Modeling of Antibiotic Resistant Gonorrhea to Determine the Economic Value of Interventions

MPH-IDV Comprehensive Paper

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Abstract

BACKGROUND: *Neisseria gonorrhoeae* is rapidly becoming resistant to antibiotics. Mathematical models have long been used to examine gonorrhea transmission dynamics, and can potentially be used to inform policy and investment decisions.
OBJECTIVE: The goal of this paper is to determine what the value of gonorrhea infection related interventions is on the public health, as well as the potential impact of interventions on slowing the emergence of antibiotic resistance.
METHODS: A model of antibiotic resistance was developed using values found in literature as well as publically available survey data. The inputs of this model were then altered to reflect what the effect of interventions could be.
CONCLUSIONS: The results of the model estimate that it would take roughly 6.5 years for resistance to a new antibiotic to develop and be a problem. However, use of condoms for both oral and vaginal sex can delay resistance emergence by many years. Doubling current condom use rates for vaginal sex could represent a $0.8 billion dollar per year value.

Background

This analysis is an attempt to estimate what the total disease burden of gonorrhea may be within the next 25 years, as well as estimating how much of the morbidity can be avoided through implementation of control strategies.

In 1995, Kretzschmar et al created a model of gonorrhea transmission, using which they tested various interventions such as contact tracing, screening, and promotion of condom use (Kretzschmar 1996). These interventions cost money and time, and so figuring out what the cost effectiveness threshold of the interventions is a potentially valuable exercise. Additionally, since then, the rise of antibiotic-resistant gonorrhea strains introduces new dynamics.

The organism *Neisseria gonorrheae* (gonorrhea) is a significant cause of genital tract infections. The burden of disease arising from gonorrhea infection includes pelvic inflammatory disease and associated complications, epididymitis, greater transmission of HIV, and ocular disease in neonates. In the past, gonorrhea has been successfully treated using antibiotics, however, resistance to antibiotics has been steadily growing, and most strains of gonorrhea are resistant to all but a few antibiotics (CDC). Needless to say, untreatable gonorrhea is a significant threat to public health, so much so that not only has the CDC has declared it one of the urgent antibiotic resistant threats, but the WHO has also listed it among its 12 priority pathogens (CDC).

The first model of gonorrhea transmission, the seminal paper from Hethcote and Yorke, had discovered that sustained transmission of gonorrhea is dependent on a subpopulation of individuals who display higher risk behaviors (Hethcote 1984). The persistence of infection is sustained due to this 'core group' of high infections. More recent models of gonorrhea have included models for antibiotic resistance (Chan 2016), site of infection (Hui 2015), asymptomatic infections as drivers of infection (Garnett 1999, Hazel 2015), and impacts of interventions (Xiridou 2016).

A position paper/review from Grad et al specifically emphasizes the need for improved modeling for improving decision-making regarding gonorrhea.

> Just as it is clear that we need technological and scientific advances—including point-of-care diagnostic testing for resistance, novel therapeutic options, and, ideally, antigonococcal vaccines—we will need better models of gonococcal transmission, which incorporate more of the details of the evolution and interactions of strains, and better understanding of the risk factors associated with antimicrobial resistance, to maximize the effectiveness of our current surveillance and interventions and to best deploy any innovations (Grad 2016).

Background: Use of modeling techniques for public policy

Models of disease transmission are recognized as valuable tools that have been used to inform policy for quite some time now. They can allow for evaluation of disease control approaches, and contribute to contingency planning (Dube 2007). One of the biggest examples of this was Ferguson et al's 2006 paper on influenza. Ferguson et al used an epidemic simulation to examine the effectiveness of interventions, using Great Britain and the US as examples (Ferguson 2006). Their simulations provided a basis for the response to the swine flu pandemic of 2009.

Model Basics

With gonorrhea, past infection is not protective against future infection. This natural history provides for us the basis of the building of the compartmental model. This would be the SIS model, where individuals return to the susceptible population after infection. Additionally, gonorrhea infection may be symptomatic or asymptomatic. Graphically, this can be represented as this, below:

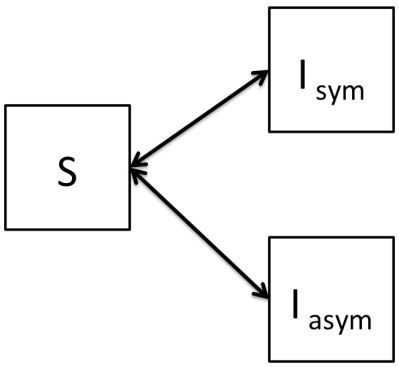


Figure 1: Compartmental model for gonorrhea infection

This can be represented with the following basic equations:

$$\frac{dS}{dt} = -\frac{\beta i S I}{N} + drecY + recA$$

$$\frac{dY}{dt} = +\frac{\beta i S (I * g)}{N} - drecY$$

$$\frac{dA}{dt} = +\frac{\beta i S (I * (1 - g))}{N} - recA$$

$$I = Y + A$$

With *S* indicating susceptible individual, *Y* indicating symptomatic infection, and *A* indicating asymptomatic infection. Recovery rates for *Y* and *A* are different. It is assumed that individuals with symptomatic infections will seek out drug treatment (*drec*), whereas asymptomatic individuals will recover naturally from infection (*rec*). The term $\frac{\beta i S I}{N}$ is the force of infection; it represents the contact rate between the susceptible portion of the population and the infected portion of the population multiplied by the chance that each contact will result in an infection. The term *g* was chosen to indicate the likelihood that an infection will be symptomatic.

With antibiotic resistance, another compartment is introduced:

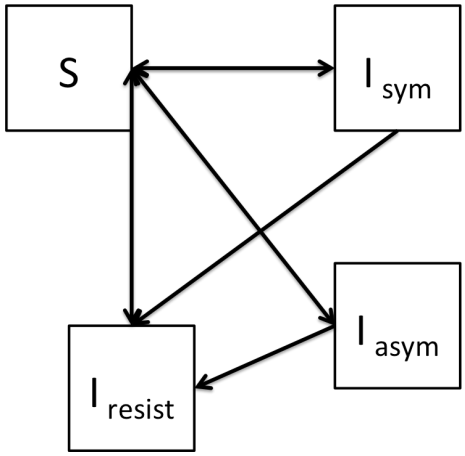


Figure 2: Compartmental model with additional compartment for resistance

The associated equations are below (with R to stand in for I_{resist}):

$$\frac{dS}{dt} = -\frac{\beta i S I}{N} - \frac{\beta i S R}{N} + drecY + recA + recR$$

$$\frac{dY}{dt} = +\frac{\beta i S Y\left(\left(1-\frac{R}{I}\right)*(g)\right)}{N} - drecY - amrR$$

$$\frac{dA}{dt} = +\frac{\beta i S A\left(\left(1-\frac{R}{I}\right)*(1-g)\right)}{N} - recA - amrR$$

$$\frac{dR}{dt} = \frac{\beta i S R\left(\frac{R}{I}\right)}{N} + amrR - recR$$

$$I = Y + A + R$$

The new term *amr* would represent the rate by which an individual's infection becomes drug resistant.

This model is of course, not ideal. A previous paper (Chan 2012) has treated gain of resistance as a probability that occurs for each drug treatment. Resistance is treated as an 'all or nothing' variable, and gain of resistance is a constant. With regards to antibiotic resistance, an attempt to think of resistance in a useful way would consider that the rise of resistance is correlated to the use of antibiotics. Modeling this would link the rise of drug resistance (*amr*) to the rise in numbers of individuals who get treated (*drecY*), with M being a constant representing some interaction between the mutation rate and acquisition of resistance mutations.

$$amr = drecY * M$$

This equation represents the increase in resistance contributed at that particular moment in time.

Checking the approach to modeling AMR

In order to test to see if this is a valid approach to modeling antimicrobial resistance would be, a rough model of resistance was implemented. The parameters used below, with assumptions about mixing rates taken from Vynnycky and White (Vynnycky 2011; Marshall 2016). This rough model does not include assumptions about site of infection or gender. Ciprofloxacin (cipro) resistance was chosen as a test case. A crude assumption of the mutation rate was calculated by assuming a

mutation frequency of 1 mutation per 10^7 bp per generation, multiplied by 15 generations a day. The assumption was made that only 5 of the 2 million bp in the NG genome would confer resistance to cipro, as resistance to cipro was generally associated with few mutations in both ParC and GyrA (Allen 2011).

Table 1: Parameter estimation for testing antibiotic resistance modeling validity

Parameter	Estimate
Population	50,000
High risk group proportion	0.02
Recovery rate (due to drug use)	12 days
Mutation rate	3.75×10^{-12} / day

The model was built in a program that solves ordinary differential equations, Berkeley Madonna (Berkeley Madonna 2017).

Based on historical CDC data, it took approximately 13 years from the first use of ciprofloxacin for 14% of *N. gonorrhoeae* strains to be resistant to cipro. At the peak use, cipro accounted for about 20% of the drugs used to treat gonorrhea (CDC). The following graph is obtained, showing that in roughly 20 years, 12% of infections will be resistant to the antibiotic. This aligns relatively closely to reality. This model does not account for gain of resistance through lateral gene transfer, which is believed to be one of the biggest ways resistance is gained (Low 2016). However, the fact that this model is extremely oversimplified cannot be overstated.

