

Minimizing Drug Resistant Cases of Gonorrhea through Cost-Effective Treatment Plans

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Abstract

Gonorrhea, caused by the bacterium *Neisseria gonorrhoeae*, is the second most common bacterial sexually transmitted infection (STI) with a reported 87 million new cases worldwide, according to the World Health Organization (WHO). Gonorrhea has developed resistance to multiple treatment therapies within the past century due to the introduction and misuse of antibiotics. This develops a posing threat of an untreatable infection of drug resistant gonorrhea and a global health crisis. We aim to study a comprehensive treatment strategy with respect to drug resistance in gonorrhea and cost effectiveness. We develop a mathematical model of gonorrhea's resistance to the two dual treatments recommended by the WHO, ceftriaxone with azithromycin and cefixime with azithromycin. Our cost benefit analysis compares several suggested treatment plans to minimize the emergence of drug resistance. We numerically simulate our model and analyze the reproductive number based on estimated parameters. As a result this study found that the costs are minimized if more than 50 % of individuals are successfully treated.

1 Introduction

Gonorrhea, an infection caused by the bacterium *Neisseria gonorrhoeae* is one of the most prevalent sexually transmitted infections (STIs). The World Health Organization (WHO) estimates that in 2018, there were 78 million cases among adults worldwide [23]. Between 2013-2018, the number of cases in the United States increased by 67% [8]. The infection can be passed by sexual touching or intercourse as well as vaginal childbirth. Areas affected by the infection, in both men and women, include the reproductive tract, oral cavity, and the rectum. Infected individuals may be symptomatic, but 55% men and 86% women with gonorrhea are asymptomatic [13]. For individuals who display symptoms, they may experience abdominal or pelvic pain or genital abnormalities. An untreated case of gonorrhea can cause future health complications ranging in severity. Scar tissue development in the fallopian tubes, ectopic pregnancy, infertility, abdominal pain, and fever may occur in women, while men may experience complications such as epididymitis or infertility. A person with untreated gonorrhea is also more likely to develop other diseases like pelvic inflammatory disease (PID) or human immunodeficiency virus (HIV) [8].

The use of antibiotic must be closely monitored during the course of treatment, due to bacteria susceptibility to the drug [7]. Development of drug resistance occurs when harmful bacteria infects the body, a portion of the bacteria will have a greater immunity to antibiotics than others. A small proportion of the bacteria may be resistant to the antibiotic and continue to multiply, grow, and develop defensive mechanisms. Antibiotic resistant bacteria have the ability to pass on their resistance to other non-resistant bacteria [7]. Other possible ways for antibiotic resistance to occur is to change cell membrane structure, neutralizing, or pumping out the antibiotic, thus causing the bacteria to become resistant [6]. The Center for Disease Control and Prevention (CDC) highly recommends to complete antibiotic treatment as prescribed from a physician to decrease the potential for drug resistance, Figure 1 was adapted from the Center of Disease Control and Prevention to depict drug-resistant development in bacteria [6].

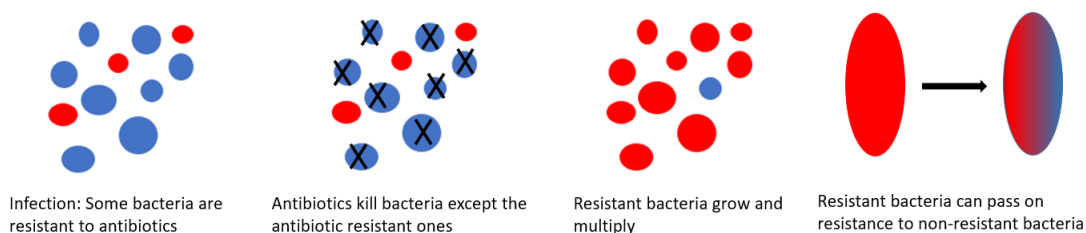


Figure 1: Antibiotic Resistance

The first course of treatment to cure gonorrhea was sulfonamides in the mid-1930s until reported cases of resistance, in Figure 1 a timeline developed from the CDC and [31] to show case the treatment and drug-resistant prevalence [2, 18, 31]. The introduction of antibiotics has caused an increase of various treatment protocols for gonorrhea, due to frequent and diverse drug-resistant strains. Penicillin was an effective antibiotic because of the gonococci being easily susceptible to it [20, 31]. Dosage for penicillin increased after 10 to 15 years which led to rising numbers

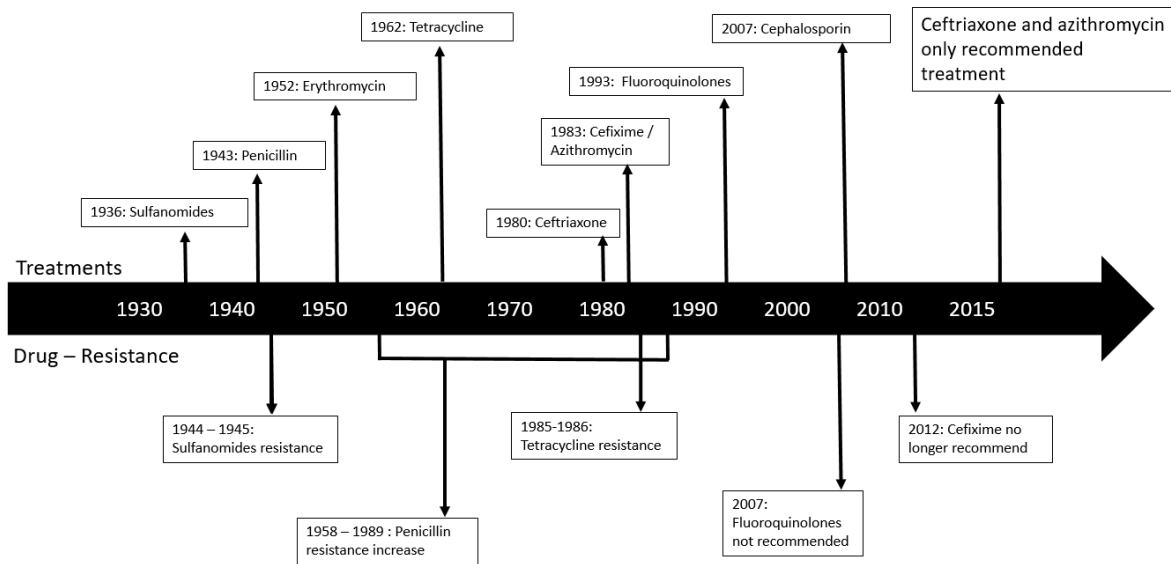


Figure 2: Treatment and Resistance Timeline

of penicillin-resistant gonorrhea [31, 34]. Aminoglycosides, macrolides, and tetracycline were used as a second line antibiotics when penicillin-resistant gonorrhea occurred. By the mid 1980s, tetracycline was no longer a recommended treatment due to reported cases of resistance [10, 31]. The introduction of ciprofloxacin, a fluoroquinolone, showed an increase of treatable gonorrhea cases, however resistance was eventually reached as well [31]. By 2007, resistance to fluoroquinolones caused the CDC to remove it as a recommended treatment [9, 25, 31]. Cefixime and ceftriaxone, third generation cephalosporin's, at low doses are now the new line of defense. Alike the previous treatments for gonorrhea, there have been reports of cefixime and ceftriaxone resistance [26, 28, 31, 35]. As of 2016, the World Health organization (WHO) recommends treatment for gonorrhea as a dual therapy of a single dose of 250 mg of ceftriaxone taken intramuscularly (IM) and a single dose of 1g of azithromycin taken orally or a single dose of 400 mg of cefixime taken orally and a single dose of 1 g of azithromycin taken orally [23]. In the United States, the CDC recommends the dual therapy consisting of ceftriaxone and azithromycin as a first line defense, and recommends cefixime only if ceftriaxone is unavailable or a known resistance to ceftriaxone exists. They emphasize the importance of dual treatment rather than use of a single antibiotic to ensure a cure in the face of antibiotic resistance, and to prevent further resistance [5].

