Adaptive guidelines for the treatment of gonorrhea to increase the effective lifespan of antibiotics: A mathematical modeling study

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Abstract

Background: The rise of gonococcal antimicrobial resistance highlights the need for strategies that extend the clinically useful lifespan of antibiotics. As there is limited evidence to support the current practice of switching empiric first-line antibiotic when resistance exceeds 5% in the population, our objective was to compare the impact of alternative strategies on the effective lifespans of antibiotics and the overall burden of gonorrhea.

Methods and Findings: We developed and calibrated a mathematical model of gonorrhea transmission among men who have sex with men (MSM) in the United States. We calibrated the model to the estimated prevalence of gonorrhea, the rate of gonorrhea cases, and the proportion of cases presenting symptoms among MSM in the United States. We used this model to project the effective lifespan of antibiotics and the number of gonorrhea cases expected under current and alternative surveillance strategies over a 50-year simulation period. We demonstrate that compared to the current practice, a strategy that 1) uses quarterly (as opposed to yearly) surveillance estimates and 2) incorporates both the estimated prevalence of resistance and the trend in the prevalence of resistance to determine treatment guidelines could extend the effective lifespan of antibiotics by 0.83 years without increasing the number of gonorrhea cases. This is equivalent to successfully treating an additional 86.8 (95% uncertainty interval: [51.7, 121.2]) gonorrhea cases per 100,000 MSM population each year with the first-line antibiotics without worsening the burden of gonorrhea.

As our model describes the transmission of gonorrhea among the U.S. MSM population, our conclusions might not be generalizable to other settings. Furthermore, to better capture the uncertainty in the characteristics of current and future antibiotics, we chose to model hypothetical drugs with characteristics similar to the antibiotics commonly used in gonorrhea treatment.

Conclusions: Our results suggest that use of data from surveillance programs could be expanded to prolong the clinical effectiveness of antibiotics without increasing the burden of the disease. This highlights the importance of maintaining effective surveillance systems and the engagement of policy makers to turn surveillance findings into timely and effective decisions.

Author Summary

Why Was This Study Done?

- Gonorrhea is the second most common notifiable disease in the United States and has developed resistance to all first-line antibiotics.
- The selection of antibiotics used for gonorrhea treatment is almost always empiric and based on guideline recommendations.
- There is limited evidence to support the current practice of switching the first-line antibiotic after resistance to it exceeds 5% in annual surveillance estimates.
- Our objective was to project how alternative strategies to inform the first-line treatment recommendations impact the lifespan of antibiotics and the overall burden of gonorrhea.

What Did the Researchers Do and Find?

- We developed a mathematical model that describes the key characteristics of gonorrhea transmission among men who have sex with men (MSM) in the United States.
- Our model estimates the lifespan of antibiotics and the incidence of gonorrhea under current and alternative strategies for changing first-line empiric antibiotic treatment.
- We found that compared to the current practice, a strategy that 1) uses quarterly surveillance estimates and 2) incorporates both the estimated prevalence of resistance and the trend in the prevalence of resistance to determine treatment guidelines could extend the effective lifespan of antibiotics without worsening the burden of gonorrhea.

What Do These Findings Mean?

- This work suggests an opportunity to optimize the use of surveillance systems to slow the spread of antibiotic-resistant strains and control the burden of gonorrhea.
- This requires enhancing the surveillance systems (for example, by allowing for more frequent reporting of estimates and a larger number of observations) and the engagement of policy makers to turn surveillance findings into timely decisions.
- Further studies are needed to investigate the generalizability of these conclusions.

Introduction

Gonorrhea remains a globally significant sexually transmitted infection (550,000 reported cases in 2017 in the United States [1] and an estimated 87 million cases worldwide in 2016 [2]), and the recent descriptions of resistance to standard treatments has raised concern about the global emergence of untreatable infections [3,4]. The threat of spread of untreatable gonococcal infections highlights the need for strategies to maximize the lifespan of existing antibiotics while providing effective treatment for infected individuals.

The selection of antibiotics used for gonorrhea treatment is almost always empiric and based on guideline recommendations, as the diagnosis is usually made by nucleic acid amplification test which does not inform on antibiotic susceptibility [5-7]. Even when culture is available, patients likely receive first-line empiric antibiotic treatment while awaiting drug-susceptibility results. In the United States, current treatment guidelines are based on the prevalence of antimicrobial resistance estimated by the Gonococcal Isolate Surveillance Project (GISP) [8], a sentinel surveillance system that monitors trends in antimicrobial susceptibilities of gonococcal strains in the United States [9].

Once the point estimate for prevalence of resistance to the first-line antibiotic exceeds 5% [8,10], the WHO guideline recommends switching to another antibiotic for empiric treatment [10]. However, there is limited evidence to support this 5% threshold. Increasing the threshold may extend the lifespan of second-line antibiotics by minimizing the use of these agents but at the cost of decreasing the probability that any given individual with gonorrhea receives effective first-line therapy. This could be associated with greater individual morbidity and may also lead to longer durations of infectiousness, facilitating further transmission of gonorrhea. In contrast, decreasing the switching threshold may increase the probability that each individual receives effective first-line therapy, but also would lead to earlier and more extensive use of second-line regimens, which would be expected to shorten their lifespan. Beyond the cross-sectional resistance proportion, other easily observed features of resistance emergence, such as tempo of change, could also be considered in designing optimal switching policy. A rapid rise in resistance proportion, for example, might prompt an earlier switch in recommended antibiotics than a slow increase [11].

In this study, we used a transmission dynamic model to compare the performance of different decision rules that could inform the recommendations for the first-line therapy of gonococcal infections. Specifically, we considered whether the current switching strategy based on the 5% threshold from annually reported surveillance efforts is outperformed by policies that i) use different thresholds for the percentage of isolates that are resistant; ii) incorporate information on the trend in the percentage of isolates that are resistant; iii) and increase the frequency and/or size of drug resistance surveys.

Methods

Treatment of gonococcal infections

We considered a scenario in which three antibiotic drugs (Drug A, Drug B, and Drug M) are available for treatment of gonorrhea. Drug A represents first-line therapy, such as ceftriaxone or azithromycin [12], and Drug B represents an alternative antibiotic that may be suitable for the first-line treatment of gonorrhea, such as zoliflodacin [13] or gepotidacin [14], both of which have been over 95% effective against urogenital gonococcal infections in phase 2 trials. Drug M represents the last-line antibiotic for gonorrhea.

We assumed that Drug B would be initially reserved for treatment of cases that fail treatment with Drug A. The selective pressure for resistance to Drug A increases as more cases of gonorrhea are treated with this drug Following the current strategy [8,10], one would remove Drug A from clinical use and replace it with Drug B once a specific threshold for resistance to Drug A is exceeded. Subsequently, those who fail first-line treatment with Drug B will be retreated with Drug M. Likewise, when the prevalence of resistance to Drug B reaches a pre-defined threshold, Drug B will be removed from the first-line therapy and Drug M will be used for both first-line and second-line therapy.

Adaptive guidelines to inform first-line treatment recommendations

An efficient strategy to guide the first-line treatment recommendations strikes a balance between the need to maximize the effective lives of Drugs A and B with the goal of treating gonococcal infections with the most effective drug available. An adaptive guideline identifies the first-line therapy drug based on cumulative observations on the resistance characteristics of the ongoing gonorrhea epidemic. In this study, we compared the performance of four types of adaptive guidelines in terms of their ability to prolong the effective life of Drugs A and B, and to prevent gonorrhea (Table 1).

Strategies ‘Threshold-Annual’ and ‘Threshold-Quarterly’ represent the guidelines that recommend switching to a new first-line drug once the resistance prevalence passes a certain threshold (e.g., 5%) [8,10]. They differ in how frequently the estimates of resistance prevalence are obtained and treatment recommendations are updated. The strategy ‘Threshold-Annual’ with a value of 5% represents the current practice as the estimates of resistance prevalence from surveillance systems (such as GISP in the United States) become available on yearly basis. The ‘Threshold-Quarterly’ policy relies on the same annual number of susceptibility tests as in ‘Threshold-Annual,’ but it distributes them over four quarters. Therefore, it might be able to detect trends in resistance more quickly but at the expense of lowering the precision in the estimates of resistance prevalence.

Strategy ‘Threshold + Trend’ seeks to detect the emergence of resistance to the first-line drug more proactively by using both estimates of resistance prevalence and the change in the resistance prevalence since the last year. Strategy ‘Enhanced Threshold + Trend’ is the same as strategy ‘Threshold + Trend’ except that the evaluation of resistance prevalence is performed quarterly with twice as many annual susceptibility tests as in the strategy ‘Threshold + Trend’. Compared to the ‘Threshold + Trend’ strategy, the ‘Enhanced Threshold + Trend’ strategy

benefits from more frequent and a larger number of observations, which might facilitate the detection of statistically significant trends.

