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RESEARCH NOTE

Association between intensity of STI screening and development of antimicrobial resistance in *N. gonorrhoeae* in 12 cities in the USA: An ecological study [version 1; peer review: 2 approved with reservations]

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Abstract

In this study, we assessed if there was a city-level association between sexually transmitted infection (STI) screening intensity in men who have sex with men and antimicrobial sensitivity in *Neisseria gonorrhoeae* in the United States, 2007 to 2013. We found positive associations between STI screening intensity and increases in minimum inhibitory concentrations for cefixime and azithromycin, but not ceftriaxone.

Keywords

N. gonorrhoeae; STI screening; antimicrobial resistance; MSM

Open Peer Review**Approval Status**

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version 3		
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16 Oct 2018	view	
version 2		
(revision)		
27 Sep 2018	view	view
version 1		
10 Aug 2018	view	view

1. **Edward Goldstein**, Harvard T.H. Chan School of Public Health, Boston, USA

2. **Ellen Stobberingh**, Maastricht University Medical Centre (MUMC), Maastricht, The Netherlands

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: Kenyon CR: Conceptualization, Formal Analysis, Investigation, Methodology, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

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Introduction

In the United States (USA) the prevalence of antimicrobial resistance in *Neisseria gonorrhoeae* has typically been higher in men who have sex with men (MSM) than men who have sex with women (MSW) and women^{1,2}. It has also frequently been noted to be highest in the West and lowest in the South¹⁻³. Resistance has characteristically emerged in the West Coast and Hawaii and then spread eastward¹⁻³. This patterning of spread has led to the view that a primary driver of resistance is the import of resistant gonococci from eastern Asia and other world regions³. In support of this theory, a number of studies have documented travel as a means of import of resistance in the USA^{4,5}. A systematic review of risk factors associated with resistance in *N. gonorrhoeae*, however, found that a history of sex with partners abroad was associated with resistance in 6 studies and was not associated with resistance in 7 studies⁶. Furthermore, the evidence that travel plays a seminal role in the emergence of resistance in MSM is not that compelling. An analysis of data from the Gonococcal Isolate Surveillance Project (GISP) 2002 to 2007, for example, found a pronounced increase in ciprofloxacin-resistance in MSM and a smaller and later increase in MSW; the association with recent travel was negative in MSM and borderline positive in MSW⁷.

Antimicrobial resistance results largely from exposure to antimicrobials^{8,9}. This has been extensively documented *in vitro* and *in vivo* but for various reasons antimicrobial pressure at a population level may be more important than at an individual level in determining risk of development of antimicrobial resistance^{8,10,11}. In the case of *N. gonorrhoeae*, extensive antimicrobial exposure in a population would be predicted to result in a high prevalence of resistance genes in the pharyngeal microbiomes that could then be taken up (via transformation) by *N. gonorrhoeae* and thereby provide it with a fitness conferring resistant phenotype in the setting of ongoing high antimicrobial consumption¹². These insights have provided the rationale for ecological level studies that have generally found strong associations between the intensity of antimicrobial use and the prevalence of resistance to that antimicrobial^{8,13}. A recent study from the USA however found no association between an increase in *N. gonorrhoeae* minimum inhibitory concentration (MIC) for azithromycin, ceftriaxone, cefixime and ciprofloxacin in the 23 GISP sites and the consumption of antimicrobials in the surrounding county³. A weakness of this study design was the use of total-consumption-of-antimicrobials by the entire county population as the explanatory variable. Since resistance has repeatedly emerged in certain MSM populations, it would be prudent to assess if this emergence is correlated with antimicrobial consumption in this group rather than the entire population. One major driver of antimicrobial consumptions in MSM is sexually transmitted infection (STI) screening. Because most *N. gonorrhoeae* and *Chlamydia trachomatis* in MSM are carried asymptotically in the anorectum and oropharynx, screening for these STIs may result in a large increase in antimicrobial exposure. A modeling study for example found that increasing annual gonorrhea/chlamydia screening in an MSM population from 3 to 50% would result in a 11-fold increase in antimicrobial exposure¹⁴. In this exploratory paper we hypothesized that the intensity of

STI testing plays a role in the genesis of resistance in MSM via the associated increase in antibiotic exposure.

Methods

We assessed if there was an ecological-city-level-association between the intensity of STI testing in MSM in the USA and the development of antimicrobial resistance in *N. gonorrhoeae*.

