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Rebecca Lebeaux April 1, 2018

100 Years Later: Modeling Why a Modern-Day Influenza Pandemic Would Still Disproportionately Affect Low and Middle-Income Countries

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Abstract

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As of the publishing of this thesis, one hundred years have passed since the last severe influenza pandemic in 1918 which caused catastrophic morbidity and mortality. Some countries and individuals faced worse health outcomes than others. Unfortunately, given the mutation rate of the influenza virus and growing globalization, another pandemic will likely occur. Previous research has extrapolated that an excess amount of deaths will occur in low and middle-income countries. This thesis used SIR models to explore what country-level and individual host factors would be most influential in causing inequities in morbidity and mortality across countries in an influenza pandemic of similar severity to the 1918 influenza pandemic. The results indicate that discrepancies in pandemic preparedness and surge capacity measures, facilitated by variant recovery and transmission rates, cause the biggest differentials in total attack rates (TAR), case-fatality rates, peak day of infection, and the number of individuals affected on the peak day of infection across countries of varying income levels. Specifically due to country-level factors, the TAR and case-fatality rate for a high-income country was 19.5% and 0.845% respectively compared to a low-income country which had a TAR of 72.1% and case-fatality rate of 2.50%. Acknowledging that vast disparities between countries can be remedied through better pandemic preparedness and surge capacity measures offers policy-makers the opportunity to alleviate the impact of another 1918-like influenza pandemic.

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Introduction

This was influenza, only influenza. Yet to a layperson at home, to a wife caring for a husband, to a father caring for a child, to a brother caring for a sister, symptoms unlike anything they had seen terrified. And the symptoms terrified a Boy Scout delivering food to an incapacitated family; they terrified a policeman who entered an apartment to find a tenant dead or dying; they terrified a man who volunteered his car as an ambulance. The symptoms chilled laypeople, chilled them with the winds of fear (Barry, 2005, p. 236).

Citizens of today's society frequently get sick. In developed countries, individuals may get a common cold or the flu multiple times a year. Meanwhile, in developing countries, individuals are more frequently stricken with serious infectious diseases such as malaria, tuberculosis, or HIV/AIDS. Regardless of the severity of an infectious disease, occasional illnesses within populations are likely occurrences.

Society, however, is less accustomed to mass outbreaks of infectious diseases that cause sickness, the worst of which are pandemics or global epidemics which occur about every 10-50 years (Vince, 2013). Infectious diseases "are a proxy for poverty and disadvantage...affect populations with low visibility and little political voice, ...cause stigma and discrimination,...impose a heavy health and economic burden,...and have a greater impact where health systems are weak" (WHO, 2012, p. 14). Likewise, pandemics exacerbate inequities of modern society such as poverty and racial/ethnic status (Quinn & Kumar, 2014).

Unfortunately, as this paper will address, an influenza pandemic is almost inevitable. Worse yet, numerous scholars and scientific leaders in the field feel that the world is not ready for another influenza pandemic (Director-General, 2011; Barry, 2005, p. 454; Fineberg, 2014; Walsh, 2017). In the book *The Great Influenza,* John Barry poses the question "How prepared are we for a new pandemic?" and subsequently responds "At this writing, we are not prepared. At all" (Barry, 2005, p. 454). While Barry's statement was made in 2005 prior to the 2009 H1N1

influenza pandemic, similar statements have been made post 2009. An international committee, chaired by Dr. Harvey Fineberg, was assembled by the World Health Organization (WHO) to assess the outcomes of the 2009 influenza pandemic. Similarly to John Barry, they said, "'the world is ill prepared to respond to a severe influenza pandemic or to any similarly global, sustained and threatening public-health emergency'" (Fineberg, 2014, p. 1336).

This thesis will assess how countries of different income levels will fare during an influenza pandemic akin in severity to the influenza pandemic of 1918-1919 using Susceptible-Infected-Recovered (SIR) models. First, country-level and individual host factors that most impact the morbidity and mortality of disease will be evaluated. Then, country-level factors will be used to establish parameter values and initial conditions for low, middle, and high-income country models. These models will be used to establish how many individuals in the given population are likely to end up unaffected, infected, or dead as well as the time course of disease. This research will enable policy-makers to analyze the predominant factors impacting influenza transmission, morbidity, and mortality in order to mitigate the impact of a future influenza pandemic.

Background

History of Influenza Pandemics

One hundred years since the writing of this thesis, the H1N1 influenza pandemic of 1918-1919 began ravaging the globe. Estimated to have killed 50-100 million people and infected a third of the world's population, the 1918 influenza pandemic was one of the deadliest events in human history (Taubenberger & Morens, 2006). It killed more people than those who died fighting in World War I and was brutal enough to decrease the life expectancy in the United

States by more than 10 years (Barry, 2005, p. 238). Secondary pneumonia is a predominant theory explaining why there were such high rates of mortality during the 1918 influenza pandemic (Brundage & Shanks, 2008).

Although colloquially referred to as the Spanish influenza, some hypothesize that the pandemic started in Haskell County, Kansas (Barry, 2005, p. 456). Carried by World War I troops traveling to various army camps, influenza spread rapidly both throughout the United States and globally (Barry, 2005, p. 457). The virus circulated throughout the globe in three waves (Taubenberger & Morens, 2006). The first wave occurred around March of 1918 and was relatively mild. This was followed by a deadly second wave from September to November of the same year. Finally, many countries had a third wave that swept through in early 1919. Unlike any other pattern of disease spread seen before, three consecutive waves of influenza caused mass morbidity and mortality (Taubenberger & Morens, 2006).

Various other influenza pandemics have occurred since the 1918 influenza pandemic. The 1957-1958 Asian Flu (H2N2) pandemic marked the first time that viral strains could be immediately recovered and a vaccine could be tested. In 1968, the H3N2 Hong Kong influenza pandemic originated in Southeast Asia (Kilbourne, 2006). Unlike the 1918 influenza pandemic during which 99% of influenza associated deaths occurred in individuals younger than sixty-five years old, only 48% of influenza-associated deaths were seen in the same age group during the H3N2 pandemic (Simonsen et al., 1998). Simonsen and colleagues hypothesize the difference in percentage of deaths by age-groups likely occurred because of the “intrinsic differences in virulence and transmissibility of strains and differences in the susceptibility of the general population to influenza infection due to previous exposure to antigenically similar strains and

aging of the human population" (Simonsen et al., 1998, p. 58). The H3N2 strain still persists in society as the most severe type of the seasonal influenza viral subtypes (Kilbourne, 2006).

The 2009 H1N1 influenza pandemic, however, has received the most intensive study as of late in fear that the pandemic would reach a severity level rivaling the 1918-1919 influenza pandemic. Dubbed the "swine flu" due to the crossover of the virus from pigs to humans, this was the first influenza pandemic of the twenty-first century. Beginning in early 2009 in Mexico and transmitted through trade and contact with the United States, the H1N1 virus spread globally. By April 25, the World Health Organization (WHO) declared H1N1 a "public health emergency of international concern" (Fineberg, 2014, p. 1336). By June 9, 73 countries reported greater than 26,000 laboratory-confirmed cases and shortly after the WHO declared the epidemic a phase six pandemic (Fineberg, 2014). A phase six pandemic signals that a pandemic is in progress and has caused "sustained community-level outbreaks in at least one other country in another WHO region" (Director-General, 2011, p. 102). It has been hypothesized that 100,000 to 400,000 people directly or indirectly died during the pandemic, which is similar to a typical seasonal influenza season (Fineberg, 2014). Unlike normal influenza seasons, however, it is estimated that sixty-two percent of all deaths occurred in individuals younger than sixty-fix (Simonsen et al., 2013). Accordingly, the 2009 pandemic caused more years of life to be lost than seasonal epidemics (i.e. younger individuals with more years of life yet to live, died) (Fineberg, 2014; Simonsen et al., 2013). Although this pandemic did not cause more deaths than seasonal epidemics, it did expose many governmental and health system weaknesses.

Biology of Influenza

Influenza is a respiratory disease caused by various strains of the influenza virus. Common symptoms of seasonal influenza infection include cough, sneezing, fever, sore throats, and muscle aches (CDC, 2017a). These symptoms frequently facilitate the airborne, droplet transmission of influenza that causes the illness to be spread relatively easily (WHO, 2018b). Seasonal influenza is an ongoing public health problem for most countries in the world. Every year approximately 3-5 million people have severe consequences of illness and about 290,000 to 650,000 die (WHO, 2018b). In the United States, it is estimated that annually approximately 10% of the population is infected with influenza (CDC Foundation, n.d.).

Influenza viruses are negative-sense, single-stranded RNA viruses that are divided into seven or eight segments (Bouvier & Palese, 2008). There are three viral types of influenza that infect humans: A, B, and C (WHO, 2018b). Within each main influenza viral type, there are also a variety of strains and subtypes. These viruses are classified by proteins on the surface of their cells that control the entrance and exit of influenza into host cells. These protein subtypes are called hemagglutinin (HA) and neuraminidase (NA), which also determine the nomenclature of the virus (Bouvier & Palese, 2008). The frequent mutations of HA and NA are responsible for the lack of lifelong immunity to influenza viruses (Bouvier & Palese, 2008). Thus far, only novel influenza A viruses have ever reached pandemic level (WHO, 2018b). Likewise, according to Walsh (2017), the "CDC [Centers for Disease Control and Prevention] ranks H7N9 as the flu strain with the greatest potential to cause a pandemic."

Influenza is not a disease specific to humans. Rather, as a zoonotic disease, it exists in many animal reservoirs but most notably birds. Novel influenza in humans occurs when there is a significant mutation of a dominant viral strain that often originated from another animal source.

This occurs through antigenic shift or when there is a reassortment of genes between humans and animals (Bouvier & Palese, 2008).

Each year, three or four viral strains are selected to be included in the seasonal influenza vaccine (CDC, 2017b). Due to the unpredictability of influenza viruses, the process of vaccine selection is challenging. Vaccines are created for both the northern and southern hemispheres due to the rapid antigenic change of influenza and alternating winter seasons when influenza most easily spreads. During the creation of the vaccine, viral strains selected must be unique, widely prevalent throughout the population, and available for vaccine creation (Stohr et al., 2012). Vaccine efficacy ranges depending on how well the strains are selected, but vaccines generally have between 40 to 60% efficacy (CDC, 2017b).

Seasonal influenza tends to cause the most morbidity and mortality in young children. Death from seasonal influenza is rare in individuals between the ages of one to sixty-five and mortality is often described as a "U"-shaped curve (Taubenberger & Morens, 2006). Individuals less than one are more likely to die because their immune system is not optimally primed for novel infection and elderly adults tend to have reduced immunity due to age or underlying medical conditions (Jabr, 2017).

In contrast to seasonal flu and other epidemics, the 1918 influenza pandemic is described as having a "W"-shaped mortality curve, which showed an additional large increase in deaths for individuals between the ages of twenty to forty years old (Taubenberger & Morens, 2006). Although no definitive reason has been found to explain this abnormal increase of deaths in this age group (Simonsen et al., 1998; Morens & Fauci, 2007; Morens et al., 2010), a vigorous response to the virus such as a "cytokine storm" or "overexuberant release of proinflammatory cytokines" (Morens & Fauci, 2007, p. 1022) may have occurred in this age group. Alternatively,

differential exposure to previous viruses (Morens & Fauci, 2007; Simonsen et al., 1998) or environmental factors such as smoking or aspirin use (Morens & Fauci, 2007) may have contributed to mortality differences between age groups.

Given the burden of influenza and ease of transmission, it is evident why influenza has caused previous pandemics that have created global disruption. These facts also explain why many researchers predict that another incidence of pandemic influenza is imminent due to its mutation pattern and cross-animal transmission pattern.

Structural Violence, Syndemics, and Disproportionate Health Impacts of Influenza

Infectious agents do not indiscriminately choose which people to infect as there constantly seems to be aggregations of particular diseases in hosts with similar attributes or risk factors. For instance, Murray et al. (2006) estimated that 96% of all mortalities in a future pandemic as severe as the 1918 influenza pandemic will occur in developing countries. They also found that during the 1918 pandemic there was over a 30-fold difference in mortality across countries. Likewise, Barrett and Brown (2008) identified multiple instances of inequities in morbidity and mortality that occurred during the 1918 influenza pandemic both within developed countries such as the United States and on a global scale. Within the United States, Markel et al. (2007) identified discrepancies between cities in mortality outcomes during the 1918 influenza pandemic. Modern pandemics have also demonstrated disparities in health outcomes by countries. Simonsen et al. (2013) identified up to a 20-fold difference in mortality rates across countries during the 2009 H1N1 influenza pandemic. Chowell and Viboud (2016) contend that there is not much conclusive evidence regarding the reasons for differences within or between countries but identify socioeconomic status, prior immunity, economic, and behavioral factors as

potential factors. However, Viboud et al. (2016) found that economic disparities such as country GDP could explain 37-99% of mortality differences across countries during the 1957-1959 influenza pandemic. Other than for geographic reasons, it is apparent that factors both at the individual and country-level must compound one another to cause disproportionate morbidities and mortality throughout populations. This thesis attempts to understand how some of these factors contribute to differential population health outcomes during influenza pandemics. This section will focus on disparities encountered by low-income individuals.

Structural violence defines the oppression and inherent social injustices contextualized in inequalities such as disparities in "access to resources, political power, education, health care, and legal standing" (Farmer et al., 2006, p. 1686). This concept aligns with the idea of syndemics in which there is a "clustering of social and health problems" that cause "some level of deleterious biological or behavioral interface that exacerbates the negative health effects of any or all of the diseases involved" (Singer et al., 2017, p. 941-942). Co-morbidities such as asthma, heart disease, immunosuppression, chronic lung disease, and extreme obesity are risk factors for secondary pneumonia, a major cause of severe influenza outcomes (CDC, 2018a), and are examples of syndemics.

To understand the magnitude of inequities caused by income inequality such as lack of access to health resources, it is necessary to understand the dynamics of disadvantaged individuals and influenza. Populations of low socioeconomic status face substantial health inequities throughout influenza pandemics such as reduced health resources (Oshitani et al. 2008; Rudge et al., 2012), inability or reluctance to skip work (Blumenshine et al., 2008; Bouye et al., 2009), and increased hospitalization rates (Lowcock et al., 2012; Quinn & Kumar, 2014). In an attempt to account for these disparities, Blumenshine et al. (2008) theorize there are three

main factors to explain differential disparities. These are 1) factors affecting the probability of coming in contact with the virus, 2) the susceptibility to infection once exposed, and 3) the ease of receiving treatment to increase chances of recovery.

Differences in exposure to disease have been documented for impoverished individuals. Individuals that live in public housing are more likely to suffer from poor health due to "unsafe drinking water, overcrowding (from urbanization and landfill waste, and inadequate ventilation), which could cause serious implications during an influenza pandemic" (Bouye et al., 2009, p. S289). Additionally, influenza often infects individuals that live in close proximity to poultry or swine and this initial transmission can cause propagation of infection to either other animals or throughout communities that rely on animal trade and slaughter for their livelihoods (Leibler et al., 2009). Likewise, Blumenshine et al. (2008) notes that individuals with lower socioeconomic status use more public transportation putting them at further exposure to infection. Impoverished individuals are also less likely to be able to stop working when there is fear of infection due to instability of finances putting them at further risk for exposure (Blumenshine et al., 2008).

Susceptibility differences during an influenza pandemic would likely be caused by factors that exacerbate chances of acquiring disease once exposed (Blumenshine et al., 2008). Factors causing differential susceptibility include psychosocial stress, malnutrition, and vaccine uptake (Quinn & Kumar, 2014). For instance, Linn et al. (2008) found that 56.6% of elderly United States adults with a total household income less than $10,000 reported receiving the influenza vaccine within the previous year compared to 73.4% of individuals with a total household income greater than or equal to $75,000. Factors related to low economic status, can lead to a decreased ability of the body's immune system to fight off viral infections. Inevitably, this can cause disproportionate hospitalization rates between individuals of varying

socioeconomic statuses (Quinn & Kumar, 2014). Between April and July of the H1N1 influenza pandemic of 2009, a Canadian study found a greater odds ratio (OR) of hospitalization in individuals who had a high school or lower education (OR = 2.28: 95% CI = 1.13-4.59) or who came from a poor neighborhood with high deprivation (OR = 2.58: CI = 1.24-5.35) (Lowcock et al., 2012).

Systemic barriers to treatment and differences in vaccine-seeking behavior prevent disadvantaged individuals from receiving equal access to care. On the individual level, "care-seeking attitudes and behavior" may play a role (Blumenshine et al., 2008, p. 711). Galarce et al. (2011) state that there are "attitudinal and health belief differences exist[ing] among different population subgroups" (p. 5284-5285) that impact vaccine beliefs. For example, individuals with a high school education were less likely to believe that the 2009 H1N1 influenza vaccine was safe (Galarce et al., 2011). Systemic barriers, as Hutchins et al. (2009) acknowledges, during an influenza pandemic may differ from barriers to vaccine acquisition for seasonal influenza as pandemic vaccine clinics "may require greater effort by individuals to seek out" (p. S264).