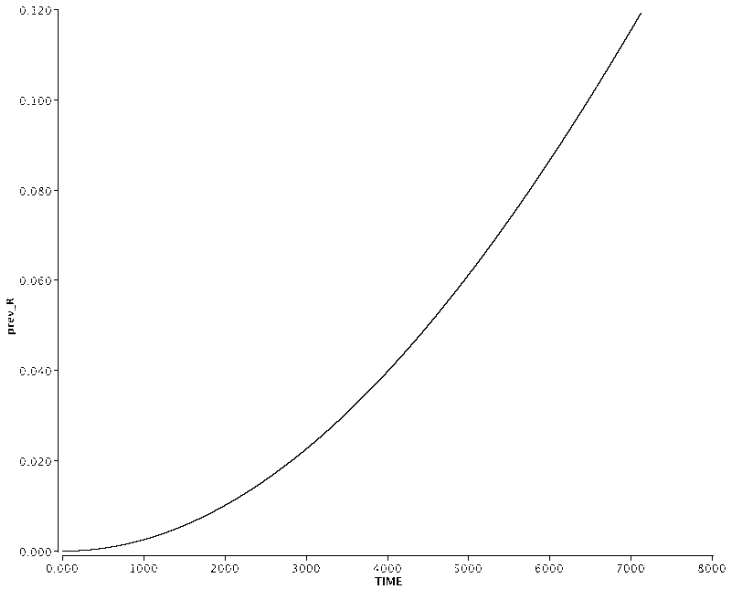


Figure 3: Prevalence of resistant strains of gonorrhea. Time is represented in days.

The final model

Below is the graphical representation of the final model being used for this analysis. The model includes asymptomatic infection, as well as site of infection (pharyngeal vs genital infection), and is split by gender. Despite being important to the disease dynamics (Hui 2015), men who have sex with men (MSM) were removed from this model for ease of programming. Pharyngeal gonorrhea was not considered for the male population, as there is no data supporting pharyngeal gonorrhea transmission through oral sex on a female. The population is further split into a high risk and low risk group, with different contact rates for each group.

Site of infection is modeled not only because of contact rate, but also because pharyngeal gonorrhea is a reservoir, but does not cause the same sequelae in individuals that genital gonorrhea does. Pharyngeal infections are assumed to be completely asymptomatic, so the patient never seeks drugs. Male infection rates are driven by both genital and oral contact rates, whereas female infection rates use only the relevant contact rate.

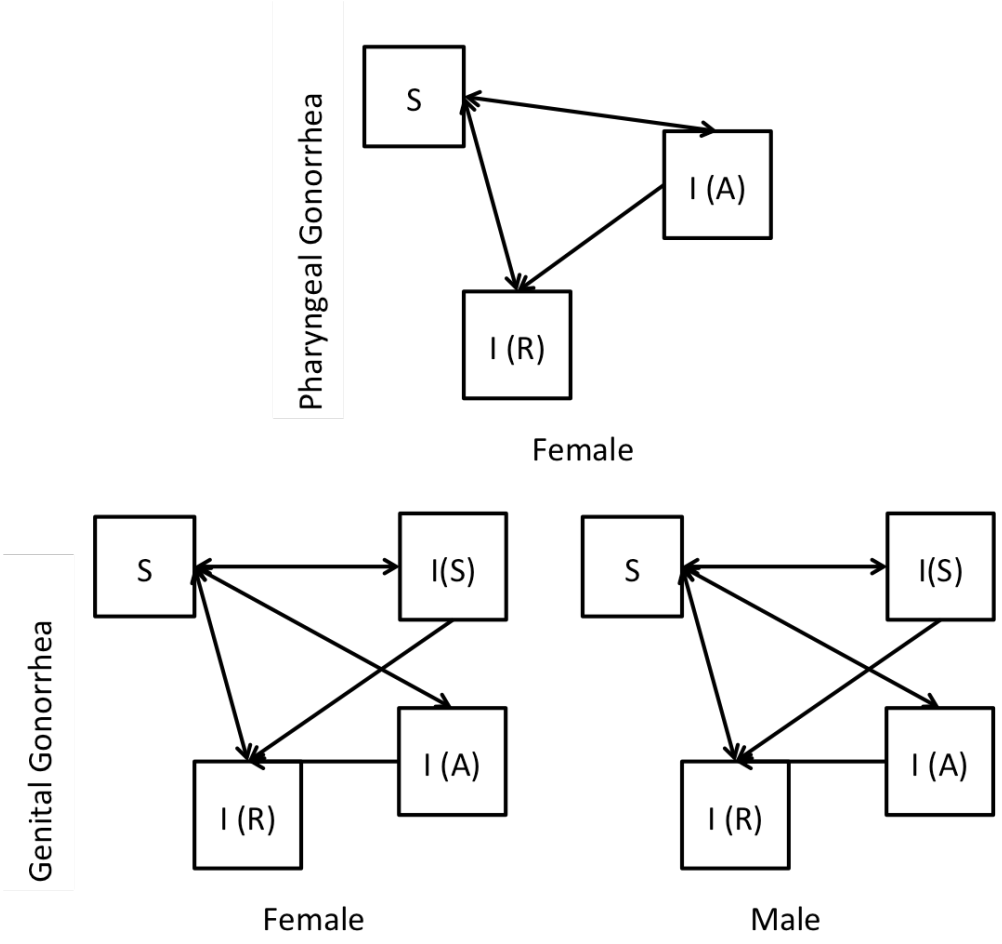


Figure 4: Final compartmental model chosen. The structure is duplicated for high and low risk groups

As before, the model was built using differential equations, and Berkeley Madonna was used to solve them. The code used for this model can be found in Appendix 1. Infection events are given a probability of causing a resistant infection or a susceptible infection, based on the proportion of the total infections that are resistant. For non-resistant infections, another proportion is applied to determine whether or not an infection will be symptomatic or not. As an asymptomatic infection in one individual may be symptomatic in others, this calculation is only used to decide what proportion of newly infected individuals end up in each compartment.

This model does not account for how an individuals' contact behavior will change based on symptoms showing or not, or what other factors may influence care seeking behavior.

Parameters

Parameters were taken from the literature, using either the most relevant modeling study, or using data taken from epidemiologic studies.

The National Health and Nutrition Examination Survey (NHANES) conducted by the CDC contain a set of questionnaires involving sexual behavior. The results of the sexual behavior survey in the 2013-2014 NHANES were released by the CDC, and used (CDC). Use of this dataset contains several flaws, in that not all respondents answered all the questions, leading cross tabulations to contain flaws. Additionally, survey respondents don't necessarily truly represent the various high-risk groups. As a result, this data was only used to obtain several of the crude rates.

Table 2: Parameter estimates for final model. Contact rates were recalculated for per-day.

Parameter	Estimate	Source
Asymptomatic chance - female	0.61	Flynn 2015
Asymptomatic chance - male	0.11	Ong 2016
Natural recovery - genital	185 days	Garnett 1999
Natural recovery- pharyngeal	140 days	Chow 2016
Drug mediated recovery	20 days	Hazel 2015
Transmission probability	0.8	Hazel 2015
AMR mutation chance - AZM	9.5×10^{-12} / day	Extrapolated -Lynagh 2015
High risk group proportion	0.028	Extrapolated – NHANES 2014
Contact rate – oral (high risk)	18.5/ yr = 0.050	Extrapolated – NHANES 2014
Contact rate – oral (low risk)	1.4/yr = 0.0038	Extrapolated – NHANES 2014
Contact rate – genital (high risk)	7.1/yr = 0.019	Extrapolated – NHANES 2014
Contact rate – genital (low risk)	1.6/yr = 0.0043	Extrapolated – NHANES 2014

Individuals defined as “high risk” for the purpose of this calculation were defined as individuals who made 3 or more partnerships per year. Contact rates are assumed to be on a new partner basis, not on a per act basis. Previous papers (Chan 2016) used multiple risk groups, so choosing 3 partnerships as the cutoff for the high- and low- risk groups was a somewhat arbitrary decision to make the coding less painful.

Oral and genital sex contact rates were calculated as follows: using the NHANES data, individuals reporting fewer than (365/3) days since performing oral sex on a new male partner were classified as ‘high risk’, and an average calculated from their answers. Individuals who answered more than (365/3) days, but less than a year, were then used to calculate the low risk group. The year cutoff was used because of an assumption that individuals in partnerships lasting longer than a year likely won’t contribute to the gonorrhea infection rate. The rates used are comparable to the rates used by others in literature.

Unfortunately, due to lack of accessible data, there is no way to compare this model to historical data to make stronger estimates of unknown parameters. As such, this model is also essentially useless, as it’s basically untested.

Results

The population was set to be 100,000 individuals, evenly split on gender. It was also assumed that the population is fixed; no entry or exit from the population. Due to the contact rates used (partnerships last less than a year), and lack of age structure, this could theoretically represent a group of young adults.

Because MSM transmission has previously been found to be important for sustaining transmission (Hui 2015), a 'fudge factor' of 20% was applied to the contact rates above. This was done to ensure that we could reach sustained endemic transmission before introducing antibiotic resistance. Using the initial calculated contact rates did not allow for sustained transmission.

The code for the model can be found in Appendix 1. The model was allowed to run to equilibrium for 65 years, then resistance was introduced, and the model run for another 25 years. The results are shown below, with rise of resistance beginning at day 23750. Additional graphs can be found in Appendix 2. The black line represents infections that are resistant to antibiotics, while the grey line represents the uninfected population.