Gonorrhea, drug-resistant gonorrhea, and drug resistance to gonorrhea can be modeled in various formats depending on the scope of the situation. If the scope is the spread of gonorrhea on a microbial level, the use of a system of ordinary differential equations (ODEs) can model the resistance to bactericidal and bacteriostatic. When the study is based on how the disease is spread throughout a given population, mathematical models such as surveillance and dynamical transmissional modeling can be used. Surveillance on the number of cases of the disease in a population can be collected and determine the rate at which a certain strain can increase in resistance [14]. For exam-

ple, a study conducted in Alberta, Canada [12,32] focused on the antibiotic resistance in gonorrhea through surveillance of antimicrobial resistance (AMR). The Alberta model looked at culture and nucleic acid amplification test (NAAT) specimens from various sites. Cultures were tested for penicillin, tetracycline, cefixime, ceftriaxone, ciprofloxacin, and azithromycin resistance. The purpose of this model is to maintain the surveillance of antimicrobial resistance in gonorrhea for the determination of treatment guidelines [12, 24, 30]. Surveillance data is also used to estimate the rate at which drug-resistant gonorrhea has spread in heterosexual males and men who have sex with men (MSM). The dynamic transmission model focused on prevalence and incidence rates, thus showing the treatment rates of heterosexual men and MSM. The rate of spread was labeled with high importance, since it details the increase of treatment rates cause a faster antibiotic resistance spread compared to having multiple partners [4]. In a study in South Africa [15–17, 19], dynamic transmission modeling was used to see sexually transmitted infection (STIs) trends. Results from dynamic transmission model may show how STIs are spread but can't account for underlying assumptions that may be unrealistic [19]. Surveillance and dynamic modeling are not the only ways gonorrhea can be modeled, but other studies have shown using a fitness cost in the population of men who had sex with men (MSM) and cefixime resistance only [29]. Another mathematical model ([27]) has looked at the rapid diagnostics for antibiotic susceptibility and the effect it has on usefulness of antibiotic treatments. Several cases were taken into consideration regarding Point-of-Care testing to determine resistance in the treatment chosen.

In contrast, our proposed model compares two dual treatments, ceftriaxone with azithromycin and cefixime with azithromycin, in a population of all sexually active Americans. The WHO recommends treating gonorrhea with a dual treatment of 1g of azithromycin and one of the following: 250 mg of ceftriaxone or 400 mg of cefixime [23]. However, the CDC only recommends a dual treatment of 1 g azithromycin and 250 mg ceftriaxone but not cefixime [7]. We aim to observe what happens to the number of drug resistant cases when we introduce a second treatment option to the current CDC recommendation. By using a SIS based model we determine the development of resistance in gonorrhea, focusing on treatment type and misuse of the treatment. The proportion of people manifesting symptoms varies between men and women, and whether or not someone shows symptoms impacts how long it takes them to get treated [8]. Our work focuses on six cases regarding time until treatment (1) female, (2) male, (3) average of presenting symptoms in female and male, (4) asymptomatic, (5) symptomatic, and (6) average of asymptomatic and symptomatic. We then find and compare the cost effective treatment plans to combat drug resistant gonorrhea in each population. In this study we also analyze the cost effectiveness of treatment strategies to treat and reduce gonorrhea cases.

2 Methods

In order to model the dynamics of gonorrhea infection we assume that there is no multi-drug resistance; a strain of gonorrhea can be resistant to ceftriaxone or cefixime, but not both. Following from the first assumption, we assume that if somebody is infected with gonorrhea, they can be cured using at least one of the two treatments in the model. Although there have been a few cases

of untreatable gonorrhea, the CDC has not received any reports of it in the United States [3, 8]. According to the CDC, azithromycin resistance is rare in the United States, and the model focuses on limiting resistant cases of the other two drugs [7]. Additionally, we assume no disease death because gonorrhea alone is not a life-threatening disease [8]. In our model, every infected person eventually develops symptoms or complications at which point we assume they immediately seek treatment. We also assume that there are no false positives/negatives in testing, and that as soon as a person is treated, although they are not yet cured, they are no longer infectious.

We use a Susceptible-Infected-Susceptible (SIS) like model which incorporates the addition of treatment classes. The class S represents our susceptible population of all sexually active Americans. Susceptible people can become infected with gonorrhea through sexual contact and move to one of the infected classes of I depending on which strain they have. If the gonorrhea strain is drug sensitive, meaning it is resistant to either ceftriaxone nor cefixime, then the infected individual moves to I_S . The individual takes t_s days to show symptoms at which point they go to the doctor and get a diagnosis after t_d days. Then, a proportion p of infected people are assigned to treatment 1, 250mg ceftriaxone plus 1g azithromycin, and the rest are assigned to treatment 2, 400mg cefixime plus 1g azithromycin. They move to T_1 or T_2 depending on which treatment is assigned. Once someone reaches the T class there are two possibilities: an individual could complete their treatment and become susceptible again after γ_1 or γ_2 days depending on their treatment class. Alternatively, the medicine could be mishandled by the doctors or stored improperly and cause the gonorrhea in their body to develop resistance to the treatment. In this case, since the individual is not cured they would move from T_1 to I_1 or from T_2 to I_2 . The patient then goes back to the doctor to get tested and after being diagnosed, they receive the alternative treatment from what they originally received. So individuals in I_1 will move to V_2 where they are given treatment 2, and individuals in I_2 will move to V_1 where they are given treatment 1. Finally they are cured and moved back to S . However, if the strain is resistant to treatment 1 from inception, they move directly from S to I_1 , and similarly if it is resistant to treatment 2 from inception they move directly from S to I_2 . From there, they follow the same path as those who developed drug resistance. The

Equation (1) represents our model:

$$\begin{aligned}
\frac{dS}{dt} &= \mu N - \frac{\beta S}{N}(I_S + I_1 + I_2) + q\gamma_1 T_1 + q\gamma_2 T_2 + \gamma_1 V_1 + \gamma_2 V_2 - \mu S, \\
\frac{dI_s}{dt} &= \frac{\beta I_s}{N} S - \mu I_s - \tau_s I_s, \\
\frac{dI_1}{dt} &= \frac{\beta I_1}{N} S - \mu I_1 - \tau_1 I_1 + (1-q)\gamma_1 T_1, \\
\frac{dI_2}{dt} &= \frac{\beta I_2}{N} S - \mu I_2 - \tau_2 I_2 + (1-q)\gamma_2 T_2, \\
\frac{dT_1}{dt} &= p\tau_s I_s - (\mu + \gamma_1) T_1, \\
\frac{dT_2}{dt} &= (1-p)\tau_s I_s - (\mu + \gamma_2) T_2, \\
\frac{dV_1}{dt} &= \tau_2 I_2 - (\mu + \gamma_1) V_1, \\
\frac{dV_2}{dt} &= \tau_1 I_1 - (\mu + \gamma_2) V_2,
\end{aligned}
\tag{1}$$

$$N = S + I_s + I_1 + I_2 + T_1 + T_2 + V_1 + V_2 \tag{2}$$

where $\beta = c\beta_c$ is transmission rate. The Figure (3) shows the schematic diagram of our model. State variables and parameter definitions, and their units of measurement are listed in Table (1).

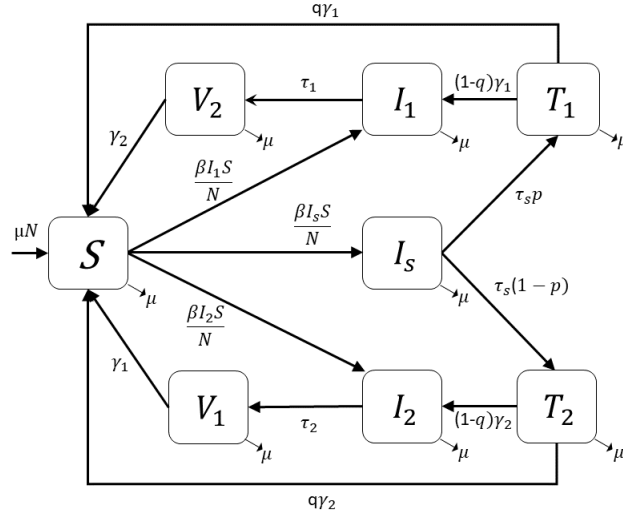


Figure 3: The Schematic of Model

Although μ is defined as the natural birth/death rate, it should be considered the start and end of sexual activity over a period of time. For example, someone who practices abstinence will not be considered part of the population, N . If later on they decide to start having sexual encounters

(that would be sufficient enough to put them at risk of contracting gonorrhoea) then they would be entered into the population and this would be considered a natural birth into the population. On the other hand, if someone who is having sexual encounters ends up abstaining from sexual encounters this would be considered as a natural death because they are being withdrawn from the population.

