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Population Based Model of Gonorrhea and Interventions Against Increased Antibiotic Resistance

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POPULATION BASED MODEL OF GONORRHEA AND INTERVENTIONS AGAINST INCREASED ANTIBIOTIC RESISTANCE

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ABSTRACT

POPULATION BASED MODEL OF GONORRHEA AND INTERVENTIONS AGAINST INCREASED ANTIBIOTIC RESISTANCE

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Gonnorrhea is an infectious sexually transmitted disease (STD) caused by the bacterium *Neisseria gonorrhoeae* that commonly reproduces in the reproductive tract.The Centers of Disease Control and Prevention (CDC) estimate that more than 700,000 individuals in the U.S. contract new gonorrheal infections per year. During recent years, there has been a progressive global increase of drug-resistant strains of gonorrhea. Therefore, there exists the necessity for health organizations to encourage the monitoring, research and development of innovative treatment regimens.

We have developed multiple mathematical models to explore the gonorrheal disease state. The first objective of model formulation was to fit the model to

established disease and population data provided by the CDC and U.S. Census Bureau and then include the presence of antibiotic resistance in the model. Additionally, we discuss intervention methods to combat this resistance. The second objective of model formulation was to use parameter sensitivity to determine specific age groups to target in effort to alter disease dynamics.

CHAPTER 1

THE CHARACTERISTICS OF GONORRHEA AND MODELING THE SPREAD OF DISEASE

Gonorrhea has been reported as the second most common infectious disease acquired in the United States [13]. The CDC (Centers for Disease Control and Prevention) estimates that there are approximately more than 700,000 acquired gonorrheal infections per year [13]. In 2010, the rate of gonorrheal infection in the United States was 100.8 per 100,000 population [4]. The highest reported rates in the United States are marked by the population age groups of adolescents (ages 15-19 years) and young adults (ages 20-24 years) [4]. In 2010, the rate of infection for adolescents was 570.9 per 100,000 population and the rate of infection for young adults was 560.7 per 100,000 population [4].

Gonorrhea is a sexually transmitted disease (STD) caused by the bacterium *Neisseria gonorrhoeae* that multiplies in the reproductive tract, which includes the cervix, uterus, fallopian tubes, and urethra [22]. Untreated gonorrhea can lead to severe complications in both women and men. In women, untreated gonorrhea can lead to pelvic inflammatory disease, which is the infection of the uterus, fallopian tubes, and other reproductive organs [13]. Pelvic inflammatory disease

can cause infertility, ectopic pregnancy, abscess formation, and chronic pelvic pain [13]. In men, untreated gonorrhea can lead to epididymitis, a condition of the ducts attached to the testicles, which can cause infertility [13]. In both men and women, it is possible for untreated gonorrhea to spread to the blood or joints and/or increase the contraction of HIV (Human Immunodeficiency Virus) [27].

The development of antibiotic resistance in *Neisseria gonorrhoeae* is an increasing public health concern. Currently in the United States, gonorrhea control strategy relies primarily on effective antibiotic therapy. Consequently, drug resistance is a significant issue requiring careful monitoring, research and scientific development of new treatment regimens. The bacterium has progressively developed resistance to sulfonilamides, penicillin, tetracycline, and ciproflaxin which were previously used as effective antibiotic treatments [22]. Currently the CDC STD treatment guidelines recommend dual therapy, which includes a cephalosporin antibiotic, typically ceftriaxone, and either azithromycin or doxycycline to treat the majority of gonococcal infections present among adults and adolescents [13]. Dual therapy is recommended so as to hinder the potential emergence of gonococcal cephalosporin resistance [13].

Surveillance of antimicrobial resistance in *Neisseria gonorrhoeae* in the United States is focused through the Gonococcal Isolate Surveillance Project (GISP). GISP was formed in 1986 to monitor trends in antimicrobial susceptibilities of strains of *Neisseria gonorrhoeae* so as to establish a rational basis for the selection

of gonococcal therapies [15]. In support of the project, the GISP advises clinicians to report any *Neisseria gonorrhoeae* specimen with decreased cephalosporin susceptibility and any gonorrhea cephalosporin treatment failure to the CDC through their state and local public health authorities [15]. Challenges of monitoring emerging antimicrobial resistance arise due to the significant decline in the capability of laboratories to use essential techniques for gonorrheal culturing required for antibiotic susceptibility testing [12]. Currently, there is an increased use of newer, non-culture-based laboratory technology, yet this technology does not provide greater reliability in comparison to culture-based techniques to perform antibiotic susceptibility testing [12]. Therefore, a greater employment of laboratory culture-based technology is sought [12].

Between 1970 to 1980 the emergence of gonococcal resistance to penicillin and tetracycline was established [22]. Within recent years, gonococcal resistance to fluoroquinolones was established [12]. Resistance was first documented in Asia then soon emerged in the United States [22]. Emergence first developed in Hawaii then continued development in surrounding western states, initially becoming prevalent in homosexual men [22]. Currently, gonococcal resistance is present in all regions of the United States [12]. This caused the CDC to discontinue recommending any fluoroquinolone regimens for the treatment of gonorrhea in 2007 [12]. Though, currently, cephalosporins remain an effective treatment for gonococcal infections, health care providers are advised to be vigilant in regards to treatment failure

[22]. Health care providers are advised to report resistance cases to state and local health departments [12]. State and local health departments are encouraged to promote the maintenance of laboratory capability to culture *Neisseria gonorrhoeae*, allowing for the testing of isolates in reference to cephalosporin resistance [12]. State and local health departments are further encouraged to develop enhanced surveillance and response protocols for gonorrhea treatment failures and to report gonococcal treatment failures to the CDC [12].

The GISP monitors antimicrobial susceptibilities in *Neisseria gonorrhoeae* through the ongoing testing of approximately 5,900 male urethral gonococcal isolates obtained annually from consecutive symptomatic men at 25 to 30 sexually transmitted disease clinics in the United States [25]. Antibiotic susceptibility is measured by minimum inhibitory concentration (MIC) [25]. MIC is defined as the lowest concentration of an antibiotic that inhibits visible growth of bacterium [25]. The GISP has analyzed MIC's to cephalosporins among gonococcal isolates collected from 2000 to 2010 [25]. Decreased antibiotic susceptibility in reference to the cephalosporins cefixime or ceftriaxone is defined by the Clinical and Laboratory Standards Institute (CLSI) as an MIC greater than 0.5 μg/mL [25].

GISP tested an average of 5,865 isolates for antibiotic susceptibility annually from 2000 to 2010 [25]. Overall, the percentage of isolates with cefixime MIC's greater than 0.25 μg/ML increased from 0.2% to 1.4% from 2000 to 2010 [25]. The percentage of isolates with ceftriaxone MIC's greater than 0.125 μg/mL increased

from 0.1% to 0.3% from 2000 to 2010 [25]. In the western region of the United States, the percentage of isolates with cefixime MIC's greater than 0.25 μg/mL increased from 0% to 3.3% and the percentage of isolates with xetriaxone MIC's greater than 0.125 μg/mL increased from 0% to 0.5% from 2000 to 2010 [25]. In the western region of the United States, the most prominent increases in cefixime MIC's were observed in Honolulu, Hawaii with an increase from 0% to 7.7% and in California with an increase from 0% to 4.5% from 2000 to 2010 [25]. An increase in ceftriaxone MIC's from 0% to 0.6% was observed in California from 2000 to 2010 [25].

Communicable diseases, both epidemic and endemic, are frequently examined in mathematical epidemiology [23]. Mathematical epidemiology involves the use of mathematical models to analyze the progression of infectious disease [23]. An infectious disease is classified as an epidemic when the number of expected disease cases, based on recent experienece, is exceeded, occurring in a community or region during a specified period of time [23]. An infectious disease is classified as an endemic when the disease is present in a community at all times but in low frequency [23]. In the mathematical modeling of disease transmission, there exist simple models, which exclude most disease-specific details, designed to highlight only general qualitative behavior [23]. Also, there exist detailed models, designed for the inclusion of disease-specifics containing short-term quantitative predictions [23]. A qualitative approach does not attempt to examine explicit solutions of a

modeling system, but does attempt to examine general behavior of the modeling system [23]. A simple model provides the general framework and structure necessary for the construction of a detailed model. Both a simple and detailed model assist in answering a variety of questions of interest raised by public health officials. A primary general topic of interest concerns the severity of an epidemic [23]. More specifically, health officials are interested in the number of individuals affected, thus requiring treatment, the longevity of the epidemic, and/or the effectiveness of quarantine or isolation in reducing the severity of the epidemic [23].

Most early developments in the mathematical modeling of communicable disease can be attributed to the work of public health physicians. The first known result in mathematical epidemiology is a defense of the practice of inoculation, commonly referred to as the introduction of a serum, vaccine, or antigenic substance into the body of a human or animal subject, to produce or boost immunity to a specific disease [3]. Daniel Bernoulli, trained as a physician, discovered this extraordinary result, recognized in 1760 [3].

