3×3 screening arm in the ITT analysis. This finding could be explained by the higher consumption of doxycycline and ceftriaxone, two antimicrobials effective against *T pallidum*, in the screening arm. Given that the incubation period of primary syphilis is typically 10–90 days and the fact that syphilis infections are frequently asymptomatic in this population, treating *N gonorrhoeae* and *C trachomatis* with either of these antimicrobials could have reduced the incidence of syphilis. This reduction in syphilis incidence should be taken into account when assessing the benefits and harms of screening for *N gonorrhoeae* and *C trachomatis* in PrEP users.

Our study had several limitations. The untreated infections bias meant that our primary analysis overestimated the incidence of *N gonorrhoeae* and *C trachomatis* infections in the non-screening arm. Controlling for this bias in our sensitivity analysis may, however, have underestimated *N gonorrhoeae* and *C trachomatis* incidence in the non-screening arm. Due to the pooling of samples used for *N gonorrhoeae* and *C trachomatis* testing, the anatomical site of infection was unknown, which might have impacted our results. Moreover, the assays used for *N gonorrhoeae* and *C trachomatis* testing do not allow to discriminate viable infections from non-viable infections. The use of such assays could lead to a better estimation of the incidence of infections and should be included in future trials. Furthermore, given the number of sex partners reported by participants, there might have been contamination between study arms. Another limitation is that the participants and physicians were not blinded. This might have resulted in altered behaviour. This RCT took place in different periods of COVID-19 restrictions. PrEP users decreased their number of partners in the periods of COVID-19 restrictions.[31] We cannot exclude that our results were impacted by changing behaviours and might thus not be representative of periods with no restrictions. In addition to the measurement bias in our outcome, we cannot dismiss the presence of selection bias in the per-

protocol estimates and in the ITT estimates due to the large number of excluded participants due to out of window visits and due to missing outcome data. Finally, the qualitative substudy was conducted among 12 PrEP users at one study site; it is possible that this small sample size did not allow us to reach saturation in the PrEP users' perceptions regarding *N gonorrhoeae* and *C trachomatis* screening, and we cannot exclude that there are variations in these perceptions between study sites.

The introduction of doxycycline post-exposure prophylaxis (PEP) could have a profound effect on STI screening.[32] By reducing the incidence of *C trachomatis* and *N gonorrhoeae*, doxycycline PEP could reduce the benefit and need for 3×3 screening for these infections. Conversely the combination of intensive screening and doxycycline PEP could have a large effect on the transmission of these infections.[32] It is also possible that the high antimicrobial consumption resulting from these interventions would do more harm than good in terms of antimicrobial resistance and microbiome damage.[33] The main reason to screen for *N gonorrhoeae* and *C trachomatis* in MSM and transgender women is to reduce the incidence of symptomatic infections and secondarily to reduce the incidence and prevalence of infections in the population. In our RCT, screening reduced the incidence of *C trachomatis* but not *N gonorrhoeae*. The effect on *C trachomatis* incidence disappeared once we controlled for the untreated infections bias. We found that screening resulted in a lower incidence of symptomatic *C trachomatis* infections but not symptomatic *N gonorrhoeae* infections. Screening was, however, associated with a 21–45% increase in consumption of antimicrobials. In conclusion, our study shows that 3×3 screening for *N gonorrhoeae* and *C trachomatis* in MSM and transgender women taking HIV PrEP could lead to a reduction in the incidence of *C trachomatis* infections but not *N gonorrhoeae* infections and comes at the cost of higher antimicrobial consumption. Therefore, more studies, including studies with doxycycline PEP arms, are needed to assess the benefits and harms of *N gonorrhoeae* and *C trachomatis* screening in this population.

Contributors

CK, SH, YVH, IDB, EF, DH, A-SS, J-CG, EP, BV, TR, and AL contributed to the conceptualisation, methodology, and funding acquisition. All authors contributed to the investigation. AT performed the formal analysis. All authors contributed to the writing of the manuscript and approved the final version. TV, AT, and CK directly accessed and analysed the underlying data and statistical analyses. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Anonymised individual participant data and a data dictionary defining each field in the dataset can be shared on approval of a written request to the corresponding author and in agreement with data sharing policy of the Institute of Tropical Medicine, Antwerp.

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