MATHEMATICAL MODELING THE ZOONOTIC AND VECTOR TRANSMISSION DYNAMICS OF WEST NILE VIRUS AS THEY RELATE TO HUMAN MORBIDITY AND MORTALITY

A Dissertation

by

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ABSTRACT

West Nile virus (WNV), an arthropod-borne flavivirus, naturally circulates between passeriform birds and mosquitoes. Other vertebrates, such as humans, may become infected during the bloodmeal of infectious mosquitoes. WNV initially invaded New York in 1999, rapidly swept west across the North American continent, and is now endemic across the continental United States. The focus of this study was to use mathematical modeling, for improving current public health understanding on how infectious cycles of birds and mosquitoes, infection and cross-infection, and environmental dynamics of WNV, along with human pathology, influences human morbidity and mortality in the Dallas, Tarrant, and Denton counties of Texas.

During a comprehensive literature review of WNV, avian pathophysiology, public health entomology, human pathophysiology, and epidemiology, we proposed a novel mathematical model. Subsequently, we developed an epidemic model of the WNV dynamics, in the avian host (American crow), mosquito vector (*Culex*), and two age classifications of humans (≤ 39 & ≥ 40). The bifurcation of human age was conducted due to the risk of humans developing neuroinvasive disease increases 1.5X for every decade of life. We also divided human infected classes into asymptomatic, West Nile Fever (WNF), and West Nile neuroinvasive disease (WNND), as WNND is the only fatal form. The model was then calibrated to observed data, from the endemic years between 2003-1012. A sensitivity analysis of each individual variable and parameter was

conducted to test influence on human morbidity and mortality. Focusing on the most sensitive variables, we conducted a multivariate analysis, in which we formulated situations such as drought, avian concentration and population fragmentation, insecticide usage, larvae side usage, and habitat modification through the reduction of standing water.

We were able to successfully simulate the endemic years, and outbreaks, between 2003 and 2012, but underestimated the outbreak year of 2012. This model illustrates the observed link between infected mosquito densities to human health outcomes. Climate changes that effect the mosquito population and their interaction with humans have been shown to be important factors influencing human morbidity and mortality. In the future this model may also be useful in predicting the effect of various disease control strategies.

DEDICATION

"We wish to pursue the truth no matter where it leads. But to find the truth, we need imagination and skepticism both. We will not be afraid to speculate, but we will be careful to distinguish speculation from fact. The cosmos is full beyond measure of elegant truths; of exquisite interrelationships; of the awesome machinery of nature."
– Carl Sagan

To my family, for fostering my imaginative and inquisitive nature

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1. INTRODUCTION

1.1 Zoonotic & Vector-borne Disease

Zoonotic diseases, or zoonoses, are infectious organisms that may be transmitted from animals to humans, accounting for more than 60% of human infectious diseases (Karesh et al., 2012). Approximately a billion human cases and millions of deaths are attributable to zoonotic diseases each year, causing hundreds of billions of dollars in economic damage over the past few decades (Karesh et al., 2012). Many of these infectious agents may be directly transmitted from an infected animal to a susceptible human through direct contact with the animal or through indirect contact via cross-infection from bodily fluids by way of food, water, air, and/or other fomites. Some of these pathogens, such as influenza, may be subsequently transmitted from human-to-human. A subset of these zoonoses is transmitted via vectors. Vectors are carriers of the infectious agent from one host to another, generally arthropods (e.g. ticks and mosquitoes), and transmit the pathogen via saliva during biting behaviors.

Many serious diseases influencing individual and population health are zoonoses. These infectious agents may be classified into agent types, including parasites (e.g. protozoa and helminths), fungi, prions, bacteria, and viruses. Parasitic diseases include toxoplasmosis and baylisascaris. Fungal infections include histoplasmosis and ring worm. The most notorious prion disease, spongiform encephalopathy, is variant

Creutzfeldt-Jakob disease. Bacterial diseases include anthrax, salmonellosis, and plague. Viral diseases include Ebola hemorrhagic fever, smallpox, and West Nile virus (WNV).

Viruses transmitted by the mosquito arthropod are referred to as mosquito-borne arboviruses. Human infection from these viruses may range from asymptomatic infection, through non-fatal morbidity due to fever and associated clinical manifestations, to fatal complications, such as hemorrhagic shock, meningitis, and encephalitis (Leake, 1998). These hemorrhagic and neurologic manifestations may lead to chronic conditions such as flaccid paralysis.

Zoonoses may naturally reside, stably established and undetected, in clustered or isolated animal populations. Occasional human cases can occur when humans interact with these infected animal populations. Localized human outbreaks can develop when groups of people begin interacting with infected animal populations and/or the contracted pathogen may be transmitted amongst the local human population. Macro geographical spread (i.e. pandemic) of zoonoses can be attributed to large-scale human population attributes and behaviors, and ecological factors. Both localized and global scale changes in human infection trends tend to be attributed to ecologic factors influencing the way humans, hosts, vectors, and pathogens interact with each other. Distinctions may be made between epidemic, endemic, and emerging infectious diseases as well. Epidemic disease is spatiotemporally separated between the occurrences of human population infections. An endemic disease has a spatiotemporally continuous presence within a given system. Emerging diseases are described by novel introduction of a pathogen into a given human population.

Emerging infectious agents manifest themselves due to many different environmental pressures. These pressures provide fundamental changes in an ecological system. The emerging disease occurs due to the novel interaction between a pathogen and an immunologically naïve human population. These infectious agents may have been present within the geographic confines of a human population or introduced. Most often, the cause of emergence is an introduction of pathogens to humans, or humans to pathogens, due to human conduct (Karesh et al., 2012). Such conduct may include human migration, changes in land usage, changes in animal production and food systems, global trade and shipping, and social issues (e.g. anti-vaccination movement and warfare). Pathogen evolution can occur in short timescales, with major changes occurring within the course of an epidemic, and even as short as a single infection. Humans may artificially pressure this evolution through improper antimicrobial practices (antimicrobial resistance) and intentional manipulation (e.g. biological weapons). Emergences may also occur due to natural phenomenon. Zoonoses require multiple species interactions to survive and proliferate. Changes in a system, which change the behavior or lifecycle of any one of these species, may lead to an ecological cascade, providing the proper circumstances for human-pathogen interaction. Examples of changes can include, but are not limited to, climate change, presence of other diseases, nutrition, and natural disasters (Karesh et al., 2012).

1.2 Avian & Mosquito Population Characteristics

Avian WNV infection, in North America, has been identified in around 300 avian species (McLean, 2006). The corvid species is particularly sensitive to severe infection and death. Public health surveillance systems use corvids as a sentinel system to detect WNV in the environment and predict human cases. Other species, such as the American Robin, capable of becoming infectious, may be responsible for the majority of viral maintenance and amplification, due to the magnitude and duration of viremia, and higher survival rates (Hamer et al., 2009). The *Culex* pipiens complex is the dominant vector for WNV in the United States, although the virus has been isolated in other mosquito complexes. These mosquitoes survive and proliferate well in urbanized habitats containing an abundance of water and biological diversity of plants and animals. *Culex* mosquitoes are ornithophilic, predominantly feeding on birds, but are also known to opportunistically feed on mammals such as humans (Hamer et al., 2009).

1.3 Study Region Population & Characteristics

For this project, the Dallas, Tarrant, and Denton Counties of Texas were employed as the study area. This is mainly due to the land mass and population size of the study area being large enough to ensure the availability of disease cases in each species of interest, the proximity of Texas A&M University to the study population, and willingness of cooperation from the state and county health departments, most likely due to the scale of the 2012 WNV outbreak. WNV interacts differently within differing environments. As this study is investigating the impact of ecology on viral transmission

and disease manifestation in humans, it is appropriate to reduce the study area to a size which ensures a reasonably uniform ecosystem.

The 2010 Census was utilized in determining an accurate representation of the human population demographics and land area. Dallas County retains the highest total population of the three counties with 2,368,139 inhabitants. The population of inhabitants <5 yrs old is 7.8%. The population of inhabitants <18 yrs old is 9.5%, and inhabitants >65 yrs old is 9.5%. The combined land/water area is 908.6 square miles. Tarrant County is the second most populated with 1,809,034 inhabitants. The population of inhabitants <5 yrs old is 7.4%. The population of inhabitants <18 yrs old is 23.3%, and inhabitants >65 yrs old is 9.9%. The combined land/water area is 902.3 square miles. Denton County is the least populated, but consists of the largest land area. The total population of Denton County is 662,614 inhabitants. The population of inhabitants <5 yrs old is 6.8%. The population of inhabitants <18 yrs old is 26.5%, and inhabitants >65 yrs old is 8.3%. The combined land/water area is 953 square miles.

1.4 Literature Review

A review of the current WNV epidemiologic and environmental health literature formed the background manuscripts in this project. I completed a literature review on the history of WNV and historical outbreaks in the United States from 1999-2012. Current epidemiologic and environmental risk factor knowledge was evaluated, in addition to noteworthy mathematical and risk assessment models, as well as viral pathogenesis and host immune response.

For this review, I employed three literature search databases: Ovid (3457 results), PubMed (4913 results), and Google Scholar (67,200 results). I also searched the Texas A&M University Medical Sciences Library for books pertaining to WNV and infectious disease modeling. The main database search terms were: West Nile virus, West Nile virus epidemiology, West Nile virus disease modeling, West Nile virus mathematical modeling, and West Nile virus disease ecology, West Nile virus in birds, equine West Nile virus, West Nile fever, and neuroinvasive West Nile virus. Multiple variations and combinations of terms were also employed in an attempt to gather the maximum number of high quality sources. Individual references within incorporated literature were pursued for further review when they pertained to this project.

English-language, peer-reviewed articles, published between the years of 1980 and 2013 were required for inclusion. For clinical information to be included they needed to be supported by at least two credible sources. There are fewer ecologic, epidemiologic, and modeling studies, so only one article was required for certain information, but each article was reviewed in its entirety to ensure validity. Articles should have cited at least 25 sources for research, and 50 sources for reviews, as a marker of the comprehensiveness of background research. As the scope of this study is the United States and the Dallas/ Fort Worth area, epidemiologic studies chosen were narrowed within borders of the continental United States. Articles were excluded when the research that they reported lacked quality or generalizability. Mathematical models were excluded when their findings and conclusions were not justified within the scope of the article.

Selected books and articles were reviewed for content on arthropod vectors, avian hosts, incidental hosts, spatial and temporal drivers of WNV amplification, environmental drivers of WNV amplification, human epidemiology, pathogen invasion, alternative routes of transmission, human pathogenesis, clinical features, disease modeling, vaccination, and disease prevention. The Global Infectious Diseases Epidemiology Network (GIDEON) database was searched for maps, tables, graphs, and figures as well as specific WNV disease information pertaining to this study.

1.5 Mathematical Modeling of Infectious Disease

There are many scientifically validated approaches to the prevention and treatment of zoonotic diseases. Sanitation, vaccination, quarantine, culling of herds, and environmental remediation are all examples of proactive forms of modern disease prevention methods. Modern medicine has allowed scientists to study how a pathogen interacts and causes disease within an individual infected organism. Data accumulation, over time, has provided a basis for statistical analysis and identification of how pathogens are transmitted through the ecosystem. A number of infectious agents have been studied to a point where they may be assessed with a systems dynamics approach. By studying the transmission dynamics of zoonoses, it is possible to identify the most efficient means of disease reduction and elimination. Quantitative analysis, through mathematical modeling, not only allows scientists to identify possible intervention strategies, but may be used to predict the spread of disease and designing efficient medications. Most recently, the rapid increase in computing power has provided

epidemiologists the capacity to build, test, and incorporate these models into public-health practice. Mathematical modeling also grants the ability to conduct experiments within a system without consuming precious time and money. The more comprehensive and accurate the parameters within a model are can influence the precision of the experiments output.

Deterministic modeling is conducted by identifying disease states (compartments) and the parameters which influence flow from one state to another. A series of differential equations is then formulated to describe the compartments. There are several approaches to analyzing deterministic mathematical models, most notably the calculation of the basic reproduction ratio (R_0), numerical analysis, interpolation, and extrapolation. The R_0 value is "the average number of secondary infections caused by a single infectious individual during their entire infectious lifetime" (Smith?, 2008). As epidemiologists are interested in population dynamics, R_0 is viewed as a threshold value. The threshold of $R_0 = 1$ infers a steady endemic state, so that <1 will indicate the disease is dying out, and >1 indicates an epidemic. Numerical analysis permits the epidemiologist to manipulate parameter values within the model and asses how the changes will affect other parameter values over time. Interpolation allows the modeler to assume data points between known points from past data collection, and extrapolation allows projection of disease occurrence into the future.

Spatial modeling is also possible. This form of modeling combines statistical and mathematical approaches integrated with geographic data. This form of modeling can illustrate past trends in physical disease movement and provide a means of identifying

possible covariates. Agent-based spatial models may also be used to simulate future geographic movement of disease over time.

1.6 Disease Surveillance & Data Acquisition

Due to their susceptibility to severe disease and death preceding infection in humans, corvids (e.g. American crow) are used as a sentinel in detecting the presence of WNV by most health agencies. The dead birds are collected and tested in a laboratory for infection. As *Culex* mosquitoes are the dominant vector for WNV, mosquito surveillance is generally based upon live trapping, and subsequent laboratory testing. WNV infection in humans is a nationally-notifiable disease, and confirmed cases are generally reported to public health or commercial laboratories. Healthcare providers may also report suspected cases.

The observational data used in validating the model was collected from the Texas Department of State Health Services, Dallas County Department of Health and Human Services, Tarrant County Department of Public Health, and Denton County Health Department, from the years 2003 – 2012. The Texas Department of State Health Services provided avian and mosquito surveillance data, along with age stratified case counts of West Nile fever and West Nile neuroinvasive disease for the three study counties. Each county provided age stratified cases counts of West Nile disease-related deaths. The observational data was integrated, analyzed for consistency with national trends, and used in comparison numerical simulation output.

1.7 Specific Aims

The goal of the manuscript "West Nile virus Epidemiology, Ecology, and Human Health in the United States" is to lay the foundation for the following manuscripts, with a review study of WNV ecology, mathematical modeling, pathophysiology, and disease manifestation. This study was conducted in order to conceptually construct a novel mathematical model, ascertain accurate parameters and variables for baseline conditions, determine reasonable adjustments to the initial modeling conditions when conducting the sensitivity analysis, and postulate hypotheses to test during the utility analysis of the model.

The goal of the manuscript "A Mathematical Model of the Zoonotic and Vector Transmission Dynamics of West Nile virus: Human Morbidity and Mortality" is to develop a novel mathematical model of WNV transmission, in order to better understand the dynamics that lead to human morbidity and mortality. Human age structure is stratified between juvenile and adult classification, accompanied by compartments for the multiple disease manifestations (i.e. asymptomatic, WNF, WNND, and death), with associated compartments to calculate disease incidence. Multiple annual simulations of the historic bird, mosquito, and human (by age group) epidemic in the Dallas, Tarrant, and Denton county area of Texas were conducted to calibrate and determine the accuracy of this novel model.

The goal of the manuscript "A Mathematical Model of the Zoonotic and Vector Transmission Dynamics of West Nile virus: Utility Analysis**"** is to understand how the dynamics that affect human morbidity and mortality may naturally vary or be controlled,

through intervention, leading to differing population health outcomes. To achieve this goal, numerical simulations are preformed of the developed WNV model. Numerical simulations are compared to surveillance data from the multiple epidemics subsequent to the initial introduction of WNV into Texas during 2002. A sensitivity analysis of the model was conducted to determine the magnitude which human morbidity and mortality changes with given changes in individual baseline variables and parameter initial conditions. Multivariate manipulation was then conducted to simulate environmental changes and human interventions.