The first contributor to modern mathematical epidemiology is owed to P.D. En'ko between the years 1873 and 1894 [3]. The foundations of the complete approach to epidemiology employing compartmental models was designed by public health physicians Sir Ross, R.A., W.H. Hamer, A.G. McKendrick, W.O. Kermack and statistician J. Brownlee between the years 1900 and 1935 [3]. A particularly

instructive example of the significant contribution of emlploying compartmental models was provided by the work of Sir Ross, R.A in reference to the communicable disease malaria [3]. Ross was awarded the second Nobel Prize in Medicine for his demonstration of the transmission dynamics of malaria between mosquitoes and humans [3]. Ross formulated a mathematical model that predicted the dismissal of malaria outbreaks provided the mosquito population maintain below a critical threshold level [3]. Field trials supported his conclusions which lead to substantial successes in disease malaria control strategies [3].

The basic compartmental models used to describe the transmission of communicable diseases are contained in a sequence of three papers produced by W.O. Kermack and A.G. McKendrick in the years 1927, 1932, and 1933 [3]. The first of these papers describes general epidemic models [3]. One model described is the Kermack-McKendrick epidemic model, which is a special case of the general epidemic model referenced in the paper [3]. The general epidemic model includes dependence on age of infection, which was employed in the mathematical modeling of HIV and AIDS (Acquired Immune Deficiency Syndrome) [3]. The Kermack-McKendrick model, proposed in 1927, is referred to as the general susceptible, infected, and recovered (SIR) model, Figure 1.1 [3]. The model provides the framework for a vast variety of mathematical epidemiologic models.

Many forms of SIR models are used to model the dynamics of a variety of infectious diseases present in a population studied over a specified period of time.

Figure 1.1: SIR Model Schematic: Three compartments of general SIR model shown. Compartments are susceptible (S), infected (I), and recovered (R).

One form of the SIR model commonly employed in the research study of infectious disease is the SEIR model. The SEIR model contains one additional compartment than the SIR model, which is the compartment representing exposed individuals, noted as E. The infected population is then split into infected individuals who incubate the disease but display no disease symptoms and the infectious individuals who do have external disease symptoms [5]. One such study used the SEIR model to explore the infectious disease Ebola hemorrhagic fever, commonly referred to as Ebola [26]. Another such study of the SEIR model was used to analyze Dengue Fever. Dengue Fever is a virus-caused disease that is spread by mosquitoes, prevalent in Latin America and Southeast Asia [34].The model focused on analyzing the fixed point and eigenvalues of the dynamical system in order to determine system behavior [34]. Model simulations were performed given formulated parameter values to show breeding rates reaching an endemic and non-endemic state [34]. These are two examples of the many uses of mathematical modeling in studying infectious diseases.

In Hethcote's review of infectious modeling he notes the numerous reviews

and books produced in reference to mathematical modeling in epidemiology. He shares that recent models of epidemiological study have involved aspects such as passive immunity, gradual loss of vaccine and disease-aquired immunity, stages of infection, vertical transmission, disease vectors, macroparasitic loads, age structure, social and sexual mixing groups, spatial spread, vaccination, quarantine, and chemotheraphy [21]. He further shares the the fact that recent epidemiological models have been formulated to study some diseases such as measles, rubella, chickenpox, whooping cough, diptheria, smallpox, malaria, rabies, herpes, and HIV/AIDS [21].

Many epidemiological model incorporate age dynamics to study specific diseases. In research by Dietz [6], [7], Hethcote [18], Anderson and May [1], [2], and Rouderfer, Becker, and Hethcote [32], the continuous age-structure model for the research study of measles and rubella vaccination strategies was proposed. In a study by Hethcote [20] was proposed the optimal ages of vaccination for measles on three continents. Halloran et al, Ferguson [17], Anderson, and Garnett [11] and Schuette and Hethcote [33]all used age-structured models to study the effects of varicella (chickenpox) vaccination programs.

The 2010 review by Funk et al. looks at the current state of behavioral disease models. Funk explains that behavioral changes can be involved in the interpretation of the disease outbreak data to explain decreases in transmission rate [31], [28], yet is often there is little detail explaining how these specific reactions are

quantified and discovered in a systematic way. In this review Funk explains applying a restrictive study to models which focus exclusively on "self-initiated, voluntary behavior" and "behavioral reactions to information from the outside world", common to many behavioral mathematical models [16]. He further explains that both the source and type of information in relation to disease presence is a major factor in determing behavioral dynamics [16].

In a research study by Hethcote, he examines the transmission dynamics and control of gonorrhea [19]. Hethcote employs a discrete SIS model, to focus on the effects of population dynamics determined by the characteristics of gonococcal disease [19]. Hethcote then develops more specific, detailed models to explore both effective screening and possible vaccination strategies [19]. Hethcote further examines the dynamics of disease in a sub-popuation of hetersexual and homosexual males and females [19]. All developed models were used to analyze the future disease state.

In this research project, we will start from a basic model, focused on the infectious population, and develop the model to include both age and behavioral dynamics. Studied in this research project was the development of three mathematical models used to capture population dynamics in reponse to the spread of gonorrhea. All mathematical models present in this research project used the framework of a general SIR/SIRS model to mimic population dynamics in response to the spread of the infectious disease. The SIR model is a compartmental

disease model which expresses the amount of individuals in specified compartments (classes) throughout a disease time course [9]. Compartments of the SIR model are susceptible (S) individuals , infected (I) individuals , and recovered (R) individuals. Individuals are classified into one of these compartments depending on the individuals contraction of the disease [24]. If an individual has not acquired the disease, then the individual is classified as susceptible. Once an individual has acquired the disease, the individual is classified as infected. When the individual is cured of the disease, the individual is classified as recovered. Each member of the population has the ability to transition from one compartment to the next compartment, progressing from the classification of susceptible to infected to recovered [24]. In formulating the mathematical model we develop differential equations for the number of individuals in each compartment. In formulating the mathematical model as a system of differential equations, the assumption exists that the epidemic process is deterministic in which the behavior of a population is solely determined by its history and by the interactions described by the model [23].

Figure 1.1 shows a flow diagram of all compartments with arrows representing transition between compartments of the typical SIR model. The model we used in the research study slightly extends this model and is called the SIRS model. The SIRS model is described similarly to the SIR model, but includes a transition rate from the recovered compartment to the susceptible compartment. The transition rate from the infected class to the recovered class may account for isolation from

the rest of the population, immunization against infection, recovery from the disease with full immunity against re-infection, or death caused by the disease [9].

Total population, denoted as N, is $N = S+I+R$. The SIRS model assumes N remains constant as total population typically does not significantly alter within a time interval in which an infectious disease is typically measured.

The SIRS model uses a set of differential equations to model infectious disease population dynamics over time. The set of differential equations used are $\frac{dS}{dt}, \frac{dI}{dt}$, and $\frac{dR}{dt}$ with solution $S(t)$, $I(t)$, and $R(t)$. Transition rates used in the general SIRS model are β, γ,and f. β represents the rate at which a susceptible individual becomes infected or contracts the disease, γ represents the rate at which an infected individual becomes recovered or is alleviated from the disease and f represents the rate at which a recovered individual becomes susceptible or "loses immunity" from the disease. The SIRS model schematic displaying each transition rate is shown in Figure 1.2.

The general SIRS model equations are then

$$\frac{dS}{dt} = -\beta SI + fR$$

$$\frac{dI}{dt} = \beta SI - \gamma I$$

$$\frac{dR}{dt} = \gamma I - fR.$$

The equations describe the population dynamics due to the presence of disease at any specified time of interest. The differential equation for the suceptible population is determined by the rate of loss due to susceptible individuals becoming

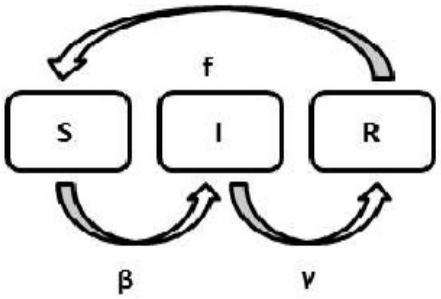

Figure 1.2: SIRS Model Schematic: Transition rates, indicated by arrows, between each compartment shown. Each compartment defined as in SIR model.

infected. In addition, the second term is the gain due to recovered individuals losing immunity from the disease. The differential equation for the infected population is determined by a rate of gain due to susceptible individuals becoming infected. In addition, the second term is the rate of population loss due to infected individuals recovering. The differential equation for the recovered population is determined by the rate of gain due to infected individuals recovering. In addition, to the second term accounts for the recovered individuals losing immunity and becoming susceptible.