Data for STI screening was taken from the 2005, 2008 and 2011 **National HIV Behavioral Surveillance MSM (NHBS-MSM) studies**. These cross-sectional surveys done in 21 cities asked respondents about STI testing in the preceding 12 months. The 2005 survey (n=10,030) asked if respondents had been tested for syphilis/gonorrhea/another-STI during the preceding 12 months (single question), the 2008 survey (n=8,175) if they had been tested for syphilis in the preceding 12 months, and the 2011 survey (n=8,012) if they had been tested for gonorrhea, chlamydia or syphilis in the previous 12 months (3 questions).

Data for the change in city geometric mean *N. gonorrhoeae* MIC between 2005 and 2013 was taken from GISP data³. Spearman's correlation was used to assess if there was an association between the prevalence of STI testing in each survey and the increase in geometric mean MIC of cefixime, ceftriaxone and azithromycin in *N. gonorrhoeae* between 2005 and 2013. These three antibiotics were chosen since these were the recommended antibiotics for *N. gonorrhoeae* therapy since 2007¹. All analyses were conducted in STATA 13.

Results

Twelve cities participated in both the NHBS-MSM and GISP surveys (n=9 for 2005, n=12 for 2008, n=12 for 2011). The intensity of self-reported STI testing in 2005 varied between 27% and 56% (median 43%, IQR 39–49). There was little change in the relative positions of the cities in terms of testing intensity between 2005 and 2008 ($\rho=0.87$, $p=0.002$) and 2005 to 2011 ($\rho=0.81$, $p=0.008$). Cities in the West tended to have higher STI testing rates than cities in the South (**Figure 1**). In 2011, the percent reporting testing for gonorrhea was strongly correlated with the percent reporting testing for chlamydia ($\rho=0.99$, $p<0.001$) and syphilis ($\rho=0.98$, $p<0.001$). In general, the *N. gonorrhoeae* geometric mean MIC for cefixime and azithromycin increased more rapidly than ceftriaxone in all cities (data not shown).

In 2005, significant positive associations were found between STI screening and the increase in MIC of cefixime ($\rho=0.88$, $p=0.002$), azithromycin ($\rho=0.93$, $p<0.001$) but not ceftriaxone ($\rho=0.27$, $p=0.491$; **Figure 1**). Likewise in 2008, there was a positive correlation between the percent reporting testing for syphilis in the prior 12 months and increase in MIC of cefixime ($\rho=0.71$, $p=0.010$), azithromycin ($\rho=0.791$, $p=0.002$) but not ceftriaxone ($\rho=0.36$, $p=0.247$). A positive association was also found for the percent reporting testing for gonorrhea in 2011 and an increase in MIC for cefixime ($\rho=0.63$, $p=0.026$) and azithromycin ($\rho=0.64$, $p=0.024$) but not ceftriaxone ($\rho=0.56$, $p=0.062$). The results for chlamydia and syphilis testing were similar (data not shown).

Figure 1. Scatter plots of change in the minimum inhibitory concentrations (MICs) between 2007 and 2013 and the percent of respondents reporting in 2005 that they had a bacterial STI test in the prior 12 months for (a) cefixime, (b) ceftriaxone and (c) azithromycin by USA city (data sources detailed in *Methods*).

Discussion

There was a roughly two-fold variation in the proportion of MSM in different cities reporting testing for bacterial STIs. The proportion testing for bacterial STIs was associated with an increase of MIC for cefixime and azithromycin but not ceftriaxone. A plausible reason for the lack of association between ceftriaxone and MIC change is that ceftriaxone has been used almost exclusively in combination with azithromycin^{3,15} and even on its own may be less susceptible to the development of resistance than cefixime and azithromycin¹⁶. These findings are compatible with the theory that screening intensity plays a role in the selection of antimicrobial resistance in *N. gonorrhoeae* in MSM.

The findings should however be regarded as tentative due to a number of methodological weaknesses: the sample size was small ($n=9$ to 12), the outcome variable (increase in geometric MIC) referred to all men sampled in GISP and not just MSM, the explanatory variable was only evaluated at three time points, the explanatory variable measured 'STI testing' and not 'STI screening' and possible confounders were not controlled for.

Increased testing could, for example, be associated with other factors that may be associated with antimicrobial resistance such as greater risk behavior, more frequent travel, HIV-infection and access to medical care. Likewise we did not control for changes over time in the percent of GISP samples derived from MSM which may have influenced the geometric mean MICs.

