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Article

Evaluating Performance of the US Surveillance Systems for Monitoring Antimicrobial-Resistant Gonorrhea: An Agent-Based Modelling Study

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Abstract: We evaluated performance of two American surveillance systems for monitoring the spread of antimicrobial-resistant (AMR) gonorrhea: the Gonococcal Isolate Surveillance Project (GISP) and the enhanced Gonococcal Isolate Surveillance Project (eGISP) which includes the non-urethral isolates in addition to the urethral ones utilized in the original surveillance system. A continuous-time agent-based model of gonorrhea transmission among the US men who have sex with men (MSM) population was developed and used for this purpose. The model accounts for susceptible and resistant strains of *N. gonorrhoeae*, symptomatic and asymptomatic infection and different transmission routes. Overall, eGISP system outperforms the original GISP system and allows to obtain a higher accuracy using a significantly lower number of isolates. Most of time, the original surveillance system determines the moment of switch to a new antibiotic later than necessary which leads to additional gonorrhea cases and spread of the resistance. Informing the gonorrhea treatment guidelines by eGISP estimates instead of the currently used GISP estimates would result in reduction of 622 (95% uncertainty interval: -4,009, 9,099) gonorrhea cases in the simulated cohort of 10,000 US MSM over a 25-year period without reduction in the lifespan of the current first-line antibiotic.

Keywords: Agent-based modelling; gonorrhea; antimicrobial resistance; surveillance

1. Introduction

The rise of antimicrobial-resistant (AMR) gonorrhea is an emerging problem in many countries. N. gonorrhoeae has already developed resistance to many classes of antibiotics used for its treatment [1]. Some of the reasons for this growth are the inappropriate use of antibiotics, mutations and low quality of the antibiotics used. The infections outside of the genital area are also believed to contribute to it as those infections are mainly asymptomatic and the bacteria exchanges genetic material with other organisms in these parts of the body [2] [3].

Untreated gonorrhea can lead to a number of health problems, such as neonatal eye infections, infertility, ectopic pregnancy, increased ability to give and receive HIV etc. [4] Also, this growth of resistance threatens our ability to treat other infections which are being cured with the same antibiotics. However, the development of new antibiotics has been rather slow over the recent years as it is not profitable for pharmaceutical companies [5]. There are few antibiotics in clinical trials [6], but none of them has reached the market yet. Therefore, accurate surveillance of AMR gonorrhea is essential as it allows to take appropriate public health actions at the right time.

In the US, the Gonococcal Isolate Surveillance Project (GISP) formed in 1986 is a sentinel surveillance system to monitor the trend in AMR gonorrhea [7]. GISP utilizes urethral isolates collected from the first 25 men diagnosed with urethral gonorrhea in a number of surveillance sites and estimates the percentage of cases which are resistant to different antibiotics used for the treatment of gonorrhea. Once that value for a current first-line drug reaches 5%, a switch to a different antibiotic is usually made according to the World Health Organization (WHO) guidelines [8] [9].

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In 2017, the enhanced Gonococcal Isolate Surveillance Project (eGISP) was established which also included pharyngeal, rectal, and endocervical isolates [7]. This was done in order to understand whether rectum and pharynx can serve as anatomic niches that foster resistance and whether the antibiotic susceptibility pattern differ between men and women [10]. Since then, a decision is made each year by the policymakers on how many surveillance sites of each system to establish [11]. However, the positive impact of this new initiative remains unknown and the number of eGISP sites has remained low over the years (8-12 eGISP sites vs. 29-32 GISP sites [12] [13] [14] [15]).

We aim to compare the performance of both surveillance systems. In order to do this, we modelled the transmission of gonorrhea among the US men who have sex with men (MSM) which is the population group that is disproportionally affected by this disease [16]. The surveillance systems of AMR gonorrhea were also modelled, and their performance was evaluated. In particular, we calculated accuracy, sensitivity and specificity of each surveillance system. We also calculated the expected change in the lifespan of the current first-line antibiotic and the total number of gonorrhea cases (both diagnosed and undiagnosed) over 25 years for the current situation when the gonorrhea treatment guidelines are informed by GISP estimates and for a situation in which they are based on eGISP estimates instead.