State Variable	Definition
N	Total Population
S	Susceptible
I_S	Drug-susceptible infection
I_1	Drug 1 - resistant infection
I_2	Drug 2 - resistant infection
T_1	First Line of Treatment 1
T_2	First Line of Treatment 2
V_1	Second Line of Treatment 1
V_2	Second Line of Treatment 2

Parameter	Definition	Units
μ	Natural birth/death rate	$\frac{1}{days}$
c	Total number of sexual encounters per time	$\frac{act}{days}$
q	Proportion of people who completed treatment	-
β_c	Probability of transmission per act	$\frac{1}{act}$
γ_1	Rate of completion of treatment 1	$\frac{1}{days}$
γ_2	Rate of completion of treatment 2	$\frac{1}{days}$
t_s	Time for symptoms to occur	days
t_d	Time to diagnostics	days
τ	Treatment rate	$\frac{1}{days}$
p	Proportion of people assigned T_1	-

Table 1: State variable, parameters and their definitions

3 Stability Analysis

In our model, we assume that the total population is constant and $N = S + I_S + I_1 + I_2 + T_1 + T_2 + V_1 + V_2$. There are four equilibrium points in this model denoted E_i with $i = 1, 2, 3, 4$ using the notation:

$$E_i = (S^*, I_S^*, I_1^*, I_2^*, T_1^*, T_2^*, V_1^*, V_2^*).$$

The *first* equilibrium point is the Disease Free Equilibrium (DFE), as implied, this is defined as the equilibrium where there are no infected individuals within the population. This means that I_s , I_1 and I_2 must be equal to zero, since there are no infected individuals then there are no treatments and thus T_1, T_2, V_1, V_2 must equal to zero as well. This leaves the entire population as susceptible. Then, the DFE is given by:

$$E_1 = (N, 0, 0, 0, 0, 0, 0, 0)$$

The *second* and *third* equilibrium points describe when the gonorrhoea bacteria become completely resistant to treatment 1 or treatment 2, respectively. This means there's only one resistant strain left. That is, the *second* equilibrium point is when only treatment 1 will cure the infection since all the bacteria have become resistant to treatment(drug) 2. Once the bacteria have become resistant to treatment 2, T_2 and V_2 will equal to zero indicating that the treatment is no longer used. It also follows that I_s and I_1 must also equal to zero because the bacteria are all strain I_2 and can only be treated by V_1 . This equilibrium is defined by:

$$E_2 = \left(\frac{N(\mu + \tau_2)}{\beta}, 0, 0, \frac{N(\mu + \gamma_1)(\beta - \mu - \tau_2)}{\beta(\mu + \gamma_1 + \tau_2)}, 0, 0, \frac{N\tau_2(\beta - \mu - \tau_2)}{\beta(\mu + \gamma_1 + \tau_2)}, 0 \right)$$

The *third* equilibrium is exactly like the second equilibrium except only treatment 2 will cure the infection since all the bacterium have become resistant to treatment(drug) 1. Similarly, T_1, V_1, I_s and I_2 will equal zero. This equilibrium is defined by:

$$E_3 = \left(\frac{N(\mu + \tau_1)}{\beta}, 0, \frac{N(\mu + \gamma_2)(\beta - \mu - \tau_1)}{\beta(\mu + \gamma_2 + \tau_1)}, 0, 0, 0, 0, \frac{N\tau_1(\beta - \mu - \tau_1)}{\beta(\mu + \gamma_2 + \tau_1)} \right)$$

The *last* equilibrium represents a mixture of drug susceptible strains as well as treatment 1 and 2 resistant strains; therefore, every treatment option is used here. So we have an interior equilibrium:

$$E_4 = \left(\frac{N(\tau_s + \mu)}{\beta}, \frac{M(\mu + \gamma_2)}{\tau_s(1-p)}, \frac{Mp(1-q)(\mu + \gamma_2)\gamma_1}{(1-p)(\tau_1 - \tau_s)(\mu + \gamma_1)}, \frac{M(1-q)\gamma_2}{\tau_2 - \tau_s}, \frac{Mp(\mu + \gamma_2)}{(1-p)(\mu + \gamma_1)}, M, \frac{M(1-q)\gamma_2\tau_2}{(\tau_2 - \tau_s)(\mu + \gamma_1)}, \frac{Mp(1-q)\tau_1\gamma_1}{(1-p)(\tau_1 - \tau_s)(\mu + \gamma_1)} \right)$$

where

$$M = \frac{N\tau_s(\beta - \tau_s - \mu)(1-p)(\tau_s - \tau_1)(\tau_s - \tau_2)(\mu + \gamma_1)}{\beta(p\tau_s(\tau_s - \tau_2)U + V + (1-p)\tau_s(\tau_s - \tau_1)W)}$$

and

$$\begin{aligned} U &= (q - 1)\gamma_1(\mu + \gamma_2 + \tau_1) + (\mu + \gamma_2 + \tau_1) + (\mu + \gamma_2)(\tau_s - \tau_1) \\ V &= (\mu + \gamma_1)(\mu + \gamma_2)(\tau_s - \tau_1)(\tau_s - \tau_2) \\ W &= \gamma_2(q - 1)(\mu + \gamma_1 + \tau_2) + (\mu + \gamma_1)(\tau_s - \tau_2) \end{aligned}$$

The basic reproductive number, R_0 is the average of secondary number of gonorrhoea caused by an infected individual from the susceptible population. Given the disease free equilibrium point $E_1 = (N, 0, 0, 0, 0, 0, 0, 0)$, R_0 can be determined from the next generation operator.

Matrix X represents the vector of infected classes of gonorrhoea. F is the vector of new infection rates of gonorrhoea, where as, V represents all other rates excluding new infection rates.

$$X = \begin{bmatrix} I_S \\ I_1 \\ I_2 \end{bmatrix}, F = \begin{bmatrix} \frac{\beta I_S S}{N} \\ \frac{\beta I_1 S}{N} \\ \frac{\beta I_2 S}{N} \end{bmatrix}, V = \begin{bmatrix} \tau_s I_S + \mu I_S \\ \tau_1 I_1 + \mu I_1 + (q-1)\gamma_1 T_1 \\ \tau_2 I_2 + \mu I_2 + (q-1)\gamma_2 T_2 \end{bmatrix}$$

For \mathcal{F} , the partial derivative of F with respect to I_S, I_1, I_2 is taken. The partial derivative of V with respect to X is given by \mathcal{V} .

$$\mathcal{F} = \begin{bmatrix} \frac{\beta S}{N} & 0 & 0 \\ 0 & \frac{\beta S}{N} & 0 \\ 0 & 0 & \frac{\beta S}{N} \end{bmatrix}, \mathcal{V} = \begin{bmatrix} \tau_s + \mu & 0 & 0 \\ 0 & \tau_1 + \mu & 0 \\ 0 & 0 & \tau_2 + \mu \end{bmatrix}$$

\mathcal{F} and \mathcal{V} evaluated at Disease Free Equilibrium are given by:

$$\mathcal{F}|_{DFE} = \begin{bmatrix} \beta & 0 & 0 \\ 0 & \beta & 0 \\ 0 & 0 & \beta \end{bmatrix}, \mathcal{V}^{-1}|_{DFE} = \begin{bmatrix} \frac{1}{\tau_s + \mu} & 0 & 0 \\ 0 & \frac{1}{\tau_1 + \mu} & 0 \\ 0 & 0 & \frac{1}{\tau_2 + \mu} \end{bmatrix}$$

Hence, the next generation matrix is given by:

$$\mathcal{F}\mathcal{V}^{-1}|_{DFE} = \begin{bmatrix} \frac{\beta}{\tau_s + \mu} & 0 & 0 \\ 0 & \frac{\beta}{\tau_1 + \mu} & 0 \\ 0 & 0 & \frac{\beta}{\tau_2 + \mu} \end{bmatrix}$$

R_0 is determined by the spectral radius of $\mathcal{F}\mathcal{V}^{-1}$. So we obtain $R_0 = \max\left\{\frac{\beta}{\mu + \tau_s}, \frac{\beta}{\mu + \tau_1}, \frac{\beta}{\mu + \tau_2}\right\}$.