We developed three mathematical models to model the population dynamics of gonorrhea using the general SIRS model equations as a starting point. Several parameters were created and added to the general SIRS model in order to tailor to the specific characteristics of gonorreal infection. Specific to each model are

data sets collected from the CDC and U.S. Census Bureau in which information concerning gonorrhea infection rates and total population are described. The primary goal of each model is to match these particular data sets by developing model equations and fitting unknown parameters. Other significant objectives of the research study are to model the effect of gonorrhea's antibiotic resistance on population dynamics and to explore parameter sensitivity in relation to population dynamics. Overall these objectives will assist in the aid of examining the future state of disease in order to allow for awareness and prevention efforts.

Each model further divides total population, as simple models progress to detailed models. The first model studies the disease course in the total population. The second model studies disease course with age-specific variables. The age-specific variables (populations) are adolescents, young adults and adults older than 25 years. The third model studies disease course in reference to behavioral age-specific populations based on the knowledge of disease contraction. The behavioral age-specific populations are adolescents, young adults and adults older than 25 both unknowing and knowing of the contraction of disease. Disease contraction among adolescents and young adults are of particular attention since gonorrheal infection rates are highest among adolescents and young adults caused by a combination of behavioral, biological, and cultural factors [13].

CHAPTER 2

MODELING GONORRHEA WITH VITAL DYNAMICS AND ANTIBIOTIC RESISTANCE

The first model used in the study considers no subdivision of total population. Model one equations are

$$\frac{dS}{dt} = -\beta SI + fR + \alpha(S + I + R) - \delta S$$

$$\frac{dI}{dt} = \beta SI - \gamma \frac{1}{1+\sigma} I - \delta I$$

$$\frac{dR}{dt} = \gamma \frac{1}{1+\sigma} I - fR - \delta R.$$

These model equations include parameters, which were added to the general SIRS model, in order to model gonorrhea and vital dynamics. Here, parameters α and δ represent total population birth and death rate, respectively. Birth and death are referred to as the vital dynamics of a population. Birth rate is defined as the measure of childbirths per 1,000 population per year and death rate is defined as the measure of deaths per 1,000 population per year. The model assumes birth and death rate are equal, thus total population remains constant with respect to time. More specifically, $\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0$. The parameter σ models the level of gonococcal antibiotic resistance. The expression $\frac{1}{1+\sigma}$ is used to measure antibiotic resistance. This expression was used due to the ease of it's effectiveness

in capturing the effect of antibiotic resistance on system dynamics. As higher σ levels of antibiotic resistance response increases, individual transition rate from the infected class to the recovered class decreases, thus affecting model parameter γ. Infected individuals transition at slower rates to the recovered class due to the individuals inability to overcome the presence of the bacterial infection in the body. Parameters β, γ,and f represent the transition rates between each compartment as previously described. The only constraint on model parameters is that they are positive.

2.1 Model Fit

The first objective of the model was to fit the model and parameters to known disease and population data. This will establish the presence of the disease state in a population extending beyond the time displayed in the data set. Virginia disease reports and total population were used in the model fitting, published by the CDC and the U.S. Census Bureau from 2001 to 2010, respectively. Virginia disease reports and total population data was chosen for use in research project due to its relevance in regards to research location. After model equations were developed, data driven equilibrium and parameter values were sought. According to the data, in effort to model disease dynamics, total population, $N(t) = S(t) + I(t) + R(t)$, must remain steady or constant at approximately 7,500 which represents the average Virginia total population from 2001 to 2010. For modeling purposes

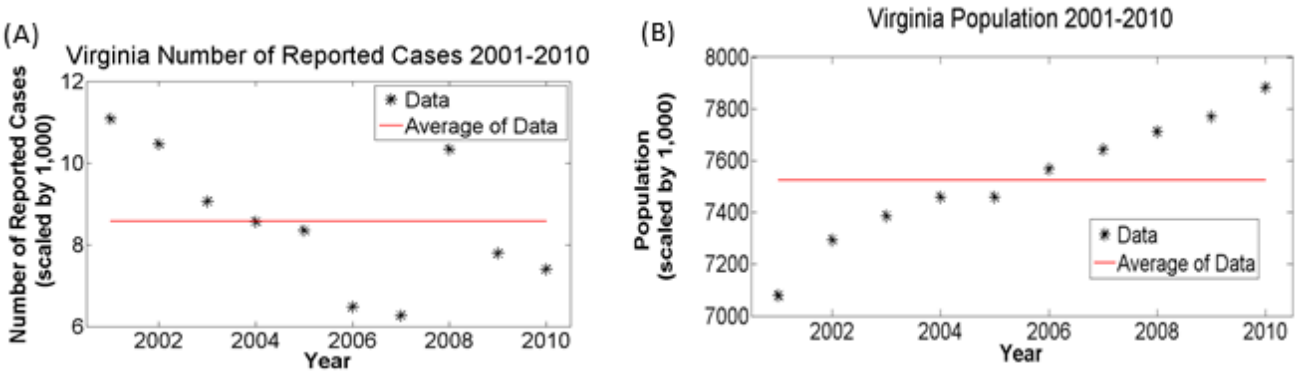

Figure 2.1: Number of Reported Gonorrhea Cases and Total Population Data for Virginia: Scatter plot represents Virginia's total number of reported cases of gonorrhea (A) and total population (B) from 2001-2010. The red line of (A) and (B) represents average value of of each data set.

we have scaled all population data by 1,000. Similarly, according to the data, the model disease dynamics of the infected population, $I(t)$, must be steady or constant at approximately 8.6, which represents the number of reported gonorrhea cases in Virginia from 2001 to 2010, scaled appropriately. Figure 2.1 displays the data representing Virginia's total population and Virginia's total reported cases of gonorrhea from 2001 to 2010, respectively. The red solid line displayed in each plot indicates the average of the data set, which we will use to determine the equilibrium values of total individuals and infected individuals in this model.

Equilibrium Values					
S	I	R			
6898.432	8.584	80.984			
Parameter Values					
β	γ	f	α	δ	σ
$4.5319*10^{-5}$	0.305	0.0247	0.00763	0.00763	0

Table 2.1: Virginia Model Equilibrium and Parameter Values: Parameter values and cooresponding equilibrium values of Virginia gonorrhea model.

The presence of the disease state is acheived at the noted target values. The specified parameter values in Table 2.1 were used to model Virginia's dynamics of disease state from years 2001 to 2010. Parameters α and δ are parameters of established values, as they represent average U.S. birth and death rate from 2001 to 2010. All other parameter values were unknown, thus data driven. Shown in Table 2.1 are the equilibrium values and parameter values produced by the model. Model equilibrium and parameter values show Virginia total population equal to 6988 and Virginia's total reported cases of gonorrhea equal to approximately 8.584. Therefore, the model data accuarately forms an approximation to the given data.

Next, we sought to model the effect of disease dynamics given an arbitrary initial amount of infected individuals, 1,000, introduced into a host population of susceptible individuals, thus modeling earlier gonococcal disease presence in

Virginia. We then were able to produce the transients for each population class, Figure 2.2. End dynamics match the Virginia total population and total disease cases data for 2006-2010. Initial conditions used for Figure 2.2 were $S(0) = 6987$, $I(0) = 1$, and $R(0) = 0$. Figure 2.2 exhibits a typical disease time course for each population class with noted equilibrium values attained.

In Figure 2.2 (A), (B), and (C) we see a gradual transition among all population states until we reach steady state. All transients are montonically increasing or decreasing to this state. At the ending time of each subplot, all populations reach values approximating the known Virginia population and infectious disease data. Note that the model assumes birth rate and death rate are equivalent, therefore total population remains constant throughout the disease time course. We know this is not historically correct, but because we are using this model for current dynamics during which we neglect increase in population, thus this figure is a qualatative description of a possible disease course.

In the study of epidemiology, the basic reproduction number, $R_0 = \frac{\beta S(0)}{\alpha+\delta} > 1$, defined as the average number of secondary infections that occur when only one infected individual is introduced into a completely susceptible host population, is often calculated [21]. This calculation is of particular interest in epidemiological study because the magnitude of R_0 allows one to determine the effort necessary to prevent an epidemic or to eliminate an infection from a population [8]. For our model parameters we get $R_0 = 20.750$.