2. Methods

2.1. Model Description

The population of the model is 10,000 MSM. The MSM population has high rates of partner numbers and high percentage of casual partners (80% according to a recent study [17]). We assumed all the contacts to be casual. The number of people reaching the sexually active age equals to the number of people leaving this population group. Individuals can get infected at rectum, pharynx and urethra. Sexual practices included in the model are kissing, oral sex, anal sex, rimming and docking. As the result, all the transmission routes were modelled: pharynx to pharynx, pharynx to urethra, urethra to pharynx, urethra to rectum, rectum to urethra, pharynx to rectum, rectum to pharynx and urethra to urethra.

The infection can occur at one site, or it can occur at two sites at the same time. A triple-site infection was not included due to its low possibility of occurrence [18]. Individuals can get infected with susceptible or resistant strain of gonorrhea. In case of a multi-site infection, the strains can be the same or different at two sites. Urethral infection was allowed to be symptomatic or asymptomatic, while rectal and pharyngeal infection was assumed to be always asymptomatic as symptomatic cases are rare [3].

The recovery pathways are shown in Figure 1. Symptomatic individuals seek the first-line treatment (ceftriaxone) at healthcare facilities and recover unless their strain was resistant or the bacteria developed resistance to ceftriaxone during the treatment, in which case the individual is re-treated with the second-line drug (ertapenem) and recover. Asymptomatic individuals can either recover naturally or get detected during the screening, after which they receive the first-line treatment and recover unless, again, their strain was resistant or the bacteria developed resistance, in which case the individual remains infectious.

The algorithm of the model can be found in the supplementary material. The model was developed using the Java-based simulation modelling tool AnyLogic (version 8.8.1 University).

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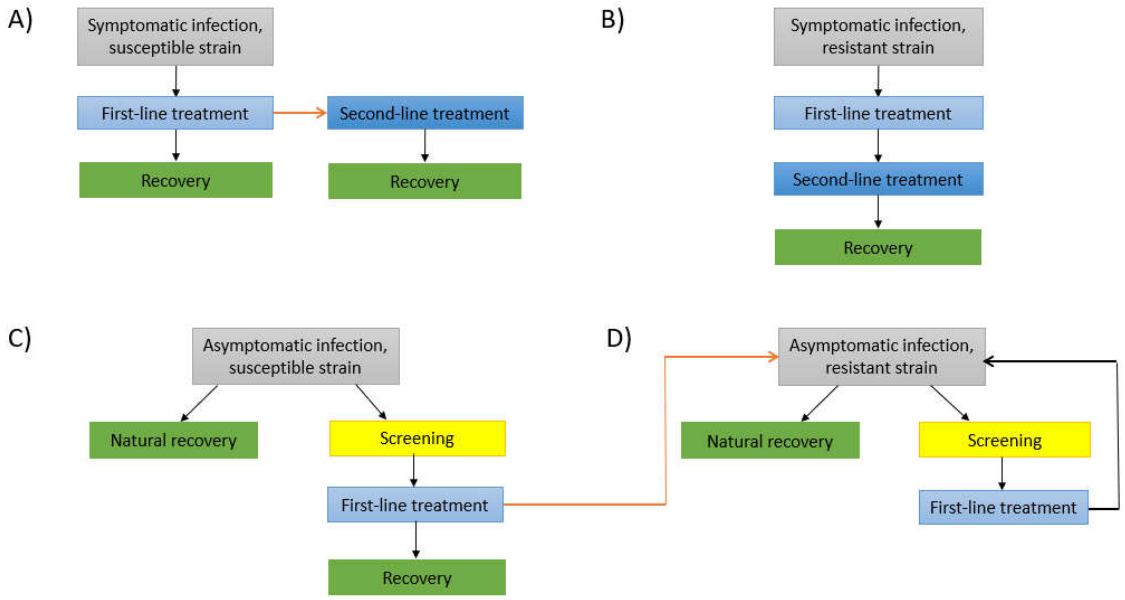

Figure 1. Recovery pathways for symptomatic versus asymptomatic infection and susceptible versus resistant strain of gonorrhea. The orange arrows represent development of resistance to ceftriaxone by *N. gonorrhoeae* while an individual is under treatment.