3.1 Stability Analysis of Equilibrium

We study the existence and stability conditions for the equilibrium points of the system.

Biologically, all of our compartment populations must be nonnegative. We observe the existence and stability condition at each equilibrium point of the system.

The Jacobian matrix of the model is:

$$J = \begin{bmatrix} \frac{-\beta I}{N} - \mu & \frac{-\beta S}{N} & \frac{-\beta S}{N} & \frac{-\beta S}{N} & q\gamma_1 & q\gamma_2 & \gamma_1 & \gamma_2 \\ \frac{\beta I_s}{N} & \frac{\beta S}{N} - (\mu + \tau_s) & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\beta I_1}{N} & 0 & \frac{\beta S}{N} - (\mu + \tau_1) & 0 & (1-q)\gamma_1 & 0 & 0 & 0 \\ \frac{\beta I_2}{N} & 0 & 0 & \frac{\beta S}{N} - (\mu + \tau_2) & 0 & (1-q)\gamma_2 & 0 & 0 \\ 0 & p\tau_s & 0 & 0 & -(\mu + \gamma_1) & 0 & 0 & 0 \\ 0 & (1-p)\tau_s & 0 & 0 & 0 & -(\mu + \gamma_2) & 0 & 0 \\ 0 & 0 & 0 & \tau_2 & 0 & 0 & -(\mu + \gamma_1) & 0 \\ 0 & 0 & \tau_1 & 0 & 0 & 0 & 0 & -(\mu + \gamma_2) \end{bmatrix}$$

The Jacobian matrix around E_2 is:

$$J|_{E_2} = \begin{bmatrix} \frac{(\mu + \gamma_1)(\mu + \tau_2 - \beta)}{\mu + \gamma_1 + \tau_2} - \mu & -(\mu + \tau_2) & -(\mu + \tau_2) & -(\mu + \tau_2) & q\gamma_1 & q\gamma_2 & \gamma_1 & \gamma_2 \\ 0 & \tau_2 - \tau_s & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \tau_2 - \tau_1 & 0 & (1-q)\gamma_1 & 0 & 0 & 0 \\ \frac{(\mu + \gamma_1)(\mu + \tau_2 - \beta)}{\mu + \gamma_1 + \tau_2} - \mu & 0 & 0 & 0 & 0 & (1-q)\gamma_2 & 0 & 0 \\ 0 & p\tau_s & 0 & 0 & -(\mu + \gamma_1) & 0 & 0 & 0 \\ 0 & (1-p)\tau_s & 0 & 0 & 0 & -(\mu + \gamma_2) & 0 & 0 \\ 0 & 0 & 0 & \tau_2 & 0 & 0 & -(\mu + \gamma_1) & 0 \\ 0 & 0 & \tau_1 & 0 & 0 & 0 & 0 & -(\mu + \gamma_2) \end{bmatrix}$$

The characteristic polynomial of the matrix $J|_{E_2}$ is:

$$p_2(\lambda) = \frac{(\lambda^2(-\mu - \tau_2 - \gamma_1) - \lambda(\beta + \gamma_1)(\mu + \gamma_1) + (\mu + \gamma_1)(\mu + \gamma_1 + \tau_2)(\mu - \beta + \tau_2))(\mu + \lambda + \gamma_1)(\lambda + \tau_1 - \tau_2)(\lambda + \tau_s - \tau_2)(\mu + \lambda)(\mu + \lambda + \gamma_2)^2}{\mu + \gamma_1 + \tau_2}$$

The eigenvalues of the characteristic polynomial are:

$$\lambda_1 = \tau_2 - \tau_s, \lambda_2 = \tau_2 - \tau_1, \lambda_3 = -\mu, \lambda_4 = -\mu - \gamma_1, \lambda_5 = \frac{a - b}{\mu + \gamma_1 + \tau_2}, \lambda_6 = -\frac{a + b}{\mu + \gamma_1 + \tau_2},$$

$$\lambda_7 = -\mu - \gamma_2, \lambda_8 = -\mu - \gamma_2.$$

where $a = \sqrt{(\mu + \gamma_1) \left(\tau_2^3 + (3\mu - \beta + 2\gamma_1)\tau_2^2 + (\mu + \gamma_1)(3\mu - 2\beta + \gamma_1)\tau_2 + (\mu + \gamma_1) \left(\mu - \frac{\beta}{2} + \frac{\gamma_1}{2} \right)^2 \right)}$
and $b = (\mu + \gamma_1)(\beta + \gamma_1)$.

From the value of λ_5 , the denominator is positive. Hence, we can see that λ_5 and λ_6 have negative real parts when $a - b < 0$. We define the reproductive number of E_2 for stability as $R_1 = \max\left\{\frac{\tau_2}{\tau_s}, \frac{\tau_2}{\tau_1}, \frac{a}{b}\right\}$.

As a result equilibrium E_2 exists when $\beta > \mu + \tau_2$, and E_2 is locally stable if $\tau_2 < \tau_s, \tau_2 < \tau_1$ and $a - b < 0$. So E_2 exists and is stable when $R_0 > 1$ and $R_1 < 1$, Figure(4).

We can calculate the Jacobian matrix around E_3 by using the same approach as E_2 . We can obtain:

The characteristic polynomial of the matrix $J|_{E_3}$ is:

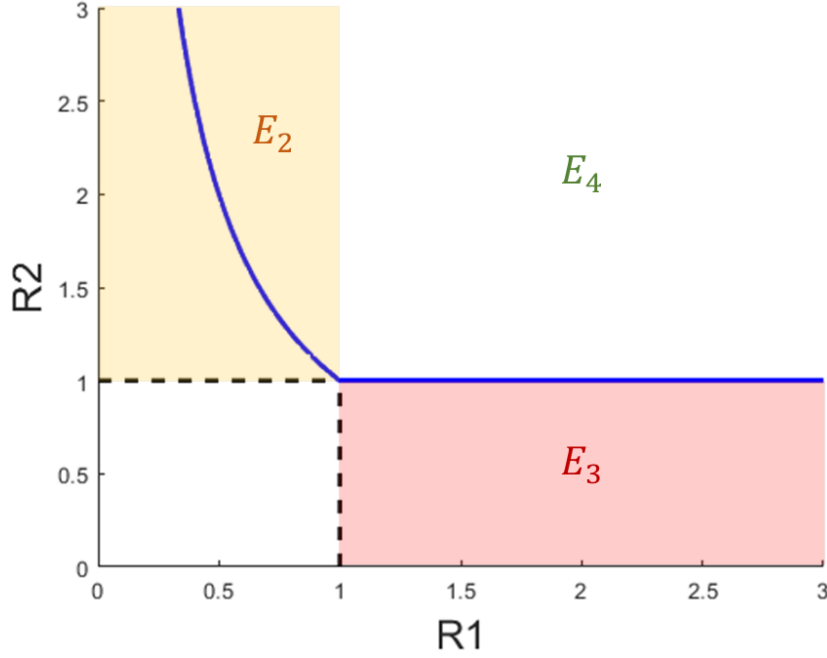


Figure 4: E_2 exists and is stable (blue line): if $R_1 < 1$ based on $R_0 > 1$.

$$p_3(\lambda) = \frac{((\lambda^2(-\mu-\tau_1-\gamma_2)-\lambda(\beta+\gamma_2)(\mu+\gamma_2)+(\mu+\gamma_2)(\mu+\gamma_2+\tau_1)(\mu-\beta+\tau_1))(\mu+\lambda+\gamma_2)(\lambda+\tau_2-\tau_1)(\lambda+\tau_s-\tau_1)(\mu+\lambda)(\mu+\lambda+\gamma_1)^2}{\mu+\gamma_2+\tau_1}$$

The eigenvalues of the characteristic polynomial are:

$$\lambda_1 = \tau_1 - \tau_s, \lambda_2 = \tau_1 - \tau_2, \lambda_3 = -\mu, \lambda_4 = -\mu - \gamma_1, \lambda_5 = \frac{c - d}{\mu + \gamma_2 + \tau_1}, \lambda_6 = -\frac{c + d}{\mu + \gamma_2 + \tau_1},$$

$$\lambda_7 = -\mu - \gamma_1, \lambda_8 = -\mu - \gamma_1.$$

Where

$$c = \sqrt{(\mu + \gamma_2) \left(\tau_1^3 + (3\mu - \beta + 2\gamma_2)\tau_1^2 + (\mu + \gamma_2)(3\mu - 2\beta + \gamma_2)\tau_1 + (\mu + \gamma_2) \left(\mu - \frac{\beta}{2} + \frac{\gamma_2}{2} \right)^2 \right)}$$

and $d = (\beta + \gamma_2)(\mu + \gamma_2)$.

