DENGUE—A REAL & INCREASING THREAT: MECHANISTIC MODELING, DETERMINANTS, & A FRAMEWORK FOR RECOMMENDATIONS

A Dissertation

by

AMBER FOREMAN BRITT

Submitted to the Graduate and Professional School of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PUBLIC HEALTH

Chair of Committee,	Rebecca Fischer
Committee Members,	Angela Clendenin
	Martial Ndeffo Mbah
	Patrick Tarwater
Head of Department,	Jennifer Griffith

May 2023

Major Subject: Public Health Sciences

ABSTRACT

Dengue is a vector-borne viral disease affecting humans that is endemic in tropical and subtropical areas worldwide. As a re-emerging disease, a growing body of literature is dedicated to the dynamic, clinico-epidemiology of dengue, complicated by the co-existence of several Dengue virus serotypes and an increase in the range and seasonality of mosquito vectors.

A spatiotemporal model was developed using an extended version of the Ross-Macdonald theory to calculate a Relative Global Dengue Basic Reproductive Model (R_0). It included temperature, rainfall, *Aedes aegypti* vector distribution, and geolocalized economic factors to evaluate disease transmission dynamics.

A literature review identified the comprehensive factors that determine the severity and determinants of the disease, the characteristics of non-traditional high-risk populations with repeated and/or prolonged exposures, and mitigation and control measures. The impact of new vaccines on the potential for limiting travel-related cases was explored through a cost-benefit analysis of a vaccine implementation program in a special population with high-risk exposures, using United States Peace Corps volunteers as a population-case study.

The mechanistic model predicts a global relative dengue outbreak risk profile and demonstrates its spatiotemporal heterogeneity by identifying areas at risk of high virus transmission throughout the various months of the year. It shows an increase in the geographic spread of the risk area during summer temperatures, demonstrating an optimal temperature and precipitation range for the genesis and proliferation of a dengue disease outbreak.

A comprehensive, One Health approach should be employed to fight the spread of dengue. A tailored pre-travel health assessment and focus on primary prevention can reduce disease risk. After establishing previous infection through a serum study, administering vaccines

for travelers to endemic and hyperendemic areas should be considered. The cost-benefit analysis revealed that no comprehensive vaccination program should be started for Peace Corps volunteers—the benefits achieved through vaccine efficacy against the risk of severe clinical disease is too low for a blanket recommendation. Dengue is and will continue to be a threat to global health; control and mitigation strategies targeting specific high-risk populations and understanding the true risk of the disease will be paramount to curb the spread.

DEDICATION

For Sully, Gabbie, Izzy, and Jonathan. You are my world, my sun, my stars, and my moon, and you fill my life with happiness. I love you all SOOO much!

ACKNOWLEDGEMENTS

This thesis is the fruit of countless hours and numerous sacrifices. First and foremost, I must thank God for his guidance and comfort through this journey. I am incredibly blessed and thankful to my husband, Jonathan, and my children, Isabelle, Gabriella, and Sullivan, for without their love and support, none of this would be possible. My children are amazing and resilient; they were patient, steadfast, helpful, and my absolute joy. I hope they are inspired to pursue their life's passion as well.

Our families have stepped in time and time again to fill the childcare gaps and provide support, laughter, and encouragement. I am forever thankful for their assistance. I am incredibly blessed with an amazing tribe, one that spans the globe and is right here in town—they have encouraged me, prayed for me, kept me accountable, reviewed for exams together, and helped with the kids. I offer my deepest and most sincere gratitude to you all for supporting me and my dreams.

I wanted to thank my dissertation committee for their guidance and support. Dr. Fischer, Dr. Ndeffo, Dr. Clendenin, and Dr. Tarwater, thank you for investing in me and my pursuits. Countless military leaders have guided, tested, and molded me into the person I am today—I would not be where I am without their encouragement and mentorship.

Finally, my father, Brian Foreman, left this earth too early. You were always in my corner. Dad, I did not finish this journey with you, but I know you were with me, cheering from heaven. I will miss you forever.

CONTRIBUTORS AND FUNDING SOURCES

Contributors

This work was supervised by a dissertation committee consisting of Professor Rebecca Fischer, Professor Angela Clendenin, and Professor Patrick Tarwater from the Department of Epidemiology and Biostatistics and Professor Martial Ndeffo-Mbah from the Department of Veterinary Integrative Biosciences at the School of Veterinary Medicine and Biomedical Sciences.

The analyses depicted in Chapter 2 were partly conducted by Mr. Sina Mokhtar, BS, from the Department of Statistics. All other work conducted for the dissertation was completed by the student independently.

Funding Source

Graduate study was supported by a fellowship from the United States Air Force and the Air Force Institute of Technology. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Department of Defense or the United States Air Force.

NOMENCLATURE

1°	Primary (first) infection
2°	Secondary (subsequent) infection
AD	Anno Domini
ADE	Antibody-Dependent Enhancement
Ae.	*Aedes*
AHRC	Agency for Healthcare Research and Quality
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
C	Celsius
CI	Confidence Interval
CDC	Centers for Disease Control and Prevention
CDSR	Cochran Database of Systematic Reviews
COA	Course of Action
COVID-19	Coronavirus Disease 2019
DENV-1	Dengue virus serotype 1
DENV-2	Dengue virus serotype 2
DENV-3	Dengue virus serotype 3
DENV-4	Dengue virus serotype 4
DHF	Dengue Hemorrhagic Fever
DSS	Dengue Shock Syndrome
EIP	Extrinsic Incubation Period
FDA	Food and Drug Administration
G-Econ	Geolocalized Economic Data
G6PD	Glucose-6-Phosphatase Dehydrogenase
GDP	Gross Domestic Product
HCT	Hematocrit

IgG	Immunoglobulin G
IgG ELISA	Immunoglobulin G Antibody Capture Enzyme-Linked Immunosorbent Assay
IgM	Immunoglobulin M
IFRC	International Federation of Red Cross and Red Crescent Societies
IHC	Immunohistochemical
INMET	National Institute of Meteorology (Brazil)
km	Kilometer
MAC-ELISA	Immunoglobulin M Antibody Capture Enzyme-Linked Immunosorbent Assay
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
mm	Millimeter
NAAT	Nucleic Acid Amplification Test
NEA	National Environmental Agency
NS-1	Dengue Virus Antigen Detection
PAHO	Pan American Health Organization
PCV	Peace Corps Volunteer
PPP	Purchasing Power Parity
PRNT	Plaque Reduction Neutralization Test
R_0	Basic Reproductive Number (R-naught)
Rmin	Minimum rainfall
Rmax	Maximum rainfall
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
SARS	Severe Acute Respiratory Syndrome
SEI-SEIR	Susceptible, Exposed, Infectious-Susceptible, Exposed, Infectious, Recovered
SD	Severe Dengue
SI	Secondary (Subsequent) Infection
U.S.	United States

TAK-003	Takeda’s Tetravalent Dengue Vaccine candidate (Qdenga®)
WHO	World Health Organization
WHOLIS	World Health Organization library catalog

TABLE OF CONTENTS

LIST OF FIGURES

Page

LIST OF TABLES

Page

1. INTRODUCTION AND LITERATURE REVIEW

Burden and Distribution of Dengue

Dengue fever is an arboviral infection spread by mosquitos that causes human diseases. Its distribution and impact have increased steadily throughout tropical and subtropical climates worldwide. This emerging infection evolved from severe outbreaks documented in less than ten countries before 1970 to endemic in more than 100 countries (Farrar et al., 2007). Globalization of trade networks, the frequency and ease of travel, and the geographical growth of favorable habitats and environmental conditions for mosquito vectors combined to make dengue the most rapidly advancing vector-borne infection in the world (Messina et al., 2019; Mulligan et al., 2015; WHO, 2021).

Leta et al. (2018) showed that 85% of the 250 countries and habitats analyzed were potentially suitable habitats for the *Aedes* mosquito—painting a grim picture for the future. There are an estimated 50 to 100 million new cases of dengue infection globally each year, and about 50% of the world's population is at risk of contracting it (Farrar et al., 2007; Gubler, 2002; WHO, 2020). This widely cited estimate is, in reality, most likely a gross underestimate of the true impact of the disease due to imprecise morbidity and mortality statistics (Gómez-Dantés & Willoquet, 2009). Several cohort and active surveillance studies in the Americas and Asia purport the true incidence to be underestimated by 11 to 250 times (Beatty, 2008).

Vector Ecology

Vector-borne diseases are responsible for more than 700,000 deaths annually, accounting for more than 17% of all infectious diseases (WHO, 2020). A vector is a living organism that can transmit infection between humans or from animals to humans (WHO, 2020). Any illness

resulting from a parasitic, viral, or bacterial infection transmitted to humans and other animals by bloodsucking arthropods (mosquitos, ticks, and fleas) is a vector-borne disease.

Dengue is transmitted through the bite of an infected female *Aedes aegypti (Ae. aegypti)* or *Aedes albopictus (Ae. albopictus)* mosquito. It is considered one of the most impactful vector-borne diseases globally (Halstead, 1992). Transmission dynamics are related to vector density, favorable environmental conditions, urbanization, and the availability of susceptible individuals. These vectors have different feeding rates and host preferences (Caminade et al., 2017). *Ae. aegypti* are day biters and lay eggs in clear water-filled containers. Additionally, they almost exclusively feed on humans, making them an essential and efficient transmitter of disease.

In contrast to other mosquito species, *Ae. aegypti's* eggs are laid above the water level and only hatch when the water surface rises and wets them (Valdez et al., 2018). *Ae. aegypti's* eggs are hardy and can survive weeks in the environment before hatching during a rainfall event, which confers a competitive advantage (Caminade et al., 2017). The strong and desiccant-resistant eggs which characterize the *Aedes* mosquito facilitated global dissemination throughout complex international trade networks (Kraemer et al., 2019). *Ae. aegypti* has a higher optimum and maximum temperature gradient than *Ae. albopictus.*

Conversely, *Ae. albopictus* feeds less frequently and on a broader range of hosts. They have a more extensive habitable range that stretches into more temperate regions, increasing the geographical spread of the vector and disease potential. These facts make it an essential secondary disease vector (Caminade et al., 2017).

The mosquitos prefer urban habitats and breed in man-made containers. Historically, the spread is associated with the adaptation to container-breeding and worldwide trade in tires and

potted plants, which provide ideal larva development habitats (Pliego Pliego et al., 2018; Reiter, 1998; Silva et al., 2020). This vector thrives in densely populated areas that lack reliable access to water supplies, waste management, and sanitation (Honorio et al., 2009).

Four Distinct Viruses and Their Global Distribution

Dengue is caused by one of four related viruses: DENV-1, DENV-2, DENV-3, and DENV-4 (WHO, 2021; CDC, 2021). Each virus serotype can affect humans; therefore, an individual can contract the Dengue virus as many as four times in his or her lifetime. Infection with one type does not confer immunity to other types, so subsequent dengue infections can occur over an individual's lifespan. Furthermore, each serotype contains three to five common strains (genotypes) that differ in virulence and can produce different disease presentations (Endy et al., 2002; Silva et al., 2020). Early serotype-specific symptoms and the sequence of successive dengue infections with a different viral strain are determinants of disease severity. Sequencing refers to the specific viral infection and then a second infection with another virus serotype (i.e., DENV1 and then DENV3, DENV4 and then DENV2, etc.). Globalization, tire trade, international travel, and the failure of environmental management means that all four Dengue serotypes are circulating in almost every tropical and subtropical region of the world, creating patterns of endemic and hyperendemic regions (Cucunawangsih & Lugito, 2017; Reiter, 1998).

Disease Presentation and Classification

Dengue infections are commonly asymptomatic or present as an undifferentiated fever or mild self-limiting illness; however, a small proportion of infections progress to severe disease with plasma leakage. According to the Centers for Disease Control and Prevention (CDC), only one in four people infected with dengue will get sick (CDC, 2021). For many who get sick, the symptoms are mild, including nausea, vomiting, rash, severe headaches, pain behind the eyes,

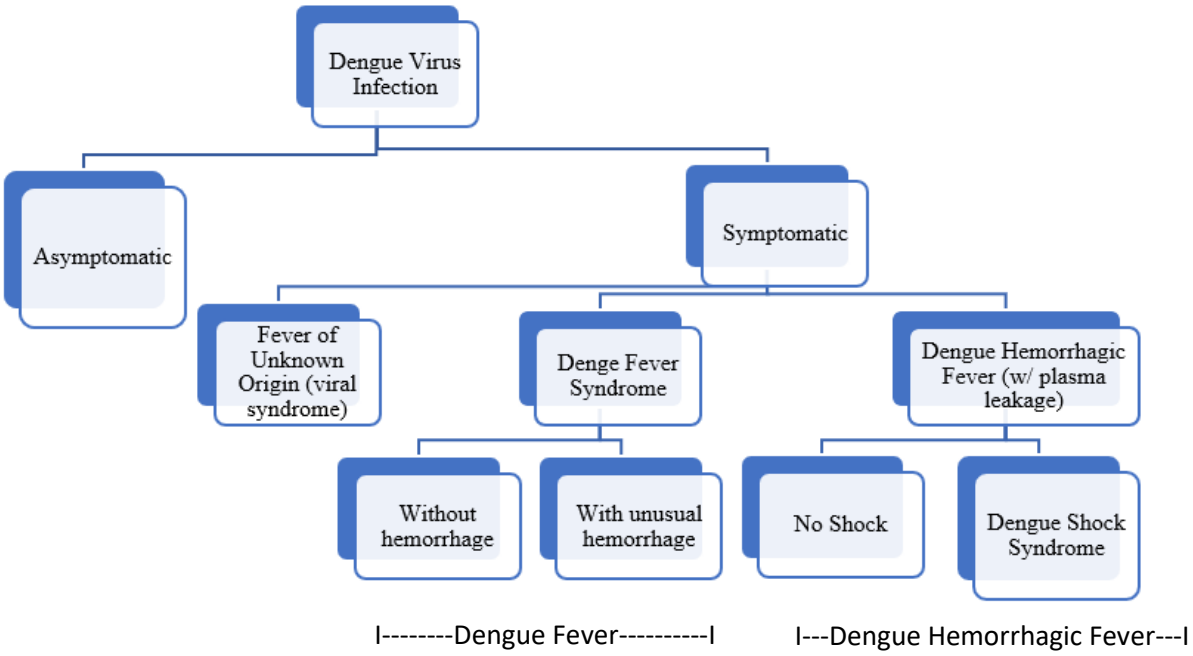
and aches and pains (typically muscle, joint, or bone pain) (CDC, 2021; Heymann, 2015; WHO, 2022). Symptoms usually last between 2 to 7 days after a 4 to 7 day incubation period (range of 3-10 days) following the bite of an infected mosquito. Dengue usually follows three phases: febrile, critical, and convalescent (CDC, 2021).

Nevertheless, a small proportion, approximately 1 out of the 20 people who get sick with dengue, will develop severe disease generally within 3-7 days after illness onset. During this phase, individuals can experience a sudden deterioration of symptoms, including severe abdominal pain, persistent vomiting, rapid breathing, fatigue, liver enlargement, or blood in vomit or stool (WHO, 2022). These complications can become fatal if plasma leakage, fluid accumulation, respiratory distress, severe bleeding, or organ impairment occur (CDC, 2021; WHO, 2022).

This severe form was previously known as dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS), characterized by excessive bleeding or clotting, increased vascular fragility, and fluid loss through increased capillary permeability (WHO, 2019). For many years, there was a distinction between classic dengue fever, DHF, and DSS, yet the latter syndromes, the life-threatening forms of dengue, have now been collapsed (Figure 1.1).

Figure 1.1

1997 Dengue Case Classification System

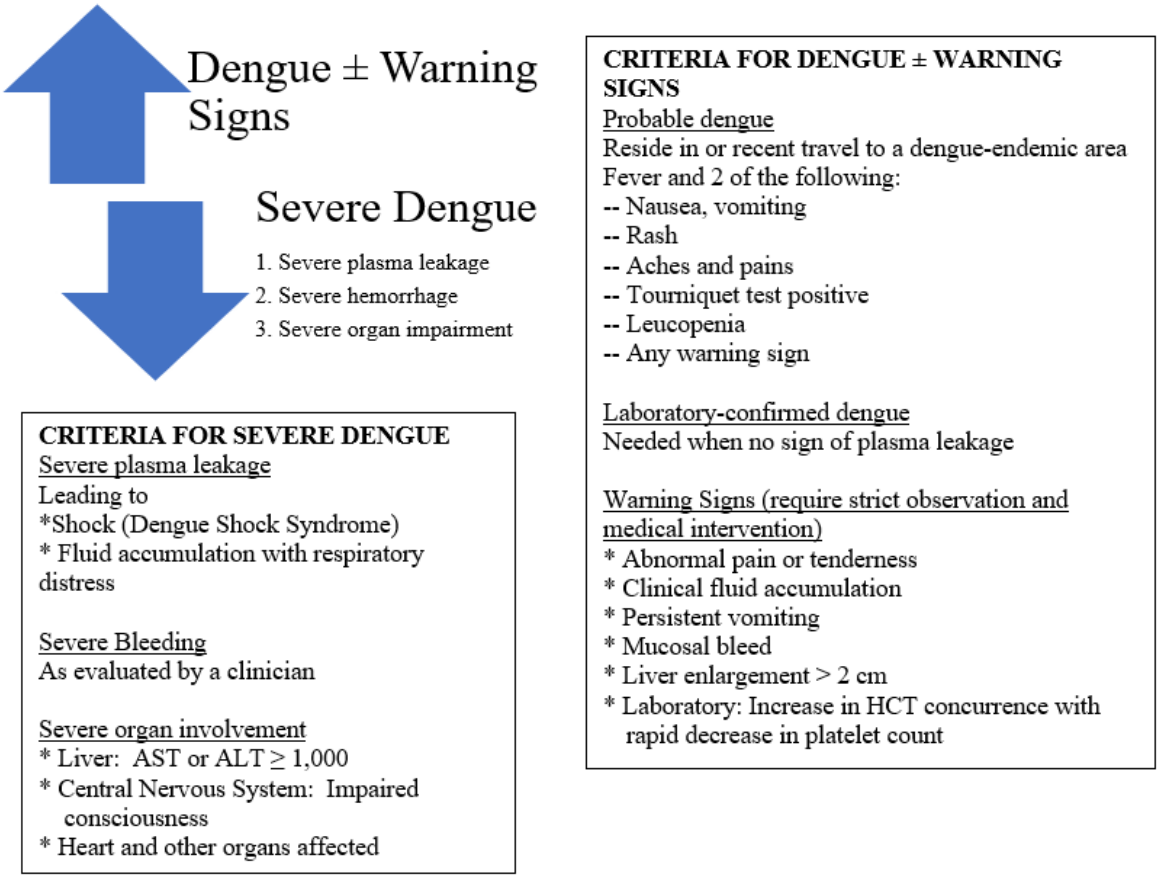


Note. Adapted from the WHO Dengue Haemorrhagic Fever: Diagnosis, Treatment, Prevention, and Control, 1997.

The clinical presentation usually falls somewhere along the disease spectrum rather than fitting in one of the distinct disease classification phases (Hadinegoro, 2012). Therefore, in 2009 the WHO devised a new classification system in which symptomatic individuals are categorized as having "dengue" if they have no major complications (Figure 1.2). Those who have complications are divided into three categories of "severe dengue": (1) plasma leakage severe enough to cause shock or respiratory distress, (2) severe bleeding, or (3) severe organ impairment (WHO, 2009).

Figure 1.2

2009 Revised Dengue Case Classifications



Note. Adapted from WHO Dengue Guidelines for Diagnosis, Treatment, Prevention, and Control, New Edition, 2009. AST = aspartate aminotransferase (a protein made by liver cells); ALT = alanine transaminase (an enzyme found mostly in the liver); HCT = hematocrit (a measure of how much of your blood is made of red blood cells).

Dengue Detection

Several diagnostic tests can identify dengue infections by detecting virus particles, viral nucleic acid, antigens or antibodies, or a combination of these techniques. The timing of the test in relation to the illness phase determines which method yields the most accurate results. Molecular tests such as the Nucleic Acis Amplification Test (NAAT), Dengue Virus Antigen Detection (NS-1), serologic tests like the IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA), IgG ELISA, and Plaque Reduction Neutralization Test (PRNT) and tissue tests, such as the Nucleic Acid Amplification Test (NAAT) or the Immunohistochemical (IHC) Analysis can all be used within the first seven days of acute symptom onset (CDC, 2021). In contrast, only serologic and tissue tests are reliable more than seven days after symptom onset, a period known as the convalescent phase (CDC, 2021).

The virus is detectable in serum, plasma, circulating blood cells, and tissues for 4-5 days after illness onset. There are several reverse transcriptase-polymerase chain reaction (RT-PCR) tests, and this method is considered the gold standard (WHO, 2021). Antigen testing can also detect a protein the virus produces—NS1 through a commercially produced rapid antigen test (WHO, 2021). Serological methods can be used to confirm the presence of a recent (presence of IgM) or past infection (IgG) through the detection of antibodies (CDC, 2011).

Mitigation and Control

The global spread of all Dengue virus serotypes has made prevention and control infinitely more problematic. There is no single tool or methodology that will be effective in controlling the vector population alone (Gubler, 2011). Human activities such as forestry, mining, and agriculture can alter ecology, lead to spillover events, and amplify the transmission of diseases. Primary prevention is the key to controlling the disease, which is best accomplished through

source reduction. This entails the prevention of breeding through mosquito habitat modification—mainly by inhibiting access to egg-laying environments, removing standing water, properly disposing of solid waste, and covering, emptying, and cleaning domestic water storage containers every week. These actionable steps help break the chain of infection (WHO, 2021). Water storage systems and urbanization are associated with poor housing, crowded living conditions, and the absence of basic services. These factors create ideal habitats for the explosion of vector populations and spillover events (Hassell et al., 2017; Reiner et al., 2016).

The Transtheoretical Model (Stages of Change) was employed in a study of homemakers from Colombia to determine behavior patterns in reducing the mosquito breeding habitat (Luna et al., 2004). Stratified focus groups revealed that homemakers were the most appropriate target of the intervention as they had the most contact with the breeding sites and that participants needed to be monitored in the action phase to empower them to rise into the maintenance stage (Luna et al., 2004). In Latin America, elementary teachers have successfully targeted students with educational campaigns about mosquito mitigation and dengue prevention efforts (Sequeira et al., 2010).

In Nicaragua, educational pamphlets with dengue facts, prevention, and mitigation strategies were passed out by teachers in elementary schools to empower youth to make positive changes in their homes (Sequeira et al., 2010). These pamphlets were translated into regional dialects and had drawings depicting local characteristics underscoring the use of culturally appropriate and tailored interventions (Huey et al., 2014).

An initiative through the International Federation of the Red Cross and Red Crescent Societies (IFRC) in Myanmar trained key individuals from remote villages after a severe dengue outbreak in 2013 (IFRC, 2014). One program graduate spoke of its impact, “I didn’t have a lot of

health knowledge before, so I was very happy to learn and I'm proud to share this information with my village. I also learned how important it is to keep your environment clean." Community health workers and gatekeepers should engage with local health authorities to report on interactions with community members, barriers and successes, and their weekly activities. Periodic refresher training or teachings on new illnesses coupled with pre-tests or focus groups can evaluate the effectiveness of the community health workers' understanding and their impact. The success of these programs is primarily due to their focus on fostering change within existing social relationships (McLeroy et al., 1988).

Businesses that employ workers outside can mandate uniforms consisting of pants and long-sleeved shirts and provide insect repellents for use at the job sites. Crawshaw et al. (2017) studied the acceptability of insecticide-treated clothing by migrant rubber tappers in Myanmar. They found that the farmworkers reported fewer mosquito bites and generally preferred the treated clothing over identical non-treated clothing. Furthermore, modifications of the workday where outdoor workers avoid the dawn and dust preferred mosquito feeding times can reduce the number of bites. Faith-based organizations are the center of many communities and can be powerful change agents. In 2019, the Philippines used Catholic churches to spearhead a clean-up campaign to prevent the spread of dengue during an outbreak (Torres, 2019).

In conjunction with the Pan American Health Organization (PAHO) and the WHO, the Costa Rican Ministry of Health developed an interactive video game that focused on vector-borne diseases and the effects of sanitation on the community. In the game, the protagonist, Fabio, roams through his hometown to find the cause of a mysterious illness that has inflicted his sister. (PAHO Pueblo Pitanga, 2013). This video game uses technology to entertain and empower children to produce behavioral change. It was developed with input from community

organizations highlighting the need for multisectoral and interinstitutional approaches to dengue mitigation and control.

Community empowerment and ownership of mosquito control programs are critical to their success. In the 1980s, sustainable *Aedes* control shifted to "community-based, integrated programs (bottom-up)," which thought that cost-effective control could best be achieved by larval source reduction conducted by occupants of the communities where transmission occurred (Gubler & Clark, 1995). The sustainability of disease control programs necessitates community ownership and the adaptation of the belief that mosquitos' habitats cannot be permitted to remain undisturbed, and it is in the communities' best interest to control the vector population. The Cuban government mobilized civil defense workers to go from house to house, implementing mosquito control practices and educating citizens about dengue (Gubler & Clark, 1995). A similar program was instituted with Colombian high school students trained to perform household visits to educate the public about Dengue risk and encourage them to break the cycle of transmission (Luna et al., 2004).

There are three types of environmental management in controlling dengue: environment modification, environmental manipulation, and changes to human habitation or behavior (Mahmud et al., 2018). While often appealing to the public's desire for action, programs that primarily rely on eliminating adult mosquitos during crisis situations have not been successful (Gubler, 1998; Newton & Reiter, 1992). Integrated vector management projects employ environmental management strategies to reduce vector breeding grounds through improved water resource use, bacterial larvicides, and larvivorous fish (WHO, 2021). The WHO (2021), in conjunction with local and national authorities, has tested a new long-lasting insecticide-treated

netting cover for household water storage containers in Cambodia. Partnerships with local and national governments are critical to the success of mosquito abatement strategies.

An integrated pest management plan targeting mosquitos at all phases of their lifecycle and destroying breeding grounds is a crucial containment step. This plan uses biological controls targeting the mosquito at different life cycle stages and the alteration of breeding grounds in a practical yet environmentally sensitive approach. *Aedes* mosquitos flourish in urban dwellings, especially in water stored for household use. These issues are confounded by uncontrolled and unplanned urbanization of much of the developing world and inadequate environmental management (Gubler, 2002). Larvicides, adulticides, mosquito dunks, and emptying of standing water rank among the most effective techniques. One of the keys to the success of this program is consistent surveillance and application of control techniques once monitored action thresholds have been met.

There has been an increased focus on genetically modified mosquitos released to suppress the wild vector population (Facchinelli et al., 2013). Absent vaccines and chemoprophylaxis, a focus on a genetic approach to control the vector population either by making female mosquitos flightless so they cannot easily reproduce or by limiting the mosquitoes' ability to acquire and transmit the pathogen has emerged (Buchman et al., 2019; Facchinelli et al., 2013). While theoretically plausible and initially promising, these genetically modified vectors present serious ethical, social, and cultural considerations (Lavery et al., 2008).

Vaccines

There are no specific chemoprophylaxis or therapeutics to prevent or treat dengue infection. One of the newest tools against dengue is the WHO's approval of Dengvaxia® in 2015—a tetravalent live attenuated yellow fever chimeric dengue vaccine (WHO, 2018). This

vaccine is approved for at-risk individuals aged 9-45 years who live in endemic areas and have had at least one laboratory-confirmed dengue virus infection (WHO, 2021). The Food and Drug Administration (FDA) has only approved the vaccine for individuals aged 9-16 in the U.S. who live in endemic areas, mainly U.S. territories, including Puerto Rico (CDC, 2022).

Several other dengue vaccines are in clinical trials (Osorio et al., 2016; Whitehead, 2016;). In 2015, the Department of Defense and Glaxo Smith Kline performed a Phase II clinical trial for a dengue vaccine in Thailand; however, when a durable immune response was not detected, the program was ended (Institute of Medicine, 2002; Rothman & Ennis, 1999; Watanaveeradej et al., 2016). In December 2022, the European Commission approved the Japanese-developed Qdenga® (TAK-003) vaccine to prevent dengue disease in individuals over four years of age (Takeda, 2022). In a series of trials, the vaccine was shown to be 80.2% effective in preventing symptomatic dengue cases in the 12 months following inoculation and preventing 90.4% of hospitalizations 18 months after vaccination (Biswal et al., 2019, 2020; Rivera et al., 2021; Takeda, 2022;).

Climatic Effects

Climate change has increased the habitable range of the mosquitos that transmit the virus (Shen et al., 2015). The United Nations (2021) Climate Change Report predicts an increase in the frequency and duration of major climatic events, perpetuating epidemic outbreaks of arbovirus diseases. Alterations to the world's ecosystems are increasing the habitable range of mosquitos and extending seasonal or year-round transmission of vector-borne illnesses.