2.2. Model Calibration

The model was calibrated using the Bayesian calibration approach. Prevalence of gonorrhea among the US MSM at three anatomical sites, prevalence of gonorrhea resistant to ceftriaxone among the US MSM at three anatomical sites and the annual rate of reported gonorrhea cases per 100,000 US MSM were used as the calibration targets.

Ceftriaxone started to be used as the first-line treatment for the MSM in the US in 2004 [19]. The estimates on prevalence of ceftriaxone-resistant gonorrhea at different anatomical sites among the US MSM obtained from [20] were collected between 2018 and 2019. Therefore, in order to model the spread of resistance to ceftriaxone, we initiated the model in 2004, assigned the initial prevalence of gonorrhea resistant to ceftriaxone to zero and ran the model for 15 years. We kept the values of the other four calibration targets constant during the simulation period because the data on them is limited and trends cannot be assessed.

At the end of calibration, a set of trajectories was selected which fit the calibration targets the most precisely. They are shown in Figure 2. The details of the calibration procedure can be found in the supplement.

2.3. Surveillance Systems

Under GISP and eGISP surveillance systems, the isolates are tested for antimicrobial susceptibility and the percentage of cases resistant to different antibiotics used for treatment of gonorrhea is estimated. A surveillance system was modelled as the sum of the percentage of diagnosed cases resistant to ceftriaxone and the estimation error which occurs because only a limited number of isolates is tested for drug susceptibility. We adapted the approach from the earlier study [9] and assumed that the estimation error follows the normal distribution with mean zero and standard deviation $\sqrt{y_t(1-y_t)/K}$, where y_t is the percentage of diagnosed cases resistant to ceftriaxone in year t and K is the average number of isolates collected from the US MSM within a certain time period. A higher value of K leads to a smaller estimation error. It was assumed that the WHO guidelines [8] are followed and the switch to a different antibiotic is made once the system detects that the percentage of cases resistant to ceftriaxone has reached 5%.

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2.4. Evaluating Performance of the Surveillance Systems

We calculated accuracy of each surveillance system, i.e. its ability to correctly detect a moment of switch to a different antibiotic. For each trajectory, accuracy was computed as $\frac{x_r-|x_r-x_s|}{x_r}$, where x_r is the year when the percentage of diagnosed cases resistant to ceftriaxone reached 5% and x_s is the year when this percentage was detected under a surveillance system. Then the average accuracy was computed for each surveillance system. Sensitivity (probability that when the percentage of diagnosed cases resistant to ceftriaxone passes 5% a surveillance system correctly detects that) and specificity (probability that if the percentage of diagnosed cases resistant to ceftriaxone is below 5% a surveillance system correctly informs that) was also calculated for both surveillance systems.

The reports published by the Centers for Disease Control and Prevention (CDC) contain data on the number of isolates from the MSM used in eGISP up to 2022 [14] [15]. The average number during those years (2018-2022) was 822 isolates and this is the value that we used in our analysis for eGISP. The total number of isolates used in GISP is typically around 5000-6000 isolates [11]. During 2018-2022, the MSM accounted on average for one third of the submitted isolates [13]. Therefore, we used the average of 1833 isolates in our calculations for GISP.

Incorrect detection can result in a number of negative consequences. Early detection results in reduced antibiotic lifespan, while late detection leads to an increased number of gonorrhea cases. We calculated the total number of gonorrhea cases (both diagnosed and undiagnosed) over 25 years for the current situation when the treatment guidelines are based on GISP estimates and compared it with the situation in which they are informed by eGISP estimates. Also, we calculated the expected change in the lifespan of the current first-line antibiotic as the difference between the year when a surveillance system detects that the percentage of diagnosed cases resistant to ceftriaxone reached 5% and the actual moment that value was reached. Only the trajectories for which the moment of switch to a different antibiotic was detected under both surveillance systems and occurred in reality during the investigated time period (2017-2042) were used. The analysis was conducted in Python (version 3.11.5).

