Supplementary material

1. Algorithm of the continuous-time agent-based model of gonorrhea transmission

Notations:

- f_i: fraction of individuals initially infected at site i;
- f_{ij}: fraction of individuals initially infected at sites i and j;
- f_{sym}: fraction of urethral cases that are initially symptomatic;
- An infectious profile: (i, r, s)
    - i is the anatomical site of infection, $i \in \{R, P, U\}$;
    - r is the resistance status that takes 0 for susceptible to ceftriaxone and 1 for resistant to ceftriaxone;
    - s is the symptom status that takes 0 for asymptomatic infection and 1 for symptomatic infection;
- β: the yearly rate of sexual acts;
- p_j: probability that infection at anatomical site j becomes symptomatic;
- $k_{i,j}$: probability of a sexual act between anatomical site i and site j;
- $d_{i,j}$: probability of transmission between anatomical site i and site j;
- t_i: average time until natural recovery at site i;
- t_s: average time between screening episodes;
- t_t: average time until seeking treatment for symptomatic urethral infection;
- t_r: average time until recovery after receiving treatment;
- p_{res}: probability of developing resistance to ceftriaxone under treatment.

1. Initialization of individuals

At the start of the simulations, a population of n susceptible agents is created.

2. Introduction of drug-susceptible strain of gonorrhea

A drug-susceptible infection is randomly introduced to the population, where f_R, f_P and f_u of individuals are allocated with infection at rectum, pharynx and urethra, respectively. Multi-site infection is also introduced, so f_{RP}, f_{RU} and f_{PU} of individuals are allocated with infection at rectum and pharynx, rectum and urethra, and pharynx and urethra, respectively.

3. Introduction of symptomatic urethral infection

A symptomatic urethral infection is randomly introduced to the population, so f_{sym} of individuals infected at urethra initially (as a single-site and multi-site infection) develop symptoms.

4. Transmission of gonorrhea

In AnyLogic, transmission of infection (as well as any other interaction between agents) is modelled by sending messages with certain information. An infected agent sends a message which contains the type of infection (e.g. urethral asymptomatic resistant) at a certain rate to randomly selected agents. Upon receiving of the message, an agent develops the infection of that type.

For simplicity, the type of infection was referred as infectious profile.

1) Individuals with infectious profile $(R, 0, 0)$ and $(R, 1, 0)$ send the following messages:
    a. $(j, r, 1)$, with $j \in \{P, U\}$, $r \in \{0,1\}$ at the rate $\beta k_{i,j} d_{i,j} p_j$.
    Individuals who received the message develop symptomatic infection at site j with resistance status r;
    b. $(j, r, 0)$, with $j \in \{P, U\}$, $r \in \{0,1\}$ at the rate $\beta k_{i,j} d_{i,j}(1 - p_j)$.
    Individuals who received the message develop asymptomatic infection at site j with resistance status r.
2) Individuals with infectious profile $(P, 0, 0)$ and $(P, 1, 0)$ send the following messages:
    a. $(j, r, 1)$, with $j \in \{R, P, U\}$, $r \in \{0,1\}$ at the rate $\beta k_{i,j} d_{i,j} p_j$.
    Individuals who received the message develop symptomatic infection at site j with resistance status r;
    b. $(j, r, 0)$, with $j \in \{R, P, U\}$, $r \in \{0,1\}$ at the rate $\beta k_{i,j} d_{i,j}(1 - p_j)$.
    Individuals who received the message develop asymptomatic infection at site j with resistance status r.
3) Individuals with infectious profile $(U, 0, 0)$, $(U, 1, 0)$, $(U, 0, 1)$ and $(U, 1, 1)$ send the following messages:
    a. $(j, r, 1)$, with $j \in \{R, P, U\}$, $r \in \{0,1\}$ at the rate $\beta k_{i,j} d_{i,j} p_j$.
    Individuals who received the message develop symptomatic infection at site j with resistance status r;
    b. $(j, r, 0)$, with $j \in \{R, P, U\}$, $r \in \{0,1\}$ at the rate $\beta k_{i,j} d_{i,j}(1 - p_j)$.
    Individuals who received the message develop asymptomatic infection at site j with resistance status r.

5. Natural recovery

The agents in the model move between different stages by undergoing the transitions. Each of these transitions has an associated rate.