A gonorrhea transmission dynamic model

To evaluate the impact of these strategies on the overall burden of gonorrhea and antibiotic lifespans, we developed a stochastic compartmental model that describes the transmission of *N. gonorrhoeae* among men who have sex with men (MSM) in the United States (Fig. 1). About 42% of gonorrhea cases in 2017 were among MSM and the emergence of resistance among this population is of particular concern [1,5]. The model is adapted from Tuite et al (2017) [15] with additional details necessary to evaluate the strategies described in Table 1.

In our model, susceptible individuals are at risk of infection with gonorrhea, and this risk varies by the prevalence of infection. Infected cases can be symptomatic or asymptomatic (Fig. 1A). Infected individuals are further divided to represent the resistance profile of the infecting strain: drug-susceptible infection (I_0), infection resistant to Drug A (I_A), infection resistant to Drug B (I_B), and infection resistant to both Drugs A and B (I_{AB}) (Fig. 1B). Asymptomatic cases do not seek treatment and remain infectious until they recover spontaneously or get detected through active screening (Fig. 1A). All symptomatic cases are assumed to seek treatment with some delay. Cases who seek treatment or are detected through screening will receive treatment with either Drug A, B, or M, depending on the current recommendation for the first-line therapy. If treated with an antibiotic to which the infecting strain is susceptible, the individual returns to the susceptible state. A portion of symptomatic individuals who fail the first-line treatment (due to receiving ineffective treatment or developing resistance) will seek retreatment with some delay. As soon as effective treatment is initiated, we assume that infected individuals no longer contribute to the force of infection (due to either negligible infectiousness and/or reduced sexual activity).

Resistance may arise while an individual receives antibiotic treatment (Fig. 1B). To account for the fitness cost associated with resistance, we assumed that compared to susceptible strains, resistant strains are less transmissible [15], at least initially. Data from GISP indicate that despite the decrease in the use of tetracycline, penicillin, ciprofloxacin, cefixime, ceftriaxone, and azithromycin in recent years, the prevalence of resistance to these antibiotics has been fairly stable [1]. To produce simulated trajectories that allow for this persistence despite reduced use of these antibiotics, we allow the fitness cost of resistance to gradually decrease, consistent with the idea that the fitness costs may be compensated (see §S1.3 of the Supplementary Information) [16]. Additional details about the model are provided in the Supplementary Information.

Model calibration and validation

We used a Bayesian approach to calibrate our model against estimates of gonorrhea prevalence, the rate of reported gonorrhea cases in 2017, and the proportion of gonorrhea cases with symptoms. This calibration approach seeks to estimate the probability distributions of unknown parameters that result in simulated trajectories with good fit to the available epidemiological data [17]. We chose prior parameter distributions based on the available data, estimates and plausible ranges extracted from the literature, and expert opinion when estimates were unavailable (see Supplementary Information for additional details).

Comparing the performance of guidelines to inform first-line treatment recommendations

We compare the performance of strategies to inform the first-line treatment recommendations (Table 1) based on the number of gonorrhea cases that could be averted with respect to the status quo (the "Threshold-Annual" strategy in Table 1 with 5% switch threshold) and the increase in the effective life of Drugs A and B. To measure the effective life of antibiotics, we note that the consumption of Drug M is inversely related to the effective lifespan of Drugs A and B. If resistance to Drug A and B rises quickly, implying a short effective lifespan for these drugs, all future cases of gonorrhea will be treated with Drug M. We therefore defined the effective lifespan of Drugs A and B as the area under the curve of the annual percentage of gonorrhea cases that are successfully treated with Drugs A or B over 50 years of simulation (i.e. $\sum_{t=1}^{50} \frac{N_A(t)+N_B(t)}{N_A(t)+N_B(t)+N_M(t)}$, where $N_A(t)$, $N_B(t)$ and $N_M(t)$ are the number of gonorrhea cases treated successfully with Drugs A, B, or M in simulation year t).

If a strategy extends the effective lifespan of Drugs A and B by ΔL years, we estimate the number of additional cases of gonorrhea that would be treated successfully with first-line antibiotics under this strategy with $S\frac{\Delta L}{L}$, where S is the number of cases successfully treated with Drugs A or B, and L is the effective lifespan of Drugs A and B under the status quo.

The simulation window of 50 years was selected to ensure enough time for the resistance to emerge against Drug A and Drug B (in a sensitivity analysis, we set the simulation window at 25 years). We summarized results using the mean and 95% uncertainty interval (i.e. the interval between 2.5th and 97.5th percentiles of realizations) across 500 simulated trajectories. For the 'Threshold + Trend' and 'Enhanced Threshold + Trend' strategies (Table 1), the two thresholds used to inform switching (i.e. threshold for resistance prevalence and the threshold for change in the resistance prevalence) are determined using the optimization algorithm described in §S4 of the Supplementary Information text.

Results

We fitted our model against gonorrhea prevalence, the rate of reported gonorrhea cases in 2017, and the proportion of gonorrhea cases with symptoms, and estimated the proportion of cases resistant to Drugs A, B or both when 5,000 annual gonorrhea cases are tested for drug resistance during each simulation (Fig. 2). We used 5,000 annual cases based on how many *N. gonorrhoeae* isolates were collected and tested through GISP in 2014 (5,093 isolates) [5].

In Fig. 3(A), we report the trade-off between increasing the effective lifespan of antibiotics and reducing the annual incidence of gonorrhea. The origin in this figure represent the status quo in which switching policies are triggered when greater than 5% of the isolates tested are resistant [8,10]. Increasing this resistance-prevalence threshold for switching to new antibiotic drugs (moving toward top-right corner of Fig. 3(A)) increases the effective lifespan of Drugs A and B by using the existing drugs for a longer period. Increasing this switching threshold, however, leads to increases in the expected number of annual gonorrhea cases, since delaying the switch to a new antibiotic drug lowers the probability of receiving an effective first-line therapy, thereby extending the expected duration of infectiousness while these cases await detection of treatment failure and

treatment with effective second-line therapy. The blue curve in Fig. 3(A) has a slope of 15.3 at the origin. This implies that the 5% switch threshold represents a sacrifice of the effective lifespan of Drugs A and B by 1 year to avert an additional 15.3 gonorrhea cases per 100,000 MSM population per year.

Fig. 3(A) also demonstrates that increasing the frequency at which first-line therapy recommendations are revisited could lead to a substantial increase in the effective lifespan of Drugs A and B without increasing the number of gonorrhea cases. Compared to the current policy, the 'Threshold-Quarterly' strategy could increase the effective lifespan of Drugs A and B by 0.82 years without increasing the number of gonorrhea cases (this is measured as the horizontal distance between the points where the curves in Fig. 3(A) crosses the x-axis). This is equivalent to successfully treating an additional 79.6 (47.4, 111.2) gonorrhea cases per 100,000 MSM population each year with Drugs A and B without worsening the burden of gonorrhea.

Fig. 3(B) shows that the 'Threshold + Trend' strategy, which uses both the resistance prevalence and the change in resistance prevalence since the last year, outperforms the 'Threshold-Annual' strategy. Compared to the status quo, the 'Threshold + Trend' strategy could increase the effective lifespan of Drugs A and B by 0.83 years (which is equivalent to successfully treating an additional 80.1 (47.7, 111.9) gonorrhea cases per 100,000 MSM population each year with Drugs A and B) without increasing the incidence of gonorrhea. Specifically, the 'Threshold + Trend' strategy which removes an antibiotic from the first-line therapy either when the resistance prevalence exceeds 10.1% or when the increase in the resistance prevalence from last year is greater than 1.6 percentage points is expected to increase the effective life of Drugs A and B while preventing gonorrhea cases compared with the status quo.

Fig. 3(C) demonstrates that the benefits of the 'Threshold + Trend' strategy can be enhanced when the evaluation of resistance prevalence is performed quarterly, and the annual number of gonorrhea cases tested for drug susceptibility is doubled. Compared to the current approach, the 'Enhanced Threshold + Trend' strategy could increase the effective lifespan of Drugs A and B by 0.88 years (which is equivalent to successfully treating an additional 85.6 (51.0, 119.5) gonorrhea cases per 100,000 MSM population each year with Drugs A and B) without worsening the burden of gonorrhea.

Discussion

We used a mathematical model of gonorrhea transmission to evaluate how different strategies to inform recommendations for the first-line treatment of gonorrhea would impact the effective lifespan of antibiotics and the incidence of gonorrhea in the U.S. MSM population. We used a Bayesian approach to calibrate the model to the estimated prevalence of gonorrhea, the rate of gonorrhea cases, and the proportion of cases presenting symptoms among MSM in the United States. We examined alternative strategies to inform the timing of shifts in first-line treatment regimen. These strategies respond to the data from surveillance systems 1) by revisiting the treatment guidelines more frequently (quarterly vs. annually), or 2) by considering not only the current resistance prevalence but also the increase in resistance prevalence since the last decision point to inform the first-line treatment recommendations. Our analysis showed that these adaptive strategies could extend the effective lifespans of existing antibiotics for the treatment of gonorrhea without exacerbating the burden of gonorrhea.

