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Screening for STIs in PrEP cohorts results in high levels of antimicrobial consumption

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Abstract

Screening for STIs in men who have sex with men receiving HIV pre-exposure prophylaxis resulted in high consumption of macrolides, extended spectrum cephalosporins, fluoroquinolones and tetracyclines. The consumption of macrolides was 52 times as high as that reported for community-level consumption in certain European countries.

Keywords

Gonorrhea (*Neisseria gonorrhoeae*), chlamydia (*Chlamydia trachomatis*), Europe, antibiotic, screening

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Background

Antimicrobial consumption (AMC) drives antimicrobial resistance (AMR) at both individual and population levels.[1] Populations with high AMC tend to have a high prevalence of AMR for a range of antimicrobial-bacterial species (bug/drug) combinations.[1,2] Emerging evidence suggests that there are AMC thresholds for AMR. For example, one study found that all populations with macrolide consumption above 2 defined daily doses per 1000 persons daily (DID) had a high prevalence of macrolide resistance in *Treponema pallidum*, whereas those consuming less than this threshold had little or no resistance.[2] These considerations mean it is crucial to monitor population-level AMC in sub-populations at high risk of AMR, such as men who have sex with men (MSM) in preexposure prophylaxis (PrEP) cohorts.[3,4] Previous analyses have estimated what AMC might be in these cohorts based on reported percentage testing positive for bacterial STIs and assuming that all testing positive received treatment.[3] In this paper we aimed to assess the AMC in a PrEP cohort for macrolides, third generation cephalosporins, fluoroquinolones and tetracyclines in DID following standard WHO methodology.

Methods

We calculated the measured AMC in a well characterized HIV PrEP cohort in Antwerp, Belgium. Between October 2015 and December 2016, 200 HIV-uninfected MSM were enrolled into a PrEP demonstration project. Of these, 179 attended each of their follow up visits every 3 months for 18 months. At each of these visits, they were tested for *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Mycoplasma genitalium* at 3 sites (rectum, urethra and pharynx) using nucleic acid amplification tests. HIV and syphilis serological tests were also conducted 3-monthly. Hepatitis C serology was assessed at baseline and at 24 months. The full details of the follow up and testing are provided elsewhere.[5–7] At each study visit, the antimicrobials prescribed for any indication were recorded in the case reporting form as well as the clinical indications for these. We used these data to calculate AMC for these 179 individuals for macrolides (ATC class J01FA), third generation cephalosporins (ATC class J01DD), fluoroquinolones (ATC class J01MA) and tetracyclines

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(ATC class J01A) in DID following standard WHO methodology.[8] We compared the fold-difference in consumption between our PrEP cohort and national community-level consumption in 2016 in the 30 European countries participating in the European Surveillance of Antimicrobial Consumption (ESAC) program (https://www.ecdc.europa.eu/en/antimicrobial-consumption/surveillance-and-disease-data/database). The antimicrobial treatments used followed current European IUSTI guidelines.[9–13] Typically, this involved doxycycline or azithromycin for chlamydia, ceftriaxone and azithromycin for gonorrhoea and benzathine penicillin for syphilis. Ethical approval for the study was provided by the institutional review board of the Institute of Tropical Medicine Antwerp and the ethics committee of the Antwerp University Hospital.

Results

The consumption of macrolides (12.05 DID) in these young (median 39 years [IQR 33-44]), otherwise healthy men was very high and two to 52-times as high as that in the 30 European countries (Figure 1). It exceeded the approximate threshold for AMR in *Treponema pallidum* by 6-fold.[2] Consumption of third generation cephalosporins (0.76 DID) was higher than that in 25 countries. Fluoroquinolone consumption (4.80 DID) was higher than all countries except one and 11-fold higher than the country with the lowest consumption (Norway). Tetracycline consumption (2.29 DID) was higher than that in 19 countries. In all comparisons AMC in this PrEP cohort exceeded the community-level consumption for Belgium. This was despite the fact that fluoroquinolone and macrolide AMC in Belgium was in the top tertile of the 30 countries.

AMC was driven by the high number of asymptomatic STIs diagnosed. A total of 99/125 (79.2%) *C. trachomatis,* 96/138 (69.6%) *N. gonorrhoeae* and 132/161 (82.0%) *M. genitalium* infections were asymptomatic. In the case of *C. trachomatis*, *T. pallidum* and *N. gonorrhoeae* all infections were treated at each study visit and thus each diagnosis represented a new infection.