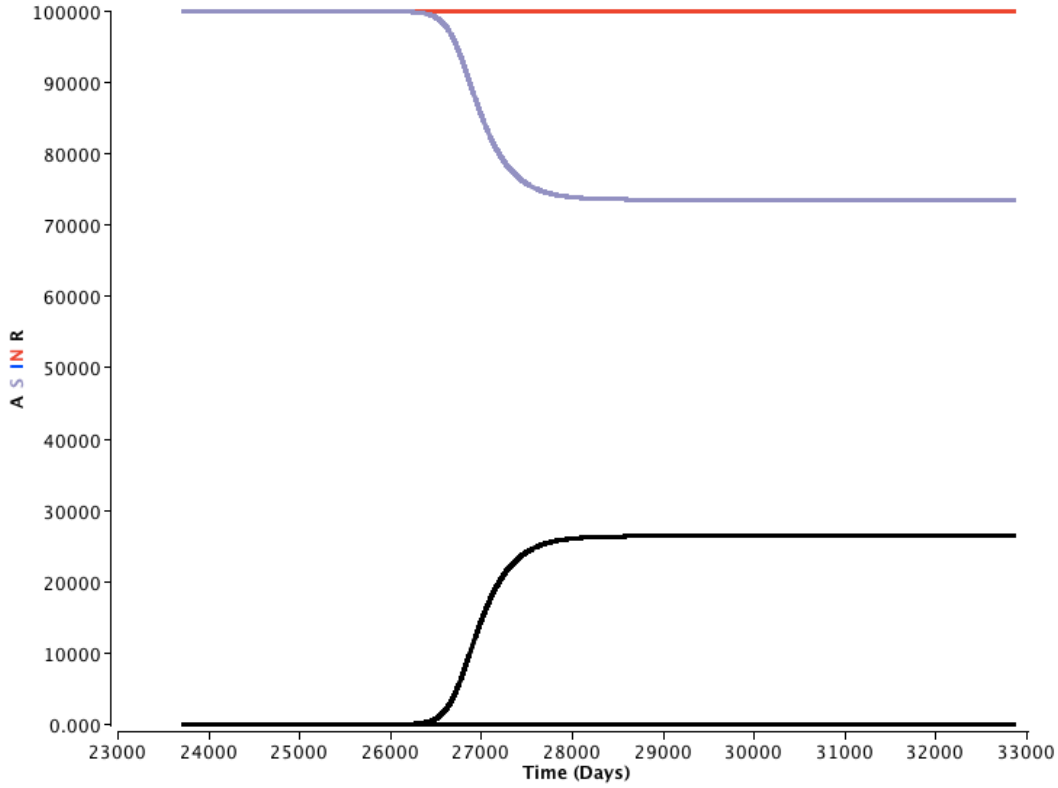


Figure 5: The grey line represents susceptible individuals, and the upper black line represents individuals infected with an antibiotic resistant infection. Red shows the population total. The time scale is 25 years, after resistance is introduced; antibiotic resistance added after infections were allowed to reach equilibrium.

Implementation of the model, as shown in Figure 5, predicts that, if gonorrhea becomes untreatable, 27% of the sexually active population will be affected. It also predicts that a significant level of resistance would take around 6.5 years to arise (around 2400 days).

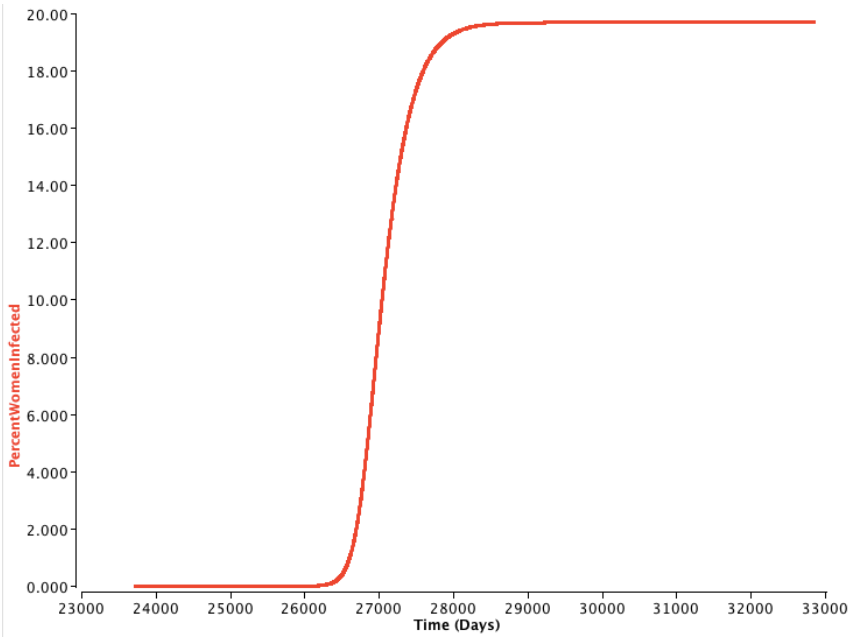


Figure 6: Percentage of women infected with gonorrhea at any given moment.

Figure 6 above shows the percentage of the population of women we would expect to see with an antibiotic resistant gonorrhea vaginal infection at any time, under the conditions given in the model. We would expect 19.6% of the population to have an untreatable gonorrhea infection, once infection reaches equilibrium.

Costs and Interventions:
Increasing Condom Use

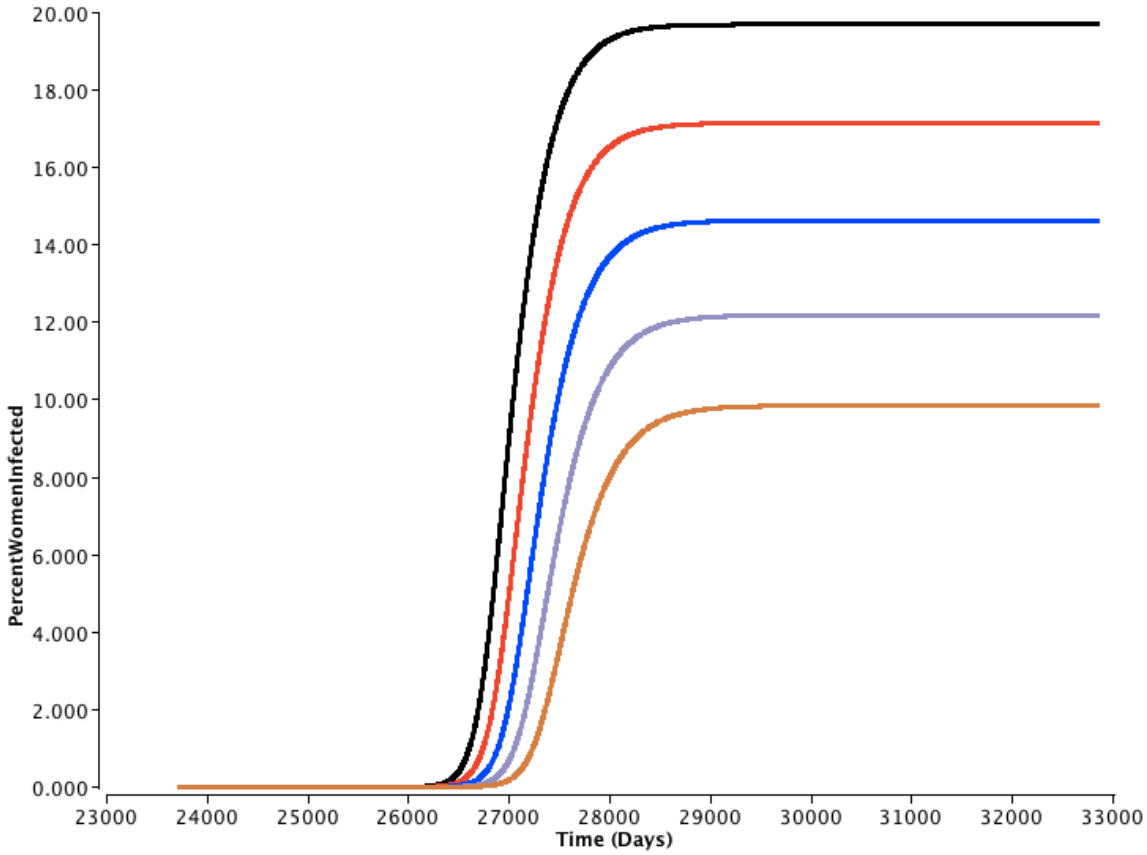


Figure 7: Percent of women infected with gonorrhea, with varying condom use rates for vaginal sex; colors represent the following percentages: Black: 0%; Red: 10%; Blue: 20%; Grey: 30%; Orange: 40%

Here, the model is run as before, only with varying levels of condom use for vaginal sex. The original model is built with the assumption that no condoms are being used at all (black line). If condom use rates are appended into the genital contact rates, we can see the type of change indicated in the graph. The most realistic level is around 20% condom usage (Reece 2010), giving us about 14.6% of women infected with gonorrhea (blue line). If condom usage can be doubled, this will drop to about 9.8% of women infected. Increasing rates of condom usage also, importantly, has the effect of delaying emergence of resistance by 2-3 years.

Assuming that women with gonorrhea have a 10% chance of developing PID (Kreisel 2017), we would expect that this would result in an additional 1.4% of the population per year diagnosed with PID. This is particularly worrying, as, as of 2014, PID prevalence in American woman aged 18-44 is at 4.4% (Kreisel 2017). An additional 1.4% would represent a 30% increase in PID diagnoses.