While understanding the impact of influenza on the individual is important, individuals exist within societies and countries that act both in accordance to their own needs on a domestic and global scale. Thus, in this thesis I will evaluate the impact of pandemic influenza from a country-level perspective by taking into account factors that most affect the severity of a pandemic within that particular country. Approaching disparities from this angle may appear to reduce the narrative of the individual to simply an average, but is necessary to explore the broader global outcomes inherent of pandemics.

Country-Level Social Injustices and Geographies of Blame

During influenza pandemics, inequities between countries are exposed as countries attempt to maintain their international image and the health of their citizens. Sparke and Anguleov (2012) list and discuss the drastic inequalities that presented themselves during the 2009 influenza pandemic: "(1) inequalities in blame for the outbreak in the media; (2) inequalities in risk management; [and] (3) inequalities in access to medicines…" (p. 726). These inequities compound the impact of influenza pandemics on countries with lower socioeconomic statuses.

"Geographies of blame" (Farmer, 2006) describe the "pathologization" (Sparke & Anguelov, 2012, p. 727) that disadvantaged individuals and locations often face during infectious disease events. This concept can be directly related to both the 1918 and 2009 influenza pandemics. In the 1918 influenza pandemic, when called the Spanish influenza pandemic, it improperly attributes blame to Spaniards for the pandemic (Barett & Brown, 2008). Rather, the flu is wrongly attributed to Spain because Spain reported on the influenza pandemic while other surrounding war-time countries did not want to publish stories on influenza to avoid morale deficits (Valentine, 2006). Likewise, although the 2009 influenza pandemic started in Mexico, it was likely the United States that propagated disease due to its global trade and travel networks (Sparke & Anguelov, 2012).

Assessing the impact of a pandemic also relates to countries' abilities to handle risk management. Sparke and Anguelov argue that low-income countries could not divulge influenza surveillance or reporting measures during the 2009 influenza pandemic as their health infrastructures were already stretched. They also identified multiple studies that cautioned against comparing case-fatality rates during the 2009 influenza pandemic across different

countries due to variant surveillance systems that caused underreporting. While International Health Regulations (IHR) were set in place "'to prevent, protect against, control and provide a public health response,'" (WHO, 2016, p. 1) they are also limited by their inabilities to enforce updated surveillance in these countries (Fineberg, 2014).

Access to antivirals and vaccines, as this paper will address, are influential in preventing catastrophic levels of morbidity and mortality during influenza pandemics and yet high-income countries are better able to stockpile than low-income countries. Gostin (2009) claims that rich countries frequently stockpile vaccines which "leaves poor countries in Africa, Asia, and Latin America much more vulnerable" (p. 10). These inequities in manufacturing or obtaining antivirals or vaccines played out during the 2009 H1N1 pandemic. Manufacturers were asked to reserve some vaccines for other countries (WHO, 2011). However, as Fidler (2010) found, high-income countries, including Australia and the United States, would not allow manufacturers to give vaccines to other countries until "domestic needs" (p. 2) were met. With regards to antivirals, low-income countries often may not have the capacity to meet healthcare demands including providing access to medications and health professionals (Oshitani et al., 2008). When the surge or sudden increase in the number of patients over a short amount of time occurs during a pandemic, health systems frequently are overwhelmed. This leads to an inability of low-income countries to treat patients with other chronic or infectious diseases that simultaneously occur during influenza pandemics (Oshitani et al., 2008).

SIR Models and Influenza

In the absence of an influenza pandemic, modeling can be used to predict global variations in health barriers and outcomes across countries. The dynamics of an influenza

epidemic can be represented by Susceptible-Infected-Recovered (SIR) models; indeed, SIR models have served as a "basis for all subsequent influenza models" (Coburn et al., 2009, p. 2). In this thesis, the simple SIR model discussed in this section will be adapted into a slightly more complicated model in the following section to better represent how different factors play a role in influenza pandemic outcomes. SIR models are a type of compartmental model. They are defined by susceptible, infected or infectious, and recovered individuals' movement through each compartment (see **Figure 1** and **Table 1**).

Table 1: Symbols for a generalized SIR model

Symbol	Definition
S	The number of susceptible individuals at time t
I	The number of infected and infectious individuals at time t
R	The number of recovered individuals at time t
β	Transmission rate or infection probability
μ	Mortality rate
ν	Recovery rate

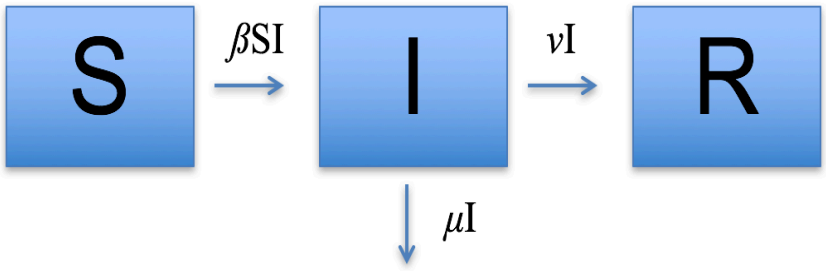

Figure 1: A generalized Susceptible-Infected-Recovered (SIR) model. Individuals within a population are classified as either susceptible (S), infected (I), or recovered (R). In this figure, individuals move from the susceptible to infected class at transmission rate β. Individuals can exit the infected class either by dying from disease at rate μ or entering the recovered compartment at rate ν.

The movement of individuals through each compartment can be represented using a set of differential equations to demonstrate the rate at which each person moves through each

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

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

$$\frac{dR}{dt} = \nu I$$

compartment throughout time. Positive terms indicate movement into a population compartment while negative signs indicate an outflow of individuals into another compartment or death.

This model has "mass action transmission" meaning the number of contacts is independent of the total number of individuals within the population (Haran, 2009, p. 13). In this model, the contact rate or number of contacts per person per unit of time consistently remains equal to one. Movement from each compartment occurs at rates β, ν, and μ. Once an infected individual enters the population, susceptible individuals will become infected at transmission rate β. Individuals that are in the infected class will either die at rate μ or recover at rate ν and enter the recovered population. This model only considers that once a person enters the recovered class, they cannot reenter the susceptible or infected class.

This type of model makes multiple assumptions, as discussed by Jones (2007). First, the population is closed and no individuals can be born into the population or die from any cause other than disease-related mortality. Second, the rate of individuals moving through the compartments is stable across time; this means that no behavioral or environmental condition will affect the rates of change over the time course of the model. Additionally, individuals are spatially distributed evenly throughout populations. Lastly, all individuals within the population are susceptible to infection. Lack of immunity to the influenza strain could cause this population-level susceptibility.

Transmissibility of Influenza and R_0

The basic reproductive number (R_0) is used to describe the transmissibility of diseases. For the purpose of this research, R_0 represented the average number of secondary cases infected with influenza from one infected person in a susceptible population (Jones, 2007) (see **Figure 2**).

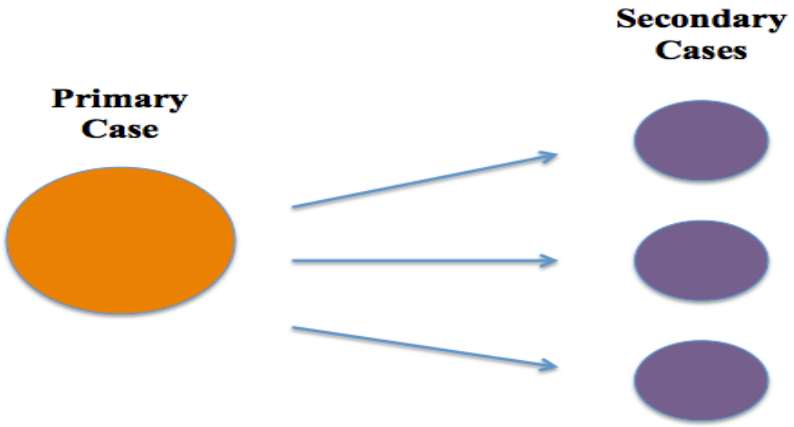

Figure 2: The reproductive number (R_0) is the average number of secondary cases that arise from one primary case. In this figure, R_0 would be three if on average every primary case infected three secondary cases.

R_0 can be calculated by multiplying the transmissibility of the infection (β) with the duration of infection ($1/v$) or the reciprocal of the recovery rate (v) (Coburn et al., 2009). In non-stochastic models, or models in which there are set parameters with no randomness, when $R_0 < 1$, no influenza outbreak will occur. This is because each infected individual is on average passing the influenza infection to less than one person. On the other hand, an $R_0 > 1$ will cause an influenza outbreak to occur.

Depending upon the transmission pattern of a given disease, the R_0 value can range from 1 to 18 for easily transmissible diseases such as whooping cough and measles (Anderson & May 1982; Keeling & Rohani, 2011). Past studies have estimated the R_0 of the 1918 influenza pandemic to be between 1.4 and 3 (Ferguson et al., 2006; Mills et al., 2004) with a median R_0 of 1.80 and an interquartile range of 1.47-2.27 (Biggerstaff et al., 2014). As a comparison,

Biggerstaff et al. (2014) estimated that the median basic reproductive number for seasonal influenza is 1.28.

Thesis Dual Group SIR Model Design and Base Model

In order to evaluate how different factors impact health outcomes between countries, a two-group model was established for a better understanding of how some factors alter populations. The model used in this thesis is an adaptation to the standard SIR model (see **Table 2** and **Figure 3**).

Table 2: Symbols used in adapted SIR model

Symbol	Definition
S_1	The number of susceptible individuals at time t in the first group
I_1	The number of infected and infectious individuals at time t in the first group
R_1	The number of recovered individuals at time t in the first group
μ_1	Mortality rate of individuals in the first group
ν_1	Recovery rate of individuals in the second group
N_1	Total number of individuals in S_1, I_1, and R_1 class at time t
S_2	The number of susceptible individuals at time t in the second group
I_2	The number of infected and infectious individuals at time t in the second group
R_2	The number of recovered individuals at time t in the second group
μ_2	Mortality rate of individuals in the second group
ν_2	Recovery rate of individuals in the second group
N_2	Total number of individuals in S_2, I_2, and R_2 class at time t
β	Transmission rate or infection probability for individuals in either susceptibility class
λ	Force of infection

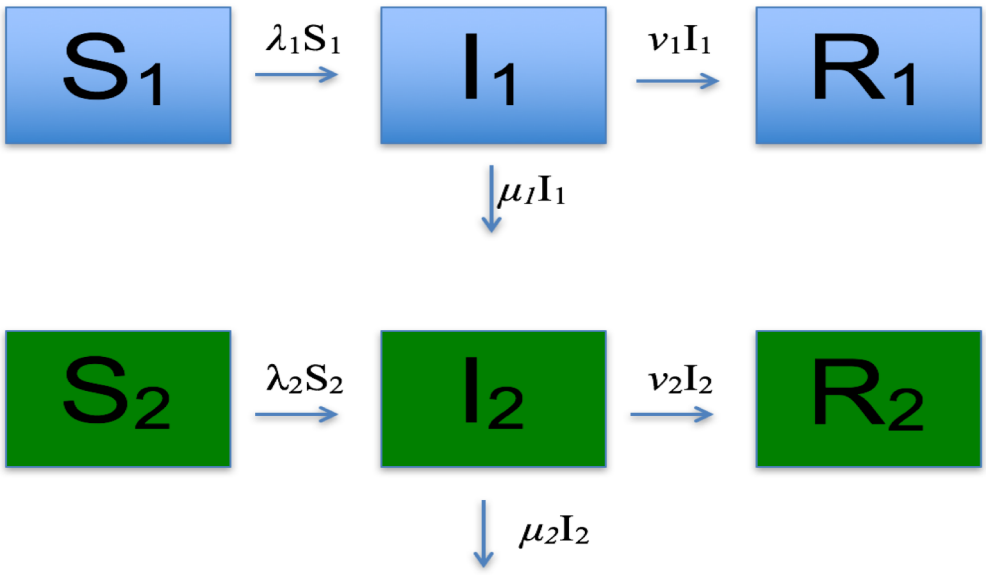

Figure 3: Individuals in this compartmental, SIR model were divided into two groups. In both groups, individuals encountered the same force of infection (λ), which controlled individuals' rate of movement from the susceptible class (S_1 or S_2) into the infected class (I_1 or I_2). Respectively, individuals in each group faced separate rates of mortality (μ_1 or μ_2) or recovery rates (v_1 or v_2) entering the recovered class (R_1 or R_2) as they exited the infected class.

Individuals within this model were broken down into two groups within one population (i.e. group 1 or 2). This allowed for differentiation of input parameters and initial conditions between the groups. All individuals entered the model as susceptible individuals in the S_1 or S_2 class unless they were initially infected with the influenza virus. A new symbol, the force of infection (λ), dictated the rate at which individuals moved from the susceptible to infected class. The force of infection was the transmission factor (β) multiplied by the proportion of infected individuals out of all individuals from both groups (N_1 and N_2). Individuals moved through each

$$N_1 = S_1 + I_1 + R_1$$
$$N_2 = S_2 + I_2 + R_2$$
$$\lambda = \beta \text{ x } (I_1 + I_2)/(N_1 + N_2)$$

$$\frac{dS_1}{dt} = -\lambda S_1 \qquad \frac{dS_2}{dt} = -\lambda S_2$$

$$\frac{dI_1}{dt} = \lambda S_1 - v_1 I_1 - \mu_1 I_1 \qquad \frac{dI_2}{dt} = \lambda S_2 - v_2 I_2 - \mu_2 I_2$$

$$\frac{dR_1}{dt} = v_1 I_1 \qquad \frac{dR_2}{dt} = v_2 I_2$$

compartment at separate rates. The force of infection (λ), however, was dependent upon the number of infected individuals in both classes. The transmission rate (β) was also the same parameter for both groups of individuals. Positive terms indicated movement into a population compartment while negative signs indicated an outflow of individuals into another compartment or death.

Separate values for the force of infection were not differentiated by group because individuals from either infected group were equally likely to infect all susceptible individuals.

Infected individuals from variant groups, however, may have left the infected class at different rates. They may have died from infection at rate μ_1 or μ_2 or recovered at rate v_1 or v_2.

Base Model Settings

To run the SIR models, I used R Studio 1.1.423 and EpiModel 1.6.1 (Jenness et al., 2017), an R package for SIR modeling. EpiModel enables the user to build deterministic compartmental models (DCMs), stochastic individual contact models (ICMs), and network models. For this thesis I created a model from a combination of the basic and two-group SIR models (EpiModel *Basic DCMs,* 2017) and adapted code using advice from the *New DCMs with EpiModel* (2017) page.

The base model (see **Figure 4**) will be referred throughout this thesis as the two-group model that has consistent parameter values and initial conditions. It can be considered the model used to demonstrate the movement of individuals between compartments in one country. The initial conditions were set at 10,000,000 susceptible individuals (S_1), 1 infected individual (I_1), and no recovered individuals (R_1) and was run for 200 time steps. Time steps in this instance represent the number of days of the epidemic. No individuals were placed in the second group (S_2, I_2, or R_2) for this base model as there were no subgroups modeled.

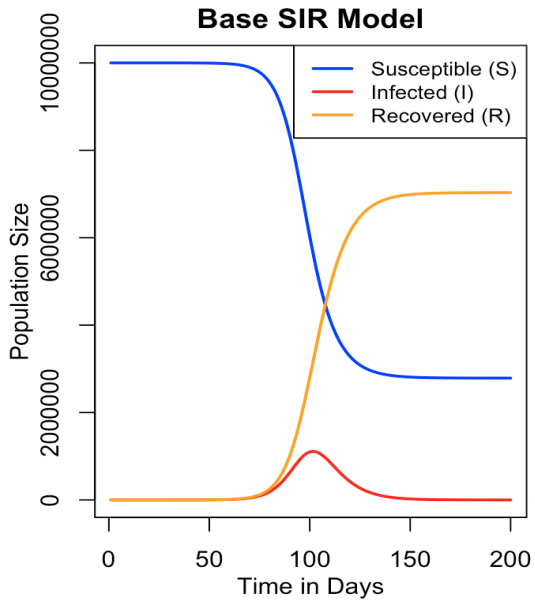

Figure 4: How individuals progressed through each compartment (S, I, and R) over the course of the influenza pandemic. There were initially 10 million susceptible (S) individuals, 1 infected individual (I), and no recovered individuals (R). By the end of the pandemic, over 7.2 million people became infected.

The parameter values for the base model were set according to prior literature regarding modeling of influenza. The R_0 for this thesis was taken from Biggerstaff et al. (2014) who found a median R_0 of 1.80 for the 1918 influenza pandemic. The recovery rate (v) is the reciprocal of the duration of infection as there is 1 recovery per person per day (Smith & Moore, 2004). The recovery rate was set at 1 recovery for every 5 days ($v_1 = 1/5$) and was adopted from Nichol et al. (2010). This falls within the CDC's stated recovery rate for influenza of 3-7 days (CDC, 2016a). Since β equals R_0 x v, β or the transmission factor became 0.36. The case-fatality rate of the 1918 influenza pandemic was found to likely be greater than 2.5% even though case-fatality rates for other influenza pandemics were less than 0.1% (Taubenberger & Morens, 2006). However, as Murray et al. (2006) established while modeling a modern-day influenza pandemic, there is variation in case-fatality rates across countries. This may be due to disproportionate outcomes or underreporting (Sparke and Anguelov, 2012). Given the inability to predict the severity of

influenza strains and lack of a succinct case-fatality rates provided in the literature, the case-fatality rate was set at 2.5%.