The relationship between vectors, the environment, human population migrations, and socio-economic determinants of disease transmission is dynamic and complex (Caldwell et al., 2021; Caminade et al., 2017; Mordecai et al., 2017; Ngonghala et al., 2021; Perkins et al., 2016;

Reiter et al., 2003; Tesla et al., 2018; Valdez et al., 2018). Modifications of weather patterns are likely to increase the intensity and duration of climatic events, including floods, droughts, tropical storms, and severe storms. Predictions concerning disease risk and impact have been somewhat controversial (Altizer et al., 2013; Patz et al., 2005; Rogers & Randolph, 2006; Siraj et al., 2014). However, global warming has already caused profound and often complex changes to the severity of some infectious diseases (Altizer et al., 2013).

Study Aims and Research Questions

Dengue's global burden and distribution are increasing due to a complex web of climatological, environmental, ecological, and socioeconomic factors. Mechanistic modeling has been employed with several vector-borne diseases, including Zika, Yellow Fever, and Dengue (Caldwell et al., 2021; Caminade et al., 2017; Mordecai et al., 2017; Ndeffo-Mbah & Pandey, 2020; Ngonghala et al., 2021; Perkins et al., 2016; Tesla et al., 2018;). Aim 1 is to develop a model that combines the temperature-dependent metabolic and reproductive traits, the ecology of precipitation and temperature, the distribution of the *Ae. aegypti*, and geolocalized socioeconomic factors to create a spatiotemporal relative risk of dengue on a 5 x 5-kilometer^2 global scale. This model allows for evaluating the impact of temperature and precipitation on the mosquito vector life cycle to determine the global relative risk of dengue infection.

Through a literature review, Aim 2 is to identify the determinates of dengue and severe dengue, to understand the effect of immunity on severe disease and the risk of disease introduction into immunologically naïve populations, to evaluate the relationship between the order of serial infections and severity, and to determine the risk of complications. Risk factors for severe dengue are explored by synthesizing past studies isolating the predominate serotypes of different outbreaks and the implication of serial infections with a secondary virus serotype.

The consequences of the circulation of all four serotypes throughout many tropical and subtropical locations and the impact of vaccines on mitigation and control efforts are discussed.

Aim 3 addresses a particular subset of individuals at risk of repeated or prolonged exposures, putting them at a higher risk of infection than others. These include individuals engaged in military service, volunteer service, disaster response, and recent immigrants traveling back to visit friends and relatives in their country of origin. A review was performed to characterize these special populations with repeated exposures to construct a framework for recommendations for pre-travel health consultations. The specific risk factors of repeated travel to endemic areas, the order of secondary infections, and prevention and mitigation measures, including the use of vaccines, are explored.

Aim 4 builds a simple cost-benefit analysis of the feasibility of implementing a Dengvaxia® vaccine program for Peace Corps volunteers serving in endemic areas worldwide. A previous study of the incidence of dengue cases in volunteers over a 14-year period and real-world costs, seropositivity conversion rates, medical evacuations, and voluntary vaccine uptake rates were derived from the literature. Furthermore, the cost-benefit analysis seeks to determine if an off-label use or exception to policy should be utilized to screen and vaccinate travelers in these groups. Considerations of the pandemic effects on dengue mitigation and control and the potential impact of vaccines, primarily the newly approved Qdenga® vaccine, on limiting the illness in travelers are evaluated.

Finally, the public health impact of dengue is characterized. Dengue is a re-emerging tropical disease whose range, severity, and impact have and will continue to grow—steps must be taken to limit its power on future generations. Control and mitigation strategies targeting

specific high-risk populations and understanding the true risk of the disease on a global scale will be paramount to curbing the spread.

2. DENGUE—AN EMERGING THREAT WORLDWIDE: A MATHEMATICAL MODEL EXPLORING GLOBAL RELATIVE RISK USING CLIMATIC, GEOLOCALIZED ECONOMIC, AND VECTOR DISTRIBUTION DATA

Background

Dengue is transmitted via the bite of an *Aedes* mosquito, but only female mosquitos bite humans and animals to obtain protein from the blood meal. After ingestion, it takes 3-5 days for the blood to be digested and the eggs to develop (Pasco County, 2022). Female mosquitos can lay up to 300 eggs at a time, live up to 2-4 weeks, and produce 2-4 egg batches (CDC, 2022). Simply put, without blood meals, mosquitos would cease to exist as this is a necessary component of their reproductive cycle.

Mosquitos use their proboscis to pierce the skin and suck up blood. As they feed, the mosquito injects saliva into its victim's skin. Sometimes, the mosquito ingests germs (parasites, bacteria, viruses, etc.) during feeding. These pathogens pass from the mosquito's gut into the body, where it is multiplied. After replication, the germ moves from the body into the salivary gland, which takes two to three weeks (CDC, 2020; Chamberlain & Sudia, 1961). The next time the female takes a blood meal, some germs pass from the mosquito's salivary gland into the blood of the person or animal being bitten.

Not every mosquito is infected with a virus—some of them cannot spread the illness, and some capable of transmitting infections have not come in contact with an infected host while this animal or person was able to transmit the pathogen. Conversely, some mosquitos are infected with several pathogens simultaneously (Rückert et al., 2017). However, there is no way of knowing if it is infectious by looking at a mosquito with the naked eye. In reality, a complicated web of factors including the infectivity of the host, the age of the mosquito, the pathogen itself, environmental conditions such as temperature and humidity, and the "load" or amount of the

germ ingested during the feeding (Carrington & Simmons, 2014; CDC, 2020). These characteristics are parameterized and studied in a mechanistic model to determine the effects of environmental, ecological, socioeconomic, and human-vector interaction on Dengue transmission.

Effect of Temperature on Mosquito Dynamics

Temperature is a strong driver of vector-borne disease transmission, but many of the parameters, mechanisms, and details of the host-pathogen systems are unknown. As an ectotherm, mosquitos depend on an external body heat source, with temperature playing an integral role in the mosquito life cycle. Traits important for disease transmission and ones linked to metabolic functions, such as reproduction, development, survival, and biting rate, are temperature-dependent (Caldwell et al., 2021; Mordecai et al., 2017). Additionally, the rates at which mosquitos acquire and transmit viruses are intrinsically linked to thermal dynamics. This transmission rate is determined by the number of blood meals remaining in the mosquito's lifespan after the point in which they become infectious—determined by the biting rate (feeding frequency), estimated vector mortality rates, and the time required to develop the virus inside the mosquito (extrinsic incubation period (EIP)) (Caminade et al., 2017).

All the temperature-dependent effects are predictable through the analysis of mechanistic models. Previous work demonstrated transmission peaks at 23-34°C for biting rate, egg-to-adult survival and development rate, adult lifespan, and fecundity for *Ae. aegypti* and *Ae. albopictus* (Mordecai et al., 2017). Studies have shown that average annual temperatures which reach a threshold of 18.25°C (64.85°F) increase transmission risk (Shen et al., 2015). The thermal response curves for *Ae. albopictus* is shifted towards the lower extremes, meaning its transmission is better suited to cooler environments than *Ae. aegypti* (Mordecai et al., 2017).

Transmission depends upon the vector's survival through the length of the EIP, becoming infectious and attacking susceptible hosts. Mosquitos exposed to higher temperatures after a blood meal containing the virus become infectious more rapidly than mosquitos in lower ambient temperature environments. Thus, higher temperatures and shortened EIP would mean more mosquitos become infectious during their lifespan (Promprou et al., 2005). At 30°C, the EIP for dengue is 12 days, but it falls to only seven days during ambient temperatures from 32-35°C (Focks et al., 1995). The direct impact of climate change on ecology and habitat necessitates ecosystem changes. When coupled with human encroachment into new areas that decrease biodiversity, climatological changes impact the emergence and spread of infectious diseases (Keesing et al., 2010).

Overall, unimodal impacts of temperature on survival, vector competence, and EIP have non-linear effects (Tesla et al., 2018). Much of the parametric data is derived from a few laboratory studies that often fail to adequately mimic the complexities of real-world behaviors and interactions. Notwithstanding, the EIP is an essential component and integral to understanding weather and climate's influence on mathematical disease transmission models (Chan & Johansson, 2012).

Effect of Rainfall on Carrying Capacity

The mosquito life cycle starts when eggs hatch into an aquatic larval and subsequent pupal stage; thus, rainfall plays a significant role in vector colonization. Rainstorms often leave standing water providing new mosquito breeding locations. However, heavy precipitation may initially flush or wash away the reproductive habitats (Benedum et al., 2018; Koenraadt & Harrington, 2008; Paaijmans et al., 2007). *Ae. aegypti* are urban mosquitos and reproduce in water collection containers used by humans. Thus, increased water storage activities during a

drought can increase water availability for mosquito breeding. For this reason, vector control and mitigation techniques emphasize eliminating standing water around living spaces and the introduction of larvicides to water sources.

An increase in rainfall creates more breeding habitats leading to more mosquitos. Heightened adult mosquito density raises the odds of a mosquito obtaining a pathogen during feeding and later transmitting it to a susceptible host (Promprou et al., 2005). A study from Thailand showed that more frequent, lighter rains might replenish breeding sites and maintain higher humidity levels, which assist in adult mosquito dispersal and survival (Promprou et al., 2005). However, heavy rainfall or flooding events may initially have detrimental effects on vector populations. Mosquitos require standing water for breeding and larval development. However, too much rainfall leads to flushing—the overflow of the breeding environment, which disrupts breeding behaviors and destroys the developing larva (Benedum et al., 2018). A study from Singapore predicted that a maximum rainfall level of 123 millimeters (mm) led to a high probability of flushing events (Benedum et al., 2018). Furthermore, analysts developed a predictive model associating temporal rainfall patterns with flushing conditions, demonstrating a statistically significant reduction in dengue infection risk following a flushing event aligned with the time lag necessitated by the mosquito development cycle (Benedum et al., 2018).

Mathematical Modeling of Dengue

Mathematical models are simplified descriptions of a system or process often used to assist in calculations and predictions. Infectious disease models are a set of equations describing the transmission of a pathogen in a population with an attempt to capture key processes while ignoring unnecessary details (Ndeffo-Mbah, 2021). Models fulfill two distinct roles: understanding and prediction (Keeling & Rohani, 2008). They are judged on accuracy,

transparency, and flexibility (Ndeffo-Mbah, 2021). Predictive models guide difficult public policy decisions. When predictive models fail to predict epidemic behavior accurately, this is a diagnostic warning signal that this disease outbreak's underlying parameters and behaviors may differ from the norm. Models can be used to understand how infectious diseases spread and how various complexities affect dynamics by analyzing individual factors or parameters (Keeling & Rohani, 2008).

Mechanistic modeling has played a role in response to most of the emerging disease threats of this century, from foot and mouth disease in Great Britain, to Severe Acute Respiratory Syndrome (SARS), to Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Saudi Arabia to Ebola in West Africa (Cauchemez et al., 2014; Keeling et al., 2001; Lipsitch et al., 2003; WHO, 2014). These models have been enhanced with laboratory-derived parameters and manipulated to assess the effects of temperature, rainfall, humidity, and other environmental impacts. When taken together, the models provide essential information on the potential future impacts of dengue due to the lengthening of the vector breeding seasons and the increase in the geographic spread of vector habitability.

For emerging outbreaks, models have been used to quickly quantify and compare policy alternatives. These forecasts help policymakers and governments determine how to utilize limited resources best. Mathematical models can estimate R-naught (R_0) and predict the final epidemic size—vital for determining the risk and implementing control strategies to reduce morbidity and mortality. Modeling Dengue risk after major climatic events, including floods and hurricanes, which include lag time for incubation periods and vector life cycle completion, could inform risks for disaster response workers. It can also help to determine the best implementation strategies for dengue vaccines (Coudeville et al., 2020).

Basic Reproductive number (R-naught (R_0))

The risk of spread of infectious disease is described by its basic reproduction number (R_0)—the average number of people that a single infected person can be expected to transmit the disease to in a fully susceptible population (Nelson & Williams, 2007). This is the primary metric used to quantify the transmission of the disease in infectious disease dynamics and provides a measure of how fast an outbreak can grow through subsequent generations. When R_0 is less than 1, the infectious individuals will no longer replace themselves, and there will be fewer infectious individuals in the current generation than in the previous generation. The epidemic will wane and eventually die out. For the reverse, the epidemic will propagate when the basic reproductive number is greater than 1. R_0 for vector-borne diseases is a dynamic model that varies in space and time and is heavily influenced by temperature and precipitation.

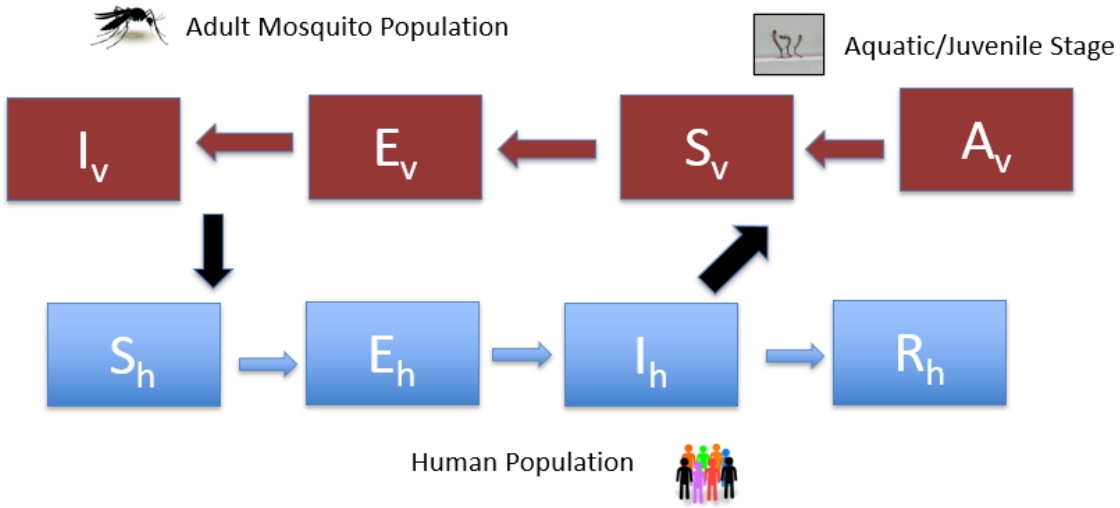
Enhanced SEI-SEIR Model

R_0 is affected by intricate biological, socio-behavioral, and environmental factors determining host-agent dynamics. The basic reproductive number can be estimated using complex mathematical models. Compartmental models offer a methodological approach to integrate the traits of disease dynamics and the course of infection. A single vector in the population is assigned to a compartment based on its current role in the transmission process. Mosquitos and humans follow an enhanced SEI-SEIR model in Dengue dynamics (Figure 2.1). Mosquitos begin in an aquatic/juvenile stage and enter the Susceptible (not infected) class through a recruitment term. They become Exposed (infected but not infectious) after biting an infectious human. After a temperature-dependent EIP, the surviving mosquitos move into the Infectious compartment where they can transmit the virus. Mosquitos eventually leave the system through a temperature-dependent mortality function and remain infectious until death.

The human population is divided into similar compartments based on disease status with the addition of the R compartment. For Dengue transmission dynamics, this R class represents the population removed from infectious dynamics through recovery from acute infection. Although not studied or analyzed here, the R compartment would also include all members who have been inoculated against the virus and, therefore, not considered infectious after exposure. Furthermore, while there are four strains of Dengue, and infection only provides lifelong immunity to that particular strain, the risk of reinfection with subsequent serotypes was not modeled here. The dynamics of the infection in a population are defined by the rate at which members move between the compartments. Biological characteristics of the disease process determine this rate—i.e., the rate that individuals recover from the illness. Additionally, the status of the population—the rate that individuals move from susceptible to infectious is determined by the number of infectious individuals in the population (Nelson & Williams, 2007).

Figure 2.1

Schematic Representation of the Enhanced SEI-SEIR Dengue Compartmental Model



Note. The red boxes represent the vector compartments according to disease status and include an aquatic juvenile stage, whereas the blue boxes represent the human compartments. A solid arrow denotes the transitions between the compartments. The black arrows represent the transmission of the virus from vectors to humans and humans to vectors. For simplicity in the model, the human population is considered stable (no births or deaths).

Research Questions

Mechanistic models have been utilized to model several vector-borne diseases based on the premises of Ross-Macdonald's theory (Amaku et al., 2016). Predicting the effects of climate change on vectors and transmission derives from understanding the links between the environment and human and vector population migrations and densities (Johnson et al., 2015). These models have been enhanced with laboratory-derived parameters and manipulated to assess the effects of temperature, rainfall, humidity, and other environmental impacts.

Specifically, this paper looks at the *Ae. aegypti* mosquito and how climatological, ecological, and socioeconomic factors drive Dengue disease dynamics. A Global Relative R_0 Model for Dengue at a 5 by 5-kilometer^2 grid resolution was constructed based on earlier works of Ndeffo-Mbah and Pandey (2020). This model includes the distribution of the *Ae. aegypti* vector, the interaction between socioeconomic factors and human-mosquito contact, and climatic factors (rainfall and temperature) on transmission dynamics. The geolocalized socioeconomic factors include measures such as prosperity, housing conditions, and availability of air conditioning. The model was used to analyze the spatiotemporal risk of Dengue by capturing the contributions of hosts, pathogens, and vectors' multiple, interacting, and often nonlinear responses to climatological factors.

Methods

This paper built upon previous mechanistic models that incorporate the *Aedes* life cycle and human disease dynamics through the analysis of temperature and rainfall-dependent trait functions into one epidemiological model (Caldwell et al., 2021; Huber et al., 2018; Li et al., 2019; Lourenço & Recker, 2014; Oidtman et al., 2019; Siraj et al., 2014; Wang et al., 2016). Initial R_0 models derived from Mordecai et al. (2017) and Ngonghala et al. (2021) were replicated to model the dynamics of dengue infection by *Ae. aegypti* with respect to temperature

and precipitation. This approach employed a Bayesian framework to fit thermal and rainfall responses for the characteristics inherent to both mosquitos and humans that drive disease transmission (Ryan et al., 2021). Johnson et al. (2015) provide a detailed background of this methodology.

Poverty has long been considered a determinant of dengue infection. Vector control, pesticide management, basic sanitation and hygiene, and the provision of safe drinking water are essential strategies that must be employed at the highest levels to fight infectious diseases effectively. However, a systematic review of English language journal articles revealed a mixed story when poverty's effects were empirically assessed (Mulligan et al., 2015). The researchers discovered that income and physical housing conditions were the most common poverty incomes associated with increased dengue infections (Mulligan et al., 2015). Nevertheless, for many, it is evident that infectious diseases thrive and persist under conditions of poverty (Nii-Trebi, 2017). The main driver of dengue infection in impoverished regions comes from the poor housing infrastructure (windows without screens, lack of piped water leading to numerous large water collection devices in which *Ae. aegypti* mosquitos are evolutionarily adapted to deposit their eggs) and rapid urbanization (Caminade et al., 2017; Gubler, 2011). Access to running potable water and proper household waste disposal were key determinates of infection during a large outbreak in Tanzania (Mboera et al., 2021). In this model, the interaction between poverty and human-mosquito contact was parameterized by the risk of exposure function.

Recognizing the link between climate change and its effect on poverty, mosquito habitats, loss of biodiversity, and extreme weather events is a critical first step in climate change and dengue policy implementation. Therefore, this dengue model was then parameterized with several high-resolution datasets (Table 2.1).

Table 2.1

Specified Databases with High Spatial Resolution that were used to Parameterize the Model

Parameter	Description & Source
Global *Aedes* Distribution (P_{ae})	Uncertainty estimates for *Ae. aegypti* mosquito distribution at 5 km x 5 km spatial resolution https://www.dropbox.com/sh/bpxcmzmmpiiav8u/AAAl3CBKnBYwXb0n1s1C4-K-a?dl=0 (Kraemer et al., 2015)
Global Climate Database (Rainfall & Temperature)	Monthly minimum, maximum, and average temperature (°C) and rainfall (mm) data from 1970-2000 at a 2.5 min spatial resolution https://www.worldclim.org/ (Fick & Hijmans, 2017)
Geolocalized Economic Data (G-econ)	Geophysically scaled dataset linking per capita gross product (GDP) at purchasing power parity (PPP) rates --Recomputed to change 1 km x 1 km to match the 5 km x 5 km resolution of other data sets http://gecon.yale.edu/sites/default/files/files/Gecon40_post_final.xls (Zhang et al., 2017)

Relative Global Dengue R_0 Model

An extended version of the classic Ross-Macdonald model was utilized to calculate a Relative Global Dengue R_0 model.

$$R_0\ Formula = \sqrt{\frac{b_v^2\ * \beta_{vh} * \beta_{hv} * \sigma_v\ * R_{se} * \kappa * f(R) * P_{ae}\left(1 - \frac{\mu_v^2}{\theta_v * \nu_v * \phi_v}\right)}{\gamma_h * \mu_v * (\sigma_v + \mu_v) * N_h}}$$

In this extended version of the classic Ross-Macdonald model, b_v is the mosquito biting rate (the number of human bites per mosquito per unit of time); β_{vh} is the transmission rate (the probability that an infectious mosquito successfully transmits the virus while taking a blood meal from a susceptible human); β_{hv} is the infection rate (the probability that an infectious human successfully transmits the virus to a susceptible biting mosquito); σ_v is the extrinsic incubation period (the rate at which vectors become infectious); γ_h is the per capita human recovery rate (days humans are infectious before they recover with immunity); μ_v is the natural mosquito death rate ($1/\mu$ = average lifespan on mosquitos); R_{se} is the risk of exposure (based on geophysical data based on economic activity and poverty factors); P_{ae} is the probability of exposure (due to *Aedes* occurrence and human populations); κ is the carrying capacity (maximum number of mosquitos a site can support); $f(R)$ is the hypothesized rainfall function; Θ_v is the number of eggs a female mosquito produces each day; ν_v is the probability of an egg surviving to become an adult; Φ_v the rate at which an egg develops into an adult mosquito; and N_h is the human population density.

Mosquito Population & Carrying Capacity (κ)

Kraemer et al. (2015) compiled a mosquito distribution database that predicts the global distribution when combined with environmental variables (Figure 2.2). This comprehensive synthesis showed that this range was the widest ever recorded—primarily due to global trade routes and the ease of international travel. As mosquitoes carry many infectious diseases, this

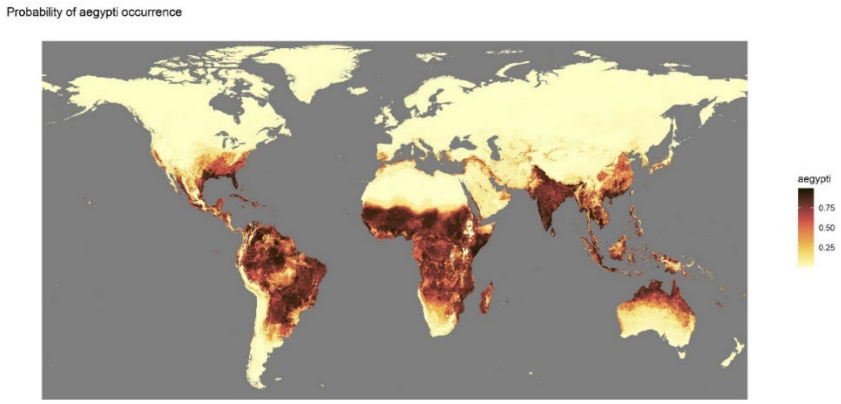
increased distribution significantly impacts the spread of disease. Quantifying the entomological baseline allows for predictions of future autochthonous infections and public health measures of control and mitigation efforts.

Mosquito Population Formula: $\alpha = \frac{\Theta_v * \nu_v * \Phi_v}{\mu_v}$

The mosquito population is a function of multiple terms, including the carrying capacity (κ-kappa) and a mosquito constant (alpha–α). Alpha represents the interaction of $\Theta_{v,}$ (the number of eggs) times ν_v (probability of surviving from egg to adult) times Φ_v (the rate of development from an egg into an adult) divided by μ_v (the natural death rate). Each of these terms is represented by a functional form affected by the temperature (measured in degrees Celsius). Carrying capacity is also influenced by the availability of suitable aquatic habitats for developing eggs. Although several distinct types of aquatic habitats contribute to the carrying capacity, only one value—an empirically derived but standardized—kappa of 20 was used in the analysis. (Perkins et al., 2016; Smith et al., 2013; Soda et al., 2018;).

Figure 2.2

The Global Probability of Ae. aegypti Occurrence



Note. Figure created using data from Kraemer et al., 2015.

Human Population

Although several estimates of human population density (N_h) exist , the data files are too large to be transformed into a usable form for our global relative risk model without a supercomputer. Worldpop.org (2018) has an estimate for each country in the world for each year during a twenty-year (2000-2020) period. The vastness of the data was beyond this project's scope; thus, a constant human population density (N_h) of 1 was used for this expanded model. The analysis assumed the maximum possible interaction between human and mosquito populations for the global relative risk model.

Precipitation

The effects of precipitation on disease transmission have yet to be widely researched or understood. Following Caldwell's et al. (2021) model, disease dynamics were evaluated based on three hypothesized biological relationships between freshwater availability and immature mosquito breeding environments (Table 2.2). The effects of rainfall on carrying capacity were assessed twice, once as a Brière function and once as a quadratic function. Minimum rainfall (R_{min}) was set at 1 mm and maximum rainfall (R_{max}) was set at 123 mm for the quadratic function, with the values set at 1 mm and 246 mm for the Brière function. This maximum value was based on Benedum et al., 2018) study in Singapore and represented a high probability of flushing mosquito larvae from the breeding habitat. Rate constants (c) of $7.86e^{-5}$ (Brière) and $5.99e^{-3}$ (quadratic) were based on rate constants from other parameters with similar functional forms (Caldwell et al., 2021). The z scaling factor value was used to restrict the maximum carrying capacity to produce model outputs based on a subsample of the total population. Similarly, Ngonghala et al. (2021) utilized this parametric methodology, which allowed the inclusion of a precipitation variable to detect rainfall's effect on carrying capacity.

Table 2.2

Dengue Carrying Capacity Model Parameter Settings for Hypothesized Rainfall Relationships

Functional Form	Rate Constant (c) value	Minimum Rainfall (R_{min}) value (mm)	Maximum Rainfall (R_{max}) value (mm)	Scaling Factor (z) value
$f(R_{Brière}) = c * R * (R-R_{min}) * \sqrt{(R_{max}-R)} * z$	$7.86e^{-5}$	1	246	0.50
$f(R_{Quadratic}) = c * (R-R_{min}) * (R- R_{max}) * z$	$5.99e^{-3}$	1	123	0.28
$f(R_{Inverse}) = \frac{1}{R} * z$	---	---	---	0.60

Note. All three functional forms were modeled, but only the Brière and Quadratic forms were utilized in our final analysis. The rainfall relationships were derived from Caldwell et al. 2021.

Temperature

Many values for the traits analyzed in this mechanistic model were derived from laboratory experiments and other recently published thermal performance curves (Mordecai et al., 2017; Ryan et al., 2021; Tesla et al., 2018). Vector competence and extrinsic incubation periods specific to dengue were modeled. Temperature-dependent rates were fit with symmetrical (Quadratic, $c(T-T_0)(T-T_m)$ or asymmetrical (Brière, $cT(T-T_0)(T_m-T)1/2$) functions. For both functional equations, T_0 and T_m are the minimum and maximum temperatures in Celsius for transmission, and c is a positive rate constant (Mordecai et al., 2017).

Exposure Risk

The link between socioeconomic factors and population risk of exposure was demonstrated through the extrapolation of data from Nordhaus et al. (2006). This project mapped the large countries' per capita gross cell product into a "gridded output" dataset. Data was compiled for 1° latitude by 1° longitude resolution cell. The economic data was based on four primary sources: (1) gross regional product, (2) regional income by industry, (3) regional employment by industry, (4) regional urban and rural population or employment along with aggregate sectoral data on agriculture and nonagricultural incomes (Nordhaus et al., 2006). The socioeconomic scales impact the availability of air conditioning and indoor plumbing, impacting human and vector interaction and vector-carrying capacity.

The Risk of Exposure Function was derived from earlier work on Yellow Fever vaccination rates and a modeling study on the spread of the Zika virus in the Americas (Ndeffo-Mbah & Pandey, 2020; Zhang et al., 2017). This functional form supplies a data-driven relationship between purchasing power parity (PPP) and the exposure risk from the *Ae. aegypti*

vector. The information was derived from historical data and geographically based economic (G-Econ) records to reflect the impact of socioeconomic factors on vector exposure (Zhang et al., 2017).