From the values of λ_5 , the denominator is positive. Hence, we can see that λ_5 has negative real parts when $c - d < 0$. We define the reproductive number of E_2 for stability as $R_2 = \max\{\frac{\tau_1}{\tau_s}, \frac{\tau_1}{\tau_2}, \frac{c}{d}\}$.

As a result, if $R_0 > 1$ and $R_2 < 1$, then the equilibrium E_3 exists and it is locally stable, Figure(5).

For E_4 , we get $M > 0$ when U, V, W is satisfied $U < 0, V > 0, W < 0$. This condition is the same as $\tau_s < \tau_1$. Then the other compartments population is positive if $M > 0$ and $\beta > \mu + \tau_s$. Hence, we have a positive equilibrium E_4 if $R_0 > 1$ and $\tau_s < \tau_1$, and $\tau_s < \tau_2$. The stability analysis of E_4 is complicated. Hence, we will be running simulations and present the results in section 4.

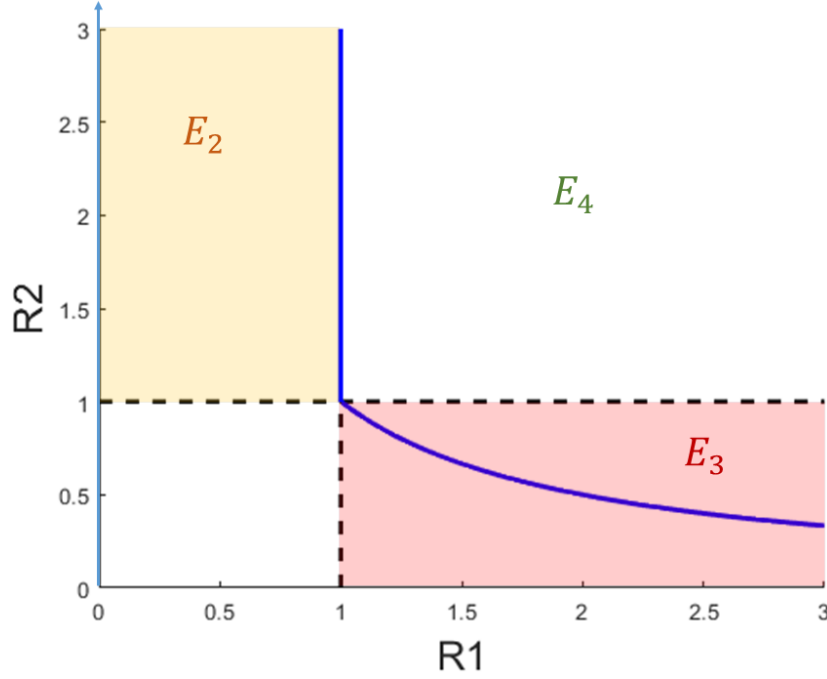


Figure 5: E_3 exists and is stable (blue line): if $R_2 < 1$ based on $R_0 > 1$.

4 Numerical Results

This section evaluates how drug resistance develops over time. All the parameter values are at the baseline in Table (2) unless stated otherwise. The numerical simulations were made using MatLab and Mathematica codes and the equations were solved using ode45.

Figure 7 represents the time-series of infection states for three different p values: $p = 0, \frac{1}{2}$, and 1. The analysis and behavior of the infected individuals is similar for different τ values; in fact, the results were not sensitive to diagnostics through culture or NAATs. Therefore, here we represent the result only for NAATs.

For the case $p = 0$, all the infected individuals are given treatment 2 (T_2), therefore, I_1 class is constant at 0 as T_2 only affects the I_2 class. While the value of t_s increases, such does the number of infected individuals from the second infected class. Due to the increment in I_2 , gonorrhea is becoming resistant to the second strain of the bacteria and therefore, treatment 1 (V_1) will be given, (see Figure (6)).

When $p = \frac{1}{2}$, half of the infected individuals are receiving treatment 1 (T_1); during the first ten days both I_1 and I_2 classes are the same. Till the first 30 days, infected classes increase; however, after 31 days, I_1 decreases whereas I_2 continues increasing but at a slower rate. Even though half of the infected individuals are receiving treatment 1 (T_1), since t_s corresponds to T_2 . Furthermore, as t_s gets bigger, I_1 decreases at a slower rate than I_s and I_2 increases since people are receiving both treatments, Figure (7a).

Parameter	Symptomatic (NAAT)	Asymptomatic (NAAT)	Symptomatic (Culture)	Asymptomatic (Culture)
μ	$\frac{1}{70 \times 365}$	$\frac{1}{70 \times 365}$	$\frac{1}{70 \times 365}$	$\frac{1}{70 \times 365}$
c	$\frac{1}{7}$	$\frac{1}{7}$	$\frac{1}{7}$	$\frac{1}{7}$
q	0.5	0.5	0.5	0.5
β_c	0.375 [11]	0.375 [11]	0.375 [11]	0.375 [11]
γ_1	$\frac{1}{7}$ [5]	$\frac{1}{7}$ [5]	$\frac{1}{7}$ [5]	$\frac{1}{7}$ [5]
γ_2	$\frac{1}{7}$ [5]	$\frac{1}{7}$ [5]	$\frac{1}{7}$ [5]	$\frac{1}{7}$ [5]
t_s	7 [5]	183 [33]	7 [5]	183 [33]
t_d	1 [21]	1 [21]	4 [21]	4 [21]
τ	$\frac{1}{8}$	$\frac{1}{184}$	$\frac{1}{11}$	$\frac{1}{187}$
p	0.6 [22]	0.6 [22]	0.6 [22]	0.6 [22]

Table 2: Parameter Value and their baseline.

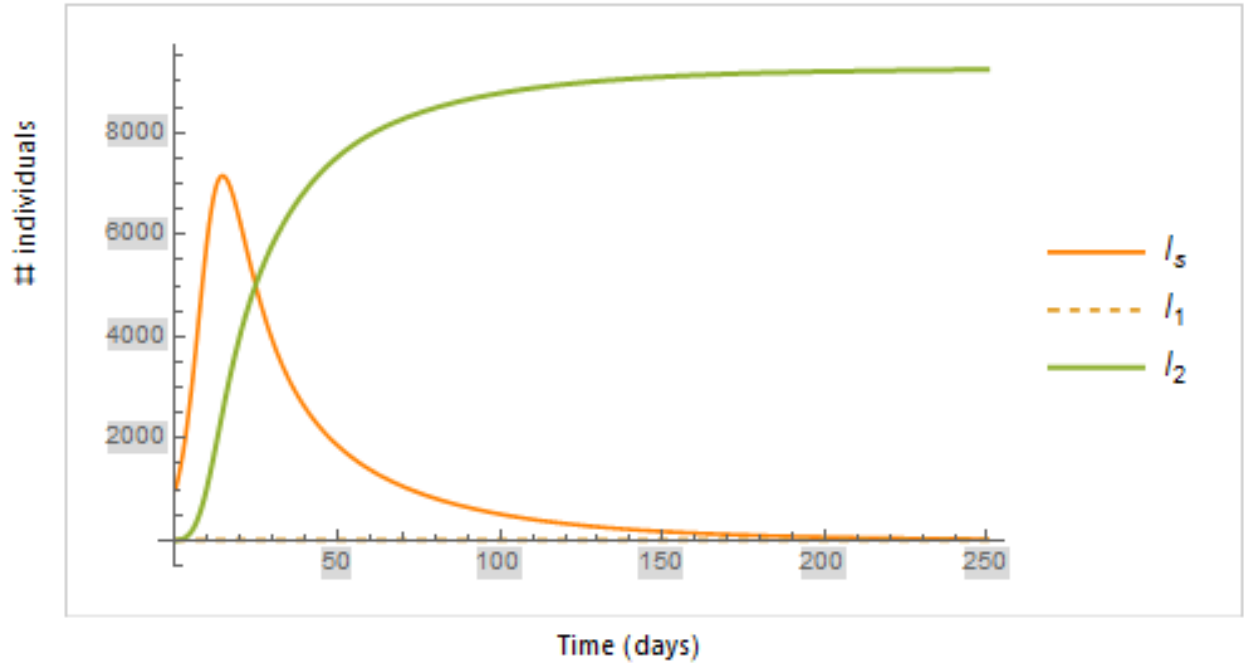


Figure 6: **Infected individuals vs. Time with $p = 0$:** All the infected individuals are given treatment 2 (T_2), therefore, I_1 class is constant at 0.