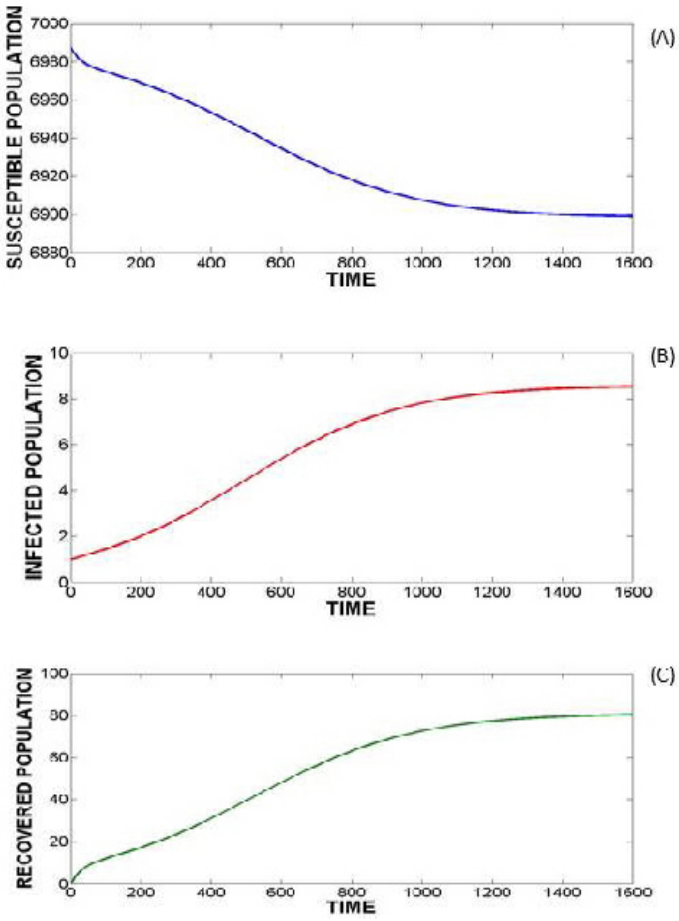

Figure 2.2: Virginia Model Transients: Subplots represent the disease state at equilibrium among the susceptible (A), infected (B), and recovered (C) population classes. Initial conditions used to create disease time course are $S(0) = 6987$, $I(0) = 1$, and $R(0) = 0$.Time values from 1591-1600 represent the disease dynamics of Virginia from 2001-2010. Population scaled by 1,000.

σ	**Equilbrium Values**			
	S	I	R	N
0	6898.432	8.584	80.984	6988
0.25	5552.417	167.96 (1856.664%)	1267.623 (1465.276%)	6988
0.5	4655.075	320.048 (90.55%)	2012.878 (58.792%)	6988.001
0.75	4014.116	465.336 (45.396%)	2508.54 (24.625%)	6987.992
1	3533.397	604.271 (29.857%)	2850.333 (13.625%)	6988.001

Table 2.2: Virginia Model Equilibrium Values at Various Levels of Antibiotic Resistance: Equilibrium values for the susceptible, infected, and recovered populations attained. Percentage increase of infected and recovered population between each consecutive level of antibiotic resistance shown in parenthesis.

2.2 Modeling Antibiotic Resistance

Another significant objective was to model the effect of antibiotic resistance on disease population dynamics. As described above, the model parameter signifying a measured level of antibiotic resistance is σ. As σ increases, the rate of transition from the infected class to the recovered class decreases. Table 2.2 presents the equilibrium values attained for the susceptible, infected, and recovered class at various values of σ.

Table 2.2 verifies that as σ increases, there is a slower transition from the infected class to the recovered class. In Table 2.2 we see a higher rate of increase of the size of the infected class as σ increases than the rate of increase of the size

of the recovered class. Note, total population, N, remains constant among all values of σ. Given the nonlinearity of the σ term, we see a decrease in the percent change as we increase σ by 0.25.

To combat resistance we looked at which disease term to target. Using σ held constant at various increased levels, we increased and decreased all other parameter values by 20% from original equilibrium state in to examine their effects on the disease dynamics. The parameter sensitivity analysis was constructed in order to discover if adjusting the parameter value β or f was more effective at controlling the infected population dynamics at specified levels of σ. More specifically, we were interested in whether the rate of contracting the disease or the rate of developing safe practice post disease is more effective in controlling disease dynamics. Both parameter values β and f are the only model parameters that are behavior-dependent. Therefore, they are practical to target and adjust in reference to parameter sensitivity analysis. Table 2.3 shows the model parameter sensitivity analysis.

In order to determine which parameter is more sensitive to parameter alteration, the percent change between the number of infected at orginal equilibrium state, displayed in Table 2.2, and the number of infectives after a 20% and increase and decrease for each parameter was calculated.

As previously described, increased values of σ cause the presence of a higher number of infected individuals. Table 2.3 also supports this claim. Table 2.3 shows

σ	**20%** β_I	**20%** β_D	**20%** f_I	**20%** f_D
0	118.843 (1273.749%)	0 (-100%)	9.829 (13.617%)	7.438 (-14.022%)
0.25	276.312 (64.430%)	5.637 (-96.645%)	190.316 (13.255%)	144.957 (-13.738%)
0.5	426.58 (33.246%)	160.49 (-49.869%)	361.484 (12.913%)	277.033 (-13.466%)
0.75	570.129 (22.491%)	308.419 (-33.737%)	524.036 (12.588%)	403.984 (-13.205%)
1	707.402 (17.043%)	449.88 (-25.565%)	678.607 (12.279%)	526.104 (-12.953%)

Table 2.3: Virginia Model Parameter Sensitivity Analysis: Total number of individuals in the infected class recorded. Displayed in parenthesis is percent change between the altered value of infected and the original value of infected present at equilibrum.Original infected values at steady state were 8.584, 167.96, 320.048, 465.336, and 604.27. Subscript I and D are used to denote percentage increase and decrease for each parameter, respectively.

that altering model parameter β produces a greater percentage increase of infectives than the percentage increase due to altering f. Because model parameter β directly effects the population size of the infected class, increasing or decreasing β will cause greater population change in comparision to model parameter f which indirectly effects population size of the infected class. As both parameters experience a 20% increase and decrease, the change in calculated percent change decreases as σ values increase.

Table 2.3 supports that model parameter β exhibits greater sensitivity to alteration in comparison to model parameter f. This parameter shows that there are greater percent increase and decrease changes present among all levels of antibiotic resistance. More specifically, Table 2.3 supports that the rate of disease transmission has a heavier influence on the dynamics of the disease state than the rate of "immunity loss" because model parameter β has a direct effect on the infected population size.

XPPAUT, a computer program tool for solving and analyzing differential equations, was used to produce the model simulations and determine the parameter values for this model [10].

CHAPTER 3

MODELING GONORRHEA WITH VITAL DYNAMICS, ANTIBIOTIC RESISTANCE, AND AGE DYNAMICS

The second model we developed expands the first model by incorporating age dynamics. Included in this model is a subdivision of total population according to age group, accompanying age group transition. Each population class of susceptible, infected, and recovered, catergorizes age groups as adolescent, young adult or older. The adolescent age group comprise a population aged 15 to 19, the young adult age group comprise a population aged 20 to 24 and the older age group comprise a population aged above 24. Gonorrhea rates among each age distribution have experienced marked differences through the progression of recent years. Reported by the CDC, gonorrhea rates were highest among adolescents and young adults in 2010 [13]. In 2010, the highest rates were recorded among women aged 15 to 19 years and 20 to 24 years. From 2009 to 2010, gonorrhea rates displayed an increase among most all age sectors [13]. The largest gonorrhea rate increases were observed among those aged 20 to 24 years and 30 to 34 years. Gonorrhea rate decreases were observed among those aged 35 to 39 years and above 54 years [13].

3.1 Model Fit

The second model equations are represented by

$$\frac{dS_A}{dt} = -(\beta_{AA}I_AS_A + \beta_{AY}I_YS_A + \beta_{AO}I_OS_A) + fR_A - \nu S_A +$$

$$\alpha(S_A + I_A + R_A + S_Y + I_Y + R_Y + S_O + I_O + R_O) - \delta S_A$$

$$\frac{dI_A}{dt} = \beta_{AA}I_AS_A + \beta_{AY}I_YS_A + \beta_{AO}I_OS_A - \gamma\frac{1}{1+\sigma}I_A - \nu I_A - \delta I_A$$

$$\frac{dR_A}{dt} = \gamma\frac{1}{1+\sigma}I_A - fR_A - \nu R_A - \delta R_A$$

$$\frac{dS_Y}{dt} = -(\beta_{YA}I_AS_Y + \beta_{YY}I_YS_Y + \beta_{YO}I_OS_Y) + fR_Y + \nu S_A - \nu S_Y - \delta S_Y$$

$$\frac{dI_Y}{dt} = \beta_{YA}I_AS_Y + \beta_{YY}I_YS_Y + \beta_{YO}I_OS_Y - \gamma\frac{1}{1+\sigma}I_Y + \nu I_A - \nu I_Y - \delta I_Y$$

$$\frac{dR_Y}{dt} = \gamma\frac{1}{1+\sigma}I_Y - fR_Y + \nu R_A - \nu R_Y - \delta R_Y$$

$$\frac{dS_O}{dt} = -(\beta_{OA}I_AS_O + \beta_{OY}I_YS_O + \beta_{OO}I_OS_O) + fR_O + \nu S_Y - \delta S_O$$

$$\frac{dI_O}{dt} = \beta_{OA}I_AS_O + \beta_{OY}I_YS_O + \beta_{OO}I_OS_O - \gamma\frac{1}{1+\sigma}I_O + \nu I_Y - \delta I_O$$

$$\frac{dR_O}{dt} = \gamma\frac{1}{1+\sigma}I_O - fR_O + \nu R_Y - \delta R_O.$$

Each population subgroup A (adolescent), Y (young adult), and O (older) is contained in compartments S, I, and R. Therefore, introduced variables of model two are S_A, I_A, R_A, S_Y, I_Y, R_Y, S_O, I_O, and R_O, which represent all age-dependent population classes. Introduced parameters of model two are β_{AA}, β_{AY}, β_{AO}, β_{YA}, β_{YY}, β_{YO}, β_{OA}, β_{OY}, β_{OO} and ν.