Calculating the mortality rate for infected individuals (μ_I) was determined once the transmission and recovery rates were established. A sensitivity analysis was completed to determine what value of μ_I would allow the case-fatality rate to be 2.5%. The case-fatality rate was found by dividing the total amount of deceased individuals from the total amount of individuals that recovered or died from infection and multiplying the result by 100%. Through this process, it was established that the mortality rate of 0.513% (μ_I = 0.00513) produced a case-fatality rate of 2.50%. Through a review of multiple studies on the 1918 influenza pandemic, Brundage and Shanks (2008) identified that the average mortality rate was <0.5% which is very close to the mortality rate selected for the base model.

Using these settings, 2,788,069 people remained susceptible (uninfected), 7,031,572 people recovered from illness, and 180,486 people died due to influenza. The peak of the epidemic occurred on day 102 with 1,109,342 people infected (see **Figure 5**). Called the total attack ratio (TAR) from Nichol et al. (2010), the TAR is the total percentage of individuals infected divided by the total individuals in the population and was 72.1% in this model.

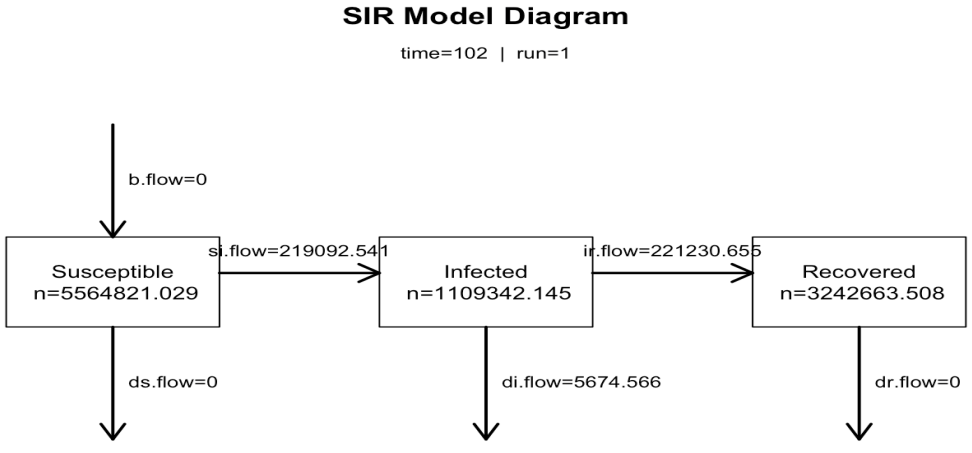

Figure 5: Output image using the basic DCM model of peak day of infection (day 102). On this day, 1,109,342 people were infected. Also demonstrated is the flow of individuals through each compartment.

Once the model was constructed, I validated my model by comparing it to the Bootsma and Ferguson (2007) model that assumed no preventative measures or treatments were used in the population. In a population of 100,000 they used an R_0 of 2, v = 1/3.5 and found a TAR of 80%. These parameter values were replicated using my model. I used the same R_0 of 2, and set v_1 = 1/3.5, μ_1= 0 , and β = 2/3.5. I found a TAR of 79.7% which is the same TAR value that Bootsma and Ferguson (2007) found in their study. This is important as it established the validity of my base model as a representative country with no access to resources. Establishing the best estimates for a country that had set characteristics and did not incorporate mitigation factors will offer insights on the importance of prevention and protection methods in further models studied in this thesis.

Modeling Country-Level and Individual Host Factors

The goal of this thesis is to understand how factors contribute to differential health outcomes during influenza pandemics for high, middle, and low-income countries. Seven factors were selected to be studied as they are a mixture of impacts that cause or are a result of income differences across countries. These factors were selected based on available literature and theoretical epidemiological importance regarding their effect on transmission, mortality, or recovery rates during an influenza pandemic. The seven factors were broken down into factors that affected populations at the country-level and individual host level. Country-level and individual host factors were modeled differently for this thesis (see **Figure 6**).

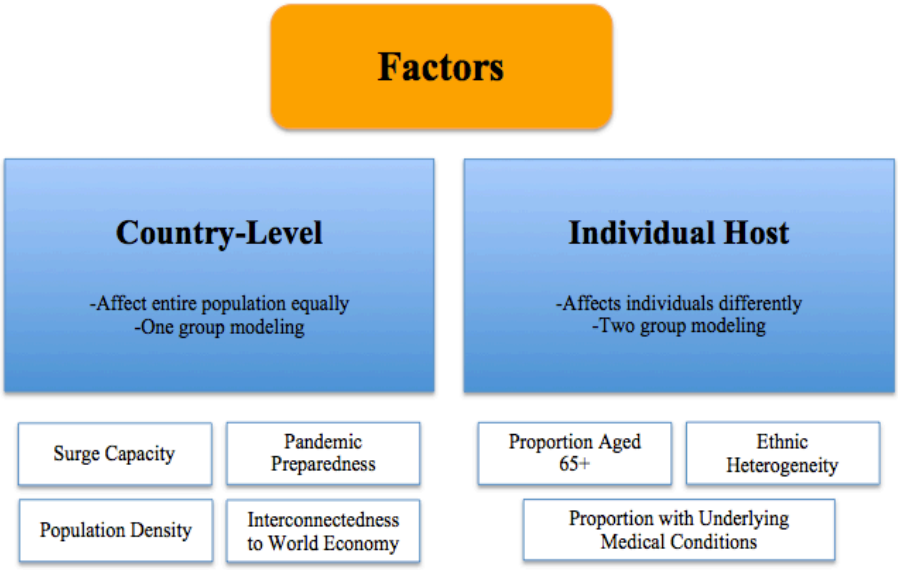

Figure 6: Seven factors divided into country-level and individual host factors due to how they impacted the population. Country-level factors included: surge capacity, pandemic preparedness, population density, and interconnectedness to the world economy. Individual host factors included: proportion of individuals sixty-five or older, ethnic heterogeneity, and proportion with underlying medical conditions.

Country-level factors are referred to as community or environmental factors in Murray et al. (2006) because they impacted all individuals within each country equally. I made the decision to change this category's name from community and environmental factors to country-level factors to clarify the extent to which these factors exist beyond the level of individual communities. This group consisted of population density, surge capacity, interconnectedness to the world economy, and pandemic preparedness. These factors were modeled with one initial group of susceptible individuals, one infected individual, and no recovered individuals unless otherwise mentioned. Additionally, μ_2 and v_2 were set to zero while μ_1 and v_1 were altered. This meant that only individuals in group 1 were analyzed and there was no flow of individuals within group 2.

Factors that affected only individuals with certain characteristics (e.g., over 65 years, immunocompromised) impacted certain subgroups' ability to respond to infection. These factors included: proportion of country with an underlying medical condition, proportion of individuals sixty-five and older, and ethnic heterogeneity. All factors in this category were modeled into two subgroups. Some individuals existed in group 1, while others were in group 2. As mentioned previously, individuals from either group could infect individuals from the other group. This was accounted for through the equation for the force of infection (λ). All scenarios started with one individual initially infected in the I_1 compartment and no individuals in either recovered compartment (R_1 or R_2). Changing the initially infected individual from group 1 to group 2 did slightly change outputs, but not substantially. Within each model μ_1, v_1, μ_2, and v_2 were altered for each factor; which allowed for individuals in each group to have separate mortality and recovery rates.

The purpose of the base model was to create a country that represents a potential low-income country that has little or no access to resources. The base model was created under the following seven assumptions regarding each factor: low population density (<175 people per square mile), low surge capacity, low interconnectedness to the global economy, a weak pandemic preparedness program, 20% of the country with an underlying medical condition, no variance in age distribution, and ethnically homogeneous. Further information regarding the operationalization of each assumption will be discussed in the following sections.

Country-level Factors

Population Density

In order to understand the spread of disease throughout countries of different income levels, it is necessary to explore spatial orientations of the population. Population density is an easily measurable factor that varies between and within countries. The range of population densities fluctuates greatly as the World Bank (2018a) reports that there are 0 people per square kilometer (PPSK) in Greenland, but 20,204 in Macau. An instance of within country variation exists in the United States. On average, the United States has 35 PPSK or 90.6 people per square mile (PPSM). However, New Jersey, the most densely populated state, has 1,225 PPSM while Alaska only has 1 PPSM (Statista, 2018b).

For the purpose of this thesis, high population density will alter β or the transmissibility of disease in addition to the rate of mortality (μ_I). This is based on the theory that individuals in high population density settings may have "more frequent and more severe" outbreaks in overcrowded settings (WHO, 2018c). Murray et al. (2006) also consider population density a potential contributor to differential mortality across communities.

Before discussing how population density could affect β and μ_I, it should be noted that many papers have shown that population density is not associated with mortality or disease spread (Mill et al., 2004; Pearl 1919; Viboud et al., 2006). However, this does not agree with the theory behind population density. Thus, to assess the factors that most greatly impact influenza pandemics, it is necessary to ascertain whether population density truly affects β and μ_I independent of other factors such as connectedness to world economy and socioeconomic status.

Pearl (1919) studied the initial explosiveness of mortality trends during the 1918 influenza pandemic throughout American cities. He found that population density did not have a

major impact on the magnitude of the original disease peak-time mortality rate. However, he did find that greater distance from a city was correlated with a decreased chance of exposure to infection. Likewise, Mills et al. (2004) identified only weak correlations between the reproductive number and population density in major cities during the 1918 influenza pandemic after looking at influenza-associated mortality. Evaluating inter-pandemic influenza epidemics in the United States between 1972 and 2002, Viboud et al. (2006) found that movement of the workforce is more of factor in disease spread than population density or size. While this study was well conceived, novel influenza strains have variant transmission patterns to seasonal epidemics based on immunity status within susceptible populations.

Other studies have found population density to be a major factor in the proliferation of disease. Gilbert et al. (2007) analyzed data from outbreaks of avian influenza in Thailand and Vietnam. They found that population density was a large factor in viral presence measured by the number of reported cases of avian influenza. Likewise, Chandra et al. (2013) used data from the 1918 influenza pandemic in India. Through evaluation of population densities across different regions, they found that areas with higher population densities had a greater percentage of population loss than areas with lower population densities. They found that the threshold for population density creating a difference in mortality depended on the number of people per square mile threshold. The decline in population was 3.72% in places with below 175 PPSM while the decline was 4.69% in places above this threshold. While this data may not exclude other factors such as socioeconomic variation, it does indicate the possibility that population density greatly impacts transmission and mortality rates. An additional limitation to this study, and some others, is that the mortality rate is derived from the number of excess deaths during the influenza pandemic.

Although literature on population density's effect on mortality and transmission rates has been mixed, theoretically population density should have an impact. Thus, the 175 PPSM threshold will be used to differentiate between low and high population density models. For the purpose of this paper, population density data will be used from the *Number of People per Square Kilometer of Land Area* data set produced by the World Bank using data from 2016 (World Bank, 2018a). The average population density of a country is 57 PPSK of land area or 148 PPSM. Average population density by country income status is shown in **Table 3**.

Table 3: Population Density by Country Income Grouping

Income Class (Defined by Gross National Income)	Population Density (People Per Square Mile of Land Area)[a]
Low-Income	127
Lower Middle-Income	337
Middle-Income	179
Upper Middle-Income	114
High-Income	88

[a] People per square mile (PPSM) data was calculated by converting population density for square kilometer from the *Number of People per Square Kilometer of Land Area* World Bank Data set. 1 square mile is equivalent to 2.589988 square kilometers (Calculateme, n.d.).

Surge Capacity

When an influenza pandemic occurs, there will be an influx of patients into healthcare centers and the ability of countries to respond to these patients at the start and peak of a pandemic amounts to differential morbidity and mortality outcomes between countries. Researchers frequently refer to the "surge" or "surge capacity" to describe the response "to a sudden increase in patient demands" (Hick et al., 2008, p. S51; Watson et al., 2013, p. 90). This

is broken down into the components of "trained personnel (staff), comprehensive supplies and equipment (stuff), facilities (structure), and, of imperative importance, integrated policies and procedures (systems)" (Barbisch & Koenig, 2006, p. 1099). Other factors contributing to surge capacity include health expenditure per capita. However, unlike with other factors, there is not a clear correlation between greater spending on health care and better health outcomes. The United States, for example, spends more on health care than any other nation, yet has a short life expectancy and poor health outcomes compared to other countries (Squires & Anderson, 2015).

For the purpose of this thesis, surge capacity will predominantly focus on the "stuff" and "structure" components. Pandemic preparedness will cover the "systems" component of surge capacity indirectly. Regarding the "staff" component, there are inherent issues with considering staff as a measure of surge capacity. Although Welzel et al. (2010) identified the number of medical staff members as a measure of surge capacity and DeLia & Wood (2008) used the number of staffed beds, Watson et al. (2013) reported that regardless of current staff levels prior to a pandemic, many may decide or be forced to not work during a pandemic.

A limitation of literature related to surge capacity is the lack of focus on low-income countries (Fischer et al., 2014; Watson et al., 2013). Watson et al. (2013) completed a comprehensive literature on papers focused on surge capacity. They found that only 4 out of the 186 (2.2%) papers assessed low-income countries, while 167 (89.8%) focused on the United States. None of the papers evaluating low-income countries provided information on modeling or quantifying surge capacity for influenza pandemics. Therefore, many papers in this field use extrapolated data from high-income countries with qualitative insights provided by papers focusing on developing countries for any analysis of low-income countries. As Oshitani et al.

(2008) acknowledges, this may underestimate the magnitude of influenza in low-income countries.

Countries that already suffer from poor health infrastructures will inevitably face further disadvantages during pandemics. For instance, chronic disease treatment or treatment for infectious diseases such as AIDS and tuberculosis may be stifled as the health system moves to halt the spread of influenza (Oshitani et al, 2008). Thus, countries that have poor health infrastructures and higher proportions of individuals with underlying medical conditions will inevitably face worse outcomes during an infectious disease epidemic.

A study by Oshitani et al. (2008) evaluated the impact of influenza pandemics on hospital beds by country. Using FluSurge 2.0 software to estimate the number of hospital admissions during an influenza pandemic, they found that a greater percentage of hospital beds would be needed for influenza patients in low-income than high-income countries. Specifically, if the influenza incidence was 35%, then in low-income countries 79.1% of hospital beds would be taken by influenza patients while only 20.8% of beds would be occupied by influenza patients in high-income countries. African countries were excluded in this study as hospital bed data had not been reported.

Other studies have focused on Sub-Saharan Africa's ability to handle an influenza pandemic. Murray et al. (2006) found that 29% of all global deaths during an influenza pandemic would come from Sub-Saharan Africa. This is a significant finding as about 17% of the world's population lives in Africa (Statista, 2018a). Murray et al. (2006) attributes these inequalities to factors related to poverty. Breiman et al. (2007) explains how poor health infrastructure would contribute to why Sub-Saharan Africa would particularly suffer during an influenza pandemic. They state that Sub-Saharan Africa has "vast geographic areas that are difficult to access; uneven

socioeconomic development; nearly transcontinental limitations in epidemiologic, surveillance, and laboratory capacity; and profound infrastructure weaknesses relating to communications and health systems and capacity of government organizations to effectively focus limited resources" (p. 1454). This analysis of Africa specifically details that poverty creates inefficiencies in health infrastructure. These systemic problems then may lead to poor outcomes during an influenza pandemic.

Studies have looked at the impacts of stockpiling resources and gaps in resource availability. Gani et al. (2005) found that if stockpiles can cover 20-25% of the population, they could reduce hospitalization rates by 50-77% in a pandemic where the R_0 value is 1.28 to 1.39. Modeling influenza resource gaps in Southeast Asia, Rudge et al. (2012) identified the impact of lacking available influenza-response resources such as antivirals, hospital beds, or ventilators. Antiviral medications may be a first line of defense against pandemic influenza depending on the strain and could be an important part of a mitigation strategy. They "may be effective for treatment and prevention of pandemic influenza, and current antiviral drugs seem to be biologically effective against 1918 and 1918-like viruses" (Blumenshine et al., 2008, p. 712). Using their models for a moderate influenza pandemic with an R_0 of 1.32, Rudge et al. (2012) found an overall attack rate of 35.6% for both situations of sufficient and not sufficient resources. However, there was a considerable difference in the case-fatality rate. Territories with no shortages of hospital resources had a case-fatality rate of 0.018%, while places with no resources suffered a case-fatality rate of 0.029%. While this model assumed a lower R_0 value than the average influenza pandemic R_0 finding of 1.80 as identified by Biggerstaff et al. (2014), the drastic difference in mortality between resource sufficient and insufficient countries will be considered while modeling surge capacity. Understanding the ability of countries to distribute

resources will help approximate why high-income countries can respond better than low-income countries during influenza pandemics.