Table 2.3

The Risk of Exposure Function Measures the Interaction Between Poverty and Human-Mosquito Contact

Risk of Exposure Function	Range of Values
1.67 -0.34*log(PPP*exp(0.47))	1.97>log(PPP*exp(0.47))<4.911
1	log(PPP*exp(0.47))<1.97
0	log(PPP*exp(0.47))>4.911

Note. Fraction of the exposed population that can be associated with the geographically based version of the per capita Gross Domestic Product based on Purchasing Power Parity (GDP per capita, PPP) (Zhang et al., 2017).

Model Parameterization

This extended version of the Ross-MacDonald function was parameterized using empirical values derived from other epidemiological, entomological, and mathematical modeling studies. The value of many vectorial parameters is uncertain, with estimates varying on geographical location, time, and temperature. Estimated values were obtained from the literature (Table 2.4) (Caldwell et al., 2021; Mordecai et al., 2017; Ngonghala et al., 2021).

Table 2.4

Dengue R_0 Model Parameter Settings for Ae. aegypti Mosquitos

Parameter	Description	Function	Constant/Formula
T	Temperature °C	--- Empirical Data	Monthly min, max, and average temperature (°C) and rainfall (mm) at various resolutions from 1970-2000 (use 2.5 min spatial resolution data for 5 km) https://www.worldclim.org/
b_v	Mosquito biting rate	Brière	2.02E-04*T*(T-13.35)*(40.08-T)^0.5
Beta_vh β_{vh}	The probability that an infectious mosquito successfully transmits the virus while taking a blood meal from a susceptible human (i.e., transmission rate)	Brière	8.49E-04*T*(T-17.05)*(35.83-T)^0.5 Value is taken from Mordecai et al., 2017
Beta_hv β_{hv}	The probability that an infectious human successfully transmits the virus to a biting susceptible mosquito (i.e., infection rate)	Quadratic	4.91E-04*T*(T-12.22)*(37.46-T)^0.5 Value is taken from Mordecai et al., 2017
Sigma_v σ_v	The rate at which vectors become infectious (extrinsic incubation period)	Brière	1.74E-04*T*(T-18.27)*(42.31-T)^0.5
Gamma_h Υ_v	Per capita human recovery rate	Constant	1/5 (days) Value is taken from Mordecai et al., 2017
Theta Θ	# of eggs a female mosquito produces per day	Brière	8.56E-03*T*(T-14.58)*(34.61-T)^0.5

Table 2.4 Continued

Parameter	Description	Function	Constant/Formula
Nu N	Probability of surviving from egg to adult	Quadratic	-5.99E-03*(T-38.29)*(T-13.56)
Phi φ	The rate at which an egg develops into an adult mosquito	Brière	7.86E-05*T*(T-11.36)*(39.17-T)^0.5
Mu μ	Natural Mosquito Death Rate	Quadratic	1/(-3.02E-01*(T-11.25)*(T-37.22))
f(R)	Modeling Precipitation	$f(R_{Brière})$ $f(R_{Quadratic})$ $f\ (R_{Inverse})$	$f(R_{Brière}) = c * R * (R-R_{min})* \sqrt{(R_{max}-R)} * z$ $f(R_{Quadratic}) = c * (R-R_{min})* (R- R_{max}) * z$ $f(R_{Inverse}) = f(R_{Inverse}) = \frac{1}{R} * z$ See values in Table 2.2 above (Caldwell et al., 2021)
Kappa/Human Population Density κ/N_h	Maximum Human to Mosquito Ratio: (vector carrying capacity/human population density)	Constant	20 Values derived from Ndeffo-Mbah and Pandey, 2020; Zhang et al., 2017; Caminade et al., 2017
R_{se}	Risk of exposure	---- Empirical Data	Estimated using geolocalized economic data from Nordhaus et al., 2006 & Zhang et al., 2017 See values in Table 2.3 above.
P_{ae}	Probability of aegypti occurrence	---- Empirical Data	Probability of *Aedes* aegypti occurrence derived from Kraemer et al., 2015

Note. These parameters were derived from Ngonghala et al. (2021) and Mordecai et al. (2017) and are specific to *Ae. aegypti* mosquitoes. R0 is the average number of secondary cases arising from a typical primary infection in an otherwise fully susceptible population. The temperature-dependent parameters were based on both the quadratic $c(T-T^m)(T-T^0)$ and Brière $(cT(T-T^0)(T^m-T)^{1/2}$ functional forms. Here T is the temperature (Celsius), c is the rate (or scaling constant), T^0 is the critical thermal minimum temperature, and T^m is the critical thermal maximum temperature.

Results

Global Relative R_0

Computational modeling determined the relative basic reproduction number (R_0) for potential dengue outbreaks on a 5-kilometer by 5-kilometer^2 global scale. Monthly average temperature and precipitation data from 1970-2000 enabled the construction of the graphics (Fick & Hijmans, 2017). Geolocalized economic data and human-mosquito interaction variables provided the final inputs into the global relative risk model. Overall, the R_0 model's projections align with the observed equatorial and tropical distribution of the Dengue virus. Dengue is present in Africa, the Americas, Asia, the Caribbean, and the Pacific (ECDC, 2021). It is endemic in over 100 countries and affects almost two-fifths of the world's population (Gubler, 2002; Messina et al., 2019). There is a significant congruence between the projected R_0 potential and the global distribution and disease burden, as reported by Bhatt et al. (2013).

The Brière Functional Form of precipitation in the R_0 model demonstrated high potential R_0 values along the equatorial regions throughout the year (Figure 2.3). Portions of sub-Saharan Africa and South America remain at risk for dengue outbreaks year-round. There is a coordinating increase in R_0 values at higher latitudes in the northern hemispheres during the summer months and lower latitudes in the southern hemisphere during the summer months.

This increase in the basic reproductive value is evident through an analysis of potential outbreak risk in Australia from November to March and dengue risk in the southern United States (U.S.) and Mexico from May through September. These locations have the *Ae. aegypti* mosquitos and temperatures conducive to vector proliferation. Global warming lengthens mosquito populations' life cycle duration and geographic reach amplifies the biting rate and breeding patterns. Mosquito metabolic and reproductive parameters vary with climatic conditions, leading to pronounced seasonal effects.

Figure 2.3

Monthly Global Relative R_0 Models using the Brière Functional Form

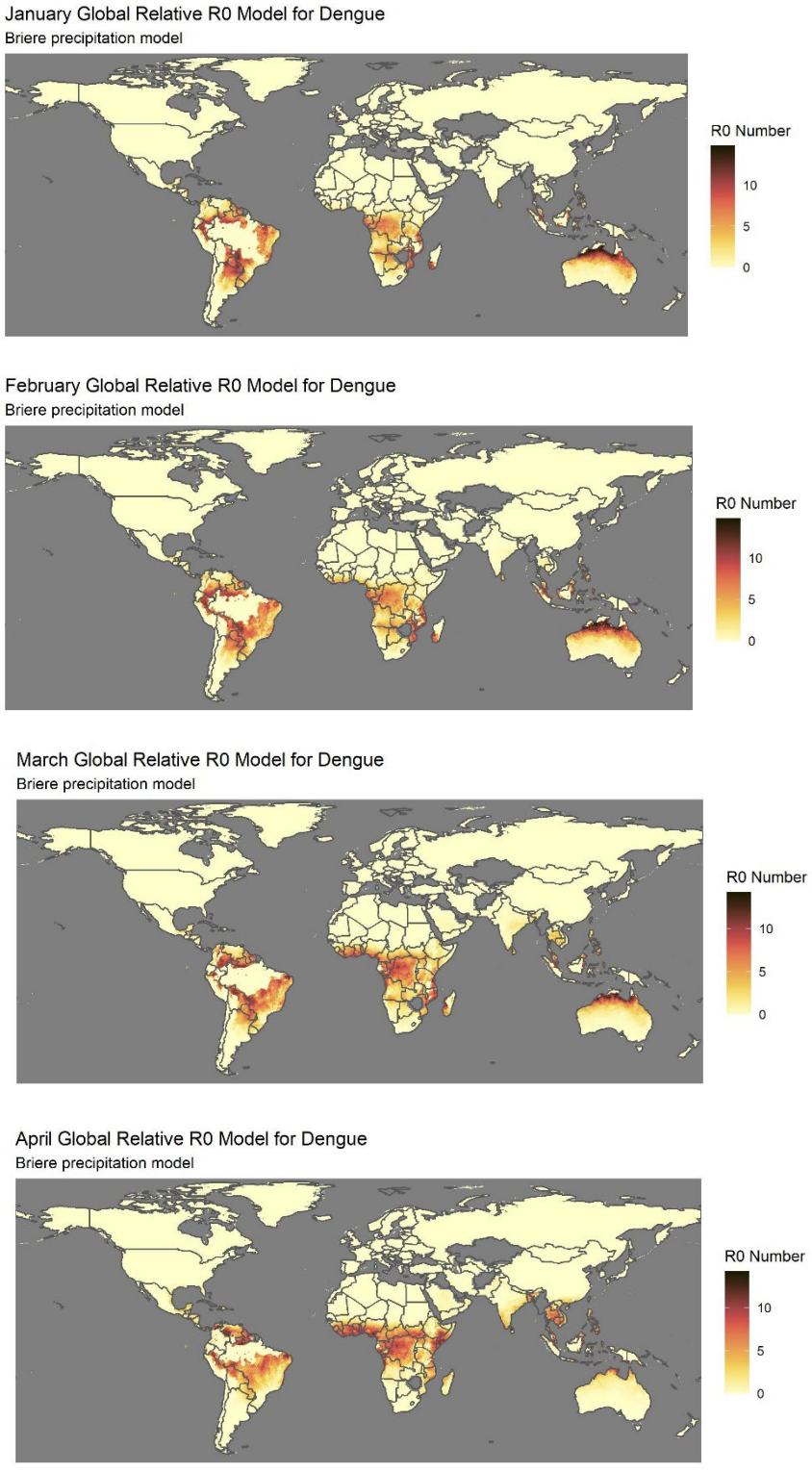


Figure 2.3 Continued

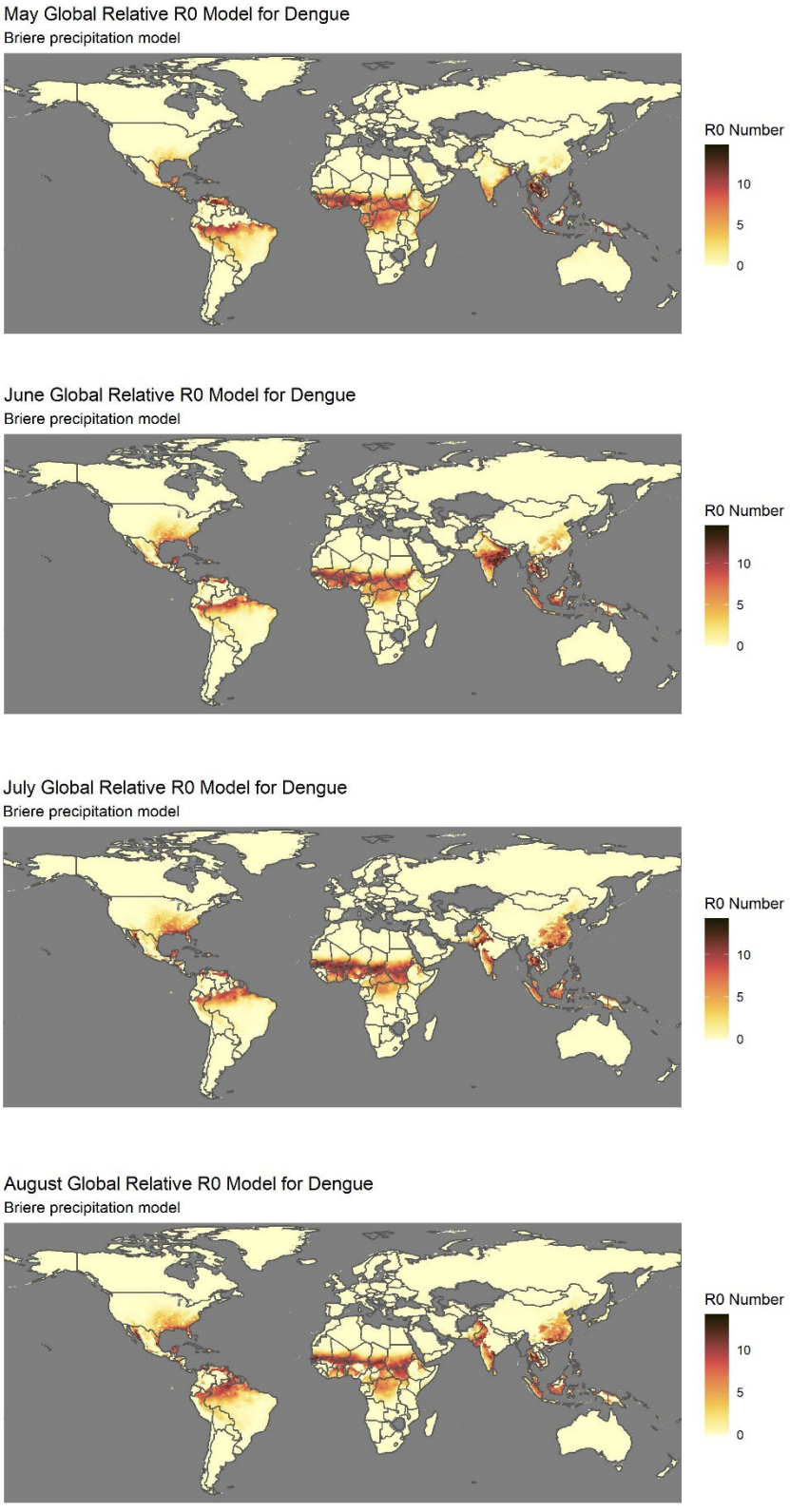
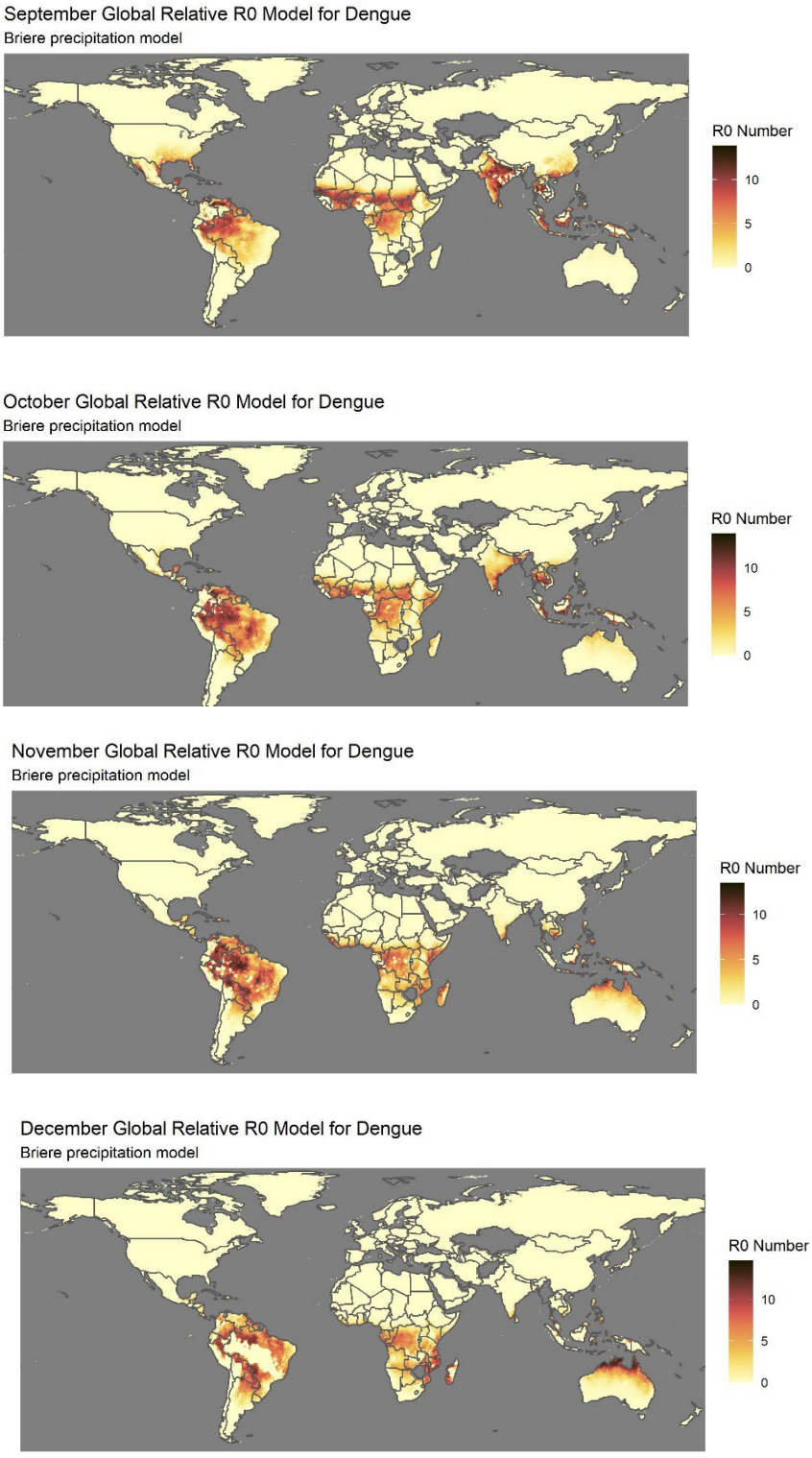


Figure 2.3 Continued



The Quadratic Precipitation model produced pronounced and strong relative R_0 values (Figure 2.4). Similar to the Brière Model, there were consistently high R_0 values along the equatorial regions throughout the calendar year. This model also produced widespread R_0 values on the South American and Australian continents during the southern hemisphere spring and summer seasons (October to April). Dengue rates and geographical spread is particularly pronounced in India from March to June. Furthermore, the Quadratic model shows the potential for Dengue spread well into the North American continent up to the Midwest from June to August. Brazil has extreme patterns of potential dengue spread throughout much of the year. Almost the entire country is at significant risk for dengue outbreaks during August and September.

Figure 2.4

Monthly Global Relative R_0 Models using the Quadratic Functional Form

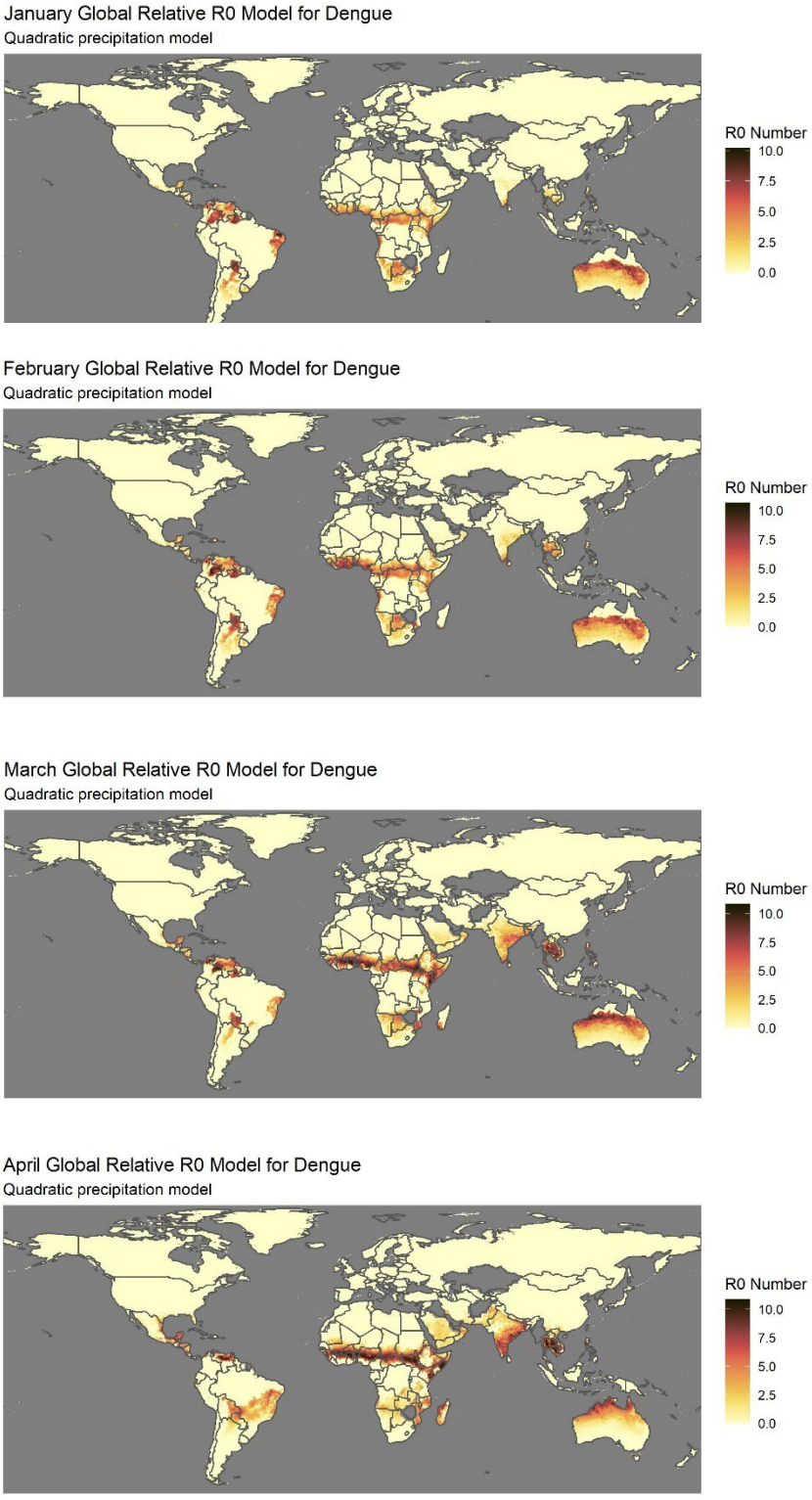


Figure 2.4 Continued

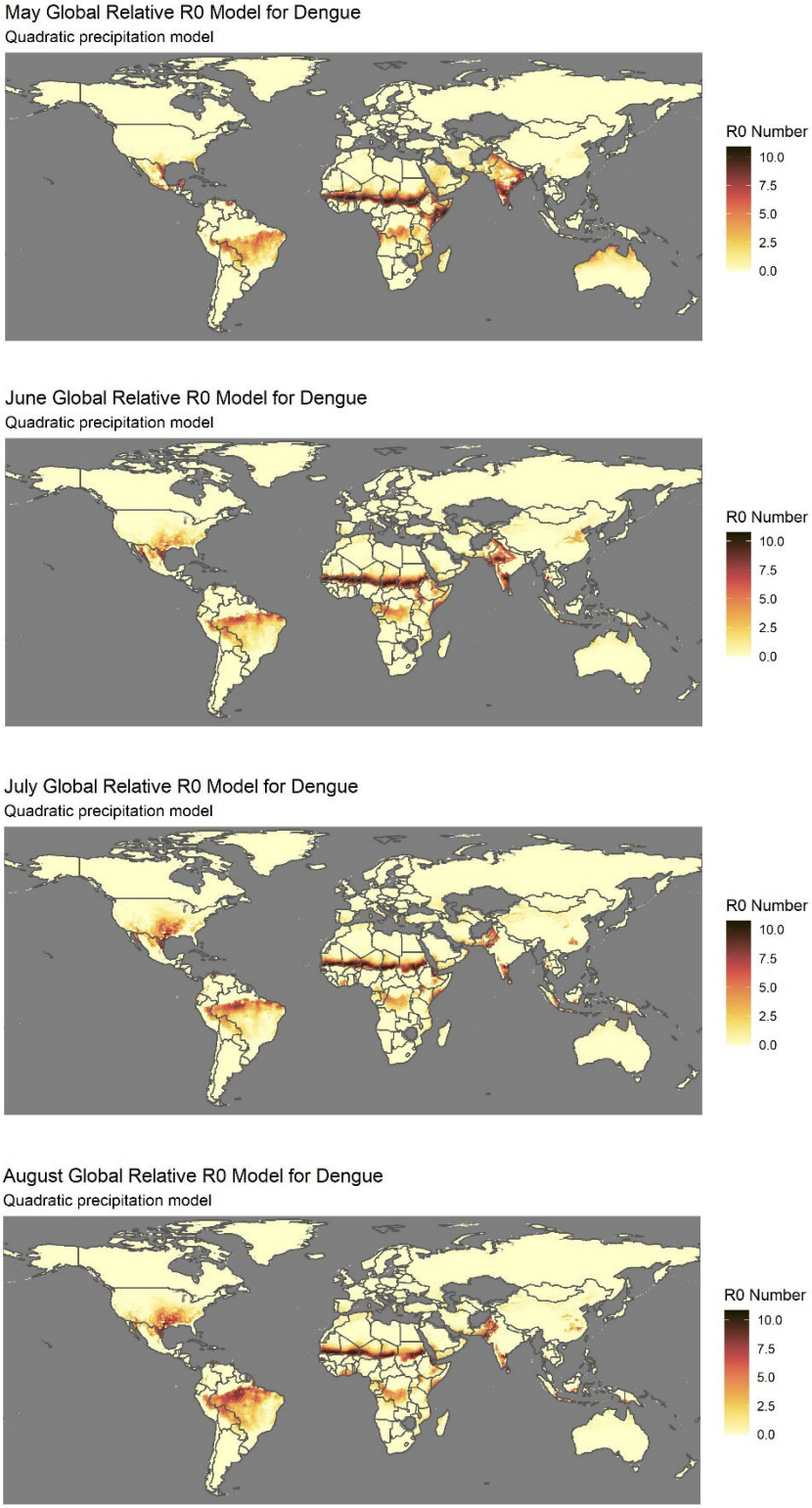
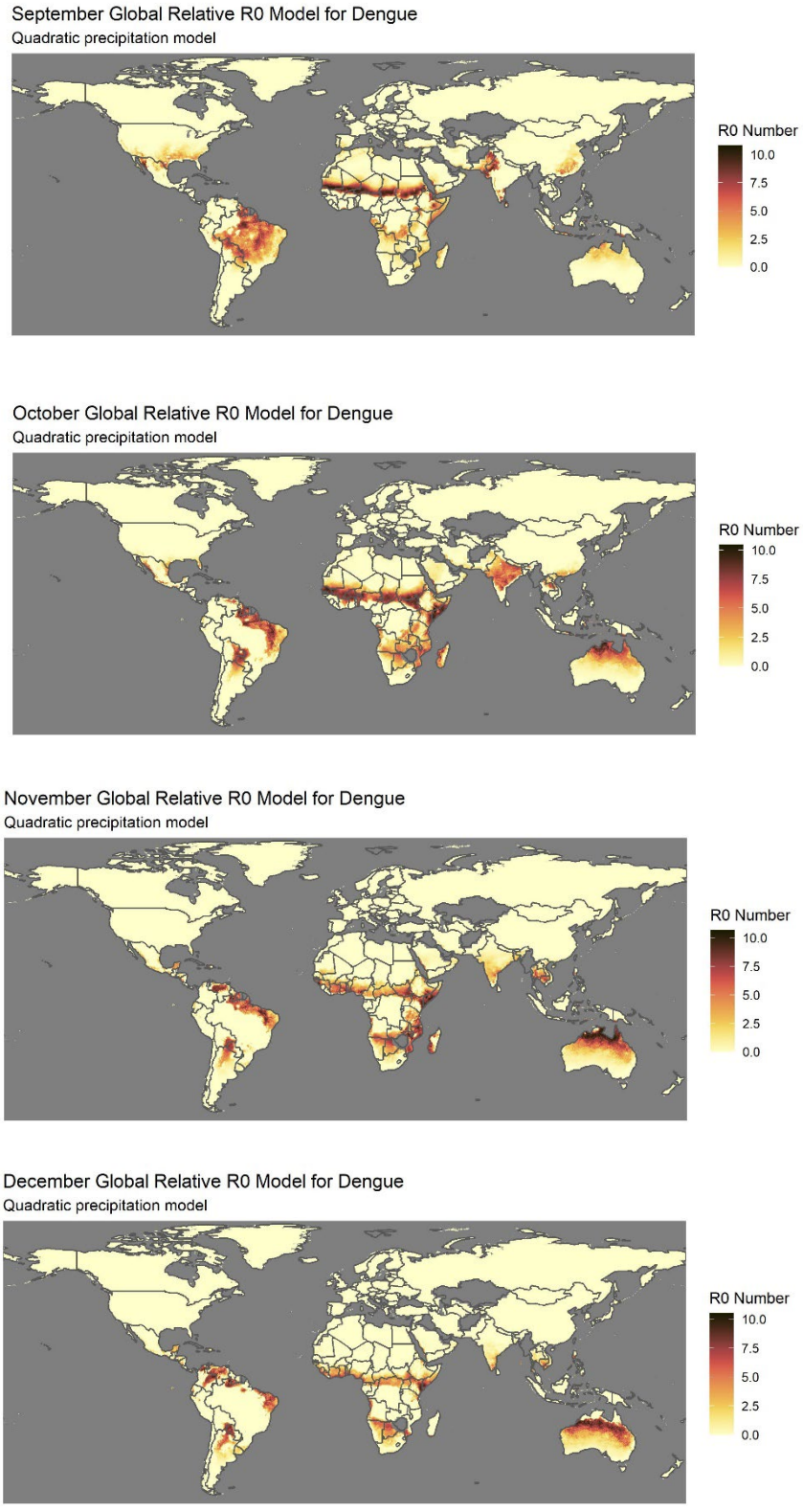


Figure 2.4 Continued



The climate in many tropical and subtropical regions supports a long vector breeding season with multiple generations, leading to year-round mosquito populations as evidenced by the continuous dengue presence (Simo et al., 2019). However, in more temperature climates, only a small number of mosquitos can survive the overwintering period leading to periods of negligible to no transmission (Keeling & Rohani, 2008). Data values were unavailable for Zimbabwe, Afghanistan, Kazakhstan, and Iraq, so no relative R_0 estimates could be generated.