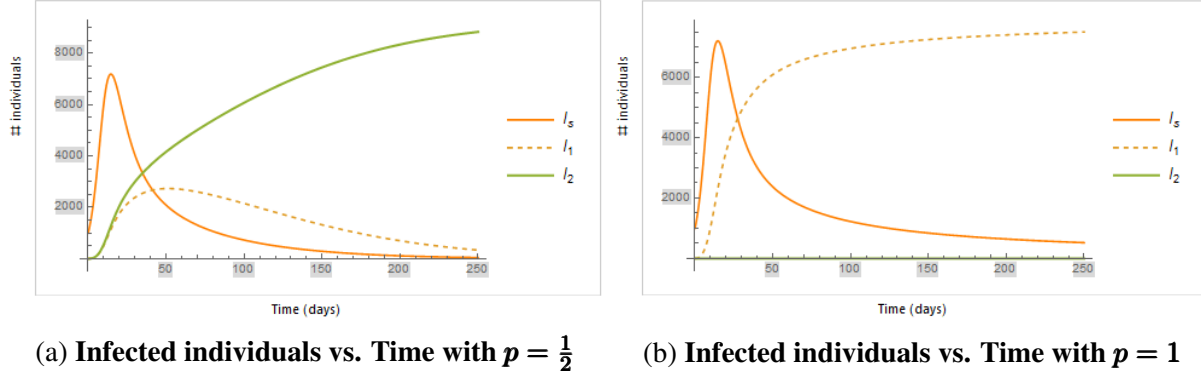


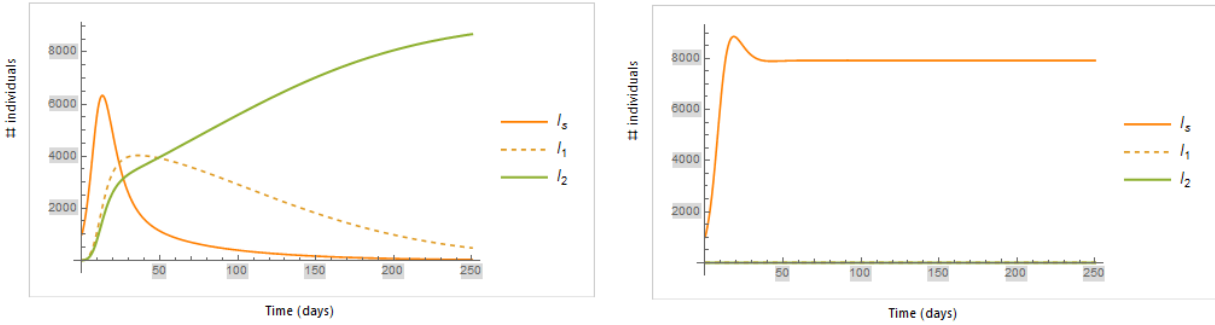
Figure 7: Infected Classes with Respect to p . Half of the infected individuals are receiving treatment 1 (T_1) and the other half T_2 . All the infected individuals are given treatment 1 (T_1), therefore, I_2 class is constant at 0.

And finally when $p = 1$, none of the infected individuals will receive the second treatment, therefore I_2 has no people as T_1 only affects the I_1 class. While the value of t_s increases, there is no change in any of the remaining two infected classes as none of them have t_s as a parameter. Since the only prescribed treatment is T_1 , the bacteria will develop resistance to it, therefore even though people are receiving that treatment, the infected individuals will belong to I_1 , Figure (7b).

Figure 8 represents the time-series of infection states for two different q values: when none of the individuals ($q = 0$) and all of the population ($q = 1$) completed their treatment. The analysis and behavior of the infected individuals is same as the p values, the results were not sensitive to diagnostics through culture or NAATs. Hence, we represent the result only for NAATs.

When $q = 0$, all the infected individuals receive second line treatments (V_1) and (V_2) since none of the individuals completed the first line treatments (T_1) and (T_2). During the first 50 days, I_1 is bigger than the other infected classes because T_1 is greater than the second treatment by 10%. However, after those 50 days, I_2 becomes greater than I_1 and it continues exceeding the infectious class 2 as t_s increases since V_2 as well as T_2 are given and the resistance increases, (see Figure (8a)).

On the other hand, when $q = 1$, all the infected individuals are only given the first line treatments (T_1) and (T_2) as all of them completed their medication. Since everyone concluded the treatments, all the infected individuals belong to I_s and the resistance is due to the strain of gonorrhea individuals have, not because they developed resistance after their medication. As t_s increases, there is no change in the graph since only I_2 has it as a parameter but there are no individuals that belong to that class, (see Figure (8b)). More specifically, the change from I_s to either I_1 or I_2 is tracked and shown in Figure (9). In all figures the red lines indicate the infected classes, while the solid red line indicating the drug susceptible strains of infections. During the first 20 days of the symptomatic individuals, there is an outbreak of both infected classes I_1 and I_2 but since T_1 is the first and more heavily prescribed treatment, I_1 grows at a faster rate than I_2 . All infection classes gradually reach an endemic equilibrium.



(a) **Infected individuals vs. Time with $q = 0$:** All the infected individuals are given the second the second line treatments (V_1) and (V_2). (b) **Infected individuals vs. Time with $q = 1$:** All the infected individuals are only given the first line treatments (T_1) and (T_2).

Figure 8: Infected Classes with Respect to q

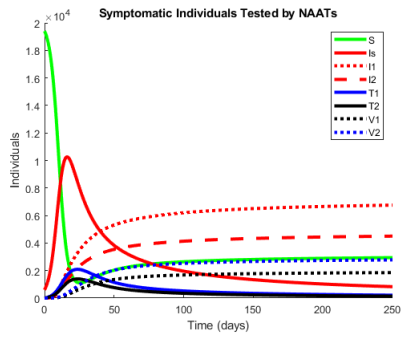
Note that for Figures (9a) and (10a), the first round of treatments, T_1 and T_2 , becomes ineffective as time continues, this is a natural result from the emergence of resistance, that is the decrease of I_s . Since symptomatic individuals take less time to go to the doctor, the time scale is shorter than the asymptomatic ones. Also note that all treatment classes are kept to a minimum (see Figures (9b) and (10b)) because asymptomatic infected individuals are not seeking diagnosis or treatment. Since asymptomatic individuals lack knowledge about their infection, they do not seek medical care as soon as the symptomatic ones; therefore, their time scale is almost 20 times greater than the one for the latter ones.

Symptomatic individuals who have taken NAATs showed the quickest example of how to get diagnosed and treated. This is due to the quick onset of symptoms which causes the individuals to become aware of the infection and allows them to get a diagnosis, in this case the relatively quicker NAATs, so therefore treatment is applied sooner than the alternative culture testing, Figure (9a).

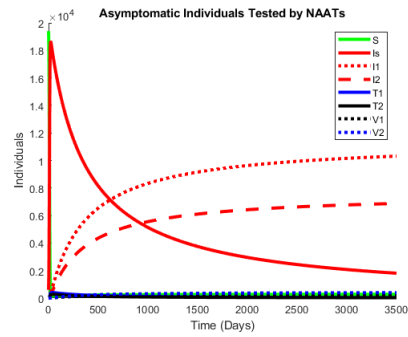
Figure (9b) shows asymptomatic individuals that are diagnosed using NAATs. This model shows the quickest example of how asymptomatic individuals get diagnosed and treated. Although these individuals get diagnosed quicker than if they were given a culture test, the time it takes for these individuals going to get diagnosed in the first place is significantly longer. This is because there are no symptoms, so the individuals do not get diagnosed, it is not until the secondary symptoms start to emerge that the individuals are aware of the disease.

