Screening is not associated with reduced incidence of gonorrhoea or chlamydia in men who have sex with men (MSM); an ecological study of 23 European countries [version 1; peer review: 2 approved]

Chris Kenyon1,2

1University of Cape Town, Cape Town, South Africa, 7925, South Africa
2Institute of Tropical Medicine, Antwerp, Antwerp, 2000, Belgium

Abstract

Background: Increasing rates of antimicrobial resistance has motivated a reassessment of if intensive screening for gonorrhoea and chlamydia is associated with a reduction in the prevalence of these infections in men who have sex with men (MSM).

Methods: Spearman's correlation was used to evaluate the country-level correlation between the intensity of self-reported sexual transmitted infection (STI) screening in MSM (both anal and urethral screening, taken from a large internet survey of MSM) and the incidence (taken from ECDC surveillance figures) and prevalence (taken from a literature review of studies estimating prevalence in MSM attending STI clinics) of gonorrhoea and chlamydia.

Results: The intensity of both anal and genital screening was found to be positively associated with country level gonorrhoea incidence rates (rho 0.74; p=0.0004; rho=0.73; p=0.0004, respectively) and Ct incidence rates (rho 0.71; p=0.001; rho=0.78; p=0.0001, respectively). No associations were found between anal or genital screening intensity and Ng prevalence in clinic populations (Table 2).

Conclusions: We found no evidence of a negative association between screening intensity and the prevalence of gonorrhoea or chlamydia in MSM. Randomized controlled trials are urgently required to evaluate if the high antimicrobial exposure resulting from intensive screening programmes is justified.

Keywords
Gonorrhoea, chlamydia, MSM, STI screening, PrEP, antimicrobial resistance
Introduction
There have been large increases in antimicrobial resistance in a number of sexual transmitted infections (STI) in the recent past. There are serious concerns that both *Neisseria gonorrhoeae* (Ng) and *Mycoplasma genitalium* may become untreatable in the not too distant future\(^1,2\). For both these bacteria as well as macrolide resistance in *Treponema pallidum*, AMR has frequently first emerged in populations with a combination of high antimicrobial consumption and dense sexual networks\(^3,4\). HIV pre-exposure prophylaxis (PrEP) cohorts have dense sexual networks and the intense screening STI typically practiced translates into high antimicrobial exposures\(^3,5,6\). Three-monthly, 3-site Ng/Chlamydia trachomatis (Ct) screening for example translates into macrolide exposures of around 4400 standard units/1000 population/year, which is many times higher than levels associated with the induction of macrolide resistance in a range of bacteria including *T. pallidum* and Ng\(^7,8\). These findings have led a number of authors to review the evidence to support Ng/Ct screening in men who have sex with men (MSM) PrEP populations.

The US Preventive Task Force, concluded that there is insufficient evidence to advocate for or against screening for Ng in men, including MSM\(^9\). In a systematic review conducted to inform these guidelines, the authors found no randomised, controlled trials or controlled observational studies that assessed the utility of NG screening in men\(^9\). In a systematic review of observational studies, we found no evidence that even the most intense Ng/Ct screening such as screening 100% of PrEP cohorts every 3 months was associated with a decline in the prevalence of these infections\(^10\). Others have argued that this lack of an effect was because the PrEP recipients were having sex with (and being reinfected by) people who were not being screened\(^10\). This generates the hypothesis that we test in this paper that populations where a high proportion of MSM are screened for Ng/Ct will have a lower prevalence of these infections than populations with less screening. We test this hypothesis in European countries because the intensity of STI screening varies widely here and data for screening and prevalence estimates were available.