Sensitivity Analysis

The robustness of the model was assessed through a series of sensitivity analyses which enabled an assessment of the confidence of the projections. Sensitivity analysis can identify important parameters and optimal measurements and evaluate the individual impacts of each variable on the system (Hamby, 1994). A correlation analysis through the construction of contour plots was generated to show the basic reproductive number as a function of temperature and precipitation. Subsequently, this helped to visualize the data better. A time-series plot of Brazil, the country with the most incident cases of dengue in the world, provided a glimpse at the variation of R_0.

Contour Plots

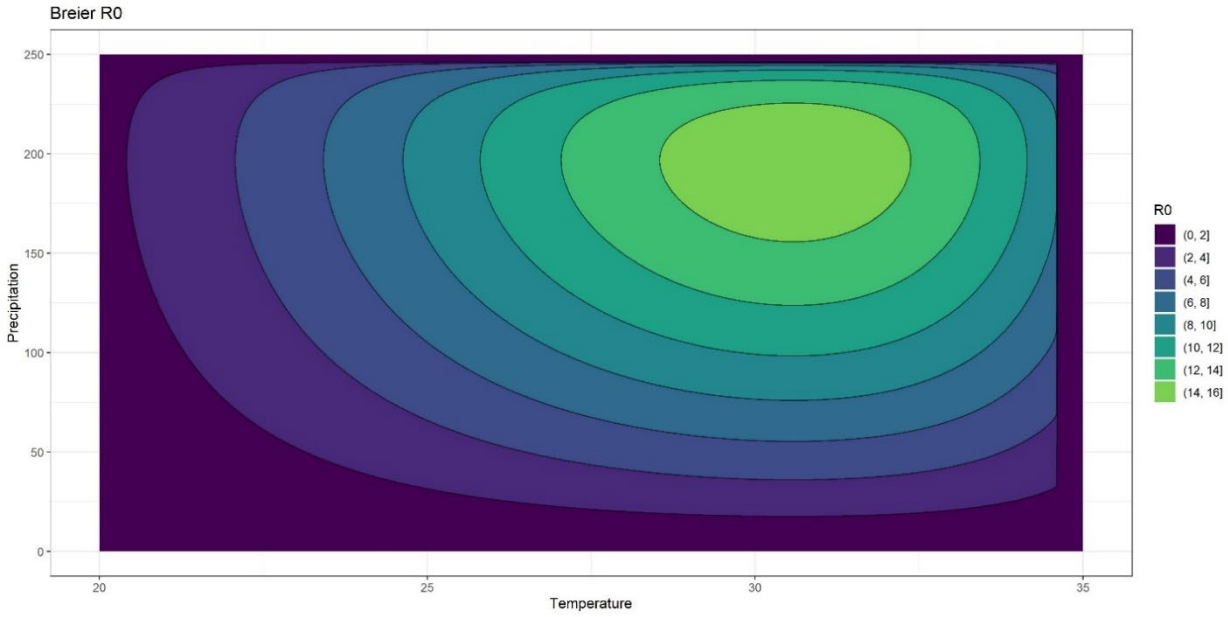
Contour plots are built on a two-dimensional plane. They are used to display the functional relationship ($z = f(x,y)$) between two continuous independent or input variables (X and Y) and a dependent or response variable (Z) (Frost, 2022; Morse, 1968). In our case, temperature and precipitation were modeled to determine the effect on R_0. The other important parameters of exposure risk (R_{se}) and probability of *Ae. aegypti* occurrence (P_{ae}) were fixed to their maximum values. The graph visually represents the relationship; precipitation in mm was plotted along the y-axis, the temperature in degrees Celsius was plotted along the x-axis, and the

contour lines and bands represent the R_0 (Z variable). The contour lines connect different combinations of variables X and Y that produce equal values of Z (Frost, 2022). They represent visual clues for which values of X and Y will maximize the response function. The contour lines' spacing indicates the change rate between the variables. For example, if the contour lines are spaced close to each other, the values change rapidly. In contrast, if the lines are spaced far apart, the R_0 (Z variable) value changes more slowly (Rapid Sigma Solutions LLP, 2022).

As illustrated below in the Brière Functional Form, the colored contour bands represent the varying ranges of the response variable—the Relative R_0 of Dengue (Figure 2.5). This contour map for the Brière Functional Form reveals a wide range of areas on the plot which reflect temperature and precipitation values that would not lend themselves to a dengue outbreak. This is shown by the dark purple shade outlining the plot—when the ambient temperature is less than 25°C and there is no significant precipitation. For temperatures from 21-35°C and rainfall of at least 30 mm, dengue outbreaks with R_0 between 2-4 could potentially occur. The contour bands representing the highest R_0 values (14,16) are found at conditions between 27-31°C at precipitation levels from 170-230 mm. The consistent spacing between the contour bands indicates a relatively constant change rate.

Figure 2.5

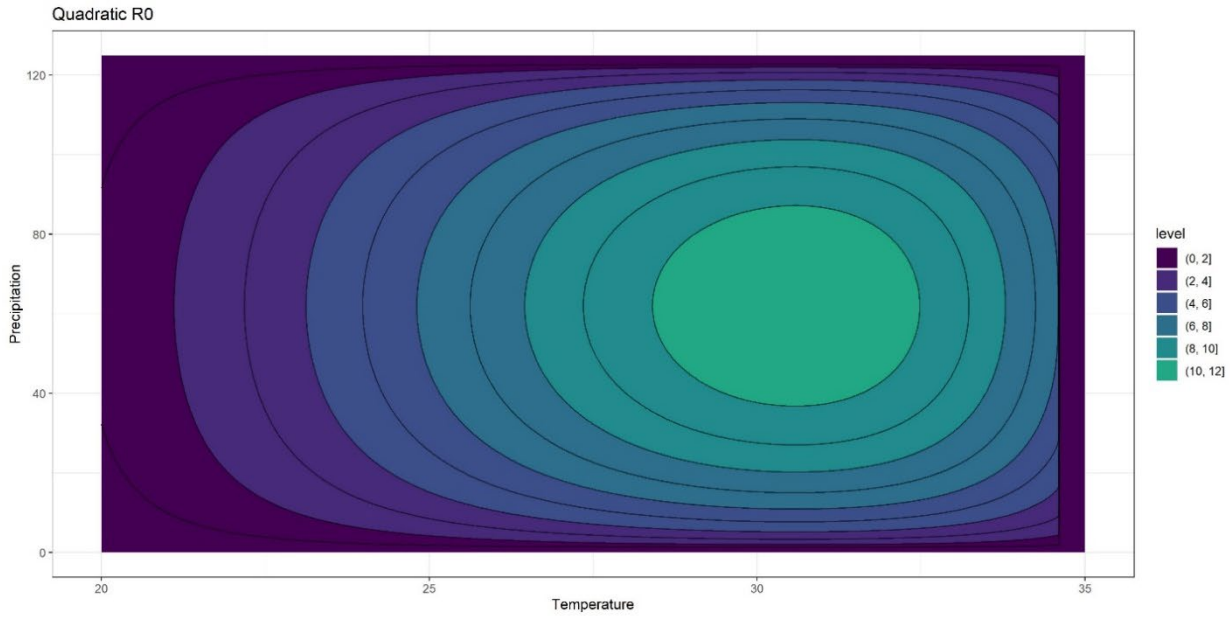
Contour Plot of R_0 Based on the Interaction Between Temperature and Precipitation using a Brière Functional Form



In the Quadratic Functional Form Contour plot, the teal innermost contour represents the highest relative R_0 values and their corresponding temperature and precipitation values (Figure 2.6). Using the quadratic functional form, the highest R_0 values occur at temperatures around 27-33°C and precipitation ranges from 40-84 mm. There is consistent spacing between the contour lines for values of $R_0 = 0, 2$ through values of $R_0 = 8, 10$ showing a relatively constant rate of change. The uppermost limit in precipitation occurs around the 118 mm mark, as precipitation values above this threshold do not consistently produce a dengue outbreak. Temperatures below 22°C and higher than 35°C are not conducive to virus transmission. These dark purple values depict environmental conditions outside the optimal temperature and precipitation values for mosquito vector survival and reproduction.

Figure 2.6

Contour Plot of R_0 Based on the Interaction Between Temperature and Precipitation using a Quadratic Functional Form



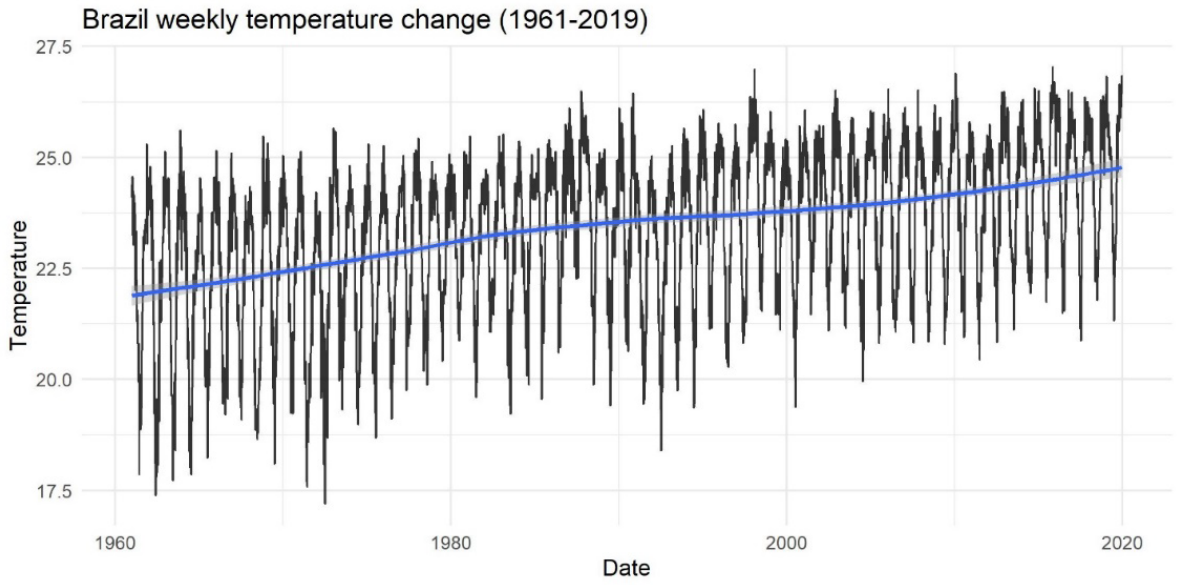
Overall, both contour plots show an interaction between temperature and rainfall on the potential for a dengue outbreak. Rain is needed for the aquatic mosquito breeding processes (Benedum et al., 2018; Koenraadt & Harrington, 2008; Paaijmans et al., 2007). Temperature is linked to numerous metabolic and reproductive traits in mosquitos (Caldwell et al., 2021; Mordecai et al., 2017). These plots underscore significant environmental implications in the model that account for the proliferation of this viral illness. Overall, an increase in both the temperature and having met a minimum precipitation threshold result in an increase in the potential magnitude of the outbreak, as evidenced by the R_0 value (Mushanyu et al., 2021).

Time Series Analysis

Brazil has the highest incidence rate of Dengue and has one of the world's most comprehensive surveillance systems, so it was chosen to analyze how the average R_0 of Dengue changed over time (Brady et al., 2015; ECDC, 2022;). A time-series sensitivity analysis was performed using data from Brazil's National Institute of Meteorology (INMET). It boasts a comprehensive network of over 265 weather stations reporting data from 1961 to 2019 (INMET, 2022). The average daily temperatures and precipitation levels were plotted at the country level for weekly and monthly time steps (Figures 2.7-2.10). This data was then used to generate weekly and monthly R_0 values using the Brière and Quadratic functional forms for precipitation (Figures 2.11-2.12).

Figure 2.7

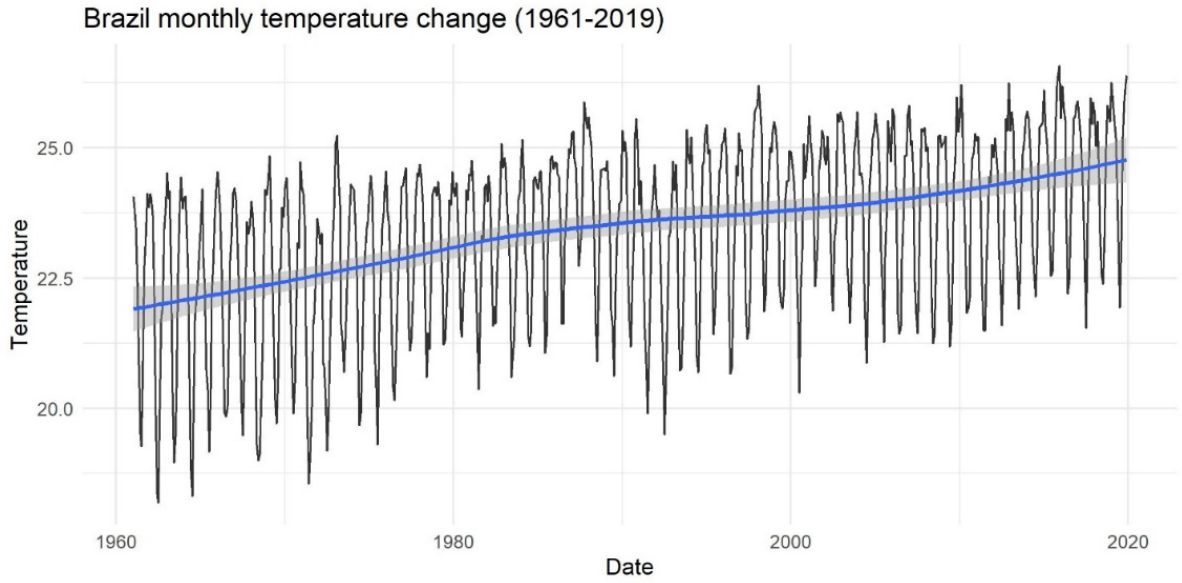
Brazil's Average Temperature Change from 1961-2019 Shows an Increase in the Average Weekly Temperature.



Note. The average weekly temperature increased from 21.5°C to 24.5°C over the nearly 60-year period. Data from INMET, 2022.

Figure 2.8

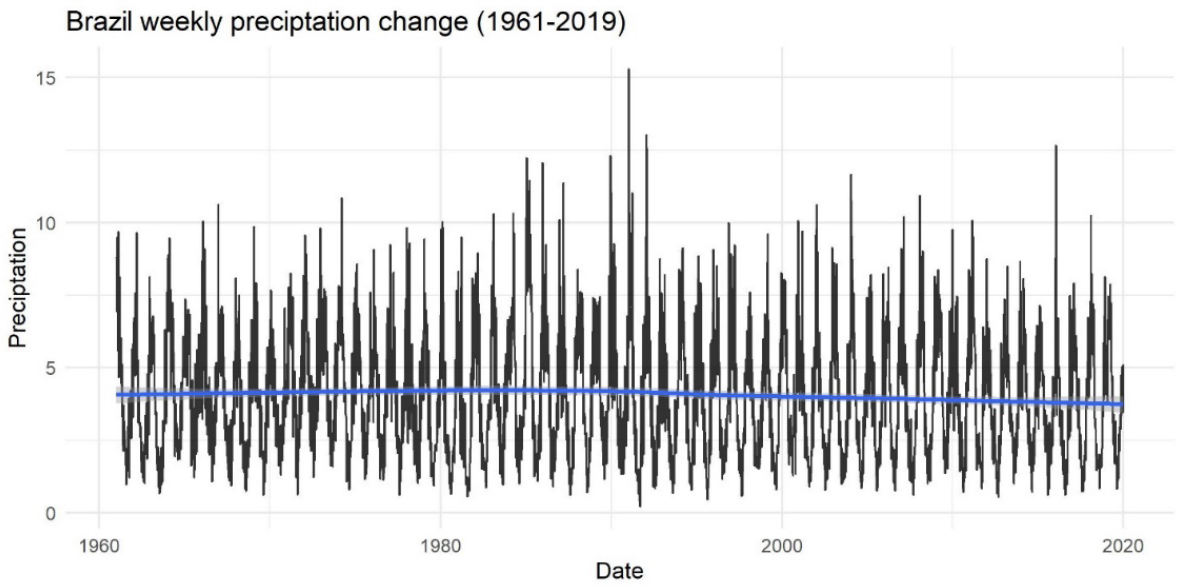
Brazil's Average Temperature Change from 1961-2019 Shows an Increase in the Average Monthly Temperature



Note. The average monthly temperature increased from 21.5°C to 24.5°C over the 58 years. Data from INMET, 2022.

Figure 2.9

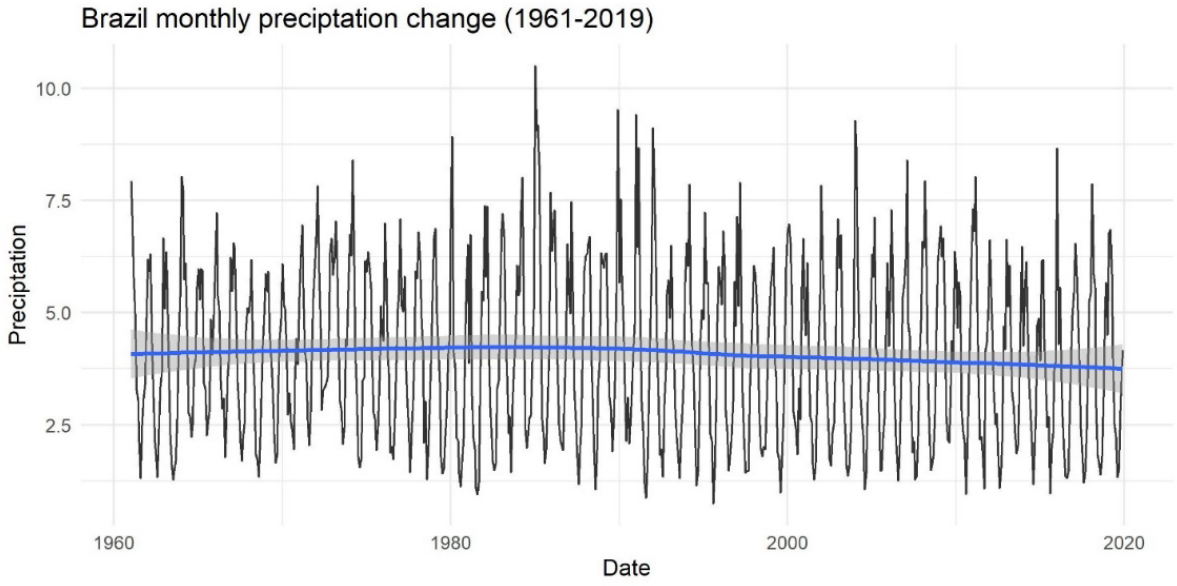
Brazil's Weekly Precipitation Change from 1961-2019 Reveals a Steady State for the Average Weekly Rainfall Amounts



Note. The average weekly rainfall remained relatively stable at around 4 mm throughout the 58-year study period. Data from INMET, 2022.

Figure 2.10

Brazil's Monthly Precipitation Change from 1961-2019 Reveals a Steady State for the Average Weekly Rainfall Amounts

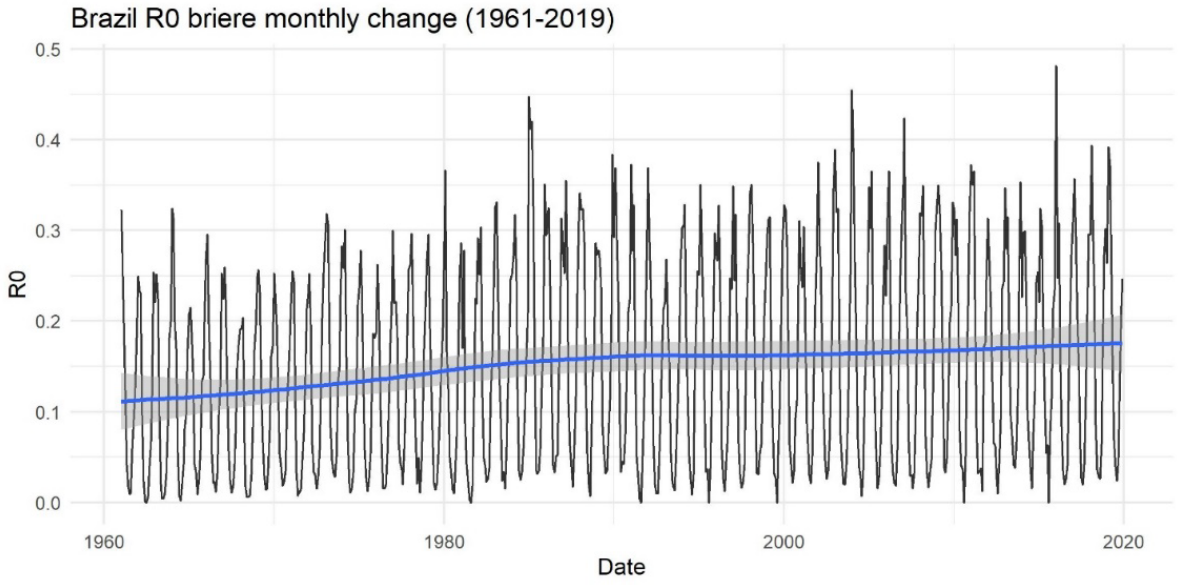


Note. The average weekly rainfall remained relatively stable at around 4 mm throughout the 58-year study period. Data from INMET, 2022.

The Brière Functional Form displays a slight increase in the R_0 over time, so as temperature increased and rainfall stayed relatively constant, the potential for outbreaks is amplified. The Quadratic Functional Form R_0 graphs show a fairly steady increase in the basic reproductive number from an average of 0.75 1 in 1961 to almost 1.5 in 2019. These results are consistent with empirical data showing an increase in dengue cases since the 1970s within Brazil (Cortes et al., 2018). The steady state of the weekly average rainfall produced sufficient breeding habitats to propagate the mosquito population. The increase in temperature led to an increase in dengue case numbers, highlighting the importance of both temperature and precipitation on the basic reproductive number.

Figure 2.11

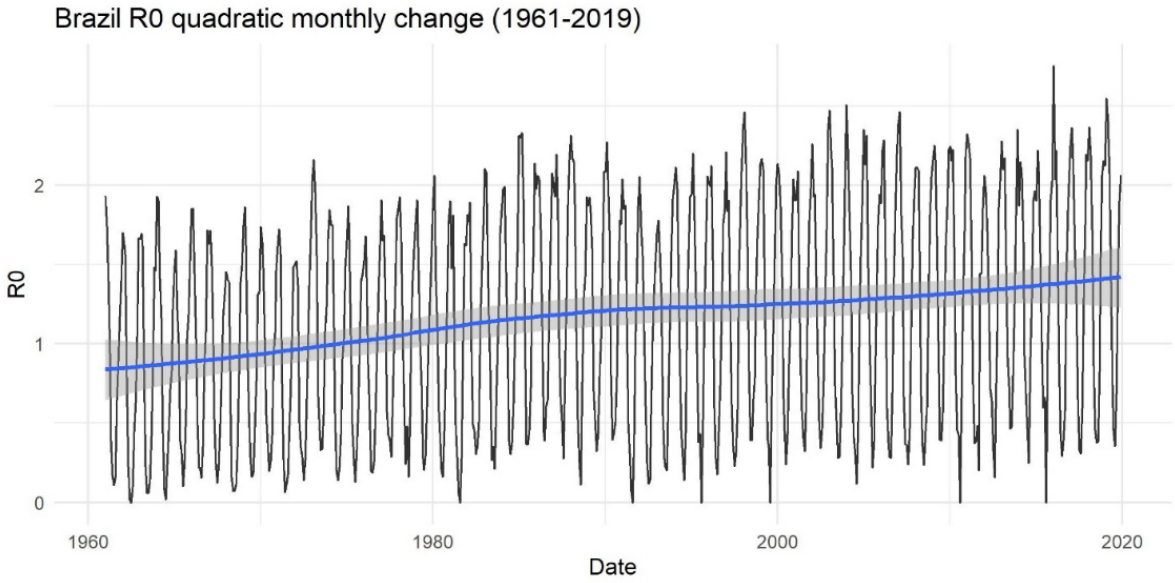
Temporal Analysis of Variations in R_0 Based on the Interaction Between Temperature and Precipitation Data from Brazil from 1961-2019 using a Brière Functional Form



Note. Data from INMET, 2022.

Figure 2.12

Temporal Analysis of Variations in R_0 Based on the Interaction Between Temperature and Precipitation Data from Brazil from 1961-2019 using a Quadratic Functional Form



Note. Data from INMET, 2022.

Discussion

A spatial-temporal relative global R_0 Dengue model was developed using climatic variables, including temperature and precipitation and their corresponding effect on mosquito metabolic, reproductive factors, and transmission dynamics, *Ae. aegypti* vector distribution and abundance, and geolocalized economic data and its interaction with human population density. The model presents a methodological framework for developing a global relative dengue outbreak risk profile and should be interpreted as thus—an indication of risk, not a predictive tool to the exact magnitude and timing of a dengue outbreak. It demonstrates the seasonality of the disease etiology by identifying areas at risk of high virus transmission throughout the various months of the year.

The R_0 model reveals an increase in the geographic spread of the risk area during summer temperatures, with the at-risk area of the map moving further from the tropical and subtropical equatorial regions into more temperate climes. Traits important for disease transmission and linked to metabolism, such as reproduction, development, survival, and biting rate, are temperature-dependent (Caldwell et al., 2021; Mordecai et al., 2017). *Aedes* are anthropophilic and their aggressiveness makes them a critical threat to humans (Caminade et al., 2017). Focusing on one geographical area—for example, Australia allows one to follow the temporal changes as the temperature and rainfall amounts vary throughout the year. Similar to a Zika risk model, the largest R_0 values on the African continent occur during the December to February rainy season, as evidenced by both the Brière and Quadratic models (Caminade et al., 2017). This comparison is especially poignant considering the similarity between the viruses and their primary vector—the *Aedes* mosquitos (Hart et al., 2017; Weger-Lucarelli et al., 2016;)

Through the application of empirical and laboratory data and high spatial resolution databases, it is clear that there is an optimal temperature and precipitation range for the genesis

and proliferation of a dengue outbreak. In this model, the effect of precipitation is most pronounced on the carrying capacity. However, there is also an undisputable link between temperature, precipitation, and human activity. The model generated is similar to other published estimates of global reach and burden of disease (Bhatt et al., 2013; Caminade et al., 2017; ECDC, 2021).

Additionally, a socioeconomic component to mosquito and human population interaction exists, including the availability of running water, air conditioning, and screens on the windows (Hallegatte et al., 2018; Nii-Trebi, 2017). *Ae. aegypti* are urban-dwelling mosquitos who prefer human hosts and enter buildings to feed and rest (Christophers, 1960). A study in Texas showed the protective factors of air conditioning and window screens on the transmission of dengue through the limitation of human-mosquito contact (Reiter et al., 2003). Thus, although it needs to be better quantified, sufficient evidence exists for an association between human-mosquito contact and economic prosperity (Perkins et al., 2016).