Individuals with infectious profile (i, r, s) with $i \in \{R, U, P\}$, $r \in \{0,1\}$ and $s = 0$ recover naturally. Time until natural recovery follows an exponential distribution with rate parameter t_i.

6. Screening of individuals

Individuals with infectious profile (i, r, s) with $i \in \{R, U, P\}$, $r \in \{0,1\}$ and $s = 0$ undergo screening. Time between screening episodes follows an exponential distribution with rate parameter t_s. Immediately after screening individuals receive the first-line treatment (ceftriaxone).

7. Seeking the first-line treatment for symptomatic urethral infection

Individuals with infectious profile $(U, 0, 1)$ and $(U, 1, 1)$ seek the first-line treatment. Time until seeking treatment for individuals with symptomatic urethral infection follows an exponential distribution with rate parameter t_t;

8. Receiving the first-line treatment, development of resistance and recovery

a) Treatment of drug-susceptible infection

Individuals with infectious profile $(R, 0, 0)$, $(P, 0, 0)$, $(U, 0, 0)$ and $(U, 0, 1)$ receive the first-line treatment as the result of infection detection during the screening or care seeking for a symptomatic urethral infection. Time until recovery after receiving the first-line treatment follows an exponential distribution with rate parameter t_r.

During the treatment, the bacteria might develop resistance to ceftriaxone with probability p_{res}, which results in changing the resistance status of infection profile to $r = 1$. If resistance is not developed, the individual recovers at that site. In case of individuals being infected at two sites, the bacteria might develop resistance with the probability p_{res} at one site or at another one. It can also develop resistance at both sites with the same probability. If resistance is not developed, the individual recovers at both sites.

b) Treatment of drug-resistant infection

Individuals with infectious profile $(R, 1, 0)$, $(P, 1, 0)$, $(U, 1, 0)$ and $(U, 1, 1)$ receive the first-line treatment which does not change their infectious profile.

9. Seeking the second-line treatment for symptomatic urethral infection

Individuals with infectious profile $(U, 1, 1)$ seek re-treatment with the second-line antibiotic (ertapenem) after the first-line treatment fails. Time until seeking re-treatment for individuals with symptomatic urethral infection follows an exponential distribution with rate parameter t_t.

10. Simulation of the surveillance systems

Before starting the simulations, it is being set whether one of the surveillance systems (GISP or eGISP) will be simulated. Once the set system detects that the percentage of cases resistant to ceftriaxone reached 5%, a switch to a different antibiotic is being made. As the result, all the cases become susceptible (r=0 for all the infectious profiles). The probability of developing resistant to ceftriaxone under treatment becomes zero (p_{res}=0).

2. Details of calibration

The model was calibrated to prevalence of gonorrhea at three anatomical sites, prevalence of gonorrhea resistant to ceftriaxone at three anatomical sites and the annual rate of reported gonorrhea cases per 100,000 US men who have sex with men (MSM). For the first six calibration targets, prevalence, the number of participants (M) and the number of positive cases (m) reported in a study used in the relevant source was obtained from [1] [2] [3] [4]. For prevalence of rectal gonorrhea and prevalence of pharyngeal gonorrhea, we pooled the data from several studies that were available in order to reflect the real-life situation better.

For the last calibration target, we took the annual rate of reported gonorrhea cases per 100,000 US MSM estimated for 2018 from the Centers for Disease Control and Prevention (CDC) report [5], and the confidence intervals as well as the values for M_7 and m_7 from [6] where they were calculated manually. The calibration targets and their associated values are listed in Table A.

i	Calibration target	Number of participants (M) and number of positive cases (m) in the source study	Data	Source
1	Prevalence of rectal gonorrhea among the US MSM	2337, 117	5.01% [4.2%, 6%]	[2, 3]
2	Prevalence of pharyngeal gonorrhea among the US MSM	4547, 231	5.08% [4.5%; 5.8%]	[3, 4]
3	Prevalence of urethral gonorrhea among the US MSM	802, 12	1.5% [0.86%; 2.6%]	[2]
4	Prevalence of rectal gonorrhea resistant to ceftriaxone among the US MSM	1553, 2	0.13% [0.03%; 0.51%]	[1]
5	Prevalence of pharyngeal gonorrhea resistant to ceftriaxone among the US MSM	1049, 7	0.67% [0.32%; 1.4%]	[1]
6	Prevalence of urethral gonorrhea resistant to ceftriaxone among the US MSM	3974, 7	0.18% [0.08%; 0.37%]	[1]
7	Annual rate of reported gonorrhea cases per 100,000 US MSM	1380, 90	6508 [5206, 7809]	[5, 6]

Table A. Calibration targets and their associated values.