2. WEST NILE VIRUS EPIDEMIOLOGY, ECOLOGY, AND HUMAN HEALTH IN THE UNITED STATES

2.1 Introduction

There are more than seventy viruses that form the genus flavivirus, a subset of the family flaviviridae (Kuno, Chang, Tsuchiya, Karabatsos, & Cropp, 1998). These viruses are comprised of positive, single-stranded, enveloped RNA viruses found in ticks and mosquitoes. West Nile Virus (WNV) shares membership of the Japanese encephalitis serocomplex with Japanese encephalitis, St Louis encephalitis (SLE), and Murray Valley encephalitis (Petersen, 2009). WNV is an Old World flavivirus naturally circulating in a transmission cycle between mosquitoes (enzootic vectors) and birds (amplifying hosts). Birds are the natural host for WNV and, by way of mosquitoes, maintain the virus within the ecosystem. Mainly horses and humans (dead-end hosts) may be infected by the bite of certain blood-feeding mosquitoes (bridge vectors), although most vertebrates are susceptible to infection if bitten by an infected mosquito (Laperriere, Brugger, & Rubel, 2011). Other vertebrates may become infected with WNV but cannot transmit the virus back to mosquitoes. The rate of WNV transmission to humans depends on the abundance of infected mosquitoes and their feeding patterns on the reservoir host, the behavior of birds and humans within the environment, and the local ecology that influences human exposure.

WNV was initially introduced to New York in 1999, presumably from the Middle East, and rapidly swept west across the North American continent, north into southern Canada, and south into Latin America by 2006 (Reisen & Brault, 2007). Major outbreaks have been noticed, after disease surveillance, occurring in 2003, 2006, 2009, and 2012 indicating a 3-year epidemic cycle. Preliminary investigation, in 1999, detected IgM antibodies which were presumed to be flaviviruses in the SLE group, and the initial perception was that the outbreak was due to the SLE virus. Investigators soon realized that in addition to human illness there was extensive mortality in the wild bird population, especially amongst the crows and other corvid species (Nelson & Williams, 2007). After Dr. Tracey McNamara conducted a serologic investigation of the dead birds at the Bronx, NY Zoo WNV was identified as the cause of the outbreak. After further analysis, the genetic structure of North American WNV isolates have been shown to be virtually identical to those from Israel (R. S. Lanciotti, 1999).

Historic outbreaks have yielded infection incidence of 2% to 55% in human populations. Generally, lower infection incidence is associated with outbreaks in the United States. Serosurveys indicate that incidence in the United States averages around 5% of the human population during outbreaks, which is considered to be too low to decrease the frequency of WNV outbreaks through protective herd immunity (E. B. Hayes, Komar, et al., 2005).

Changes in ecology and human demographics have shown the potential to drive disease incidence much higher. In particular, an infected individual's risk of neuroinvasive disease increases with age. WNV was recognized as a cause of

neuroinvasive disease in the elderly as early as the 1950's, and during the early years of the United States outbreak, it was noticed that the incidence of neuroinvasive disease increases approximately 1.5 fold, for an individual, every decade of their life making age the principal risk factor for developing WNND (O'Leary et al., 2004). In the U.S., after the recognition of WNV posing a public health problem, several programs have been implemented to address the issue. State and local health departments have instituted vector control programs, disease surveillance, public service announcements, mosquito and bird monitoring, and laboratory assay capability.

Several mathematical models have been constructed to explain the transmission dynamics of WNV between mosquitoes and birds. A few have integrated dead end hosts, such as horses, but a model which accounts for human morbidity and mortality is needed to project the severity of future outbreaks and test the efficacy of interventions.

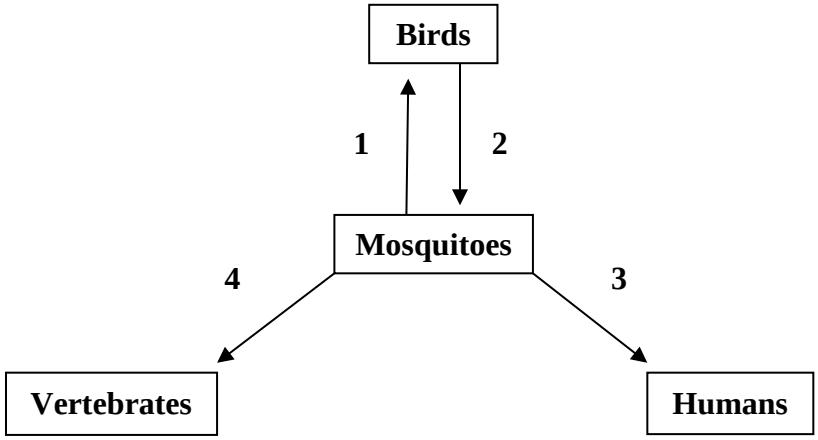

Figure 1: WNV life cycle. 1.) Mosquitoes incubate virus in the midgut and transmit virus through salivary glands during bloodmeal. 2.) Infected birds build viremia to a level of transmission. Some species die and some do not show signs of disease. Transmission to mosquitoes occurs during bloodmeals. 3.) Humans may become infected but are considered "dead-end" hosts. They do not build viremia to a level of transmission. 4.) Most other vertebrates may also become infected, and are considered "dead-end" hosts.

2.2 Epidemiology and Ecology

"The ecology of vector and host populations is a critical pathway through which environmental variability influences virus transmission and ultimately disease risk to humans" (Chuang & Wimberly, 2012). WNV is maintained in a transmission cycle between *Culex* mosquitoes and passeriform birds, an order of birds consisting of the majority of bird species. Viral infection of dead-end hosts, such as humans and horses, occurs when an infected mosquito cannot attain a blood meal from a bird and opportunistically feeds on other vertebrates (Komar, 2003; Weaver & Reisen, 2010) Figure 1. Although the virus has been found in 43 other mosquito species, mosquitoes in the genus *Culex* are the primary WNV vectors worldwide (Murray, Walker, & Gould, 2011; Turell, O'Guinn, & Oliver, 2000).

WNV was initially discovered in Uganda in 1937. After many years of WNV circulating throughout Africa, the Middle East, and Europe, the virus was introduced to an immunologically naïve western hemisphere. Without immunity to WNV in any vertebrates, the virus traversed the continental states, invading Canada, Mexico, and South America within four years of the 1999 introduction to the United States (Reisen & Brault, 2007). Regional human epidemics typically include a year of viral introduction with a low infection rate, followed by female mosquito overwintering, which leads to epidemic levels of viral amplification in birds the following year. Virus is readily produced at high loads within several avian species that produce viremia levels capable of infecting moderately susceptible mosquito species (Reisen & Brault, 2007). A three-year epidemic pattern has been recognized in the human population. This is most likely attributed to declining avian herd immunity leading to renewed viral amplification in the newly susceptible, immunologically naïve, avian hosts (Reisen & Brault, 2007).

WNV strains are associated with one of two genetic lineages (I or II) (R. S. Lanciotti, 1999; Robert S. Lanciotti et al., 2002). Human outbreaks of WNV are generally associated with lineage I and include three sublineages. Sublineage (a) is distributed in Africa, the Middle East, Europe, and the Americas. Sublineage (b), found in Australia, and is also known as KUNV. Sublineage (c) strains are isolated in India (Petersen & Roehrig, 2001). Lineage II is maintained in enzootic (affecting animals) cycles.

Risk factors for humans contracting WNV include populations with more vegetation, agriculture, open or grassy areas, habitat fragmentation by roads, poor

drainage, wetlands, streams and open water. WNV-positive birds and mosquitoes can also be important human risk indicators (Rochlin, Turbow, Gomez, Ninivaggi, & Campbell, 2011). Middle class suburban neighborhoods or "inner suburbs" provide the appropriate combination of environmental factors for WNV transmission to humans (Rochlin et al., 2011; Ruiz, Walker, Foster, Haramis, & Kitron, 2007). Higher biological diversity in rural and affluent communities may protect against transmission to humans. The avian host "dilution effect," proposes that areas, such as inner suburbs, containing a high population of mosquitoes, and low habitability of birds and other vertebrate hosts will increase the probability that humans will come into contact with infected mosquitoes (Swaddle & Calos, 2008). Low biological diversity of animal species ultimately leads to a greater probability of humans becoming the source of a blood meal from these infected mosquitoes, leading to disease transmission.

Climactic changes play a pivotal role in the intensity of WNV transmission. Warmer climates with an abundance of water and vegetation serve as the ideal breeding grounds for mosquitoes. Environmental temperature influences many factors in the effectiveness of WNV transmission (Hartley et al., 2012; Konrad & Miller, 2012; Laperriere et al., 2011). Ambient temperature increases the efficiency of the mosquito gonotrophic cycle by increasing the biting rate of females and reducing the duration of time between blood meal and the laying of eggs. After eggs are laid, the birth and mortality rates of both larvae and adult mosquitoes depend on ambient temperature (Rubel et al., 2008). Fluctuations in temperature also directly affect rates of virus amplification within the mosquito vector. The extrinsic incubation period is the lapse in

time between a mosquito's ingestion of an infectious blood meal and the point in time when that mosquito is capable of viral transmission. This period is an important parameter in the rate of disease transmission (Reisen, Fang, & Martinez, 2006). The extrinsic incubation period of WNV in the mosquito is inversely correlated with temperature between 10° and 30°C (Reisen, Fang, et al., 2006). The amount of ambient standing water evaporation is driven by temperature, and the number of infections in birds, humans, and other vertebrates is negatively correlated with precipitation due to population dilution (Crowder et al., 2013). When water is scarcer, populations of the vector and principal host concentrate in areas with a sustained water source. During hot, dry periods, these areas are generally urban, suburban, and agricultural centers that use water for irrigation. Mosquito biting activity and the percentage of the mosquito population in diapause (i.e. hibernation) is a direct result of the photoperiod (i.e. length of daylight) (Rubel et al., 2008).

It is possible for WNV to survive during colder periods with low to no transmission between birds and mosquitoes. Most likely WNV has been persisting over winters by: infected overwintering female mosquitoes, continued transmission, chronic infections in birds, and migratory birds (Reisen & Brault, 2007). On several occasions WNV has been isolated from overwintering female *Culex* mosquitoes while WNV-infected birds and mosquitoes are collected throughout the year in warmer climates. Corvids (e.g. crows, ravens, and jays) succumb rapidly during acute infection, but other avian taxa recover. High levels of persistent RNA have been found in the spleen, kidney and lungs of these recovered birds. Warblers are susceptible to WNV infection, and virus

may overwinter at southern latitudes and then be carried north during the warbler migration (Reisen & Brault, 2007). Different passeriform families play specific roles in the transmission and human understanding of WNV. Whereas birds that are fairly unaffected by infection aid in the maintenance of the virus, birds that succumb quickly aid human surveillance efforts. Due to their susceptibility to severe disease and death preceding infection in humans, corvids are used as a sentinel in detecting the presence of WNV by health agencies. In some cases nearly 50% of dead birds tested during a mass death period were positive for WNV and were far easier to track than humans in the early days of infection (Nelson & Williams, 2007).

WNV outbreaks are unpredictable and necessitate surveillance systems with capabilities of detecting ongoing WNV transmission activity with regard to person, place and time. These systems must be maintained to ensure the ability to respond to outbreaks with effective interventions. These efforts consist of the complementary epidemiological and environmental surveillance of humans, birds, and mosquitoes (Nasci et al., 2013). Human WNV disease burden is quantified through epidemiologic surveillance and identifies seasonal, geographic, and demographic disease patterns in human populations. WNV activity is also monitored within the environment, specifically in mosquitoes and birds, to identify future risks for human population health (Nasci et al., 2013).

WNV infection is a nationally-notifiable disease. Cases are reportable in nearly all states and territories of the United States. Confirmed cases are generally reported to public health or commercial laboratories and healthcare providers may also report suspected cases. The respective health departments are tasked with ensuring that the

reported cases then meet the national case definitions provided by the CDC (CDC, 2013b). These passive surveillance systems depend completely on clinician diagnostic efficacy. They must be able to identify probable WNV, conduct the appropriate diagnostic testing, and report confirmed cases to their respective public health authority (CDC, 2013b). WNV disease is underestimated in epidemiological and environmental surveillance systems. This is mainly due to incomplete diagnosis and reporting in humans, and the impossibility of capturing of all infected birds and mosquitoes. Due to substantial associated morbidity and mortality, WNND case reports in humans are considered the most accurate. Reports of WNF should be assumed inadequate and under-represented and they are not generalizable between geographic areas or over time (CDC, 2013b).

A few WNV epidemiological trends have been noticed. The frequency of documented human WNV outbreaks has increased over the past decade, and cases of human neuroinvasive disease and fatality rates in birds coincide with these outbreaks (Murray et al., 2011). This trend may be attributed to surveillance bias, as it has been shown that surveillance of human morbidity and mortality is inadequate in certain study locations and is presumably better in others. Human infections typically begin around June as the infected population of birds and mosquitoes reaches its peak. In September, a decline in infection occurs as evening temperatures fall and mosquito activity slows (Haley, 2012). High childhood attack rates in rural Nile villages are thought to provide protection of the older population from neuroinvasive disease due to acquired immunity. North Americans lack the background immunity in bird and human populations leading

to more neuroinvasive disease cases (Reisen & Brault, 2007). Generally, elderly individuals are at the highest risk for neuroinvasive disease and death. However, several other risk factors have been identified for death, including cardiovascular disease, hypertension, history of cancer, chronic obstructive pulmonary disease, chronic renal disease, diabetes, history of alcohol abuse, and immune suppression (Lindsey, Staples, Lehman, & Fischer, 2012; Murray et al., 2011).

Currently, there is not a licensed human WNV vaccine. Prevention of disease transmission to humans is conducted through public health action (Haley, 2012). Prevention of disease in humans must focus on prevention of exposure. Public education, control of mosquito populations through elimination of breeding sites, and physical distancing of humans from mosquitoes have been effective in mitigating outbreak severity and adverse health outcomes (Murray et al., 2011). The CDC promotes the five 'Ds' for WNV prevention: Dusk, Dawn, Draining, Dress, and DEET. Dusk and Dawn are the highest risk times for exposure to infected mosquitoes, Draining standing water decreases mosquito breeding, Dressing in long sleeves and trousers when outdoors provides a physical barrier from bites, and mosquito repellent containing DEET provides a chemical barrier (CDC, 2013b; Murray et al., 2011).

The first vector-borne epidemic model was proposed in 1908, known as the Ross-Macdonald malaria model. Although the vast majority of WNV modeling has been conducted via statistical investigation, several veterinary mathematical models have been constructed for assessing control strategies against WNV (Blayneh, Gumel, Lenhart, & Clayton, 2010; Bowman, Gumel, van den Driessche, Wu, & Zhu, 2005;

Wonham & Lewis, 2008). Models commonly simulate the seasonal cycles of bird, equine, and occasionally human WNV cases along with environmental parameters (Laperriere et al., 2011). Generally, these models consist of compartmentalized systems converted into ordinary differential equations for numerical analysis (Abdelrazec, Lenhart, & Zhu, 2013; Cruz-Pacheco, Esteva, Montano-Hirose, & Vargas, 2005; Foppa & Spielman, 2007; Simpson et al., 2012). These models may be used for simulating temporal changes of disease within differing populations. They may also be used to test epidemiologic hypotheses or intervention strategies by manipulation of the model parameters through computer simulation before implementation. Other forms of modeling include the use of Geographic Information Systems to conduct a geospatial-temporal analysis.