In the absence of rapid drug-susceptibility testing to determine the resistance profile of a gonococcal infection, the treatment of gonorrhea remains empiric and based on population surveillance. Historically, once the estimated resistance prevalence for the recommended first-line antibiotic exceeds 5%, it is replaced in the guidelines by a regimen with lower levels of population-wide resistance [8,10]. Our analysis suggests that the optimal choice of this threshold requires a tradeoff between the effective lifespan of antibiotics and the incidence of gonorrhea. Increasing this switch threshold would increase the effective lifespan of existing antibiotics but could also increase the burden of gonorrhea; conversely, decreasing this switch threshold would prevent more gonorrhea cases but the at the expense of reducing the effective lifespan of existing antibiotics. Using our mathematical model, we estimated that the 5% switch threshold currently used represents a tradeoff of forgoing a year of the effective life of existing antibiotics to avert an additional 15.3 cases of gonorrhea per year per 100,000 MSM population. Different decision rules could improve this relationship.

Our analysis has a number of limitations. Our mathematical model describes the transmission of *N. gonorrhoeae* only among men who have sex with men (MSM) in the United States. The burden of gonorrhea and drug-resistant gonorrhea is particularly high in this sub-population [1,5] and hence, our conclusions might not be generalizable. For populations with lower burden of the disease, the benefits of adaptive strategies might diminish as the consequences of making suboptimal decisions would be less severe. While data from surveillance systems indicate an upward trend in the rate of gonorrhea cases among the MSM [1], we assumed that the incidence and prevalence of gonorrhea among this population are expected to be relatively stable around the 2017 estimates (**Fig. 2**). We did not model specific antibiotics and instead chose to model hypothetical drugs with characteristics similar to the antibiotics commonly used in treatment of gonorrhea. This allowed us to better capture the uncertainty in the characteristics of current and future antibiotics drugs (e.g. probability of resistance from treatment).

Current CDC treatment guidelines for gonorrhea recommend dual therapy with ceftriaxone and azithromycin, but our decision model assumes that first-line therapy consists of only one antibiotic, such as those now in place in the UK [18]. Although our approach considers single antibiotic treatment for clarity, it can be extended to scenarios in which combination therapy is the first-line gonorrhea treatment. We assumed that once an antibiotic treatment for gonorrhea is abandoned because of the level of resistance, it will not be reintroduced. However, alternative stewardship and diagnostic strategies (e.g. the use of sequence-based diagnostics to identify the resistance profile [19]) suggest the possibility of reintroduction of these antibiotics. For example, a recent modeling study suggests that cefixime, which had previously been removed from clinical use due to increasing levels of resistance, could be reintroduced to treat a minority of cases, assuming that cefixime resistance incurs a fixed fitness cost [20].

Our model did not account for site-specific infections although the percent of infections that are asymptomatic varies by anatomic sites [21-23]. While we assumed that estimates of resistance prevalence calculated from GISP data are representative of the MSM population, GISP includes isolates from the first 25 men (not only MSM) who have been diagnosed with urethral gonorrhea after attending sexually transmitted disease clinics in select U.S. cities. Our model assumes complete adherence to the first-line treatment guidelines. While the actual treatment regimens used in the population may differ from the recommended guidelines, recent studies estimate the

adherence to the CDC guideline for the treatment of gonorrhea to be around 80% [24]. Relaxing these assumptions could improve the accuracy of projections made by our model, but it is not expected to significantly affect the comparative evaluation of strategies considered here.

Enhancing surveillance systems to enable more frequent reporting and evaluation of more gonococcal isolates would increase the cost of surveillance. While the cost-effectiveness of these proposed changes needs to be studied, the analysis presented here highlights the importance of maintaining effective surveillance systems and the engagement of policy makers to turn surveillance findings into timely decisions to better control the spread of drug-resistant gonorrhea [25]. In the future, decision support tools like the one we proposed in this paper could help policymakers to respond more efficiently to the rise of antibiotic-resistant gonorrhea, in a way that could prolong the effective lifespan of existing antibiotics and control the burden of the disease.

While we await a breakthrough (new antimicrobial agents, novel molecular assays to determine susceptibility to antimicrobial agents, or a gonococcal vaccine), it is important to optimize the use of surveillance systems to minimize the burden of gonorrhea and to slow the spread of antibiotic-resistant strains. We demonstrated the potential for data from surveillance programs to be used in a more efficient and active way to prolong the effective lifespans of existing antibiotics without increasing the burden of the disease.

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Figures

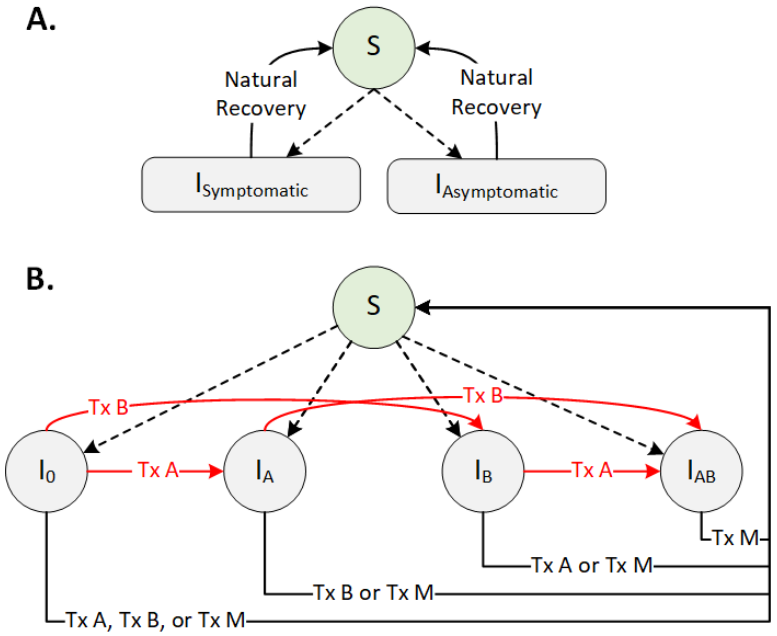

Fig. 1: A stochastic gonorrhea transmission model. Dotted arrows represent new infection and red arrows represent resistance acquisition while under treatment. S represents susceptibles, I_0 represents drug-susceptible infections, and I_A, I_B, and I_{AB} represent infections resistant to Drug A, B, and both. Tx A, Tx B, and Tx M denote treatment with drugs A, B, and M. The expanded model structure is provided in the Supplementary Information (Fig. S1). The model is adapted from [15] with additional details necessary to evaluate the strategies in Table 1.