During the calibration, the simulations were run for 15 years and a total of 45,000 runs were performed. Only the trajectories that satisfied the conditions listed below during the entire simulation were kept.

1. Annual rate of reported gonorrhea cases per 100,000 US MSM is greater than 500 and less than 11000.
2. Prevalence of rectal gonorrhea among the US MSM is greater than 2% and less than 8%.
3. Prevalence of pharyngeal gonorrhea among the US MSM is greater than 2.5% and less than 8%.
4. Prevalence of urethral gonorrhea among the US MSM is greater than 0.3% and less than 4%.
5. Prevalence of rectal gonorrhea resistant to ceftriaxone among the US MSM is less than 2%.
6. Prevalence of pharyngeal gonorrhea resistant to ceftriaxone among the US MSM is less than 2%.
7. Prevalence of urethral gonorrhea resistant to ceftriaxone among the US MSM is less than 2%.
8. Percentage of symptomatic cases is greater than 50%.

For each kept trajectory, seven functions (likelihoods) were computed according to the formula:

$$L_i = m_i \ln p_i + (M_i - m_i)\ln(1 - p_i), \quad i = 1,..7.$$

Here p_i is the value of the output i at the end of simulation, M_i is the number of participants used in the source study i and m_i is the number of positive cases used in the source study i (Table A).

Then the function L_{Total} was calculated for each kept trajectory as:

$$L_{Total} = \sum_{i=1}^{7} L_i.$$

Finally, we selected 70 trajectories for which the value of L_{Total} was the highest.

3. Model parameters

The values of the parameters that remain constant during the simulations are listed in Table B. Sexual acts such as anal fingering and sharing sex toys which potentially involve contacts between saliva and rectum were also included in rimming (pharynx to rectum route and rectum to pharynx route), so the probability of a sexual act between these two sites was increased accordingly [7].

Parameter	Value	Source
Total MSM population (n)	10,000	
Probability that rectal infection becomes symptomatic (p_R)	0	Assumption
Probability that pharyngeal infection becomes symptomatic (p_p)	0	Assumption
Probability of a sexual act between two anatomical sites		[7]
$k_{P,P}$	0.83	
$k_{P,U}$	0.825	
$k_{P,R}$	0.6	
$k_{U,R}$	0.478	
$k_{U,U}$	0.03	
$k_{R,U}$	0.478	
$k_{R,P}$	0.6	
$k_{U,P}$	0.825	

Table B. The values of the parameters that remain constant during the simulations.

The prior distributions and posterior intervals of the parameters of the model that were determined during the calibration are listed in Tables C-E. For assigning prior distributions for the fractions of people infected at different anatomical sites and the yearly rate of sexual acts we took the mean value (x) from the published literature [8] [9] and then assigned a distribution as uniform($x - 0.2x$, $x + 0.2x$). In case a histogram that we obtained after a round of calibration was left-skewed or right-skewed, we extended the range to the right or to the left, respectively.

Parameter	Prior distribution (all uniform)	Mean and 95% posterior interval	Source to inform prior distribution
Fraction of individuals initially infected at rectum (f_R)	[0.04008, 0.06012]	0.05 (0.04, 0.059)	[8]
Fraction of individuals initially infected at pharynx (f_P)	[0.04064, 0.06096]	0.052 (0.042, 0.06)	[8]
Fraction of individuals initially infected at urethra (f_U)	[0.012, 0.018]	0.015 (0.012, 0.018)	[8]
Fraction of individuals initially infected at rectum and pharynx (f_{RP})	[0.0016, 0.0024]	0.002 (0.002, 0.002)	[8]
Fraction of individuals initially infected at rectum and urethra (f_{RU})	[0.00048, 0.00072]	0.0006 (0.0005, 0.0007)	[8]
Fraction of individuals initially infected at pharynx and urethra (f_{PU})	[0.00032, 0.00048]	0.0004 (0.00032, 0.00047)	[8]
Fraction of urethral cases that are initially symptomatic (f_{sym})	[0.01, 0.3]	0.16 (0.019, 0.3)	Assumption

Table C. Prior distributions and posterior intervals of the initialization parameters.