2.3 Pathophysiology in Humans

Mosquitoes inoculate WNV into the capillary bed of a vertebrate host as they probe the host's skin and obtain a blood meal. The skin and mucous membranes form the initial barriers against viral invasion, but the female mosquito's proboscis penetrates them. The innate response to a virus consists of various humoral and cellular immune reactions, involving an interferon (IFN) response, the complement system, natural antibodies, phagocytosis, cytotoxic mechanisms, and apoptosis (Arjona & Fikrig, 2008). Antibodies can neutralize the infectivity of viruses by mechanically blocking the virus entry pathway in a process called neutralization (Klasse & Burton, 2007). The formation

of antibodies specific to WNV and their subsequent "memory" constitute the adaptive immune response.

After a mosquito successfully inoculates the reservoir or incidental vertebrate host, dendritic cells residing in the epidermis, known as Langerhans cells (LC), become infected and activate. This process prompts the infected cells to migrate to the respective lymph node through an afferent lymphatic (Johnston, Halliday, & King, 2000). In order to recognize pathogen-associated molecular patterns (PAMPs) from viral proteins and nucleic acids, cells utilize extracellular and cytoplasmic pathogen recognition receptors (PRRs) (Akira, Uematsu, & Takeuchi, 2006). As little as one viral component may be recognized as a PAMP and trigger innate immune activation (Johnston, Halliday, & King, 1996; Johnston et al., 2000). After a cell recognizes the viral epitope, PRRs initiate rapid responses, involving genomic effects. These effects result from rapid activation of transcription factors and interferon regulatory factors (IRFs). Activation leads to the production of several cytokines and induction of antiviral, inflammatory, and adaptive responses (Arjona & Fikrig, 2008).

Type 1 IFNs, IFN-β, and IFN-α are the major cytokines generated after WNV infection. These cytokines facilitate the generation of an innate response and eventually lead to the development of adaptive immunity to WNV. Type 1 IFNs also induce effector molecule expression influencing protein synthesis, cell growth, and cell survival (Theofilopoulos, Baccala, Beutler, & Kono, 2005). IFN-β can be induced from secondary sites of viral infection including the central nervous system (CNS). This

indicates multiple cell types, including neurons, can recognize WNV infections (Arjona & Fikrig, 2008).

Although IFN-α may prevent the initial cellular infection by WNV, it does not inhibit the viral replication after viral invasion of the cell. Expression of one or more viral proteins can inhibit the IFN-α response (Diamond et al., 2000; Lucas et al., 2003; Morrey et al., 2004). DC-SIGN, DC-SIGN-R, and integrin $\alpha_\upsilon\beta_\varepsilon$ aid in attachment of WNV to host cells. Once bound to the cell membrane, WNV enters the cell through receptor-mediated endocytosis. The viral and endosomal membranes then fuse, and the viral nucleocapsid is released into the cytoplasm (Samuel & Diamond, 2006). WNV replication interferes with an early step in the signal transduction pathway required for cellular activation (Guo, Hayashi, & Seeger, 2005). Within infected cells, IFN does not induce efficient phosphorylation of Janus kinase 1 and Tyrosine kinase 2. Consequently, the signal transducers and activators of transcription factors remain latent. Ultimately, the induction of immune serum globulins (ISGs) becomes insufficient to establish an antiviral state.

The first location of viral amplification is a lymph node. Within the node, the virus is released from the LC and delivers virus that infects macrophages and dendritic cells. WNV spreads systemically via the efferent lymphatics to the bloodstream and disseminates throughout the body (Arjona & Fikrig, 2008). Subsequent infection occurs in peripheral tissues such as the spleen, kidneys, and brain (Samuel & Diamond, 2006). TNF-α can promote inflammation and permeability of the blood-brain-barrier (BBB) and in turn facilitate CNS infections (Samuel & Diamond, 2006; Wang et al., 2004).

Infection of neural tissue may lead to a potentially fatal condition called West Nile meningoencephalitis characterized by the swelling of the brain, and the membranes covering the brain and spinal cord. Inflammation and permeability of the BBB can lead to mechanical tissue damage of the fragile neurons. Viral invasion of neurons subsequently leads to cell death via viral load and immune response. The swelling of the brain and its protective barrier due to edema and cellular apoptosis may also cause neuronal damage, leading to impaired cognitive function and flaccid paralysis. Neuroinvasive disease occurs in an estimated <1% of infected humans, yet accounts for around 100% of fatalities (case fatality ranging from 3% to 15%). Asymptomatic cases and West Nile fever account for an estimated 80% and 20%, respectively.

During WNV infection, macrophages are also involved in humoral and cell-mediated immune responses. Once a virus is phagocytized, macrophages digest proteins and process the antigens for surface presentation on the major histocompatibility complex (MHC). These molecules are in turn presented to Th1 cells. Macrophages also respond to WNV infection by secreting antiviral and proinflammatory cytokines (Garcia-Tapia, Loiacono, & Kleiboeker, 2006; Rios et al., 2006; Shirato, Miyoshi, Kariwa, & Takashima, 2006). Natural Killer (NK) cells respond by secreting the IFN-γ that activate macrophages and DCs, shaping the adaptive immune response toward the $CD4^+$ Th1-type immunity (Andoniou, Andrews, & Degli-Esposti, 2006). NK cells recognize and kill host somatic cells that are opsonized with antibody through neutralization. The NK cells also secrete antiviral and inflammatory cytokines (Andoniou et al., 2006).

The expression of antiviral and inflammatory cytokines and chemokines leads to the activation and recruitment of lymphocytes into the infected tissue. This expression represents a link between innate and adaptive immunity (Lobigs, Mullbacher, & Regner, 2008). The second wave of the IFN response activates many ISGs (Lobigs et al., 2008). $CD4^+$ Th1 lymphocytes provide helper function to B-cells staging a humoral response (Bishop & Hostager, 2001). These lymphocytes can also limit viral replication through cytokines and kill virus-infected cells by Fas- and granule exocytosis-mediated cytotoxic mechanisms (Heller, Gurer, & Munz, 2006). $CD4^+$ T-cell help is required for IgM-to-IgG antibody isotype switching. This process is a critical component of the adaptive immune response against the WNV (Vieira & Rajewsky, 1988). Antibodies can neutralize the infectivity of flaviviruses. Opsonization interferes with attachment, internalization, and fusion of the virus by inhibiting the conformational changes in the E protein associated with membrane fusion, effectively neutralizing the viral threat (Jost & Pierson, 2009; Klasse & Burton, 2007).

After the body clears the virus and foreign antigen is absent from the system, a down regulation of the immune response occurs. A subsequent increase of antibody concentration ensues in the plasma as antibodies are no longer interacting with antigen. The excess antibodies act to control, through feedback, the production of new antibody proteins. Over time, the short-lived effector T and B-cells die and decrease in number to pre-infection concentrations. Memory cells, with extended life spans, are retained at levels sufficient to scan the circulatory system for future infections. It is thought that humans may form a lifelong immunity to WNV, although this is currently contested.

2.4 Clinical Manifestations in Humans

Around 80% of human WNV infections are asymptomatic, although, due to the sub-clinical attributes leading to under reporting, this number is difficult to estimate (Mostashari et al., 2001). When symptoms develop, around 20% of persons have self-limited West Nile fever (WNF). WNF tends to be characterized by the acute onset of fever, headache, fatigue, malaise, muscle pain and weakness, gastrointestinal symptoms, and/or a temporary macular rash (C. G. Hayes, 1989; Watson et al., 2004). It takes a an average of 1-2 weeks for a case to recover from WNF and median time of 60 days for a person to fully recover to pre-WNF vitality (Flatau, Kohn, Daher, & Varsano, 1981; E. B. Hayes, Sejvar, et al., 2005).

Neuroinvasive disease develops in less than 1% of WNV infections for the entire human population. Meningitis, encephalitis, or paralysis may manifest in these circumstances. Neuroinvasive disease is more likely to be reported than WNF because of the severity of the signs and symptoms, and the possibility of death, although there have been cases of misdiagnosed individuals who died and donated their organs for transplant (Mostashari et al., 2001). The main known risk factor for neuroinvasive disease is advanced age. Risk of encephalitis is also higher among transplant recipients and others who are immunocompromised (Beckham & Tyler, 2009). Manifestation of WNV encephalitis ranges from mild confusion to coma and death. Severe tremors and Parkinsonism have also manifested in some cases (Pepperell et al., 2003; Sejvar et al., 2003). Infection of motor neurons may cause acute asymmetric flaccid paralysis that may persist for several years (E. B. Hayes, Sejvar, et al., 2005). Brainstem and high

cervical spinal cord infection may lead to death after diaphragmatic and intercostal muscle paralysis causes respiratory failure (E. B. Hayes, Sejvar, et al., 2005).

2.5 Discussion

There have been a number of WNV wakeup calls for public health professionals in the United States over the past decade. Although public health and mosquito control programs continually become more efficient in areas that conduct them, and zoonotic and vector surveillance have become priorities in several major metropolitan areas where substantial outbreaks have occurred, further understanding of the dynamic WNV ecology must be pursued so that we may increase competency in resource allocation.

Now that WNV has become endemic in the United States and has been shown to be prevalent in rural areas as well as urban, rural counties should join in conducting surveillance and implementing control measures. As the average age of United States citizens increases, it becomes ever more important to protect the aging population from morbidity and mortality due to WNV infection. To educate the population on the risk of infection and development of neuroinvasive disease, an increase in the number of public service announcements conveying proper personal protections may be needed.

The One Health initiative, mathematical modeling of WNV ecology, and other interdisciplinary ventures can facilitate the future comprehensive understanding and unified response to this persistent disease threat. Cooperative efforts by ornithologists, entomologists, medical professionals, public health professionals, and many other disciplines may support this pursuit. This integrated knowledge may aid physicians and

public health professionals to mitigate, prepare for, respond to, and recover from the inevitable future outbreaks.

In the future, efforts should be directed towards disease detection and modeling. Mathematical modeling of WNV has not been conducted to portray long-term predictions of human WNV disease burden by combining the life cycles, environmental conditions, and pathophysiology of birds, mosquitoes, and humans. A model which accounts for these factors may add to the development of comprehensive ecologic knowledge related to how the interactions of environmental factors lead to WNF, WNND, and disease-related mortality in humans within different age strata. By considering geospatial population focalization of different species, and their overlap with others, one may provide illumination on disease amplification within a given area and subsequent transmission into others over time and space. The practical applications are numerous, including forecasting disease, testing hypotheses, and testing the efficacy of disease interventions.

3. A MATHEMATICAL MODEL OF THE ZOONOTIC AND VECTOR TRANSMISSION DYNAMICS OF WEST NILE VIRUS: HUMAN MORBIDITY AND MORTALITY

3.1 Introduction

West Nile virus (WNV) initially invaded New York in 1999 and rapidly swept west across the North American continent, north into southern Canada, and south into Latin America by 2006 (Reisen & Brault, 2007). Historic outbreaks have yielded 2% to 55% infection incidence in human populations (E. B. Hayes, Komar, et al., 2005). Generally lower infection incidence is associated among outbreaks in the United States with serosurveys indicating that human prevalence of acute infection averages around 5% during an outbreak, which is considered to be too low to decrease the frequency of WNV epidemics or modulate their intensity through protective immunity (E. B. Hayes, Komar, et al., 2005). Changes in ecology and human demographics have shown the potential to drive disease incidence much higher. For example, an infected human's risk of neuroinvasive disease increases with age. WNV was recognized as a cause of neuroinvasive disease in the elderly as early as the 1950's, and during the early years of the United States outbreak it was noticed that the incidence of neuroinvasive disease increases approximately 1.5 fold for an individual every decade of their life. This results in a risk approximately 30 times greater for a person over 80 years of age than for someone younger than 10 years old (O'Leary et al., 2004).

In the United States, a three-year epidemic pattern has been recognized in the human population, and is most likely attributed to declining avian herd immunity leading to renewed explosive viral amplification (Reisen & Brault, 2007). In 2012, Texas had the largest outbreak of neuroinvasive disease since the introduction of WNV to the state in 2002, with 844 confirmed cases (CDC, 2013a). The majority of cases occurred in the Dallas/Fort Worth area; thus, our study is focused on this region. Surveillance data for model calibration was acquired from the Texas Department of state Health Services and from each of the Dallas, Tarrant, and Denton counties health departments.

Mathematical modeling of disease ecology traces back to Daniel Bernoulli's work with smallpox in 1760. Epidemic modeling of vector-borne disease began in 1908 with a malaria model proposed by Sir Ronald Ross. He published his "The Prevention of Malaria" in 1911, which later earned his work a Nobel Prize (Smith?, 2008). Half a century later, with the contributions of George Macdonald in 1957, the model is now known as the Ross – Macdonald malaria model. In 2001, Thomas and Urena introduced the initial WNV transmission model, investigating pesticide efficiency in relation to the reduction of human neuroinvasive WNV (Thomas & Urena, 2001). In 2005, WNV modeling dynamics were broadened to include humans into the enzootic transmission cycle with the incorporation of five disease state compartments for humans which allowed for simulating hospitalization, due to severe WNV symptoms, prevalence over time (Bowman et al., 2005). Models based upon temperature dependent, seasonal cycles, of vector-borne disease have been presented in the past several years, targeting such variables in the mosquito population as the gonotrophic cycle (i.e. egg development),

biting rate of females, birth and mortality rates of both larvae and adults, and the viral extrinsic incubation period (Laperriere et al., 2011; Rubel et al., 2008). In 2010 a WNV model of the Mediterranean population (Europe and Africa) began the integration of human age structure into the dynamics of disease progression (Durand, Balanca, Baldet, & Chevalier, 2010).

Models have not been constructed to portray long-term predictions of human WNV disease burden by combining the life cycles, environmental conditions, and pathophysiology of birds, mosquitoes, and humans of different age strata. Therefore we propose a deterministic compartmental model for the dynamics of WNV. This model adds to the development of comprehensive ecologic knowledge related to which factors in the transmission and infection process lead to West Nile fever (WNF), West Nile neuroinvasive disease (WNND), and disease-related mortality within different age strata. The proposed model has numerous practical applications, including forecasting disease, testing hypotheses, and testing the efficacy of disease interventions.

The goal of this paper is to develop a novel mathematical model of WNV transmission by stratifying human age structure, and incorporating compartments for the multiple disease manifestations and associated compartments to calculate disease incidence, in order to understand the dynamics that lead to human morbidity and mortality. Multiple annual cycles of the historic bird, mosquito, and human (by age group) epidemic in the Dallas, Tarrant, and Denton county area of Texas were conducted to calibrate and determine the accuracy of this novel model.

3.2 Methods

3.2.1 WNV Surveillance Data

WNV was first detected in Texas in 2002. After the initial outbreak the virus became endemic with a three-year epidemic cycle recognized after a decade of human surveillance based upon clinical and laboratory reporting to the state and local health departments Table 1. Although the surveillance methods employed do not wholly represent the actual burden of disease for birds, mosquitoes, and humans they provide valuable data for model validation.

		2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Age: ≤39	WNF	4	4	5	7	8	3	2	0	0	122
	WNND	18	5	4	13	6	2	8	0	1	69
	Death	0	0	0	0	0	0	0	0	0	0
Age: ≥40	WNF	20	3	25	37	19	3	11	0	2	376
	WNND	62	11	26	67	23	6	27	0	0	261
	Death	5	0	1	10	0	0	5	0	0	32

Table 1: Human surveillance data. Observed yearly incidence (2003 – 2012) of West Nile fever (WNF), West Nile neuroinvasive disease (WNND), and disease-related mortality by age group in the combined Dallas, Tarrant, and Denton counties. Shading indicates major outbreak years.

The surveillance data used for this study was narrowed to the Dallas, Tarrant, and Denton counties of Texas due to the abundance of neuroinvasive cases and deaths in these counties. The data was acquired from the Texas Department of State Health Services and from each of the Dallas, Tarrant, and Denton counties health departments.