Symptomatic individuals that are diagnosed using a culture test get the result after 4-5 days. This is due to the amount of time for the culture test takes to make an accurate enough diagnosis, see Figure (10a). Asymptomatic individuals tested by cultures, have a slow diagnosis and treatment process. Although these individuals get diagnosed slower than if they were given a NAAT, the time it takes for these individuals going to get diagnosed in the first place is still significantly longer, Figure (10b). By comparing Figures (9a) and (10a), we observe that a slight decrease in diagnosis time will decrease the cases of drug resistant gonorrhoea strains, while barely any change occurs between the two testing methods for asymptomatic patients in Figures (9b) and (10b). Although culture diagnostics offer a more accurate diagnosis, the use of NAATs will decrease the overall

resistant strains since the treatment is given sooner.

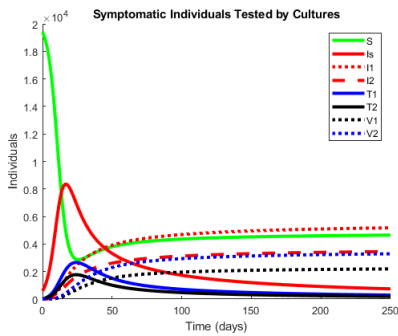


(a) Symptomatic NAATs

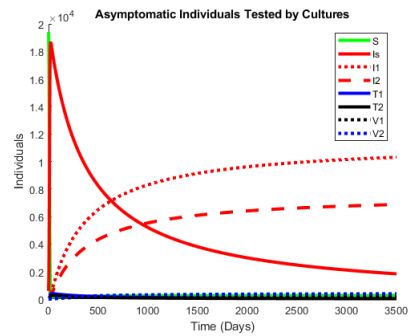


(b) Asymptomatic NAATs

Figure 9: Comparing NAATs diagnosis and treatment of symptomatic and asymptomatic infected individuals. The quick way of diagnosis and treatment. Because of the relatively quicker NAATs, treatment is applied sooner than the alternative culture testing.



(a) Symptomatic Culture



(b) Asymptomatic Culture

Figure 10: Comparing culture method to diagnosis and treatment of symptomatic and asymptomatic infected individuals. The slow approach of diagnosis and treatment of asymptomatic individuals.

5 Cost Analysis

When analyzing strategies to combat antibiotic resistant bacteria, the financial cost must be taken into account. Minimizing cost is important to ensure that treatments are accessible to everyone who needs them, including the poor or uninsured. Furthermore, lower costs makes it easier for governments to implement strategies to lower the overall prevalence of the disease and drug resistant strains. Based on the assumptions of our model, it is obvious that drug resistant cases can be minimized by making sure the treatment compliance is perfect. However, the treatment compliance for gonorrhea is relatively low [CITE]. One of the major reasons for treatment non-compliance is the cost associated with the treatment [CITE]. If a treatment is not affordable, people are discouraged from seeking medical attention or completing their treatment of antibiotics. For this reason, we consider the financial cost of diagnosing and treating gonorrhea in the United States.

The cost function for our model is given by:

$$\begin{aligned}
 C(T) = & C_0 \int_0^T (\tau_s I_S(t) + \tau_1 I_1(t) + \tau_2 I_2(t)) dt \\
 & + C_1 \int_0^T (p\tau_s I_S(t) + \tau_2 I_2(t)) dt \\
 & + C_2 \int_0^T ((1-p)\tau_s I_S(t) + \tau_1 I_1(t)) dt
 \end{aligned} \tag{3}$$

We develop the cost function for our model to give the total cost of diagnosis and treatment for a population of infected individuals. Here, C_0 is the cost of diagnosis, C_1 is the cost of treatment 1, and C_2 the cost of treatment 2. The actual values of these variables are $(C_0, C_1, C_2) = (\$104.02, \$30.46, \$39.256)$ in terms of average dollars per individual [1]. We calculate the value of C_0 by adding the cost of being seen by a nurse and doctor to the mean cost of a NAATs test and a culture test while C_1 and C_2 are derived from the direct medical costs to a patient without insurance for each medication [1].

The time interval goes from $[0, T]$ where T is defined in terms of days. The expressions $(\tau_s I_S(t) + \tau_1 I_1(t) + \tau_2 I_2(t))$ denotes the rate that people are tested and treated; $(\tau_s p I_S(t) + \tau_2 I_2(t))$ denotes the rate that people are given treatment 1, and $(\tau_s (1-p) I_S(t) + \tau_1 I_1(t))$ denotes the rate of which people are given treatment 2.

The cost per case of drug resistant gonorrhea averted after T days is evaluated by calculating the variation in cost effectiveness at the end of a year using the Average Cost-Effectiveness Ratio (ACER) given by:

$$ACER(t) = \frac{C_p - C_b}{I_b - I_p} = \frac{\Delta C}{\Delta I}.$$

This method defines a baseline policy, which is the current policy in place, and compares it to alternative policies to see if the new policy can not only minimize cost but simultaneously reduce resistance. New policy corresponding to the minimum ACER is deemed the most cost-effective

since it minimizes cost incurred per averted case.

The baseline values, C_b and I_p , are calculated using the current parameter values in the United States. The alternative policies are developed by defining a parameter vector, $P_v = (t_d, p, q)$, which are the values we want to control and varying those values. Since t_d and p depend on policy rather than biology, they can be easily changed. The value t_d is dependent on which diagnostic test is used, so recommending either NAATs or cultures would change its value. The value of p refers to the proportion of people assigned to treatment 1, so it could be altered by changing the recommended treatment protocol. The parameter q , which is the proportion of successful treatment, was also chosen since it is the driving force of creating resistance. This parameter was chosen because it could potentially change from factors such as better antibiotic education, accessibility, or better storing methods of the antibiotics.

For our purposes, all ACER values are evaluated over the course of one year. The baseline parameters reflect the current baseline policy, that is, $P_v = (1, 1, .5)$ [8]. The proposed policy parameters of p and q will both vary from 0 to 1 in increments of .1. While t_d alternates between 1 and 4, indicating the use of either diagnostic test. These values are used to calculate both C_p and I_p . We evaluate what combinations of values of P_v will reduce the number of incidences of drug resistant cases of infection within a population in a cost-effective manner. It is important to note that I_p and I_b are calculated using only the number of drug resistant cases, so the analysis below does not apply to the overall prevalence of gonorrhea.

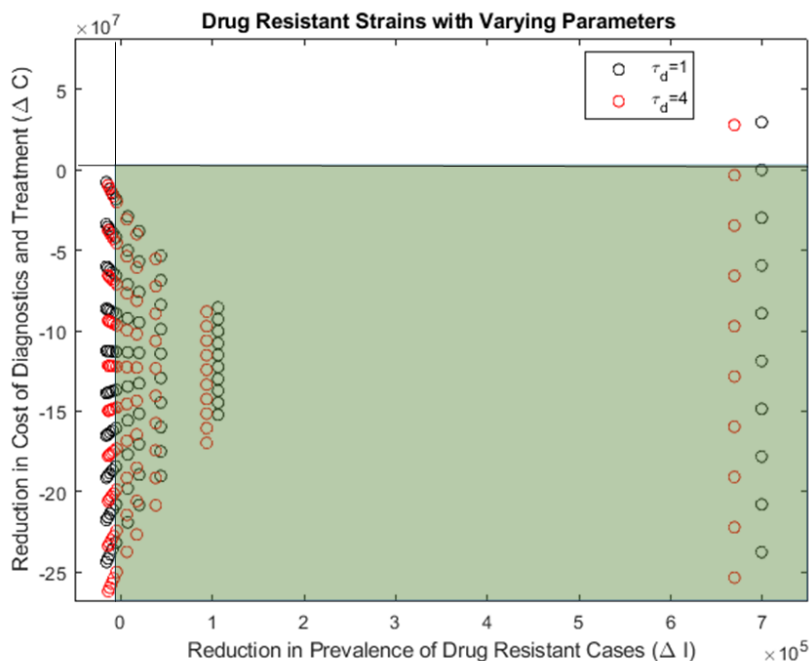
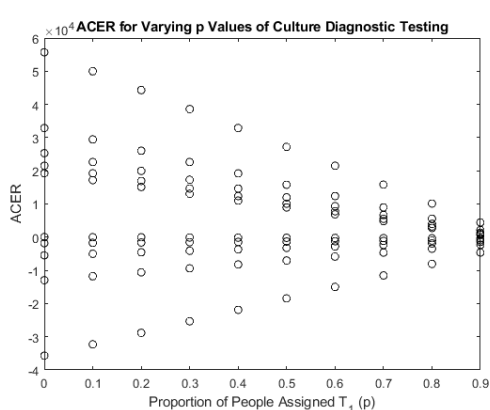