The β parameters each represent the rate of gonorrheal infection between each age-dependent population class. Each rate is specific to the interaction between each pair of age-dependent population classes. Thus β_{AA} describes the rate of gonorrheal infection contracted from an infected adolescent to a susceptible adolescent, β_{AY} describes the rate of gonorrheal infection contracted from an infected young adult to a susceptible adolescent, β_{AO} describes the rate of gonorrheal infection contracted from an infected older to a susceptible adolescent, etc. CDC reports that, within recent years, the largest increases of gonorrheal infection are observed among young adults [4]. As a result β parameters β_{YA}, β_{YY}, and β_{YO} used in the model were chosen to be largest in comparison to all other β parameters because these parameters describe the rate that young adults contract gonorroheal infection from all age groups.

The parameter ν represents the rate of transition of age among each age-dependent population class. As each subgroup ages, there is transition to and from cooresponding classes. All subgroups transition in the order of adolescent, young adult, older. The model neglects the time delay previous to entering the adolescent class, therefore introduced population members are included in the susceptible adolescent (SA) aged-dependent population class. It was necessary that the parameter ν be chosen so as to reasonably increase total population, $N = S_A + I_A + R_A + S_Y + I_Y + R_Y + S_O + I_O + R_O$, at each time step as the model assumes no decreases or significant increases in total population within the small

Year	A Reported Cases	Y Reported Cases	O Reported Cases
2006	9.6104	11.0465	14.5446
2007	9.826	11.1418	14.0688
2008	9.7069	10.8747	12.6013
2009	8.6996	10.0645	10.9468
2010	8.825	10.5619	11.1591

Table 3.1: Gonorrheal Disease by Age Group Data: Data represents the total number of reported cases of gonorrhea, or total number of infected, from 2006-2010 for each age-dependent population. Reported older gonorrhea cases found by taking the sum of number of reported gonorrhea cases for those individuals aged 25 and older. Note that all data was scaled by 10,000.

specified time span modelled.

Similar to the Virginia model, there were three objectives to explore with this age-dependent model. The first objective was to fit the given model to known data, the second objective was to observe population dynamics in reponse to increased levels of antibiotic resistance, and the third objective was to observe parameter β and f sensitivity in reference to their effect on the population dynamics of the infected classes.

Shown is the known data, reported by the CDC, Table 3.1, and model fit, Figure 3.1. The scatter plot of each age-dependent population represents the data of total U.S. reported gonorrheal cases from 2006-2010. The solid line represents

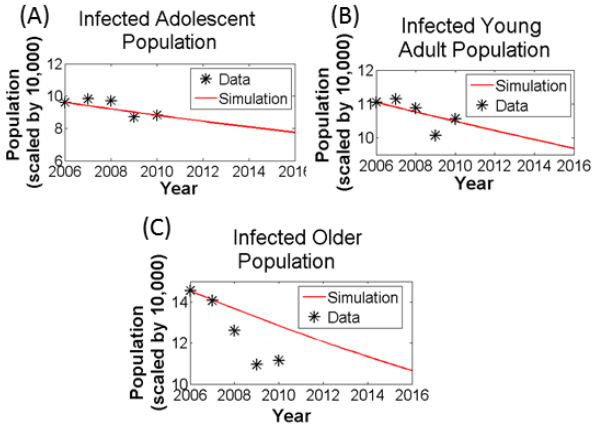

Figure 3.1: Age Dynamics Model Data Fit: Data of the total U.S. reported cases of each age-dependent population is represented as a scatter plot. Cooresponding model simulation represented as a solid line. Here the residual error is 0.529, 0.386, and 9.254 for plots (A), (B), and (C), respectively.

the model data acquired applying appropriate parameters and initial conditions. The objective of this data overlay is to closely match actual and model data so that model data may represent actual data in effort to conduct analysis regarding future disease trends. This fit was obtained using parameters and initial conditions described in Table 3.2 and Table 3.3. The initial conditions were determined using the infected population data, Table 3.1, and total U.S. population data for 2006. The initial recovered population of each aged-class was formed by taking 3% of total population, an observation characteristic of the first model. The initial susceptible population of each age- dependent class was formed by subtracting both the infected and recovered population from U.S. total population, which yields the remaining total population.

In effort to model the population dynamics of U.S. gonorrheal cases, it was necessary to first find the value of the model parameter ν. We simulated the system with only age-related dynamics to determine the parameter ν. Only parameters α, δ, and ν were non-zero because these parameters control population dynamics without regards to the influence of disease. We found $\nu = 0.0001$ properly models U.S. total population data, from 2006 to 2016.

After the model parameter ν was found, the full disease model was used to fit the data of the number of U.S. reported cases of gonorrhea from 2006-2010. The number of reported cases of each age-dependent population group translate as the size of each cooresponding infected class. All β parameters were estimated in order

Parameter	Parameter Value
β_{AA}	$4.097*10^{-6}$
β_{AY}	$4.903*10^{-7}$
β_{AO}	$7.179*10^{-10}$
β_{YA}	$4.097*10^{-7}$
β_{YY}	$8.9029*10^{-6}$
β_{YO}	$1.218*10^{-6}$
β_{OA}	$1.097*10^{-10}$
β_{OY}	$1.9029*10^{-9}$
β_{OO}	$1.18*10^{-10}$
f	0.00247
ν	0.0001
γ	0.0305
α	0.000763
δ	0.000763
σ	0

Table 3.2: Age Dynamics Model Parameters: Displayed are model parameters used for model fit. All parameters account for scaling of population by 10,000.

	S	**I**	**R**
Adolescent	2019.2416	9.6104	62.748
Young Adult	1967.0745	11.0465	61.179
Older	18598.3003	14.5447	575.655

Table 3.3: Age Dynamics Model Initial Conditions: Displayed are initial conditions used for model fit. Initial conditions determined by 2006 total U.S. reported cases of gonorrhea and 2006 total U.S. population. U.S. Census Bureau estimates total 2006 U.S. population were 2091.6, 2039.3, and 19188.5 for adolescents, young adults, and older, respectively. All population scaled by 10,000.

to fit the data. In effort to estimate all β parameters, data reported from the CDC in reference to gonorrheal infection rates specific to each age distribution were used to obtain general initial estimates. All β parameters were then individually tweaked from the initial estimate until they matched the number of reported cases during the years 2006, 2007, 2008, 2009, and 2010 in which data was collected. All other parameters were recycled from the Virginia model and scaled appropriately in accordance with all other scaled model parameter values of the age dynamics model.

3.2 Modeling Antibiotic Resistance

Objective two of the model observes age-dependent infective class population dynamics in reponse to increased σ values. Recall, as σ values are increased, the

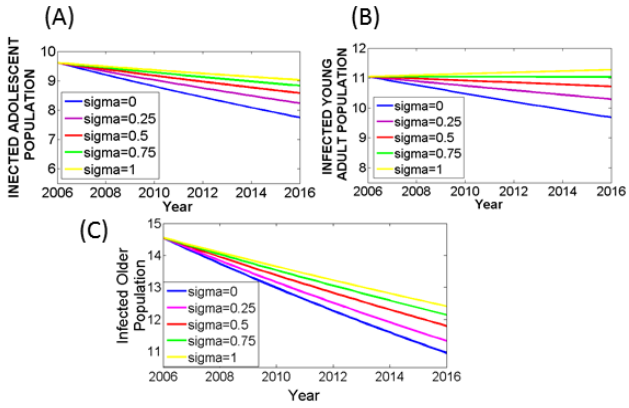

Figure 3.2: Age Dynamics Model Antibiotic Resistance: Displayed in each graph (A-C) is the total number of infectives of each age-dependent population at specified values of σ, labeled by color.

expression $\gamma\frac{1}{1+\sigma}$ decreases. Therefore, higher levels of antibiotic resistance cause a lower transition rate from the infected class to the recovered class. Figure 3.2 shows the age-dependent infective class population in response to increased σ values.

Each plot was scaled appropriately to give an accuarate estimate of increase in the infective population between each σ value. The σ values chosen, $\sigma = 0, 0.25, 0.75, 1$, were used so as to capture a vast range of infected population data among all age distributions. Recall, as σ levels increase, the model term $\gamma\frac{1}{1+\sigma}$ decreases, causing individuals of the infected class to persist at longer time intervals within this class. Figure 3.2 (C) and (B) show that the older age-dependent population experiences the lowest rates of gonorrheal infection as σ levels increase,

while, the young adult age-dependent population experiences the highest rates of gonorrheal infection as σ levels increase. The slope of each graph for σ in the older population has a higher negative value than the slope of each plot in (A) and (B). Plot (A) actually experiences a postive slope at $\sigma = 0.75$ and $\sigma = 1$, unlike plots (B) and (C), which experience no positive slope at any values of σ. Because the young adult population experiences the highest rate of disease contraction at each increased level of antibiotic resistance, this infected group may start to increase if antibiotic resistance increases significantly.