These data included yearly case count of West Nile fever (WNF), West Nile neuroinvasive disease (WNND), and WNV related deaths, all stratified by age group for the years 2003-2012. To examine whether the virus was continuously in circulation throughout this time period, bird and mosquito surveillance data were also gathered from the state. The human surveillance data were compared to the numerical simulations for our model for model validation.

3.2.2 Model Development

A deterministic compartmental model was developed to simulate the dynamics of WNV in bird, mosquito, and human populations during individual years. This model was constructed to postulate which parameters may fluctuate, and to what degree, to produce an outbreak year. The model is based on the WNV model developed by Laperriere et al. in 2011 which simulates the life cycles of birds, mosquitoes, and humans as well as the infection cycle between birds and mosquitoes with humans as dead-end hosts (Laperriere et al., 2011). Due to the increased risk of developing neuroinvasive disease with advanced age, we consider two distinct age classes for humans: juveniles (≤ 39 years old) and adults (≥ 40 years old). Moreover, we consider multiple states of infection (WNF, WNND, and asymptomatic infection) in the human population, and a simplified treatment of seasonality in which time-dependent parameters are replaced by a constant yearly average.

Let $S_B(t)$,$E_B(t)$,$I_B(t)$, and $R_B(t)$ denote the number of susceptible, exposed (infected but not yet infectious), infectious, and recovered birds at time t, where $t \geq 0$,

respectively. Let $L_M(t)$ denote the number of mosquito larvae at time t ≥ 0 and $S_M(t)$, $E_M(t)$, and $I_M(t)$denote the number of susceptible, exposed, and infectious mosquitoes at time t ≥ 0, respectively. Due to the short average lifespan of mosquitoes we assume infected mosquitoes will die prior to recovery from infection. Let $S_h(t)$, $E_h(t)$, $I_{h1}(t)$, $I_{h2}(t)$, $I_{h3}(t)$and $R_h(t)$denote the number of susceptible, exposed, infected (asymptomatic), infected (WNF), infected (WNND), and recovered juvenile humans at time t ≥ 0, respectively. Similarly, let $S_H(t)$, $E_H(t)$, $I_{H1}(t)$, $I_{H2}(t)$, $I_{H3}(t)$and $R_H(t)$ denote the number of susceptible, exposed, infected (asymptomatic), infected (WNF), infected (WNND), and recovered adult humans at time t ≥ 0, respectively. Finally, denote the total bird, mosquito, juvenile human, and adult human populations at time t ≥ 0 by $N_B(t) = S_B(t) + E_B(t) + I_B(t) + R_B(t)$, $N_M(t) = S_M(t) + E_M(t) + I_M(t)$, $N_h(t) = S_h(t) + E_h(t) + I_{h1}(t) + I_{h2}(t) + I_{h3}(t) + R_h(t)$, and $N_H(t) = S_H(t) + E_H(t) + I_{H1}(t) + I_{H2}(t) + I_{H3}(t) + R_H(t)$, respectively. The variables for the model along with their units are described in Table 2.

Suppose that $\Lambda_B > 0$ represents the constant recruitment rate of birds into the population, while $d_B > 0$ and $\mu_B > 0$ denote the natural and disease-related death rate for birds. Susceptible birds (S_B) become exposed (E_B) after being bitten by an infectious mosquito (I_M). As in Laperriere, this mosquito-to-bird transmission is modeled using frequency-dependent transmission with parameter $\beta_{MB} > 0$. The average latent period for birds is $1/\alpha_B$ days, after which an exposed bird (E_B) becomes infectious (I_B). Birds will remain infectious for an average of $1/\gamma_B$days

before recovering (R_B) and gaining immunity to reinfection. The dynamics of the bird population are illustrated in Figure 2.

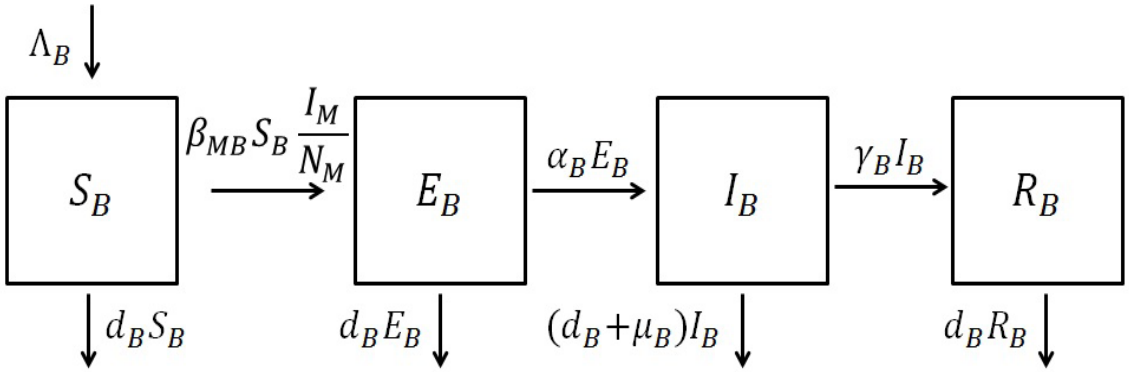

Figure 2: Compartmental model of avian WNV dynamics

Suppose that $b_L > 0$ and $d_L > 0$ represent the birth and death rates of mosquito larvae, respectively. The rate at which mosquito larvae (L_M) will become susceptible adult mosquitoes (S_M) is given by b_M. Since we are not considering vertical transmission of WNV all newborn mosquitoes are assumed to be susceptible. Suppose that $d_M > 0$ is the natural death rate of mosquitoes. Susceptible mosquitoes (S_M) become exposed (E_M) after biting an infectious bird (I_B). As in Laperriere, the bird-to-mosquito transmission is modeled using frequency-dependent transmission with parameter $\beta_{BM} > 0$. Note that $\beta_{BM} \neq \beta_{MB}$ since the probability of transmission from an infectious bird to a susceptible mosquito is not the same as the probability of transmission from an infectious mosquito to a susceptible bird. The

average latent period for mosquitoes is $1/\alpha_M$ days, after which an exposed mosquito (E_M) becomes infectious (I_M). Due to their short average lifespan, we assume that mosquitoes will die prior to recovery from infection. The dynamics of the mosquito population are illustrated in Figure 3.

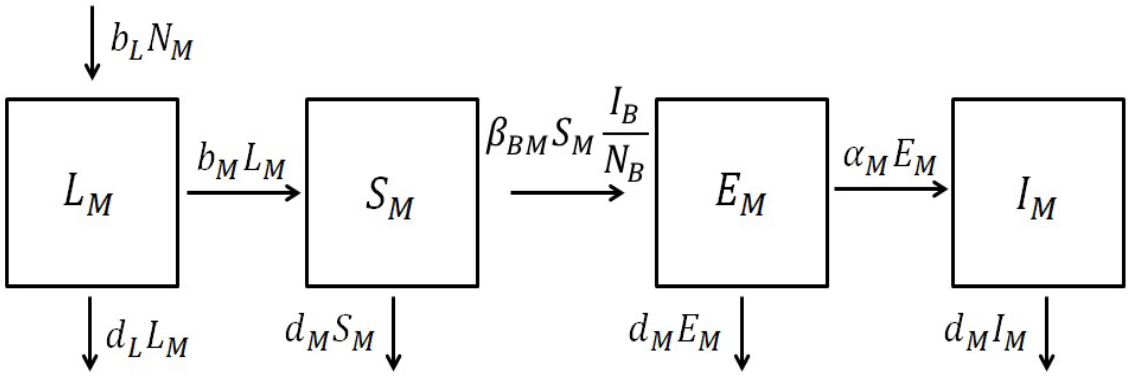

Figure 3: Compartmental model of mosquito WNV dynamics

Suppose that $\Lambda_h > 0$ represents the constant recruitment rate of juvenile humans into the population, and $d_h > 0$ represents the natural death rate of juvenile humans. Susceptible juvenile humans (S_h) become exposed (E_h) after being bitten by an infectious mosquito (I_M). As in Laperriere, the mosquito-to-human transmission is modeled using frequency-dependent transmission with parameter $\beta_{MH} > 0$. The average latent period for juvenile humans is $1/\alpha_h$ days, after which an exposed juvenile human (E_h) becomes infected. The probability that an exposed juvenile human will develop WNF is denoted by $p_1 \in (0, 1)$. Thus, the rate at which exposed

juvenile humans (E_h) become infected with WNF (I_{h2}) is given by ($\alpha_h p_1 E_h$). The probability that an exposed juvenile human will develop neuroinvasive disease is denoted by $p_2 \in (0, 1)$. Thus, the rate at which exposed juvenile humans (E_h) become infected with neuroinvasive disease (I_{h3}) is given by ($\alpha_h p_2 E_h$). It follows that the rate at which exposed juvenile humans become infected with no symptoms (I_{h1}) is given by $\alpha_h(1 - p_1 - p_2)E_h$. The recovery rates for infected juvenile humans in states I_{h1}, I_{h2}, and I_{h3} are γ_{h1}, γ_{h2}, and γ_{h3}, respectively. Juveniles infected with neuroinvasive disease suffer an increased risk of death associated with infection. The disease-related death rate for juvenile humans is denoted by μ_h and the number of juvenile disease-related deaths at time $t \geq 0$ is denoted by $D\_h(t)$. Similar notation is used for the model parameters related to adult humans, with the exception of a capital H subscript. However, the probability that an exposed adult human (E_H) develops neuroinvasive disease (I_{H3}) is denoted by $p_3 \in (0, 1)$. Since adult humans have a greater risk of developing neuroinvasive disease, it follows that $p_3 > p_2$. The dynamics of the human population are illustrated in Figure 4. All of the model parameters with their units are summarized in Table 2.

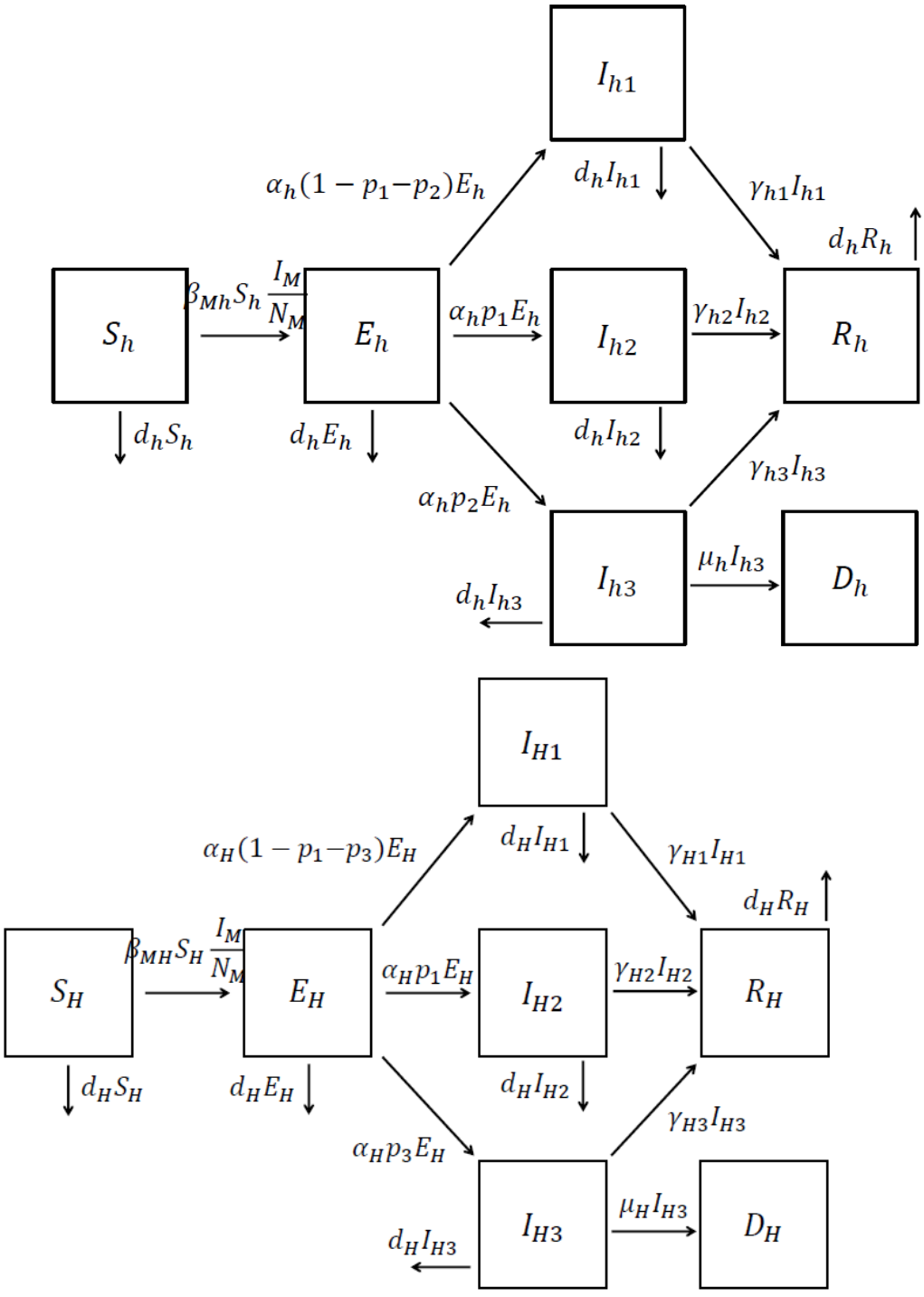

Figure 4: Compartmental model of juvenile & adult WNV dynamics

Parameters	Definition	Units	Baseline Value
$\mathbf{b_L}$	Larvae birth rate	Larvae/(Mosquito)(Day)	0.0434
$\mathbf{d_L}$	Larvae death rate	1/Day	0.1436
$\mathbf{b_M}$	Mosquito birth rate	Mosquito/(Larvae)(Day)	0.00434
$\mathbf{d_M}$	Mosquito death rate	1/Day	0.01436
$\boldsymbol{\beta_{BM}}$	Bird-to-mosquito transmission	1/Day	0.00434
$\boldsymbol{\alpha_M}$	Mosquito duration of incubation	1/Day	0.0469
$\boldsymbol{\Lambda_B}$	Bird recruitment	Birds/Day	294
$\mathbf{d_B}$	Bird natural death rate	1/Day	3.425×10^{-4}
$\boldsymbol{\beta_{MB}}$	Mosquito-to-bird transmission	1/Day	0.5601
$\boldsymbol{\alpha_B}$	Bird duration of incubation	1/Day	0.3333
$\boldsymbol{\mu_B}$	Bird disease-related death rate	1/Day	0.0923
$\boldsymbol{\gamma_B}$	Bird recovery rate	1/Day	0.3077
$\boldsymbol{\Lambda_h}$	Juvenile recruitment	Humans/Day	220.5
$\boldsymbol{\Lambda_H}$	Adult recruitment	Humans/Day	220.5
$\boldsymbol{\beta_{MH}}$	Mosquito-to-human transmission	1/Day	1.3079×10^{-5}
$\mathbf{d_{H\ \&\ h}}$	Human natural death rate	1/Day	3.914×10^{-5}
$\boldsymbol{\alpha_{H\ \&\ h}}$	Human duration of incubation	1/Day	0.125
$\boldsymbol{\gamma_{H1\ \&\ h1}}$	Recovery rate for $I_{H1\ \&\ h1}$	1/Day	0.1429
$\boldsymbol{\gamma_{H2\ \&\ h2}}$	Recovery rate for $I_{H2\ \&\ h2}$	1/Day	0.0541
$\boldsymbol{\gamma_{H3\ \&\ h3}}$	Recovery rate for $I_{H3\ \&\ h3}$	1/Day	0.0714
p1	Probability of exposed developing $I_{H2\ \&\ h2}$	Dimensionless	0.20
p2	Probability of exposed developing $_{Ih3}$	Dimensionless	0.005
p3	Probability of exposed developing I_{H3}	Dimensionless	0.0175
$\boldsymbol{\mu_h}$	Juvenile disease-related death rate	1/Day	7.143×10^{-5}
$\boldsymbol{\mu_H}$	Adult disease-related death rate	1/Day	0.0071

Table 2: Parameter values for the WNV model with units and associated baseline values

The WNV model consists of 23 ordinary differential equations (ODE's) which are given in Figure 5. The "dot" notation denotes differentiation with respect to time. That is $\dot{S}_B = dS/dt$.