Future studies that wish to evaluate the screening-resistance hypothesis could assess if there is an association between bacterial STI screening intensity and resistance in *N. gonorrhoeae* in bigger samples in the USA or elsewhere. Testing this hypothesis in Europe would be instructive since the proportion of MSM reporting anal screening for bacterial STIs in the prior 12 months in 38 different European countries ranges from 9.1% in Romania to 79.6% in Malta (median 18.5%, IQR 13.5–28.4)¹⁷. Furthermore whilst two of these countries that report high STI screening rates in MSM (the United Kingdom¹⁷ and the Netherlands¹⁷) have found an association between resistance in *N. gonorrhoeae* and MSM^{18,19}, other countries in Europe have not found this association¹⁵.

The recent emergence of combined azithromycin/ceftriaxone resistant *N. gonorrhoeae* provides additional motivation to better characterize the underlying determinants of the differential emergence of resistance in MSM and other populations²⁰. If screening intensity is found to play a role then this could be taken into account in development of an optimal STI screening strategy.

Data availability

Data for STI screening: [National HIV Behavioral Surveillance MSM \(NHBS-MSM\) studies](#)

GISP data: Technical appendix of [3](#)

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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Open Peer Review

Current Peer Review Status: ? ?

Version 1

Reviewer Report 24 September 2018

<https://doi.org/10.5256/f1000research.16982.r38243>

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Ellen Stobberingh

Care And Public Health Research Institute (CAPHRI), Maastricht University Medical Centre (MUMC) , Maastricht, The Netherlands

The manuscript describes the association between STI screening and antimicrobial resistance development of *N. gonorrhoeae*. Although of interest there are several questions which need to be answered:

Material and Methods:

- The number of participants reduced over time: 10,030 in 2005 and 8,012 in 2011. Also there was a difference in participation rate in the different cities.
What is the influence of the decreased participation rate over time and the variation in the participation in the different cities on the interpretation of the data?
- In 2008 (only syphilis) and in the two other years in addition *N. gonorrhoeae*, other STI or Chlamydia were tested. What was the reason for this difference?
- How many *N. gonorrhoeae* isolates were included in the different years?
- Was the microbiological method to isolate, identify and antibiotic susceptibility testing over testing similar over time? Which method was used for susceptibility testing?
- Please provide range and GM MIC values of the three antibiotics testing in the different years,

Figure 1:

- The horizontal axis mentioned an increase in MIC. What was the reference MIC?

Dicussion:

- Was there a change in therapy over time among the participants. All three antibiotics are mentioned in the guidelines, but is there information concerning the therapy prescribed

over time in the different cities / participants?

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

Partly

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

Partly

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

Partly

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

I cannot comment. A qualified statistician is required.

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

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My expertise includes microbiology, bacteriology, and antimicrobial susceptibility

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

Author Response 25 Sep 2018

Chris Kenyon, Institute of Tropical Medicine, Antwerp, Antwerp, Belgium

The manuscript describes the association between STI screening and antimicrobial resistance development of *N. gonorrhoeae*. Although of interest there are several questions which need to be answered:

Material and Methods:

- The number of participants reduced over time: 10,030 in 2005 and 8,012 in 2011. Also there was a difference in participation rate in the different cities. What is the influence of the decreased participation rate over time and the variation in the participation in the different cities on the interpretation of the data?

Reply:

Indeed both the decline in the absolute number of participants and the variation by city could introduce biases. This additional limitation has been added to the discussion.

- In 2008 (only syphilis) and in the two other years in addition *N. gonorrhoeae*,

other STI or Chlamydia were tested. What was the reason for this difference?

Reply:

These differences reflect differences in the questions asked in the various surveys. In 2008, for example, respondents were asked if they had been tested for syphilis in the preceding 12 months, whereas in the 2011 survey they were asked if they had been tested for gonorrhea, chlamydia or syphilis in the previous 12 months. This is made clear in the methods section.

- How many *N. gonorrhoeae* isolates were included in the different years?

Reply:

Between 2005 and 2013, 44,144 isolates were tested. The report does not detail the breakdown of number tested by year.

- Was the microbiological method to isolate, identify and antibiotic susceptibility testing over testing similar over time? Which method was used for susceptibility testing?

Reply:

There were small changes in the laboratory protocol used. The protocol used and these changes are detailed in the Kirkcaldy et al report as follows [1]:

"Gonococcal isolates collected at each sentinel clinic are subcultured at the clinic's local public health laboratory on supplemented chocolate medium and frozen in Trypticase soy broth containing 20% glycerol.

Isolates are shipped monthly to one of the regional reference laboratories, where they are tested for Beta-lactamase production and susceptibility to azithromycin, penicillin, tetracycline, ciprofloxacin, spectinomycin, cefixime, and ceftriaxone using the agar dilution method.