Methods

**Data sources**

**STI screening intensity.** Country level STI screening prevalence were obtained from the European MSM Internet Survey (EMIS), which was an internet-based survey of over 160 000 MSM from 38 countries living in Europe\(^11\). The survey was conducted between June and August 2010. In the section where participants were asked about STI testing in the past 12 months, they were asked 3 questions that are relevant to Ng/Ct screening: Did you provide a urine sample for STI screening? Was urethral swab inserted into your penis for STI screening? Was a swab inserted into your anus for STI screening? EMIS combined the results from the first two questions into one variable reporting the proportion of respondents reporting ‘urethral STI screening’ – via either urine or urethral swab. The third question provided the proportion with ‘anal STI screening’. Typically, these urethral and anal samples are tested for Ng/Ct.

**Ng/Ct prevalence/incidence.**

1. National Ng and Ct incidence estimates for men in 2010 were taken from European Centre for Disease Prevention and Control (ECDC) figures\(^12\). These incidence estimates are based on national surveillance systems. The ECDC does not provide incidence estimates separately for MSM and thus we used the estimates for all men. MSM do however constitute a high proportion of diagnoses in all men\(^11\).

2. Systematic review of Ng/Ct prevalence in MSM
   Ng/Ct prevalence estimates for MSM were taken from a published literature review of pharyngeal and anorectal Ng and Ct prevalence estimates in MSM (and other populations)\(^13\). All studies listed in PubMed reporting prevalence of extragenital Ng and Ct in MSM up to 1 December 2015 were included. A total of 53 studies were included of which 18 were from 6 European countries (Table 1). For the four European countries with more than one study we selected the study reporting prevalence estimates from 2010 or as soon after this year as possible. All selected studies were prevalence estimates established by Nucleic Acid Amplification Testing of MSM clients attending STI clinics.

Data analysis

In all analyses the correlation between screening intensity and Ng/Ct prevalence/incidence was tested using Spearman’s correlation. The statistical analyses were performed in STATA 13.

Results

**STI screening**

The proportion of respondents in each of the 23 countries reporting anal STI screening varied widely from 6.5 to 70.6% to (median 17.3%, IQR 11.8–47.1; Table 1). Likewise, there were large variations in the proportion reporting genital STI screening (range 37.0 to 94.0%, median 63.6 IQR 50.0–85.0%). There was a strong correlation between the proportions reporting anal and genital STI screening (rho=0.81; p<0.0001).

**Incidence of Ng and Ct based on ECDC estimates**

For 19 countries with data, the incidence of Ng for men in 2010 ranged between 1.2 and 42.2 cases per 100 000 men per year (median 7.2, IQR 3.6–18.3). There was an even wider distribution in estimated Ct incidence for the 18 countries with data (range 0 to 383.7, median 24.8, IQR 1.3–201).

**Prevalence of Ng/Ct in MSM based on STI clinic attendees**

There was less variance in the prevalence estimates of Ng and Ct in MSM (Table 1). Rectal Ng: median 5.5%, IQR 4.6–7; pharyngeal Ng: median 5.4%, IQR 3.9–6.5; urethral Ng: median 1.9%, IQR 1–3.4. Rectal Ct: median 7.3%, IQR 6.5–10.0; pharyngeal Ct: median 1.3, IQR 0.8–1.7; urethral Ct: median 3, IQR 2.5–5.3; Table 1.

**Correlation between screening intensity and Ng/Ct incidence/prevalence**

The intensity of both anal and genital screening was found to be positively associated with country level Ng incidence rates
No associations were found between anal or genital screening intensity and Ng prevalence in clinic populations (Table 2).

**Discussion**

A key reason for screening for Ng and Ct in MSM is to reduce the incidence and prevalence of these infections. In this analysis, we did not find evidence of a negative correlation between the intensity of STI screening in MSM and the incidence/prevalence of Ng/Ct. Instead, we found evidence of a positive association between the intensity of screening in MSM and the estimated incidence rate for men. This positive association may be explained by the fact that incidence estimates are influenced by the intensity of screening – countries with more intensive screening programmes would be expected to diagnose more asymptomatic Ng and Ct infections which lead to higher incidence estimates.