According to the 2010 US Census, females in the 18-44 age range account for 18.3% of the population, giving us 56 million individuals (Census 2010). 1.4% of this is 817,600 individuals. The CDC estimates that each case of PID results in an average cost of $3,202 (Kreisel 2017). Thus, assuming that the population stays the same by the time gonorrhea becomes fully untreatable, under this model, the expected costs for PID treatment due to untreated gonorrhea then sit at $2.62 billion per year. If condom use could be doubled to being used 40% of the time (orange line), this cost would drop to $1.75 billion per year.

Under this model, spending $0.87 billion per year on doubling condom use for gonorrhea prevention (or some other equivalent intervention) would then be considered cost saving, especially because none of the other sequelae that gonorrhea causes are being considered. With a cash discount rate of 3%, this value 15 years in the future is worth a $0.56 billion investment today, if a doubling of condom use can be induced and permanently sustained.

Unfortunately, the literature is not optimistic about the effectiveness of condom education and promotion campaigns (Lopez 2013). Therefore, alternately, in this model, increasing the condom use rate effectively the same as reducing the chance of transmission, so this can also be effectively thought of as developing a gonorrhea vaccine that is 20% effective. Accomplishing this would be worth at least a $0.56 billion investment today, not even taking into consideration other the other benefits that would come with reduced gonorrhea transmission, such as reduced epididymitis, reduced rates of HIV transmission, and reduced neonatal complications.

A search through the literature indicated that this number is within an acceptable and believable range. In 2006, Chesson's analysis had estimated that federally funded gonorrhea prevention programs had likely cut gonorrhea rates by 75%. This program cost $4.3 billion, and was estimated to have averted $8.1 billion in direct medical costs, thus being considered cost saving (Chesson 2006).

Table 3: Expected costs of gonorrhea due to PID, under specified conditions. Bolded is the status quo.

Condom Use Rate (Vaginal Sex)	Additional PID cases	Estimated Cost of PID
0%	1064000	$3,406,928,000
20%	**817600**	**$2,617,955,200**
40%	548800	$1,757,257,600

Condom Use for Oral Sex

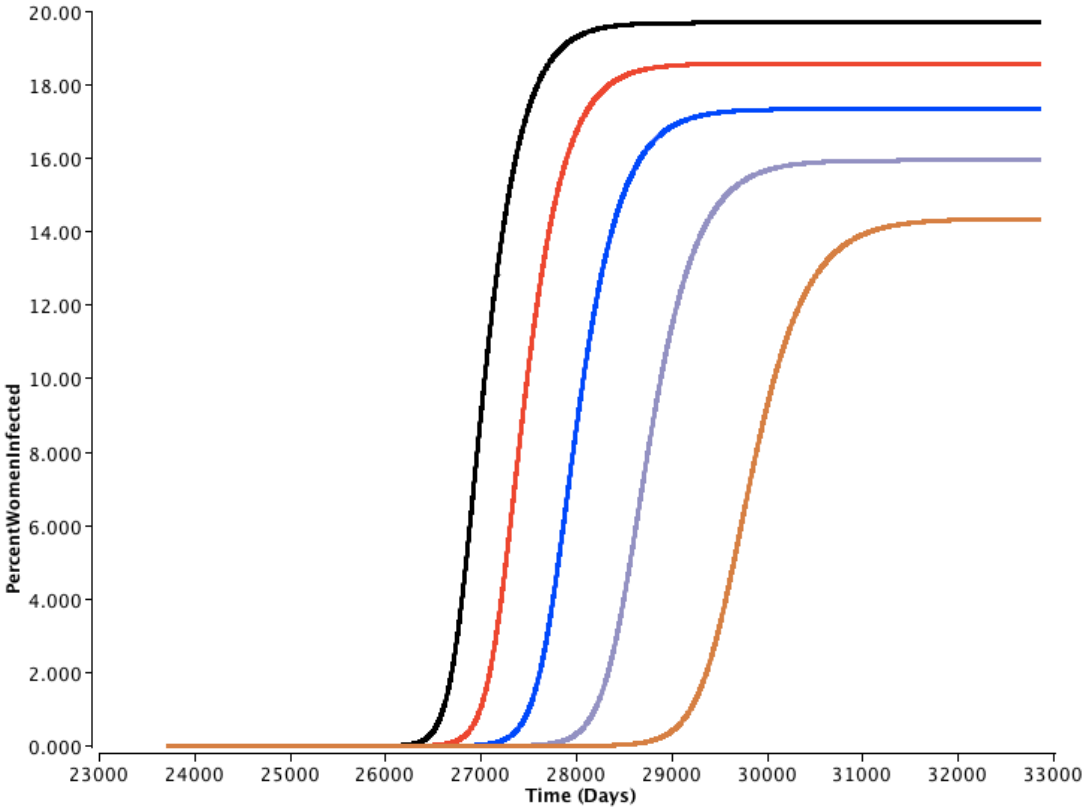


Figure 8: Percent of women infected with gonorrhea, with varying condom use rates for oral sex; colors represent the following percentages: Black: 0%; Red: 10%; Blue: 20%; Grey: 30%; Orange: 40%

The above figure show how using protection for oral sex may alter the emergence of resistance, as well as change the prevalence of vaginal infections, even assuming no condoms are being used for vaginal sex. Each subsequent line represents a 10% increase in condom use in oral sex. We can see that increasing condom use for oral sex by 40% will delay emergence of resistance by 9 years, as well as reducing prevalence of vaginal infection by 30%.

Applying a similar analysis as above yields similar results – a 40% increase in condom usage for oral sex would result in cost savings of $0.9 billion.

Table 4: Expected costs of gonorrhea due to PID. Bolded is the status quo.

Condom Use Rate (Oral Sex)	Vaginal Gonorrhea Rate	Additional PID cases	Estimated Cost of PID
0%	**0.019**	**1,064,000**	**$3,406,928,000**
20%	0.017	952,000	$3,048,304,000
40%	0.014	784,000	$2,510,368,000

However, no substantial literature exists in promotion of safe oral sex practices.

Conclusions

This model of antibiotic resistant gonorrhea transmission represents what would happen if gonorrhea were to become resistant to our last-line drugs, and if we did not take further steps to stem resistance development. Further manipulations of this model could inform where efforts could be focused.

Within this model, introducing interventions that would reduce genital transmission rates of gonorrhea by 20% would effectively delay emergence of resistance by 2-3 years, as well as prevalence. This reduced prevalence is well worth a $0.56 billion investment in today's dollars. This $0.56 billion threshold is the threshold at which an intervention will be cost saving. It should be noted that even if an intervention is not cost *saving* does not mean that it is not cost *effective.* The cost value calculated here is based on money alone. In truth, averting 100,000 cases of PID would also avert several thousand cases of infertility and chronic pelvic pain (Yeh 2003). The improvements in the quality of life for those individuals would be worth far more than the estimated $3,202 direct medical cost per case of PID. Additionally, the delayed time to resistance is priceless, as it would give additional time to develop new drugs and treatments, which can allow us to even further delay the onset of the post-antibiotic era.

Limitations: Model

The adage "garbage in, garbage out" acutely applies to all work involving computer simulations. The model can only be as good as the assumptions made going into it. Because this model has been so heavily simplified, it's really only useful for giving broad ideas of what kind of possibilities may occur.

Because the sequelae associated with gonorrhea tends to have a greater economic impact on women, this model looks only at partnerships involving women. This was partly chosen out of convenience. Unfortunately, this is a flawed way to look at gonorrhea transmission. MSM typically represent a high-risk group for gonorrhea, yet were removed from this model. This is especially flawed, as increasing antibiotic resistance is commonly first detected in this population (Unemo 2014). In fact, initially, using the calculated contact rates, transmission could not be sustained. This finding is similar to Hui 2016, where transmission couldn't be sustained in just the heterosexual population alone. A 'fudge factor' of 20% had to be added in order to cause a sustainable infection. Because of this, the 'true' effect of interventions likely won't be seen. Additionally, many interventions are targeted towards certain risk

groups, so if those risk groups are not modeled, the effectiveness of those interventions also cannot be modeled.

With regards to development of full antibiotic resistance, this model gives a generous estimate of that time scale. As this model only accounts for resistance rising de novo, and how it may spread in the population, it doesn't come close to reflecting reality. In reality, since resistant genes can be acquired through lateral gene transfer, we would expect resistance to arise much faster than indicated in the model, as gonococcal bacteria pick up genes from other gonococci and the environment. However, the model also only assumes that one drug will be used to treat gonorrhea, and that drug will be used until exhausted. In reality, guidelines and recommendations would change such that emergence of resistance can be delayed for as long as possible. Knowledge of the antibiogram of an area can allow for smarter treatment choices, which reflect treatment paradigms not represented in this model.

There is also an assumption of population mixing in this model. In reality, geographic variations in gonorrhea transmissions are significant; resistant gonorrhea rates in large, coastal metropolitan areas like San Francisco and New York are higher than in the rural South, even though both areas have relatively high gonorrhea prevalence (CDC).

This model contains no age structure, as well as no entry or exit from the population. To that end, it's intended to be represent a sexually active population that has not yet 'settled down', where individuals who exit the population are immediately replaced by identical individuals. This isn't truly representative of any population, but was done for simplicity. Much more variability would be seen if a changing age structure was introduced.