Climate changes that increase the duration of the mosquito breeding seasons and their geographical reach are part of a complex web of interrelated factors that affect economic prosperity (WHO, 2008). Economically distressed individuals are more vulnerable to "shocks and stressors" that adversely affect their economic situation (Hallegatte et al., 2018). Even slight variations in the distribution and burden of diseases will deteriorate the economic well-being of entire communities and profoundly affect the flow of people falling into poverty (Hallegatte et al., 2018)

Inverse Functional Form

Models were constructed using the Inverse Functional Form for precipitation and Global Relative R_0 maps were generated. However, there were practical issues with interpreting the

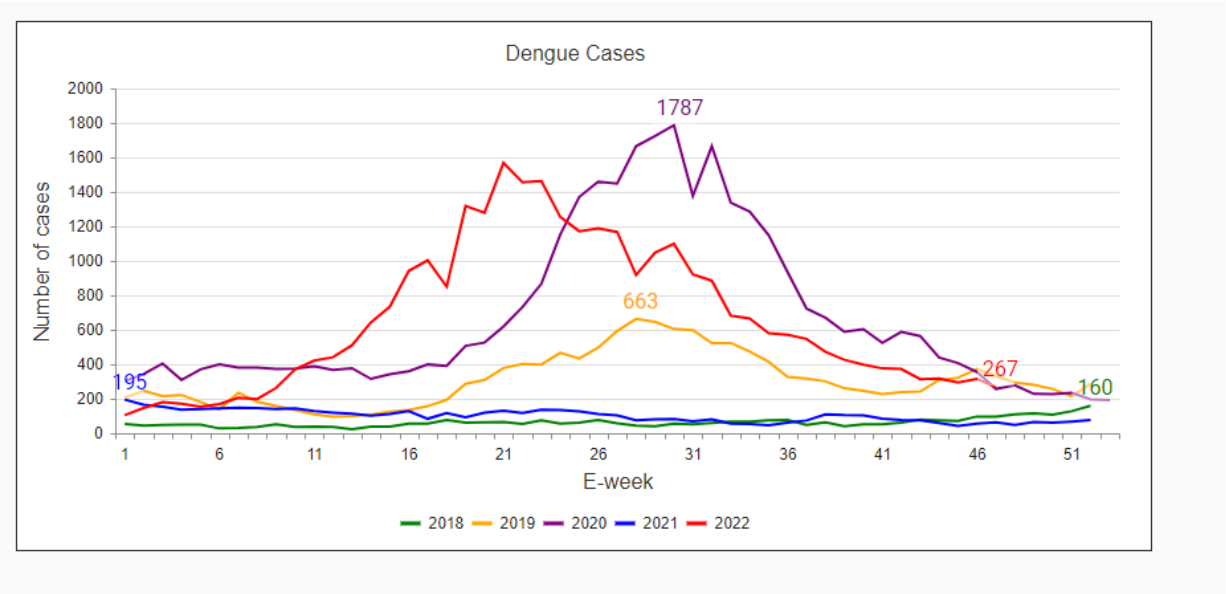
Inverse Functional Form products. Most importantly, zero rainfall would yield an R_0 value of infinity in this functional form. This signifies that no precipitation would be the ideal condition for virus transmission (i.e., no rainfall produces virus transmission); however, rainfall is a necessary part of the vector life and breeding cycle. Thus, this assertion of the model is, in fact, false, defying both entomological norms and empirical observation. For this reason, the Inverse Functional forms were not utilized in the final iteration and discussion of the Global Relative R_0 Model for Dengue.

Model Validation

Model parameters that exert the most influence on the outcome of a model are identified through sensitivity analysis (Hamby, 1994). Model validation was performed by comparing relative R_0 risk to empirical data on dengue outbreaks in Brazil and Singapore—two countries with a high number of reported cases (National Environmental Agency (NEA), 2022). The most substantial risk of a dengue outbreak occurs during April in both Sub-Saharan Africa and India. Data from the Singapore Ministry of Health and NEA show the greatest number of dengue cases from May to August, corresponding to the highest risk for dengue outbreaks in this area generated by the model (NEA, 2022) (Figure 2.13). The model is further validated by comparing Dengue surveillance data from two Brazilian cities from 2001 to 2014 to the projected Dengue R_0 values generated by the Brière and Quadratic forms of the basic reproductive number equations (Cortes et al., 2018). The highest incidence was observed from December through May and the lowest number of cases was from July through September, which correlates to the predicted values from the Brière Functional Form for precipitation (Cortes et al., 2018).

Figure 2.13

The Temporality of Dengue Cases in Singapore from 2018-2022



Note. Data compiled by the Communicable Disease Division, Ministry of Health (NEA, 2022). Figure retrieved 28 November 2022.

Limitations

There are several limitations to this form of mathematical modeling for dengue outbreaks. Only a handful of studies inform the metabolic and reproductive parameters of the mosquitos and the interaction of temperature and precipitation on these values (Caldwell et al., 2021; Caminade et al., 2017; Mordecai et al., 2017; Ngonghala et al., 2021). The projections of the model were based on average monthly temperatures and rainfall when in all actuality, there is great heterogeneity of temperature and precipitation during this time frame. Therefore, uncertainty in these estimates may underestimate the impact of environmental factors on Dengue transmission, thus miscalculating the global R_0 risk. Further development of Dengue models based on calibrations from field-based data would provide a more accurate relative R_0 determination.

Additionally, only parameters specific to *Ae. aegypti* mosquitos, the primary vector of the Dengue virus, were used in modeling computations. However, a more complete model would also include *Ae. albopictus* distribution models. These secondary vectors are likely to increase the geographical reach and distribution of the virus (Kraemer et al., 2019). This is because the predicted global distribution of the two species differs in their optimal climatic conditions with *Ae. albopictus* generally tolerating lower temperatures (Caminade et al., 2017; Mordecai et al., 2017). *Ae. aegypti* are primarily found in the tropical and subtropical equatorial regions and in northern Brazil and Southeast Asia. This species is notably absent in most of Europe and temperate areas of North America (Kraemer et al., 2019). In contrast, *Ae. albopictus's* range extends further into temperate regions, including further north in the U.S. and China, southern Europe, southern Brazil, and Japan (Brady et al., 2015; Kraemer et al., 2019; Lounibos et al., 2002; Tsuda & Takagi, 2001).

A further limitation was the use of a standard mosquito carrying capacity (Kappa) to human population density value of 20. The actual vector carrying capacity would vary with human population density and socioeconomic status. This data does not currently exist at a local level and thus would be impossible to extrapolate to our global model. An early iteration of the model was run using empirical data for several different types of aquatic habitats contributing to the carrying capacity. Analysis was performed on a temporary and constant rain-fill habitat (Perkins et al., 2016; Smith et al., 2013; Soda et al., 2018). The constant and temporary habitat functional forms were adjusted from the 1-degree by 1-degree resolution to 5-kilometer by 5-kilometer^2 units at the equator. (Soda et al., 2018; Veregin, 2022). However, this computation overestimated the R_0 values in most countries compared to literature values; therefore, the choice was made to use a standard value for these calculations (Liu et al., 2020).

One of the assumptions inherent in a basic reproductive model is that the population is fully susceptible. This is misleading as Dengue's endemicity is so widespread and large populations are affected each year. Furthermore, our model failed to evaluate the different serotypes of Dengue—each one able to infect the same individual—and ignored the immunity conferred from recovery from one strain of the virus.

Application

Mathematically derived basic reproductive number models can estimate infectious disease risk and interpret surveillance data. This Global Relative R_0 Model for Dengue synthesizes the seasonality in vector breeding and population dynamics, temperature impacts on mosquito traits, and socioeconomic factors contributing to human-mosquito contact. It can help to inform the timing and intensity of vector control and mitigation efforts. The model's environmental and socio-economic components could predict the disease transmission dynamics

and inform the relative magnitude of the outbreak. This model projects an outbreak's relative risk and magnitude but does not project a future outbreak's precise location, timing, or size.

The introduction of mosquitos into new locations through trade routes, human travel, and climate change introducing new suitable habitats can lead to novel outbreaks. These maps can pinpoint focus areas for vector surveillance and control. Rapid response protocols to limit the introduction of new species ameliorates human health risks. Recent economic downturns and the interruption of critical vector control services and surveillance infrastructure during the global COVID-19 pandemic enabled unrestrained disease proliferation.

Travel medicine professionals could use the Global Relative Risk Models to help educate and convey the potential risk of infection to travelers during specific time periods and to specific locations. The results could aid military and humanitarian aid organizations in optimally timing future exercises or training missions. Additionally, they can inform planners of needed force health protection measures, including insecticide-treated clothing, repellents, and mosquito nets. However, the model results should be interpreted cautiously, especially concerning the assumptions and limitations of the equation.

3. DENGUE—DETERMINATES OF DISEASE SEVERITY AND RISK FACTORS

Background

The first documented evidence of dengue can be traced back to the third century A.D. in China, where it was referred to as "water poison" and was thought to be related to flying insects associated with water (Gubler, 1998; Silva et al., 2020). Dengue infection is caused by a virus with the same name belonging to one of four distinct viral serologic types (serotypes): DENV-1, DENV-2, DENV-3, and DENV-4, that are phylogenetically distinct and often geographically clustered (CDC, 2021; Coffey et al., 2009; WHO, 2021). Humans can be infected by each viral serotype and become affected four times in their lifetime. Each serotype is comprised of three to five common strains (genotypes). The different viral types vary in virulence and their resulting infections can produce clinical syndromes that differ in presentation (Endy et al., 2002; Silva et al., 2020). During an outbreak, one serotype usually emerges as the predominate serotype; however, evidence suggests that many outbreaks are conglomerations of geographically localized clusters of multiple Dengue virus serotypes (Endy et al., 2002).

Research Aims and Questions

If one cannot tell which mosquitos are infectious by looking at them and if dengue infection is an emergent threat worldwide, how does one know their individual level of risk? Should concerns about dengue infection factor into one's travel decision? What factors affect the spectrum of dengue illness presentation—a continuum that ranges from subclinical to self-limiting, mild diseases to ones that require hospitalization and could ultimately cause death?

This review aims to identify the determinates of dengue and severe dengue in order to understand the risk factors for hospitalizations, manifestations of severe disease, and complications. The issue of recurrent infections with different strains of the Dengue virus and

whether the sequence of infections impacts the severity of the illness presentation are explored. Characteristics of immunity and introduction of the virus into naïve populations and its implications on the future trajectory of disease burden are studied.

Methods

A quasi-systematic effort was undertaken to comprehensively identify hotspots of dengue transmission, high-risk populations, characteristics of high-risk populations, and control measures. A literature review was conducted using the following databases: the National Institutes of Health Medical Database (PubMed), the Cochran Database of Systematic Reviews (CDSR), and the World Health Organization (WHO) library database (WHOLIS). Free text keywords using combinations of the following words: Dengue, secondary infections, seroprevalence, antibody-dependent immunity, vaccines, risk assessment, and travel were utilized. Primary papers were read, and a systematic review of citations was explored to uncover additional information sources. This iterative process was repeated until citations were exhausted.

Data were collected to summarize dengue's disease presentation and classification, immunity and immunologically naïve populations, sequence and severity of different serotypes, characteristics of frequent high-risk travelers, prevention and mitigation factors, and vaccine recommendations. Further review of risk assessments and pre-travel health assessments were conducted. This paper synthesizes contemporary academic literature to determine dengue and severe dengue risk factors.

Findings

Human Genetic Factors

The WHO definitions of dengue with or without warning signs and severe dengue were updated in 2009 to better classify and quantify the true disease burden. Classification is just one step in understanding the etiology of the disease. One of the hallmarks of the expansion of dengue over the past 40 years has been the intensity of the infections with multiple serotypes circulating at the same time or the presence of serial occurrences of dengue outbreaks in successive transmission seasons (Halstead, 1992). A 1981 outbreak in Cuba with severe dengue disease suggested that individuals of African ancestry (blacks) may possess inherent genetic resistance to the virus similar to the malaria parasite resistance (Bravo et al., 1987; Coffey et al., 2009; Halstead et al., 2001). Research indicates that determinates of disease risk are part of a complex web of interactions, including viral and immunological factors such as cytokine expression, activation and proliferation of immune cells, and human genetic factors (Coffey et al., 2009).

Several studies have shown the propensity of certain ethnic populations to develop severe manifestations of the disease, while others only have mild forms (Bravo et al., 1987; Coffey et al., 2009; Halstead, 1992). A study from Haiti showed that 85% of children aged 6-13 years living in Port-au-Prince had dengue antibodies, but there were no reported dengue cases for the youth in the city (Fink et al., 2006). However, the mainly Caucasian U.S. military personnel had 185 reported dengue cases with laboratory confirmation. This suggests that Haitian children are less susceptible to endemic dengue than Caucasian adults (Coffey et al., 2009; Fink et al., 2006). In Asia, individuals of Chinese heritage had significantly higher morbidity rates (9.0 cases per 100,000 people) compared to Malaysian (2.9 cases per 100,000) compared to individuals from

India (2.4 cases per 100,000) in retrospective outbreak studies (Shekhar & Huat, 1992a, 1992b). These studies purport that ethnicity determines infection susceptibility and suggest that human genetic factors could play a part in determining dengue disease outcomes. Blood type and a complex series of immune responses, including a variety of antigenic and histocompatibility complexes, antibody isotypes, and single nucleotide polymorphisms, are also thought to play a role in the susceptibility and severity of disease (Coffey et al., 2009; Fink et al., 2006; Kalayanarooj et al., 2007).

Sequence and Severity

Severe illness does occur in initial cases of infection—mainly if the strain is virulent, as seen in Thailand at the turn of the 21st century (Anantapreecha et al., 2005). A 2002 study from Brazil showed that high mean virus titers of DENV-3 contributed to severe illness leading to deaths in both primary and secondary cases (De Araujo et al., 2009). Dengue infection does confer immunity, but only to the infecting viral serotype. Any secondary infection with a different Dengue serotype is a risk factor for severe dengue (Cherian et al., 1994; De Carvalho Bittencourt et al., 2012; Fried et al., 2010; Guzman et al., 2010, 2013; Halstead et al., 1969, 1970; Ocasionez et al., 2006; Pancharoen et al., 2001; Porter et al., 2005; Tantracheewathorn & Tantracheewathorn, 2007; Thomas et al., 2008; Vaughn et al., 2000). Thus, though often mild and self-limiting, dengue can be a severe and even fatal disease with a preponderance of evidence showing repeated exposures with different serotypes having the highest risk for severe illness manifestations.

Nevertheless, not all infection sequences have the same risk for severe illness (WHO, 2022). Studies from Thailand suggested that secondary infection with DENV-2 was 5-7 times more likely to become severe dengue when compared to secondary DENV-1 or DENV-3 infection

(Endy et al., 2004; Vaughn et al., 2000). Furthermore, the sequence of DENV-1 followed by DENV-2 had the greatest risk of severe disease (Table 3.1) (Alvarez et al., 2006; Anantapreecha et al., 2005; De Carvalho Bittencourt et al., 2012; Graham et al., 1999; Guzman et al., 1999, 2012; Kourí et al., 1998; Ocasionez et al., 2006; Sangkawibha et al., 1984; Thomas et al., 2008). Additional studies with DENV-3 as the causative agent of a secondary infection revealed a substantial risk of severe dengue (Anantapreecha et al., 2005; Chungue et al., 1990; De Araujo et al., 2009; Gubler et al., 1979; Guzman et al., 2012).

Table 3.1

A Summary of Severe Dengue (SD) Outbreaks as a Secondary Infection (SI) with Sequencing Information

Timeline of Study	Country	Population at Risk & Study Results	Sequence of Infection	References
2001 - 2002	Cuba	Epidemic in Cuba with SD (n=78 DHF/DSS patients)	DENV-1 → DENV-3 led to the most severe infections	Alvarez et al., 2006
1997	Cuba	DENV-2 epidemic after 15-year lull in disease activity; previous epidemics in 1997 (DENV-1) & 1981 (DENV-II); all 12 decedents has SI (n=3,012 cases with 205 SD/12 fatalities)	DENV-1 → DENV-2; all fatalities were adults with SI	Guzman et al., 1999; Kourí et al., 1998
2003	Cuba	Following the 2011-2012 epidemic, a seroprevalence study of a 1% sample of residents in the Playa District of Havana (n=1758)	7.2% of pop with DENV-3; DENV-1 → DENV-3 most likely for SD	Guzman et al., 2012
1994 - 1996	Thailand	Children at two hospitals (n=168) with acute Dengue; higher viremia titer was a marker for SD	DENV-2 as SD; SI led SD	Vaughn et al., 2000
1999 - 2002	Thailand	DENV-1 & DENV-3 induced SD in 1° & 2° cases; DENV-2 & DENV-4 caused SD in 2° cases (n=2,715 patients in 6 hospitals)	All 4 serotypes; SD in 1° & 2° cases with DENV-1 → DENV-3 highest risk for SD	Anantapreecha et al., 2005
1998 - 2000	Thailand	Prospective study of 2,000 school kids (n=154 cases); All DENV produced SD, but DENV-3 produced more severe symptoms compared to other serotypes	All four serotypes; SD only as SI	Endy et al., 2004
1976	Central Java, Indonesia	Serum analyzed (n=69; 4 fatalities); DENV-1, DENV-3, & DENV-4 were all detected	DENV-3 led to SD & death	Gubler et al., 1979

Table 3.1 Continued

Timeline of Study	Country	Population at Risk & Study Results	Sequence of Infection	References
1989 - 1990	French Polynesia	DENV-3 outbreak following mild outbreaks in 1971 (DENV-2), 1975 (DENV-1), & 1979 (DENV-4) (n=213 cases of SD/7 fatalities)	DENV-1 → DENV-3; SD as a SI	Chungue et al., 1990
1995 - 1996	Indonesia	A prospective study with 22% initial dengue antibodies; 20.1% prevalence increased with the age of kids; 536 incident cases (n=1,837 4–9 year-olds);	All 4 serotypes; all SD were SI; DENV-2→ DENV-1 led to SD	Graham et al., 1999
2005 - 2006	Martinique	Adult patients at single hospital (n=146; 11 with SD; 4 fatalities)	SD as a SI; DENV-2 as SI had worse outcomes	Thomas et al., 2008
2010	Martinique	Patients over age 15 (n=44; 12 with SD) with lab samples positive for dengue at one hospital; dendritic cells count was not a predictor of SD	DENV-2 as SI most likely to cause SD	De Carvalho Bittencourt et al., 2012
2002	Brazil	Patients hospitalized with DENV-3; 52.2% of fatal cases were 1° cases (n=42 patients 23 fatalities)	SD in 1° & 2° cases; SD had higher mean virus titers; DENV-3 was particularly severe strain	De Araujo et al., 2009
1998-2004	Colombia	1998 DENV-1 predominated; DENV-3 predominated 2001-2003; wide presence of DENV-2 in 2000-2001 lead to more SD (n=1452 serum samples with 596 cases)	All 4 serotypes; Increase in 1° infection each year; DENV-2 led to more SD	Ocasionez et al., 2006

Note. 1° = primary; 2° = secondary.

Increasing global travel, expanding vector habitats, and the circulation of numerous serotypes within the same communities complicate the epidemiology of dengue and create risk for lifetime exposure to multiple viral types, thereby enhancing the likelihood of severe dengue in specific populations. The global spread of all Dengue virus serotypes has made prevention and control infinitely more problematic—due to the increase in the endemic range of the virus and the increased probability of severe infections from secondary cases. There is no single tool or methodology that will be effective in controlling the vector population alone (Gubler, 2011).

Antibody-Dependent Enhancement

For individuals who do not experience their first natural dengue infection before vaccination, the vaccines carry an increased risk of severe or hemorrhagic disease because a subsequent infection has a higher probability of severe disease. It is generally understood that a secondary infection provokes antibody-dependent enhancement (ADE) (Halstead, 1982; Libraty et al., 2009; Whitehead, 2016). ADE is an immune process wherein antibodies resulting from a prior infection's immune memory can worsen the condition instead of clearing the virus. In dengue ADE, the responding IgG antibodies recognize and bind to the virus but cannot neutralize it. These bound antibodies act as a "trojan horse," allowing the pathogen to enter monocyte cells through normal phagocytic processes or may activate other immune components that can exacerbate the immune response (Huisman et al., 2009). The infection of the monocytes is associated with an increase in virus replication and a heightened risk of severe disease (Melanson et al., 2019). Observations from studies of severe infections in children perpetuated the theory that pre-existing immunity can predispose individuals to a more serious secondary infection (Halstead, 1982). This notion of pre-existing humoral immunity as a significant risk factor in severe manifestations of the diseases was later reinforced by several studies (Burke &

Kliks, 2006; Graham et al., 1999; Huisman et al., 2009; Kliks et al., 1988; Sangkawibha et al., 1984).

Immunity and Immunologically Naïve Populations

Infection with one serotype confers lifelong immunity to that serotype and limited, transient protection against subsequent infection with any of the other serotypes (Dussart et al., 2012; WHO, 2022). A concomitance of evidence suggests that a subsequent infection with another serotype (secondary infection) increases the risk of developing a severe illness. A study of primary school children in Thailand showed that homologous immunity was long-lasting. However, cross-protective immunity was minimal within a year, leading to potential outbreaks with different genotypes (Endy et al., 2002).

The scope and duration of climatic events increase the geographical range and transmission windows of vector-borne diseases. The complex interaction of human migration patterns, poverty, vector density, and environmental conditions can lead to explosive outbreaks when the virus encounters an immunologically naïve human population. An outbreak in Greece in the late 1920s resulted in more than one million people (90% of Athens) falling ill with an unusually high occurrence of hemorrhagic fever due to sequential and almost simultaneous exposure to DENV-1 and DENV-2 (Louis, 2012; Schaffner & Mathis, 2014). Infected travelers to non-endemic areas where mosquito vectors are present can be the source case—triggering an outbreak and subsequent autochthonous transmission (Massad et al., 2018; Senda et al., 2018; Wilder-Smith, 2018).

Discussion

Dengue and severe dengue should be approached through a One Health framework. One that, per the CDC, is “a collaborative, multisectoral, and transdisciplinary approach—working at

the local, regional, national, and global levels to achieve optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment" (CDC, 2022d). One Health is a lens through which we should see the world to understand the connections and complex interactions that drive disease patterns, ecology, environment, and animal and human migrations. The severity of dengue infections depends on the interactions of a complex web of mosquito vector, environmental, human genetic, and virus serotype factors. Alterations in the agent, host, or environment will inevitably drive changes in other parts of the epidemiological triad. These changes are further complicated by the progressive evolution of viral and microbial hosts and issues of population influxes, human and vector migrations, and drug resistance (Chala & Hamde, 2021).

The determinants of dengue infection are vast and complex. An increased understanding of a particular strain in a confined geographical area or the interaction with a certain subset of populations allows better predictions about outbreak severity, duration, and disease prognosis. A second infection with a different serotype can lead to severe infections. Sometimes a particularly virulent strain can cause complications in primary infection. Many individuals may be unaware of previous exposure to a strain of Dengue due to subclinical or mild infection. Even those who are aware may not fully understand the risk of subsequent infections or fail to comply with personal protective measures.

Summary

Globalization has been the principal driver of economic systems, including a transnational flow of knowledge, people, goods, animals, and arthropod vectors (Gubler, 2011). The spread of all Dengue virus serotypes has made prevention and control infinitely more problematic. It also potentially produces more resistant and intense viruses easily spread by air

travel. There is no single tool or methodology that will be effective in controlling the vector population alone (Gubler, 2011). The presentation and severity of dengue infections depend on the strain, the presence of antibodies from a previous infection, the interval between infections, and the infection sequencing. While many primary infections are subclinical, secondary infections and those of a particularly virulent strain can lead to severe disease and even death. A better understanding of host genetic interactions and antibody-dependent enhancement might lead to breakthroughs in therapeutics and vaccines.

4. SPECIAL POPULATIONS WITH REPEATED HIGH-RISK EXPOSURES: CHARACTERISTICS AND A FRAMEWORK FOR RECOMMENDATIONS

Background

As a re-emerging tropical disease, a growing body of literature has been dedicated to the emergence of Dengue serotypes throughout the world, an increase in the vector range and seasonality, the discovery of dengue in previously unaffected populations and locations, and characteristics that place individuals at greater risk for severe dengue—the most complex and life-threatening form. However, no cohesive synthesis of the pathogenesis of the disease and its impact on specific non-traditional populations at risk of frequent and/or prolonged exposures. In this context, high-risk populations denote populations not living in dengue-endemic areas.

Dengue is often underreported, partly due to the non-specific febrile presentation, the self-limiting nature of the illness (which is often mild), and frequent subclinical infections. Further complicating reporting is that laboratory capacity and access to diagnostics are under-resourced in areas where dengue is endemic and most of the infections occur. While various control and prevention measures exist, no specific pharmaceutical agent exists to treat, cure, or prevent dengue. Treatment is supportive at most, and infection prevention relies largely on vector avoidance. Primary prevention and education are paramount to stopping the spread of the disease and risk assessments could strengthen individual compliance with personal protective measures.

Research Questions & Methods

This review identifies and characterizes special non-traditional populations with repeated and/or prolonged exposures. What makes an individual more susceptible to contact with the mosquito, exposure to the virus, and developing the disease? If specific traits, behaviors, or characteristics place individuals at greater risk, what prevention and control strategies can they

employ? Are there knowledge gaps in understanding the etiology of dengue disease and is education about risks a sufficient intervention? Why might some individuals potentially understand the risk but still be unlikely to follow prevention and mitigation guidelines?

Synthesizing the clinco-epidemiology of dengue with available prevention and mitigation measures, including the use of vaccines, allows for the development of a framework for recommendations for travelers with repeated high-risk exposures. The framework will also briefly include barriers to vaccine behaviors and recommended pre-travel threat assessment meeting items. Using the same methods outlined in Chapter 3, data were collected to determine the characteristics of frequent high-risk travelers, prevention and mitigation members, and vaccine recommendations.

Findings

Characteristics of Repeated High-Risk Exposures

Humanitarian aid workers, disaster response workers, Peace Corps volunteers, missionaries, and military service members are at a heightened risk for dengue infection due to recurrent and long-term travel. These individuals often have extended travel duration, a higher likelihood of visiting rural or remote areas, and have continued close contact with locals (McCarthy, 2001; Rowe et al., 2017). Serosurveys have produced incidence rates of 1.12 cases of Dengue per 1,000 volunteer-months in Peace Corps volunteers and a disease prevalence rate of 93% from missionaries returning from posts in Jamaica (Ferguson et al., 2016; Moncayo et al., 2015; Wilder-Smith, 2018).

Dengue has played a detrimental role in U.S. military operations since the Spanish American War, plaguing troops in the Asian and South Pacific theaters, Somalia, and Haiti leading to attack rates of up to 80% and convalescence of up to three and half weeks (Gibbons et

al., 2007). Military service members assigned to Special Operations units deployed to Africa, Southeast Asia, and South and Central America were screened for dengue with a preliminary 13.2% (55 of 414) seropositivity rate (Caci et al., 2014). A different seropositivity study of dengue among 494 U.S. military service members assigned to Puerto Rico from 1 January to 1 June 2015 revealed a 66.8% positivity rate (72.7% for members who were born or resided in a Dengue endemic country before deployment as opposed to 26.8% to those born or lived in a non-endemic country) (Pollett et al., 2022). Furthermore, 78.2% of the study sample had antibodies to more than one strain of Dengue, while the rest had only one strain—representing a primary infection (Pollett et al., 2022).

Dengue on the African continent is widely underreported, but a French military study from 2011 to 2014 in Djibouti established the circulation of DENV-3 for the first time along with DENV-1 and DENV-2 (Le Gonidec et al., 2016). The emergence of new serotypes of Dengue in the region elevates the concern for increased severity of dengue outbreaks from secondary infections (Melanson et al., 2019). Dengue impacting troops has been documented in a wide range of areas by several militaries—parallel examples of reports of dengue infections affecting militaries throughout the world can be seen in Australian troops in Papua New Guinea & East Timor, Italian troops in East Timor, and U.S. military members in Haiti, the Philippines, Somalia, and French Guiana (Bullard, 2004; Hayes et al., 1995; Kitchener et al., 2002; Meynard et al., 2008; Peragallo et al., 2003; Trayers et al., 2008; Trofa et al., 1997; Zemke et al., 2019). Dengue threatens the military mission abroad and presents a potential for ill service members to import the virus back to American communities when they return (Kitchener, 2010). Imported dengue into naïve areas is a known but *unquantifiable* threat—one that has seen international

travel implicated in autochthonous cases in France and the U.S. (Murray et al., 2013; Ruche et al., 2010; Senda et al., 2018).

International business travelers are at increased risk through repeated trips to the same location or multiple trips to various endemic areas. Since Dengue vectors are primarily urban dwellers, even business travelers are at risk of repeated exposures when work takes them to endemic areas (Chen et al., 2018). Many foreign economic hubs have populations of 15 to 20 million people. Business travel encompasses approximately 14% of all international travel, with 17% of corporate travelers from a conglomerate of forty-eight multinational corporations reporting having traveled for at least 30 days or more each year (Chen et al., 2018). The potential of dengue in this community is unknown but potentially substantial.

Travelers visiting friends and relatives (VFRs) is another category of high-risk travel. This recently coined acronym refers to immigrants from developing countries who fall ill with infectious diseases after returning home to their native lands (Bacaner et al., 2004). Travelers VFRs may also experience asymptomatic chronic infections acquired before migration (Monge-Maillo et al., 2014). A 1990 CDC study showed that 73% of typhoid infections were acquired abroad, and 77% of patients reported that their international trip was to visit family (McCarthy, 2001; Mermin et al., 1998). Another study from Spain showed that this cohort was frequently diagnosed with malaria, latent tuberculosis, chronic viral hepatitis, filariasis, intestinal parasites, and dengue (Monge-Maillo et al., 2014).