### Table 1. Prevalence of sexual transmitted infection (STI) screening, STI incidence and prevalence in European countries with available data.

| Country       | Screening Prevalence in 2010 (%) | STI Incidence in men 2010 (cases/100 000/year) | STI Prevalence in MSM attending STI clinics (%) |
|---------------|----------------------------------|-----------------------------------------------|-----------------------------------------------|
|               | Urethral Anal Ng Ct | Urethral Rectal | Pharyngeal | Urethral Rectal Pharyngeal |
| Bulgaria      | 39.2 10.0 2.7 .5 | 56.6 20.6 1.9 4.6 5.5 | 3.4 8 1.5 | doi.org/10.1136/sextrans-2012-050929 |
| Cyprus        | 59.9 17.3 .5 | 71 40.0 13.2 383.7 | 2.6 2.6 0 | doi.org/10.1136/sti.73.6.493 |
| Czech Rep.    | 67.2 19.6 10.4 | 58.4 14.2 6.5 40.5 | 41.4 11.8 4.6 1.4 |
| Germany       | 56.6 20.6 1.9 4.6 5.5 | 3.4 8 1.5 | 9.5 | doi.org/10.1136/0956462413466455 |
| Denmark       | 71 40.0 13.2 383.7 | 2.6 2.6 0 | 41.9 9.1 1.2 0 |
| Estonia       | 58.4 14.2 6.5 40.5 | 41.4 11.8 4.6 1.4 | 64 14.9 26 33.8 |
| Greece        | 41.4 11.8 4.6 1.4 | 52 15.2 9.5 | 85 70.6 20.9 37.5 |
| Spain         | 52 15.2 9.5 | 89 37.9 7.2 201 | 87 63.0 3.4 5.5 3.9 4.3 10.1 1.7 doi.org/10.1177/0956462414521165 |
| Finland       | 89 37.9 7.2 201 | 91 67.2 20.5 104.7 0 4.1 3.3 1.7 6.6 8 | doi.org/10.1136/sextrans-2012-050929 |
| Lithuania     | 63.6 13.3 18.3 15.7 | 56.6 20.6 1.9 4.6 5.5 | 3.4 8 1.5 | doi.org/10.1136/0956462413466455 |
| Luxembourg    | 41.9 9.1 1.2 0 | 64 14.9 26 33.8 | 68.9 9.5 1.5 |
| Latvia        | 64 14.9 26 33.8 | 85 70.6 20.9 37.5 | 60 16.9 3.6 |
| Malta         | 85 70.6 20.9 37.5 | 87 63.0 3.4 5.5 3.9 4.3 10.1 1.7 doi.org/10.1177/0956462414521165 |
| Netherlands   | 87 63.0 3.4 5.5 3.9 4.3 10.1 1.7 doi.org/10.1177/0956462414521165 | 84 47.2 15 353.8 | 92 59.0 13.3 333.3 |
| Norway        | 84 47.2 15 353.8 | 37 8.9 1.5 2.2 | 68.9 9.5 1.5 |
| Poland        | 37 8.9 1.5 2.2 | 69 19.7 1.9 2.7 | 45 6.5 4.1 .7 |
| Portugal      | 68.9 9.5 1.5 | 60 16.9 3.6 | 92 59.0 13.3 333.3 |
| Romania       | 45 6.5 4.1 .7 | 60 16.9 3.6 | 68.9 9.5 1.5 |
| Sweden        | 92 59.0 13.3 333.3 | 50 29.0 4.1 | 50 29.0 4.1 |
| Slovenia      | 50 29.0 4.1 | 94 67.9 42.2 4.7 9 5.2 5.3 6.5 2.2 doi.org/10.1258/ijsa.2012.011378 |
| Slovakia      | 60 16.9 3.6 | 94 67.9 42.2 4.7 9 5.2 5.3 6.5 2.2 doi.org/10.1258/ijsa.2012.011378 |
| United Kingdom| 94 67.9 42.2 4.7 9 5.2 5.3 6.5 2.2 doi.org/10.1258/ijsa.2012.011378 | 87 63.0 3.4 5.5 3.9 4.3 10.1 1.7 doi.org/10.1177/0956462414521165 |

*N. gonorrhoeae - Neisseria gonorrhoeae, C. trachomatis - Chlamydia trachomatis*
To deal with this bias and the fact that the ECDC Ng/Ct incidence estimates do not provide incidence estimates for MSM, we also evaluated the association in MSM attending STI clinics. Here we found no evidence of an association between screening intensity and prevalence.