Looking at historical models, estimates of all aspects of the models are widely varying. For example, there exists very little data about how increasing resistance may affect natural recovery from gonorrhea infection. The transmission rates for oral sex are likely to be different from male-to-female as compared to female-to-male, but the data for those transmission events is lacking. Additionally, estimates of the proportion of asymptomatic infections greatly vary, even in the existing models (Kretzsmacher 1996, Hazel 2015). Better data gathering in the future would address these limitations. Model developers should interact with health officials and lab scientists to obtain the highest quality data. With better data, various rates could be estimated through model fitting rather than through extrapolation of statistics or reliance on literature.

Limitations: Cost-effectiveness

As discussed earlier, the true value of preventing antibiotic resistant gonorrhea infection is much higher than estimated here. Delaying emergence of resistance by several years is invaluable, as it could provide the time necessary for development of new drugs or treatments. Additionally, the value of any intervention that improves safe sex practices has value beyond just what gonorrhea prevention would deliver. Improving condom use rates would also have the effect of reducing transmission of other STDs, including HIV and chlamydia, as well as reducing unwanted pregnancies.

Limitations: Modeling of antimicrobial resistance

Everything should be as simple as possible, but not simpler. – Einstein

Given the grave threat that antibiotic resistant infections pose, there have been many previous attempts at modeling antibiotic resistance, both from the pharmacokinetic perspective and from a population perspective, but none that combine the two.

Previous population-level models of antibiotic resistant gonorrhea give susceptible strains a possibility of becoming resistant. More sophisticated models will relate the rate of resistance to the rate of drug use. While models are always oversimplifications of reality designed to assist in decision-making, the base assumptions of how resistance occurs in this case are faulty.

In existing models like the ones reviewed by Spicknell et al, antibiotic resistance is treated as a separate category in a compartmental model, much like how it was presented above. Spicknell present various model structures that focuses mostly on the population dynamics of the bacteria within the host – competition between sensitive and resistant strains. While this interaction no doubt plays an important role in the dynamics of an antibiotic resistant infection, Spicknell does not mention a sorely overlooked factor in the modeling of drug resistance (Spicknell 2013).

Antibiotic resistance is not an 'on/off' switch for bacteria. Development of drug resistance is oftentimes the result of gradual accumulation of resistance mutations. However, determination of the whether a bacterial strain is classified as 'antibiotic resistant' is based off of the minimum inhibitory concentration (MIC). This MIC level is the concentration of antibiotic necessary to kill or inhibit growth. If the MIC is

above a certain level set by standard setting agencies (breakpoints set by CLSI in the US and EUCAST in the European Union), then the strain is considered 'resistant'. Thus, it's entirely theoretically possible to have a bacterial strain that is difficult to treat, but not technically 'antibiotic resistant'. Failure to fully treat this strain only contributes to the rise of resistance, as it will then have future opportunities to accumulate even more resistance mutations.

Resistant strains also are not necessarily truly untreatable by a drug, but rather could also take a longer or stronger drug regimen to fully eradicate. This pattern of drug resistance is currently seen in diseases such as malaria – emergence of strains of *Plasmodium falciparum* that take a longer time to clear with artemisinin treatment have been of particular concern (Ashley 2014). Given the ranges of MICs shown by different strains of *N. gonorrhoeae*, it's not at all unreasonable to see this as a contributor to the rise of resistance.

In their review on antimicrobial drug dosage design, Gehring et al emphasize the importance of understanding the dynamic nature of drug exposure and effect to derive clinical treatment strategies (Gehring 2013). This view should be expanded to those doing population level modeling design as well. Lack of appropriate modeling of the pharmacodynamics of antimicrobial agents in population models makes these models less useful. Properly designed drug regimens must be employed with resistant infections or risk hastening resistance. If overly simple models are used to design these regimens, these drug regimens will not be as effective, and perhaps even harmful. A properly designed resistance model could lead to better predictive power as well as clearer ideas of where to focus research efforts, development of better drug regimens, and drug use policies.

Future Directions: Proposed Individual-Based Model

The limitations of using a differential equation based model are clear. Interactions in real life aren't truly random, and stochasticity likely has a strong effect on the true interactions. Here, a framework is proposed in which an antibiotic resistance model can be improved. This framework is similar to the chlamydia model for testing chlamydia vaccine usefulness developed by Gray et al, in that bacterial dynamics within individuals should be considered in the model (Gray 2006).

The proposed model is an agent (individual) based model. This should be the chosen antibiotic resistance model due to the degree of complexity and heterogeneity involved. Even if resistance itself could be effectively modeled through differential equations, it can't be appropriately expressed without linking it directly to

individuals interacting with other individuals in a population. Additionally, the agent-based model can accommodate the more continuous nature of the attributes associated with heterogeneity.

The agent-based, open-source modeling software, NetLogo, provides a user-friendly interface where variables can be changed to show how they may affect the outcome of running the model (Wilensky 1999). Several other individuals have previously used NetLogo to model disease transmission (Escobar 2015; Prats 2016). Netlogo thus provides a convenient basis with which to start building the model.

In the structure of this model, bacteria and people will be modeled separately. Bacteria have an associated resistance characteristic to them that determines how quickly they will be cured. The resistance characteristic will be affected by the drug use of the individual. Infection of another person leads to duplication of the bacteria's current resistance levels.

Bacteria states can be conceptually as seen in Figure 9:

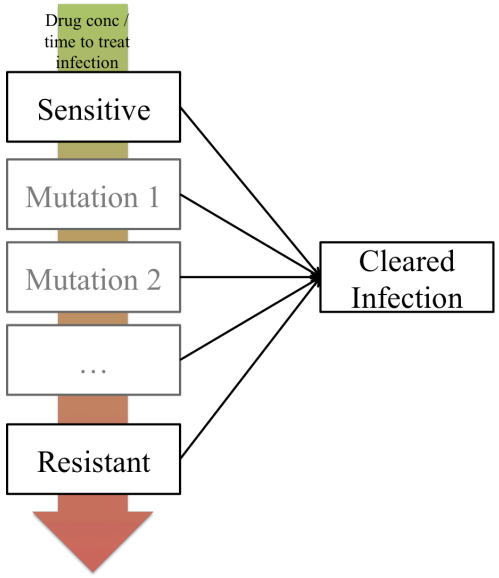


Figure 9: Bacteria transition states

At each compartment, a bacterium has a chance to either gain further mutations to make it more resistant, or to die and be cleared from the body. The concentration of drug needed at each state to clear the infection increases the further down it goes, until the bacteria has accumulated enough mutations to become resistant. Alternately, a bacterium can also go directly from [sensitive] to [resistant] through acquisition of resistance genes through lateral gene transfer.

Human states can be modeled as seen in Figure 10.

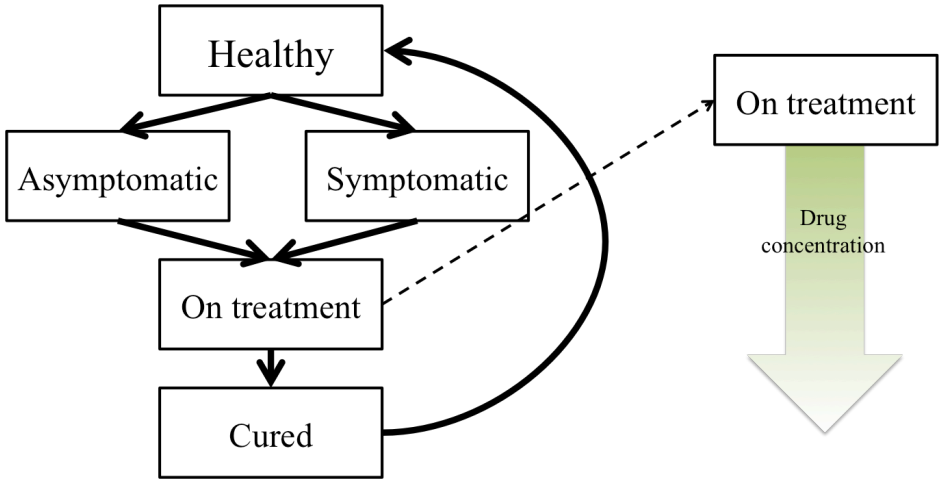


Figure 10: Human transmission states

Individuals can move between these compartments, with different parameters to describe what conditions must be satisfied to move into a different compartment. For example, contact with an infected person is necessary to move an individual to either an asymptomatic or symptomatic infection. To go onto treatment, the individual either has to seek care, or will discover their infection during routine testing, or maybe even just never gets treated. Because past infection with gonorrhea is not protective against future infection, cured individuals go back into the pool of healthy individuals.

In the [on treatment] compartment, the individual is assigned a drug concentration in the beginning that slowly decreases over time. This is meant to simulate the current recommended treatment, which is a single oral dose of 1g azithromycin and an intramuscular injection of 250mg ceftriaxone (CDC). Because these drugs are only delivered once, their concentrations in the body will decrease at some rate over time. This dosage should then interact with the bacteria model compartments.

Future Directions: Interventions and Cost Effectiveness.

A more exhaustive examination of various interventions and their effectiveness should be done. Doing so can give us information about whether or not a particular intervention will be cost saving or, if not, how cost-effective it is. Potential interventions to test could include condom promotion, education, increasing availability of testing services, provision of point-of-care over-the-counter testing kits, and implementing test of cure as standard practice. Other conditions that could be tested could look at synergistic effects of implementing two different interventions at once.