Parameter	Prior distribution (all uniform)	Mean and 95% posterior interval	Source to inform prior distribution
Probability that urethral infection becomes symptomatic (p_U)	[0.33, 0.94]	0.76 (0.52, 0.93)	[10-13]
Yearly rate of sexual acts (β)	[64, 96]	19.9 (8.5, 42)	[9]
Probability of transmission between two anatomical sites			Assumption
$d_{P,P}$	[0.001, 0.1]	0.035 (0.003, 0.093)	
$d_{P,U}$	[0.001, 0.1]	0.058 (0.008, 0.098)	
$d_{P,R}$	[0.001, 0.1]	0.044 (0.003, 0.094)	
$d_{U,R}$	[0.001, 0.1]	0.051 (0.008, 0.095)	
$d_{U,U}$	[0.001, 0.1]	0.054 (0.003, 0.099)	
$d_{R,U}$	[0.001, 0.1]	0.059 (0.014, 0.096)	
$d_{U,P}$	[0.001, 0.1]	0.047 (0.006, 0.09)	
$d_{R,P}$	[0.001, 0.1]	0.048 (0.004, 0.096)	

Table D. Prior distributions and posterior intervals of the transmission parameters.

Parameter	Prior distribution (all uniform)	Mean and 95% posterior interval	Source to inform prior distribution
Average time until natural recovery at different anatomical sites (years)			Assumption
t_R	[1/12, 5]	2.26 (0.59, 4.6)	
t_U	[1/12, 5]	2.5 (0.36, 4.77)	
t_P	[1/12, 5]	3 (1, 4.87)	
Average time until seeking treatment for symptomatic urethral infection (t_t) (days)	[3, 11]	6.9 (3.5, 10.7)	[11]
Average time between screening episodes (t_s) (years)	[1, 10]	14.4 (9.42, 17.7)	Assumption
Average time until recovery after receiving treatment (t_r) (days)	[1, 14]	7.7 (1.7, 13.5)	Assumption
Probability of developing resistance to ceftriaxone under treatment (p_{res})	[0.00000001, 0.01]	0.0048 (0.001, 0.009)	Assumption

Table E. Prior distributions and posterior intervals of the recovery parameters.

The probabilities of transmission between two anatomical sites that we obtained are of the same order of magnitude for all the transmission routes. It was the highest for and rectum to urethra route (anal sex) and the lowest for pharynx to pharynx route (kissing). Our calibration results indicate that the actual time between screening episodes is much longer that the one recommended by the CDC (at least annually for sexually active MSM [14]). The probability of developing resistance to ceftriaxone that we obtained is a bit lower than the actual one because we did not account for cefixime being ocassionally used as the first-line treatment (when ceftriaxone was not an option) between 2004 and 2007 and 2008 and 2012 [15] [16]. For the yearly rate of sexual acts we obtained a much lower range than our prior distribution that was formed based on the mean value reported in [9]. However, [9] focused on a specific population group: young, internet-using MSM. Finally, our results indicate that it takes longer to recover naturally from asymptomatic gonorrhea at pharynx than it does at rectum or urethra.

The histograms of the posterior distributions are shown in Figures A-C.