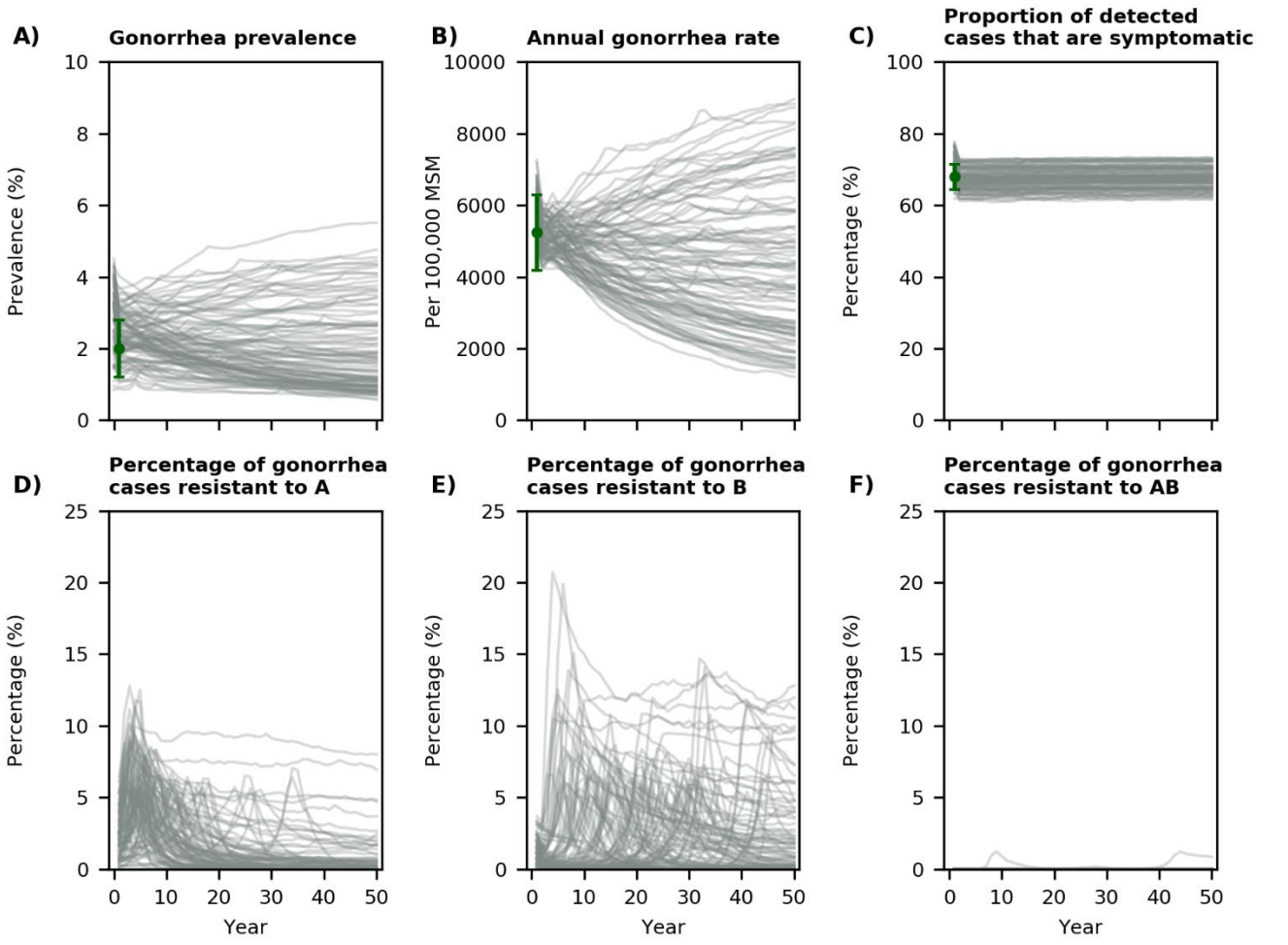

Fig. 2: Displaying 100 simulated trajectories from the calibrated model. The green dots in panels A-C represent the data or estimates the model is calibrated against: gonorrhea prevalence (2.0% [1.2%, 2.8%] [26,27] of MSM), the estimated rate of gonorrhea cases in 2017 (5,241.8 cases per 100,000 MSM [1]), and the proportion of gonorrhea cases among MSM that are symptomatic (67.9% [64.4-71.4%] [28]). In these simulated trajectories, the first-line treatment is changed when more than 5% of the annual gonorrhea cases are resistant to the first-line drug.

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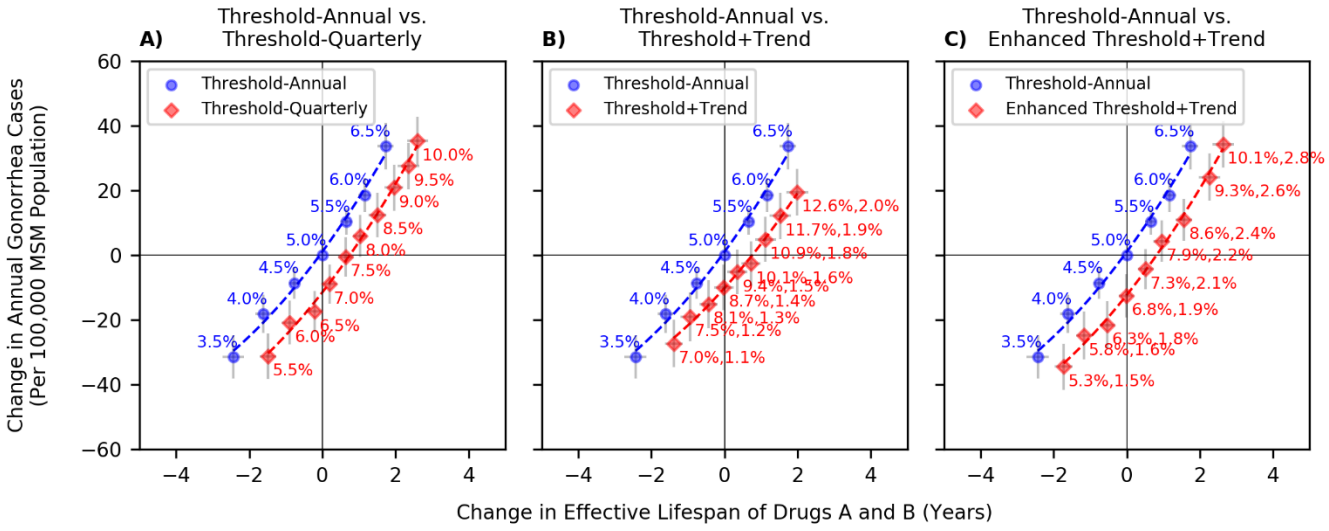

Fig. 3: Comparing the performance of policies in Table 1 with respect to the current policy. The origins in these figures reflect the current policy that recommends switching the antibiotic used for empiric treatment once the estimated resistance prevalence exceeds 5% [8,10]. The numbers on the curves of 'Threshold-Annual' and 'Threshold-Quarterly' strategies represent the threshold of resistance prevalence to switch the first-line therapy of gonorrhea, and the two numbers on the curves of 'Threshold+Trend' and 'Enhanced Threshold+Trend' strategies represent the two thresholds used to inform switching: resistance prevalence (first %) and percentage point change in the resistance prevalence (second %).

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Tables

Table 1: Adaptive guidelines to inform first-line treatment recommendations for gonorrhea

Strategies	Frequency of Decision Making	Annual Number of Tests for Resistance	Epidemiolocal Estimates Used for Decision Making	Policy Examples
Threshold-Annual	Annually	5,000	Estimate of resistance prevalence	Switch to a new first-line drug when the point estimate of the proportion of resistant isolates exceeds τ%.
Threshold-Quarterly	Quarterly	5,000	Same as Threshold	Same as Threshold
Threshold + Trend	Annually	5,000	Estimate of resistance prevalence and change in the estimate of resistance prevalence	Switch to a new first-line drug when point estimate of the proportion of resistant isolates exceeds τ% or the change in the estimate of resistance since the last decision point exceeds θ percentage point.
Enhanced Threshold + Trend	Quarterly	10,000	Same as 'Threshold + Trend'	Same as 'Threshold + Trend'

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Supplementary Information

S1 Additional model details

S1.1 Model population

We developed a stochastic compartmental model to simulate the transmission of gonorrhea among the MSM population of age 14 or older in the United States (Fig. S1). A meta-analysis of U.S. population-based surveys estimated the proportion of MSM among male 13 and older at 3.9% [1]. According to the 2015 U.S. Census, the size of the male population of age 14 and older is 125,092,000 [2]. Therefore, we approximate the MSM population of age 14 and older at 4,878,588. We assumed that an individual stays in the model for an average of 35 years (representing the period when an individual could be sexually active).

S1.2 Simulation approach

To construct the model, we introduce the following notation:

- $i \in \{0, A, B, AB\}$: resistance profile an infection ($i = 0$, drug-susceptible; $i = A$, resistance to Drug A; $i = B$, resistance to Drug B; and $i = AB$, resistance to both Drug A and Drug B);
- $s \in \{0,1\}$: symptom status ($i = 0$, asymptomatic, and $i = 1$, symptomatic);
- t: epidemic time;
- $N(t)$: population size at time t;
- $S(t)$: number of susceptibles at time t;
- $I_{(i,s)}(t)$: number of infected cases with resistance profile i and symptom status s at time t;
- $W_{(i,s)}(t)$: number of diagnosed cases at time t waiting to receive the first-line therapy;
- $W'_{(i,s)}(t)$: number of diagnosed cases at time t waiting to receive the second-line therapy.

The state of the gonorrhea epidemic at any given time t can be identified by a discrete-time Markov chain $\{(S(t), I_{(i,s)}(t), W_{(i,s)}(t), W'_{(i,s)}(t), i \in \{0, A, B, AB\}, s \in \{0,1\}: t = 0, \Delta t, 2\Delta t, 3\Delta t, \dots\}$, where Δt is the time-step of the simulation (e.g. $\Delta t = 1$ day). To generate epidemic trajectories for this model, we use Monte Carlo simulation to sample from this Markov chain using the following approach. Consider a particular compartment Z in which members depart due to J events each of which is occurring at the rate $\mu_j, j \in \{1,2, \dots, J\}$. For example, members of Susceptible compartment may leave due to 1) infection with the susceptible strain, 2) infection with Drug-A resistant strain, 3) infection with Drug-B resistant strain, or 4) infection with a strain resistant to both drugs (i.e. $J = 4$) (see Fig. S1). If the number of individuals in compartment Z at time t is $Z(t)$, then the number of individuals that leave this compartment due to events $j \in \{1,2, \dots, J\}$ follows a multinomial distribution with total counts of $Z(t)$ and probabilities $(p_0, p_1, p_2, \dots p_J)$, where $p_0 = 1 - e^{\sum_{j=1}^{J} \mu_j \Delta t}$ is the probability of not leaving the compartment Z during $[t, t + \Delta t]$, and $p_j = \frac{\mu_j}{\sum_{k=1}^{J} \mu_k \Delta t} e^{\sum_{k=1}^{J} \mu_k \Delta t}$ is the probability of leaving the compartment Z during $[t, t + \Delta t]$ due to the event $j \in \{1,2, \dots, J\}$.