Isolates were inoculated on Difco GC medium base supplemented with 1% IsoVitalEx enrichment (Becton-Dickinson Diagnostic Systems, Sparks, MD). During 2005 to 2007, the lowest azithromycin concentration tested was 0.008 ug/ml; this increased to 0.03 ug/ml in 2008.

The routine testing range for azithromycin extended to 16.0 ug/ml during 2005 to 2013. Laboratories were asked to conduct agar dilution testing to identify an endpoint for isolates with an MIC of 16.0ug/ml on the initial testing run. Testing to an endpoint was not conducted on three isolates collected during 2005 to 2013. In the absence of Clinical and Laboratory Standards Institute (CLSI) breakpoints for gonococcal azithromycin susceptibility or resistance, we defined reduced azithromycin susceptibility for this analysis as an MIC of 2.0 ug/ml. Quality assurance processes are described in detail in the GISP protocol. To ensure accuracy and reproducibility of antimicrobial susceptibility results from the regional reference laboratories, a set of seven control *N. gonorrhoeae* strains with known MICs of various antimicrobials are included with each susceptibility run. In addition, reference laboratories test a CDC-provided panel of 15 unidentified strains twice yearly to compare results and ensure consistency among laboratories. The results obtained from the testing of control strains and CDC-provided panels are used for internal quality assurance."

- Please provide range and GM MIC values of the three antibiotics testing in the different years,

Reply:

This data is not provided in the paper that reports the GISP results [1]. In the online Technical Appendix file of this paper the following data is however reported:

<https://doi.org/10.3201/eid2310.170488>

The geometric MIC of cefixime (Table 1), ceftriaxone (Table 2) and azithromycin (Table 3) by site and year. Table 8 presents the median and interdecile range of the 3 antimicrobials by site.

Figure 1:

- The horizontal axis mentioned an increase in MIC. What was the reference MIC?

Reply:

The horizontal axis is the change in MIC between 2007 and 2013.

Discussion:

- Was there a change in therapy over time among the participants.
All three antibiotics are mentioned in the guidelines, but is there information concerning the therapy prescribed over time in the different cities / participants?

Reply:

This information is not provided in the report.

References:

1. Kirkcaldy RD, Bartoces MG, Soge OO, Riedel S, Kubin G, Del Rio C, et al. Antimicrobial Drug Prescription and Neisseria gonorrhoeae Susceptibility, United States, 2005-2013. *Emerg Infect Dis*. 2017;23(10):1657-63. Epub 2017/09/21. doi: 10.3201/eid2310.170488. PubMed PMID: 28930001; PubMed Central PMCID: PMC5621530

Competing Interests: I have no competing interests

Reviewer Report 20 August 2018

<https://doi.org/10.5256/f1000research.16982.r37099>

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Edward Goldstein

Center for Communicable Disease Dynamics (CCDD), Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA

The paper under review studies the association between the frequency of STI screening in MSM and changes in geometric mean MICs for certain antibiotics in *N. gonorrhoeae* samples in select US cities. An important potential source of bias in such analysis could be reverse causality, namely places with higher prevalence of drug resistance for gonorrhea, as well as syphilis in MSM may initiate more STI screening efforts. Below are some questions/suggestions to the author.

1. Please define geometric mean MIC. Also, since one refers to geometric mean, it might be more reasonable to examine fold changes (increase or decreases) in geometric mean MIC (or logarithm of thereof) in the correlation analysis.

2. Nine cities reported STI screening information in 2005 (Figure 1), and 12 cities reported STI screening information in 2013. The reviewer would suggest to correlate the frequency of STI screening in 2013 with

- Geometric mean MICs in 2013
- (Fold) change in geometric mean MICs between 2009 and 2013
- (Fold) change in geometric mean MICs between 2005 and 2013

For the 2005 screening frequencies, it would be interesting to correlate them with geometric mean MICs (in 2013, and possibly 2005), and not only changes in thereof.

3. In ref. 3, no association was found between rates of antibiotic prescribing and geometric mean MICs. Perhaps the results of the paper under review are affected by reverse causality, namely places with higher prevalence of drug resistance for gonorrhea, as well as syphilis in MSM may initiate more STI screening efforts. For example, the California sites had both high geometric mean MIC for ciprofloxacin in 2005 (ref. 3), and high frequency of screening (see also¹). Currently, this possibility is not mentioned in the Discussion. The reviewer was also wondering if there is a correlation between the fold change in screening frequency and the fold change in geometric mean MICs between 2005 and 2013.

4. Are other variables in NHBS-MSM surveys (possibly rate of change of sexual partners, or a number of recent sexual partners) correlated with geometric mean MICs/changes in thereof?