2.5. Sensitivity Analysis

Since it is difficult to estimate how long it would take for bacteria to develop resistance to a particular antibiotic, we investigated whether our choice of the simulation duration has affected our conclusions for accuracy, sensitivity and specificity of each surveillance system.

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3. Results

Comparison of the trajectories from the calibrated model to the calibration targets is shown in Figure 2.

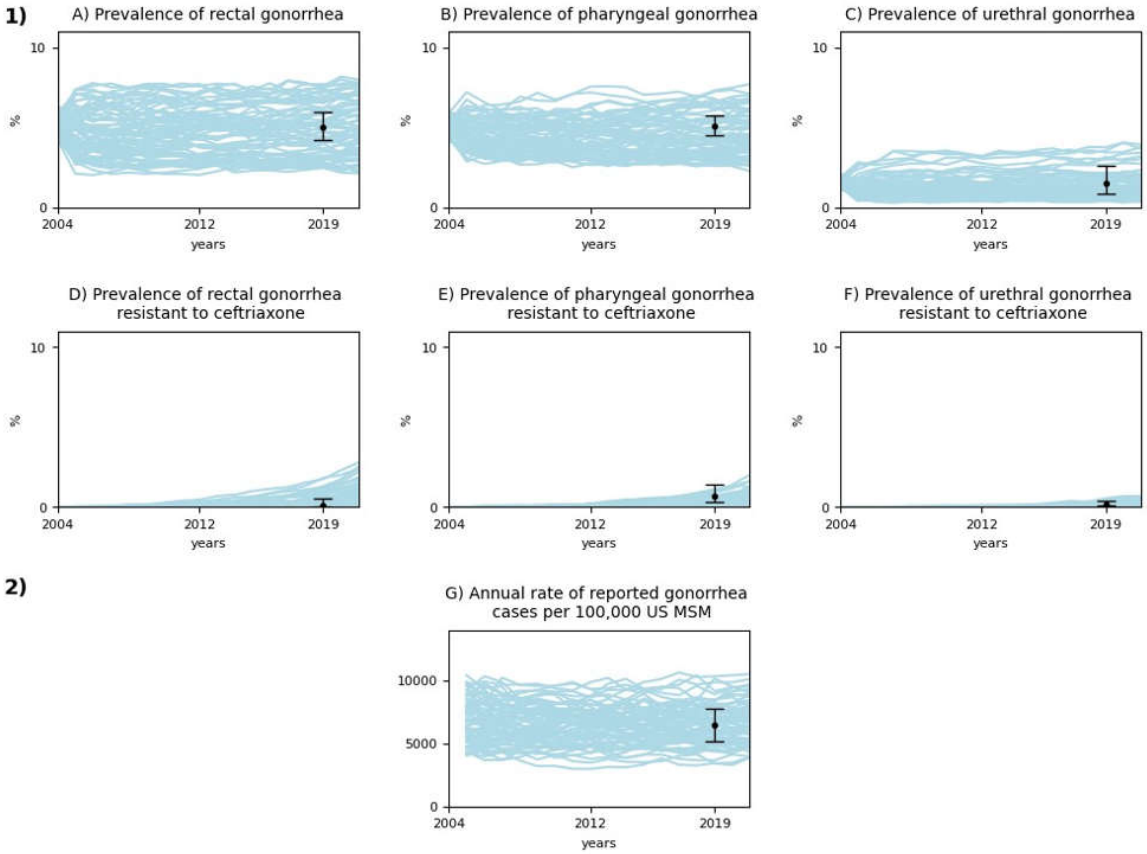

Figure 2. Comparison of the trajectories from the calibrated model to the calibration targets. The black dots and bars represent the estimates the model was calibrated against and the 95% uncertainty intervals. Panel 1: prevalence of rectal gonorrhea among the US MSM (5.01% [4.2%, 6%] [21] [22]), prevalence of pharyngeal gonorrhea among the US MSM (5.08% [4.5%; 5.8%] [22], [23]), prevalence of urethral gonorrhea among the US MSM (1.5% [0.86%; 2.6%] [21]), prevalence of rectal gonorrhea resistant to ceftriaxone among the US MSM (0.13% [0.03%; 0.51%] [20]), prevalence of pharyngeal gonorrhea resistant to ceftriaxone among the US MSM (0.67% [0.32%; 1.4%] [20]), prevalence of urethral gonorrhea resistant to ceftriaxone among the US MSM (0.18% [0.08%; 0.37%] [20]). Panel 2: annual rate of reported gonorrhea cases per 100,000 US MSM (6508 [5206, 7809] cases [24] [25]).

The model fit well to the calibration targets. The posterior distributions of the parameters can be found in Tables C-E in the supplement. The histograms of the posterior distributions are shown in Figures A-C in the supplement. Since many parameters related to gonorrhea transmission are unknown (e.g. probability of transmission between different anatomical sites, probability of developing resistance to ceftriaxone etc.), the results that we obtained provide some insight.