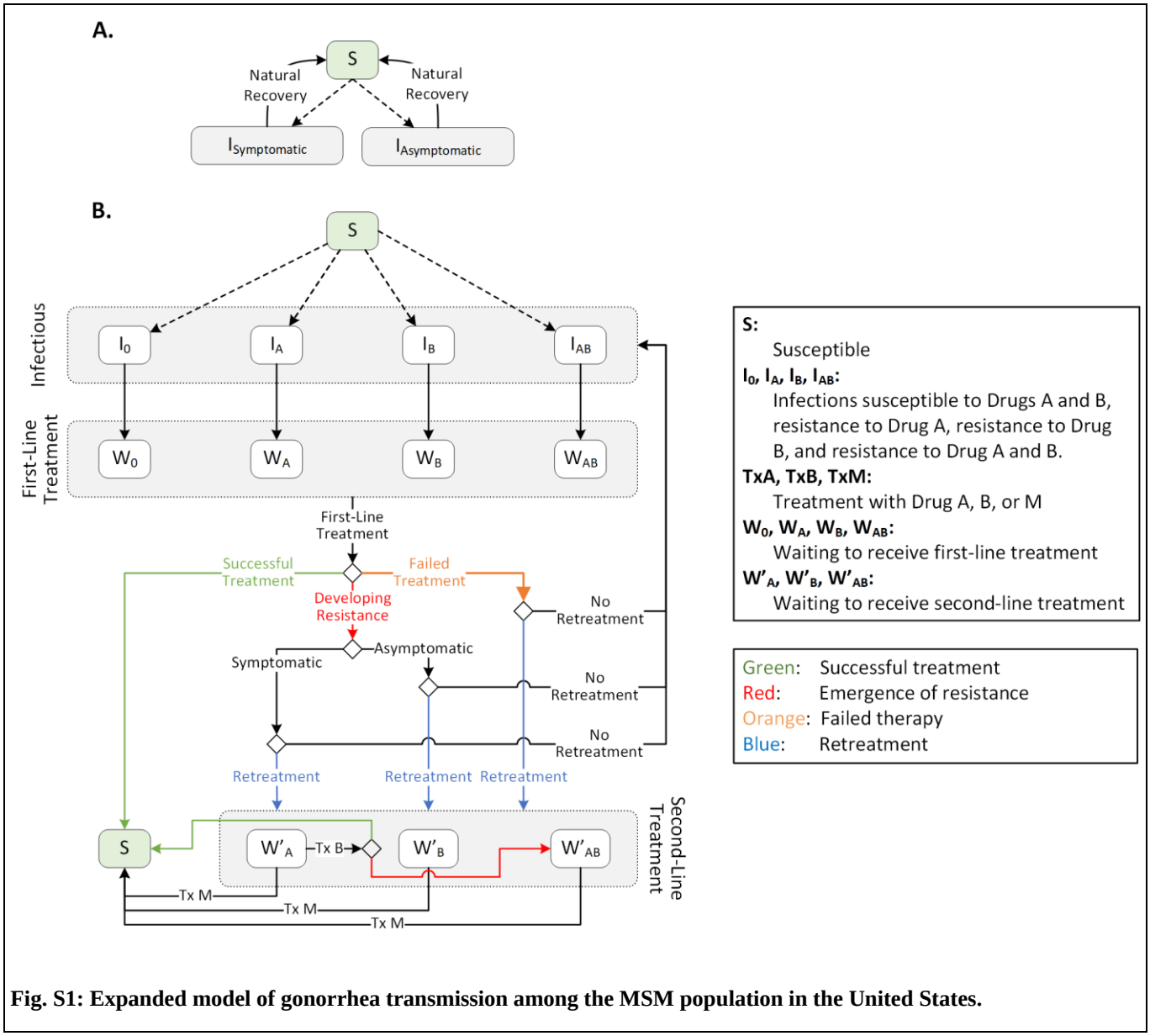

Fig. S1: Expanded model of gonorrhea transmission among the MSM population in the United States.

To identify the new epidemic state at the next time step, we first sample from the multinomial distributions associated to each compartment and then use these realizations to calculate the new epidemic state given the current epidemic state. The events that drive the epidemic are represented by black arrows in Fig. S1. For example, the number of susceptibles at time $t + \Delta t$ can be calculated as:

$$S(t+\Delta t) = S(t)$$
$$- \text{ new infections susceptible to Drugs A and B}$$
$$- \text{ new infections resistant to Drug A}$$
$$- \text{ new infections resistant to Drug B}$$
$$- \text{ new infections resistant to Drug A and Drug B}$$
$$+ \text{ new population members .}$$

S1.3 Calculating the rate of infection

We calculate the daily rate of infection with resistance profile $i \in \{0, A, B, AB\}$ at time t as:

$$\mathcal{F}_i(t) = \beta_i(t) \sum_{s\in\{0,1\}} \frac{I_{(i,s)}(t) + W_{(i,s)}(t) + W'_{(i,s)}(t)}{N(t)}, \quad (1)$$

where $\beta_i(t)$ is the transmission parameter for resistance profile $i \in \{0, A, B, AB\}$. We let $\beta_0(t) = \beta$ and $\beta_i(t) = \gamma_i(t)\beta$ for $i \in \{A, B, AB\}$, where $0 \leq \gamma_i(t) \leq 1$ represents the fitness cost associated with the resistance profile $i \in \{A, B, AB\}$. To allow fitness cost to decrease over time, we let the relative transmissibility of the resistance profile $i \in \{A, B, AB\}$ increase over time according to:

$$\gamma_i(t) = b_{i,min} + \frac{1 - b_{i,min}}{1 + e^{-b_i(t-t_{i,0})}}. \quad (2)$$

Here, $b_{i,min} \geq 0$, $b_i \geq 0$, and $t_{i,0} \geq 0$,. **Fig. S2** displays how $\gamma(t)$ changes over time and how the parameters of this function (i.e. $b_{i,min}$, b_i, and $t_{i,0}$) impact this behavior. These parameters are determined through the calibration procedure described below.

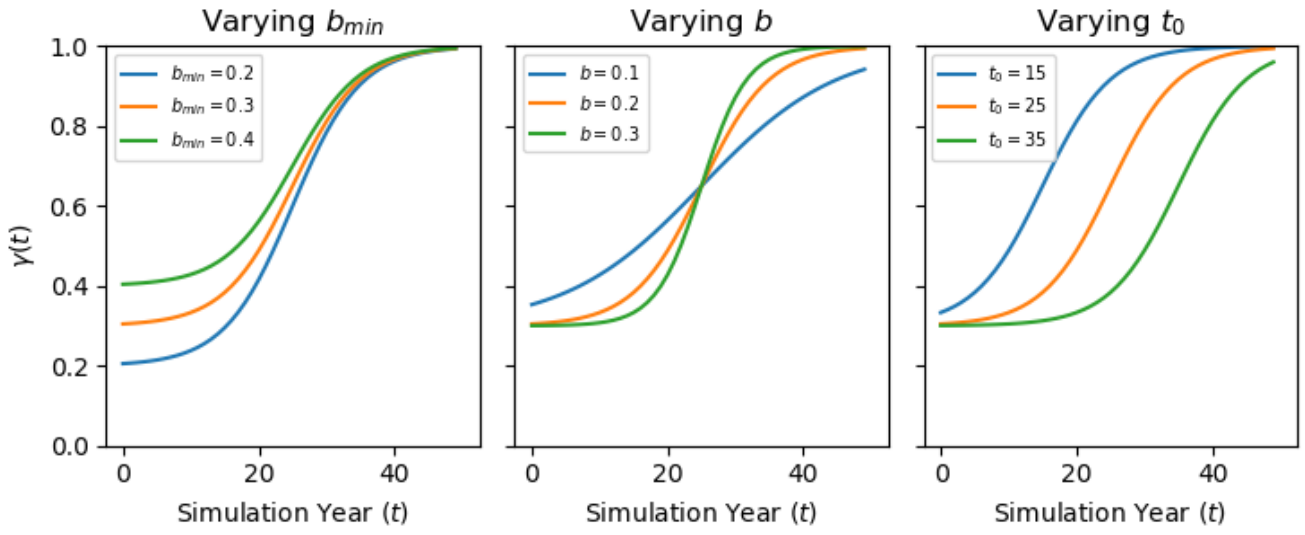

Fig. S2: Behavior of function $\gamma(t)$ (defined in Eq. (2)) over time. In these figures, the non-varying parameters are set at the default values $(b_{min}, b, t_0) = (0.3, 0.2, 25)$.

S2 Sampling error in estimating the resistance prevalence

The decision about which antibiotic to include in the first-line treatment recommendation is based on estimates of resistance prevalence obtained from surveillance systems, such as GISP [3], by evaluating a limited number of gonorrhoeae isolates for drug susceptibility. Hence, the estimates of resistance prevalence are affected by sampling error. To account for this sampling error when evaluating the policies of Table 1 using our simulation model, we use the following approach. Let y_t be the proportion of gonorrhea cases in the simulation year t that are resistant. Since not all cases are tested for drug-susceptibility, we assumed that p_t can be observed with some noise:

$$\hat{y}_t = y_t + \epsilon_t.$$

Here we assume that ϵ_t follow a normal distribution with mean 0 and standard deviation $\sqrt{y_t(1-y_t)/N}$, where N is the number of gonorrhea cases tested for drug-susceptibility. Fig. 2D-F displays the estimated proportion of cases resistant to Drugs A, B or both when $N = 5{,}000$ of annual gonorrhea cases are tested for drug resistance during each simulation. This assumption is informed by how many *N. gonorrhoeae* isolates are collected and tested through GISP in 2014 (5,093 isolates) [3].