Interconnectedness to World Economy

Globalization has enhanced the spread of microbes through increased travel and trade allowing infectious diseases to spread beyond countries' borders (Frenk et al., 2011). According to Ali and Keil (2006), the increase of infectious disease spread is a result of changing modes of transportation, the number of individuals traveling, and the new methods of entering countries. Air travel has had a large impact on the spread of diseases as incubation periods are often longer than a flight which allows microbes to travel undetected by the host to a new location (Ali & Keil, 2006). While understanding trade and travel within countries is important, Ferguson et al. (2006) found that border or travel constraints must be more than 99% effective to reduce the transmission of influenza viruses by more than a couple weeks. Additionally, they found that reducing border crossings 10-fold at the beginning of an epidemic would be surpassed once the global prevalence of the influenza virus increases 10-fold. Thus, understanding the connectedness of countries to the world economy is integral to understanding how quickly countries are likely to receive initial influenza cases as they likely will not be able to prevent influenza's entrance into the country.

The zoonotic transmission of influenza between animals also enhances the likelihood that influenza will spread across borders as novel strains of influenza are often initially passed to humans by swine or birds through antigenic drift or shift (Bouvier & Palese, 2008). Leibler et al. (2009) explains the predominant methods in which wild avian species pass influenza to humans using poultry as an intermediate viral host. Poultry pass influenza virus that mutated in either the

wild avian flocks or poultry population enough to transmit and infect humans predominantly through poultry workers. This concern is exacerbated by the growing pork and poultry production industries. Globally, pork production is predicted to increase by 2% in 2018 to 113.1 million tons and exports will increase by 3% (USDA, 2017). Likewise, broiler meat (poultry) production is set to increase by 1% to 91.3 million tons in 2018 and exports are predicted to grow by 3% (USDA, 2017).

The severe acute respiratory syndrome (SARS) epidemic of 2002-2003 and the 2009 H1N1 influenza pandemic demonstrate how the interconnectedness of countries spread SARS from Asia and H1N1 influenza from Mexico. Beginning in the Guangdong province of China, in November of 2002, many individuals became infected with an unknown respiratory illness which was later called SARS (NPR, n.d.). The illness was transmitted by hotel guests on February 21, 2003 in Hong Kong and inevitably spread to Vietnam, Singapore, Ireland, Germany, and Canada (NPR, n.d.). By the end of July 2003, the epidemic was contained but had spread to 32 countries and infected 8,099 people (NPR, n.d.). Within a span of six months in 2009, H1N1 influenza spread from Mexico to the United States through trade and travel and continued into 73 countries (Fineberg, 2014). The spread of microbes propagated by travel and trade in recent years establishes the connection between airborne transmission of diseases and commerce between countries.

The SARS epidemic of 2003 and 2009 H1N1 influenza pandemic both demonstrate the woes of globalization. The SARS epidemic began in China and spread through other countries quickly. An analysis by Keogh-Brown and Smith (2008) found that the greatest economic loss in GDP, investments, and the service sector were in China and Hong Kong, the countries hit hardest by the epidemic. Other countries, however, that saw cases of SARS including Canada and

Singapore also experienced short-term economic consequences. During the 2009 H1N1 influenza pandemic, both tourism and pork product exportation were affected. Rassy & Smith (2013) estimated that $US 2.8 billion USD was lost to tourism, a major component of their service sector and, along with the economic disaster of the previous year, caused a "virtual halt" (p. 824) of the tourism industry. While fear perceptions of influenza from pork products was unfounded due to the lack of evidence that pork consumption can infect humans (CDC, 2017c), many countries, including the United States and Japan, avoided buying meat from Mexico (Rassy & Smith, 2013). This amounted to $27 million in lost revenue for Mexico (Rassy & Smith, 2013).

Lee and McKibben (2004) state there are three main ways that SARS impacted the global economy, but their analysis can relate more generally to all respiratory disease epidemics. First, they hypothesize that consumer demand for services such as retail and travel sales decrease. Second, foreign investment money declines as confidence in the country's growth and stability are questioned. Lastly, disease prevention and ultimately the costs associated with eliminating disease are expensive. Underlying the economic consequences of pandemics is inevitably the fear associated with becoming infected by the disease. Unequal economic circumstances created during or after a pandemic may also explain why differential outcomes are exacerbated between countries.

Evaluating economic connectedness is necessary to understand which countries are likely to be most adversely impacted by a major influenza epidemic within the country. Low and middle-income countries predominantly rely on trade and service industries and thus are more greatly economically impacted by trade and travel restrictions (McKibben & Sidorenko, 2006). Fortunately, while low and middle-income countries may suffer worse economically during an

influenza pandemic, they generally have a lower McKinsey Global Institute (MGI) Connectedness Index (Manyika et al., 2016). This index evaluates the flow of people, data, services, goods, and finance and ranks countries by each subsect of their economy. As all categories evaluated by the MGI could contribute to the spread of influenza pandemics, overall country ranking of world connectedness will be used for this thesis. The MGI Connectedness Index considers the "size of each flow for a country relative to its own GDP or population (flow intensity) as well as its share of each total global flow. Combining these measures avoids making large and diversified economies appear closed simply due to the extent of economic activities taking place within its own borders" (Manyika et al., 2016, p. 11). Using data collected in 2014 and published in 2016, the MGI found that Singapore, the Netherlands, and the United States were the most interconnected countries with MGI indices of 64.2, 54.3, and 52.7 respectively. Within the top ten connected countries, six were European and two were in Asia. The Seychelles was at the bottom of the list with a score of 1.1.

As this thesis makes broad assumptions regarding countries by income levels, general estimates for connectedness index scores will be used relative to one another in modeling interconnectedness. In order to establish how global interconnectedness affects health outcomes, I will consider a very interconnected country one with a MGI Connectedness Index rating between 10.0 and 64.2 (the range of the top twenty-five most connected countries). Moderately connected countries will have index scores between 2.0 and 10.0 (the range of countries ranked twenty-six through eighty-one). Countries with low levels of interconnectedness will be any with an MGI Connectedness Index less than 2.0.

For this thesis, it will be assumed that greater economic connectedness will increase the likelihood of spread of disease into a country. This will be assumed because trade and travel

have been identified as risks leading to the proliferation and appearance of infectious diseases and pandemics (Suk et al., 2014). Geographic location and location of country of origin will play a significant role in a future pandemic, but for the purposes of this thesis, this model will assume geographic independence regarding the pandemic's country of origin. Using the MGI, a greater global connectedness ranking will affect the number of infectious individuals I_1 at the start of the pandemic. Evaluating global economic connectedness will help demonstrate how the initial entry of virus into countries will affect differential population-level health outcomes.

Pandemic Preparedness

Although governments may not initially be able to influence entry of influenza within or into their country, generally governments have some control over how they respond to pandemics. Countries that respond better and faster to the threat of influenza within their country will likely have better health outcomes. According to Lee and Fidler (2007), "surveillance, protection of the population from the circulating virus, effective response to outbreaks, and communication" (p. 218) are the four necessary functions that governments must coordinate in order to protect citizens from an influenza pandemic. The factor of pandemic preparedness will be considered a result of strong governmental planning prior to and during a pandemic.

Flaws in implementing preparedness measures have created distinct groups of countries that either do, do not, or are unable to follow the IHR. The IHR were established in 2005 "'to prevent, protect against, control and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks…'" (WHO, 2016, p. 1). This extends to infectious and noninfectious dangers (Kasolo et al., 2013). All 193 Member States of the WHO and one State Party are bound by the IHR (Director-General, 2011)

and the first full enactment of the IHR occurred during the 2009 H1N1 influenza pandemic (Fineberg, 2014). At the time of the 2009 H1N1 pandemic, 74% of countries had preparedness plans established (Director-General, 2011). However, according to the Director-General of the WHO (2011) many State Parties were not able to meet IHR guidelines for preparedness plans and infrastructure improvements by the 2012 deadline. Out of 194 State Parties, 66% responded to the WHO questionnaire sent out prior to 2012. Of the reporting State Parties, only 58% had "developed national plans to meet core capacity requirements" (p. 13) and 10% had been able to meet the IHR requirements. Gostin and Katz (2016) found that only 64 countries had fully implemented IHR by 2014. This follows the major criticism of the IHR which is the inability for the WHO to impose sanctions on countries that are unable to meet country guidelines (Fineberg, 2014). This ineptitude to act, in part, has caused differential levels of pandemic preparedness.

Pandemic preparedness for influenza has specifically been a focus of the WHO. The *WHO Checklist* (2005) was released for improving country-level preparation. The checklist includes a variety of measures that are "essential" for countries to implement including early warning surveillance, communication, risk assessment, public health measures, and health services, while ethical issues, general surveillance, vaccine programs, and evaluation are "desirable" (WHO*,* 2005). 89 countries currently have influenza preparedness plans publically available through the WHO website (WHO, 2018a), but that does not mean they are all equally effective. While the list of traits that are necessary for pandemic preparedness are exhaustive, the directly-related mitigation factors of vaccine availability and ability to enforce social distancing measures will be predominantly evaluated while modeling this factor.

Vaccines, even when only partially effective against a novel pandemic influenza strain, can still greatly reduce the total number of infected individuals within a population (Ferguson et

al., 2006). Ferguson et al. (2006) created a model to evaluate how pandemic mitigation strategies in the United States and England would reduce the spread of a pandemic. They found that vaccines need to be distributed within the first 120 days of a pandemic to be effective. As they also identify that it generally takes vaccine manufacturers longer than four months to produce a vaccine, it becomes obvious that countries need a stockpile of vaccines prior to pandemics. Luckily, even if stockpiled vaccines are "poorly matched to circulating strains" (p. 5935) of influenza, disease spread can be reduced to less than 10% even with an R_0 equal to 1.9 if children are vaccinated primarily (Germann et al., 2006).

During the pandemic, the government may also decide to enact measures to keep citizens from coming in contact with infected individuals. Certain measures may include "limiting large groups of people coming together, closing buildings, and canceling events" (Public Health Dept. of Santa Clara, n.d., p. 1) but could also include border control (Ferguson et al., 2006). Ferguson et al. (2005) considers the impact of 90% school and 50% workplace closures within a 5 kilometer radius of a detected case in addition to an 80% quarantine of the immediate space surrounding infectious individuals. They found that area quarantine, in combination with prophylactic drug treatment of individuals located near an infected individual and school and workplace closures could increase the likelihood of epidemic containment to 90% when the R_0 is 1.8. Ferguson et al. (2006) found that border control could delay the peak of an epidemic in the United States. Regarding antiviral use in conjunction with social distancing measures, Germann et al. (2006) found that for an R_0 of 1.8, the United States would need a stockpile of 51 million antiviral drugs for 281 million Americans to mitigate the attack rate to approximately 10%. The amount of antiviral drugs needed for mitigation, however, decreased significantly with every decrease in R_0.

While mitigation factors can be effective at reducing severe population health outcomes, prior research indicates that they must be applied early and effectively. Reluga (2010) asserted that utilization of social distancing measures by individuals are most effective when the basic reproductive number is close to 2. Markel et al. (2007) discussed how mitigation factors other than pharmaceutical interventions affected population health outcomes in United States cities during the 1918 influenza pandemic. They found that cities had large discrepancies in excess deaths per 100,000 both in magnitude of the first peak of infection and in overall mortality rates. For instance, New York City had the lowest excess mortality burden of Eastern seaboard cities with 452/100,000 individuals. The success was attributed at least in part to "mandatory case reporting and rigidly enforced isolation and quarantine procedures" (Markel et al., 2007, p. 651). On the other hand, Pittsburgh suffered from high excess mortality (807/100,000) likely due to its limited and slow mitigation responses. Thus, while nonpharmaceutical interventions can cause substantial differences in health outcomes, research declares that they must be applied with appropriate discretion to be effective.

Therefore, countries with strong pandemic preparedness should make efforts to reduce the R_0 value of a pandemic through measures such as social distancing and vaccination to reduce the initial surge of cases and limit the need for other resources. Multiple papers have also used a decreasing R_0 to establish the strength of a mitigation program (Ferguson et al., 2005; Ferguson et al., 2006; Mills et al., 2004). For this thesis, reduction of R_0 and hence the transmission factor (β), will be the outcome of strong vaccine production capabilities and social distancing measures. Ability to mitigate the effect of a pandemic within the country may be a contributing factor to why high-income countries tend to have better health outcomes than low-income countries.

Individual Host Factors

Proportion of Country with Underlying Medical Conditions

Different countries inherently have variant proportions of individuals in the population with underlying medical conditions and this may substantially alter morbidity and mortality rates by country. Both developing and developed countries face health burdens due to the epidemiologic transition which is a result of industrialization. For instance, cardiovascular disease causes 5-10% of deaths in less developed regions including Sub-Saharan Africa and South America as opposed to around 50% of deaths in Western Europe and North America (Yusuf et al., 2001). The types of cardiovascular disease deaths, however, vary due to the risk factors in the region (i.e. nutritional cardiomyopathies versus old age) which may in part be explained by the epidemiologic transition (Yusuf et al., 2001). According to McKeown (2009) the "epidemiologic transition describes changing patterns of population distributions in relation to changing patterns of mortality, fertility, life expectancy, and leading causes of death" (p. 1). As part of the transition, infectious diseases slowly fade as the leading cause of morbidity and mortality as urbanization brings wealth and food surplus to societies consequently leading to better public health services and nutrition (Gaziano, 2010). This leads to the third stage of the epidemiologic transition in which man-made diseases such as cardiovascular disease and cancer occur once individuals increasingly make unhealthy lifestyle choices (Gaziano, 2010). According to Yusuf et al. (2001), countries are at varying stages in the epidemiologic transition generally with developing (i.e. low and middle-income) countries in the earlier stages and developed (i.e. high-income or industrialized) countries at the latter stages of the epidemiologic transition. For countries transitioning from developing to developed, there often exists a high prevalence of both chronic and infectious diseases (Yusuf et al., 2001).

Given the predominance of chronic conditions as leading causes of death globally (WHO, 2017), it is no surprise that many studies have found associations between pre-existing medical conditions and severe health outcomes of influenza. Underlying conditions of consideration for this research will include conditions considered by the CDC to put individuals at-risk for complications from influenza such as chronic respiratory diseases, immunosuppression, chronic kidney disease, chronic neurological diseases, cardiovascular disease, lung disease, and extreme obesity (CDC, 2018a).

Individuals with chronic conditions frequently have higher hospitalization and mortality rates from influenza than other individuals within the population. Campbell et al. (2010) used 2009 pandemic influenza surveillance in England to quantify the risk of hospitalization due to influenza in individuals with pre-existing conditions such as chronic respiratory diseases, immunosuppression, chronic kidney disease, and chronic neurological diseases. They found that having one of these pre-existing conditions increased risk of hospitalization 10- to 20-fold. Additionally, they found an OR of 1.6 (95% CI: 0.9-2.9) for death in individuals with one or more chronic conditions in hospitalized individuals and had a 1.5 OR (95% CI: 1.1-2.1) of having any severe outcome compared to patients with no underlying medical condition. Van Kerkhove et al. (2011) found that the OR for death after influenza-related hospitalization was significantly higher for those with respiratory disease, diabetes, cardiac disease, renal disease, liver disease, neurological disease, or patients who were immunocompromised. Likewise, during the 2009 influenza pandemic in Mexico, it was estimated that 70% of all hospitalized individuals had a pre-existing condition (Echevarria-Zuno et al., 2010). Although not a disease alone, obesity has also been shown to be a notable risk factor for more severe outcomes of novel influenza as it can lead to other underlying conditions such as cardiovascular disease. A study in

California identified that half of patients twenty years or older hospitalized during the 2009 H1N1 influenza pandemic were obese (Louie et al., 2011). These results suggest that the prevalence of underlying conditions and the distribution of that burden globally is central to understanding how a 1918-like influenza pandemic would impact the world today.

Although no estimates for proportions of individuals with pre-existing conditions have been directly calculated for all countries, approximate rates of underlying conditions have been found for some countries and can be extrapolated for other countries. The United States (U.S.) has well-documented rates of underlying medical conditions. As of 2000, 45% of the U.S. population was found to have a chronic condition (Anderson & Horvath, 2004). That number is likely higher currently due to the increasing prevalence of obesity and diabetes. Additionally, a more recent study by Claxton et al. (2016) found that 27% of all Americans younger than 65 had a pre-existing condition. Health conditions defined for the Claxton et al. (2016) study were characteristics that would have made the participants ineligible for health insurance before the Affordable Care Act. Regarding obesity, the Organization for Economic Cooperation and Development (OECD), often considered '"a club of mostly rich countries"' (Buttonwood, 2017), found that on average in 2015 that 19.5% of individuals fifteen and older were obese in OECD countries (OECD, 2017). In the United States, the obesity rate was 38.2% (OECD, 2017).

As a result of pre-existing conditions, two key parameters in the SIR model will be impacted, the recovery rate, v_2, and mortality rate, μ_2. As related to mortality, Campbell et al. (2010) found that the OR for death increased to 1.6 given hospitalization, so the case-fatality rate will be adjusted accordingly. For the recovery rate, it will be assumed that individuals with chronic conditions will have a prolonged duration of infection as individuals as they are more likely to be hospitalized or die (Campbell et al., 2010; Echevarria-Zuno et al., 2010; Louie et al.,

2011). Understanding the proportion of individuals with chronic conditions by country will enable a better understanding of how co-morbidities at the individual level compound population-level outcomes.