Travelers VFRs may be at higher risk for severe dengue due to previous infections during childhood (Ericsson et al., 2006). Furthermore, they are more likely to have prolonged contact with locals, may travel last minute to attend funerals or visit sick relatives, spend more time in the country and be less likely to adhere to mitigation measures due to their familiarity with the

region. Additionally, children of travelers VFR who grew up in the developed world may be at a particularly elevated risk of diseases if they lack immunity (McCarthy, 2001). A GeoSentinel Surveillance Network study showed that migrants who return to highly prevalent Dengue areas to visit friends and relatives have a higher risk of severe dengue due to previous exposure to the virus (Ericsson et al., 2006).

These special populations' characteristics and travel patterns place them at high risk for infection acquisition. For each of these populations, the sequence of infection and the potentially high seroprevalence of past dengue infections increase the probability of severe disease. Special considerations should be given to preventing and mitigating dengue infections for them.

Prevention and Mitigation Measures

Frequent, high-risk travelers have unique travel patterns and geographic locations, which make them ideal candidates for pre-travel medical appointments. These appointments should focus on risk identification, mitigation, and pre-travel interventions including the potential administration of vaccines. A large-scale study of British volunteers returned from overseas assignments concluded that pre-travel educational appointments should focus on the prevention of diarrhea, personal security, communicable diseases, and accidents through easily implemented advice (no ice, use separate cutting boards for meat and vegetables, and hand hygiene) (Bhatta et al., 2009).

Currently, no specific chemoprophylaxis prevents infection with dengue or therapeutics to treat the infection once contracted. In general, a pre-exposure prophylaxis medication taken by travelers does not stop the individual from getting bitten by the mosquito vectors and acquiring the infection. However, theoretically, the drug would block the virus from replicating, thereby preventing clinical disease (Institute of Medicine, 2002; Schwartz, 2012). This is a promising

future solution for high-risk travelers. Without this innovation, primary prevention of mosquito bites and elimination of habitats is the best control measure.

Larva source reduction and targeted treatment of mosquito breeding habitats are essential steps in the multiprong approach needed for mitigation and control. The mosquito population thrives in densely populated areas that lack reliable access to water supplies, waste management, and sanitation (Honorio et al., 2009). Eliminating mosquito egg breeding sites--flipping over any trash or debris where water has collected and covering and cleaning items used for rainwater collection are simple but effective steps (European CDC, 2021). Using mosquito nets, windows with screens, and removing standing water from the immediate vicinity of the living quarters would also be very effective.

After eliminating the breeding sites, reducing contact (mosquito bites) between mosquitos and human hosts is the next best prevention layer (Debboun & Strickman, 2013; Lasluisa et al., 2019). This is part of the U.S. military's six-component approach to travel or deployment medicine which reiterates preparation, education, personal protective measures, vaccines and chemoprophylaxis, and surveillance to prevent infectious diseases (Murray & Horvath, 2007). Activities that alleviate the risk of vector-borne disease infection include proper clothing—sleeves down, pants tucked into boots, undershirts tucked into pants, use of mosquito repellants, and bed nets impregnated with insecticides. Goodyer et al. (2010) provided an expert review of effective arthropod bite avoidance techniques, concluding that the most substantial evidence exists for using insecticide-treated mosquito nets and insecticide-treated clothing as a valuable adjunct to repellant applied to the skin (Table 4.1).

Table 4.1

A Summary of Evidence for Topically Applied Repellents

Type & Location of Topically Applied Repellent	Strength of Evidence	Quality of Evidence	Notes
DEET (N, N-diethyl-meta-toluamide)			
Dermal application for mosquito avoidance	Good evidence to support its use	Evidence from 1 or more randomized control trial(s)	Reapplication times vary by individual mosquito species; Effective broad-spectrum repellent
Application of DEET to wristbands	Good evidence to support the recommendation AGAINST its use	Evidence from 1 or more randomized control trial(s)	Wristbands provide no protection for uncovered or untreated skin
Icaridin/Picaridin Sec-butyl-2-(2-hydroxyethyl) piperidine-1-carboxylate			
Dermal application for mosquito avoidance	Moderate evidence to support its use	Evidence from 1 or more randomized control trial(s)	Provides good protection against *Anopheles* species
IR3535 ethyl butylacetylaminopropionate			
Dermal application for the avoidance of mosquitos	Moderate evidence to support its use	Evidence from 1 or more well-designed clinical trial(s) without randomization, case-control analysis of cohort study	Results are based on five limited field studies. As effective as DEET with *Aedes* species

Table 4.1 Continued

Type & Location of Topically Applied Repellent	Strength of Evidence	Quality of Evidence	Notes
PMD—Lemon Eucalyptus (Corymbia citriodora) Extract *p*-methane 3, 8-diol			
Dermal application for mosquito avoidance	Good evidence to support its use	Evidence from 1 or more randomized control trial(s)	Highly recommended alternative to DEET at concentrations >20%
Citronella (*Cymbopogon* grasses extract)	Poor evidence to support its use	Lower quality: Consensus evidence, evidence from one authority or report from expert communities, single case studies	Not recommended for use when engaging in vigorous activities or in areas of high mosquito density; Repellent only effective <2 hours
Neem Oil (Fruit and Seed Extract) Azadirachta indica	Moderate evidence to support a recommendation AGAINST its use	Lower quality: Consensus evidence, evidence from one authority or report from expert communities, single case studies	More studies must be conducted; It can cause dermatitis and long-term exposure can impair fertility
Essential Oils (Mixtures containing thyme oil, geraniol, peppermint oil, cedar oil, patchouli, and clove)	Moderate evidence to support a recommendation AGAINST its use	Lower quality: Consensus evidence, evidence from one authority or report from expert communities, single case studies	Variable formulations affect the efficacy

Note. Table adapted from Goodyer et al., 2010.

Dengue Vaccines

In 2015, after more than a half-century of research, a tetravalent live attenuated yellow fever chimeric dengue vaccine was licensed (Halstead, 2016). The WHO approved Dengvaxia® for at-risk individuals aged 9-45 years who live in endemic areas and have had at least one laboratory-confirmed dengue virus infection (WHO, 2021). Several other dengue vaccines are in clinical trials (Osorio et al., 2016; Whitehead, 2016). In December 2022, the European Commission approved the Japanese-developed Qdenga® (TAK-003), a vaccine to prevent dengue disease in individuals over four years of age (Takeda, 2022). In a series of trials, the vaccine was shown to be 80.2% effective in preventing symptomatic dengue cases in the 12 months following inoculation and preventing 90.4% of hospitalizations 18 months after vaccination (Biswal et al., 2019, 2020; Rivera et al., 2021; Takeda, 2022).

However, the Dengvaxia® vaccine carries an increased risk of severe or hemorrhagic infection in those individuals who experience their first natural infection with dengue after vaccination (Halstead, 2016). The FDA has only approved the vaccine for individuals aged 9-16 in the U.S. who live in endemic areas (2020). In 2015, the Department of Defense and Glaxo Smith Kline performed a Phase II clinical trial for a dengue vaccine in Thailand; however, when a durable immune response was not detected, the program ended (Institute of Medicine, 2002; Rothman & Ennis, 1999; Watanaveeradej et al., 2016).

The threat of travel-acquired dengue necessitates a tested and proven vaccine to prevent severe cases and the disease's introduction into previously unaffected areas. The cocirculation of multiple strains of Dengue in the same area or travelers' propensity to have repeated exposures leading to secondary infections all indicate why a vaccine could be an effective tool in the fight against dengue. Lim et al. (2016) provided an overview of what a dengue vaccine might look like

for travelers or individuals with repeated exposures compared to dengue vaccines for an endemic population (Table 4.2).

For example, the CDC has approved Dengvaxia® for children (the most vulnerable population) in endemic areas. Nonetheless, travelers of all ages are likely to be immunologically naïve. Furthermore, international travelers, particularly those whose careers or interests lead to frequent and/or prolonged high-risk exposures, are more likely to be adults than children (Wilder-Smith & Deen, 2008). Since repeated exposures are more likely to cause a severe dengue infection, this particular category of travelers who have already been afflicted with a primary infection might greatly benefit from a vaccine.

Due to an increased risk of severe disease in immunologically naïve individuals, a pre-vaccination examination with highly specific screening tests is recommended (WHO, 2018). Screening can be performed through conventional serological testing for IgG antibodies. If an individual were to have evidence of a previous infection, then vaccination is an option for seropositive individuals traveling to a highly endemic area (Wilder-Smith, 2018). The recommendation of vaccination is coupled with the lack of highly effective prevention measures and the low compliance with current strategies (coils, repellents, and insecticide-impregnated clothing) amidst an increasingly high incidence of dengue infection (Wilder-Smith, 2018).

Table 4.2

Characteristics of Dengue Vaccines for Travelers

Dengue Vaccine Characteristics and Implications	
Vaccine indication	• All ages • Immunological naïve travelers • Length of travel: short-term travelers vs. those with frequent and/or prolonged high-risk exposures • Differing disease risk levels and duration of exposure during travel • Endemicity of virus in the travel location • Type of housing or activities that increase the risk of mosquito bites
Efficacy	• High efficacy (due to potentially short travel duration) • Protection against both mild and severe disease, as both will impact travel plans and purpose • Protection against infection to limit transmission as ill travelers would not return home bearing the virus as a "souvenir"
Time to Protection	• Rapid onset of protection as many times travelers make rapid plans (potentially traveling for funerals or sick family members) or make travel appointments/receive vaccines until immediately preceding departure
Duration of Protection	• Protection for the duration of the entire travel period (at a minimum) • Longer duration of protection for repeat travelers and expatriates due to length of stay in endemic or hyperendemic areas
Doses and Schedule	• Single dose or few numbers of doses with a compressed schedule (Full course should ideally not take months or years); Increases the likelihood of compliance • Possible boosters before travel events • Ability to co-administration the immunization with another vaccine without adverse effects • Fewer doses may result in less total cost in visits and vaccine prices
Safety, precautions, and contraindications	• Low risk of complications from vaccination • Potential use in special populations (immunocompromised and pregnant individuals)

Note. Chart derived from Lim et al., 2016.

Knowledge and Perception of Risk

Intrapersonal beliefs about the severity of the illness, the perceived threat, and the likelihood of being affected by dengue are important behavioral indicators. Despite acknowledging that many travelers are inherently at a higher risk for developing dengue infections, researchers have shown that this risk is underestimated (Allwinn et al., 2008). The self-limiting nature of the illness and lack of access to laboratories while traveling are just a few of the multifactorial reasons for underreporting dengue infections. Additionally, although travelers like aid workers and the military with frequent high-risk exposures had a greater knowledge of vector-borne diseases and mitigation strategies as compared to international vacationers—compliance with control measures was often low (Bacaner et al., 2004; Bhatta et al., 2009; Cobelens et al., 2002; Dahlgren et al., 2009; Goesch et al., 2010; Moore et al., 1995; O'Leary et al., 2002; Rowe et al., 2017; Visser & Edwards, 2013; Wilder-Smith, 2018).

A large-scale study of Chinese international travelers revealed a need for knowledge about vector-borne disease threats and an absence of mosquito repellants or insecticides (Zhang et al., 2011). Another multi-site survey of travelers at departure gates at airports in Europe, Asia, South Africa, and the U.S. revealed that almost one in four travelers visiting a high-risk area for vector-borne disease had an inaccurate perception of the true risk of illness (Van Herck et al., 2004). There must be a balance between personal protective measures and the unique demands of traveling based on travel purpose and duration—the needs and attitudes of the business traveler may differ from those of the Peace Corps volunteer and disaster relief worker. Tailored personal prevention methods and risk communication are crucial to prevention. Knowledge about the risk is essential, but either forgetfulness, competing interests, or side effects of medications can inhibit compliance with preventive measures (Laver et al., 2001).

Pre-Travel Health Assessments

A pre-travel health consultation is "intended to educate, motivate, and equip travelers to respond to the health risks posed by their trips" (Noble et al., 2012). Ideally, this consultation takes place in a travel medicine clinic with trained providers and sufficient lead time to administer the full course of any vaccination or pre-exposure prophylaxis. The CDC has an extensive list of resources and advice, breaking recommendations down into reasons for travel, travelers with special considerations (including chronic illnesses, last-minute travelers, and pregnant travelers, among others), and general tips (CDC, 2022b). Their Yellow Book is a biannual publication for health professionals to guide travel medicine consultations with current guidelines, pretravel vaccine recommendations, destination-specific health threats, FDA-approved drugs, and recommendations for treating infectious diseases in the face of increasing antimicrobial resistance (CDC, 2022c).

While there are a myriad of options, a minimum set of issues should be discussed at the appointment consultation (Table 4.3). Ideally, the pre-travel health assessment starts with a questionnaire to understand the unique needs and circumstances of the pending trip. A provider should review the relevant medical history and current medications to discuss the trip's risks (Noble et al., 2012). This questionnaire can be paired with a knowledgeable travel health professional and access to computerized travel health databases and published literature (Leggat, 2006). To be the most effective, risk information must be presented in an "understandable, unbiased, tailored to their individual situation, and compares the benefits and risks of potential courses of action" (Noble et al., 2012). Risk levels for specific illnesses and the degree of confidence with that assessment should be conveyed during the travel threat assessment.

Additionally, travelers should be provided with post-trip instructions, including signs and symptoms to be aware of and the importance of sharing recent travel history if seeking medical care.

Table 4.3

Key Components of Pre-Travel Health Consultations

Component	Key Aspects
Health Background	
Past Medical History	• Age • Gender • Underlying health conditions • Blood disorders that are contraindications to certain prophylaxis (i.e., no Primaquine if G6PD deficient) • Allergies (especially any pertaining to vaccines, eggs, or latex) • Medications (use and ability to maintain a sufficient supply for the duration of the travel)
Immunization History	• Routine vaccines • Travel vaccines • Need for boosters • Titers needed and sufficient time for laboratory completion
Prior Travel History	• Experience with malaria chemoprophylaxis (need to continue malaria treatment after return) • Experience with altitude • Illnesses related to prior travels
Special Conditions	• Pregnancy (including trimester) • Breastfeeding • Disability or handicap • Immunocompromising conditions or medications • Older age • Psychiatric condition • Seizure disorder • Recent surgery • Recent cardiopulmonary or cerebrovascular event • History of Guillain-Barré syndrome • Severe allergies

Table 4.3 Continued

Component	Key aspects
Trip Details	
Itinerary	• Countries and specific regions, including order of countries if >1 country • Rural or urban • Lodging Accommodation Type
Timing	• Trip duration • Season of travel • Time to departure
Reasons for travel	• Tourism/Adventure • Business • Visiting friends and relatives • Volunteer, missionary, or aid work • Research or education • Pilgrimage • Seeking health care (medical tourism)
Special Activities	• Disaster relief • Medical care (providing or receiving) • High altitude • Diving • Cruise ships • Rafting or other water exposure • Cycling • Extreme sports • Spelunking • Anticipated interactions with animals • Anticipated sexual encounters
Risk Assessment	• Establish the probability of an adverse event based on epidemiological evidence • Stratify the risks (common; treatable/avoidable; fatal) • Select Interventions -- Evidence-based & effective -- Compare benefits and risks of adverse events and intervention • Administer the intervention(s) and recommendation(s)
Post Travel Guidance	• Contact your health provider if you become ill • Provide your vaccination and travel history • Report any injuries, close contact with animals, or bug bites • Relay any pertinent travel activities or encounters

Note. Table adapted from CDC Yellow Book (2022b)& Noble et al., 2012

A pre-travel health consultation to an endemic or hyperendemic dengue area should include information on the current risk of the disease, advice on preventing primary contact with the vector (proper wear of long sleeves and pants, repellants, and insecticide-impregnated clothing), and characteristics of the mosquitos—dengue mosquitos *(Aedes)* are day biters and urban dwellers. Additionally, simple steps for habitat modification, including cleaning out water storage containers, dumping over containers that contain standing water, and removing garbage and debris from your immediate vicinity, should be explained.

The U.S. military employs a multilayered approach to pre-deployment health assessments. Standardized guidance is provided on the following topics: food and waterborne diseases, including diarrhea and Hepatitis A; environmental threats, including heat and cold, altitude, and pollution; animal, plant, and water, including conditions such as Rabies or Schistosomiasis as appropriate; person-to-person illnesses including Ebola, Influenza, etc.; psychological stressors; and common injuries. In the Air Force, these threat briefings are performed by the installation Public Health Flight as part of a comprehensive pre-deployment health and readiness evaluation. The current military deployment health system is evidence-based. It has successfully decreased the ratio of disease-associated to battle-associated deaths in the US military, from 10:1 during the Spanish-American War to 1:1 in World War I, to 0.14:1 in the Vietnam War, and to <0.01:1 in the Persian Gulf War (Murray & Horvath, 2007; Smallman-Raynor & Cliff, 2004).

Barriers to Compliance

Dengue's prevalence is increasing—it is the world's most rapidly advancing vector-borne infection (Mulligan et al., 2015). The rapid spread is attributed to various factors, including the ease of modern air travel, the link between infectious diseases and poverty, human encroachment

due to mining, forestry, and agriculture, and climate change. The mere understanding of a disease risk does not equate to adherence to mitigation measures for various reasons. An Australian study cited cost as a prohibitive factor for pre-travel medication and vaccinations, especially among younger travelers. An aversion to needles and a lack of perceived benefit were also mentioned (Rowe et al., 2017). Furthermore, discussions about sensitive topics, including sexual activity and food and water precautions, could be difficult due to cultural barriers or stigmas.

Although vaccines are cost-effective and have saved countless lives, they are often maligned and surrounded by controversy, with growing evidence of vaccine delays or refusals (De Figueiredo et al., 2020; Salmon & Dudley, 2020). The WHO listed vaccine hesitancy as one of the "Ten threats to global health in 2019" (WHO, 2019b). Therefore, the 5C's of vaccine hesitancy: complacency (low knowledge/awareness concerning the severity and risk of vaccine-preventable illness), a lack of confidence (in vaccines and trust in the health system potentially due to belief in misinformation), constraints (any number of real or perceived psychological, financial or structural barriers), calculation (the extent to which individuals engage and search for information about vaccines) and collective responsibility (a willingness to protect others/social benefit) must be countered with risk communication and effective vaccination campaigns (Betsch et al., 2018).

Reñosa et al. (2021) employed the Theory of Planned Behavior to evaluate vaccine hesitancy, develop a framework that seeks to increase individual caretakers' intention to vaccinate, and empathetically listen to caretakers' attitudes and norms and perceived behavior controls. This framework could be employed to educate travelers about the risks and benefits of dengue vaccines. Vaccines would ensure the health and safety of the individual traveler and the

long-term security of their home communities by preventing the introduction of the virus into previously unaffected areas.

Summary

The global spread of all Dengue virus serotypes has made prevention and control infinitely more problematic. There is no single tool or methodology that will be effective in controlling the vector population alone (Gubler, 2011). The presentation and severity of dengue infections depend on the strain, the presence of antibodies from a previous infection, the interval between infections, and the infection sequencing. While many primary infections are subclinical, secondary infections and those of a particularly virulent strain can lead to severe disease and even death.

Characteristics inherent to travelers with repeated high-risk exposures lead them to more severe illness manifestations. A comprehensive, One Health approach should be employed to fight the spread of dengue infections. Disease control and prevention must employ a holistic approach utilizing best practices and methodologies that target every level of the socioecological framework into well-structured, strategically resourced plans (McLeroy et al., 1988). While vector control, habitat modifications, biological controls, and regulations significantly impact disease spread, individual travelers have limited control over these macro-level solutions.

Therefore, one of the best prevention methods is a tailored pre-travel health assessment covering a myriad of topics, including illness risk, primary prevention of vector contact, and health history as described in the developed framework. After establishing previous infection through a serum study, administering vaccines for travelers to endemic and hyperendemic areas should be considered. Travel health providers must be aware of barriers to mitigation strategies,

including noncompliance, inaccurate risk perception, and vaccine hesitancy. Dengue is a real and present threat whose reach will expand with travel, trade, and the expansion of the habitable range of the vector.

5. DENGUE VACCINE IMPLEMENTATION PROGRAM—A COST-BENEFIT ANALYSIS

Background

Various types of economic evaluations exist, and the overall goal of the analysis determines which tool or method to use. Many economists evaluate situations based on both inputs and outputs of the system—collectively referred to as *costs*—what must be given up and *consequences*—the overall benefits expected to be received (Burnham et al., 1998; Drummond et al., 2015). Cost is not a concern for efficacy evaluations, whereas a straight cost analysis does not consider outcomes. The best tools for the simultaneous measurement of multiple outcomes are cost-benefit and cost-utility analysis. The output of a cost-utility analysis is quality of life, whereas the result of a cost-benefit analysis is often measured monetarily (Burnham et al., 1998).

Peace Corps Volunteer Characteristics

Several concomitant issues allow for an interesting analysis of the utility of a vaccine for individuals with frequent and/or prolonged exposures. This will be explored by examining a group of Peace Corps volunteers (PCV) in high-risk dengue areas. PCVs are one subset of travelers with repeated or long-term exposures. Volunteers must be at least 18 years of age and typically spend three months in training within their host country before being assigned to a community to serve a 24-month commitment working on a defined development project (Peace Corps, 2023). Besides the length of service, additional risk factors include living with host families, engagement in direct contact with local populations, participating in outdoor work, being assigned to rural areas with limited infrastructure and minimal vector control, and living in housing similar to those of their community members—ones that often lack air conditioning, screened windows, and access to indoor running water (Ferguson et al., 2016; Sánchez-González et al., 2021).

Historical Precedence

A study of PCVs from 2000-2014 identified 1,448 cases of dengue from 49 of the 91 countries where the organization was active (Table 5.1). The Peace Corps Epidemiological Surveillance System defined a case as having a clinically apparent infection with laboratory confirmation by a positive NS1 antigen test, the presence of IgM antibodies, or a four-fold increase in IgG antibodies during the 14-year analysis period. The average incidence rate was 1.12 cases per 1,000 volunteer months, with a peak of 1.71 cases per 1,000 volunteer-months in 2007—this analysis included volunteers living in endemic and non-endemic dengue areas (Ferguson et al., 2016). Dengue cases were reported from all seven Peace Corps regions throughout the world, with the highest rate of dengue coming from Timor-Leste (11.32 cases per 1,000 volunteer-months), Cambodia (10.39 cases per 1,000 volunteer-months), and the Dominican Republic (9.86 cases per 1,000 volunteer-months) (Ferguson et al., 2016).

Table 5.1

The Global Incidence Rate of Dengue per 1,000 Peace Corps Volunteer-Months by Region from 2000-2014

Region	Total Volunteer-Months	Cases Meeting the Dengue Case Definition	Rate per 1,000 Volunteer-Months (95% CI)
Africa	529,546	62	0.12 (0.09-0.15)
Central America	179,766	458	2.55 (2.32-2.79)
Caribbean	67,846	374	5.51 (4.97-6.10)
Europe & Central Asia	260,964	7	0.03 (0.01-0.06)
East & South Asia	85,665	286	3.34 (2.96-3.75)
Pacific Islands	51,826	119	2.30 (1.90-2.75)
South America	122,832	142	1.16 (0.97-1.36)
Overall Total	1,298,445	1448	1.12 (1.06-1.17)

Note. Adapted from Ferguson et al., 2016. CI = Confidence Interval.

The official Peace Corps policy is that mosquito-borne illnesses are a risk in tropical areas and they supply malaria prevention medication which is mandatory for volunteers. Furthermore, for vector-borne diseases that do not have vaccines or chemoprophylaxis, they recommend "consistently applying mosquito repellant, wearing protective clothing regularly treated with insecticide (permethrin), and sleeping under an insecticide-treated bed net" (Peace Corps Medical Care, 2022).

Dengue Vaccine Considerations

The recent approval of Dengvaxia® by the WHO and CDC and Qdenga® (TAK-003) by Indonesia and the European Commission adds a new tool to the arsenal (Takeda, 2022; WHO, 2021). This is coupled with the knowledge that the geographic spread of the virus is increasing, that secondary infections are a risk factor for severe disease, and that the circulation of all four serotypes to almost every tropical and subtropical region of the world increases the likelihood of serial infections. (Endy et al., 2002; Guzman et al., 2013; WHO, 2022). The biggest issue would be that the dengue vaccine is only approved in the U.S. for individuals aged 9-16 who live in endemic areas (CDC, 2021). The CDC website explicitly states that the FDA has not approved the dengue vaccine for use in travelers (CDC, 2021).

Potential Courses of Action

However, to perform the cost-benefit analysis, one will assume that a specific policy exception was granted for Peace Corps members stationed in areas of high dengue endemicity. Potential courses of action for review by this cost-benefit analysis include: (1) do nothing—keep the status quo and perform no additional testing or vaccinations (2) perform serological testing on all PCVs going to an endemic area but not offer vaccinations (3) perform serological testing on all PCVs going to an endemic area and mandate vaccination for those who have evidence of

previous infection (4) offer a sensitive medical screening questionnaire to all PCVs going to a high-risk area and only perform serological testing on those with potential evidence of previous infection (5) perform serological testing on all at-risk PCVs and offer voluntary vaccinations (6) complete the serological testing on all at-risk PCVs and require vaccination for any individual with evidence of previous infection (Table 5.2).

Table 5.2

Potential Course of Action Explored in the Vaccine Implementation Cost-Benefit Analysis

Course of Action	Implementation Characteristics
1	Do nothing new—perform no additional testing or vaccinations
2	Serologic testing on all PCVs going to endemic areas
3	Serologic testing on all PCVs going to endemic areas & mandate vaccinations
4	Health survey screener, serologic testing on those identified as having evidence of prior infection
5	Serologic screening on identified at-risk PCVs & offer voluntary vaccines
6	Serologic screening on identified at-risk PCVs & mandate vaccines

Another commonly employed option in inoculation cost-benefit analysis is to vaccinate all eligible volunteers irrespective of previous disease history. However, several studies have shown an enhanced risk of severe dengue infection in immunologically naive individuals (Biswal et al., 2020; Branswell, 2019; Coudeville et al., 2020; Halstead, 2016; Huisman et al., 2009; WHO, 2021;). Thus, in this instance, mass inoculation would neither be medically indicated nor ethically justifiable. For these reasons, this COA was not included in the cost-benefit analysis.

Methods

Denominator Determination

The full operational capacity of Peace Corps worldwide is 7,000 volunteers (Peace Corps, 2022). Based on the known distribution of the Dengue virus and the location of nations that host volunteers, approximately 87% of the assignments are in endemic areas (Peace Corps, 2022). Only approximately 13% of volunteers serving in Eastern Europe & Central Asia live in regions with habitats unsuitable to vector survivability (Peace Corps, 2022). Therefore, the analysis will work off the assumption that there are 6,090 volunteer positions in areas at risk for Dengue virus exposure.

Costs for Dengue Screening and Vaccinations

Travel medicine clinics provide risk education and individual recommendations based on health history, laboratory work, and vaccinations. Peace Corps reimburses volunteers for pre-travel clearance and screenings. Therefore, medical practices and clinics offering travel medicine consultation services were reviewed to determine potential costs for implementing a screening and vaccination program—these costs are defined in Table 5.3. An office visit, the laboratory fee for the antibody exam, and a venipuncture fee would be required for the screenings for prior infection (Travel and Immunization Clinic City of Portland, 2023). Dengvaxia® was the vaccine

used for this analysis. The vaccine is available from the CDC at a retail price of $100.98 per dose, and a full course consists of three doses (performed at six-month intervals—0, 6, and 12 months) (CDC, 2023). The health survey screening was added as an additional itemized cost of $65 (Kelsey-Seybold Clinic, 2023).

Table 5.3

The Estimated Individual Cost for Dengue Screening and Vaccinations

Office Visit[1]	Screening Test for Dengue Antibodies	Blood draw Fee[1]	Return Office Visit[1]	Vaccine Administration Fee[1]	Vaccination Cost[2]	Admin cost—Health Survey[3]
$100	$176	$22.78	$50 x 3 doses = $150	$20.00 x 3 doses = $60	$100.98 x 3 doses = $302.94	$65
Summary Costs for the Different Strategies						
Total Visit & Lab fees = $298.78			Total Vaccine cost= $512.94			Total Visit & Health Survey =$165

Note. 1. Travel and Immunization Clinic City of Portland, 2023; 2. CDC Dengvaxia, 2023; 3. Kelsey-Seybold Clinic, 2023

Health Survey Screenings

The analysis will be simplified by assuming that the health survey is very sensitive in identifying people who meet the criteria of potential prior exposure to dengue. An individual with a documented medical history of previous infection with dengue would be identified by the health survey for confirmatory screening. Survey questions would include having lived in or having prior visits to tropical and subtropical areas where mosquito bites were observed on the individual and having traveled to tropical and subtropical areas and experienced mild flu-like symptoms consistent with dengue infection. The first question reveals a plausible link between the location, mosquito vector, and potential for subclinical or asymptomatic illness. The second question connects mild dengue symptoms after travel to potential risk areas.