These findings are open to a number of interpretations. Firstly, screening intensity may be negatively associated with Ng/Ct rates but we missed this association due to methodological issues. Our estimates of screening intensity were based on a single cross-sectional source. Although EMIS had a large sample size and the accuracy of its prevalence estimates for other variables has been validated in other studies, these screening estimates may be inaccurate and may have changed over time.

As noted above, the STI incidence estimates were for all men and were likely strongly influenced by practices such as screening intensity. The STI prevalence estimates in MSM were all taken from men attending STI clinics and thus are likely higher than

Table 2. Spearman’s correlation between prevalence of sexual transmitted infection (STI) screening (anal and urethral) and prevalence of Neisseria gonorrhoeae and Chlamydia trachomatis (pharyngeal, rectal and urethral). All P-values were greater than 0.1.

| STI prevalence | Anal testing | Urethral testing |
|----------------|--------------|------------------|
| N. gonorrhoeae  |              |                  |
| Pharyngeal     | -0.70        | -0.70            |
| Rectal         | 0.40         | 0.40             |
| Urethral       | 0.40         | 0.40             |
| C. trachomatis |              |                  |
| Pharyngeal     | 0.50         | 0.50             |
| Rectal         | -0.20        | -0.20            |
| Urethral       | 0.30         | 0.30             |
general populations of MSM. The study design of each of the 6 studies contributing Ng and CT prevalence estimates differed somewhat further limiting the extent to which comparisons can be made between prevalence estimates derived from these studies. We could find no comparable data on the prevalence of Ng or Ct in general MSM populations.

Alternatively, screening intensity as measured may not be associated with reduced Ng/Ct rates in MSM. Randomized controlled trials of the efficacy of screening for Ct in women on the prevalence of Ct have produced equivocal results\(^ {17-20}\). Although no RCTs have been conducted in MSM, a systematic review of observational studies revealed that Ng/Ct screening, even when conducted at 3-sites every 3-months, was not associated with reductions in the prevalence of Ng or Ct\(^ {11}\). If we consider Ng, numerous aspects of the way it circulates in contemporaneous populations of MSM may explain why screening has little or no effect on prevalence. Symptomatic disease is thought to typically occur soon (2–21 days) after infection and if symptoms do not develop the infection (particularly in the pharynx and rectum) tends to persist in a low abundance, low infectious state for up to 6 months\(^ {21}\). Highly exposed individuals develop a type-specific immunity, but this immunity is largely ineffective in low exposure individuals\(^ {22,23}\). As a result, the vast majority of Ng infections are asymptomatic and self-limiting in MSM PrEP populations\(^ {11,21}\). Similar considerations apply to Ct. In the case of Ct there is however better evidence that treatment of Ct results in "arrested immunity" and thereby paradoxically increases the probability of reinfection\(^ {24,25}\). If screening results in ‘arrested immunity’ it may paradoxically increase Ng/Ct prevalence/symptomatic disease. The sexual networks of PrEP recipients are very dense (up to a mean of 18 partners per 3 months\(^ {26}\)) and this is responsible for generating the high prevalences of Ng and Ct. Removing individuals piecemeal from this network for screening and treating has no effect on the underlying determinant of high prevalence. As a result, the probability of reinfection and prevalence remaining high.

Mathematical models of Ng and Ct transmission in European countries like Belgium have thus found that the sexual network of MSM was so dense that current levels of Ng screening were having little to no effects on Ng prevalence\(^ {27}\). In contrast, a modelling study from the United States found that 6-monthly screening of an expanded number of PrEP recipients could avert 40% of Ng and Ct infections\(^ {28}\). This study did not however model pharyngeal transmission of Ng (which plays a major role in transmission) and did not model the impact of immunity or Ng’s ability to adapt to antibiotic pressure. These omissions may explain the discrepancy between its finding and that of the systematic review of observational studies which found that even 3-monthly screening was not associated with a decline in Ng or Ct prevalence\(^ {11}\).