Proportion of Individuals Sixty-Five and Older

Influenza can infect individuals of all ages, but generally does not at the same rate. Variant age distributions between countries may impact the severity of health outcomes in countries with different income levels. Despite the high prevalence of chronic conditions in elderly adults (Christ & Diwan, 2008), this section will detail why during influenza pandemics elderly individuals die at a decreased rate than anticipated. This may be a contributing factor to explain why high-income countries have lower mortality rates than low-income countries.

During the 1918 influenza pandemic, for instance, mortality rates formed a "W"-shape with the highest death rates in the youngest and oldest individuals and a distinctive spike in individuals twenty to forty years old (Taubenberger & Morens, 2006). As Morens et al. (2010) and Morens and Fauci (2007) explain, this is surprising because more young adults than expected died and mortality in elderly individuals was "less pronounced" (p. 1023) than individuals of any other age. Morens and Fauci (2007) clarified that, while there was an association between mortality and age, mortality was not as high as expected in the elderly population.

Simonsen et al. (1998) found a distinct difference in mortality between individuals younger than or greater than 65. They found that during the 1918 influenza pandemic, 99% of deaths likely caused by influenza were in individuals younger than sixty-five. In addition, "the absolute risk of influenza-associated mortality was higher among persons <65 than those ≥ 65"

(Simonsen et al., 1998, p. 54). They also found that the risk ratio of death in those greater than sixty-five to younger than sixty-five was 0.3 to 1 meaning that individuals older than sixty-five had a significantly reduced chance of dying from influenza than younger adults.

Results suggest that regardless of the high proportion of underlying medical conditions in elderly individuals, adults sixty-five and older likely have some immune advantage during influenza pandemics. Data from the 2009 influenza pandemic seem to also indicate that lower than expected rates of mortality in the elderly occurred. Shrestha et al. (2011) found that during the 2009 H1N1 pandemic in the United States, there were 4.2 deaths per 100,000 in individuals sixty-five and older compared to an overall death rate of 4.1 per 100,000. This is significantly lower than the average death rate from 1990 to 1999 from influenza in individuals over sixty-five which was 22.1 deaths per 100,000 people. Murray et al. (2006) found through looking at data for 27 countries, some US states, and Indian provinces that if an influenza pandemic were to occur today, some countries would have "almost no excess mortality in individuals aged over 60 years" while others may have "substantial mortality in the same age group" (Murray et al., 2006, p. 2213). Murray et al (2006) also made predictions of age distribution and mortality across countries if an influenza pandemic occurred in modern times. They predicted that only 7% of all deaths would occur in individuals sixty years or older while 58% and 28% of deaths would occur in those 15-44 and individuals younger than fifteen respectively. They suggest that deaths of individuals 15-40 years old would be caused by high mortality rates while there would be a larger population of individuals younger than fifteen years old who would face a moderate mortality rate.

Data on the proportion of individuals older than sixty-five for 180 countries was acquired from the World Bank (2018b) dataset. The average percentage of individuals older than sixty-

five has a wide range across countries but the mean is 8%. On average, 17% of the population in high-income countries is greater than or equal to sixty-five while low-income countries only have 3% of their population sixty-five and older. Although it is still likely that the proportion of elderly individuals dying in a pandemic will be increased due to a high proportion of elderly individuals with underlying medical conditions, it will be assumed that this group will have an immune advantage due to prior exposure to an antigenically similar influenza strain. The mortality rate (μ_2) and recovery rate (v_2) for elderly individuals will be reduced in the model, to account for this prior exposure to disease and will reduce the severity and duration of infection. Through accounting for prior immunity to the virus, countries with larger percentages of individuals greater than or equal to sixty-five (high-income countries) will likely reduce their mortality and morbidity compared to countries with lower percentages (low-income countries).

Ethnic Heterogeneity and Minority Populations

Another factor that may impact pandemic influenza outcomes across countries is how ethnic heterogeneity reduces access to health care and can cause societal inequalities. Ethnic diversity has been shown to be largely negative in many instances and high proportions of ethnic heterogeneity may affect morbidity and mortality totals for different countries. Easterly and Levine (1997) found that high ethnic diversity is related to "low schooling rates, underdeveloped financial systems, … and insufficient infrastructure" (p. 1203). They evaluated African countries and found there was a correlation between low economic growth and ethnic diversity. They concluded that this trend was not unique to Africa. Alesina et al. (2003) compiled literature based on the United States and also found that, in more ethnically diverse locations, public goods

were less well distributed and community trust was reduced. Churchill and Smyth (2017) also have identified a link between increased poverty and high ethnic or linguistic heterogeneity.

Similarly to structural violence caused by income or wealth status, racial or ethnic status can create disadvantaged individuals throughout countries. Citing multiple studies, Hutchins et al. (2009) states that minority populations have "higher rates of injuries, poor health conditions, adverse health outcomes, and lack of access to health care" (p. S261). Minorities may also suffer from stigmatization and unequal care over the course of inpatient care (Blumenshine et al., 2008). According to Barrett & Brown (2008) stigmatization within populations can reduce health care seeking, cause an increase of disease spread among disadvantaged individuals, reduce the cooperation between susceptible individuals and health or governmental experts, and cause an exacerbation of societal panic.

Minority groups also disproportionately suffer from influenza due to a variety of factors. Hutchins et al. (2009) states that racial or ethnic minorities may face worse health outcomes because minority groups tend to have higher rates of pre-existing health conditions, less access to health care, lower rates of seasonal influenza vaccination, and greater socioeconomic barriers to implement pandemic interventions in their homes or communities. Likewise, Van Kerkhove et al. (2011) summarizes hypotheses from papers as to why influenza-related health disparities occur including "a higher prevalence of chronic medical conditions known to increase risk of severe influenza, delayed or reduced access to healthcare, cultural differences in healthcare-seeking behavior and approaches to health, potential differences in genetic susceptibility, and social inequalities" (p. 8-9). According to Hutchins et al. (2009), ethnic/racial minorities also have a greater risk of secondary pneumonia independent of pre-existing conditions. They argue that the increased chance of secondary infection may be caused by "lower pneumococcal

vaccination coverage and differential access to health care" (Hutchins et al., 2009, p. S264). As this paper already considers chronic conditions, the factor of ethnic heterogeneity will reflect how minority groups suffer from differences in healthcare access, healthcare-seeking behavior, and social inequalities.

Studies conducted in high-income countries including the United States, Canada, Australia, and New Zealand have shown a significant difference between morbidity and mortality totals during the 2009 H1N1 (Dee et al., 2011; Tricco et al., 2012; Van Kerkhove et al., 2011) and 1918 influenza pandemics (Frost, 1920; Garrett, 2008; Groom et al., 2009; Hutchins et al., 2009) between minority and non-minority populations. Of interest, Dee et al. (2011) found that during the 2009 H1N1 influenza pandemic in the United States, minorities had age-adjusted hospitalization rates of pediatric cases that were two times greater than those for Whites. Evaluating data on individuals from nineteen countries admitted to the hospital during the 2009 H1N1 pandemic, Van Kerkhove (2011) found that individuals from minority populations or vulnerable groups had a risk ratio for death of 2.4 (IQR 1.2-3.8). Data, however, was not consistent across all countries as Mexico and Thailand reported less severe outcomes for minority populations than the general population. As Hutchins (2009) acknowledged, Frost (1920) and Garrett (2008) both found that minority population suffered in cities in the U.S. during the 1918 influenza pandemic. Groom et al. (2009) identified that influenza outcomes in American Indians and Native Alaskans were more severe in 1918 and are still present in modern influenza outbreaks.

As high ethnic group diversity may be harmful to countries, the fractionalization or measure of evaluating the number of ethnicities within a country will be considered. Alesina et al. (2003) created an ethnic fractionalization index that evaluates the diversity of ethnicities

within populations based on anthropological insights. The values given to each country vary from 0-1 with 0 being a perfectly homogeneous country and 1 being completely heterogeneous. The mean for the 180 countries available was 0.435. The country with the greatest fractionalization was Liberia at 0.9084 while Comoros was completely homogenous at 0.0000, meaning that all individuals were of the same ethnic group. Westernized countries including Sweden and Japan tended to have lower ethnic fractionalization, while Sub-Saharan African countries such as the Democratic Republic of Congo had higher ethnic fractionalization score.

This model for ethnic heterogeneity will establish intervals for ethnic fractionalization scores to understand how variant populations throughout countries may partially explain why there are differential health outcomes between countries. Countries with ethnic fractionalization scores between 0.00 and 0.3 will be considered relatively homogeneous countries. Moderately heterogeneous countries will have indices between 0.3001 and 0.6000. Highly heterogeneous countries will have an ethnic fractionalization score between 0.6001 and 1.000. These varying values of ethnic heterogeneity will impact the number of individuals in each susceptible population group.

Results by Country-Level and Individual Host Factor

This section will detail how each country-level and individual host factor will impact countries' abilities to respond to influenza pandemics. The operationalization of how each factor was modeled along with the parameters and initial conditions used are discussed and can be viewed in **Table 4** and **Table 5**. Descriptive population-level health outcome measures by factor are also detailed. Comparisons between factors will be considered in the discussion section.

Table 4: Input Parameters and Initial Conditions by Country-Level Model

	Base Model	High Pop. Density	High Surge Capacity	Moderate Surge Capacity	Highly Connected	Moderately Connected	High Prep.	Moderate Prep.
S_1	10,000,000	10,000,000	10,000,000	10,000,000	10,000,000	10,000,000	10,000,000	10,000,000
I_1	1	1	1	1	40	20	1	1
β	0.36	0.396	0.36	0.36	0.36	0.36	0.28	0.32
R_0	1.8	1.98	1.44	1.62	1.8	1.8	1.4	1.6
μ_1	0.00513	0.00651	0.00213	0.00394	0.00513	0.00513	0.00513	0.00513
v_1	1/5	1/5	1/4	1/4.5	1/5	1/5	1/5	1/5

Note: Values for $R_1, S_2, I_2, R_2, \mu_2, v_2$ are not shown as they are 0 in all models and are only used in subgroup modeling. Pop. stands for population and prep. stands for preparedness

Table 5: Input Parameters and Initial Conditions by Individual Host Model

	Base Model	High UMC	Moderate UMC	High 65+	Mod. 65+	Low 65+	High Het.	Med. Het.	Low Het.
S_1	10,000,000	9,000,000	7,000,000	8,300,000	9,300,000	9,700,000	8,000,000	4,500,000	1,500,000
I_1	1	1	1	1	1	1	1	1	1
S_2	0	1,000,000	3,000,000	1,700,000	700,000	300,000	2,000,000	5,500,000	8,500,000
β	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36
R_0^A	1.8	2.16	2.16	1.44	1.44	1.44	2.16	2.16	2.16
μ_1	0.00513	0.00513	0.00513	0.00513	0.00513	0.00513	0.00513	0.00513	0.00513
μ_2	0	0.00695	0.00695	0.00171	0.00171	0.00171	0.0106	0.0106	0.0106
v_1	1/5	1/5	1/5	1/5	1/5	1/5	1/5	1/5	1/5
v_2	0	1/6	1/6	1/4	1/4	1/4	1/6	1/6	1/6

A: Subgroup R_0 value shown.

Note: UMC stands for underlying medical conditions, mod. stands for moderate, prop. stands for proportion, and het. stands for heterogeneity

Population Density

Population density was operationalized into high (>175 PPSM) and low (<175 PPSM) population density. Low population density used the same parameters as the base model. For

high population density, β was increased by 10% to 0.396. Increasing the population density by 10% increased the R_0 value to 1.98. I increased the case-fatality rate by 26% to 3.15% which is in line with the findings of Chandra et al. (2013) who found a decline in mortality of 4.69% in high population density (>175 PPSM) and 3.72% in low population density (<175 PPSM) countries. This was facilitated by an increased mortality rate (μ_1) of 0.00651.

The peak day of infection occurred on day 85 with 1,407,694 people infected. The peak day of infection occurred 17 days before the peak day of infection in the low population density model (see **Figure 7**). The TAR for the high population density model was 78.0%.

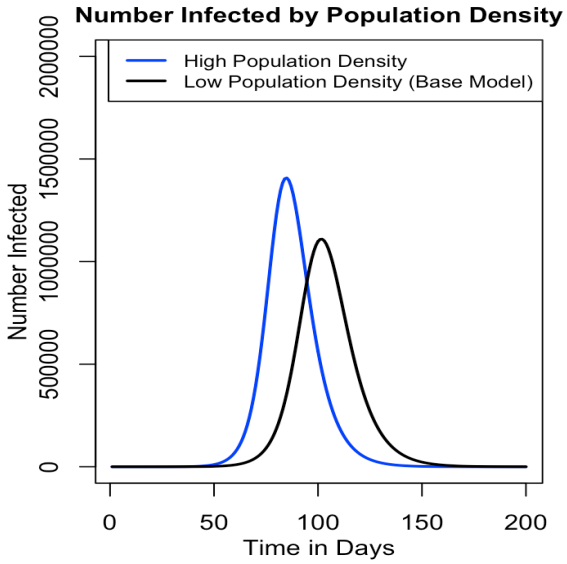

Figure 7: Number of infected individuals over time in the low and high population density models. The peak of infection for high (>175 PPSM) population density (blue) occurred at day 85 which was 17 days earlier than in the low (<175 PPSM) population density model (black). 1,109,342 were infected on this peak day in the low population density model and 1,407,694 were infected in the high population density model. The TAR for the low population density model was 72.1% and was 78.0% in the high population density model.

As identified through the literature review, there were no strong conclusions regarding increased transmission in high versus low population density areas despite the high theoretical likelihood that population density is an important factor. To test the high population density model with no transmission rate increase, only the mortality rate (μ_1) was altered to 0.00651 and

β was held constant at 0.36. The recovery rate and all initial conditions remained the same as the base model. Only changing the mortality rate did not cause a significant difference in health outcome measures from the base model. While the literature was mixed regarding population density, this thesis's goal is to address all possible factors affecting the severity of a modern-day influenza pandemic in low, middle, and high-income countries. Thus, it was assumed for the purpose of this thesis that population density did affect both the mortality and transmission rates.

Surge Capacity

Low, moderate, and high surge capacity was modeled. The low surge capacity model had the same characteristics as the base model. The high surge capacity model had a case-fatality rate of 1.0% based on the 60% reduction identified by Rudge et al. (2012). This equated to a mortality rate (μ_1) of 0.213%. It was estimated that with moderate surge capacity, the case-fatality rate would be decreased by 30% to 1.75% making the mortality rate (μ_1) 0.00394 (0.394%). The recovery rate was decreased by half a day (ν_1 =1/4.5) for the moderate surge capacity scenario and by a full day (ν_1 =1/4) in the high surge capacity scenario given the effectiveness of early antiviral treatment (CDC, 2018b). This decreased the R_0 to 1.62 and 1.44 in the high and moderate surge capacity models respectively.

Both the moderate and high surge capacity scenarios increased the time to the peak day of infection and reduced the total number of individuals infected over the low surge capacity model (see **Figure 8**). The moderate surge capacity scenario saw the peak day of infection occur after 115 days with 804,568 individuals infected. The TAR was 64.2%. In the high surge capacity scenario, the peak day occurred on day 137 with 504,594 individuals infected and a TAR of 53.3%.

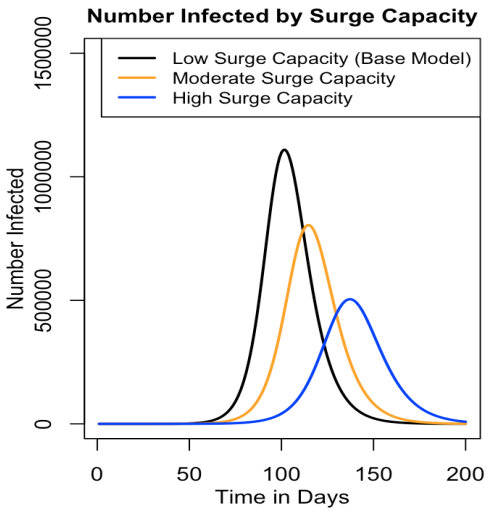

Figure 8: The number of infected individuals by low, moderate, and high surge capacity capabilities. The low surge capacity model (black) had the same characteristics as the base model. The moderate surge capacity scenario (orange) had a case-fatality rate of 1.75% and TAR of 64.2%. Peak day of infection occurred on day 115 with 804,568 individuals infected. In the high surge capacity scenario (blue), the peak day of infection occurred on day 137 with 504,594 individuals infected. The TAR was 53.3% and the case-fatality rate was 1.00%

Interconnectedness to the World Economy

Interconnectedness to the world economy was modeled for countries that were considered as having a low, moderate, or high connectedness to the world economy. Country's connectedness were defined by the MGI Connectedness Index as discussed earlier. The low connectedness to the world economy model was the same as the base model. A moderately connected country had an increase in initial infected individuals to 20 ($I_1 = 20$) and a highly connected country started with 40 initial individuals infected ($I_1 = 40$).