Objective three of the age dynamics model was to observe model parameter β and f sensitivity in reference to their effect on the age-dependent population dynamics of the infected classes. Sensitivity analysis of β's and f model parameters was performed in effort to determine which parameter contributes most to the population dynamics of the infected class among all age groups. Recall that the parameter β's describe the transition rates from the susceptible class to the infected class and model parameter f describes the transition rate from the recovered class to the susceptible class. Similar to model one, all parameters were increased and decreased by 20% from their original values noted in Table 3.2. The number of infected within each age-dependent population class at each specified level of σ was recorded for 2016 after model parameter increase and model parameter decrease. The purpose of recording nformation for 2016 is to infer future disease state trends. The analysis of parameter sensitivity follows, Table 3.4.

	I_A σ=0	% Change	I_A σ=0.25	% Change	I_A σ=0.5	% Change	I_A σ=0.75	% Change	I_A σ=1	% Change
β_{AAI}	7.788	**0.486**	8.379	**8.112**	8.727	**12.602**	8.984	**15.918**	9.182	**18.473**
β_{AAD}	7.618	-1.707	8.097	4.473	8.433	8.809	8.682	12.021	8.873	14.486
β_{AYI}	7.768	0.228	8.257	6.538	8.56	10.447	8.853	14.228	9.048	16.744
β_{AYD}	7.73	-0.262	8.217	6.022	8.558	10.422	8.81	13.673	9.004	16.176
β_{AOI}	7.749	-0.017	8.237	6.280	8.579	10.692	8.832	13.957	9.026	16.460
β_{AOD}	7.749	-0.017	8.237	6.280	8.579	10.692	8.832	13.957	9.026	16.460
	I_Y σ=0	% Change	I_Y σ=0.25	% Change	I_Y σ=0.5	% Change	I_Y σ=0.75	% Change	I_Y σ=1	% Change
β_{YAI}	9.697	-1.830	10.307	4.380	10.734	8.704	11.051	11.915	11.294	14.375
β_{YAD}	9.671	-2.061	10.279	4.096	10.706	8.421	11.021	11.611	11.264	14.072
β_{YYI}	10.026	**1.534**	10.657	**7.924**	11.099	**12.401**	11.426	**15.712**	11.678	**18.264**
β_{YYD}	9.353	-5.281	9.941	0.673	10.354	4.856	10.659	7.945	10.894	10.325
β_{YOI}	9.684	-1.929	10.293	4.238	10.72	8.562	11.036	11.763	11.279	14.224
β_{YOD}	9.684	-1.929	10.293	4.238	10.72	8.562	11.036	11.763	11.279	14.224

Table 3.4: Age Dynamics Model Parameter Sensitivity: Displayed are number of infected in 2016 within the adolescent and young adult populations after noted disease transmission rates experience percent increase and decrease, denoted by subscript I and D, respectively. Original values are 7.750, 9.875, and 10.652 infected A, Y, and O, respectively.

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Model parameters β_{OA}, β_{OY}, β_{OO}, and f and variable I_O were not included in the sensitivity table, Table 3.4, due to their very insignificant change in the number of infectives after they were increased and decreased by 20%. Also, I_Y and I_O are not included for the β_A's because there was no significant change in these variables when the β_A's were increased and decreased. Similarly, I_A and I_O are not included for the β_Y's. Similar to model one, Table 3.4 shows an increased number of infected individuals among all age-dependent populations as σ is increased. This is due to the fact that higher levels of antibiotic resistance cause a lessening of the individual's ability to become recovered. The model is most sensitive to a 20% increase and decrease of β_{AA} and β_{YY}. These parameters experience the greatest overall percent change among all levels of σ. Both $\beta_{AA}$and β_{YY} have the largest average percent change among all other β parameters displayed in Table 3.4. Recall, β_{AA} describes the rate of disease contraction from an infected adolescent to a susceptible adolescent and β_{YY} describes the rate of disease contraction from an infected young adult to a susceptible young adult. Therefore, it can be concluded that a 20% change in the rate of infection within each individual adolescent and young adult population has the greatest effect on disease dynamics. Table 3.4 also shows that model parameter β_{AA} is the most sensitive parameter, experiencing the greatest percentage change among all values of σ, or, more specifically, β_{AA} displays the largest average percent change

in comparison to all other β parameters. It can be concluded that a 20% change in the rate adolescents contract gonorrhea from other adolescents will have the greatsest impact on disease dynamics within their own age group. Thus, in order to combat the growth of disease due to antibiotic resistance, sexual health efforts must focus adolescent disease awareness and prevention.

3.3 Aggressive Screening

Often those individuals with gonococcal infections experience mild symptoms or an absence of symptoms, which is the primary cause for disease incline. More commonly, individuals experience no symptoms [4]. Even if symptoms of health complications appear, typically one to fourteen days after infection, symptoms are often very non-specific and mistaken for more common health infections, frequently excluding any sexually transmitted infections [4].

The aggressive screening model extends the age dynamics model by including disease awareness to influence behavioral dynamics related to whether or not an individual knows that they have gonococcal infection. This model further subdivides each infected aged class into both knowing individuals of gonoccocal infection and unknowing individuals of gonoccocal infection. Aggressive screening will allow the unknowing individual to transition to the knowing individual at a faster rate. Model equations are represented by

$$\frac{dS_A}{dt} = -(\beta_{AA}I_{AU}S_A + \rho\beta_{AA}I_{AK}S_A + \beta_{AY}I_{YU}S_A + \rho\beta_{AY}I_{YK}S_A + \beta_{AO}I_{OU}S_A +$$

$\rho\beta_{AO}I_{OK}S_A) + fR_A - \upsilon S_A + \alpha(S_A + S_Y + S_O + I_{AK} + I_{AU} + I_{YK} + +I_{YU} +$

$I_{OU} + I_{OK} + R_A + R_Y + R_O) - \delta S_A$

$\frac{dI_{AU}}{dt} = \beta_{AA}I_{AU}S_A + \rho\beta_{AA}I_{AK}S_A + \beta_{AY}I_{YU}S_A + \rho\beta_{AY}I_{YK}S_A + \beta_{AO}I_{OU} +$

$\rho\beta_{AO}I_{OK}S_A - \nu I_{AU} - t_A I_{AU} - \delta I_{AU}$

$\frac{dI_{AK}}{dt} = -(\gamma\frac{1}{1+\sigma}I_{AK}) - \nu I_{AK} + t_A I_{AUK} - \delta I_{AK}$

$\frac{dR_A}{dt} = \gamma\frac{1}{1+\sigma}I_{AK} - fR_A - \nu R_A - \delta R_A$

$\frac{dS_Y}{dt} = -(\beta_{YA}I_{AU}S_Y + \rho\beta_{YA}I_{AK}S_Y + \beta_{YY}I_{YU}S_Y + \rho\beta_{YY}I_{YK}S_Y + \beta_{YO}I_{OU}S_Y +$

$\rho\beta_{AO}I_{OK}S_Y) + fR_Y + \nu S_A - \upsilon S_Y - \delta S_A$

$\frac{dI_{YU}}{dt} = \beta_{YA}I_{AU}S_Y + \rho\beta_{YA}I_{AK}S_Y + \beta_{YY}I_{YU}S_Y + \rho\beta_{YY}I_{YK}S_Y + \beta_{YO}I_{OU}S_Y +$

$\rho\beta_{YO}I_{OK}S_Y + \nu I_{AU} - \nu I_{YU} - t_Y I_{YU} - \delta I_{YU}$

$\frac{dI_{YK}}{dt} = -(\gamma\frac{1}{1+\sigma}I_{YK}) + \nu I_{AK} - \nu I_{YK} + t_Y I_{YUK} - \delta I_{YK}$

$\frac{dR_Y}{dt} = \gamma\frac{1}{1+\sigma}I_{YK} - fR_Y + \nu R_A - \nu R_Y - \delta R_Y$

$\frac{dS_O}{dt} = -(\beta_{OA}I_{AUK}S_O + \rho\beta_{OA}I_{AK}S_O + \beta_{OY}I_{YUK}S_O + per\beta_{OY}I_{YK}S_O + \beta_{OO}I_{OUK}S_O +$

$\rho\beta_{AO}I_{OK}S_O) + fR_O + \nu S_Y - \delta S_O$

$\frac{dI_{OU}}{dt} = \beta_{OA}I_{AU}S_O + \rho\beta_{OA}I_{AK}S_O + \beta_{OY}I_{YU}S_O + \rho\beta_{OY}I_{YK}S_O + \beta_{OO}I_{OU}S_O +$