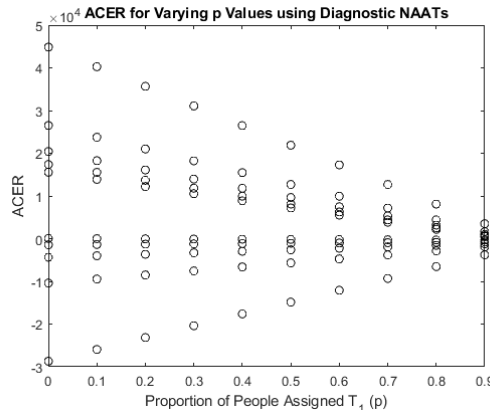
Figure 11: Cost Effectiveness Plane

The ACER numerator, $C_p - C_b$, tells us how much more expensive the proposed treatment is com-

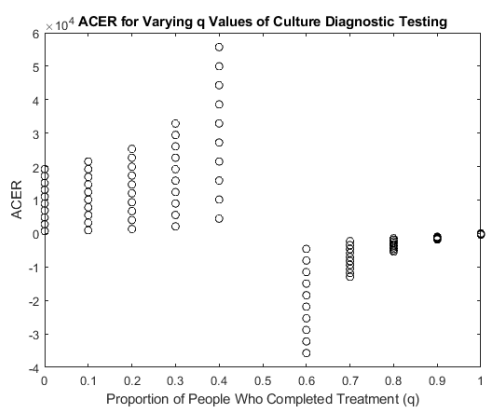
pared to the baseline treatment after one year, therefore negative ΔC values represent a reduction of cost when switching policies. On the other hand, the denominator, $I_p - I_b$, represents the number of averted drug resistant cases when implementing each new policy, so we favor positive values of ΔI . For these reasons, we choose to analyze only the cases of P_v where the points in Figure (11) lie in the fourth quadrant (green shaded region). As seen in the graph, a majority of the alternative proposed treatments are more cost-effective for reducing drug resistant gonorrhoea than the baseline treatment.



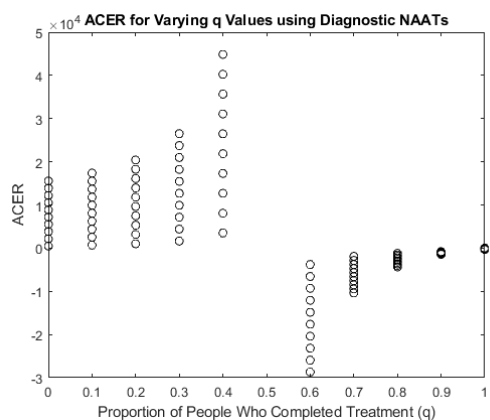
(a) Varying p with only culture testing



(b) Varying p with only NAAT testing



(c) Varying q with only culture testing



(d) Varying q with only NAAT testing

Figure 12: Diagnosis Testing with Optimizing Parameters p, q

Figure 12a shows how the ACER value changes over different p values from 0 to 1 in increments of 0.1 using the t_d values associated with culture testing. We can see that as p decreases so does our ACER value. This shows a savings as treatment 2 is favored over treatment 1, sense Lower ACER values indicate lower cost per individual. Similarly, Figure 12b shows that the same is true when using t_d values associated with NAAT testing. The baseline parameter value for p is 1 and therefore not shown in the graph. In Figure 12c and 12d, we observe positive ACER values when q is less than 0.5, and negative ACER values when q is greater than 0.5 when using either NAAT or culture tests. The baseline values of q is 0.5 so it is not shown in either graph.

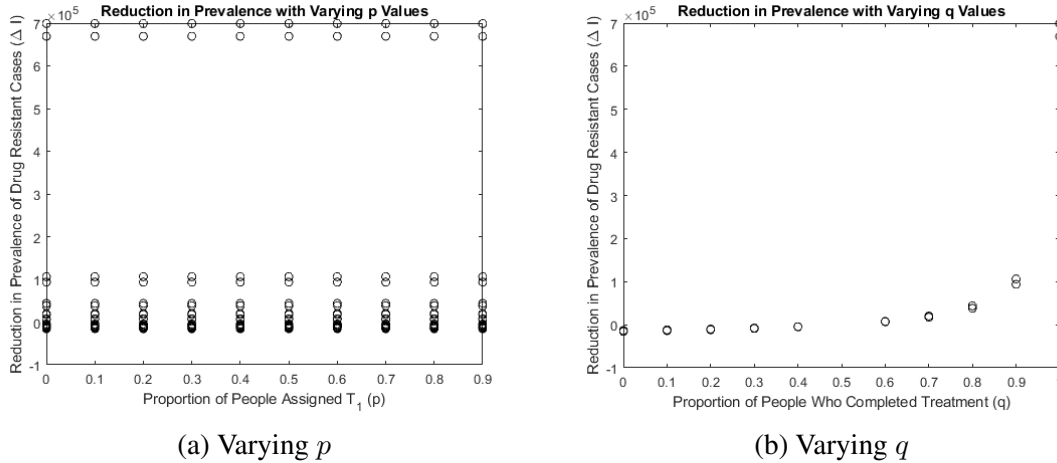


Figure 13: Prevalence over varying values of q and p

Even though the cost of treatment 2 is lower compared to baseline, as showed in Figure 11 (a), changing the value of p does not change the prevalence of drug resistant gonorrhea. However, according to Figure 11 (b), the value of q has a major influence on the number of cases averted. When q is less than 0.5, varying its value does not have a large impact on reducing the number of overall cases, but as q increases after 0.5 we observe drastic increases in the number of averted cases. From this analysis, we can conclude that scientists and policymakers should focus their efforts on finding methods to reduce noncompliance in order to lower financial costs and prevalence related to drug resistant gonorrhea.

6 Discussion

The purpose of this study was to investigate a cost-effective method for reducing the prevalence of drug-resistance gonorrhea. We proposed a dual-treatment strategy that would target drug-resistant strains of gonorrhea with a secondary layer of treatment. To study this a mathematical SIS-based model was developed, where there are 3 strains of gonorrhea that are susceptible to at least one of the treatments proposed. Furthermore, we performed a cost analysis to find the treatment ratios and compliance proportions which yield the lowest total medical costs.

Our study finds that costs and prevalence of resistant strains of gonorrhea are minimized if more than 50% of individuals are successfully treated. We also find that cost is minimized as more individuals are given treatment 2 but does not have a major impact on the number of drug resistant cases. Currently in the United States, the CDC recommends that everyone receive treatment 1 [8]. If this policy was modified to match our findings, medical expenses would decrease. To increase the number of people successfully completing their treatment, we could suggest improved education on the importance of medical professionals storing medications properly and clearly explaining to patients the importance of finishing their entire course of antibiotics.

This model could be expanded to account for whether or not a person is symptomatic since this is

a major factor in time until treatment. Since asymptomatic individuals are unaware they have gonorrhea, they are more likely to pass it on to someone else or develop complications. Similarly, the model could be altered to specify gender. Men and women have different transmission rates and rates of showing symptoms, so the dynamics would likely behave differently. Furthermore, certain types of people who have many more sexual partners than average are responsible for most cases of gonorrhea. These people make up what is known as the core group, and sometimes different treatment strategies are recommended for this particular group which could also be implemented into the model.

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