The case-fatality rate, TAR, and number of infected individuals on the peak day of infection remained consistent while the peak day of infections decreased with increasing connectedness (see **Figure 9**). The case-fatality rate for all models was 2.50% with a TAR of 72.1%. The moderately connected scenario had a peak day of infection on day 82 with 1,109,691

infected while the highly connected scenario had a peak day of infection on day 78 with 1,109,846 infected.

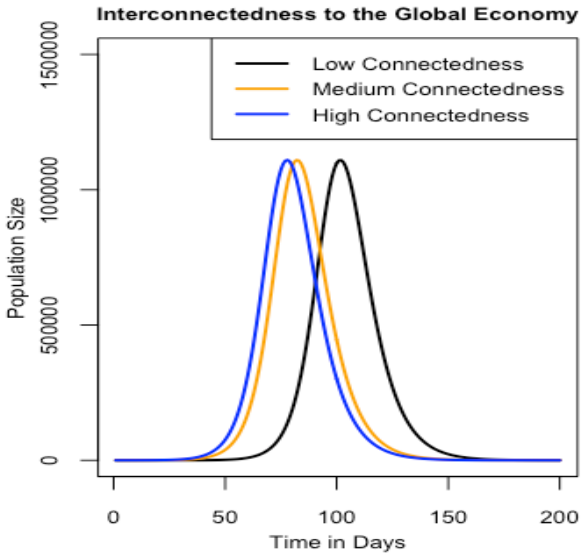

Figure 9: The number of infected individuals by low, moderate, and high connectedness to the world economy. The case-fatality rate, TAR, and number of infected individuals on the day of peak infection were stagnant across the three scenarios. The peak day of infection for the low (black), moderate (orange), and high (blue) connectedness models were day 102, 82, and 78 respectively. This signified that an increase in connectedness to the world economy decreased the number of days until the peak of the infection.

Pandemic Preparedness

Low, moderate, and high pandemic preparedness scenarios were modeled based on reductions in the basic reproductive number, R_0. Low pandemic preparedness kept the ascribed R_0 of 1.8, while in the moderate and high pandemic preparedness models the R_0 decreased to 1.6 and 1.4 respectively. To operationalize these R_0 decreases, β was decreased to 0.32 and 0.28 for each given the relationship between R_0 and β ($R_0 = \beta/v_1$). A second change that was made to the base model was an increase in the number of steps or time modeled ($t = 400$). This was to accommodate the longer timespan of the pandemic preparedness models due to the decreasing R_0 value.

The case-fatality rate remained 2.50% for all scenarios, but the TAR, peak day of infection, and number of individuals infected on the peak day of infection changed (see **Figure 10**). Moderate pandemic preparedness had its peak infection on day 133 with 749,301 people infected. The high pandemic preparedness scenario's peak day of infection was on day 194 with 401,042 people infected. The TAR for the moderate preparedness scenario was 62.7% and was 48.9% for the high preparedness scenario.

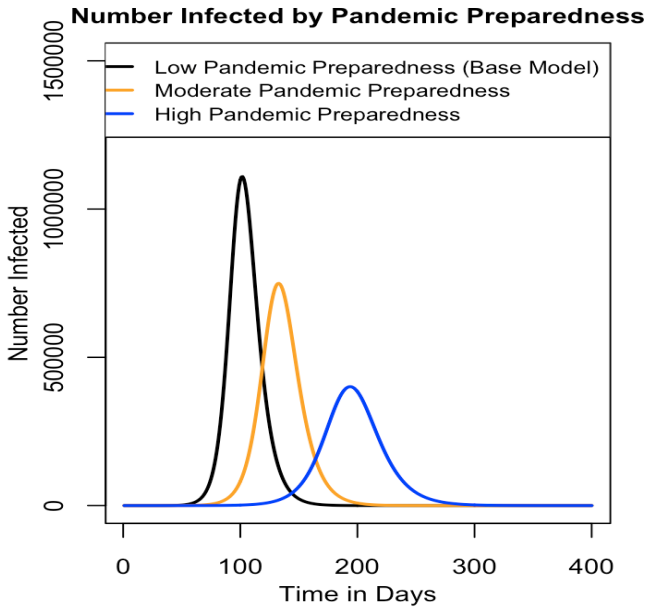

Figure 10: The number infected by the level of pandemic preparedness in the country. Low pandemic preparedness had the same characteristics as the base model (black) with 72.1% infected and a peak day of infection on day 102. The peak day of infection was extended to day 133 and 194 for the moderate (orange) and high (blue) pandemic scenarios respectively. The TAR decreased with increasing pandemic preparedness levels from 72.1% to 62.7% and 48.9% respectively.

Proportion of Country with Underlying Medical Condition

The proportion of a country with an underlying medical condition was modeled as low, moderate, and high proportions of individuals with these chronic conditions. The base model assumed that 20% of individuals had these chronic conditions based on the average levels of

obesity in OECD countries (OECD, 2017). The moderate proportion scenario had 10% more individuals with underlying medical conditions than the base scenario (S_1 = 9,000,000 and S_2 =1,000,000) and the high proportion scenario had 30% more individuals than the base model with underlying medical conditions (S_1 = 7,000,000 and S_2 =3,000,000).

The case-fatality rate was made to be 60% greater in the population of individuals with underlying medical conditions to match the findings from Campbell et al. (2010). This made the case-fatality rate 4.00% in a population with 10,000,000 individuals with a mortality rate of 0.695% (μ_2 = 0.00695). The recovery rate was also decreased in this subpopulation so that recovery occurred once every six days (ν_2 = 1/6). This increased the R_0 in this subpopulation to 2.16. All other parameters and initial values remained the same as the base model.

The moderate and high proportion of individuals with underlying medical conditions model displayed variant characteristics than the low proportion model (see **Figure 11**). The scenario in which there was a moderate proportion of individuals with an underlying medical condition had an overall case-fatality rate of 2.65% and TAR of 73.4%. The peak day of infection occurred on day 100 with 1,166,348 infected. In the scenario where a high proportion of individuals had underlying medical conditions, the peak day of infection occurred on day 97 with 1,278,564 individuals infected. The TAR was 75.8% and the case-fatality rate was 2.95%.

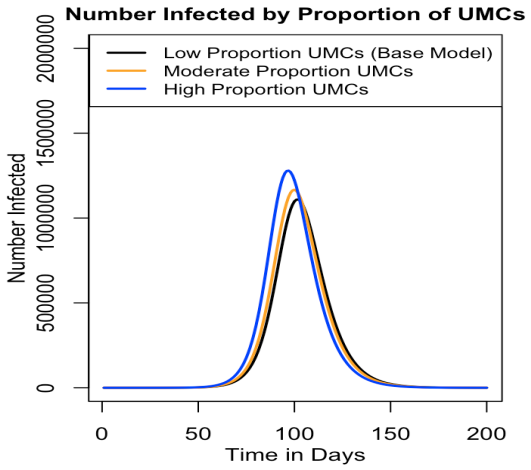

Figure 11: Number of individuals infected by proportion of underlying medical conditions (UMCs). Individuals in countries with a high proportion of underlying medical conditions (blue) had the highest rate of deaths with a 2.95% case-fatality rate and a TAR of 75.8%. There was less than 5 days of change in the peak day of infection between scenarios but the greatest number of individuals infected on the peak day occurred in the high proportion of individuals with underlying medical conditions model.

Proportion of Individuals 65 and Older

The proportion of individuals sixty-five and older was modeled by no, low, moderate, and high proportions of individuals sixty-five and older. Individuals who are sixty-five and older were considered partially immune to the virus because their immune system had been previously exposed to this viral strain. The elderly population was split into their own separate group and their mortality rate was reduced by 2/3 to 0.171% ($\mu_2 = 0.00171$) based on the reduction in mortality rate identified by Simonsen et al. (1998). The recovery rate was also reduced by one day to account for a shorter recovery period in individuals that are immune ($v_2 = 1/4$). 3%, 7%, and 17% of individuals were considered sixty-five or older in the low, moderate, and high proportion models based on the World Bank's *Population ages 65 and above (% of total)* (2018b) data set for low, middle, and high-income countries. For the low proportion of individuals with underlying medical conditions model, 9,700,000 were placed in the S_1 group and 300,000 were initially put in S_2 group. S_1 for the moderate and high proportion of individuals sixty-five or older models was 9,300,000 and 8,300,000, while S_2 was 700,000 and 1,700,000 respectively.

All population health outcomes remained similar in all models (see **Figure 12**). The TAR for high to low proportion of individuals sixty-five or older ranged from 69.7% to 71.7%. Likewise, there were small reductions to case-fatality rates with the lowest reduction in the high proportion of individuals sixty-five or older model at 2.19%. Peak day of infected individuals

ranged within one week of the base model. Number of infected individuals ranged from 1,001,216 to 1,090,470 compared to the 1,109,342 individuals infected in the base model.

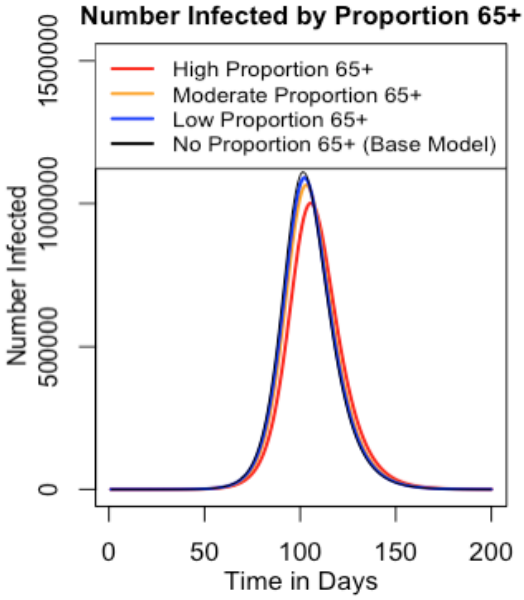

Figure 12: Number of individuals infected by proportion of individuals aged sixty-five or older. No significant differences in peak time of infection, case-fatality rates, or TAR were seen in the high (red), moderate (orange), or low (blue) proportions of individuals 65 or older models. There was, however, a significant decrease in the number of individuals infected on the peak day of infection in the high proportion of individuals sixty-five or older model.

Ethnic Heterogeneity and Minority Populations

The amount of ethnic heterogeneity within a country was measured as homogeneous or low, moderate, or high heterogeneity. This measure was used to determine how much cultural barriers such as self or community-imposed limited access to health care and social inequalities acted as factors during influenza pandemics. The homogeneous scenario had the same parameters and initial conditions as the base model. The relative distinctions of heterogeneity were determined using the ethnic fractionalization groupings from Alesina et al. (2003). The low ethnically heterogeneous model had a majority population that made up 80% of the country (S_1 = 8,000,000 and S_2 = 2,000,000), the moderately heterogeneous model had a majority population

that made up 45% (S_1 = 4,500,000 and S_2 = 5,500,000), and the highly heterogeneous scenario was composed of one majority group of 15% (S_1 = 1,500,000 and S_2 = 8,500,000). The case-fatality rate in the minority population (group 2) was 2.4 times higher than in the base model (Van Kerkhove et al., 2011). The 6.00% case-fatality rate was adjusted by increasing the length of recovery by one day (ν_2 = 1/6) and altering the mortality rate to 0.106% (μ_2 = 0.0106) in a population of 10,000,000 susceptible individuals with these characteristics. This made the R_0 = 2.16 in the group 2 population.

The case-fatality rate and TAR for each decreasing level of ethnic homogeneity increased, while the peak day of infection stayed relatively stagnant (see **Figure 13**). The low ethnically heterogeneous scenario had a 3.20% case-fatality rate and a peak day of infection on day 99 with 1,210,256 individuals infected. The TAR was 74.4%. In the moderately heterogeneous model, the case-fatality rate was 4.41% with a peak day of infection on day 94. During the peak day of the infection, 1,390,014 were infected and the TAR was 78.0%. In the highly heterogeneous model, the case-fatality rate was 5.46% with a peak day of infection on day 91 with 1,545,332 people infected and a TAR of 80.6%.

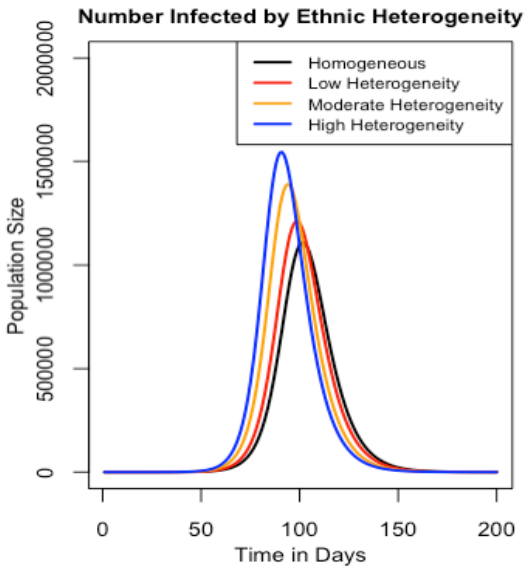

Figure 13: Then number of infected individuals by the level of ethnic heterogeneity within the population. A completely homogeneous country (black) had the same characteristics as the base model with a case-fatality rate of 2.50% and TAR of 72.1%. In increasing order of ethnic heterogeneity, the low ethnically heterogeneous (red) scenario had a case-fatality rate of 3.20% and TAR of 74.4%, the moderately heterogeneous scenario (orange) had a case-fatality rate of 4.41% and a TAR of 78.0%, and the highly heterogeneous country (blue) had a case-fatality rate of 5.46% with a TAR of 80.6%.

Modeling Countries by Income Level—Country-Level Factor Analysis

In order to build model countries by income level to establish discrepancies in health outcomes for low, middle, and high-income countries, it was necessary to combine the values of the parameters from each factor. For the purposes of this thesis, only country-level factors were considered in the low, middle, and high-income models. These factors affect all individuals within populations and are necessary for a better understanding of differential health outcomes caused by a severe influenza pandemic.

Four model countries were constructed based on typical characteristics of high, middle, and low-income countries. Low, middle, and high-income countries were defined by the *World Bank Country and lending groups* (2018c) data set. The characteristics of these four models are detailed in **Figure 14**. The low-income country model was assumed to have the characteristics of the base model as previous research had demonstrated that countries with full susceptibility and no mitigation strategies would have similar epidemic outcomes to the base model. A dense (>175 PPSM) and non-dense (<175 PPSM) middle-income country were selected as there was

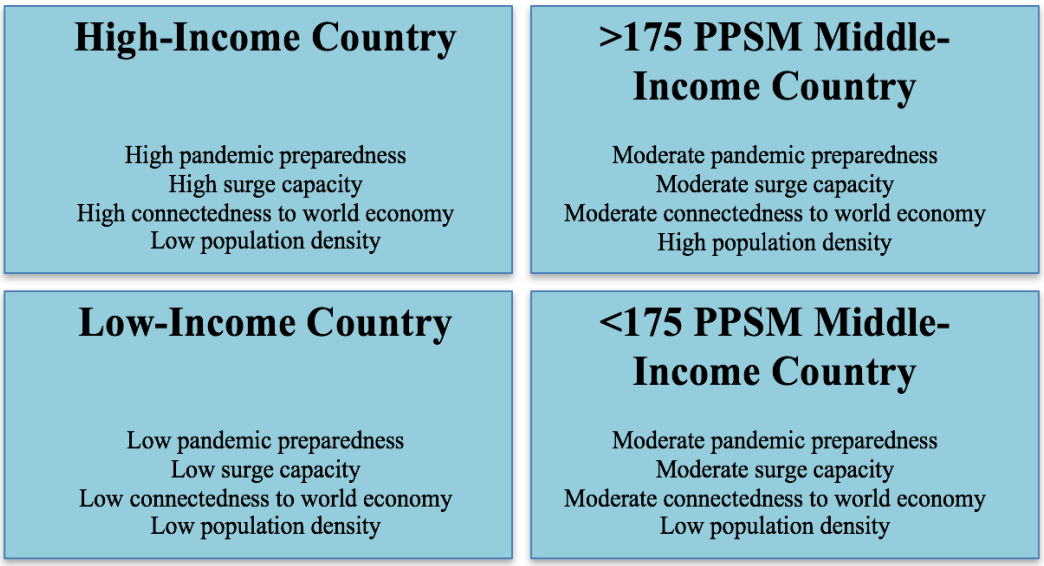

Figure 14: Four main models were used to establish how country-level factors differ across a high-income, low-income, densely populated middle-income, and less densely populated middle-income country. All four models started with 10 million susceptible individuals, one infected individual, and no recovered individuals.

disagreement in the literature regarding the importance of population density as a factor. Additionally, the population density of upper middle-income countries was less than the 175 PPSM threshold while the population density of middle-income countries was greater than 175 PPSM (Calculateme, n.d.; World Bank, 2018a). This created a need to evaluate both low and high population density countries to establish better representative countries.