Birds:

1.	$\dot{S}_B = \Lambda_B - d_B S_B - \beta_{MB} S_B \frac{I_M}{N_M}$	Susceptible Birds
2.	$\dot{E}_B = \beta_{MB} S_B \frac{I_M}{N_M} - (d_B + \alpha_B) E_B$	Exposed Birds
3.	$\dot{I}_B = \alpha_B E_B - (d_B + \mu_B + \gamma_B) I_B$	Infectious Birds
4.	$\dot{R}_B = \gamma_B I_B - d_B R_B$	Recovered Birds
5.	$\dot{D}_B = \mu_B I_B$	Disease-related Bird fatalities

Mosquitoes:

6.	$\dot{L}_M = b_L N_M - (d_L + b_M) L_M$	Mosquito Larvae
7.	$\dot{S}_M = b_M L_M - d_M S_M - \beta_{BM} S_M \frac{I_B}{N_B}$	Susceptible Mosquitoes
8.	$\dot{E}_M = \beta_{BM} S_M \frac{I_B}{N_B} - (d_M + \alpha_M) E_M$	Exposed Mosquitoes
9.	$\dot{I}_M = \alpha_M E_M - d_M I_M$	Infectious Mosquitoes

Figure 5: Ordinary differential equations

Humans ≤ 39:

10. $\dot{S}_h = \Lambda_h - d_h S_h - \beta_{MH} S_h \frac{I_M}{N_M}$	Susceptible Juvenile Humans
11. $\dot{E}_h = \beta_{MH} S_h \frac{I_M}{N_M} - (d_h + \alpha_h) E_h$	Exposed Juvenile Humans
12. $\dot{I}_{h1} = \alpha_h (1 - p_1 - p_2) E_h - (d_h + \gamma_h) I_{h1}$	Infected (Asymptomatic)
13. $\dot{I}_{h2} = \alpha_h p_1 E_h - (d_h + \gamma_{h2}) I_{h2}$	Infected (WNF) Juvenile Humans
14. $\dot{I}_{h3} = \alpha_h p_2 E_h - (d_h + \mu_h + \gamma_{h3}) I_{h3}$	Infected (WNND) Juvenile Humans
15. $\dot{R}_h = \gamma_{h1} I_{h1} + \gamma_{h2} I_{h2} + \gamma_{h3} I_{h3} - d_h R_h$	Recovered Juvenile Humans
16. $\dot{D}_h = \mu_h I_{h3}$	Disease-related Juvenile Fatalities

Figure 5: Continued

Humans ≥ 40:

17. $\dot{S}_H = \Lambda_H - d_H S_H - \beta_{MH} S_H \frac{I_M}{N_M}$	Susceptible Adult Humans
18. $\dot{E}_H = \beta_{MH} S_H \frac{I_M}{N_M} - (d_H + \alpha_H) E_H$	Exposed Adult Humans
19. $\dot{I}_{H1} = \alpha_H (1 - p_1 - p_3) E_H - (d_H + \gamma_H) I_{H1}$	Infected (Asymptomatic)
20. $\dot{I}_{H2} = \alpha_H p_1 E_H - (d_H + \gamma_{H2}) I_{H2}$	Infected (WNF) Adult Humans
21. $\dot{I}_{H3} = \alpha_H p_3 E_H - (d_H + \mu_H + \gamma_{H3}) I_{H3}$	Infected (WNND) Adult Humans
22. $\dot{R}_H = \gamma_{H1} I_{H1} + \gamma_{H2} I_{H2} + \gamma_{H3} I_{H3} - d_H R_H$	Recovered Adult Humans
23. $\dot{D}_H = \mu_H I_{H3}$	Disease-related Adult Fatalities

Figure 5: Continued

3.2.3 Initial Conditions

The initial American crow density was estimated based upon the land area being considered, Farnsworth et al. (2005), and Laperriere et al. (2011). Using the average of 15 birds/km^2, for an area of 7,158.5km^2, we calculate an estimated initial population of 107,377 birds (Census Bureau, 2010; Farnsworth et al., 2005; Laperriere et al., 2011). The initial conditions for *Culex* mosquitoes are set for a 7% infection prevalence of overwintering female mosquitoes (Reisen, Barker, et al., 2006). The population density of mosquitoes was calculated at 40,000 per acre (Haramis, 2011). A susceptible human population in Dallas, Tarrant, and Denton counties of 4,850,000 was obtained from the 2010 census and divided equally between the two age groups (Census Bureau, 2010). All other disease states for birds, mosquitoes and humans were assumed to be initially zero. These initial conditions are given in Table 3.

Variable	Definition	Units	Initial Condition
S_B	Susceptible Birds	Birds	15/km2 * 7158.46814 (sq. km) = 107377
E_B	Exposed Birds	Birds	0
I_B	Infectious Birds	Birds	0
R_B	Recovered Birds	Birds	0
D_B	Disease-related Bird fatalities	Birds	0
L_M	Mosquito Larvae	Larvae	0
S_M	Susceptible Mosquitoes	Mosquitoes	40,000mos/acre (640acres/sq. mi.) 2,763.9sq. mi. (93%) = $6.578x10^{10}$
E_M	Exposed Mosquitoes	Mosquitoes	0
I_M	Infectious Mosquitoes	Mosquitoes	7 % of overwintering
S_h	Susceptible Juvenile Humans	Humans	2,425,000
E_h	Exposed Juvenile Humans	Humans	0.00
I_{h1}	Infected (Asymptomatic)	Humans	0.00
I_{h2}	Infected (WNF) Juvenile Humans	Humans	0.00
I_{h3}	Infected (WNND) Juvenile Humans	Humans	0.00
R_h	Recovered Juvenile Humans	Humans	0.00
D_h	Disease-related Juvenile Fatalities	Humans	0.00
S_H	Susceptible Adult Humans	Humans	2,425,000
E_H	Exposed Adult Humans	Humans	0
I_{H1}	Infected (Asymptomatic) Adult Humans	Humans	0
I_{H2}	Infected (WNF) Adult Humans	Humans	0
I_{H3}	Infected (WNND) Adult Humans	Humans	0
R_H	Recovered Adult Humans	Humans	0
D_H	Disease-related Adult Fatalities	Humans	0

Table 3: Variables for the WNV model with units and associated initial conditions

3.2.4 Infection and Cross-infection

Birds and mosquitoes may infect one another, during the blood meal of a female mosquito. This is referred to as cross-infection. Female mosquitoes may feed on other vertebrates, inoculating but not contracting the virus, as most other vertebrates do not develop a level of viremia capable of transmission. We employ human subjects for this study.

The force of transmission between mosquitoes-birds, birds-mosquitoes, and mosquitoes-humans are considered a function of an average photoperiod and temperature:

- $\beta_{MB}(\bar{T}) = \bar{\delta}_M k(\bar{T}) p_M \phi_B$
- $\beta_{BM}(\bar{T}) = \bar{\delta}_M k(\bar{T}) p_B$
- $\beta_{MH}(\bar{T}) = \bar{\delta}_M k(\bar{T}) p_M \phi_H$

The average photoperiod was calculated for the geographic latitude of Dallas/Fort Worth in order to estimate the average fraction of active, non-diapausing, mosquitoes ($\bar{\delta}_M$). The average temperature of the area ($\bar{T}$) was calculated over the course of a year for estimating the average biting rate ($k(\bar{T})$) and other mosquito parameters. The probability of viral transmission, (p_M) by mosquitoes and (p_B) by birds, and initial values for the frequency of vector interaction, (ϕ_B) vector-bird and (ϕ_H) vector-human, were set as constant (Laperriere et al., 2011).

3.2.5 Parameter Estimation

3.2.5.1 Mosquito: Vector

Parameters utilized within this WNV model are represented in Table 3. Mosquito and transmission parameters were adapted and calculated based upon a model from Rubel et al. (2008) and Laperriere et al. (2011), as these equations were constructed from U.S. WNV data for the *Culex* species (Laperriere et al., 2011; Rubel et al., 2008). The baseline mosquito parameters, calculated as functions of average annual temperature and photoperiod, are represented in Table 3. Bird and human parameters were collected from peer-reviewed literature and publically available census data (Census Bureau, 2010).

3.2.5.2 Birds: Amplifying Host

The bulk of dead birds reported in the Dallas/Fort Worth tri-county area belonged to the species *Cyanocitta cristata* (blue jay) and *Corvus brachyrhynchos* (American crow). As corvids are highly susceptible to morbidity and mortality from WNV infection they are used for sentinel surveillance. Although they most likely play a nominal role in viral amplification, the majority of avian pathogenesis information available is directed towards the American crow (Hamer et al., 2009). For these reasons, the American crow was chosen to represent the avian population in this particular WNV model.

The normal life span of an American crow has been estimated to be 8 years (mortality rate: $d_B = 1/(8 * 365) \approx 0.00034\ days^{-1}$) and the reproductive success

has been reported to be 2 offspring per bird pair, each year (recruitment rate: $\Lambda_B = [(107{,}377/2) \times 2]/365 \approx 294/day$) (Chamberlain-Auger, Auger, & Strauss, 1990; Clapp, Klimkiewicz, & Futcher, 1983). Experimental studies have shown that, once exposed, the average duration of incubation for birds is 3 days ($1/\alpha_B = 3\ days$), the average recovery rate is 3.25 days ($\gamma_B \approx 0.3077 days^{-1}$), and probability of disease-related mortality estimated to thirty percent (disease-related mortality rate: $\mu_B = (0.30/3.25) \approx 0.0923\ days^{-1}$) (E. B. Hayes, Komar, et al., 2005; Laperriere et al., 2011; McLean, 2006).

3.2.5.3 Humans: Dead-end Host

The human population has been stratified by age, as this variable is the leading risk factor for developing neuroinvasive disease and mortality. The population estimate for the Dallas/Fort Worth metropolitan area was provided by the 2010 census ($N_H = 4{,}850{,}000$) and the population divided equally between the two age strata ($\leq 39\ or\ \geq 40 yrs$) (Census Bureau, 2010). All human parameters have been acquired from published, peer reviewed literature and the only significant difference between the juvenile and adult parameters will be the proportion developing neuroinvasive disease. The recruitment rate of humans was set equal for both the juvenile and adult populations and retrieved from the 2010 census. The average human recruitment rate for 2005-2010 was ($\Lambda_{H\&h} = 80{,}470.6/365 \approx 220.4/day$) (Census Bureau, 2010). The natural death rate was calculated based upon a 70-year lifespan ($d_{H\&h} = 1/(70 * 365) \approx 0.000039\ days^{-1}$). The duration of viral incubation and rate of recovery from the

asymptomatic and febrile forms of infection were taken from a clinical study (Murray et al., 2011). The average values for these durations were used in this model. The normal duration of viral incubation is 8 days ($1/\alpha_{H\&h} = 1/8 \approx 0.1250\ days^{-1}$). The duration of asymptomatic infection is difficult to calculate and is assumed to be 7 days ($\gamma_{H1\&h1} = 1/7 \approx 0.1429\ days^{-1}$). The duration of WNF has a large variance in time and can be as mild as one week or last one month or more (Murray et al., 2011). WNF may cause prolonged morbidity, is rarely associated with mortality, and is often misdiagnosed as some other form of febrile illness. An average value of 18.5 days was employed for WNF in this model ($\gamma_{H2\&h2} = 1/18.5 \approx 0.0541\ days^{-1}$) (Murray et al., 2011). The probability calculations of exposed individuals developing each form of West Nile disease were based upon the assumption that 20% of infected individuals develop WNF ($p_1 = 0.2$) and an average, over the entire human population, of 0.75% developing WNND. We set the probability of WNND for juveniles as 0.05% ($p_2 = 0.005$) and adults as 1.75% ($p_3 = 0.0175$). The probability of developing the asymptomatic form was calculated as $(1 - (p_1 + p_2))$ for juvenile humans and $(1 - (p_1 + p_3))$ for adult humans. The recovery rate from WNND was set to 14 days ($\gamma_{H3\&h3} = 1/14 \approx 0.0714\ days^{-1}$) (Flatau et al., 1981). The adult disease-related death rate was calculated based upon a 90% probability of survival ($\mu_{H\&h} = 0.10/14 \approx 0.0071\ day^{-1}$). The juvenile disease-related death rate was calculated based upon a 99.5% probability of survival ($\mu_{H\&h} = 0.005/14 \approx 0.00036\ day^{-1}$).

3.2.6 Simulation and Calibration

Numerical simulations of the WNV model were performed in the software package MATLAB R2012b using the initial conditions in Table 2 and baseline parameter values in Table 3 (MATLAB, 2012). A time series analysis was conducted over the course of single year and month periods. Beginning with completely susceptible bird and human populations, frequency of infection is driven by the initially infected overwintering mosquitoes and the force of infection. At the end of a specified time period, the incidence was calculated. Disease prevalence over time, population densities in each disease state, and total population densities were also simulated and charted. The surveillance data obtained from the state and local health departments was then charted for each disease state. To calibrate the model, the probability of vector contact (ϕ) was adjusted in the expression for β_{MH} to reduce the mean-square error. As the surveillance data for WNF and WNND is presumably incongruent with the true incidence of disease, we calibrated the model using the incidence of disease-related mortality. The probability of vector-host interaction was scaled until the simulated incidence of disease-related mortality matched the observed, reported incidence as closely as possible.

3.3 Results

The summarized data received from the state and local health departments, illustrates the surveillance imprecision that is present in most WNV surveillance systems. Bird and mosquito cases are impossible to represent accurately and may only be used as indicators of virus in the environment. Numerical simulations illustrate a

major reduction in avian population due to their high probability of disease-related mortality. This is in concordance with other studies conducted on avian WNV disease (McLean, 2006). The avian population appears to rapidly succumb to WNV early on and either recover or die, leaving the surviving birds with permanent immunity. The virus, during the avian amplification and following several weeks, is transmitted back to the mosquito population for further viral propagation.

Our simulations are centered on the hypothesis that a WNV model may produce accurate population estimates of human morbidity and mortality within differing age strata. Due to the nonspecific nature of WNV disease manifestation, human disease representation through surveillance is challenging. With an estimated 20% of all infected humans developing WNF, and approximately 1% developing WNND, it is apparent that within the data there are reporting flaws. The reported WNND incidence is higher than WNF in this study region. This particular inaccuracy is most likely attributable to WNF cases being misdiagnosed, cases not seeking healthcare due to mild symptoms, and other healthcare administrative issues. As a result, model calibration must be conducted using the more severe form of WNV disease manifestation (WNND and death), while the WNF cases are extrapolated from these results and compared to the unbound incidence. During the calibration process, major changes in human morbidity and mortality were noticed with small adjustments of the probability of contact. The model is fitted with the average of one death within a given non-outbreak year in the adult population corresponding to 12 WNND cases (surveillance avg. 11.0) and 139 WNF cases (surveillance avg. 8.67) in a given non-outbreak year for the in the adult population

Figures 6&7. The juvenile incidence of 3 WNND (surveillance avg. 3.0), 139 WNF (surveillance avg. 3.33), and 0 dead (surveillance avg. 0.0) are represented in Figures 6&8.