5. In the Discussion, it is mentioned that “the sample size was small (9 or 12)”. Currently, only 9 cities are used in the correlation analysis, as far as the reviewer could see.

References

1. Centers for Disease Control and Prevention CDC: Increases in fluoroquinolone-resistant *Neisseria gonorrhoeae* among men who have sex with men--United States, 2003, and revised recommendations for gonorrhea treatment, 2004. *MMWR Morb Mortal Wkly Rep.* 2004; **53** (16): 335-8 [PubMed Abstract](#)

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

Partly

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

Partly

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

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?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious Disease Epidemiology

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

Author Response 25 Sep 2018

Chris Kenyon, Institute of Tropical Medicine, Antwerp, Antwerp, Belgium

The paper under review studies the association between the frequency of STI screening in MSM and changes in geometric mean MICs for certain antibiotics in *N. gonorrhoeae* samples in select US cities. An important potential source of bias in such analysis could be reverse causality, namely places with higher prevalence of drug resistance for gonorrhea, as well as syphilis in MSM may initiate more STI screening efforts. Below are some questions/suggestions to the author.

1. Please define geometric mean MIC. Also, since one refers to geometric mean, it might be more reasonable to examine fold changes (increase or decreases) in geometric mean MIC (or logarithm of thereof) in the correlation analysis.

Reply:

The geometric mean MIC has now been defined in the methods section.

2. Nine cities reported STI screening information in 2005 (Figure 1), and 12 cities reported STI screening information in 2013. The reviewer would suggest to correlate the frequency of STI screening in 2013 with

- Geometric mean MICs in 2013

- (Fold) change in geometric mean MICs between 2009 and 2013
- (Fold) change in geometric mean MICs between 2005 and 2013

For the 2005 screening frequencies, it would be interesting to correlate them with geometric mean MICs (in 2013, and possibly 2005), and not only changes in thereof.

Reply:

The third NHBS survey was in 2011 (not 2013) and thus we have assessed Spearman's correlation between percent reporting screening for any STI in the previous 12 months and MIC for the three antimicrobials in the following year (2012):

Azithromycin: Rho 0.45; P=0.141

Cefixime: Rho 0.31; P=0.325

Ceftriaxone: Rho=0.64; P=0.026

We also assessed Spearman's correlation between percent reporting screening for any STI in the previous 12 months (2011 survey) and the fold change in geometric mean MIC for the three antimicrobials between

a) 2005 and 2013:

Azithromycin: Rho 0.77; P=0.003

Cefixime: Rho 0.82; P=0.001

Ceftriaxone: Rho=0.61; P=0.034

b) 2009 and 2013:

Azithromycin: Rho 0.33; P=0.299

Cefixime: Rho -0.50; P=0.100

Ceftriaxone: Rho=0.58; P=0.047

3. In ref. 3, no association was found between rates of antibiotic prescribing and geometric mean MICs. Perhaps the results of the paper under review are affected by reverse causality, namely places with higher prevalence of drug resistance for gonorrhea, as well as syphilis in MSM may initiate more STI screening efforts. For example, the California sites had both high geometric mean MIC for ciprofloxacin in 2005 (ref. 3), and high frequency of screening (see also¹). Currently, this possibility is not mentioned in the Discussion. The reviewer was also wondering if there is a correlation between the fold change in screening frequency and the fold change in geometric mean MICs between 2005 and 2013.

Reply:

Thank you for this interesting suggestion which has been added to the discussion.

4. Are other variables in NHBS-MSM surveys (possibly rate of change of sexual partners, or a number of recent sexual partners) correlated with geometric mean MICs/changes in thereof?

Reply:

Whilst we agree this would be interesting to investigate, we did not assess these correlations in this small study.

5. In the Discussion, it is mentioned that “the sample size was small (9 or 12)”. Currently, only 9 cities are used in the correlation analysis, as far as the reviewer could see.

Reply:

The sample size for 2005 was 9 and therefore in Figure 1, where one of the variables is from 2005, only 9 data points can be used. There were however 12 data points for the other 2 surveys and these were used in the analyses using these surveys.

References:

1. Kirkcaldy RD, Bartoces MG, Soge OO, Riedel S, Kubin G, Del Rio C, et al. Antimicrobial Drug Prescription and Neisseria gonorrhoeae Susceptibility, United States, 2005-2013. Emerg Infect Dis. 2017;23(10):1657-63. Epub 2017/09/21. doi: 10.3201/eid2310.170488. PubMed PMID: 28930001; PubMed Central PMCID: PMC5621530.

Competing Interests: I have no competing interests

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