To create the income level models, parameter or initial condition values from every country-level factor had to be considered. Any value that differed from the base model was changed for every income model. For example, consider β for the densely populated (> 175 PPSM) middle-income country model. The model's four primary characteristics included: high population density, moderate surge capacity, moderate pandemic preparedness, and moderate connectedness to the world economy. This meant that β, μ_1, I_1, and v_1 had to be altered. For the parameter settings, an additive and subtractive process was used in conjunction with the base

model. Specifically for the transmission rate, β for high population density was 0.396 while the β for moderate pandemic preparedness was 0.32. The base model setting for β was 0.36. Therefore, the population density β setting was 0.036 greater than the base model β setting and the β setting for pandemic preparedness was 0.04 less. To the base model β, 0.036 was added to 0.36 and then 0.04 was subtracted. This additive and subtractive process gave a β setting for the densely populated middle-income country of 0.356. This same process was used for μ_1 and v_1. For the initial number of individuals infected (I_1), I_1 was set to the exact value for the interconnectedness to the world economy factor (I_1 =20 for the densely populated middle-income country) as no other factor altered the initial number of infected individuals. Any parameter that was not changed from the base model retained the base model value.

Results of Modeling by Income Status of Country

To evaluate how countries of varying income status would fare in an influenza pandemic akin to the 1918 influenza pandemic, all country-level factors were modeled together for a high, densely populated middle, less populated middle, and low-income country. All models retained the 10 million susceptible individuals (S_1 =10,000,000) in the initial population and individuals were placed only into group 1 as opposed to two groups. To compare parameters and initial conditions of the models, see **Table 6**.

Table 6: Input Parameters and Initial Conditions by Country Income Level Models

	Base/Low-Income	>175 PPSM Middle-Income	<175 PPSM Middle-Income	High-Income
S_1	10,000,000	10,000,000	10,000,000	10,000,000
I_1	1	20	20	40
R_1	0	0	0	0
β	0.36	0.356	0.32	0.28

R_0	1.8	1.60	1.44	1.12
μ_1	0.00513	0.00532	0.00394	0.00213
v_1	1/5	1/4.5	1/4.5	1/4

High-Income Country Model

The high-income country model involved altering all parameters. β was set to 0.28 due to the reduction in R_0 caused by high pandemic preparedness. μ_1 was set to 0.00213 and v_1 decreased by one day to 1/4 due to the high surge capabilities of high-income countries. The R_0 became 1.12. Due to the decreased R_0, the length of the epidemic increased and the timescale was expanded to t = 500 days. The initial infected individuals (I_1) was set to 40 because high-income countries are generally well-connected to the world economy. No changes were made due to population density because high-income countries on average have population densities lower than 175 PPSM (World Bank, 2018a).

Using these settings, the high-income country model produced a TAR of 19.4% and case-fatality rate of 0.845%. The peak day of infection occurred on day 309 with 51,681 individuals infected (see **Figure 15**).

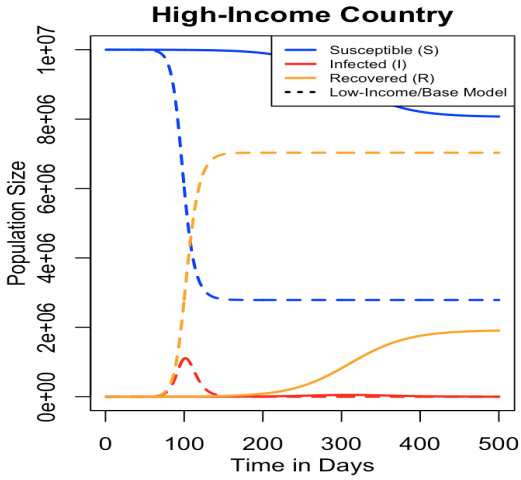

Figure 15: How individuals moved through each compartment in a high-income country versus in a low-income country (base model). Individuals in high-income countries (solid lines) moved into the the infected class (red) at a much slower pace than in low-income countries (dashed lines). The case-fatality rate for high-income countries was 0.845% while in the low-income country it was 2.50%. Likewise, the TAR for the high-income country was 19.4% while the TAR in low-income countries was 72.1%.

Middle-Income Countries

The densely populated (>175 PPSM) middle-income country involved changing all parameters from the base model. β was changed to 0.356 after accounting for the decreased value from possessing a moderate surge capacity and the increased value for population density. μ_1 was increased to 0.532% (0.00532) in accordance with the increased surge capacity and high population density. v_1 was decreased to 1/4.5 because of the country's ability to have moderate surge capacity. This made the R_0 value 1.60. The initial number of infected individuals was set to 20 due to middle-income countries' moderate connectedness to the world economy.

The less densely populated (<175 PPSM) middle-income country model did not involve adjusting for population density. In this case, $\beta = 0.32$ and $\mu_1 = 0.00394$. This made $R_0 = 1.44$. No other parameter values were different from the densely populated middle-income model.

The output values were drastically different for the middle-income countries based on the calculation for population density (see **Figure 16, 17, & 18**). The densely (>175 PPSM) populated country model produced a case-fatality rate of 2.34% while the less (<175 PPSM) populated model had a case-fatality rate of 1.74%. Likewise, the TAR of the densely populated model was 62.9%, while it was 52.8% in the less densely populated model. The peak day of infection occurred on day 96 for the densely populated model with 756,715 people infected, but occurred on day 125 with 484,800 people infected for the less populated model.

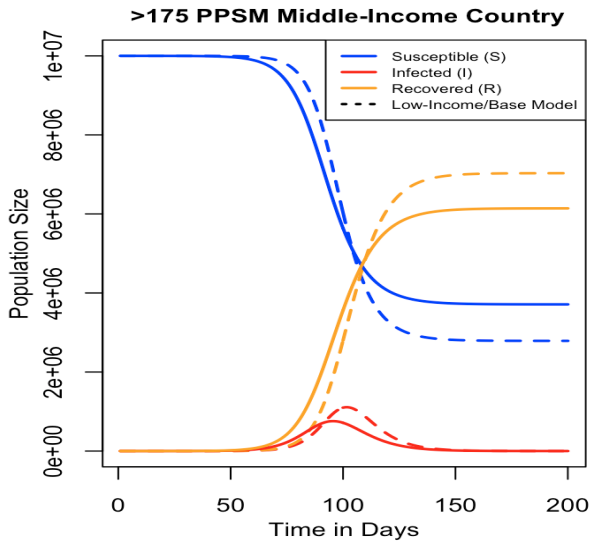

Figure 16: Flow of individuals through each compartment in a high density (>175 PPSM) middle-income country versus a low-income country. Individuals in a high density middle-income country (solid lines) fared only slightly better than individuals in a low-income country (dashed lines). The TAR for the densely populated middle-income country was 62.9% with a case-fatality rate of 2.34% compared to the 72.1% TAR of a low-income country with a case-fatality rate of 2.50%. The peak day of infection for the densely-populated middle-income country occurred six days prior to the peak day of infection in the low-income country.

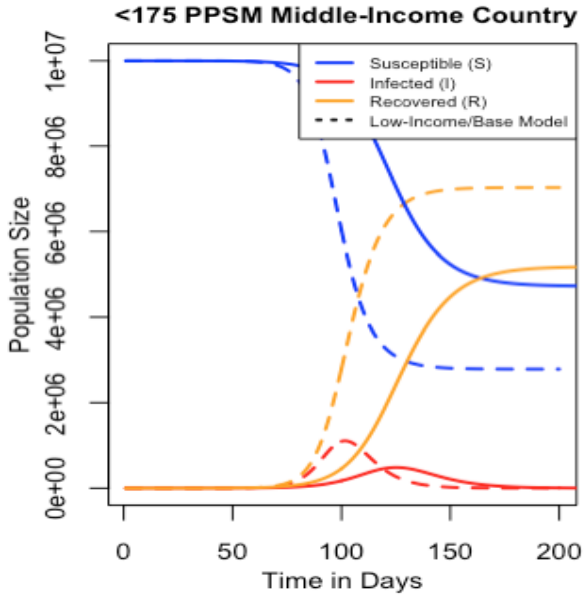

Figure 17: Flow of individuals through each compartment in a low density (<175 PPSM) middle-income country versus a low-income country. Individuals in a low density middle-income country (solid lines) had better population-health outcomes than individuals in low-income countries (dashed lines). 52.8% of individuals in this densely populated middle-income

country were infected with a case-fatality rate of 1.74% while 72.1% of individuals in a low-income country were infected and 2.50% died.

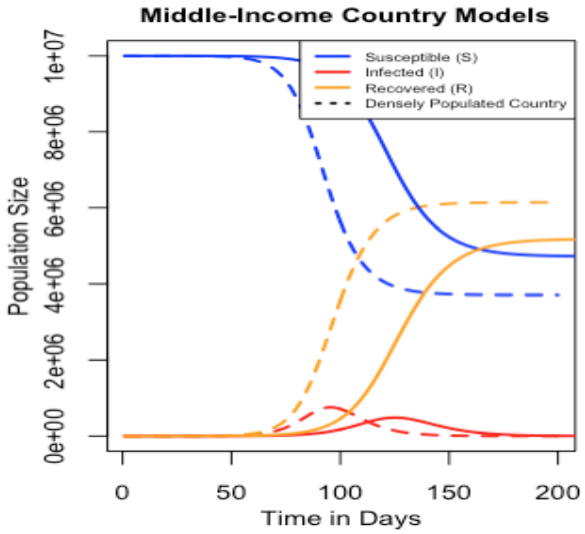

Figure 18: Flow of individuals through each compartment in the low (<175 PPSM) versus high (>175 PPSM) population density middle-income country models. The high population density model (dashed lines) showed an earlier peak of infection and higher TAR than the less densely populated middle-income country (solid lines) model.

Evaluating Impacts of Parameters and Initial Conditions on Each Income Country Model

This next section evaluates which parameter or initial condition adjustment caused the largest difference in population-level health outcomes across the country income models. Understanding the adjustment of parameters or initial condition (β, μ_1, I_1, and ν_1) in conjunction with income level models may help explain why certain factors such as pandemic preparedness and surge capacity cause more severe epidemic outcomes than population density and interconnectedness to the world economy.

The previously established parameter and initial condition values from the high ($\beta = 0.28$, $\mu_1 = 0.00213$, $I_1 = 40$, and $\nu_1 = 1/4$), densely populated middle ($\beta = 0.356$, $\mu_1 = 0.00523$, $I_1 = 20$, and $\nu_1 = 1/4.5$), less densely populated middle ($\beta = 0.32$, $\mu_1 = 0.00394$, $I_1 = 20$, and $\nu_1 = 1/4.5$), and low-income ($\beta = 0.36$, $\mu_1 = 0.00513$, $I_1 = 1$, and $\nu_1 = 1/5$) country models were utilized in this

analysis. In each subsection below, one parameter or initial condition was "controlled for." This meant that one parameter or initial condition was selected to be held constant throughout the high, middle, and low-income country models. Meanwhile, all the parameter or initial condition values from the original income country model remained the same. For instance, controlling for the transmission factor *(ß*) in the high-income country model entailed setting *ß*=0.36 instead of the prior 0.28 value. The other parameters and initial conditions set for the high-income model ($\mu_1 = 0.00213$, $I_1 = 40$, and $\nu_1 = 1/4$) remained the same. This process was conducted for all income models and for all parameter or initial condition values changed throughout this thesis. The specific parameter and initial condition values selected as "controlled for" came from the value for that parameter or initial condition in the base or low-income country model.

Controlling for the Transmission Factor (ß)

ß was set to 0.36 for each country scenario while all other parameters and initial conditions were kept constant (see **Figure 19**). Making this change did not alter the values for the low-income model as *ß* was previously set to 0.36. This adjustment did not significantly change the case-fatality rate for any of the models. For the high-income model, however, the TAR increased to 53.5% and the basic reproductive number increased (R_0) to 1.44. Additionally, the peak day of infection increased to day 103 with 504,660 people infected. The R_0 for both middle-income country models increased to 1.62. The densely populated middle-income country had a TAR increase to 63.9% and a peak day of infection at day 93 with 789,648 infected. Meanwhile, the less densely populated middle-income country had a 64.2% TAR with a peak day of infection on day 92 with 804,712 people infected.

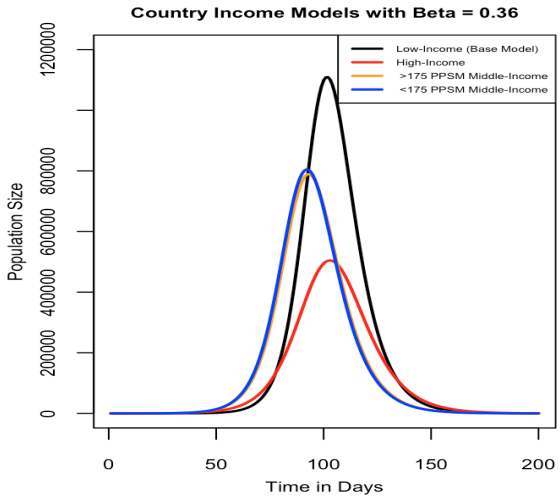

Figure 19: Number of infected individuals by country income level adjusting the transmission factor (*β*) to one constant value (0.36). The high-income (red) country model predicted the lowest number of individuals infected with 53.5% infected at an R_0 of 1.44. Both middle-income models (blue and orange) showed similar characteristics when controlling for the transmission factor. The low-income model (black) remained unadjusted.

Controlling for the Mortality Rate (μ_1)

The mortality rate (μ_1) was set to 0.513% ($\mu_1 = 0.00513$) for all models (see **Figure 20**). This did not alter the low-income country model as it already used $\mu_1 = 0.00513$. The case-fatality rates were similar between the high-income and middle-income countries models ranging between 2.01 and 2.26%. The high-income country still had a late peak day of infection at day 337 with 41,439 people infected and a TAR of 17.5%. The densely populated middle-income country had a TAR of 62.9% and a peak day of infection on day 95 with 758,858 people infected. The less populated middle-income country's TAR was 52.3% with a peak day of infection on day 126 with 473,307 people infected.

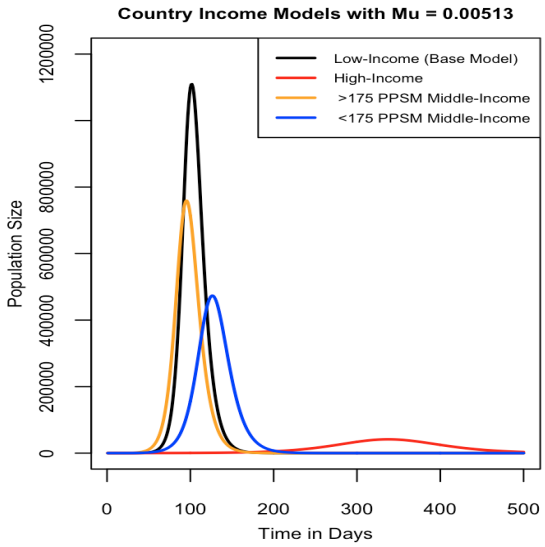

Figure 20: Number of infected individuals after adjusting for a consistent mortality rate of μ_1 = 0.00513 (0.513%). This alteration did not greatly change any model's original epidemic outcome factors with regards to TAR or number of infected individuals on the peak day of infection. The case-fatality rate, however, did increase for the high-income (red) and less populated (orange) middle-income country models. The peak day of infection for the high-income country occurred almost a month later than its original peak day.

Controlling for Number of Initially Infected Individuals (I_1)

To test the impact of changing the number of infected individuals, I_1 was set to 1 in all models (see **Figure 21**). Again, this did not alter the base model as I_1 was already set to 1. The case-fatality rate and TAR did not change significantly from the original model for any of the models. In all cases, setting I_1 =1 increased the time until the peak of infection. For the high-income country, the peak of infection occurred on day 442 with 51,647 people infected. In the densely populated middle-income country scenario, the peak day of infection occurred on day 199 with 757,147 people infected. In the less populated middle-income country, the peak day of infection occurred on day 157 with 482,797 infected people.

While evaluating the impact of changing the initial number of infected individuals, it became evident that the number of infected individuals predominantly only affected the peak day

of infection. Even if in the high-income country model I_1 was changed to 100,000, the TAR only increased to 25.1% and there was no change to the case-fatality rate.

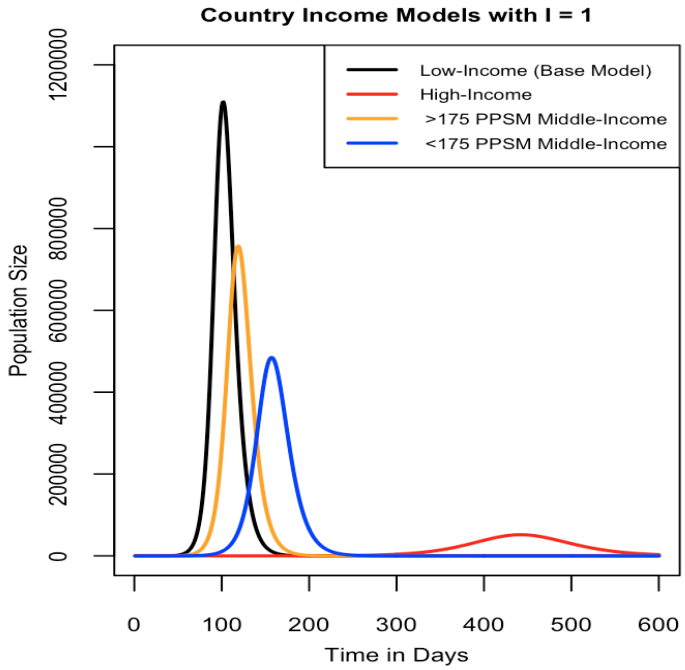

Figure 21: Number of infected individuals for each country level income model when one infected individual entered the population. There was little change to any characteristic of these models except for the peak day of infection. The most dramatic change to the peak day of infection occurred in the high-income model (red). The peak day of infection increased from day 309 to day 442. In the densely-populated middle-income model (orange), the peak day of infection also increased by more than 100 days from day 96 to 199. There was also a delay of infection in the less populated middle-income country (blue), but was less pronounced than in the densely populated middle-income country.