Based on the findings of this study and those reviewed here we conclude that we cannot exclude the possibility that intense screening (at least 3-site, 3-monthly) may have a small to moderate influence on Ng/Ct prevalence in MSM. Randomized controlled trials are urgently required to test this hypothesis. In the interim, given the mounting evidence that Ng/Ct screening does not have a large effect on prevalence but does result in high levels of antimicrobial exposure, consideration should be given to reducing the intensity or stopping Ng/Ct screening in MSM in a phased and controlled manner that allows a detailed evaluation of the risks and benefits of screening.

Data availability
Underlying data
All data underlying the results are available as part of the article and no additional source data are required.

Grant information
The author declared that no grants were involved in supporting this work.

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Eline L Korenromp
Avenir Health, Geneva, Switzerland

Nico Nagelkerke
Independent, Innsbruck, Austria

General Comments:
This is a useful study, well designed, analyzed, and written, ending in a well-reasoned call for improving the evidence base for gonorrhea and chlamydia screening programs.

The discussion adds particular value, comparing and contrasting findings from empirical studies with predictions by modelling studies. This part could possibly be structured better (e.g. I found it confusing to see reference 11 discussed twice on page 6). The authors might add a general statement about the value of mathematical models to answer complex epidemiological questions such as this. For example "This illustrates that mathematical models to assess health interventions may be wrong for reasons that are not always obvious, and underlines the importance of empirical evidence".

The specific comments below may serve to improve readability and interpretation.

Methods:
Page 3, right column, top: ‘A total of 53 studies were included of which 18 were from 6 European countries’. I suppose the remaining 35 studies were from other European countries, or also non-European? Perhaps just drop ‘European’ from this sentence, so to avoid this confusion.

While, according to reference 14, a large proportion of Gc/Ct diagnoses takes places in MSM, it is unlikely that this reflects actual incidence, especially with regard to Ct which is highly prevalent, often asymptomatically, in the heterosexual population (e.g. in adolescent girls). This may be worth mentioning (in Introduction or Discussion) – to put the importance of MSM in the overall epidemic in context.

Results:
Page 4: ‘No associations were found between anal or genital screening intensity and Ng prevalence in clinic populations’. You found the same for CT, right? Please add that.

Discussion:
Page 4: The authors offer as a possible explanation for the observed positive (and not, the hoped negative) association that screening makes people susceptible to reinfection. To me a more basic explanation in this ecological analysis based on cross-sectional data, is screening programs are likely targeted to regions and populations with high prevalence. Reverse causality: the high prevalence is likely the cause rather than the effect of the screening program being there.

Page 5: ‘To deal with this bias ... we also evaluated the association in MSM attending STI clinics’: Not clear, the association between what and what? You mean, between national screening intensity and prevalence in MSM attending STI clinics? Please rephrase, and refer back to Table 2 here.

Page 5: ‘As noted above, the STI incidence estimates were for all men and were likely strongly influenced by practices such as screening intensity’. A more general limitation of these incidence estimates based on national surveillance data is that NG and Ct incidence is hardly measurable, and case notifications are no good indication of underlying incidence of these infections, which are most often asymptomatic and not presenting to clinics. Besides variations in screening intensity, variations across countries in health care access and population awareness of STIs contribute to varying case notification rates, which do not reflect true variations in underlying incidence, and so may bias (or at least dilute the power) of the ecological analysis.

Page 6: ‘... limiting the extent to which comparisons can be made between prevalence estimates’: Please consider to rephrase as ‘... limiting the extent to which correlations could be assessed between screening intensity and prevalence across these studies’

Page 6: About the systematic review of observational studies, quoted as reference 11, could you summarize how this differs from your current study, in methodology, scope, populations covered and/or other aspect?