Discussion

Although gonococcal AMR has not been limited to one demographic group, it is remarkable how it has typically emerged in core-groups with high antimicrobial exposure such as MSM and sex workers in Asia.[4] The prevalence of reduced gonococcal susceptibility to azithromycin (MIC >1 mg/L) has increased from 2 to 12% in the past 6 years in Belgium – a finding which has been found to be associated with MSM sexual orientation in Belgium and elsewhere[14,15] but not according to a survey of gonococcal AMR in Europe.[16] We have also noted 100% genotypic macrolide resistance in circulating *Treponema pallidum* in our clinic and frequent outbreaks of macrolide-resistant *Enterobacteriaceae* such as *Shigella flexneri* in our MSM population and elsewhere.[17,18] Our findings of high macrolide consumption in MSM on PrEP provide

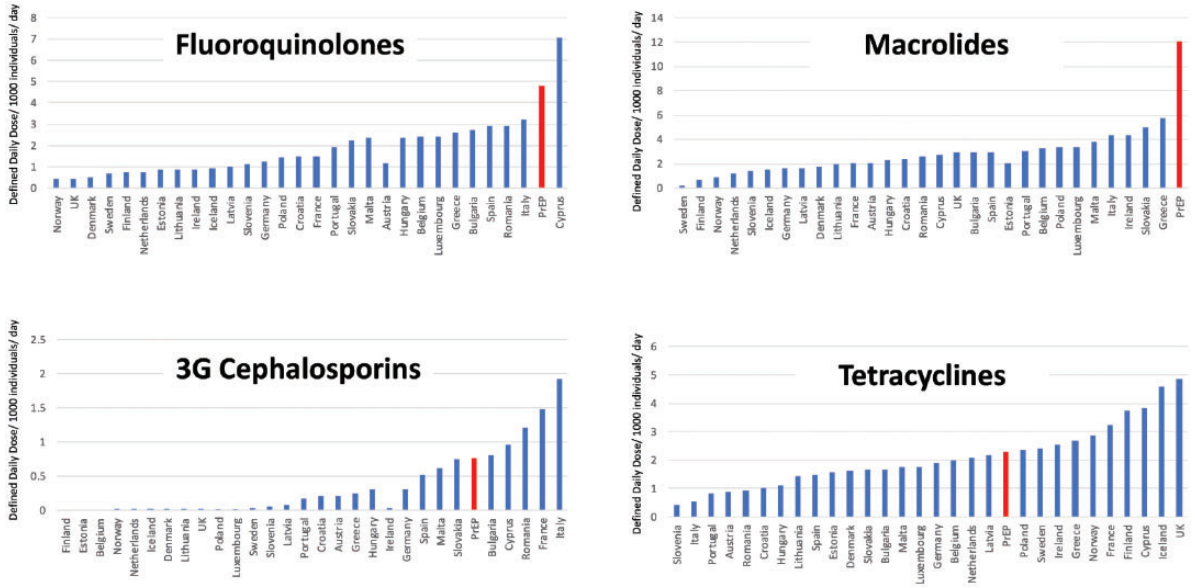

Figure 1. Antimicrobial consumption of macrolides, fluoroquinolones, third generation (3G) cephalosporins and tetracyclines in men receiving preexposure prophylaxis (PrEP depicted as red bars) in Belgium (2015 to 2018) as compared with national community consumption in 30 European countries in 2016.

a possible explanation for these linked findings. We should note that our consumption estimates are likely underestimates as they do not include antimicrobials obtained from other prescribers such as general practitioners and those consumed off-label. The fact that NAAT-based tests *for N. gonorrhoeae/C. trachomatis* may stay positive for up to two weeks post treatment may mean that participants could receive double treatment if they had their tests repeated by another health provider within this time period. A further limitation is that the study protocol initially advocated treating all those testing positive for *M. genitalium*. This practice was halted approximately 6-months into the study when it became apparent that this was having no effect on prevalence of *M. genitalium* or symptomatic infections from this organism. In addition European IUSTI guidelines, published in 2016, discouraged screening for asymptomatic *M. genitalium* infections.[9] We acknowledge that it could be argued that it is inappropriate to compare AMC in a PrEP cohort with national populations that have very different age structures and comorbidity profiles. The rationale for doing so is that reasonable data is available for national AMC in European countries and this has been shown in a number of studies to be strongly correlated with antimicrobial resistance in a wide range of bug/drug combinations.[1,19] In other words, European countries with high AMCs have been shown to have elevated prevalences of AMR for a range of bacteria.[1,19,20] Our study reveals AMC higher than these countries. This increases the probability that there is a selection pressure for the emergence of antimicrobial resistance in our PrEP cohort.

It is also relevant to note that there is a good rationale for screening for HIV, hepatitis C and syphilis in PrEP cohorts. These are all infections that have the potential for severe clinical sequelae in a considerable proportion of infections, they are typically not cleared by the host and their treatment with first-line therapies does not entail a high risk of inducing AMR in bacterial STIs such as *N. gonorrhoeae*.[21] The rationale for screening for chlamydia and gonorrhoea is less evident. No randomized controlled trials have been conducted and a systematic review of observational studies revealed no effect of screening on the prevalence of these infections.[22] This is important because ecological studies have also found that the intensity of gonorrhoea/chlamydia screening in MSM to be associated with gonococcal AMR.[14,23] Our findings of high antimicrobial consumption resulting predominantly from the detection of asymptomatic STIs via screening provide a possible explanation for the association between screening intensity and AMR. These findings provide further motivation to conduct randomized controlled trials to assess the risks and benefits of screening for chlamydia/gonorrhoea screening in MSM.

Declaration of conflicting interests

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