Controlling for the Recovery Rate (v_1)

In all country-level models, v_1 was set to one recovery for every five days (1/5). This did not alter the base model as v_1 was already set to 1/5. This greatly affected the TAR, case-fatality rate, peak day of infection, number of individuals affected on the peak day of transmission, and basic reproductive number (see **Figure 22**). The R_0 for the high-income country model was 1.4 while the R_0 for middle-income countries was 1.6. The TAR for the high-income countries rose

to 50.2% and case-fatality rate increased to 1.05%. The peak day of infection occurred on day 140 with 431,532 people infected. In the densely populated middle-income country model, the peak day of infection occurred on day 84 with 1,071,383 people infected with a TAR of 71.3% and case-fatality rate of 2.59%. For the middle-income country with less than 175 PPSM, the peak day of infection occurred on day 106 with 763,736 people infected. The TAR became 63.0% and the case-fatality rate was 1.93%.

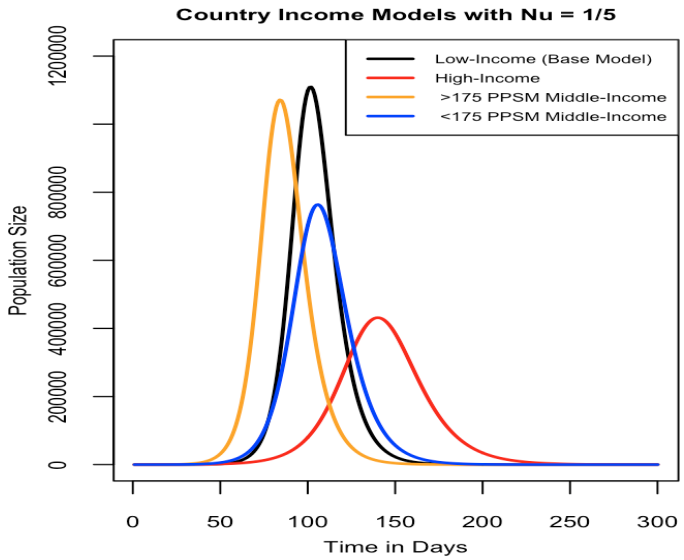

Figure 22: Number of infected individuals by country income level with a recovery rate (ν_1) of one infection for every five days. Recovery rate distinctly altered the behavior of all models. Of interest, the TAR of the high-income country (red) was elevated to 50.2% and had a peak day of infection in almost half the duration of the model when the recovery rate is one recovery for four days. There was also an increase in TAR for the middle-income country models (blue and orange).

Discussion

This thesis has explored how different country-level and individual host factors affect population-level health outcomes in an influenza pandemic as severe as the 1918 pandemic in modern-day high, middle, and low-income countries. Through building SIR models representative of countries of different income levels, I found that high-income countries would

have less severe mortality and infection outcomes than low or middle-income countries in a modern-day pandemic similar in severity to the 1918 influenza pandemic. There have already been multiple papers detailing how disparities and inequalities experienced during the 1918 influenza pandemic (Frost, 1920; Garrett, 2008; Groom et al, 2009) and a modern-day pandemic (Murray et al., 2006) caused differential health outcomes within and between countries. This thesis, however, explored what factors contribute to modern inequalities that cause differential pandemic influenza-related mortality and morbidity. Policy-makers should consider the magnitude of these factors while creating initiatives that protect citizens.

While SIR modeling is effective, it does offer some limitations. The primary concerns stem from generalizations. Selecting values for parameters can be subjective, but published values from literature were incorporated in this thesis whenever possible. Additionally, assumptions made in the modeling process inevitably impacted this research's findings. For example, there is mixed literature on the influence of population density, but I made the assumption based on theory and limited literature that population density does have an effect on mortality and transmission rates. In future research, the seven factors that I selected could be updated as more information becomes available to better replicate reality. If more time allowed, other factors, including household transmission, sex, asymptomatic versus clinical cases, or geography, would have been considered as these have been considered as possible factors related to influenza mortality and transmission. Individual host factors could have also been added into the low, middle, and high-income country models if further subgroups were created. Finally, the pattern of disease spread through SIR models is likely not fully representative of how disease networks work as individuals have behavioral responses that cannot be boiled down to differential equations. With more time, a spatiotemporal model would have been constructed.

Bearing these limitations in mind, my thesis produced a number of interesting results. Prior to evaluating how factors impact morbidity and mortality across low, middle, and high-income models, the base or low-income country was modeled. Specifically, the base model considered a low-income country had low population density (<175 people per square mile), low surge capacity, low interconnectedness to the global economy, a weak pandemic preparedness program, 20% of the country with an underlying medical condition, no individuals sixty-five or older, and ethnic homogeneity. Using these base factor assumptions, I evaluated how different factors independently mitigate or aggravate country income models.

The base model assumptions used in this thesis were made in conjunction with prior literature which identified similar TARs, mortality rates, and case-fatality rates. Although the base model may have seemed to have a high TAR (72.1%), this model aligned well with other models when there is no population-level immunity to a virus and no preventative or treatment measures invoked. Nichol et al. (2010) built a seasonal influenza outbreak model within a college population given that 0% of the population was vaccinated. As it is likely that few individuals will have immunity to a novel influenza strain, at the start of the epidemic it was assumed that the majority of individuals would be susceptible in my model (CDC, 2016b). They found a TAR of 69% with day 47 as the peak day of infection with 3,450 people in the population. Likewise, Bootsma and Ferguson (2007) found that, without any prevention methods or reactive control measures, 80% of individuals would become infected with a R_0 of 2 and Ferguson et al. (2006) found that 55-68% of all individuals would become infected with an R_0 between 1.7 and 2. As the base model aligned well with models created to demonstrate full susceptibility and a lack of mitigation strategies, it was assumed to be a valid model to represent how an influenza pandemic would affect low-income countries.

The epidemic outcome variables (i.e. TAR, case-fatality rate, peak day of infection, number of individuals infected on the peak day of infection) depicted the relevance of country-level factors (see **Table 7**). This thesis found that interconnectedness to the global economy and

Table 7: Country-Level Factor Models' Epidemic Outcomes

	Base Model	High Pop. Density	High Surge Capacity	Moderate Surge Capacity	Highly Connected	Moderately Connected	High Prep.	Moderate Prep.
TAR	72.1%	78.0%	53.3%	64.2%	72.1%	72.1%	48.9%	62.7%
Case-fatality rate	2.50%	3.15%	1.0%	1.75%	2.50%	2.50%	2.50%	2.50%
Peak Day of Infection	102	85	137	115	78	82	194	133
Number Infected at Peak Day	1,109,342	1,407,694	504,594	804,568	1,109,846	1,109,691	401,042	749,301

population density are noteworthy factors during an influenza pandemic, but not as influential as pandemic preparedness or surge capacity. As discussed in the section focused on controlling parameters, this outcome predominantly arises because neither factor directly changes the recovery or transmission rate. Connectedness to the world economy did not impact any factor other than peak day of infection which concurs with findings by Ferguson et al. (2006). This result is also worth celebrating as border control measures would have to be greater than 99% effective in order to reduce the entrance of influenza by a few weeks (Ferguson et al., 2006). Having high population density increased the basic reproductive number to almost two and sequentially increased the TAR to 78%. Conclusively, high population density produced similar results to having an influenza strain with high transmissibility, while connectedness to the world economy delayed the peak day of infection.

Depending on the goals of respective countries to prioritize reducing the number of individuals infected or dying, either improving pandemic preparedness or increasing surge capacity should be prioritized. High pandemic preparedness is the most effective measure for reducing the TAR, increasing the time until the peak day of infection, and reducing the number of individuals infected on the peak day of infection. The importance of these attributes cannot be understated. Reducing the TAR from 72.1% to 48.9%, inevitably reduces the amount of mortalities and morbidities caused by the pandemic. Increasing the time until the peak day of infection by 92 days allows more time for researchers to create a pandemic-specific influenza vaccine as it takes at least four months for vaccines to be manufactured (Ferguson et al., 2006). The longer time until peak infection also reduces the amount of stress put on the health care system. During this time, antivirals can be stockpiled and hospitals can begin preparations for the surge of patients. For reducing the mortality and case-fatality rates, having high surge capacity is ideal and can reduce the mortality rate to 0.213% and case-fatality rate to 1.00%. Having a high surge capacity also drastically lowers the TAR from 72.1% to 53.3%, but only increases the peak day of infection by 35 days. Ultimately, countries that have high pandemic preparedness with high surge capacity can best improve population-level health outcomes.

This thesis found that individual host factors vary considerably in their impact on the TAR, case-fatality rate, peak day of infection, and number of individuals affected on the peak day of infection (see **Table 8**). Out of the traits that vary by host studied, ethnic heterogeneity

Table 8: Individual Host Factor Models' Epidemic Outcomes

	Base Model	High UMC	Moderate UMC	High Prop. 65+	Mod. Prop. 65+	Low Prop. 65+	High Het..	Moderate Het.	Low Het.
TAR	72.1%	75.8%	73.4%	69.7%	71.1%	71.7%	80.6%	78.0%	74.4%
Case-fatality rate	2.50%	2.95%	2.65%	2.19%	2.38%	2.45%	5.46%	4.41%	3.20%

Peak Day of Infection	102	97	100	106	103	102	91	94	99
Number Infected at Peak Day	1,109,342	1,278,564	1,166,348	1,001,216	1,065,153	1,090,470	1,545,332	1,390,014	1,210,256

Notes: UMC stands for underlying medical conditions, mod. stands for moderate, prop. stands for proportion, and het. stands for heterogeneity

caused the greatest magnitude changes in health outcomes and produced a TAR of 81%. The increased mortality rate (0.513% to 1.06%) for individuals in minority populations, as up to 85% of individuals within the population were considered minority individuals, contributed to ethnic heterogeneity becoming the predominant individual host factor. The case-fatality rate also rose significantly to 5.46% in the model with high ethnic heterogeneity. High underlying medical conditions also appeared to be a strong factor driving increased case-fatality rates and TARs. The proportion of individuals sixty-five and older did not seem to cause a major change in the epidemic dynamics. The results for proportions of individuals with underlying medical conditions and sixty-five and older clarifies that age distribution of countries likely does not impact overall health outcomes, but rather is important to understanding individual-level health. While these outcomes are largely a result of the parameter values selected, the values for differential mortality or case-fatality rates were based on real-life research. Thus, the results suggest that culture and society's implications on individuals are the most important factors that vary by host in understanding population-level health outcomes.

Country-level factors were then used to build low, middle, and high-income country models that looked at morbidity and mortality caused during an influenza pandemic. **Modeling countries by low, middle, and high-income levels demonstrated that the high-income country model will fare the best in an influenza pandemic of similar magnitude to the 1918**

influenza pandemic (see **Figure 23** and **Table 9**). The high-income country model reduced the TAR to 19.4%, decreased the case-fatality rate to 0.845%, increased the peak day of infection by

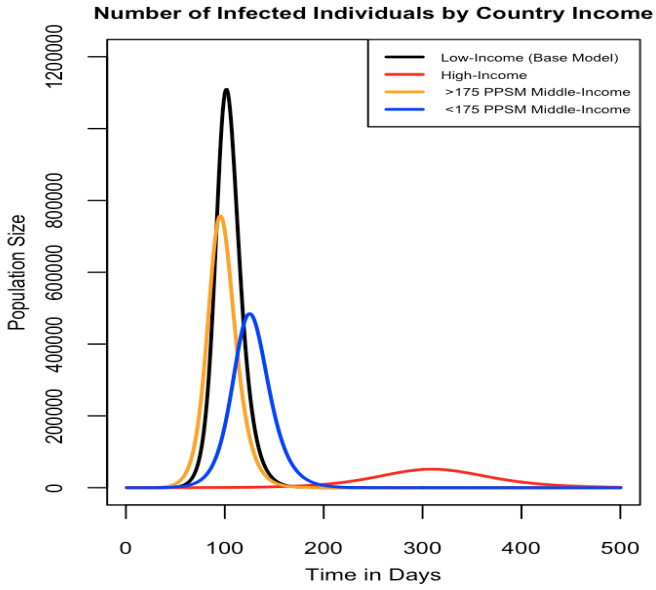

Figure 23: Number of infected individuals within all model income groups. The high-income country model (red) had the latest peak day of infection but the lowest TAR, case-fatality rates, and individuals infected on the peak day of infection. The middle-income country models (orange and blue) also produced better epidemic outcomes than the low-income country model (black), but resembled the low-income country model more than the high-income country model.

Table 9: Country Income Level Models' Epidemic Outcomes

	Base/Low-Income	>175 PPSM Middle-Income	<175 PPSM Middle-Income	High-Income
TAR	72.1%	62.9%	52.8%	19.4%
CFR	2.50%	2.34%	1.74%	0.845%
Peak Day of Infection	102	96	125	309
Number Infected at Peak Day	1,109,342	756,715	484,800	51,681

more than 200 days, and reduced the number of individuals infected on the peak day. Middle-income country models differed greatly due to the change in population density. This indicates the importance of further research to establish the impact of population density on communities and countries as population density created a distinct difference in epidemic outcomes. The results also demonstrated that population-level health outcomes in middle-income countries were more similar to low-income than high-income countries.

In order to understand which parameters created the greatest magnitude changes to epidemic outcomes, I evaluated how parameters and initial conditions affected the income country models. By holding all but one parameter and initial condition constant while adjusting only one in the income models, altering the transmission factor (β) and the recovery rate (v_1) changed the models the most. Using the high-income country model for comparison, adjusting β to 0.36 increased the TAR to 53.5% from 19.4%, while the case-fatality rate remained consistent. Altering the transmission factor essentially reverted the peak day of infection (day 103) to that of the base model (day 102). This meant that the high-income country no longer had the advantage of increasing the time until the surge. Changing v_1 to one recovery for five days in the high-income country model increased the case-fatality rate to 1.05% and decreased the peak day of infection to day 140. Increasing the average recovery time per person identified that this increased the case-fatality more than just adjusting the mortality rate. In terms of interventions, this result suggests prioritizing faster as opposed to better treatment for infected individuals. Ultimately, this thesis found that reducing the recovery or transmission rate of influenza most effectively reduces morbidity and mortality burdens caused by influenza pandemics.

These findings suggest that mitigation strategies for influenza pandemics should specifically aim to reduce the transmission and recovery rates as opposed to reducing the

number of individuals entering the country or decreasing the mortality rate. Specifically, this should be completed through pandemic preparedness and surge capacity measures. Focusing resources and attention to these types of interventions will enable countries to best reduce morbidity and mortality caused directly or indirectly by severe influenza pandemics. Attention to socially disadvantaged individuals should also be prioritized. While many high-income countries already have high levels of pandemic preparedness and surge capacity, it is necessary for low and middle-income countries to invest in strengthening services and policies as well.

Conclusion

Ultimately, the results depicted in this thesis offer a somewhat heartening reality; proper pandemic preparedness and a high surge capacity make a drastic impact on the course of an influenza pandemic within countries. While low and middle-income countries may suffer from disproportionate amounts of individuals with underlying medical conditions, high ethnic fractionalization, and high population density, pandemic preparedness and surge capacity can and should be improved. These conclusions are not exclusive to influenza pandemics, but are applicable to many disease pandemics including SARS or Ebola.

When considering which intervention strategies to employ in countries with low resources, it is likely beneficial to prioritize nonpharmaceutical interventions. As Markel et al. (2007) detailed while exploring the impacts of the 1918 influenza pandemic in the United States, nonpharmaceutical interventions can have large impacts on population health outcomes between countries. Government-enforced mitigation measures such as quarantine and school closures may be logistically challenging to enact, but likely are more fiscally feasible for low and middle-

income countries than acquiring pharmaceutical interventions such as antivirals, vaccines, and other health resources. Additionally, nonpharmaceutical interventions reduce disadvantaged countries' reliance on other countries during influenza pandemics. This concern was evidenced in the 2009 H1N1 influenza pandemic when high-income countries decided not to give away vaccines away until their own citizens received the vaccine (Fidler, 2010). While there will still be discrepancies between countries by income level if not all resources are shared, nonpharmaceutical interventions are the best self-sustainable options for low and middle-income countries during influenza pandemics.

Regardless of the disease causing a pandemic, high-income countries will likely fare better than low or middle-income countries both in short and long-term population health and economic outcomes at this time. While the WHO will likely try to orchestrate a coordinated response, health is not truly currently ensured as a human right. The greatest reductions in global morbidity and mortality will occur if countries are able to share resources such as data, drugs, and healthcare workers. Then, once more countries become truly altruistic, maybe the world will no longer be unprepared for a major influenza or infectious disease pandemic.

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