Wright and Pritt (2012) identified dengue as the most common cause of febrile illness in travelers. PCVs are 59% female and 93% have a bachelor's degree. Many have previous international volunteer experience, participated in an international student exchange program, and have worked or traveled abroad (Peace Corps, 2023). Therefore, analysis was concluded at 15% and 50% levels for people who completed the health survey and were identified as recommended for laboratory screening.

Seroprevalence Determination

Dengue seroprevalence studies for healthy Americans living in non-endemic areas are non-existent. The relative youth of the Peace Corps population combined with the extensive travel and international experience of volunteers was combined to estimate a 1% seropositivity level. Seroprevalence rates from endemic areas are as high as 76.6% in a cohort of 1,200 participants in the State of Morales, Mexico (Amaya-Larios et al., 2014). A study among U.S. military troops in Puerto Rico revealed a 6.8% positivity rate (Pollett et al., 2022). Therefore,

there is potential for healthy young adults to have experienced a previous infection with Dengue is not zero, and the 1% estimate is reasonable.

Voluntary Vaccine Rates

Recently, a stated-preference survey instrument detected a 94% compliance rate for getting a zero-cost tick-borne-encephalitis vaccine among respondents traveling to a location with the highest risk level for exposure (Poulos et al., 2022). In the study, 6% of people stated they would not receive the vaccine at any risk level (Poulos et al., 2022). This study, along with one from Malaysia showing high acceptance of a dengue vaccine by scientists and the public, was combined to fix the 94% voluntary vaccine parameter used in the calculation (Arham et al., 2022).

Dengue Detection and Treatment Costs

Hospitalization rates for dengue depend highly on the Dengue strain and the individual's health. Several studies have placed the mean hospital stay at 4.88 ± 2.74 days and 4.9 days (Mallhi et al., 2017; Prattay et al., 2022). For this study, we used the 4.88-day average from the Mallhi et al. (2017) study to determine the cost of a hospitalized case of severe dengue in international locations and the U.S.

Per the Agency for Healthcare Research and Quality (AHRQ), an average hospital stay costs $11,700 per day in 2016 (Freeman & Heslin, 2018). For comparison, in a large multispecialty southern hospital, a one-day dengue admission in 2020 cost $14,228.37 and a 2019 three-day inpatient stay was $23,394 (Marie C., personal communication). Thus, the actual cost of a hospitalized case of dengue can vary greatly. Nonetheless, we used the average rate for the AHRQ for calculations to determine the prices to account for the varying severity of illness and, therefore, the corresponding level and cost of care.

A study from Puerto Rico set the cost of an ambulatory case—one that only requires an office visit, laboratory work, and therapeutic medication at $315 ($252 -$378) and the cost of a hospitalized case at $2,132 ($1,705-$2,558) (España et al., 2021). These figures are a good proxy for clinical costs throughout much of the developing world where the Peace Corps has volunteer posts and thus were used in all local cost evaluations. In Tables 5.6-5.9, the cost of an ambulatory case and a hospital stay for cases of severe disease is combined into the "Sick Care Cost" metric, which has calculations for local and U.S. total costs.

Medical evacuation services transport sick patients either short distances within countries or longer distances when a higher echelon of care is needed. Some volunteer sites are really remote and are in areas that are not easily accessible, so air medical evacuations are common for severe illness or injury to volunteers (Peace Corps Medical Care, 2022). Prices range from $20,000 for domestic flights to more than $200,000 for international flights (Costhelper.com, 2023). Owing to the remote nature of many Peace Corps locations and the high costs of dispatching medical evacuation flights from a vetted and trusted entity, the average cost is closer to the $200,000 price tag than the $20,000 (Mike R, personal communication). Therefore, the $180,000 amount was chosen to account for the skewed costs of medical evacuations for sick or injured PCVs.

There were 1448 cases in PCVs over a 14-year period, averaging 104 cases each year (Ferguson et al., 2016). Approximately 5-10% of dengue infections result in severe disease (Peeling et al., 2010). This computes to an estimate of 6 patients at the 5% level and 11 patients at the 10% threshold of developing the most serious form of the disease without intervention. For simplicity, we will assume that all 104 individuals are seen initially at a medical clinic—counted as an ambulatory case. A patient with severe disease will require hospitalization either in the

country (locally) or be returned to the U.S. but not both. Those requiring hospitalization in the U.S. will have the medical evacuation expenditure added to the overall cost. These costs are enumerated and calculated in Table 5.4.

Table 5.4

The Estimated Annual Cost of Dengue Illness in a Cohort of Peace Corps Volunteers

Patients with Severe Dengue	Hospital Stay in developing world[1]	Hospital Stay Cost * Duration of Stay for U.S.[2]	Medical evacuation[3]	Cost of Ambulatory Case[1]
Cost	$2,132	$11,700 per day * 4.88 days = $57, 096	$180,000	$315
5% threshold of progression to severe disease = 6 patients a year	$12,792	$342,576	$1,080,000	104 cases a year * $315 = $32,760
10% threshold of progression to severe disease = 11 patients a year	$23,452	$628,056	$1,980,000	104 cases a year * $315 = $32,760

Note. 1. España et al., 2021; 2. Freeman & Heslin, 2018; 3. Costhelper.com, 2023

Vaccine Efficacy

A recent study revealed that the Dengvaxia® vaccine efficacy for seropositive individuals against symptomatic infection was 61.0% (95% Confidence Interval (CI) 29.6-86.5) in the year following the third dose (Salje et al., 2021). The efficacy waned to 39.4% (95% CI 0.2-63.0) at the 6-year mark (Salje et al., 2021). However, most PCVs complete their 27-month service commitment and return home to non-endemic areas in the U.S., so our analysis focused on the 61.0% efficacy rate that would be predicted for the year that they are still serving at their assigned location after the one year needed to complete the vaccine series. These overall rates are lower than the efficacy rates of 82% (95% CI 67%-90%) for virologically confirmed disease, 79% (95% CI 69%-86%) for hospitalization, and 84% (95% CI 63%-93%) for severe disease reported by the CDC (CDC, 2021b). However, these rates are specific to children 9-16 years old, which does not fit the 18 years and over age profile of PCVs. Therefore, the calculations of averted disease for this analysis are based on the Salje et al. (2021) study and enumerated in Table 5.5. Based on the annual average of 104 cases, there would be 3 cases averted at the 5% level and 6 cases averted at the 10% progression to severe disease level, respectively. Additionally, all expenditures were determined annually for each course of action (Tables 5.6 and 5.7).

Table 5.5

The Estimated Annual Cost of Dengue Illness During the Implementation of a Dengvaxia® Vaccine Campaign

Patients with Severe Dengue	Hospital Stay in developing world[1]	Hospital Stay Cost * Duration of Stay for U.S.[2]	Medical evacuation[3]	Cost of Ambulatory Case[2]
Cost	$2,132	$11,700 per day * 4.88 days = $57, 096	$180,000	$315
5% threshold of progression to severe disease = 3 patients a year	$6,396	$171,288	$540,000	41 cases a year * $315 = $12,915
10% threshold of progression to severe disease = 5 patients a year	$10,655	$285,480	$900,000	41 cases a year * $315 = $12,915

Note. 1. España et al., 2021; 2. Freeman & Heslin, 2018; 3. Costhelper.com, 2023. Dengvaxia® has an overall 61% efficacy against clinical disease (Tully & Griffiths, 2021).

Results

The first course of action (COA) maintaining the status quo costs $45,552 assuming that 5% of cases that progress to severe infection and are treated within the country of assignment and $56,212 under the 10% of cases progressing assumption with local treatment. Medical costs become exponentially more expensive when medical evacuation back to the U.S. is needed yielding $1,453,336 and $2,640,816 at the 5% and 10% scenarios. This represents the current baseline rate—which is used in the calculation to determine the potential savings of the other COAs.

COA 2, the implementation of lab screening for all volunteer posts in endemic areas has a total cost at the local level of $1,865,122 at the 5% level and $1,875,782 for the 10% progression to severe disease. The screening costs—the office visit and lab screening are $1,819,570 in total. COA 2 shows the price of blanket screening for all volunteers to determine their seropositive status, thus allowing a better understanding of their individualized risk profile to encourage better compliance with Peace Corps-mandated vector avoidance recommendations. This strategy does not include a vaccination component. Since immunizations are not a component of this strategy, the overall cost will not have a discounted rate of 61% of severe dengue cases avoided by individual vaccinations.

COA 3 includes screening all volunteers assigned to a dengue-endemic area and mandatory vaccinations for the predicted 1% of volunteers who have evidence of prior infection. The health screening costs $395,850 and employs two scenarios, one, assuming 15% of people would screen positive (914 individuals identified) and the other, with 50% screening positive (3,045 individuals identified). This targeted pool identifies 61 PCVs for vaccination, which is larger than the number of positive dengue cases in the more targeted screenings in COA 5 (9

people who are seropositive at the 15% level and 30 people at the 50% screening level) & COA 6 (10 people who are seropositive at 15% level and 31 people at the 50% screening level).

The overall medical costs in COAs 3, 5 & 6 are discounted to reflect the Dengvaxia® vaccine's 61% efficacy level for the varying scenarios. At the 5% threshold to severe disease, three patients must be hospitalized (in the absence of vaccines, six patients a year require hospitalization), and five patients are hospitalized (versus 11 in the scenarios without vaccines) at the 10% progression to severe disease level.

The projected price of COA 3 is assuming 15% of PCVs screening positive on the health survey and mandatory vaccines for the 1% of individuals projected to be seropositive $1,890,016 for local cases at the 5% progression threshold and $2,594,908 for cases that must be medically evacuated and treated in the U.S., and $1,894,280 for local cases at the 10% progression threshold and $3,069,100 for cases being medically evacuated and treated in the U.S. If one assumes that 50% of the volunteers would screen positive on the health survey and then 1% of them would require vaccination after laboratory confirmation than the total costs are $1,890,016 for local cases and $2,594,908 for cases requiring evacuation at the 5% progression to severe disease levels. The prices rise to $1,894,280 for locally hospitalized and $3,069,100 for medical evacuation and U.S. hospitalization under the same screening parameters but at the 10% progression to severe disease rate.

COA 4 incorporates the cost of a health survey to determine which volunteers may have been exposed to offer a more targeted screening. This health survey costs $395,850 but allows for more targeted laboratory screening. Analysis performed at the 15% and 50% screened positive thresholds identifies 914 and 3,045 individuals for laboratory testing. There are savings in this program if we assume 15% and 50% of respondents are recommended for laboratory

screening, with price tags of $1,186,65 and $605,285. A drawback to this strategy is that many cases are asymptomatic or subclinical, so there is the potential that someone with a history of dengue might be overlooked due to the lack of universal screening. As in the second strategy, individual volunteers will better understand the risk of severe dengue based on their seropositivity status. However, vaccinations that would lower their future risk of severe dengue are not offered to them, and there are no subsequent cost savings.

COAs 5 and 6, which included health surveys, laboratory screening, and vaccinations, had very similar results due to low seropositivity projections for those needing vaccination and a predicted high voluntary vaccination rate at price tags of $4,616 at the 1% seropositivity assuming 15% of volunteers being recommended to be screened. For COA 4, if 94% of the seropositive people request a vaccine, the price is $1,230,307 (local) and $1,935,199 (U.S.) at the 5% disease progression to severe disease level. If 50% of the volunteers are recommended for testing and 1% are seropositive, and 94% of those who are seropositive request a vaccine, these inoculations would cost $15,388. The total costs at the more severe 10% disease progression threshold are $1,668,347 (local) and $2,843,763 (U.S.) levels. The expenditures are slightly higher for mandatory vaccines in COA 6. Both of these strategies offer complete protection to the volunteers by giving them a full picture of their risk profile and offering/mandating vaccination against dengue which can prevent hospitalization from severe dengue.

Table 5.6.

Simple Cost-Benefit Analysis of the Six Program Implementation Strategies Assuming 15% of PCVs would Screen Positive on the Health Survey and 1% Seropositivity Rate and 5% Progression to Severe Dengue

Course of Action	Office Visit Cost	Lab Fees Screening/ Blood draw	Vaccine Costs	Health Survey	Sick Care Cost	Medevac	Total
1. No changes, status quo	$0	$0	$0	$0	Local $45,552 U.S. $375,336	Local $0 U.S $1,080,000	Local $45,552 U.S. $1,455,336
2. Lab screening for all	$609,000	$1,210,570	$0	$0	Local $45,552 U.S. $375,336	Local $0 U.S. $1,080,000	Local $1,865,122 U.S. $3,274,906
3. Lab screening and mandatory vaccine for all	$609,000	$1,210,570	1% = 61 people $31,289	$0	Local $39,156 U.S. $204,048	Local $0 U.S. $540,000	Local $1,890,016 U.S. $2,594,908
4. Health history survey/ screening	$609,000	15% = 914 people $181,685	$0	$395,850	Local $45,552 U.S. $375,336	Local $0 U.S. $540,000	Local $1,232,087 U.S. $2,101,871
5. Lab screening based on health surveys and voluntary vaccination	$609,000	15% = 914 people $181,685	1% = 9 people $4,616	$395,850	Local $39,156 U.S. $204,048	Local $0 U.S. $540,000	Local $1,230,307 U.S. $1,935,199
6. Lab screening based on health surveys and mandatory vaccination	$609,000	15% = 914 people $181,685	1% = 10 people $5,129	$395,850	Local $39,156 U.S. $204,048	Local $0 U.S. $540,000	Local $1,230,820 U.S. $1,935,712

Note. Sick care costs include ambulatory care for all patients (n=104 in scenarios without vaccines) plus the cost of local or U.S. hospitalization.

Table 5.7

Simple Cost-Benefit Analysis of the Six Program Implementation Strategies Assuming 15% of PCVs would Screen Positive on the Health Survey and 1% Seropositivity Rate and 10% Progression to Severe Dengue

Course of Action	Office Visit Cost	Lab Fees Screening/ Blood draw	Vaccine Costs	Health Survey	Sick Care Cost	Medevac	Total
1. No changes, status quo	$0	$0	$0	$0	Local $56,212 U.S. $660,816	Local $0 U.S $1,980,000	Local $56,212 U.S. $2,640,816
2. Lab screening for all	$609,000	$1,210,570	$0	$0	Local $56,212 U.S. $660,816	Local $0 U.S. $1,980,000	Local $1,875,782 U.S. $4,460,386
3. Lab screening and mandatory vaccine for all	$609,000	$1,210,570	1% = 61 people $31,289	$0	Local $43,420 U.S. $318,240	Local $0 U.S. $900,000	Local $1,894,280 U.S. $3,069,100
4. Health history survey/ screening	$609,000	15% = 914 people $181,685	$0	$395,850	Local $56,212 U.S. $660,816	Local $0 U.S. $900,000	Local $1,242,747 U.S. $2,747,351
5. Lab screening based on health surveys and voluntary vaccination	$609,000	15% = 914 people $181,685	1% = 9 people $4,616	$395,850	Local $43,420 U.S. $318,240	Local $0 U.S. $900,000	Local $1,234,571 U.S. $2,409,391
6. Lab screening based on health surveys and mandatory vaccination	$609,000	15% = 914 people $181,685	1% = 10 people $5,129	$395,850	Local $43,420 U.S. $318,240	Local $0 U.S. $900,000	Local $1,235,084 U.S. $2,409,904

Note. Sick care costs include ambulatory care for all patients (n=104 in scenarios without vaccines) plus the cost of local or U.S. hospitalization.

Table 5.8

Simple Cost-Benefit Analysis of the Six Program Implementation Strategies Assuming 50% of PCVs would Screen Positive on the Health Survey and 1% Seropositivity Rate and 5% Progression to Severe Dengue

Course of Action	Office Visit Cost	Lab Fees Screening/ Blood draw	Vaccine Costs	Health Survey	Sick Care Cost	Medevac	Total
1. No changes, status quo	$0	$0	$0	$0	Local $45,552 U.S. $375,336	Local $0 U.S $1,080,000	Local $45,552 U.S. $1,455,336
2. Lab screening for all	$609,000	$1,210,570	$0	$0	Local $56,212 U.S. $375,336	Local $0 U.S. $1,080,000	Local $1,865,122 U.S. $3,274,906
3. Lab screening and mandatory vaccine for all	$609,000	$1,210,570	1% = 61 people $31,289	$0	Local $39,156 U.S. $204,048	Local $0 U.S. $540,000	Local $1,890,016 U.S. $2,594,908
4. Health history survey/ screening	$609,000	50% = 3,045 people $605,285	$0	$395,850	Local $45,552 U.S. $375,336	Local $0 U.S. $540,000	Local $1,655,687 U.S. $2,594,908
5. Lab screening based on health surveys and voluntary vaccination	$609,000	50% = 3,045 people $605,285	1% = 30 people $15,388	$395,850	Local $39,156 U.S. $204,048	Local $0 U.S. $540,000	Local $1,664,679 U.S. $2,525,471
6. Lab screening based on health surveys and mandatory vaccination	$609,000	50% = 3,045 people $605,285	1% = 31 people $15,901	$395,850	Local $39,156 U.S. $204,048	Local $0 U.S. $540,000	Local $1,665,192 U.S. $2,369,571

Note. Sick care costs include ambulatory care for all patients (n=104 in scenarios without vaccines) plus the cost of local or U.S. hospitalization.

Table 5.9

Simple Cost-Benefit Analysis of the Six Program Implementation Strategies Assuming 50% of PCVs would Screen Positive on the Health Survey and 1% Seropositivity Rate and 10% Progression to Severe Dengue

Course of Action	Office Visit Cost	Lab Fees Screening/ Blood draw	Vaccine Costs	Health Survey	Sick Care Cost	Medevac	Total
1. No changes, status quo	$0	$0	$0	$0	Local $56,212 U.S. $660,816	Local $0 U.S $1,980,000	Local $56,212 U.S. $2,640,816
2. Lab screening for all	$609,000	$1,210,570	$0	$0	Local $56,212 U.S. $660,816	Local $0 U.S. $1,980,000	Local $1,875,782 U.S. $4,460,386
3. Lab screening and mandatory vaccine for all	$609,000	$1,210,570	1% = 61 people $31,289	$0	Local $43,420 U.S. $318,240	Local $0 U.S. $900,000	Local $1,894,280 U.S. $3,069,100
4. Health history survey/ screening	$609,000	50% = 3,045 people $605,285	$0	$395,850	Local $56,212 U.S. $660,816	Local $0 U.S. $900,000	Local $1,666,347 U.S. $3,170,951
5. Lab screening based on health surveys and voluntary vaccination	$609,000	50% = 3,045 people $605,285	1% = 30 people $15,388	$395,850	Local $43,420 U.S. $318,240	Local $0 U.S. $900,000	Local $1,668,347 U.S. $2,843,763
6. Lab screening based on health surveys and mandatory vaccination	$609,000	50% = 3,045 people $605,285	1% = 31 people $15,901	$395,850	Local $43,420 U.S. $318,240	Local $0 U.S. $900,000	Local $1,669,456 U.S. $2,844,276

Note. Sick care costs include ambulatory care for all patients (n=104 in scenarios without vaccines) plus the cost of local or U.S. hospitalization.

Discussion

COA1—continuing the status quo is the best strategy. The vaccine efficacy (61% overall) is simply too low, the projected seropositivity level in this population and corresponding individuals identified as vaccine candidates is minimal, and the laboratory screening costs are too high to justify screening and vaccinating this population. This also aligns with the literature showing that vaccination is only recommended and effective in highly endemic areas and populations (Coudeville et al., 2020; Halstead, 2016). PCVs do not meet this high endemicity threshold.

Furthermore, the costs of treating and medically evacuating dengue patients with severe disease or complications are not considerable overall. At the 15% health survey screening positive level for both the 5% and 10% progression to severe disease thresholds in COAs 5 & 6, there are small potential savings in the overall cost for severe dengue cases that have to be referred to the U.S. However, this is still not the recommended pathway forward as these savings are eliminated in the 50% screening positive scenarios. Once more information is known about the true baseline level of risk (i.e., the number of PCVs who are seropositive for dengue upon entry into service) and the if the incidence of cases and severe cases were to increase, then the calculations and recommendations could change.

There is great potential for increased dengue incidence, PCVs were pulled from service during the pandemic in 2020 and Peace Corps is just now reopening offices and placing new volunteers. These volunteers are walking into a “post” pandemic new normal in villages where community-level vector control strategies were likely discontinued due to a lack of funds, human resources, economic devastation, and stay-at-home orders. This is true of dengue and other vector-borne diseases.

In COAs 2 & 4 PCVs will know they are at heightened risk and can adhere better to mitigation and control measures. However, knowledge does not equal behavior change, so a disease-reduction component was not added to these strategies during valuation. Nonetheless, I feel that there is value added in doing a pilot seroprevalence study to identify the risk in a healthy adult population—this would better characterize the seropositivity of the average PCV and represent the true disease risk. Evaluating these potential courses of action allowed for computing the total costs associated with a screening program. It also showed that vaccine costs are relatively low so screening should only occur if there is an intent/ability to vaccinate. Furthermore, there is projected to be little difference between voluntary (94%) and mandatory vaccinations; thus, mandatory vaccinations are the better approach. Potentially, waivers could be introduced on a case-by-case basis for individuals who do not wish to be inoculated.

Future studies could potentially reach a different conclusion in a smaller cohort of military service members or full-time international disaster response workers. This is especially important for military operations where missions could be jeopardized or delayed due to ill service members. The implementation costs are more likely to be tolerated and justified in this high-threat, high-reward population. Another cost-benefit analysis with the Qdenga® vaccine could potentially yield different results, as it does not require laboratory screening and only requires two doses for a complete series.

Assumptions and Limitations

Dengvaxia® requires three doses administered at 0, 6, and 12 months. Therefore, the second and third doses will likely be administered within the host country during the volunteer's service. For simplicity in the model, the cost of the booster doses was not discounted to account for this fact. The logistics of getting vaccines into some areas of the developing world, along

with getting the volunteers to a clinic (or conversely sending a medical officer to the volunteer's site), would play a role in the cost calculation for the booster administration. This could be expensive, so a constant rate for booster vaccines was maintained.

Every effort was undertaken to determine the most realistic parameter projections based on the current scientific evidence. The hospitalization rates and dengue risk were treated as homogeneous throughout the entire endemic area of Peace Corps assignments; however, there is great heterogeneity of prices and outbreak potential based on specific Dengue virus circulation levels, housing types, availability of hospital services, and the dengue level with the local population. Furthermore, these parameter assumptions should be considered dynamic and be updated to reflect future understandings and calculations.

The Peace Corps dengue data was based on volunteers' experiences from 2000-2014 (Ferguson et al., 2016). However, dengue disease has increased 8-fold over the past two decades (WHO, 2022). Thus, the calculations will likely vary in the coming years as the risk of dengue illness continues to grow and the number of individuals with previous exposures also increases. Consequently, the number of people requiring vaccines and the potential for severe cases and hospitalization will increase.

6. PUBLIC HEALTH SIGNIFICANCE

Dengue is a growing public health problem that occurs at a nexus of unprecedented population growth, unplanned urbanization, poor public health infrastructure, and climate change increasing the habitable range and breeding seasons of vectors. Modern air transport of people, animals, and commodities allows one to be virtually anywhere in the world in only a few short hours, potentially introducing new pathogens to previously unaffected areas plays a significant role as well (Gubler, 2011). Prior to World War II, dengue was primarily a disease of the tropics; epidemics were sporadic, geographically limited, and had long interepidemic periods (Gubler, 1998). All four serotypes of Dengue are circulating throughout the world. While infection with one serotype provides lifelong immunity, a secondary infection increases the risk of severe dengue (Guzman et al., 2013; Halstead et al., 1969, 1970). Thus, if there is an increase in dengue infections, there is likely to be an increase in secondary infections and severe dengue. These diseases have catastrophic effects on individuals and wreak chaos on communities' social fabric and economic stability.

A mechanistic model explored the *Ae. aegypti* mosquito distribution and characteristics and how climatological and ecological factors drive Dengue virus dynamics. The study constructed a Global Relative Risk R_0 Model consistent with the presence and circulation of the Dengue Virus and illness in human and vector populations. This simplistic model shows the effect of precipitation and temperature on the genesis and proliferation of dengue outbreaks creating a valuable tool for military planners, epidemiologists, disaster and humanitarian relief workers, and travel medicine providers. It allows military commanders and relief organization leaders to understand transmission dynamics and vector ecological factors to implement control measures that safeguard their charges. This mechanistic model could also predict dengue

potential in disaster response and humanitarian activities to implement effective control measures. Finally, the model aggregates the contributions of multiple, interacting, and often nonlinear underlying responses of hosts, pathogens, and vectors to climate change.

Determinants of dengue infection, including host genetic and immunologic characteristics and the role of secondary infections, were explored to better understand the true risk of disease. The attributes of travelers with repeated and/or prolonged high-risk exposures that place them at a heightened risk for severe dengue were enumerated. These factors were combined to establish a framework of recommendations, including pre-travel health assessments, primary prevention of vector contact, and the potential administration of vaccines. A cost-benefit analysis of implementing a screening and vaccination program for Peace Corps volunteers did not yield a recommendation for vaccine screening in this population. However, the exercise showed the potential utility and cost savings of implementing a screening and vaccination strategy for other special groups of high-risk travelers, such as the military or international aid workers.

Globalization has been the principal driver of a global economic system, including a transnational flow of knowledge, goods, people, and animals. All four serotypes of Dengue circulate simultaneously throughout the tropics, and recombination produces more resistant viruses, which are spread through airline travel and globalization of trade to immunologically naïve populations. This framework seeks to protect individuals with an ever-increasing risk of dengue infection amidst a backdrop of increasing international travel.

The Novel Coronavirus (COVID-19) and monkeypox pandemics underscore new pathogens' global mobility and reach in immunologically naïve populations and highlight the most critical vulnerabilities globally. The increase in the intensity and duration of major climatic events, hurricanes, floods, droughts, etc., alter the land and push humans and animals into direct

contact in novel areas and mechanisms. Disease control and prevention must employ a One Health and holistic approach utilizing best practices and methodologies that target every level of the socioecological framework into well-structured, strategic plans that are properly resourced (McLeroy et al., 1988). Amid political infighting juxtaposed with a highly mobile and connected world, partnerships, collaborations, and capacity building will be necessary components of mitigation, control, and preparedness toolkits, especially for those in developing nations.

Dengue prevention and control is a tremendous undertaking; mosquitos are impervious to local and international boundaries, mosquitos breeding in neighboring garden pots will fly to nearby homes, chemical insecticide application in one area can shift mosquitos into adjacent areas that do not employ this method of environmental control. The same logic can be applied to attacking prevention and control in a disjointed manner—unless policies aimed at curbing global warming and poverty are enacted, more and more communities will be affected by *Aedes* mosquitoes and the diseases they harbor, which will expand endemic and hyperendemic areas leading to a higher probability of severe dengue cases across a wider swath of the globe.

REFERENCES

Allwinn, R., Hofknecht, N., & Doerr, H. W. (2008). Dengue in Travellers Is Still Underestimated. *Intervirology, 51*(2), 96-100. https://doi.org/10.1159/000131667

Altizer, S., Ostfeld, R. S., Johnson, P. T. J., Kutz, S., & Harvell, C. D. (2013). Climate Change and Infectious Diseases: From Evidence to a Predictive Framework. *Science*, 341(6145), 514-519. https://doi.org/10.1126/science.1239401

Alvarez, M., Rodriguez-Roche, R., Bernardo, L., Vázquez, S., Morier, L., Gonzalez, D., Castro, O., Kourí, G., Halstead, S. B., & Guzman, M. G. (2006). Dengue hemorrhagic Fever caused by sequential dengue 1-3 virus infections over a long time interval: Havana epidemic, 2001-2002. *The American Journal of Tropical Medicine and Hygiene*, *75*(6), 1113–1117

Amaku, M., Azevedo, F., Burattini, M. N., Coelho, G. E., Coutinho, F. a. B., Greenhalgh, D., Lopez, L. F., Motitsuki, R. S., Wilder-Smith, A., & Massad, E. (2016). Magnitude and frequency variations of vector-borne infection outbreaks using the Ross–Macdonald model: Explaining and predicting outbreaks of dengue fever. *Epidemiology & Infection*, *144*(16), 3435–3450. https://doi.org/10.1017/S0950268816001448

Amaya-Larios, I. Y., Martínez-Vega, R. A., Mayer, S. V., Galeana-Hernández, M., Comas-García, A., Sepúlveda-Salinas, K. J., Falcón-Lezama, J. A., Vasilakis, N., & Ramos-Castañeda, J. (2014). Seroprevalence of Neutralizing Antibodies Against Dengue Virus in Two Localities in the State of Morelos, Mexico. *The American Journal of Tropical Medicine and Hygiene*, 91(5), 1057–1065. https://doi.org/10.4269/ajtmh.14-0145

Anantapreecha, S., Chanama, S., A-Nuegoonpipat, A., Naemkhunthot, S., SA-Ngasang, A., Sawanpanyalert, P., & Kurane, I. (2005). Serological and Virological Features of Dengue Fever and Dengue Haemorrhagic Fever in Thailand from 1999 to 2002. *Epidemiology and Infection*, 133(3), 503–507.