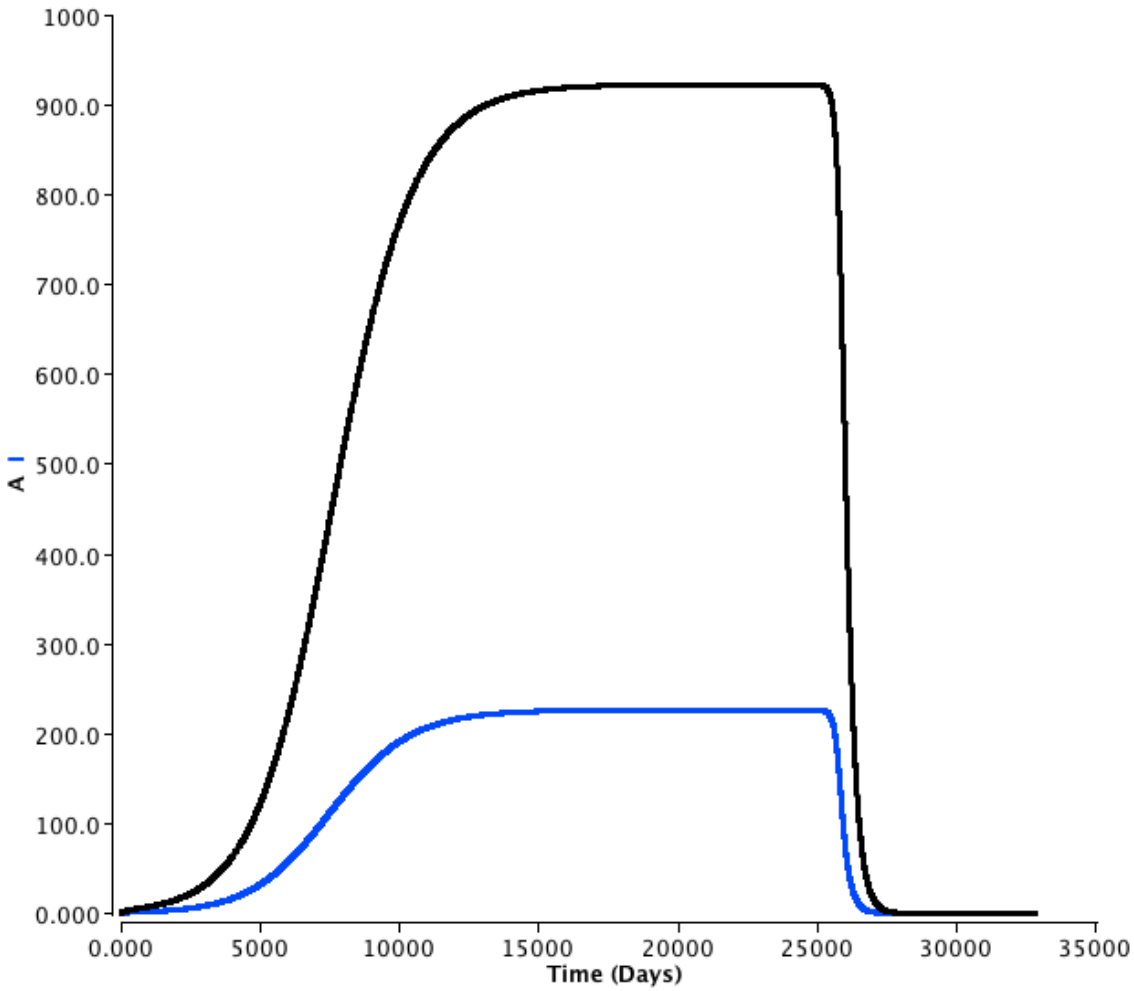
Appendix 1: Berkeley Madonna Code

```
METHOD RK4

STARTTIME = 365*65
STOPTIME=365*90
DT = 1

{Equations}

{Pharyngeal Infection: No drug recovery, since no drugs for pharyngeal, since
all pharyngeal is asymptomatic}

{High risk group. F indicates Female, M indicates male. P indicates pharyngeal;
G indicates genital. S, A, I, R indicate individual components.}

d/dt(S_F_P_H) = recP*A_F_P_H + recP*R_F_P_H - lambdaPF*S_F_P_H
d/dt(A_F_P_H) = (lambdaPF*S_F_P_H*(1 - amrPerc)) - recP*A_F_P_H
d/dt(R_F_P_H) = lambdaPF*S_F_P_H*(amrPerc) - recP*R_F_P_H

d/dt(S_F_G_H) = -lambdaGF*S_F_G_H + recG*A_F_G_H + d_rec*I_F_G_H + recG*R_F_G_H
d/dt(I_F_G_H) = lambdaGF*S_F_G_H*(1 - amrPerc)*(1 - asymlikF) - d_rec*I_F_G_H -
amr*I_F_G_H
d/dt(A_F_G_H) = lambdaGF*S_F_G_H*(1 - amrPerc)*(asymlikF) - recG*A_F_G_H
d/dt(R_F_G_H) = lambdaGF*S_F_G_H*(amrPerc) - recG*R_F_G_H + amr*I_F_G_H

d/dt(S_M_G_H) = d_rec*I_M_G_H + recG*A_M_G_H + recG*R_M_G_H - lambdaGF*S_M_G_H
- lambdaPF*S_M_G_H
d/dt(I_M_G_H) = lambdaGF*S_M_G_H*(1 - amrPerc)*(1 - asymlikM) +
lambdaPF*S_M_G_H*(1 - amrPerc)*(1 - asymlikM) - d_rec*I_M_G_H - amr*I_M_G_H
d/dt(A_M_G_H) = lambdaGF*S_M_G_H*(1 - amrPerc)*(asymlikM) +
lambdaPF*S_M_G_H*(1- amrPerc)*(asymlikM) - recG*A_M_G_H
d/dt(R_M_G_H) = lambdaGF*S_M_G_H*amrPerc + lambdaPF*S_M_G_H*amrPerc -
recG*R_M_G_H + amr*I_M_G_H

{Low risk group. Same nomenclature applies.}
d/dt(S_F_P_L) = -lambdaPL*S_F_P_L + recP*A_F_P_L + recP*R_F_P_L
d/dt(A_F_P_L) = lambdaPL*S_F_P_L*(1-amrPerc) - recP*A_F_P_L
d/dt(R_F_P_L) = lambdaPL*S_F_P_L*(amrPerc) - recP*R_F_P_L

d/dt(S_F_G_L) = -lambdaGL*S_F_G_L + recG*A_F_G_L + d_rec*I_F_G_L + recG*R_F_G_L
d/dt(I_F_G_L) = lambdaGL*S_F_G_L*(1-amrPerc)*(1-asymlikF) - d_rec*I_F_G_L -
amr*I_F_G_L
d/dt(A_F_G_L) = lambdaGL*S_F_G_L*(1-amrPerc)*(asymlikF) - recG*A_F_G_L
d/dt(R_F_G_L) = lambdaGL*S_F_G_L*(amrPerc) - recG*R_F_G_L + amr*I_F_G_L

d/dt(S_M_G_L) = -lambdaGL*S_M_G_L - lambdaPL*S_M_G_L + d_rec*I_M_G_L +
recG*A_M_G_L + recG*R_M_G_L
d/dt(I_M_G_L) = lambdaGL*S_M_G_L*(1-amrPerc)*(1-asymlikM) +
lambdaPL*S_M_G_L*(1-amrPerc)*(1-asymlikM) - d_rec*I_M_G_L - amr*I_M_G_L
d/dt(A_M_G_L) = lambdaGL*S_M_G_L*(1-amrPerc)*(asymlikM) + lambdaPL*S_M_G_L*(1-
amrPerc)*(asymlikM) - recG*A_M_G_L
d/dt(R_M_G_L) = lambdaGL*S_M_G_L*amrPerc + lambdaPL*S_M_G_L*amrPerc +
amr*I_M_G_L - recG*R_M_G_L

{Calculating numbers to be used for graphs. The /2 for women are used because
the women are modeled twice, so must be merged into one.)
S = ((S_F_P_H + S_F_G_H  + S_F_P_L + S_F_G_L)/2 ) + S_M_G_L + S_M_G_H
S_H = (( S_F_P_H + S_F_G_H)/2) + S_M_G_H
S_L = ((S_F_P_L + S_F_G_L)/2) + S_M_G_L

A = ((A_F_P_H + A_F_G_H + A_F_P_L + A_F_G_L)/2) + A_M_G_L+ A_M_G_H
A_H = ((( A_F_P_H + A_F_G_H)/2)+ A_M_G_H)
A_L = ((A_F_P_L + A_F_G_L)/2)+A_M_G_L
```

```
I = (I_F_G_H + I_M_G_H + I_F_G_L + I_M_G_L )
I_H = ( I_F_G_H + I_M_G_H)
I_L = ( I_F_G_L + I_M_G_L )

R = (((R_F_P_H + R_F_G_H + R_F_P_L + R_F_G_L)/2)+ R_M_G_H + R_M_G_L )
R_H = ( ((R_F_P_H + R_F_G_H)/2) + R_M_G_H)
R_L = (((R_F_P_L + R_F_G_L)/2) + R_M_G_L )

N = S + A + I + R

PercentWomenInfected = ((R_F_G_H + R_F_G_L) / 50000)*100

Inf_H = A_H + I_H + R_H
Inf_L = A_L + I_L + R_L
Infected = Inf_H + Inf_L

N_H = S_H + A_H + I_H + R_H
N_L = S_L + A_L + I_L + R_L

prev_H = Inf_H/  N_H
prev_L = Inf_L / N_L
prevalence = (A+I+R) /N

{Introducing emergence of resistance. Alter 365*65 to change when to introduce
resistance.}

amrPerc = IF (TIME < (365*65)) THEN 0 ELSE R/ (N-S)

{Infection Rate }

PH = 0.05 *1.2 *(1-oralcondom)
GH = .019 *1.2 *(1-condom_use)
PL = .0038 *1.2 *(1-oralcondom)
GL = .0043 *1.2 * (1-condom_use)

{Condom use rates. Use Batch runs to change these values.}
oralcondom = 0
condom_use = 0

{Population contact rates}
hrg = 0.028
lrg = 0.972

mixH = ((PH*hrg)/(PH*hrg + PL*lrg))
mixGH = (GH*hrg /(GH*hrg + GL*lrg))

mixL = 1 - mixH
mixGL = 1 - mixGH

mixrateP = mixH*prev_H + mixL*prev_L
mixrateG = mixGH*prev_H + mixGL*prev_L

lambdaPF = mixrateP*PH*trans
lambdaGF = mixrateG*GH*trans
lambdaPL = mixrateP*PL*trans
lambdaGL = mixrateG*GL*trans

trans = 0.8

{Likelihood of asymptomatic infection}

asymlikF = 0.61
asymlikM = 0.11

{Natural recovery rate (per day)}
```

```
recG = (1/185)
recP = (1/140)

{Drug mediated recovery rate(per day)}
d_rec = 1/20

{Resistance gain: mutation rate * generations per day *number of resistance
giving mutations }

M = (1/10^7)*16*(14/2000000)

{going from 1 -> R. This is *I}

amr = M*I

{Initial conditions}

init S_F_P_H =50000*hrg
init A_F_P_H = 0
init R_F_P_H = 0

init S_F_G_H =50000*hrg
init I_F_G_H = 0
init A_F_G_H = 0
init R_F_G_H = 0

init S_M_G_H = 50000*hrg
init I_M_G_H = 0
init A_M_G_H = 1
init R_M_G_H = 0

init S_F_P_L = 50000*lrg
init A_F_P_L = 0
init R_F_P_L = 0

init S_F_G_L = 50000*lrg
init I_F_G_L = 0
init A_F_G_L = 0
init R_F_G_L = 0

init S_M_G_L = 50000*lrg
init I_M_G_L = 0
init A_M_G_L = 0
init R_M_G_L = 0
```