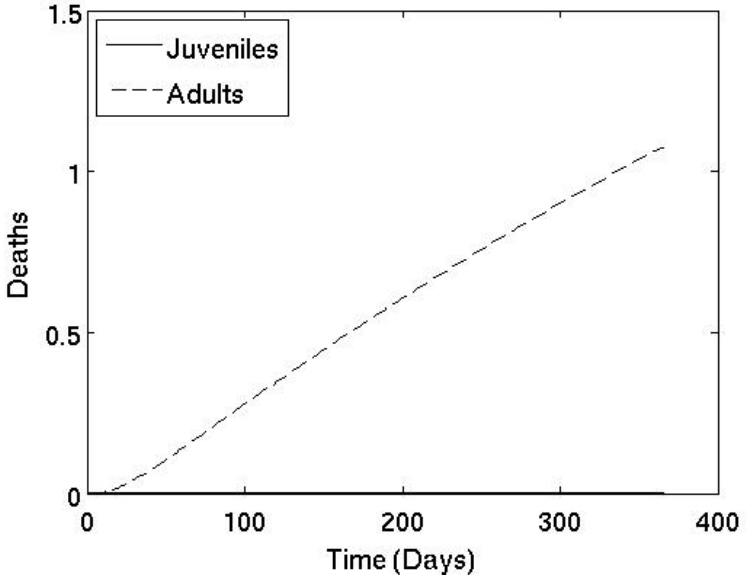

Figure 6: Annual adult and juvenile disease-related death incidence

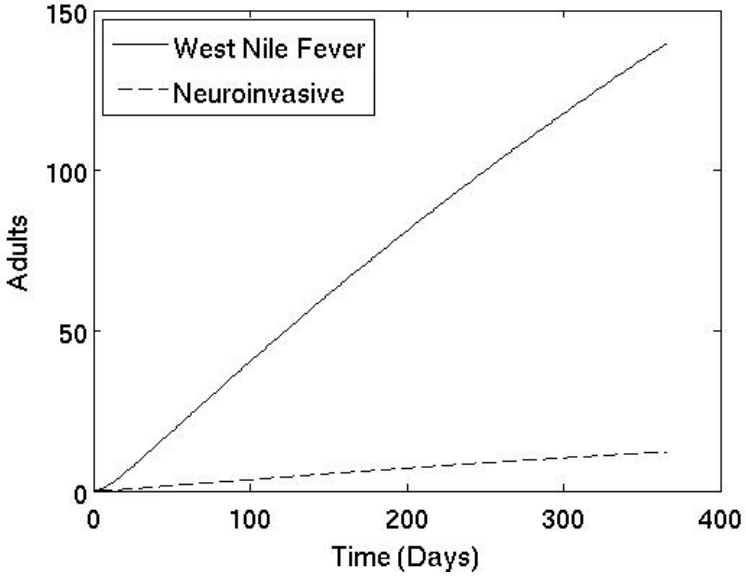

Figure 7: Annual adult WNF and WNND incidence

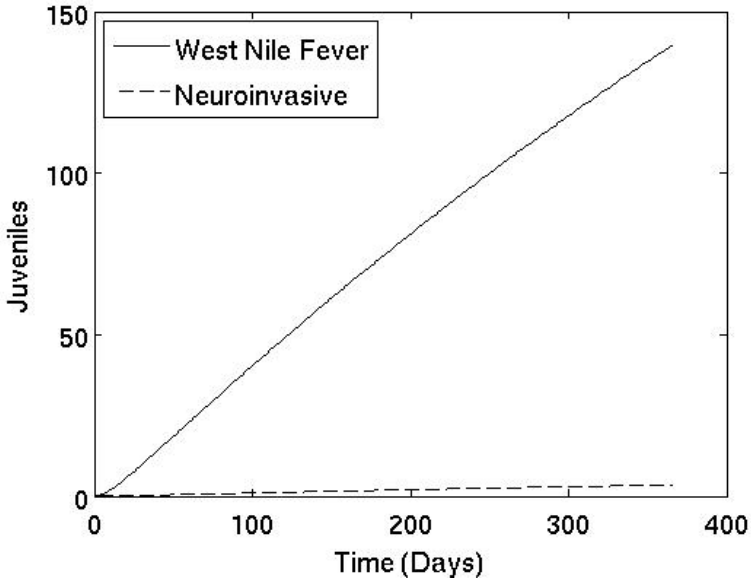

Figure 8: Annual juvenile WNF and WNND incidence

3.4 Discussion

In this manuscript, we establish the ability of an infectious disease model to reflect WNV human morbidity and mortality cases in differing age strata based upon environmental, avian, and mosquito disease determinants. Although this model is fairly complex, it is built upon the assumptions of preceding models (e.g. Laperriere et al. 2011) and is structured to be built upon in the future. Numerical simulations of our model may be conducted on any computer using MATLAB or STELLA.

In a corresponding manuscript, we conduct a utility analysis of the model presented in this manuscript. To illuminate the different ways to utilize our model, we perform numerous simulations for a parameter sensitivity analysis on human morbidity and mortality. We may also mold situations, by altering several parameters, in order to see how the combination of factors affects human morbidity and mortality. Simulations may be based on differing geographic locations, mean ambient temperature, further stratification of ages, contact probabilities, disease state probabilities, progression of disease, and many more. A utility analysis may also be able to simulate such environmental events as drought, initial avian population concentration, and long-term changes in the average annual temperature. Furthermore, this WNV model may be capable of conducting analysis of disease control strategies such as insecticide and larvicide usage, or of possible future vaccines.

Future modeling efforts may be directed towards extending our model to include additional age strata, bird species, seasonal immigration of birds, and ecologic factors that influence mosquito and human behavior. As the U.S. population ages over time, we

may observe higher incidence of disease due to a larger concentration of elderly individuals in the population. The addition of immunosuppression and other special classifications within the population may also provide insight as this is the second highest risk factor for the development of WNND. By furthering the age stratification of the human population, we may be able to represent the elderly and immunocompromised with more precision. By considering these two subgroups as equivalent to healthy juveniles provides a dilution effect of subgroup specific morbidity and mortality when determining population dynamics. Our model may also be extended to an additional form of morbidity, acute flaccid paralysis, after further research is conducted into the condition. Multiple avian and mosquito species may also be incorporated into future modeling efforts. As various species have diverse pathophysiologic responses to WNV, the addition these populations may provide further insight on disease maintenance within the environment and subsequent transmission into the human population.

Environmental aspects that affect avian, mosquito, and human behavior and interaction should be included in future modeling efforts. The abundance of water for hydration and breeding may be considered along with the segmentation of populations. By considering geospatial population focalization of different species, and their overlap with others, one may provide further illumination on disease amplification within a given area and subsequent transmission into others over time and space.

To further develop WNV modeling, we must focus more effort on determining the probability of contact within the vector-host and vector-dead end host relationship.

This parameter is the most difficult to measure, yet plays the most pivotal role in the transmission of disease.

4. A MATHEMATICAL MODEL OF THE ZOONOTIC AND VECTOR TRANSMISSION DYNAMICS OF WEST NILE VIRUS: UTILITY ANALYSIS

4.1 Introduction

West Nile virus (WNV) initially invaded New York in 1999 and rapidly swept west across the North American continent, north into southern Canada, and south into Latin America by 2006 (Reisen & Brault, 2007). After nearly a decade of WNV disease surveillance throughout the United States, a three-year epidemic pattern has been recognized in the human population. This phenomenon is postulated to be attributed to declining avian herd immunity leading to renewed explosive viral amplification (Reisen & Brault, 2007). Historic outbreaks throughout the world have yielded 2% to 55% infection in human populations with a generally lower infection prevalence associated during outbreaks in the United States, which averages 5% prevalence (E. B. Hayes, Komar, et al., 2005). Although changes in ecology and human demographics have shown the potential to drive disease prevalence much higher, this prevalence is considered to be too low to develop herd immunity (E. B. Hayes, Komar, et al., 2005).

Several modeling efforts have been conducted to determine the transmission dynamics of WNV over the past 15 years, each building upon its predecessor (Bowman et al., 2005; Durand et al., 2010; Thomas & Urena, 2001). We previously designed a deterministic compartmental model, similar in construct to the Laperriere et al., 2011

model, for the dynamics of WNV transmission (Laperriere et al., 2011). This model was developed to simulate human disease incidence and mortality during an individual year based upon parameters affecting the life cycles of birds, mosquitoes, juvenile humans (≤39 yrs old), adult humans (≥40 yrs old) and the infection cycle between birds and mosquitoes, with humans as dead-end hosts. The two age classifications of humans are due to the increased risk of developing neuroinvasive disease and death with advanced age. Risk of West Nile neuroinvasive disease (WNND) increases approximately 1.5 fold for an individual every decade of their life. This results in a risk approximately 30 times greater for a person over 80 years of age than for someone younger than 10 years old (O'Leary et al., 2004). In both the juvenile and adult populations, infected individuals are classified as asymptomatic, infected with West Nile Fever (WNF), or infected with WNND.

Here we manipulate some of the model parameters for comparison to a decade of localized surveillance data. To assess the utility of this model, multiple annual simulations of bird, mosquito, and human (by age group) WNV disease in the Dallas, Tarrant, and Denton county area of Texas will be conducted to test model parameter sensitivity with respect to human morbidity and mortality. Combined parameter manipulation will also be conducted to simulate environmental changes (e.g. mean ambient temperature, drought, and pesticide spraying). The simulations will be combined into a utility analysis for evaluation of model effectiveness during application.

The goal of this paper is to perform numerical simulations of a model of WNV transmission previously developed by Christopher Laine and Glen Lahodny, Jr. in order

to understand how the dynamics that affect human morbidity and mortality may naturally vary or be controlled, through intervention, leading to differing population health outcomes. Numerical simulations are compared to surveillance data from the multiple epidemics subsequent to the initial introduction of WNV into Texas during 2002.

4.2 Methods

4.2.1 West Nile Virus Model

The WNV model is illustrated in Figure 2, 3, and 4. The model consists of 23 ordinary differential equations (ODE's) describing the life cycles of birds, mosquitoes, juvenile humans (≤39 yrs old), adult humans (≥40 yrs old) and the infection cycle between birds and mosquitoes, with humans as dead end hosts. The American crow is used as the bird host in this model due to the abundance of scientific literature regarding their pathophysiology. *Culex* mosquitoes are used in the majority of WNV modeling studies since they are the most common carriers and transmitters of WNV in the study area. Numerical simulations of the model were performed using MATLAB version R2012B (MATLAB, 2012). The model parameters along with their units and baseline values are summarized in Table 2. The baseline model parameters are unchanged from the original model.

Vector-host interaction was scaled until the simulated incidence of disease-related mortality matched the observed, reported incidence as closely as possible. The model was fitted with the average of one adult disease related death within a given non-

outbreak year. This corresponds to 12 WNND cases and 139 WNF cases in a given non-outbreak year in the adult population. The corresponding juvenile incidence of 3 WNND, 139 WNF, and 0 disease-related deaths were also acquired from numerical simulation.

4.2.2 Surveillance Data

We employed surveillance data from Dallas, Tarrant, and Denton counties of Texas acquired directly from the Texas Department of state Health Services and from each of the individual county health departments Table 1. Surveillance data included yearly incidence of West Nile fever (WNF), West Nile neuroinvasive disease (WNND), and deaths, all stratified by age group (i.e. juvenile and adult) for the years 2002-2012. After the initial outbreak, the virus became endemic in Texas and a three year epidemic cycle became apparent. We use the average incidence for the outbreak years of 2003, 2006, and 2009 for simulation comparison.

4.2.3 Individual Variable Modification

Each of the parameters that we modified was adjusted over a spectrum of biologically-feasible values. For each point considered in the spectrum of values, a numerical simulation was performed using MATLAB and the outcomes of adult WNND, adult disease related mortality, and juvenile WNND were reported and charted.

Juvenile death was not charted after simulation due to the fact that the number of juvenile disease-related deaths never reached 1 individual disease-related fatality.

The initial susceptible avian population concentration may change drastically over consecutive years. After major outbreaks, nearly 40% of an entire avian species may perish from disease (McLean, 2006). Those that are able to recover develop a long-lasting immunity to WNV. For our simulations, an initial susceptible avian population of 107,377 was set in the area of interest based upon a calculated population of 15 birds per km^2 (Laperriere et al., 2011) and a land area of about 7,158.5 km^2 (Census Bureau, 2010). The initial susceptible avian population was then adjusted to 25%, 50%, 75%, 150%, 200%, and 400% of the baseline 107,377, for a total of 7 simulations. A recruitment rate correction was calculated into each simulation to allow for an annual recruitment rate of 2 birds per bird pair. Avian migration occurs in many species. Although American crows do not tend to be as migratory in southern latitudes, they may be influenced to change location due to environmental pressures. The initial daily migration was set to 0 with a birth rate of 294 birds per day. To apply the added adjustment for daily migration we multiplied 125%, 150%, 175%, 200%, 225% and 250% of the original birth rate value for a total of 7 simulations.

Previous experimental studies have shown that ambient temperature fluctuation throughout the year affects many mosquito parameters including the gonadotropic cycle and extrinsic incubation period of WNV within the mosquito (Laperriere et al., 2011; Rubel et al., 2008). The annual mean annual temperature for the Dallas/Fort Worth area

is 67.25°F. For the sensitivity analysis, we began simulation at 60°F and increased the mean annual temperature by 2°F until 76°F, for a total of 10 simulations.

When considering disease growth within a system there must be either an introduction of a pathogen from outside of the normal system or for the system to begin at some level of infection. Our previous simulations have considered a 7% initial infection prevalence of the mosquito population due to overwintering. We adjusted this prevalence from 7% through 52%, increasing prevalence by 5% per simulation for a total of 10 simulations. As the number of initially infected mosquitoes has no influence on the behavior of mosquitoes there was no need to add the probability of contact into simulation.

Natural mosquito and larval death depend on environmental temperature (Rubel et al., 2008). Although humans cannot directly adjust the mean ambient temperature for a given year, we may influence mosquito and larval death by vector control activities. Control activities, may also be directed towards reducing larval birth rates. The mosquito and larval death rates corresponding to a mean annual temperature of 67.25°F are $d_M \approx 0.01436$ days^{-1} and $d_L \approx 0.1436$ days^{-1}, respectively. These rates were each adjusted to 25%, 50%, 75%, 150%, 200%, 400%, 600%, 800%, and 1,000% of their baseline values for a total of 10 simulations for each parameter. A larval birth rate of $b_M \approx 0.0434$ days^{-1} was initiated and adjusted to 400%, 200%, 150%, 75%, 50%, 25%, 12.5%, 6.25%, and 3.125% of their baseline values for a total of 10 simulations.

When considering any change in the avian or mosquito population, the probability of vector-avian contact will most likely change to some degree as well. We

consider this individual parameter for model sensitivity purposes. An initial vector-avian probability of contact was set to 30 based upon previous studies (Laperriere et al., 2011). The probability of contact was then adjusted to 25%, 50%, 75%, 150%, 200%, and 400% of the baseline value, for a total of 7 simulations. Just as in considering changes in the vector-avian probability of contact (ϕ), the same applies to vector-human contact probability. An initial vector-avian probability of contact was set to 0.0007 based upon our previous study (Lane and Lahodny, 2014). The probability of contact was then adjusted to 25%, 50%, 75%, 150%, 200%, and 400% of the baseline value, for a total of 7 simulations.

4.2.4 Multivariate Modification

Climactic variation plays a fundamental role in the intensity of WNV transmission. Temperate climates with an ample supply of water and vegetation serve as the ideal habitats for mosquitoes and birds. When water is scarce during extended hot, dry periods, populations of the vector and the avian host concentrate in areas with a sustained water source such as urban and suburban centers that use water for irrigation (Rubel et al., 2008). To simulate a drought situation, we adjusted initial avian concentration and migration by 25%, 50%, 75%, 150%, 200%, and 400% of the baseline value, for a total of 7 simulations. We also took the probability of vector-avian contact and multiplied it by the squared value of 25%, 50%, 75%, 150%, 200%, and 400% against the respective baseline value for these 7 simulations.