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The comparison of the performance of GISP and eGISP surveillance systems is presented in Figure 3.

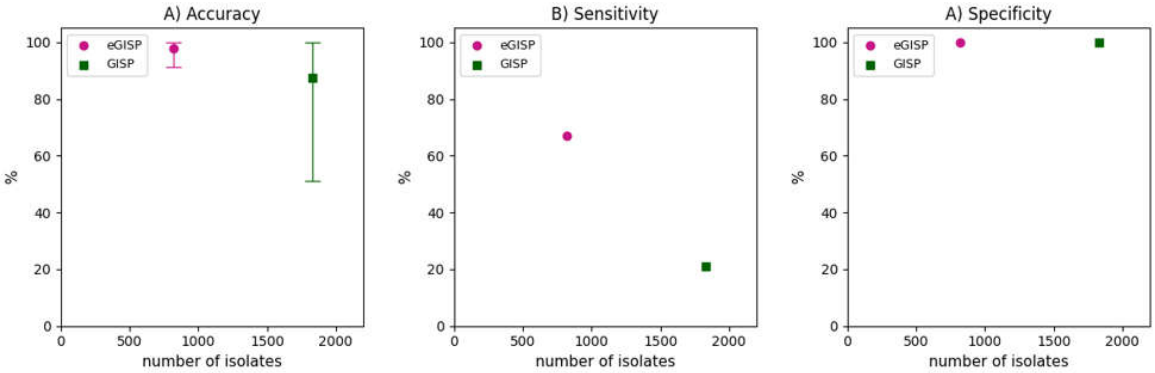

Figure 3. Performance of GISP and eGISP surveillance systems. The bars represent the 95% uncertainty intervals.

Our results indicate that accuracy of GISP system is 87.5% (95% uncertainty interval: 51%, 100%), while for eGISP system it is 98% (91%, 100%). Currently, more than twice less isolates are used in eGISP than in GISP. Despite that, the forecasted value for accuracy for the enhanced surveillance system is more than 10% higher and the uncertainty range is significantly shorter than it is for the original system. GISP demonstrates a low sensitivity of 21%, while for eGISP it is 67%. The specificity for both systems is 100%. Most of time, the original surveillance system determines the moment of switch to a new antibiotic later than necessary which leads to spread of the resistance.

Table 1 shows the expected change in the lifespan of the current first-line antibiotic (ceftriaxone) and the total number of projected gonorrhea cases (diagnosed and undiagnosed) under the scenarios in which the gonorrhea treatment guidelines are based on either GISP or eGISP estimates.

Table 1. Expected change in the lifespan of the current first-line antibiotic (ceftriaxone) and total number of projected gonorrhea cases (diagnosed and undiagnosed) over 25 years under GISP-informed and eGISP-informed gonorrhea treatment guidelines. The mean and 95% uncertainty intervals are reported. The simulations were run in the simulated cohort of 10,000 US MSM. .