$\rho\beta_{AO}I_{OK}S_O + \nu I_{YU} - t_O I_{OU} - \delta I_{OU}$

$\frac{dI_{OK}}{dt} = -(\gamma\frac{1}{1+\sigma}I_{OK}) + \nu I_{YK} + t_O I_{OUK} - \delta I_{OK}$

$\frac{d_{RO}}{dt} = \gamma\frac{1}{1+\sigma}I_{OK} - fR_O + \nu R_Y - \delta R_O.$

The added model parameters t_A, t_Y, and t_O represent the behavioral transition rate from the unknowing infected individual to the knowing infected individual of each age-dependent population present in all infected class equations. The subscript of each rate denotes the cooresponding age-dependent population. This transitional rate represents the rate of action an infected individual becoming informed of gonococcal infection, thus influencing individual behavior to stop the spread of disease and seek medical attention. Therefore, the value $-\gamma\frac{1}{1+\sigma}$ is only included in the infected knowing population class of each age-dependent population because an individual may only recover from disease contraction once that individual has developed knowledge of contracting the disease. Once an unknowing individual becomes a knowing individual, that individual may begin recovery from disease. The added parameter value ρ is used to account for the drop in the rate of disease transmission for an unknowing individual compared to the rate of disease transmission for a knowing individual. Therefore, $0 < \rho < 1$, since the model assumes that knowing infected individuals are characterized by smaller disease transmission rates than unknowing infected individuals among all age-dependent populations. Rather than developing new transmission rates, we take $\rho = 0.25$, which was discovered in regards to the model fitting process. Note that the parameter ν is defined as in the age dynamics model. Therefore, unknowing infected individuals and knowing infected individuals transition are also capable of transitioning between each age-dependent population class. In this model, all

terms in each equation are defined as is the age dynamics model with the exception of terms involving t_A, t_Y, t_O, and ρ. With these added parameters, this model now exhibits three types of transitions. There is a transition of class, age, and awareness of disease.

The three objectives of this model include fitting the given model to known data, comparing the model to the age dynamics model in reference to infected and infected knowing individuals, respectively, and observing parameter t_A, t_Y, and t_O sensitivity in reference to their effect on the population dynamics of the infected unknowing and knowing age-dependent population classes. Sensitivity analysis was key in the employment of model three in which to discover the model parameter, t_A, t_Y, or t_O, to cause the largest percent change in the number of infected unknowing individuals among all values of σ.

3.3.1 Model Fit

The first objective was to fit the aggressive screening model to the same data as we fit to the age dynamics model. The model fit follows, Figure 3.3, along with the new parameters $\rho = 0.25$, $t_A = t_Y = t_O = 0.009$ and initial conditions used, Table 3.5.

Model simulations shown in Figure 3.3 show the fit of model's three system to the established data. Note that the established data represents the total number of knowing infected individuals in each age-dependent infective population class.

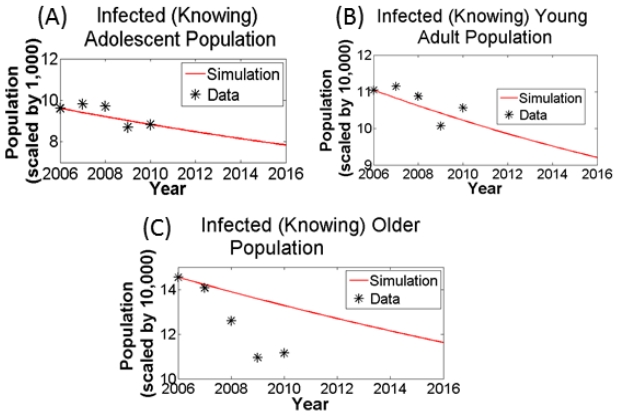

Figure 3.3: Aggressive Screening Model Data Fit: Data of the total U.S. reported cases of each age-dependent population is represented as a scatter plot. Coore-sponding model simulation represened as a solid line. Model shows similar fit to data as Virginia model. Here the residual error is 0.525, 0.346, and 13.131 for plots (A), (B), and (C), respectively.

	S	**I Unknowing**	**I Knowing**	**R**
Adolescent	2008.7416	10.5	9.6104	62.748
Young Adult	1953.5745	13.5	11.0465	61.179
Older	18585.0503	13.25	14.5447	575.655

Table 3.5: Aggressive Screening Model Initial Conditions: Shown are initial conditions used for model fit. Recall, initial conditions represent disease dynamics of age-dependent population classes cooresponding to 2006. Initial conditions scaled by 10,000.

Therefore, these data values, in reference to 2006, were used as model three initial values of the infected knowing population class. As characterized by the age dynamics model, the recovered population data values represent approximately 3% of total population of each age-dependent population. The infected unknowing population data values were arbitrarily chosen in effort to fit the established data, assuming both the adolescent and young adult populations contain a greater number of individuals unaware of disease contraction supported by their higher infection rates in comparison to the older infected population class. It is assumed that adults (older) are more knowledgable and responsible in regards sexual health awareness and prevention compared to the adolescent and young adult population. The susceptible population initial data values must equal total population of each age-depedent population excluding the infected unknowing, infected knowing and recovered population classes.

The second objective of the model was to compare both infected and infected knowing transients for both the non-screening and screening model, Figure 3.4.

Figure 3.4 shows that the models display similar data pertaining to the number of infected adolescent individuals seen in plot (A). The models show deviation from one another pertaining to the number of infected young adult and older population seen in plot (B) and (C). All plots shows that deviation increases as time increases. Therefore, both models will display similar adolescent population dynamics and dissimilar young adult and older population dynamics given the

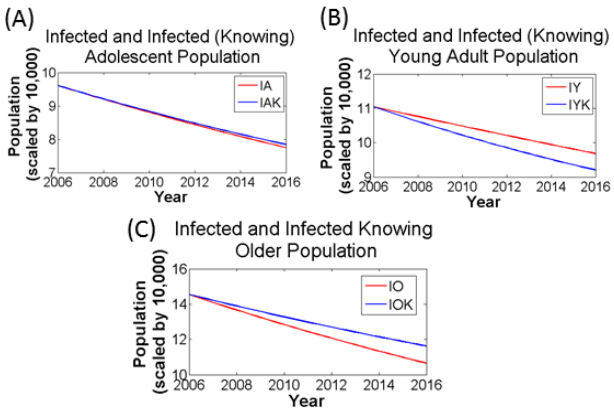

Figure 3.4: Age Dynamics and Aggressive Screening Model Transient Comparisons: Transients for both model infected and infected knowing shown for each age-dependent population, indicated by colors blue and red, respectively. Recall, all data scaled by 10,000.

same initial conditions and parameters, characteristic of each model. Because the residual error of the young adult and older population in the aggressive screening model is smaller than in the age dynamics model, the aggressive screening model provides a more accurate depiction of the presence of U.S. gonorrhea from 2006-2010.

3.3.2 Modeling Antibiotic Resistance

The third objective of the model was to perform model parameter sensitivity analysis on parameters t_A, t_Y, and t_O. The goal is to discover which parameter is most sensitive to percent change. To conduct sensitivity analysis, one parameter was increased by 50%, while the other two parameters were kept at original value. The unknowing infected adolescent, young adult, and older population was recorded among all levels of σ, shown in Table 3.6 . The model parameter which causes the greatest change in the number of unknowing infected individuals of each age-dependent population will determine the target age-dependent population for aggressive disease screening initatives.

In Table 3.6 the enlarged percentage values show the highest percentage change at each transitional percentage increase. Recall, data cooresponds to the year 2016. Table 3.6 shows a percent decrease of infected unknowing individuals among all values of σ for all population groups. As unknowing infected individuals of each population experience an increase in their discovery rate of disease

$\sigma_{=0}$	I_{AU}	% Change	I_{YU}	% Change	I_{OU}	% Change	$\sigma_{=0.25}$ I_{AU}	% Change	I_{YU}	% Change	I_{OU}	% Change
t_A	10.262	-4.290	15.504	-0.013	12.038	0.000	10.269	-4.279	15.52	-0.006	12.038	0.000
t_Y	10.719	-0.028	14.856	-4.192	12.037	-0.008	10.726	-0.019	14.871	-4.188	12.037	-0.008
t_O	10.722	0.000	15.5	-0.038	11.508	-4.403	10.728	0.000	15.517	-0.026	11.508	-4.403
$\sigma_{=0.5}$	I_{AU}	% Change	I_{YU}	% Change	I_{OU}		$\sigma_{=0.75}$ I_{AU}	% Change	I_{YU}	% Change	I_{OU}	% Change
t_A	10.273	-4.277	15.531	-0.006	12.038	0.000	10.276	-4.285	15.538	-0.013	12.038	0.000
t_Y	10.73	-0.019	14.882	-4.185	12.037	-0.008	10.733	0.028	14.89	-4.183	12.037	-0.008
t_O	10.732	0.000	15.527	-0.032	11.508	-4.403	10.36	-3.502	15.535	-0.032	11.509	-4.394
$\sigma_{=1}$	I_{AU}	% Change	I_{YU}	% Change	I_{OU}	% Change						
t_A	10.278	-4.284	15.545	-0.006	12.038	0.000						
t_Y	10.735	-0.028	14.896	-4.181	12.037	-0.008						
t_O	10.738	0.000	15.541	-0.032	11.509	-4.394						

Table 3.6: Aggressive Model Parameter Sensitivity: Total number of un-knowing individuals of each population's infected class recorded. Percentages in table represent calculated percent change from the original value of infected unknowing A, Y, and O, respectively. Original values are 10.722, 15.506, and 12.038 of A, Y, and O, respectively.

contraction, the number of unknowing infected individuals decline. The model parameter sensitivity analysis explains that as the level of antibiotic resistance rises, the number of unknowing individuals increase, though individuals are transitioning at a 50% higher rate into the knowing infected class among all populations. Thus, higher levels of antibiotic resistance prove to be a catalyst in reference to gonorrheal disease presence.