A high level of biological diversity in rural and affluent communities may reduce the risk of WNV transmission to humans. The avian host "dilution effect," proposes that urban areas and inner suburbs that contain high populations of mosquitoes, accompanied with low habitability of birds and other vertebrates, will amplify WNV transmission to humans, as low biological diversity of vertebrate species ultimately leads to a greater probability of humans becoming the source of a blood meal (Swaddle & Calos, 2008). As there will be the same initial concentration of birds, but segregated away from humans, our simulation of the avian host dilution effect adjusted both the vector-avian and vector-human probabilities of contact. The original vector-human contact probability was multiplied by 0.25, 0.50, 0.75, 1.50, 2.00, and 4.00; the vector-avian contact was then set as the multiplicative inverse of the vector-human contact for 7 simulations.

Environmental remediation against arboviral disease is most commonly conducted via comprehensive vector control which targets the mosquito at multiple stages of the life cycle. Most integrated vector management efforts consist of a series of community and personal level prevention activities. These activities include the spreading of insecticides and larvicides, water management and habitat modification, and the CDC's five "D's" for individual prevention: Dusk, Dawn, Draining, Dress, and DEET (CDC, 2002). Individual prevention can be explained by using the previously simulated probability of vector-human contact. For both insecticide and larvicide usage, we employed the mosquito and larval death simulations, but modified both the vector-avian and vector-human probabilities of contact by multiplying an adjustment value to

the original probability. For each simulation, both probabilities of contact adjustments were set as the multiplicative inverse of the originally altered values (e.g. 25% corresponds 4 and 1,000% corresponds 0.10). To account for water management and habitat modification we altered the larval birth simulations by adjusting both probabilities of contact. Each was set as equivalent to the original adjustment values (e.g. 3.125% = 0.03125 and 400% = 4).

4.3 Results

4.3.1 Simulation: Individual Variable Modification

Each variable modification was conducted without probability of contact adjustment for the purpose of sensitivity analysis. After simple adjustment of the initial susceptible avian population concentration, with the birth rate correction, we noticed static human morbidity and mortality Table 4. When migration was simulated, we received minimal changes in morbidity and mortality. No disease state accrued another person. The minimum percentage of change for each disease state to increase or decrease by 1 individual is +/- 8.20% for adult WNND, + 93.0% for disease related mortality and +/- 28.7% for juvenile WNND. As the normal annual incidence of disease related mortality is 1 case any decrease will account in 0 cases in the study area. At the maximum level of 250% adjustment in daily migration, adult WNND increased 1.56%, death increased 1.47%, and juvenile WNND increased 1.72% Table 5. Vector-avian probability was similarly minimal in change. At the minimum level of adjustment of 0.25x, adult WNND decreased -3.12%, death decreased -3.13%, and juvenile WNND

decreased -3.16%. At the maximum adjustment 4x, adult WNND increased 1.15%, death increased 1.16%, and juvenile WNND increased by 1.15% Table 6.

Initial Susceptible Avian Population Concentration, S(0)						
% Adjustment	**Adult WNND**	**% Change**	**Death**	**% Change**	**Juvenile WNND**	**% Change**
25	12.19	0.00	1.075	0.00	3.48	0.00
50	12.19	0.00	1.075	0.00	3.48	0.00
75	12.19	0.00	1.075	0.00	3.48	0.00
Baseline Value	12.19	0.00	1.075	0.00	3.48	0.00
150	12.19	0.00	1.075	0.00	3.48	0.00
200	12.19	0.00	1.075	0.00	3.48	0.00
400	12.19	0.00	1.075	0.00	3.48	0.00

Table 4: Initial susceptible avian population concentration, S(0). Percentage adjustment of variable from baseline value; associated yearly incidence of adult and juvenile WNND, and disease-related death; percentage change in yearly incidence from baseline

Probability of Vector-Avian Contact, ϕ						
% Adjustment	**Adult WNND**	**% Change**	**Death**	**% Change**	**Juvenile WNND**	**% Change**
25	11.81	-3.12	1.0413	-3.13	3.37	-3.16
50	12.04	-1.23	1.0613	-1.27	3.44	-1.15
75	12.14	-0.41	1.0701	-0.46	3.47	-0.29
Baseline Value	12.19	0.00	1.075	0.00	3.48	0.00
150	12.25	0.49	1.0803	0.49	3.5	0.57
200	12.28	0.74	1.0831	0.75	3.51	0.86
400	12.33	1.15	1.0875	1.16	3.52	1.15

Table 5: Probability of vector-avian contact, ϕ**.** Percentage adjustment of parameter from baseline value; associated yearly incidence of adult and juvenile WNND, and disease-related death; percentage change in yearly incidence from baseline

Avian Daily Migration						
% Adjustment	**Adult WNND**	**% Change**	**Death**	**% Change**	**Juvenile WNND**	**% Change**
Baseline Value	12.19	0.00	1.075	0.00	3.48	0.00
125	12.23	0.33	1.0785	0.33	3.5	0.57
150	12.27	0.66	1.0815	0.60	3.51	0.86
175	12.3	0.90	1.0842	0.86	3.51	0.86
200	12.33	1.15	1.0866	1.08	3.52	1.15
225	12.36	1.39	1.0888	1.28	3.53	1.44
250	12.38	1.56	1.0908	1.47	3.54	1.72

Table 6: Avian daily migration. Percentage adjustment of parameter from baseline value; associated yearly incidence of adult and juvenile WNND, and disease-related death; percentage change in yearly incidence from baseline

Mean annual environmental temperature plays a minimal role in disease related mortality. The changes are most prominent in morbidity. Noticeable changes in adult WNND begins at temperatures just above 64°F and just below 70°F. Juvenile WNND changes begin just above 60°F and just below 74°F Table 7. At an average of 90°F it would take 150days (5months) for the human population to reach their first disease related death.

Mean Annual Ambient Temperature						
Adjustment Value	**WNND**	**% Change**	**Death**	**% Change**	**WNND**	**% Change**
67.25°F	12.19	0.00	1.075	0.00	3.48	0.00
60°F	8.25	-32.32	0.7238	-32.67	2.36	-32.18
62°F	9.39	-22.97	0.8249	-23.27	2.68	-22.99
64°F	10.48	-14.03	0.9218	-14.25	2.99	-14.08
66°F	11.54	-5.33	1.0162	-5.47	3.3	-5.17
68°F	12.59	3.28	1.1107	3.32	3.6	3.45
70°F	13.69	12.31	1.2089	12.46	3.91	12.36
72°F	14.87	21.99	1.314	22.23	4.25	22.13
74°F	16.15	32.49	1.4276	32.80	4.61	32.47
76°F	17.52	43.72	1.5493	44.12	5.01	43.97

Table 7: Mean annual ambient temperature. Percentage adjustment of parameter from baseline value; associated yearly incidence of adult and juvenile WNND, and disease-related death; percentage change in yearly incidence from baseline

When taking into account prevalence of mosquito infection over time, we noticed that there may be differing infection prevalence at the end of different years, depending on the given conditions of the respective year. This prompted our adjustment of initial infection prevalence within the mosquito population. We began the prevalence at 7% and adjusted until the initial mosquito population was 52% infectious. Immediate dramatic increases in human morbidity and mortality became apparent with a 65% increase in all disease states with the first 5% increase in mosquito prevalence. By the level of 52% initial infection prevalence, morbidity and mortality increased by 583% Table 8.

Percentage of Overwintering Mosquitoes Infectious						
Adjustment Value	**AdultWNND**	**% Change**	**Death**	**% Change**	**Juvenile WNND**	**% Change**
7%	12.19	0.00	1.075	0.00	3.48	0.00
12%	20.15	65.30	1.778	65.40	5.76	65.52
17%	28.06	130.19	2.4763	130.35	8.02	130.46
22%	35.95	194.91	3.1733	195.19	10.27	195.11
27%	43.84	259.64	3.8696	259.96	12.53	260.06
32%	51.72	324.28	4.5653	324.68	14.78	324.71
37%	59.59	388.84	5.2608	389.38	17.03	389.37
42%	67.46	453.40	5.956	454.05	19.28	454.02
47%	75.33	517.97	6.6509	518.69	21.524	518.51
52%	83.2	582.53	7.3457	583.32	23.77	583.05

Table 8: Percentage of overwintering mosquitoes infectious. Percentage adjustment of parameter from baseline value; associated yearly incidence of adult and juvenile WNND, and disease-related death; percentage change in yearly incidence from baseline

Without considering probability of vector contact, mosquito simulations gave anomalous output addressed in the discussion. The mosquito death rate indicates a minimal role in disease related mortality. A decrease in adult WNND begins at a 400% increase in the mosquito death rate, while juvenile WNND begins at an 800% increase Table 9. Larval simulation shows the reverse of the expected output due to internal model calculation; this anomaly is corrected once probability of contact is adjusted within simulation. Larval death is illustrated in Table 10 and larval birth in Table 11.

Mosquito Death						
% Adjustment	**WNND**	**% Change**	**Death**	**% Change**	**WNND**	**% Change**
25	12.38	1.56	1.0912	1.51	3.54	1.72
50	12.32	1.07	1.086	1.02	3.52	1.15
75	12.26	0.57	1.0806	0.52	3.5	0.57
Baseline Value	12.19	0.00	1.075	0.00	3.48	0.00
150	12.05	-1.15	1.063	-1.12	3.44	-1.15
200	11.9	-2.38	1.0499	-2.33	3.4	-2.30
400	11.11	-8.86	0.983	-8.56	3.18	-8.62
600	9.91	-18.70	0.8797	-18.17	2.83	-18.68
800	7.94	-34.86	0.7104	-33.92	2.27	-34.77
1000	5.13	-57.92	0.464	-56.84	1.46	-58.05

Table 9: Mosquito death. Percentage adjustment of parameter from baseline value; associated yearly incidence of adult and juvenile WNND, and disease-related death; percentage change in yearly incidence from baseline

Larval Death						
% Adjustment	**WNND**	**% Change**	**Death**	**% Change**	**WNND**	**% Change**
25	7.29	-40.20	0.654	-39.16	2.08	-40.23
50	9.91	-18.70	0.88	-18.14	2.83	-18.68
75	11.34	-6.97	1.0025	-6.74	3.24	-6.90
Baseline Value	12.19	0.00	1.075	0.00	3.48	0.00
150	13.14	7.79	1.1559	7.53	3.76	8.05
200	13.66	12.06	1.1993	11.56	3.9	12.07
400	14.47	18.70	1.2682	17.97	4.13	18.68
600	14.75	21.00	1.2922	20.20	4.21	20.98
800	14.9	22.23	1.3044	21.34	4.26	22.41
1000	14.98	22.89	1.3117	22.02	4.28	22.99

Table 10: Larval death. Percentage adjustment of parameter from baseline value; associated yearly incidence of adult and juvenile WNND, and disease-related death; percentage change in yearly incidence from baseline

Larval Birth						
% Adjustment	**WNND**	**% Change**	**Death**	**% Change**	**WNND**	**% Change**
3.125	15.22	24.86	1.3319	23.90	4.35	25.00
6.25	15.11	23.95	1.3223	23.00	4.32	24.14
12.5	14.88	22.07	1.3034	21.25	4.25	22.13
25	14.45	18.54	1.2667	17.83	4.13	18.68
50	13.63	11.81	1.1976	11.40	3.9	12.07
75	12.89	5.74	1.134	5.49	3.68	5.75
Baseline Value	12.19	0.00	1.075	0.00	3.48	0.00
150	10.97	-10.01	0.9706	-9.71	3.13	-10.06
200	9.93	-18.54	0.8808	-18.07	2.84	-18.39
400	6.99	-42.66	0.6266	-41.71	2	-42.53

Table 11: Larval birth. Percentage adjustment of parameter from baseline value; associated yearly incidence of adult and juvenile WNND, and disease-related death; percentage change in yearly incidence from baseline

The probability of vector-human contact plays the largest role in the amplification or reduction of human morbidity and mortality of any single non-pathophysiologic parameter. A linear nature is associated between contact and disease. Immediate changes in adult WNND and at the minimum of adjustment of 0.25x adult WNND decreased about 75% while at the maximum adjustment of 4x WNND increased to 300% of its original value Table 12.

Probability of Vector-Human Contact						
% Adjustment	**Adult WNND**	**% Change**	**Death**	**% Change**	**Juvenile WNND**	**% Change**
25	3.05	-74.98	0.2688	-75.00	0.87	-75.00
50	6.1	-49.96	0.5375	-50.00	1.74	-50.00
75	9.15	-24.94	0.8063	-25.00	2.61	-25.00
Baseline Value	12.19	0.00	1.075	0.00	3.48	0.00
150	18.29	50.04	1.6124	49.99	5.23	50.29
200	24.38	100.00	2.1497	99.97	6.97	100.29
400	48.75	299.92	4.2983	299.84	13.93	300.29

Table 12: Probability of vector-human contact. Percentage adjustment of parameter from baseline value; associated yearly incidence of adult and juvenile WNND, and disease-related death; percentage change in yearly incidence from baseline

4.3.2 Simulation: Multivariate Modification

During multivariate modification, we simulate scenarios that may occur in the study area. Each scenario is conducted with the addition of at least one probability of contact adjustment. The scenarios that we simulate are drought, the avian host dilution effect, insecticide usage, larvicide usage, and habitat modification trough reduction of standing water.

To structure a drought effect on an urban and semi-urban area that maintains water irrigation, we targeted three variables within the model: the initial susceptible avian population concentration, avian migration, and probability of vector-avian contact. Drought simulation illustrated a minimal change in human morbidity and mortality Table 13. This outcome is to be suspected as the individual variables only showed minute change in the human population. Although humans are nominally affected by these conditions, the avian population shows large changes, but this is beyond the scope of this particular study.

Drought								
% Avian Concentration Adjustment	**% Avian Migration Adjustment**	**% V-A Contact Adjustment**	**Adult WNND**	**% Change**	**Death**	**% Change**	**Juvenile WNND**	**% Change**
25	25	6.25	11.37	-6.73	1.0036	-6.64	3.25	-6.61
50	50	25	11.79	-3.28	1.0392	-3.33	3.37	-3.16
75	75	56.25	12.04	-1.23	1.0616	-1.25	3.44	-1.15
Baseline Value	Baseline	Baseline	12.19	0.00	1.075	0.00	3.48	0.00
150	150	225	12.4	1.72	1.093	1.67	3.54	1.72
200	200	400	12.55	2.95	1.1056	2.85	3.58	2.87
400	400	1600	12.91	5.91	1.1374	5.80	3.69	6.03

Table 13: Drought. Percentage adjustment of parameter from baseline value; associated yearly incidence of adult and juvenile WNND, and disease-related death; percentage change in yearly incidence from baseline

The avian host dilution effect was simulated by maintaining a static avian population and segregating birds from humans to varying degrees. To illustrate a higher density of birds in the human vicinity, we set the probability of vector-avian contact at 4x and vector-human contact at 0.25x. The mathematical inverse of each was calculated as the avian population was diluted to a final vector-avian contact set at 0.25x and vector-human contact at 4x. Dilution has an immediate impact on human morbidity with large changes at each end of the spectrum. Human mortality shares the same trend and nearly reaches the surveillance outbreak levels. At the simulations maximum level of avian integration, human morbidity and mortality drops by about 74.7% across the board while at the maximum level of avian segregation, morbidity and mortality increases by about 287% across all health states Table 14.