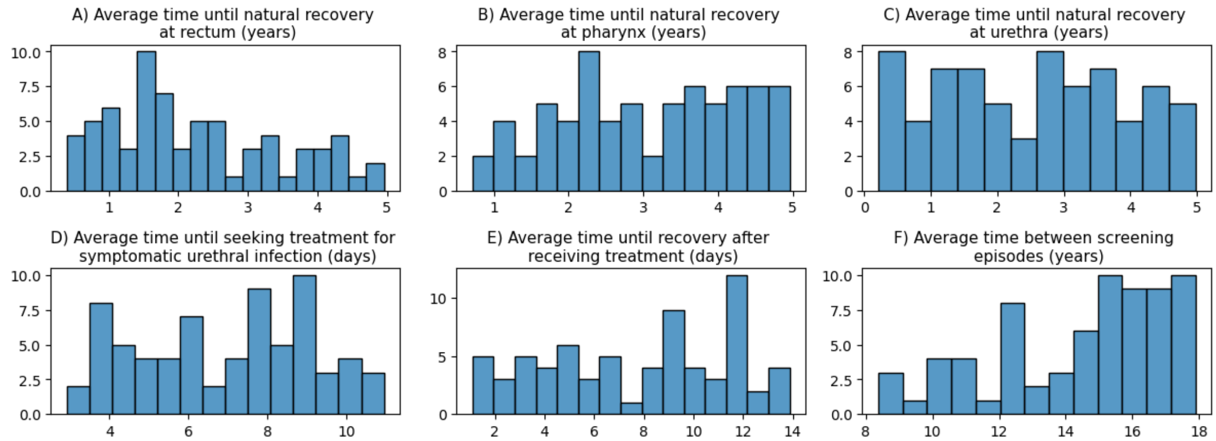

Figure A. Histograms of the posterior distributions for the average time until events that take place during the simulations.

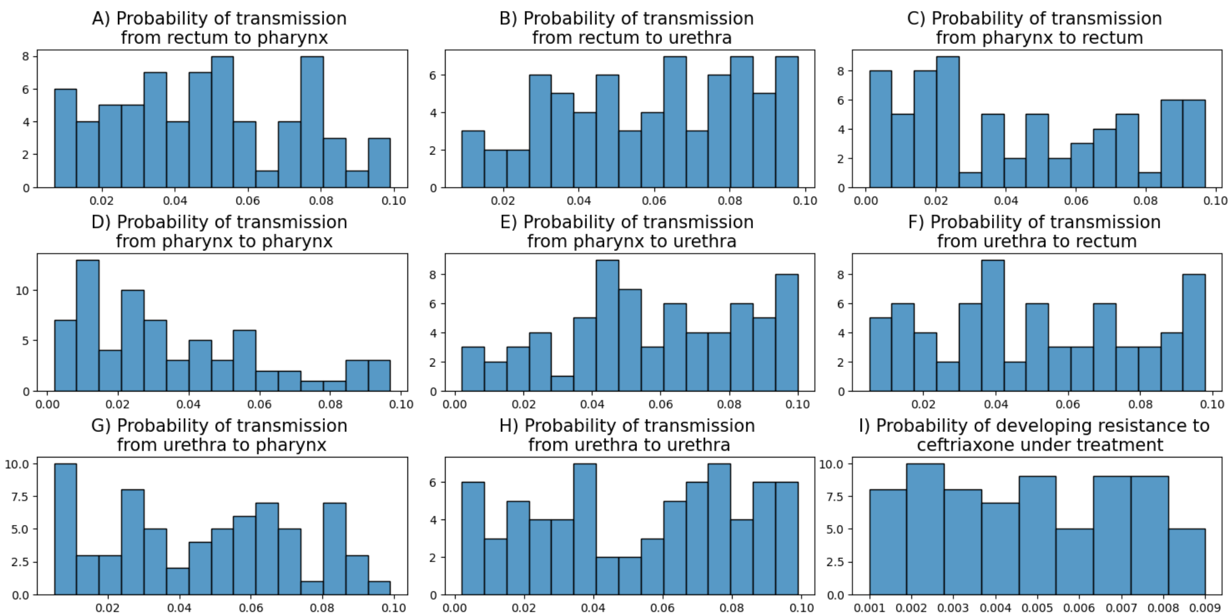

Figure B. Histograms of the posterior distributions for the probabilities of transmission between anatomical sites and probability of developing resistance to ceftriaxone under treatment.