S3 Model calibration

The model is calibrated against estimates of gonorrhea prevalence (2.0% [1.2%, 2.8%] [4,5]), the annual gonorrhea rate in 2017 (5,241.8 cases per 100,000 MSM [6]), and the proportion of gonorrhea cases with symptoms (67.9% [64.4-71.4%] [7]). To approximate the likelihood of these observations given a simulated trajectory, we chose a pseudolikelihood function consisting of three components:

S3.1 Component 1: Likelihood of gonorrhea prevalence

We assume that the 2.0% [1.2%, 2.8%] [4,5] prevalence estimate is obtained by confirming gonorrhea in $\hat{s}$ individuals out of a total of $\hat{S}$ individuals evaluated for gonorrhea (hence, $\hat{s}/\hat{S}$=0.02 and $\hat{S}$). To calculate the likelihood of observing this outcome in year t if a given simulated trajectory represents the reality, we assumed that $\hat{s}$ follows a binomial distribution with $\hat{S}$ trials and success probability τ_t, where τ_t is the prevalence of gonorrhea in year t of the simulation:

$$L_1 = \sum_{t=1}^{10} \binom{\hat{S}}{\hat{s}} \tau_t^{\hat{s}} (1-\tau_t)^{\hat{S}-\hat{s}}.$$

Here $\hat{S}$ can be approximated by noting that the half-length of the confidence interval for the estimated prevalence is:

$$HL = t_{\hat{S}-1,\alpha/2} \sqrt{\frac{\mu(1-\mu)}{\hat{S}}},$$

where $\mu = \hat{s}/\hat{S}$ and $t_{\hat{S}-1,\alpha/2}$ is the upper $\alpha/2$ critical point for the *t*-distribution with $\hat{S}-1$ degrees of freedom. By using $HL = \frac{0.028-0.012}{2} = 0.08$, $\alpha = 0.05$, and $\hat{s}/\hat{S}$=0.02 in the above equation, we estimate $\hat{S}$ at 1176.

S3.2 Component 2: Likelihood of annual rate of reported gonorrhea cases

No confidence interval was reported for the estimated 5,241.8 cases of gonorrhea per 100,000 MSM in 2017 [6]. We assume that this estimate was with 20% error which is equivalent to having a reported confidence interval of [4193.4 - 6290.2]. We assume that the estimate of 5,241.8 cases of gonorrhea per 100,000 MSM in 2017 [6] is calculated as $\hat{k}/\hat{K} \times 100{,}000$, where $\hat{k}$ is the number of gonorrhea cases observed in a sample MSM population of size $\hat{K}$. To calculate the likelihood of observing this outcome in year t if a given simulated trajectory represents the reality, we assumed that $\hat{k}$ follows a binomial distribution with $\hat{K}$ trials and success probability ρ_t, where ρ_t is the proportion of the simulated population year t that got diagnosed with gonorrhea:

$$L_2 = \sum_{t=1}^{10} \binom{\hat{K}}{\hat{k}} \rho_t^{\hat{k}} (1-\rho_t)^{\hat{K}-\hat{k}}.$$

Here $\hat{K}$ can be approximated by noting that the half-length of the confidence interval for the estimated annual rate of reported gonorrhea cases is:

$$HL = 100{,}000 \times z_{\alpha/2} \sqrt{\frac{\mu(1-\mu)}{\hat{K}}},$$

where $\mu = \hat{k}/\hat{K}$ and $z_{\alpha/2}$ is the upper $\alpha/2$ critical point for the standard normal distribution. By using $HL = \frac{6290.2-4193.4}{2} = 1048.4$, $\alpha = 0.05$, and $\hat{k}/\hat{K} = 0.05242$ in the above equation, we estimate $\hat{K}$ at 1736.

S3.3 Component 3: Likelihood of proportion of gonorrhea cases that are symptomatic

The estimate for the proportion of gonorrhea cases with symptoms (67.9% [64.4-71.4%] [7]) is obtained from a study where $\hat{r} = 466$ of $\hat{R} = 686$ gonorrhea cases presented symptoms. To calculate the likelihood of observing this outcome in year t if a given simulated trajectory represents the reality, we assumed that $\hat{r}$ follows a binomial distribution with $\hat{R}$ trials and success probability y_t, where y_t is the proportion of gonorrhea cases in year t of the simulation that are symptomatic:

$$L_3 = \sum_{t=1}^{10} \binom{\hat{R}}{\hat{r}} y_t^{\hat{r}} (1-y_t)^{\hat{R}-\hat{r}}.$$

S3.4 Total pseudolikelihood

To summarize, we calculate the natural logarithm of the likelihood of observations given a simulated trajectory as:

$$\ln L = \ln L_1 + \ln L_2 + \ln L_3.$$

To improve the efficiency of the calibration procedure, we terminate the simulation of a trajectory once any of the following conditions is met:

1. Gonorrhea prevalence falls out of the range [0.5%, 5%].
2. Annual rate of reported gonorrhea cases falls out of the range [1,000, 8,000],
3. Annual percentage of gonococcal infections that are symptomatic less than 50%.

Also, to make sure that resistance to Drugs A and B emerges during the simulation horizon (50 years), we eliminate trajectories where the prevalence of resistance to Drug A never reached 5%.

Table S1: Prior distributions and posterior intervals of model parameters

Parameter	Prior Distribution (All Uniform)	95% Posterior Interval	Sources to Inform Prior Distribution
Transmission parameter (β)	[0, 10]	(1.92, 6.41)	Assumption
Duration of infection (without treatment) (months)	[1, 60]	(5.1, 58.4)	[8]
Time until screened for infection (years)	[0.5, 5.0]	(0.6, 2.0)	[8,9]
Time until seeking treatment for a symptomatic infection (days)	[1, 14]	(1.4, 13.7)	[7,8,10]
Time until retreatment (days)	[1, 14]	(1.7, 13.6)	[7,8]
Probability that an infection will be symptomatic	[10%, 90%]	(38.1%, 67.9%)	[8,9,11]
Probability of retreatment after treatment failure with symptomatic infection	[80%, 100%]	(81.7%, 98.9%)	[9]
Probability of developing resistance while receiving Drug A	$10^{[-6,\ -4]}$	$10^{(-5.98,\ -4.02)}$	[9]
Probability of developing resistance while receiving Drug B	$10^{[-6,\ -4]}$	$10^{(-5.95,\ -4.02)}$	[9]
Relative transmissibility of the strain resistant to Drug A ($\gamma_A(t)$)			
$b_{A,min}$	[0, 1]	(0.06, 0.98)	
b_A	[0, 0.2]	(0.006, 0.182)	
$t_{A,0}$	[0, 30]	(1.0, 29.3)	
Relative transmissibility of the strain resistant to Drug B or both drugs ($\gamma_B(t)$ and $\gamma_{AB}(t)$)			
$b_{B,min}$ and $b_{AB,min}$	[0, 1]	(0.05, 0.97)	
b_B and b_{AB}	[0, 0.2]	(0.013, 0.190)	
$t_{B,0}$ and $t_{AB,0}$	[0, 40]	(1.3, 37.8)	
Initial gonorrhea prevalence	[1%, 5%]	(1.3%, 4.3%)	[4,5]
Initial proportion of gonococcal infections that are symptomatic	[0%, 50%]	(1.2%, 47.2%)	Assumption
Initial proportion of gonococcal infections resistant to Drug A	[0%, 4%]	(0.1%, 3.9%)	[3,12]
Initial proportion of gonococcal infections resistant to Drug B	[0%, 4%]	(0.2%, 3.9%)	[3,12]

S3.5 Projections and estimating posterior distributions

To build a set of trajectories to evaluate the performance of strategies in Table 1, we used a sampling / importance sampling algorithm to approximate the posterior distributions of model parameters [13,14]. We first simulate $N_0 = 100{,}000$ epidemic trajectories, each of which uses parameter values that are randomly drawn from the prior probability distribution of epidemic parameters listed in Table S1. These prior distributions are mainly informed by