Appendix 2



This is a close up of only asymptomatic and symptomatic gonorrhea infections in the equilibrium-reaching phase of the model. This is to demonstrate that the model has run to equilibrium before introducing antibiotic resistance at time = 23750. Additionally, the approximate prevalence rate of around 225 symptomatic infections/ 100,000 individuals aligns somewhat closely to the CDC reported gonorrhea rate of 250 cases/ 100,000 individuals (recalculated for sexually active adults aged 18-44 using reported gonorrhea rates in 2014). Because of this alignment, we can be reasonably confident that this model is somewhat representative of reality.

Citations

1. Allen VG, Farrell DJ, Rebbapragada A, et al. Molecular analysis of antimicrobial resistance mechanisms in Neisseria gonorrhoeae isolates from Ontario, Canada. *Antimicrob Agents Chemother*. 2011;55(2):703-712. doi:10.1128/AAC.00788-10.
2. Arepeva M, Kolbin A, Kurylev A, Balykina J, Sidorenko S. What should be considered if you decide to build your own mathematical model for predicting the development of bacterial resistance? Recommendations based on a systematic review of the literature. *Front Microbiol*. 2015;6(APR). doi:10.3389/fmicb.2015.00352.
3. Ashley E a., Dhorda M, Fairhurst RM, et al. Spread of Artemisinin Resistance in Plasmodium falciparum Malaria. *N Engl J Med*. 2014;371(5):411-423. doi:10.1056/NEJMoa1314981.
4. Berkeley Madonna (2017) by R. Macey, G. Oster, T. Zahley
5. Buono SA, Watson TD, Borenstein LA, Klausner JD, Pandori MW, Godwin HA. Stemming the tide of drug-resistant Neisseria gonorrhoeae: The need for an individualized approach to treatment. *J Antimicrob Chemother*. 2015;70(2):374-381. doi:10.1093/jac/dku396.
6. CDC. 2014 Sexually Transmitted Diseases Surveillance. Centers for Disease Control and Prevention. https://www.cdc.gov/std/stats14/default.htm. Accessed March 14, 2017.
7. CDC. "NHANES - National Health and Nutrition Examination Survey Homepage." Centers for Disease Control and Prevention. N.p., 21 July 2009. Web. 14 Mar. 2017.
8. CDC. Increases in Fluoroquinolone-Resistant Neisseria gonorrhoeae Among Men Who Have Sex with Men. Centers for Disease Control and Prevention. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5316a1.htm. Accessed March 14, 2017.
9. US Census Bureau. Age and Sex Composition: 2010. https://www.census.gov/prod/cen2010/briefs/c2010br-03.pdf.
10. Chow EPF, Camilleri S, Ward C, et al. Duration of gonorrhoea and chlamydia infection at the pharynx and rectum among men who have sex with men: a systematic review. *Sexual Health*. 2016. doi:10.1071/sh15175.
11. Reece M, Herbenick D, Schick V, Sanders SA, Dodge B, Fortenberry JD. Condom Use Rates in a National Probability Sample of Males and Females Ages 14 to 94 in the United States. *The Journal of Sexual Medicine*. 2010;7:266-276. doi:10.1111/j.1743-6109.2010.02017.x.
12. Chaitra Gopalappa, Ya-Lin A. Huang, Thomas L. Gift KO-, Edusei, Melanie Taylor and VG. Cost-Effectiveness of Screening Men in Maricopa County Jails for Chlamydia and Gonorrhea to Avert Infections in Women. *Sex Transm Dis*. 2016;8(5):583-592. doi:10.1002/aur.1474.Replication.
13. Chan CH, McCabe CJ, Fisman DN. Core groups, antimicrobial resistance and rebound in gonorrhoea in North America. *Sex Transm Infect*. 2012;88(3):200-204. doi:10.1136/sextrans-2011-050049.
14. Chesson HW. Estimated effectiveness and cost-effectiveness of federally funded prevention efforts on gonorrhoea rates in the United States, 1971-2003, under various assumptions about the impact of prevention funding (Structured abstract). *Sex Transm Dis*. 2006;33(10 Supplement):140-144. doi:10.1097/01.olq.0000194575.79728.72.
15. D'Agata EMC, Dupont-Rouzeyrol M, Magal P, Olivier D, Ruan S. The impact of different antibiotic regimens on the emergence of antimicrobial-resistant bacteria. *PLoS One*. 2008;3(12):4-12. doi:10.1371/journal.pone.0004036.

16. Dube C, Garner G, Stevenson M, Sanson R, Estrada C, Willeberg P. the Use of Epidemiological Models for the Management of Animal Diseases. *OIE*. 2007
17. Eames KTD, Keeling MJ. Modeling dynamic and network heterogeneities in the spread of sexually transmitted diseases. *Proc Natl Acad Sci*. 2002;(Track II).
18. Escobar E, Durgham R, Dammann O, Stopka TJ. Agent-based computational model of the prevalence of gonococcal infections after the implementation of HIV pre-exposure prophylaxis guidelines. *Online J Public Health Inform*. 2015;7(3):e224. doi:10.5210/ojphi.v7i3.6104.
19. Ferguson NM, Cummings DAT, Fraser C, Cajka JC, Cooley PC, Burke DS. Strategies for mitigating an influenza pandemic. *Nature*. 2006;442(7101):448-452. doi:10.1038/nature04795.
20. Flynn C, Anschuetz G, Asbel L, Madera R, Johnson CC. Influence of Insurance Status and Demographic Features on Recognition of Symptomatic and Asymptomatic Gonorrhea Cases. *Sex Transm Dis*. 2015;42(8):419-421. doi:10.1097/OLQ.0000000000000308.
21. Garnett GP, Mertz KJ, Finelli L, Levine WC, St Louis ME. The transmission dynamics of gonorrhoea: modelling the reported behaviour of infected patients from Newark, New Jersey. *Philos Trans R Soc Lond B Biol Sci*. 1999;354(1384):787-797. doi:10.1098/rstb.1999.0431.
22. Gehring R, Riviere JE. Limitations of MIC as the sole criterion in antimicrobial drug dosage regimen design: The need for full characterization of antimicrobial pharmacodynamic profile especially for drug-resistant organisms. *Vet J*. 2013;198(1):15-18. doi:10.1016/j.tvjl.2013.07.034.
23. Ghani AC, Swinton J, Garnett GP. The role of sexual partnership networks in the epidemiology of gonorrhea. *Sex Transm Dis*. 1997;24(1):45-56. doi:10.1097/00007435-199701000-00009.
24. Gómez-Gardeñes J, Latora V, Moreno Y, Profumo E. Spreading of sexually transmitted diseases in heterosexual populations. *Proc Natl Acad Sci*. 2008;105(5):1399-1404. doi:10.1073/pnas.0707332105.
25. Gong Z, Lai W, Liu M, et al. Novel genes related to ceftriaxone resistance found among ceftriaxone-resistant Neisseria gonorrhoeae selected in vitro. *Antimicrob Agents Chemother*. 2016;60(4):Accepted manuscript. doi:10.1128/AAC.00149-15.
26. Grad YH, Goldstein E, Lipsitch M, White PJ. Improving Control of Antibiotic-Resistant Gonorrhea by Integrating Research Agendas Across Disciplines: Key Questions Arising From Mathematical Modeling. *J Infect Dis*. 2016;213(6):883-890. doi:10.1093/infdis/jiv517.
27. Gray RT, Beagley KW, Timms P, Wilson DP. Modeling the impact of potential vaccines on epidemics of sexually transmitted Chlamydia trachomatis infection. *J Infect Dis*. 2009;199(11):1680-1688. doi:10.1086/598983.
28. Hazel A, Marino S, Simon C. An anthropologically based model of the impact of asymptomatic cases on the spread of {Neisseria} gonorrhoeae. *J R Soc Interface*. 2015;12(106):20150067. doi:10.1098/rsif.2015.0067.
29. Hethcote HW, Yorke JA. Gonorrhea transmission dynamics and control. *Biomathematics*. 1984;56(5):1-105. http://yorke.umd.edu/papers/Hethcote-Yorke-Gonorrhea-Transmission-and-Control-1984.pdf.
30. Holmes KK, Levine R, Weaver M. Effectiveness of condoms in preventing sexually transmitted infections. *Bull World Health Organ*. 2004.
31. Hui B, Fairley CK, Chen M, et al. Oral and anal sex are key to sustaining gonorrhoea at endemic levels in MSM populations: a mathematical model. *Sex Transm Infect*. 2015;(0):1-5. doi:10.1136/sextrans-2014-051760.