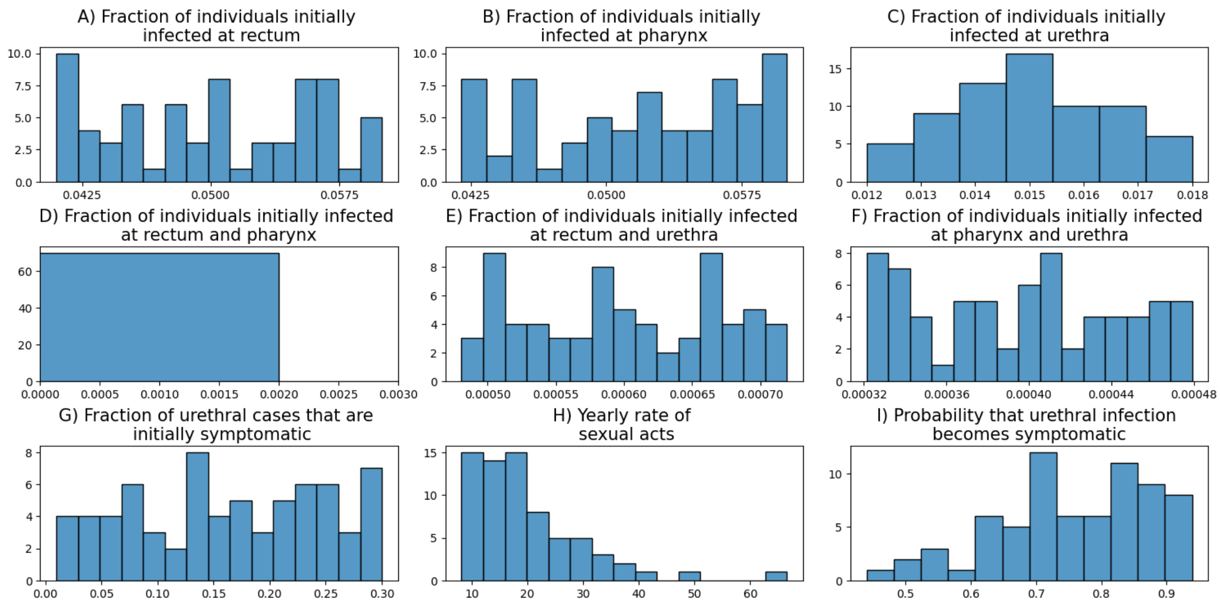

Figure C. Histograms of the posterior distributions for fractions of individuals initially infected at different anatomical sites, yearly rate of sexual acts and probability that urethral infection becomes symptomatic.

4. Results of sensitivity analysis

In our main analysis, year 2017 was the start point of the simulation horizon and year 2042 was its end point. In the sensitivity analysis, we varied the end point to investigate the impact that the simulation duration has on our conclusions for accuracy, sensitivity and specificity. From Figure D it is evident that the conclusions are robust to the choice of the simulation duration.

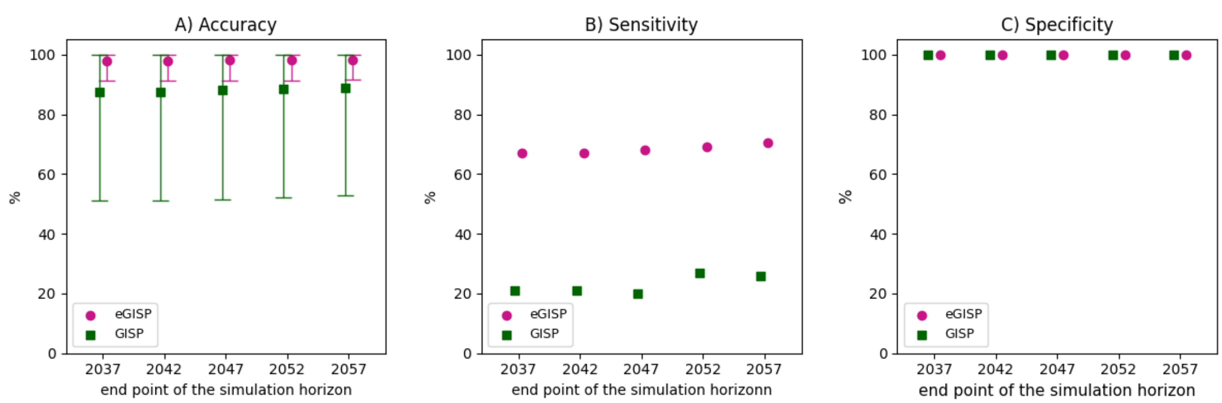

Figure D. Performance of GISP and eGISP surveillance systems under different simulation durations. The bars represent the 95% uncertainty intervals.

References

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