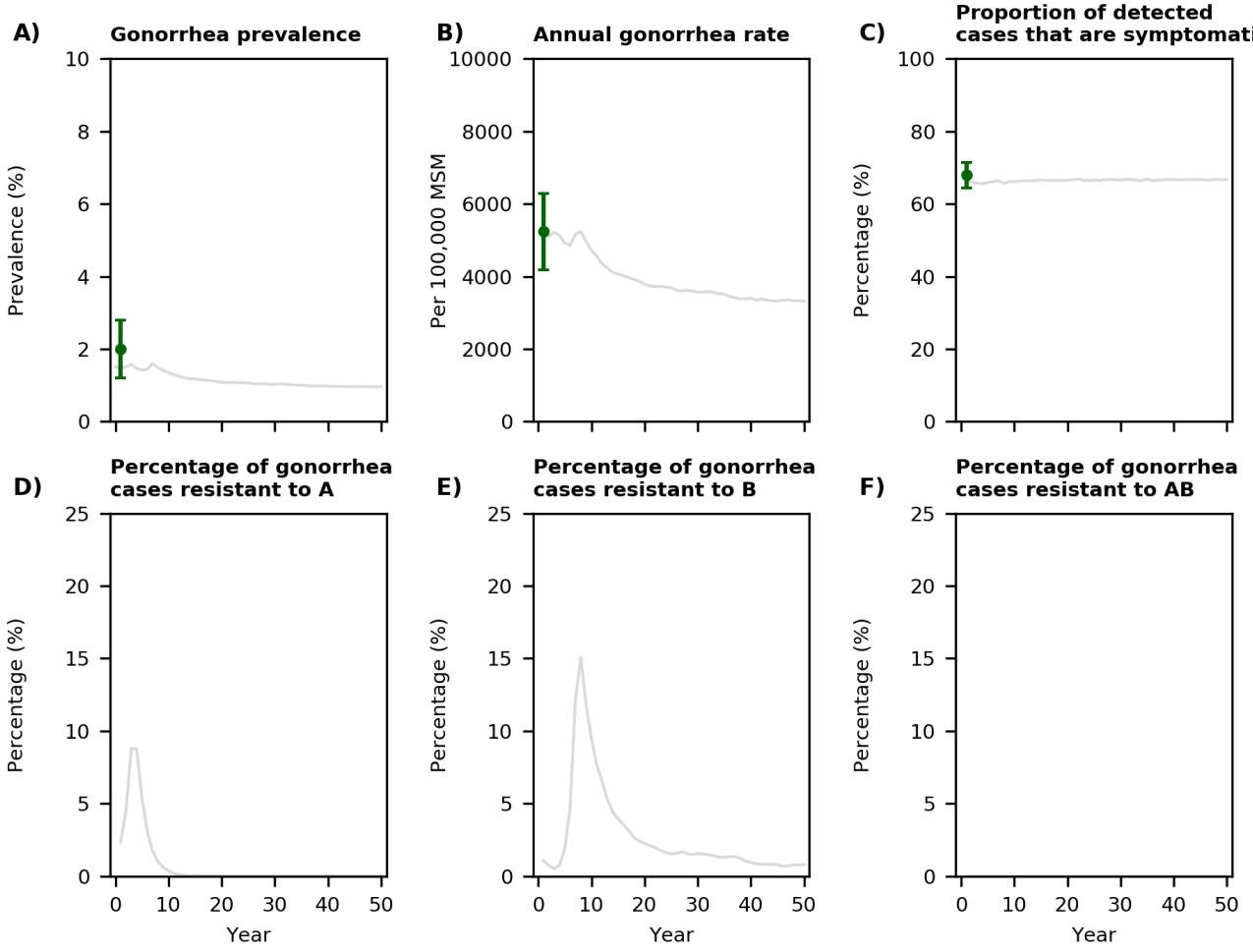

Fig. S3: Displaying an illustrative simulated trajectory from the calibrated model. The green dots in panels A-C represent the data or estimates the model is calibrated against: gonorrhea prevalence (2.0% [1.2%, 2.8%] [4,5] of MSM), the estimated rate of gonorrhea cases in 2017 (5,241.8 cases per 100,000 MSM [6]), and the proportion of gonorrhea cases among MSM that are symptomatic (67.9% [64.4-71.4%] [7]). In these simulated trajectories, the first-line treatment is changed when more than 5% of the annual gonorrhea cases are resistant to the first-line drug.

estimates extracted from existing scientific literature. When such estimates are not available, we identified prior distributions by experimenting with the model ("hand-fitting") to ensure the model can produce simulated trajectories that are consistent with past observations.

Let $\ln L_i$ be the total pseudolikelihood for the simulation trajectory $i \in \{1,2,..N_0\}$. We calculated the likelihood weight of this trajectory as:

$$w_i = \frac{e^{\ln L_i}}{\sum_{j=1}^{N_0} e^{\ln L_j}}.$$

After calculating w_i for each simulated trajectory, we draw 500 trajectories, with replacement and based on likelihood weights w_i. We used the parameter values associated with these 500 trajectories to calculate the mean and

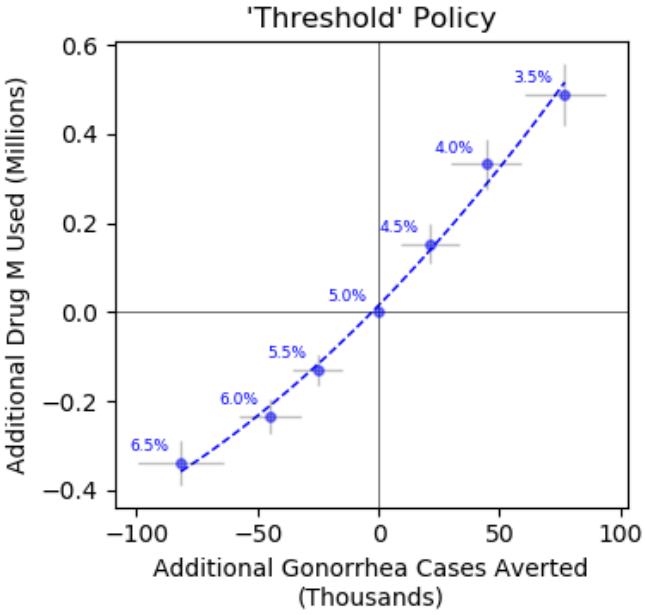

Fig. S4: The impact of chaning the switch threshod of the 'Threshold' policy (Table 1) on the consumption of Drug M and the cases of gonorrhea averted over the 50 years of simulation.

95% posterior intervals of model parameters (Table S1). Fig. S3 displays an illustrative simulation run from the calibrated model.

S4 Identifying 'Threshold- Trend' strategies

Here we propose an algorithm to identify parameters of 'Threshold-Trend' strategies, τ and θ (see Table 1) that result in a superior performance compared to the 'Threshold-Annual' strategy.

Let $q(\tau, \theta)$ and $v(\tau, \theta)$ denote, respectively, the change in gonorrhea cases and in the effective lifespan of Drugs A and B under the 'Threshold-Trend' strategy with parameter (τ, θ) compared to the 'Threshold-Annual' strategy with $\tau = 5\%$. As discussed in the main text, minimizing $q(\tau, \theta)$ (i.e. averting more cases) may lead to decreasing $v(\tau, \theta)$ (i.e. lowering effective lifespan of Drugs A and B), and vice versa. To construct a single objective function that could be optimized, we use the net monetary benefit framework [15] and defined our objective function as $\omega q(\tau, \theta) - v(\tau, \theta)$, where ω represents the decision maker's willingness to increase the consumption of Drug M by one dose to avert an additional gonorrhea case over the next 50 years.

The slope of the curve at the origin of Fig. S4, which is 5.5, could be an estimate for ω if a decision maker chooses to follow the 'Threshold-Annual' strategy with 5% switch threshold. Higher switch thresholds correspond to lower ω (moving to the lower left corner of Fig. S4) and higher switch thresholds correspond to higher ω (moving toward the upper right corner of Fig. S4). We use $\tau(\omega)$ and $\theta(\omega)$ to make it explicit that these thresholds are functions of ω. Assuming that ω takes value over $[\omega_L, \omega_U]$, our goal is to characterize functions $\tau(\omega)$ and $\theta(\omega)$ that minimizes:

$$\int_{\omega_L}^{\omega_H} \left[\omega q\big(\tau(\omega), \theta(\omega)\big) - v\big(\tau(\omega), \theta(\omega)\big)\right] d\omega.$$

Assuming that $\tau(\omega) = \tau_0 e^{\tau_1 \omega}$ with $\tau_0 \geq 0$, and $\tau_1 \leq 0$, and $\theta(\omega) = \theta_0 \tau(\omega)$ with $0 \leq \theta_0 \leq 1$, we solve the following optimization problem to characterize $\tau(\omega)$ and $\theta(\omega)$:

$$\min_{\tau_0, \tau_1, \theta_0} \int_{\omega_L}^{\omega_H} \left[\omega q\big(\tau(\omega), \theta(\omega)\big) - v\big(\tau(\omega), \theta(\omega)\big)\right] d\omega \tag{1}$$

$$\begin{aligned} \text{Subject To: } & \tau(\omega) = \tau_0 e^{\tau_1 \omega}, \\ & \theta(\omega) = \theta_0 \tau(\omega), \\ & \tau_0 \geq 0, \\ & \tau_1 \leq 0, \\ & 0 \leq \theta_0 \leq 1. \end{aligned}$$

We solve the optimization problem (1) using a stochastic approximation algorithm described below.

S4.1 Stochastic approximation algorithms

The goal of stochastic approximation (SA) algorithms [16,17] is to find the minimizer of a function

$$f(x) = \mathrm{E}_{\xi}[F(x, \xi)], \tag{2}$$

which is the expected value of a stochastic function $F(\cdot)$ that depends on a random variable ξ. An example of $F(\cdot)$ could be the total number of gonorrhea cases during the next 20 years. It is a stochastic function since its value depend on many random events (represented by ξ) that may occur during this period. A simple version of SA algorithms generates the sequence of iterates:

$$x_{n+1} = x_n - p_n \frac{y_n}{\|y_n\|}, \tag{3}$$

where y_n is an unbiased estimate of the derivative of f at x (i.e. $\nabla f(x_n)$), $\|y\|$ is the Euclidean norm of the vector y, and p_n is a sequence of positive step sizes with the properties that $p_n \to 0$ and $\sum_n p_n = \infty$ (e.g., $p_n = \frac{a_0 b}{n+b}$, with $a_0 \geq 0$ and $b \geq 1$).