Page 6: ‘These omissions may explain the discrepancy between its finding and that of the systematic review of...’ This sentence may be clearer if written as: ‘... between its prediction, and our and the earlier systematic review of observational studies’.

Conclusion:
The first concluding sentence is a perhaps optimistic twist to a negative finding, which may surprise some readers (such as me). It does serve as a good introduction to the authors’ call for randomized trials to test the impact of screening in MSM. For readability, the authors may consider to a few word changes: ‘Based on the findings of this study and those reviewed we conclude that we can STILL not exclude...’.

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

Is the study design appropriate and is the work technically sound?
Yes
Are sufficient details of methods and analysis provided to allow replication by others?
Yes

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

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

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 19 March 2019

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Hamish McManus
The Kirby Institute, The University of New South Wales (UNSW Sydney), Sydney, Australia

Basil Donovan
The Kirby Institute, The University of New South Wales (UNSW Sydney), Sydney, Australia

This is a well written study aimed to measure correlation between country-level sexually transmissible infection (STI) screening intensity in MSM, and country-level incidence of *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT) in MSM in European countries. The study sought to address a hypothesised association between risk of reinfection by unscreened cases and the intensity of screening in those populations. This hypothesis is consistent with no prior studies having detected negative correlation between screening and prevalence of STIs. While the study is ultimately unable to draw conclusions on the association between screening intensity and prevalence, its importance lies in potentially motivating discussion and further examination of this topic. One of the most important points it illustrates is that findings based on cross-sectional data such as these are open to a number of interpretations, and hence motivate more thorough analyses using longitudinal data.

In part the reason for the fairly limited conclusions and presentation of a range of interpretations of the findings lies with limitations of the ecological source data. For example, the source data used for incidence estimation should be interpreted cautiously. The ECDC estimates cited are, precisely, national-level notification rates for the general male population rather than incidence
rates for the respective MSM population. This is problematic for several reasons. Firstly, the association between increased screening intensity and notification rates has been established by previous studies and estimates of incidence based directly on notification rates need to be adjusted accordingly to reflect this.\(^1\)\(^2\) And, secondly, it is not made clear what effect the use of general male population ECDC estimates rather than MSM specific estimates has on results. Although authors suggest that the ECDC estimates are strongly weighted by MSM, this statement is not supported. While MSM are disproportionately represented in NG/CT notifications, it is still probable that the strength of correlation between screening in this population and general incidence rates could be reduced substantially given that MSM comprise a very low (<7%) proportion of the male population.

In part to address these limitations (“To deal with this bias and the fact that the ECDC NG/CT incidence estimates do not provide incidence estimates for MSM” [P5]), the correlation between screening and prevalence estimates in MSM from STI clinics was also evaluated. However, this analysis is relatively limited, and we are not sure that it addresses these concerns successfully. Specifically, the prevalence results do not improve the interpretability of the incidence results. Also, they are based on complete results from only 4 countries (2 of which are not included in the incidence comparison) which is likely to limit the levels of correlation capable of being determined.

To overcome the limitations of this ecological study, the author concludes that randomised controlled trials are urgently required. However, as this would require abandoning STI screening for some of the participants, such a trial would be ethically dubious and contrary to current clinical guidelines. Alternatively, longitudinal administrative data can be subject to retrospective cohort analysis. Using this technique, we were able to determine a true national increase in the incidence of NG in MSM but, after controlling for test frequency, this could be explained by increasing partner numbers and condomless anal sex.\(^3\)

However, the statistical analyses in Kenyon’s study are appropriate and robust. More complex methods may have been inappropriate for the broad ecological source data used. Appropriately, the conclusions drawn are careful and, in that regard, supported by the results. This study should proceed to being indexed for the reason that it motivates discussion and should motivate more rigorous research into these growing epidemics.

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

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

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

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

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

Are the conclusions drawn adequately supported by the results?
Yes

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

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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