Scenario	Expected change in the lifespan of the current first-line antibiotic (years)	Total number of projected gonorrhea cases
GISP-informed gonorrhea treatment guidelines	2.29 (0, 8)	62,610 (24,292, 194,609)
eGISP-informed gonorrhea treatment guidelines	0.38 (0, 1.43)	61,987 (24,022, 194,609)

Utilizing both surveillance systems does not reduce the lifespan of the current first-line antibiotic. Basing the treatment guidelines on GISP estimates increases the lifespan of ceftriaxone by 2.29 (0, 8) years, while basing them on eGISP estimates increases it by 0.38 (0, 1.43) years. The GISP system prolongs it that significantly due to the frequent delayed (or significantly delayed) detection of the moment of switch to a new antibiotic. There were 62,610 (24,292, 194,609) gonorrhea cases in the simulated cohort of 10,000 US MSM over 25 years under GISP-informed gonorrhea treatment guidelines and 61,987 (24,022, 194,609) gonorrhea cases under eGISP-informed guidelines.

The results of sensitivity analysis (Figure D in the supplement) demonstrate that out conclusions for accuracy, sensitivity and specificity of both surveillance systems are robust to the choice of the simulation duration.

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4. Discussion

This study evaluates the performance of GISP and eGISP surveillance systems. The eGISP system demonstrates higher accuracy and sensitivity than GISP system even with significantly lower number of isolates used. Informing the gonorrhea treatment guidelines by eGISP estimates results in fewer gonorrhea cases than basing them on the currently used GISP estimates without reduction in the lifespan of the current first-line antibiotic (ceftriaxone).

Our results demonstrate that including the extragenital isolates in the surveillance is more important for the accurate monitoring of the spread of AMR gonorrhea than increasing the surveillance size. Also, our findings support the assumption made in the recent years that rectum and pharynx can serve as a niche for the growth of antimicrobial resistance [2] [3]. Through the calibration procedure, we have estimated many parameters used in the model which can reduce uncertainty around them, especially for the ones for which no data is available (e.g., probability of developing resistance to ceftriaxone, transmission probabilities between different anatomical sites etc.).

When it comes to the non-urethral isolates, currently many isolate collection attempts fail due to a number of factors such as poor viability, growth problems or transport problems [11]. However, technical assistance with improving culture yields can resolve this problem [11]. In the recent years, there were cases of "super gonorrhea", when urethral symptoms have disappeared after the treatment, but the pharyngeal specimen remained positive to *Neisseria gonorrhoeae* and resistance to the first-line treatment used has been indicated [26]. In case of a clinic participating in eGISP instead of GISP, those cases of great concern would be more likely identified and treated.

Our findings should be interpreted in the context of a number of limitations. It was assumed that ceftriaxone was prescribed in each case as the first-line treatment. However, less effective cefixime was also used occasionally as the first-line drug between 2004 and 2007 and 2007 and 2012 if ceftriaxone was not an option [27] [28]. In addition, according to the recent data [29], adherence to the gonorrhea treatment guidelines by the healthcare practitioners in general is around 80% for male patients. Including the partnership formation and the associated condom usage would further increase the accuracy of our results. Also, we assumed that the WHO guidelines on the moment of switch to a new antibiotic are always followed. In reality, there have been rare instances of a first-line drug being replaced before reaching the recommended 5% threshold [30]. However, all the assumptions mentioned above are not expected to have a major impact on our conclusions, especially, given the comparative nature of our research.

From the public health perspective, this is the first evaluation of the performance of the US surveillance systems of drug-resistant gonorrhea. The outcomes of this work can be used by the policymakers who form the national guidelines for the surveillance of AMR gonorrhea as well as the gonorrhea treatment guidelines. This is expected to reduce the number of gonorrhea cases and spread of the resistance.

Data availability statement: All relevant data are within the manuscript and its supplement.

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