The derivative estimate $y_n = (y_n^1, y_n^2, \dots, y_n^K)$ can be obtained by:

$$y_n^i = \frac{F\big(x_n^i + \epsilon_n e_i, \xi\big) - F(x_n^i - \epsilon_n e_i, \xi)}{2\epsilon_n}, i = 1,2, \dots, K, \tag{4}$$

where e_i is a vector with 1 in the i^{th} element and 0 elsewhere and ϵ_n is a sequence of positive step sizes with the property that $\epsilon_n \to 0$. ϵ_n is selected such that it approaches 0 at a slower rate than p_n (e.g., $\epsilon_n = {c_0}^{-4}\sqrt{n}$, with $c_0 \geq 0$). One way to reduce the noise in estimating the derivatives is to use the same stream of random numbers in generating the realizations $F\big(x_n^i + \epsilon_n e_i, \xi\big)$ and $F(x_n^i - \epsilon_n e_i, \xi)$ when calculating y_n^i's. The pseudo-code of this algorithm is provided in Table S2.

S4.2 Optimization settings

To find $(\tau_0, \tau_1, \theta_0)$ that optimizes problem (1), we applied the stochastic approximation algorithm in Table S2 with the following settings:

$$F(\tau_0, \tau_1, \theta_0; \xi) = Q(\tau_0, \tau_1, \theta_0; \xi) + \Upsilon([\mathrm{neg}(\tau_0)]^2 + [\mathrm{neg}(-\tau_1)]^2 + [\mathrm{neg}(\theta_0)]^2 + [\mathrm{neg}(1 - \theta_0)]^2), \tag{5}$$

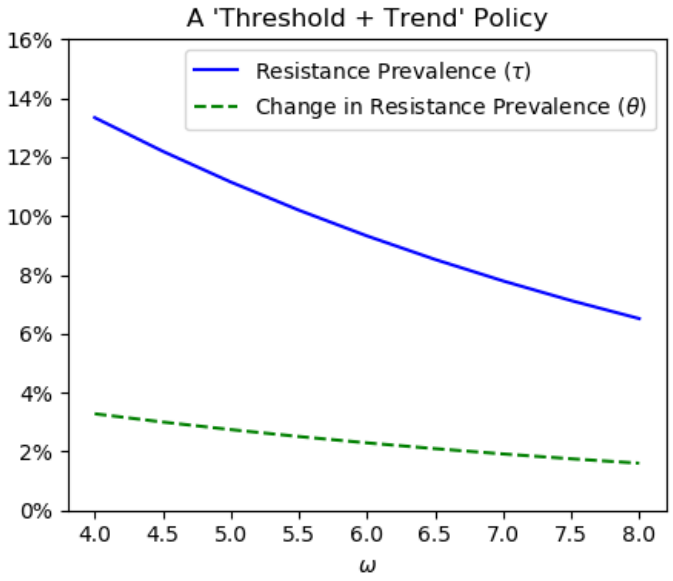

Fig. S5: A 'Threshold-Trend' Policy uses two thresholds to inform switching: resistance prevalence ($\boldsymbol{\tau}$) and percentage point change in the resistance prevalanece ($\boldsymbol{\theta}$). Here $\boldsymbol{\omega}$ represents years of the effective lifespan of Drugs A and B that a decision maker is willing to sacrifice to avert an additional gonorrhea case per 100,000 MSM population per year.

where $\text{neg}(x) = x$ if $x < 0$, and $\text{neg}(x) = 0$ if $x \geq 0$, Υ is the penalty factor to penalize a $(\tau_0, \tau_1, \theta_0)$ that violates the feasibility constraints of the optimizes problem (1), and

$$Q(\tau_0, \tau_1, \theta_0; \xi) = \frac{1}{3}\sum_{i=1}^{3} [\omega_i q(\tau(\omega_i), \theta(\omega_i); \xi) - v(\tau(\omega_i), \theta(\omega_i); \xi)] \quad (6)$$

is an approximation for the objective function (1).

In Eq. (6), we set $\omega_1, \omega_2, \omega_3$ to the slope of the curve in Fig. S4 at the smallest threshold, the 5% threshold, and the largest threshold, respectively (3.5, 5.5, 7.5). For the results presented here, we applied stochastic approximation algorithm in Table S2 with $N = 1000$, $M = 200$ and selected $\Upsilon = 10^6$ for the penalty factor in Eq. (5). To optimize a policy, we ran the algorithm with $a_0 \in \{0.05, 0.1\}$, $b \in \{10, 25, 50\}$ and $c_0 \in \{0.05, 0.1\}$ and selected $(\tau_0, \tau_1, \theta_0)$ that resulted in the highest f^* across all combinations of a_0, b, and c_0.

Table S2: Stochastic Approximation algorithm to find the minimum (x^*) of a function $f(x) = \mathbf{E}_\xi[F(x, \xi)]$

1. Choose the number of iterations N.
2. Choose an initial value for x (denoted by x_0)
3. Choose step size rule: $p_n = \frac{a_0 b}{n+b}$, with $a_0 \geq 0$ and $b \geq 1$.
4. Choose Step size rule for derivatives: $\epsilon_n = c_0 \sqrt[-4]{n}$, with $c_0 \geq 0$.
5. For $n = 0$ to N:
   a. Set f_n to a realization of $f(x)$ at x_n (i.e. $F(x_n, \xi)$).
   b. Estimate the derivative of f at x_n according to Eq. (4).
   c. Set $x_{n+1} \leftarrow x_n - p_n \frac{y_n}{\|y_n\|}$.
6. Return $x^* = \sum_{n=N-M}^{N} x_n / M$ and $f^* = \sum_{n=N-M}^{N} f_n / M$, where M is the number of last iterations to use to calculate x^* and f^* (e.g., $M = 0.2N$).

S5 Sensitivity Analysis

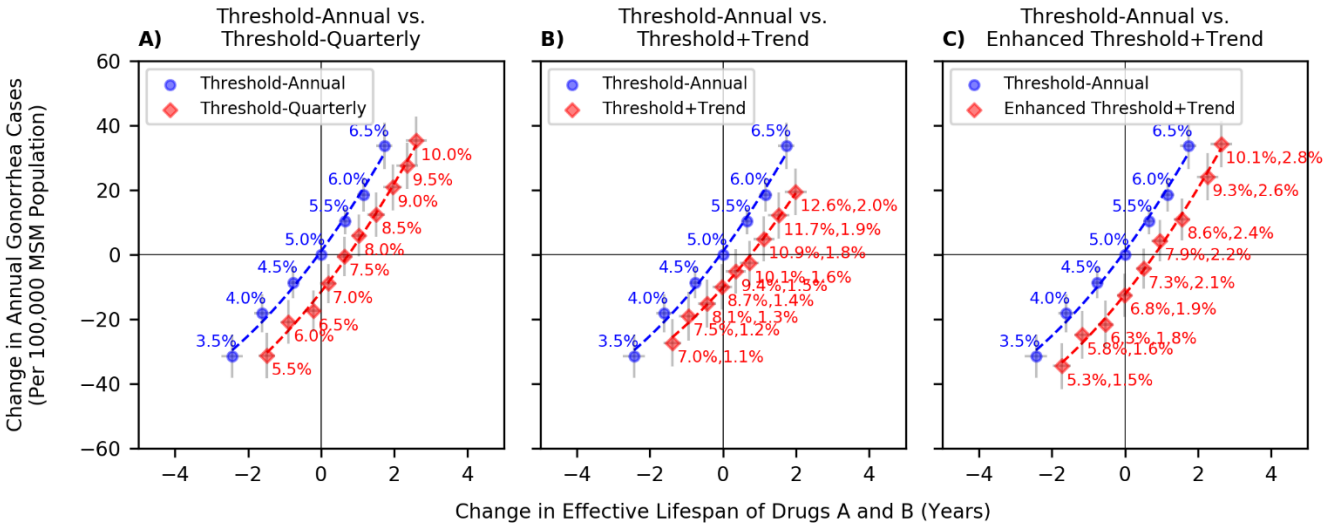

Fig. S6: Comparing the performance of policies in Table 1 with respect to the current policy over a 25-year simulation window. The origins in these figures reflect the current policy that recommends switching the antibiotic used for empiric treatment once the estimated resistance prevalence exceeds 5% [8,10]. The numbers on the curves of 'Threshold-Annual' and 'Threshold-Quarterly' strategies represent the threshold of resistance prevalence to switch the first-line therapy of gonorrhea, and the two numbers on the curves of 'Threshold+Trend' and 'Enhanced Threshold+Trend' strategies represent the two thresholds used to inform switching: resistance prevalence (first %) and percentage point change in the resistance prevalence (second %).

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