Avian Host Dilution Effect							
% V-A Contact Adjustment	**% V-H Contact Adjustment**	**Adult WNND**	**% Change**	**Death**	**% Change**	**Juvenile WNND**	**% Change**
400	25	3.08	-74.73	0.2719	-74.71	0.88	-74.71
200	50	6.14	-49.63	0.5417	-49.61	1.76	-49.43
133.33	75	9.18	-24.69	0.8094	-24.71	2.62	-24.71
Baseline Value	Baseline Value	12.19	0.00	1.075	0.00	3.48	0.00
66.67	150	18.17	49.06	1.6019	49.01	5.19	49.14
50	200	24.08	97.54	2.1226	97.45	6.88	97.70
25	400	47.23	287.45	4.1642	287.37	13.49	287.64

Table 14: Avian host dilution effect. Percentage adjustment of parameter from baseline value; associated yearly incidence of adult and juvenile WNND, and disease-related death; percentage change in yearly incidence from baseline

Integrated vector management encompasses several vector control strategies. Here we simulate three separate approaches to mosquito intervention: insecticide usage, larvicide usage, and habitat modification trough reduction of standing water. By incorporating the vector-human probability of contact, we addressed the anomalous output simulated by individual variable modification. For the simulation of insecticide usage, we adjusted the mosquito death rate between 25% and 1,000%. For each value we multiplied the mathematical inverse of the death rate against probability of vector-avian and vector-human contact. Immediate changes in morbidity and mortality become apparent on each side of the spectrum. At a 25% death rate morbidity and mortality increases by about 311% across all health states. Incidence of adult WNND becomes effectively zero at 800% and juvenile WNND at 400% Table 15. Larval death due to larvicide spraying is simulated in the same manner and follows the same trend, but shows a slightly reduced impact on morbidity and mortality. At a 25% death rate, morbidity and mortality increases by about 143% across all health states. Incidence of

adult WNND becomes 1 case at 1,000% and juvenile WNND becomes effectively zero at 600% Table 16. In order to simulate the effects from habitat modification trough reduction of standing water, we adjusted larval birth with from 400% to 3.125% with both probabilities of contact adjustments set equivalent to the birth rate adjustment. Again, immediate changes in morbidity and mortality become apparent on each side of the spectrum. At 400% of the original larval birth rate, morbidity and mortality increases by about 133% across all health states. Incidence of adult WNND becomes effectively zero at 6.25% and juvenile WNND at 12.5% Table 17.

Insecticide Usage								
% V-A Contact Adjustment	**% V-H Contact Adjustment**	**% Mosquito Death Adjustment**	**Adult WNND**	**% Change**	**Death**	**% Change**	**Juvenile WNND**	**% Change**
400	400	25	50.09	310.91	4.41	310.23	14.31	311.21
200	200	20	24.83	103.69	2.1884	103.57	7.09	103.74
133.33	133.33	75	16.41	34.62	1.4463	34.54	4.69	34.77
Baseline	Baseline	Baseline	12.19	0.00	1.075	0.00	3.48	0.00
66.67	66.67	150	7.98	-34.54	0.7041	-34.50	2.28	-34.48
50	50	200	5.87	-51.85	0.5184	-51.78	1.68	-51.72
25	25	400	2.69	-77.93	0.238	-77.86	0.77	-77.87
16.67	16.67	600	1.58	-87.04	0.1402	-86.96	0.45	-87.07
12.5	12.5	800	0.94	-92.29	0.0842	-92.17	0.27	-92.24
10	10	1000	0.49	-95.98	0.0441	-95.90	0.14	-95.98

Table 15: Insecticide usage. Percentage adjustment of parameter from baseline value; associated yearly incidence of adult and juvenile WNND, and disease-related death; percentage change in yearly incidence from baseline

Larvicide Usage								
% V-A Contact Adjustment	**% V-H Contact Adjustment**	**% Larvae Death Adjustment**	**Adult WNND**	**% Change**	**Death**	**% Change**	**Juvenile WNND**	**% Change**
400	400	25	29.56	142.49	2.6515	146.65	8.45	142.82
200	200	20	19.97	63.82	1.7733	64.96	5.71	64.08
133.33	133.33	75	15.18	24.53	1.3416	24.80	4.34	24.71
Baseline	Baseline	Baseline	12.19	0.00	1.075	0.00	3.48	0.00
66.67	66.67	150	8.71	-28.55	0.7655	-28.79	2.49	-28.45
50	50	200	6.74	-44.71	0.5922	-44.91	1.93	-44.54
25	25	400	3.51	-71.21	0.3075	-71.40	1	-71.26
16.67	16.67	600	2.36	-80.64	0.2064	-80.80	0.67	-80.75
12.5	12.5	800	1.77	-85.48	0.155	-85.58	0.51	-85.34
10	10	1000	1.42	-88.35	0.124	-88.47	0.4	-88.51

Table 16: Larvicide usage. Percentage adjustment of parameter from baseline value; associated yearly incidence of adult and juvenile WNND, and disease-related death; percentage change in yearly incidence from baseline

Habitat Modification Trough Reduction of Standing Water								
% V-A Contact Adjustment	**% V-H Contact Adjustment**	**% Larvae Birth Adjustment**	**Adult WNND**	**% Change**	**Death**	**% Change**	**Juvenile WNND**	**% Change**
3.13	3.13	3.13	0.44	-96.39	0.0385	-96.42	0.13	-96.26
6.25	6.25	6.25	0.88	-92.78	0.0773	-92.81	0.25	-92.82
12.5	12.5	12.5	1.77	-85.48	0.1549	-85.59	0.51	-85.34
25	25	25	3.5	-71.29	0.3071	-71.43	1	-71.26
50	50	50	6.73	-44.79	0.5914	-44.99	1.92	-44.83
75	75	75	9.62	-21.08	0.8467	-21.24	2.75	-20.98
Baseline	Baseline	Baseline	12.19	0.00	1.075	0.00	3.48	0.00
150	150	150	16.54	35.68	1.4631	36.10	4.73	35.92
200	200	200	20	64.07	1.775	65.12	5.71	64.08
400	400	400	28.34	132.49	2.5386	136.15	8.1	132.76

Table 17: Habitat modification trough reduction of standing water. Percentage adjustment of parameter from baseline value; associated yearly incidence of adult and juvenile WNND, and disease-related death; percentage change in yearly incidence from baseline

4.4 Discussion

After a system dynamics sensitivity analysis of each environmental parameter within this WNV model, we have demonstrated that the epidemic model may reflect human population health status changes. When considering each of the individual parameters independently of all others, we noticed that, other than the fact that birds are required for perpetuation of WNV, the population as a whole has little influence on human morbidity and mortality. Viral preservation within the system is an extremely important factor in maintaining the endemic state of disease. The individual factor that plays the most integral role in human population health has shown to be the vector-human probability of contact. This is an evident finding as the only possible way to contract WNV, in this model, is to come into contact with an infectious mosquito.

Since the probability of contact between infected mosquitoes and susceptible humans is the fundamental component of all WNV-related disease in the human population, the next intuitive step is to identify the situations which influence the extent in which these two populations interact, and the degree of infection within the mosquito population. In simulations of drought, we increased the amount of birds in the system. By doing so, this increases the likelihood that a mosquito will feed off of its natural host, but does not influence the amount of bloodmeals, and therefore, does not influence the mosquito population. In fact the only reason, within this model, human morbidity and mortality increases is due to the avian population not dying off as rapidly and maintaining an infectious avian population for a longer period of time. Drought may have other effects outside of the scope of this model. Extended drought may bring about

mosquito population migration leading to larger population densities over time. By including other avian species with differing pathophysiology, we could see longer infectious time periods and lower fatality which could lead to higher levels of WNV in the mosquito population. The avian host dilution effect performed a greater role in the influence of human disease. This increase is completely driven by mosquito behavior and their increased propensity to opportunistically feed off of humans within urban/semi-urban settings.

When considering the mosquito population and vector control strategies, it is important to consider model structure. By adjusting the birth or death solely within the larval or susceptible population compartments, it reduces the denominator of infectious mosquitoes to total population. This fraction is multiplied against probability of contact to form the probability of infectious contact. Probability of contact must also be taken into consideration; otherwise anomalous output will ensue with higher infectious contact with a lower population. After making the correct adjustments to the probability of vector-human contact, we were able to effectively test the efficacy intervention strategies. By spraying insecticides and larvicides, and reducing the habitability of mosquitoes, the model illustrates rapid reduction in human morbidity and mortality. This is accountable to the reduction in contact with humans, but also reduction in avian infection. It must be understood that these strategies also increase the level of immunologically naive birds, so changes in the virus or the mosquito resistance to interventions may lead to problems in the long-term that we must address. Overall the best strategy for curtailing the transmission of the WNV to humans is to not get bitten.

The CDC promotes the five ‘Ds’ for WNV prevention: Dusk, Dawn, Draining, Dress, and DEET. Dusk and dawn are the highest risk times for exposure to infected mosquitoes, by separating oneself during these periods through dressing appropriately and the application of DEET provides a physical and chemical barrier to mosquito contact (CDC, 2013b; Murray et al., 2011).

The major difficulty in modeling WND in this format is that the true probability of contact is nearly impossible to calculate. By conducting basic simulations, we may test straightforward concepts. While testing intervention strategies, we may demonstrate how one tactic may influence disease in the population but implementation of an integrated vector management system proves to be difficult. Future research should be conducted into obtaining good measures for this parameter. We have noticed a linear relationship with the probability of vector-human contact and all forms of WNV disease. We were able to determine that the probability of contact would need to be 6x greater to reach the three-year epidemic average and 32x greater to reach the 2012 outbreak intensity. We were unable to reasonably adjust any compartment or parameter to attain a 32x expansion in disease and conclude that in all probability there is an interactive and amplifying effect over time from multiple conditions leading to one massive outbreak.

5. CONCLUSIONS

5.1 Public Health Relevance

WNV is now an endemic disease across continental North America. Due to the favorable climatic conditions, and the abundance of competent vectors and hosts, the virus appears to be fully assimilated into the ecosystem. Without a human vaccination, we must approach disease prevention through environmental remediation, comprehensive vector management, and personal protections. This model shows that it is possible to substantially reduce human morbidity and mortality through the use of these prevention strategies. With future research into species interactions, this form of modeling may become useful to physicians and public health practitioners in forecasting disease incidence for upcoming months, so that they may plan accordingly. Additional adjustments may be made to parameter values, making this model useful anywhere in the United States. Mathematical modeling may also be used for many other infectious diseases that are endemic and emerging. This form of mathematical modeling may be used for cost benefit analyses, risk and failure analyses, and vulnerability analyses. By focusing on key variables and parameters a public health professional may simulate a breakdown in public health infrastructure, or identify the most sensitive points in the structure that must be safeguarded.

5.2 Limitations

As in most studies, this project has several limitations. This model is deterministic and averages incubation periods, recovery periods, and parameters that are dependent on seasonality. Although the model is calibrated to a decade worth of surveillance data, the data is limited, with small case counts. The surveillance data for WNF is not useful for calibration, as it is vastly underestimated. During model calibration, the model had to be fit by adjusting the frequency of vector-human contact. It is nearly impossible to obtain an accurate value of this parameter, as we are considering an entire population, and the value may change over time and location.

The breadth of this model is also limited. We only consider one avian species, the American crow. This species, along with other corvids, is known to succumb rapidly to WNV. By using multiple species, or another species that does not succumb as rapidly to the virus, we may see differing results. Species that do not rapidly die will carry the virus for an extended period in the ecosystem, increasing the likelihood of transmission. This model only considers the asymptomatic, WNF, WNND, and death health outcomes. Juveniles are not as likely to develop WNND, and when they do, they are far less likely to die from infection. Juveniles are more likely to develop a prolonged flaccid paralysis. The incidence of paralysis has been too low to include in this particular study. In future studies, a greater stratification of age in the human population, and geographic compartmentalization of the study area, may illuminate a more complete understanding of the dynamics that lead to human morbidity and mortality.

5.3 An Ecological Understanding of WNV Disease

The manuscript, “West Nile virus Epidemiology, Ecology, and Human Health in the United States,” illuminates some key complexities of WNV ecology, pathophysiology, and clinical manifestations. The manuscript also proposes a future research approach that should enhance insight into WNV transmission, human WNV infection, and disease progression. This insight is essential, as a further understanding of the dynamic WNV ecology must be pursued so that we may increase competency in resource allocation.

WNV has become endemic in the United States, and has been shown to be prevalent in rural areas as well as urban. Factors such as the photoperiod, temperature, water abundance, food supply, and access to a blood meal directly influence the presence and proliferation of WNV within an ecosystem. Other environmental factors, such as drought, urbanization, and avian demographics, may possibly be linked to the transmission of WNV into the human population. To protect the aging population of the United States, who hold an increased risk of developing neuroinvasive disease and subsequent death, interdisciplinary ventures should be employed as a unified response to this persistent disease threat. To achieve this, an increased effort in disease detection and modeling should be pursued. With a greater collective knowledge into the reality of the magnitude of infection in birds, mosquitoes, and humans, modelers may achieve a higher degree of output accuracy. In the past, mathematical modeling of WNV has not been conducted to portray long-term predictions. Future models must combine the environmental conditions, life cycles, and pathophysiology of birds, mosquitoes, and

humans in order to determine levels of WNF, WNND, and disease-related mortality in humans within different age strata, within a given geographic area.

5.4 Modeling

The manuscript, "A Mathematical Model of the Zoonotic and Vector Transmission Dynamics of West Nile virus: Human Morbidity and Mortality," successfully establishes the ability of an infectious disease model to reflect WNV human morbidity and mortality cases in differing age strata, based upon environmental, avian, and mosquito disease determinants. The mean square error of WNND and disease related mortality cases have been minimized to reflect the historical endemic cycle of WNV in the Dallas/Fort Worth area. To analyze the model's many variables and parameters, and assess the degree to which each influences human morbidity and mortality, a sensitivity analysis was performed by manipulating values from a low value to high, straddling the benchmark. Once the sensitivity analysis was conducted the data became useful in identifying key parameters for public health officials to monitor as high risk factors or, potential mitigation and control points.

A secondary analysis was performed, in which we simulated possible conditions and circumstances, by altering several parameters, in order to assess the combination of factors effects on human morbidity and mortality. Future simulations may be based on differing geographic locations, fluctuating ambient temperature, further stratification of ages, contact probabilities, disease state probabilities, progression of disease, and many more. Control strategies may also be tested to assess feasibility, efficacy, and economic

return on investment. In the future better surveillance practices may aid in refining this model with accurate WNF and paralysis case counts.

5.5 Analysis

The manuscript, "A Mathematical Model of the Zoonotic and Vector Transmission Dynamics of West Nile virus: Utility Analysis," demonstrated that the epidemic model may reflect human population health status changes, after a system dynamics sensitivity analysis of each environmental parameter within this WNV model.

The utility analysis illuminated many fascinating concepts. Other than the fact that birds are required for perpetuation and amplification of WNV in the environment, the population as a whole has little influence on human morbidity and mortality. The individual factor that plays the most integral role in human population health has shown to be the probability of vector-human contact. There appears to be a linear relationship between the probability of vector-human contact and all forms of WNV disease in humans. The major difficulty in modeling WND in a deterministic format is that the true probability of contact for a population is nearly impossible to calculate. Future research should be conducted into obtaining good measures for this parameter.

When considering the mosquito population and vector control strategies, it is important to consider model structure. When adjusting each parameter, the corresponding effect on the probability of contact must also be taken into consideration. After making the correct adjustments to the probability of contact, we were able to effectively test the relationship between environmental conditions and the efficacy

intervention strategies. By conducting basic simulations, we may test straightforward concepts, but with higher degrees of complexity it becomes difficult to make accurate adjustments to the contact probabilities. Within the model, climate changes that effect the mosquito population and their interaction with humans have been shown to be important factors influencing human morbidity and mortality. This model may also be useful in predicting the effect of various disease control strategies.

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