32. IDSA. Potential Emergence of Multi-Drug Resistant Gonorrhea Cephalosporins are the last line of. *IDSA Call to Action*. 2010:2010-2011.
33. Johnson LF, Geffen N. A Comparison of Two Mathematical Modeling Frameworks for Evaluating Sexually Transmitted Infection Epidemiology. *Sex Transm Dis*. 2016;43(3):139-146. doi:10.1097/OLQ.0000000000000412.
34. Kenyon CR, Osbak K, Vandenbruane M. What is the appropriate therapy for asymptomatic gonorrhoea in men who have sex with men? *Int J STD AIDS*. 2016;27(9):812-813. doi:10.1177/0956462416642933.
35. Kreisel K, Torrone E, Bernstein K, Hong J, Gorwitz R. Prevalence of Pelvic Inflammatory Disease in Sexually Experienced Women of Reproductive Age — United States, 2013–2014. *MMWR Morb Mortal Wkly Rep*. 2017;66(3):80-83. doi:10.15585/mmwr.mm6603a3.
36. Kretzschmar M, Van Duynhoven YT, Severijnen AJ. Modeling prevention strategies for gonorrhea and Chlamydia using stochastic network simulations. *Am J Epidemiol*. 1996;144(3):306-317.
37. Lewis DA. Will targeting oropharyngeal gonorrhoea delay the further emergence of drug-resistant Neisseria gonorrhoeae strains? *Sex Transm Infect*. 2015:sextrans-2014-051731-. doi:10.1136/sextrans-2014-051731.
38. Lopez LM, Otterness C, Chen M, Steiner M, Gallo MF. Behavioral interventions for improving condom use for dual protection. *Cochrane Database Syst Rev*. 2013;10(10):CD010662. doi:10.1002/14651858.CD010662.pub2.
39. Low N, Unemo M, Skov Jensen J, Breuer J, Stephenson JM. Molecular Diagnostics for Gonorrhoea: Implications for Antimicrobial Resistance and the Threat of Untreatable Gonorrhoea. *PLoS Med*. 2014;11(2). doi:10.1371/journal.pmed.1001598.
40. Lynagh Y, Mac Aogáin M, Walsh A, Rogers TR, Unemo M, Crowley B. Detailed characterization of the first high-level azithromycin-resistant Neisseria gonorrhoeae cases in Ireland. *J Antimicrob Chemother*. 2015;70(8):2411-2413. doi:10.1093/jac/dkv106.
41. Marshall J. Modeling of Infectious Disease Class. 2016.
42. Metcalf CJE, Edmunds WJ, Lessler J. Six challenges in modelling for public health policy. *Epidemics*. 2015;10:93-96. doi:10.1016/j.epidem.2014.08.008.
43. Moghadas S, Haworth-Brockman M, Isfeld-Kiely H, Kettner J. Improving public health policy through infection transmission modelling: Guidelines for creating a community of practice. *Can J Infect Dis Med Microbiol*. 2015;26(4):191-195. http://www.pulsus.com/journals/pdf_frameset.jsp?jnlKy=3&atlKy=13592&isArt=t&jnlAdvert=Infdis&adverifHCTp=&sTitle=Improving public health policy through infection transmission modelling: Guidelines for creating a Community of Practice, Pulsus Group Inc&HCt.
44. Nordgren J, Sharma S, Bucardo F, et al. Genomic epidemiology of gonococcal resistance to extended spectrum cephalosporins, macrolides, and fluoroquinolones in the US, 2000-2013. *J Infect Dis*. 2014:1-17.
45. Ong JJ, Fethers K, Howden BP, et al. Asymptomatic and symptomatic urethral gonorrhoea in men who have sex with men attending a sexual health service. *Clin Microbiol Infect*. 2017. doi:10.1016/j.cmi.2017.02.020.
46. Perlroth DJ, Glass RJ, Davey VJ, Cannon D, Garber AM, Owens DK. Health Outcomes and Costs of Community Mitigation Strategies for an Influenza Pandemic in the United States. *Clin Infect Dis*. 2010;50(2):165-174. doi:10.1086/649867.
47. Prats C, Montañola-Sales C, Gilabert-Navarro JF, et al. Individual-based modeling of tuberculosis in a user-friendly interface: Understanding the epidemiological role of

population heterogeneity in a city. *Front Microbiol*. 2016;6(JAN):1-13. doi:10.3389/fmicb.2015.01564.
48. Price MJ, Ades AE, De Angelis D, et al. Risk of pelvic inflammatory disease following chlamydia trachomatis infection: Analysis of prospective studies with a multistate model. *Am J Epidemiol*. 2013;178(3):484-492. doi:10.1093/aje/kws583.
49. Scott N, McBryde E, Kirwan A, Stoové M. Modelling the impact of condom distribution on the incidence and prevalence of sexually transmitted infections in an adult male prison system. *PLoS One*. 2015;10(12):1-14. doi:10.1371/journal.pone.0144869.
50. Smith KJ, Cook RL, Ness RB. Cost comparisons between home- and clinic-based testing for sexually transmitted diseases in high-risk young women. *Infect Dis Obstet Gynecol*. 2007;2007(di). doi:10.1155/2007/62467.
51. Spicknall IH, Foxman B, Marrs CF, Eisenberg JNS. A modeling framework for the evolution and spread of antibiotic resistance: Literature review and model categorization. *Am J Epidemiol*. 2013;178(4):508-520. doi:10.1093/aje/kwt017.
52. Trecker MA, Hogan DJ, Waldner CL, Dillon J-AR, Osgood ND. Revised simulation model does not predict rebound in gonorrhoea prevalence where core groups are treated in the presence of antimicrobial resistance. *Sex Transm Infect*. 2015;91(4):300-302. doi:10.1136/sextrans-2014-051792.
53. Unemo M, Shafer M. Antimicrobial Resistance in Neisseria gonorrhoeae in the 21st Century : Past , Evolution , and Future. *Clin Microbiol Rev*. 2014;27(3):587-613. doi:10.1128/CMR.00010-14.
54. Unemo M, Shafer WM. Antibiotic resistance in Neisseria gonorrhoeae: origin, evolution, and lessons learned for the future. *Ann N Y Acad Sci*. 2015:1-15. doi:10.1111/j.1749-6632.2011.06215.x.Antibiotic.
55. Warner L, Newman DR, Kamb ML, et al. Problems with condom use among patients attending sexually transmitted disease clinics: Prevalence, predictors, and relation to incident gonorrhea and chlamydia. *Am J Epidemiol*. 2008;167(3):341-349. doi:10.1093/aje/kwm300.
56. Weinstock H, Workowski K a. Pharyngeal gonorrhea: an important reservoir of infection? *Clin Infect Dis*. 2009;49(12):1798-1800. doi:10.1086/648428.
57. Wilensky, U. NetLogo. http://ccl.northwestern.edu/netlogo/ 1999. Center for Connected Learning and Computer-Based Modeling, Northwestern University, Evanston, IL.
58. Wilkinson AL, Pedrana AE, El-Hayek C, et al. The Impact of a Social Marketing Campaign on HIV and Sexually Transmissible Infection Testing Among Men Who Have Sex With Men in Australia. *Sex Transm Dis*. 2016;43(1):49-56. doi:10.1097/OLQ.0000000000000380.
59. Vynnycky E, White RG. An introduction to infectious disease modelling. Oxford: Oxford Univ. Press; 2011.
60. Xiridou M, Lugnér A, de Vries HJC, et al. Cost-effectiveness of dual antimicrobial therapy for gonococcal infections among men who have sex with men in the Netherlands. *Sex Transm Dis*. 2016;43(9):542-548. doi:10.1097/OLQ.0000000000000480.
61. Yeh J, Hook E, Goldie S. A Refined Estimate of the Average Lifetime Cost of Pelvic Inflammatory disease. *Sex Transm Dis*. 2002:143-204.