At each level of σ, t_A, t_Y, and t_O experience the greatest percent change in relation their cooresponding populations. For example, at $\sigma = 0$ the greatest percent changes are -4.290%, -4.192%, and -4.403%, diagonal entries enlarged. Similarly, at $\sigma = 0.25$ the greatest percent changes are -4.279%, -4.188%, and -4.403%. All other increased values of σ display similar information. Therefore, it can be confirmed that the most significant change in the number of infected unknowing age-dependent populations is witnessed by increasing each cooresponding population behavioral parameter by 50%. Table 3.6 also shows that the behavioral parameter from most sensitive to least sensitive are t_O, t_A, and t_Y. For example, at $\sigma = 0.75$ the percent change in the number of each population group of unknowing infected individuals is -4.394%, -4.285%, and -4.183%, describing the cooresponding percent change in the parameter most sensitive to least sensitive, respectively. These results conclude that the t_O is the most sensitive behavioral parameter. Because we assume the older population group is more responsible and knowledgable of sexual health and wellness, we conclude that it is

more practical to target initiatives toward the adolescent population. This population currently has high disease contraction rates and we would assume more receptive to disease awareness and prevention due to a lack of sexual health and wellness knowledge and sexual experience. Therefore, health organizations must focus agressive screening efforts geared toward the young adult population so as to control an incline of disease contraction. Health organizations must seek extensive gonorrheal awareness programs tailored to the young adult population in order to inform the population of necessary disease screening and protection.

CHAPTER 4

SUMMARY AND CONCLUSION

Recent CDC estimates suggest that adolescents and young adults, who represent only 25% of the sexually experienced U.S. population, acquire nearly half of all sexually transmitted diseases[13]. Adolescents and young adults are at higher risk of aquiring sexually transmitted diseases (STD's) due to behavioral, biological, and cultural factors [13]. Higher prevalence of sexually transmitted diseases among this population group likely reflects multiple barries to accessing quality STD prevention services [30]. Intervention efforts must address key aspects of the social and cultural conditions that affect sexual risk-taking behavior present in the adolescent and young adult population. In effect, strategies require design to improve these social and cultural condition to inhibit an incline in population disease contraction.

The CDC aims to improve the health of populations disproportionally affected by sexually transmitted disease by funding efforts to improve health equity, which is defined as the absence of disparities in health among population groups in a social hierarchy [14]. CDC's Division of STD Prevention (DSTDP) Community Approaches to Reducing Sexually Transmitted Diseases (CARS) is a current initiative to enable funding receipients to extend the reach of prevention services [14].

The goal of CARS is to "use community engagement methods and partnerships to build local STD prevention and control capacity in supporting the planning, implementation, and evaluation of innovative, interdisiplinay interventions to reduce STD disparities, promote sexual health, and advance community wellness" [14]. It is evident that a greater number of similar efforts concerning sexually transmitted disease disparties are required in order to advance national health equity.

The purpose of all models developed in the research study was to study small and wide-scale population dynamics in response to the acquirement of gonorrheal infection. This research topic is of national primary concern due to the emergence of antibiotic resistance of gonococcal infection and it's characterization by mild or absence of physical symptoms. Therefore, there is a possibility of rapid disease increase among all U.S. age-dependent populations. All developed models employed in the research study support the necessity of large-scale gonorrheal infection awareness, screening and prevention efforts, targeting dispartities within the adolescent and young adult populations.

The age-independent model fit to the established data describing Virginia's total number of reported cases of gonorrhea from 2001-2010. With this model we studied the system's population dynamics resulting from increased levels of antibiotic resistance. It was shown that higher levels of antibiotic resistance cause a larger percent increase in the size of the infected class and a smaller percent

increase in the size of the recovered class. Also the model dynamics are most sensitive to alteration in β, causing a greater percentage change in infected individuals among all levels of antibiotic resistance. Therefore, a change in disease transmission rate will exhibit more impact on the infected class compared to a change in "immunity loss", equivalent to unsafe practices causing a transition back into the susceptible population .

The age dynamics model extends the Virginia model by including age classes. We fit this model's dynamics to the established data of total U.S. reported cases of gonorrhea from 2006-2010 of each age group. With this model we to studied the population dynamics resulting from increased levels of antibiotic resistance. As in the first model, we confirmed an increasing rate of all age-dependent population infected classes and a decreasing rate of all age-dependent population recovered classes resulting from increased σ values. Population groups of adolescents and young adults experienced the greatest increase in disease presence between each increased level of antibiotic resistance. We performed parameter sensitivity analysis of model parameter f and the β parameters respective to year 2016. Parameter sensitivity analysis concluded that the model was most sensitive to alteration in β_{AA} among levels of σ. Thus we concluded that rate of disease transmission increased or decreased by 20% within the adolescent population will have the greatest effect on the change of disease dynamics as antibiotic resistance increases.We finally concluded that this population must be a primary target in

relation to gonorrheal disease awareness and prevention promotions.

The last model was extended by dividing all age-dependent population infected classes into unknowing and knowing individuals. This model was, again, fit to the established data of total U.S. reported cases of gonnorrhea from 2006-2010. Comparing the residual error of both models, the aggressive screening model proves more reliable in representing the U.S. gonorrheal disease state from 2006-2010. A final sensitivity analysis was used to determine which age-dependent population to target in reference to disease early detection and screening efforts. Sensitivity analysis concluded that the adolescent age group should be targeted. Therefore, increasing the rate in which the un-informed adolescent becomes informed will have the most influence on the disease dynamics. This information suggests that intervention methods highlighting the details of screening practices tailored to the adolescent population should prove successful and therefore, require immediate attention in effort to dissolve the high rate of transmission of gonoccoal infection especially among adolescents.

Future work concerning the extension of these models developed to represent the recent U.S. disease state of gonorrheal infection may include further subdivisions of each age-dependent infective class and the creation of a dynamic model parameter σ. New models may include age-dependent population infective classes further subdivided according to the disparities of disease presence. Subdivisions of sex, race, and geographical region are of particular interest due to substantial

inequalites specific within each subdivision of population. Reported by the CDC, in 2010 the rate of gonococcal infection among women was 106.5 per 100,000 population compared to 94.1 per 100,000 population amongst men. In 2010, the CDC reported a gonococal infection rate of 432.5 per 100,000 population amongst African Americans compared to 23.1 per 100,000 population among whites, 105.7 per 100,000 population amongst American Indians/Alaska Natives, and 49.9 per 100,000 population amongst Hispanics [27]. Reported by the CDC, in 2010 the rate of gonococcal infection was amongst the Southern U.S. was 134.2 per 100,000 population compared to the Midwest of 108.5 per 100,000 population, the Northeast of 77.4 per 100,000 population, and the West of 58.7 per 100,000 population [27]. Extending the last model to include further subdivisions of all infected classes will aid in analyzing, monitoring and developing predictions regarding future disease state trends specific to disparities present in our population. Awareness, screening, and prevention methods must be accuaretly tailored in effort to combat the growing disparities of disease contraction.

Newly formed models may also incorporate the presence of a dynamic σ. There exist biological factors and mechanisms by which microorganisms influence and develop antibiotic resistance [29]. The new model equation, $\frac{d\sigma}{dt}$, may incorporate these biological details to model the level of antibiotic resistance. The inclusion of a dynamic σ will allow for the simultaneous monitoring of antibiotic resistance levels and population size of the infectious class among all subgroups.

Overall, all developed models succeed in accurately representing the U.S. recent gonorrheal disease state trends. Models may be further analyzed in developing future predictions necessary to aid in disease intervention. Models conclude that targeting the disease transmission rate of the young adult population is primary to alleviating the severely disproportionate rate young adults contract gonococcal infection. The formulated models highlight the urgency of health organizations to ensure the vast expansion of sexual health equity, primarily among adolescents and young adult populations.

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VITA

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