Arham, F. A., Amin, L., Mustapa, M. A. C., Mahadi, Z., Yaccob, M., Arham, A. D., & Norizan, N. S. (2022). To do or not to do?": Determinants of stakeholders' acceptance on dengue vaccine using PLS-SEM analysis in Malaysia. *BMC Public Health*, 22(1), 1574 SpringerLink. https://link.springer.com/article/10.1186/s12889-022-13967-3

Bacaner, N., Stauffer, B., Boulware, D. R., Walker, P. F., & Keystone, J. S. (2004). Travel Medicine Considerations for North American Immigrants Visiting Friends and Relatives. *JAMA*, 291(23), 2856-2864. https://doi.org/10.1001/jama.291.23.2856

Beatty, M. E. (2008). Estimating the global burden of dengue. In *Abstract Book: Dengue 2008.* The Second International Conference on Dengue and Dengue Haemorrhagic Fever. Phuket, Thailand.

Benedum, C. M., Seidahmed, O. M., Eltahir, E. A. B., & Markuzon, N. (2018). Statistical modeling of the effect of rainfall flushing on dengue transmission in Singapore. *PLoS Neglected Tropical Diseases*, *12*(12), e0006935. https://doi.org/10.1371/journal.pntd.0006935

Betsch, C., Schmid, P., Heinemeier, D., Korn, L., Holtmann, C., & Böhm, R. (2018). Beyond confidence: Development of a measure assessing the 5C psychological antecedents of vaccination. *PloS one*, 13(12), e0208601. https://doi.org/10.1371/journal.pone.0208601

Bhatt, S., Gething, P. W., Brady, O. J., Messina, J. P., Farlow, A. W., Moyes, C. L., Drake, J. M., Brownstein, J. S., Hoen, A. G., Sankoh, O., Myers, M. F., George, D. B., Jaenisch, T., Wint, G. R. W., Simmons, C. P., Scott, T. W., Farrar, J. J., & Hay, S. I. (2013). The global distribution and burden of dengue. *Nature*, 496(7446), Article 7446. https://doi.org/10.1038/nature12060

Bhatta, P., Simkhada, P., Van Teijlingen, E., & Maybin, S. (2009). A Questionnaire Study of Voluntary Service Overseas (VSO) Volunteers: Health Risk and Problems Encountered. *Journal of Travel Medicine*, *16*,(5) 332–337. https://doi.org/10.1111/j.1708-8305.2009.00342.x

Biswal, S., Borja-Tabora, C., Vargas, L. M., Velásquez, H., Alera, M. T., Sierra, V., Rodriguez-Arenales, E. J., Yu, D., Wickramasinghe, V. P., Moreira, E. D., Fernando, A. D., Gunasekera, D., Kosalaraksa, P., Espinoza, F., López-Medina, E., Bravo, L., Tuboi, S., Hutagalung, Y., Garbes, P., … Tricou, V. (2020). Efficacy of a tetravalent dengue vaccine in healthy children aged 4–16 years: A randomised, placebo-controlled, phase 3 trial. *The Lancet*, 395(10234), 1423–1433. https://doi.org/10.1016/S0140-6736(20)30414-1

Biswal, S., Reynales, H., Saez-Llorens, X., Lopez, P., Borja-Tabora, C., Kosalaraksa, P., Sirivichayakul, C., Watanaveeradej, V., Rivera, L., Espinoza, F., Fernando, L., Dietze, R., Luz, K., Venâncio da Cunha, R., Jimeno, J., López-Medina, E., Borkowski, A., Brose, M., Rauscher, M., … Wallace, D. (2019). Efficacy of a Tetravalent Dengue Vaccine in Healthy Children and Adolescents. *New England Journal of Medicine*, 381(21), 2009–2019. https://doi.org/10.1056/NEJMoa1903869

Brady, O. J., Smith, D. L., Scott, T. W., & Hay, S. I. (2015). Dengue disease outbreak definitions are implicitly variable. *Epidemics*, 11, 92-02. https://doi.org/10.1016/j.epidem.2015.03.002

Branswell, Helen. (2019). FDA approves the first vaccine for dengue fever, but with major restrictions. *STAT*, https://www.statnews.com/2019/05/01/fda-dengue-vaccine-restrictions/ (2019, accessed 10 April 2022)

Bravo, J. R., Guzmán, M. G., & Kourí, G. P. (1987). Why dengue haemorrhagic fever in Cuba? I. Individual risk factors for dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS). *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 81(5), 816–820. https://doi.org/10.1016/0035-9203(87)90041-1

Buchman, A., Gamez, S., Li, M., Antoshechkin, I., Li, H.-H., Wang, H.-W., Chen, C.-H., Klein, M. J., Duchemin, J.-B., Paradkar, P. N., & Akbari, O. S. (2019). Engineered resistance to Zika virus in transgenic Aedes aegypti expressing a polycistronic cluster of synthetic small RNAs. *Proceedings of the National Academy of Sciences*, 116(9), 3656–3661. https://doi.org/10.1073/pnas.1810771116

Bullard, S. (2004). The great enemy of humanity. Journal of Pacific History 39(2):203-220

Burke, D. S., & Kliks, S. (2006). Antibody-Dependent Enhancement in Dengue Virus Infections. *The Journal of Infectious Diseases*, 193(4), 601–603. https://doi.org/10.1086/499282

Burnham, B. R., Wells, T. S., & Riddle, J. R. (1998). A Cost-Benefit Analysis of a Routine Varicella Vaccination Program for United States Air Force Academy Cadets. *Military Medicine*, 163(9), 631–634. https://doi.org/10.1093/milmed/163.9.631

Caci, J. B., Blaylock, J. M., De La Barrera, R., Griggs, A. N., Lin, L., Jarman, R. G., Thomas, S. J., & Lyons, A. (2014). Seroprevalence of dengue fever in US Army special operations forces: Initial results and the way ahead. *Journal of Special Operations Medicine*, 14(3):111–5

Caldwell, J. M., LaBeaud, A. D., Lambin, E. F., Stewart-Ibarra, A. M., Ndenga, B. A., Mutuku, F. M., Krystosik, A. R., Ayala, E. B., Anyamba, A., Borbor-Cordova, M. J., Damoah, R., Grossi-Soyster, E. N., Heras, F. H., Ngugi, H. N., Ryan, S. J., Shah, M. M., Sippy, R., & Mordecai, E. A. (2021). Climate predicts geographic and temporal variation in mosquito-borne disease dynamics on two continents. *Nature Communications*, 12(1), 1233. https://doi.org/10.1038/s41467-021-21496-7

Caminade, C., Turner, J., Metelmann, S., Hesson, J. C., Blagrove, M. S. C., Solomon, T., Morse, A. P., & Baylis, M. (2017). Global risk model for vector-borne transmission of Zika virus reveals the role of El Niño 2015. *Proceedings of the National Academy of Sciences*, 114(1), 119–124. https://doi.org/10.1073/pnas.1614303114

Carrington, L. B., & Simmons, C. P. (2014). Human to Mosquito Transmission of Dengue Viruses. *Frontiers in Immunology*, 5. https://www.frontiersin.org/articles/10.3389/fimmu.2014.00290

Cauchemez, S., Fraser, C., Van Kerkhove, M. D., Donnelly, C. A., Riley, S., Rambaut, A., Enouf, V., van der Werf, S., & Ferguson, N. M. (2014). Middle East respiratory syndrome coronavirus: Quantification of the extent of the epidemic, surveillance biases, and transmissibility. *The Lancet Infectious Diseases*, *14*(1), 50–56. https://doi.org/10.1016/S1473-3099(13)70304-9

Centers for Disease Control and Prevention. (2020). Mosquitoes in the United States. https://www.cdc.gov/mosquitoes/about/mosquitoes-in-the-us.html

Centers for Disease Control and Prevention. (2021). Testing for Dengue. https://www.cdc.gov/dengue/healthcare-providers/testing/index.html

Centers for Disease Control and Prevention. (2021b). Vaccine Safety and Efficacy Data. https://www.cdc.gov/dengue/vaccine/hcp/safety-efficacy.html

Centers for Disease Control and Prevention. (2022). Dengue https://www.cdc.gov/dengue/about/index.html

Centers for Disease Control and Prevention. (2022b). CDC Yellow Book. https://wwwnc.cdc.gov/travel/page/yellowbook-home-2020

Centers for Disease Control and Prevention. (2022c). Travelers' Health: Travel Advice. https://wwwnc.cdc.gov/travel/page/traveler-information-center

Centers for Disease Control and Prevention. (2022d). One Health. https://www.cdc.gov/onehealth/index.html

Centers for Disease Control and Prevention. (2023). CDC Vaccine Price List. https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html

Chala, B., & Hamde, F. (2021). Emerging and Re-emerging Vector-Borne Infectious Diseases and the Challenges for Control: A Review. *Frontiers in Public Health*, 9, 715759. https://doi.org/10.3389/fpubh.2021.715759

Chamberlain, R. W., & Sudia, W. D. (1961). Mechanism of Transmission of Viruses by Mosquitoes. *Annual Review of Entomology*, 6(1), 371–390. https://doi.org/10.1146/annurev.en.06.010161.002103

Chan, M., & Johansson, M. A. (2012). The Incubation Periods of Dengue Viruses. *PLoS ONE*, *7*(11), e50972. https://doi.org/10.1371/journal.pone.0050972

Chen, L. H., Leder, K., Barbre, K. A., Schlagenhauf, P., Libman, M., Keystone, J., Mendelson, M., Gautret, P., Schwartz, E., Shaw, M., MacDonald, S., McCarthy, A., Connor, B. A., Esposito, D. H., Hamer, D., & Wilson, M. E. (2018). Business travel-associated illness: A GeoSentinel analysis. *Journal of Travel Medicine*, *25*(1), 10.1093/jtm/tax097 https://doi.org/10.1093/jtm/tax097

Cherian, T., Ponnuraj, E., Kuruvilla, T., Kirubakaran, C., John, T. J., & Raghupathy, P. (1994). An epidemic of dengue haemorrhagic fever & dengue shock syndrome in & around Vellore. *Indian J Med Res* 100:51–56

Christophers, S. R. (1960). *Aedes aegypti* (L.), The yellow fever mosquito: its life history, bionomics, and structure. Cambridge: University Press

Chungue, E., Spiegel, A., Roux, J., Laudon, F., & Cardines, R. (1990). Dengue-3 in French Polynesia: preliminary data. *Medical Journal of Australia,* 152:557–558

Cobelens, F. G. J., Groen, J., Osterhaus, A. D. M. E., Leentvaar-Kuipers, A., Wertheim-van Dillen, P. M. E., & Kager, P. A. (2002). Incidence and risk factors of probable dengue virus infection among Dutch travellers to Asia. *Tropical Medicine & International Health*, *7*(4), 331–338. https://doi.org/10.1046/j.1365-3156.2002.00864.x

Coffey, L. L., Mertens, E., Brehin, A.-C., Fernandez-Garcia, M. D., Amara, A., Després, P., & Sakuntabhai, A. (2009). Human genetic determinants of dengue virus susceptibility. *Microbes and Infection,* 11(2), 143–156. https://doi.org/10.1016/j.micinf.2008.12.006

Cortes, F., Turchi Martelli, C. M., Arraes de Alencar Ximenes, R., Montarroyos, U. R., Siqueira Junior, J. B., Gonçalves Cruz, O., Alexander, N., & Vieira de Souza, W. (2018). Time series analysis of dengue surveillance data in two Brazilian cities. *Acta Tropica*, 182, 190–197. https://doi.org/10.1016/j.actatropica.2018.03.006

Costhelper.com. (2023). Air Ambulance Cost. https://health.costhelper.com/air-ambulances.html

Coudeville, L., Baurin, N., & Shepard, D. S. (2020). The potential impact of dengue vaccination with, and without, pre-vaccination screening. *Vaccine*, *38*(6), 1363–1369. https://doi.org/10.1016/j.vaccine.2019.12.012

Crawshaw, A. F., Maung, T. M., Shafique, M., Sint, N., Nicholas, S., Li, M. S., Roca-Feltrer, A., & Hii, J. (2017). Acceptability of insecticide-treated clothing for malaria prevention among migrant rubber tappers in Myanmar: a cluster-randomized non-inferiority crossover trial. *Malaria Journal,* 16:92

Cucunawangsih, & Lugito, N. P. H. (2017). Trends of Dengue Disease Epidemiology. *Virology: Research and Treatment*, 8, 1178122X17695836. https://doi.org/10.1177/1178122X17695836

Dahlgren, A., DeRoo, L., Avril, J., Bise, G., & Loutan, L. (2009). Health Risks and Risk-Taking Behaviors Among International Committee of the Red Cross (ICRC) Expatriates Returning From Humanitarian Missions. *Journal of Travel Medicine*, *16*(6), 382–390 https://doi.org/10.1111/j.1708-8305.2009.00350.x

De Araujo, J. M., Schatzmayr, H. G., de Filippis, A. M., Dos Santos, F. B., Cardoso, M. A., Britto, C., Coelho, J. M., & Nogueira, R. M. (2009). A retrospective survey of dengue virus infection in fatal cases from an epidemic in Brazil. *Journal of Virological Methods* 155:34–38

Debboun, M., & Strickman, D. (2013). Insect repellents and associated personal protection for a reduction in human disease. *Medical Veterinary Entomology*, 27:1–9

De Carvalho Bittencourt, M., Martial, J., Cabie, A., Thomas, L., & Cesaire, R. (2012). Decreased peripheral dendritic cell numbers in dengue virus infection. *Journal of Clinical Immunology,* 32:161–172

De Figueiredo, A., Simas, C., Karafillakis, E., Paterson, P., & Larson, H. J. (2020). Mapping global trends in vaccine confidence and investigating barriers to vaccine uptake: A large-scale retrospective temporal modelling study. *The Lancet*, 396(10255), 898–908. https://doi.org/10.1016/S0140-6736(20)31558-0

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). Methods for the Economic Evaluation of Health Care Programmes. Oxford University Press.

Dussart, P., Baril, L., Petit, L., Beniguel, L., Quang, L. C., Ly, S., Azevedo, R. D. S. S., Meynard, J. B., Vong, S., Chartier, L., Diop, A., Sivuth, O., Duong, V., Thang, C. M., Jacobs, M., Sakuntabhai, A., Nunes, M. R. T., Huong, V. T. Q., Buchy, P., & Vasconcelos, P. F. D. C. (2012). Clinical and Virological Study of Dengue Cases and the Members of Their Households: The Multinational DENFRAME Project. *PLoS Neglected Tropical Diseases*, *6*(1), e1482. https://doi.org/10.1371/journal.pntd.0001482

Endy, T. P., Nisalak, A., Chunsuttiwat, S., Libraty, D. H., Green, S., Rothman, A. L., Vaughn, D. W., & Ennis, F. A. (2002). Spatial and Temporal Circulation of Dengue Virus Serotypes: A Prospective Study of Primary School Children in Kamphaeng Phet, Thailand. *American Journal of Epidemiology*, 156(1), 52–59. https://doi.org/10.1093/aje/kwf006

Endy, T. P., Nisalak, A., Chunsuttitwat, S., Vaughn, D. W., Green, S., Ennis, F. A., Rothman, A. L., & Libraty, D. H. (2004). Relationship of Preexisting Dengue Virus (DV) Neutralizing Antibody Levels to Viremia and Severity of Disease in a Prospective Cohort Study of DV Infection in Thailand. *The Journal of Infectious Diseases*, 189(6), 990–1000. https://doi.org/10.1086/382280

Ericsson, C. D., Hatz, C., Leder, K., Tong, S., Weld, L., Kain, K. C., Wilder-Smith, A., von Sonnenburg, F., Black, J., Brown, G. V., & Torresi, J. (2006). Illness in Travelers Visiting Friends and Relatives: A Review of the GeoSentinel Surveillance Network. *Clinical Infectious Diseases*, *43*(9), 1185–1193. https://doi.org/10.1086/507893

España, G., Leidner, A. J., Waterman, S. H., & Perkins, T. A. (2021). Cost-effectiveness of dengue vaccination in Puerto Rico. *PLoS Neglected Tropical Diseases*, 15(7), e0009606. https://doi.org/10.1371/journal.pntd.0009606

European Centre for Disease Prevention and Control. (2021). *Aedes aegypti*-Factsheet for experts. https://www.ecdc.europa.eu/en/publications-data/geographical-distribution-dengue-cases-reported-worldwide-2020

European Centre for Disease Prevention and Control. (2022). Dengue Worldwide Overview. https://www.ecdc.europa.eu/en/dengue-monthly

Facchinelli, L., Valerio, L., Ramsey, J. M., Gould, F., Walsh, R. K., Bond, G., Robert, M. A., Lloyd, A. L., James, A. A., Alphey, L., & Scott, T. W. (2013). Field cage studies of progressive evaluation of genetically engineered mosquitos. *PLoS Neglected Tropical Diseases* Jan 17

Farrar, J., Focks, D., Gubler, D., Barrera, R., Guzman, M. G., Simmons, C., Kalayanarooj, S., Lum, L., McCall, P. J., Lloyd, L., Horstick, O., Dayal-Drager, R., Nathan, M. B., Kroeger, A., & Group, on behalf of the W. D. S. W. (2007). Editorial: Towards a global dengue research agenda. *Tropical Medicine & International Health*, 12(6), 695–699. https://doi.org/10.1111/j.1365-3156.2007.01838.x

Ferguson, R. W., Henderson, S. J., Lee, E. A., & Jung, P. (2016). Dengue in Peace Corps Volunteers, 2000–14. *Journal of Travel Medicine,* 1-4 https://doi.org/10.1093/jtm/taw010

Fick, S. E., & Hijmans, R. J. (2017). WorldClim 2: New 1-km spatial resolution climate surfaces for global land areas. *International Journal of Climatology*, *37*(12), 4302–4315. https://doi.org/10.1002/joc.5086

Fink, J., Gu, F., & Vasudevan, S. G. (2006). Role of T cells, cytokines and antibody in dengue fever and dengue haemorrhagic fever. *Reviews in Medical Virology*, 16(4), 263–275. https://doi.org/10.1002/rmv.507

Focks, D. A., Daniels, E., Haile, D. G., & Keesling, J. E. (1995). A simulation model of the epidemiology of urban dengue fever: Literature analysis, model development, preliminary validation, and samples of simulation results. *The American Journal of Tropical Medicine and Hygiene*, *53*(5), 489–506. https://doi.org/10.4269/ajtmh.1995.53.489

Food and Drug Administration. (2023). Dengvaxia®. https://www.fda.gov/vaccines-blood-biologics/dengvaxia

Freeman, W. J., & Heslin, K. C. (2018). Overview of U.S. Hospital Stays in 2016: Variation by Geographic Region.

Fried, J. R., Gibbons, R. V., Kalayanarooj, S., Thomas, S. J., Srikiatkhachorn, A., Yoon, I. K., Jarman, R. G., Green, S., Rothman, A. L., & Cummings, D. A. (2010). Serotype-specific differences in the risk of dengue hemorrhagic Fever: an analysis of data collected in Bangkok, Thailand from 1994 to 2006. *PLoS Neglected Tropical Diseases,* 4:e617

Frost, J. (2022). Statistics by Jim Making Statistics Intuitive. https://statisticsbyjim.com/jim_frost/

Gibbons, R. V., Kalanarooj, S., Jarman, R. G., Nisalak, A., Vaughn, D. W., Endy, T. P., Mammen, M. P., & Srikiatkhachorn, A. (2007). Analysis of repeat hospital admissions for dengue to estimate the frequency of third or fourth dengue infections resulting in admissions and dengue hemorrhagic fever, and serotype sequences. *American Journal of Tropical Medicine and Hygiene*, 77:910–913

Goesch, J. N., Simons de Fanti, A., Béchet, S., & Consigny, P. H. (2010). Comparison of knowledge on travel related health risks and their prevention among humanitarian aid workers and other travellers consulting at the Institut Pasteur travel clinic in Paris, France. *Travel Medicine and Infectious Disease*, *8*(6), 364–372. https://doi.org/10.1016/j.tmaid.2010.09.005

Gómez-Dantés, H., & Willoquet, J. R. (2009). Dengue in the Americas: Challenges for prevention and control. *Cadernos de Saúde Pública*, 25(suppl 1), S19–S31. https://doi.org/10.1590/S0102-311X2009001300003

Goodyer, L. I., Croft, A. M., Frances, S. P., Hill, N., Moore, S. J., Onyango, S. P., & Debboun, M. (2010). Expert Review of the Evidence Base for Arthropod Bite Avoidance, *Journal of Travel Medicine*, 17(3):182–192, https://doi.org/10.1111/j.1708-8305.2010.00402.x

Graham, R. R., Juffrie, M., Tan, R., Hayes, C. G., Laksono, I., Ma'Roef, C., Erlin, Suturyo, Porter, K. R., & Halstead, S. B. (1999). A prospective seroepidemiologic study on dengue in children four to nine years of age in Yogyakarta. Indonesia I. Studies in 1995-1996. *American Journal of Tropical Medicine and Hygiene*, 61(3), 412-419.

Gubler, D. J. (1998). Dengue and Dengue Hemorrhagic Fever. *Clinical Microbiology Reviews*, *11*(3), 480–496. https://doi.org/10.1128/CMR.11.3.480

Gubler, D. J. (2002). Epidemic dengue/dengue hemorrhagic fever as a public health, social and economic problem in the 21st century. *Trends Microbiology,* 2002;10:100–103

Gubler, D. J. (2011). Dengue, urbanization and globalization: the unholy trinity of the 21st century. *Tropical Medicine & Health,* 39 (4 Suppl): S3-S11. https://doi.org/10.2149/tmh.2011-S05

Gubler, D. J., & Clark, G. C. (1995). Community involvement in the control of *Aedes aegypti*. *Acta Tropica,* 61:169-179

Gubler, D. J., Suharyono, W., Lubis, I., Eram, S., & Sulianti Saroso, J. (1979). Epidemic dengue hemorrhagic fever in rural Indonesia. I. Virological and epidemiological studies. *American Journal Tropical Medicine and Hygiene,* 28:701–710

Guzman, M. G., Alvarez, M., & Halstead, S. B. (2013). Secondary infection as a risk factor for dengue hemorrhagic fever/dengue shock syndrome: An historical perspective and role of antibody-dependent enhancement of infection. *Archives of Virology*, 158(7), 1445–1459. https://doi.org/10.1007/s00705-013-1645-3

Guzman, M. G., Alvarez, M., Rodriguez, R., Rosario, D., Vazquez, S., Valdes, L., Cabrera, M. V., & Kourí, G. (1999). Fatal dengue hemorrhagic fever in Cuba, 1997. *International Journal of Infectious Diseases,* 3:130–135

Guzman, M. G., Alvarez, A., Vazquez, S., Alvarez, M., Rosario, D., Pelaez, O., Cruz, G., Rodriguez, R., Pavon, A., Gonzalez, A., Morier, L., Ruiz, D., Kourí, G., & Halstead, S. B. (2012). Epidemiological studies on dengue virus type 3 in Playa municipality, Havana, Cuba, 2001–2002. *International Journal of Infectious Diseases,* 16(3):e198–e203

Guzman, M. G., Halstead, S. B., Artsob, H., Buchy, P., Farrar, J., Gubler, D. J., Hunsperger, E., Kroeger, A., Margolis, H. S., Martínez, E., Nathan, M. B., Pelegrino, J. L., Simmons, C., Yoksan, S., & Peeling, R. W. (2010). Dengue: A continuing global threat. *Nature Reviews*, Microbiology, 8(12 Suppl), S7-16. https://doi.org/10.1038/nrmicro2460

Hadinegoro, S. R. S. (2012). The revised WHO dengue case classification: Does the system need to be modified? *Paediatrics and International Child Health*, *32*(sup1), 33–38. https://doi.org/10.1179/2046904712Z.00000000052

Hallegatte, S., Fay, M., & Barbier, E. B. (2018). Poverty and climate change: Introduction. *Environment and Development Economics*, 23(3), 217–233. https://doi.org/10.1017/S1355770X18000141

Halstead, S. B. (1982). Immune Enhancement of Viral Infection. *Immunity and Concomitant Immunity in Infectious Diseases*, *31*, 301–364. https://doi.org/10.1159/000406537

Halstead, S. B. (1992). The XXth century dengue pandemic: Need for surveillance and research. *World Health Statistics Quarterly*, 45(2–3), 292–298

Halstead, S. B. (2016). Licensed Dengue Vaccine: Public Health Conundrum and Scientific Challenge. *The American Journal of Tropical Medicine and Hygiene*, *95*(4), 741–745. https://doi.org/10.4269/ajtmh.16-0222

Halstead, S. B., Nimmannitya, S., & Cohen, S. N. (1970). Observations related to pathogenesis of dengue hemorrhagic fever. IV. Relation of disease severity to antibody response and virus recovery. *The Yale Journal of Biology and Medicine*, *42*(5), 311–328

Halstead, S. B., Scanlon, J. E., Umpaivit, P., & Udomsakdi, S. (1969). Dengue and Chikungunya Virus Infection in Man in Thailand, 1962–1964: IV. Epidemiologic Studies in the Bangkok Metropolitan Area. *The American Journal of Tropical Medicine and Hygiene*, *18*(6), 997–1021. https://doi.org/10.4269/ajtmh.1969.18.997

Halstead, S. B., Sun, W., Kanesa-Thasan, N., Russell, K., Putvatana, R., Streit, T. G., Lafontant, J. G., Watts, D. M., & Hayes, C. G. (2001). Haiti: Absence of dengue hemorrhagic fever despite hyperendemic dengue virus transmission. *The American Journal of Tropical Medicine and Hygiene*, 65(3), 180–183. https://doi.org/10.4269/ajtmh.2001.65.180

Hamby, D. M. (1994). A review of techniques for parameter sensitivity analysis of environmental models. *Environmental Monitoring and Assessment*, 32(2), 135–154. https://doi.org/10.1007/BF00547132

Hart, C. E., Roundy, C. M., Azar, S. R., Huang, J. H., Yun, R., Reynolds, E., Leal, G., Nava, M. R., Vela, J., Stark, P. M., Debboun, M., Rossi, S., Vasilakis, N., Thangamani, S., & Weaver, S. C. (2017). Zika Virus Vector Competency of Mosquitoes, Gulf Coast, United States. *Emerging Infectious Diseases*, 23(3), 559–560. https://doi.org/10.3201/eid2303.161636

Hassell, J. M., Begon, M., Ward, M., & Fevre, E. M. (2017). Urbanization and Disease Emergence: Dynamics at the Wildlife–Livestock–Human Interface. *Trends in Ecology and Evolution,* 32(1), 55-67

Hayes, C. G., Wallace, M. R., Iriye, C., Sanchez, J. L., Burans, J. P., Sharp, T. W., Thornton, S. A., DeFraites, R. F., Arthur, R. R., Batchelor, R. A., Rozmajzl, P. J., Hanson, R. K., & Wu, S. J. (1995). Dengue Fever in U.S. Troops during Operation Restore Hope, Somalia, 1992–1993. *The American Journal of Tropical Medicine and Hygiene*, 53(1), 89–94. https://doi.org/10.4269/ajtmh.1995.53.89

Heymann, D. L. (2015). Control of Communicable Diseases Manual: An Official Report of the American Public Health Association. 20th edition. Washington, DC: APHA Press, an imprint of the American Public Health Association

Honorio, N. A., Codeco, C. T., Alves, F. C., Magalhaes, M. A., & Lourenco-De-Oliveira, R. (2009). Temporal distribution of *Aedes aegypti* in different districts of Rio de Janeiro, Brazil, measured by two types of traps. *Journal of Medical Entomology*, Sep;46(5):1001-14

Huber, J. H., Childs, M. L., Caldwell, J. M., & Mordecai, E. A. (2018). Seasonal temperature variation influences climate suitability for dengue, chikungunya, and Zika transmission. *PLOS Neglected Tropical Diseases*, *12*(5), e0006451. https://doi.org/10.1371/journal.pntd.0006451

Huey, S. J., Tilley, J. L., Jones, E. O., & Smith, C. A. (2014). The contribution of cultural competence to evidence-based care for ethnically diverse populations. *Annual Review of Clinical Psychology*, 10, 305–338. https://doi.org/10.1146/annurev-clinpsy-032813-153729

Huisman, W., Martina, B. E. E., Rimmelzwaan, G. F., Gruters, R., & Osterhaus, A. D. M. E. (2009). Vaccine-induced enhancement of viral infections. *Vaccine*, *27*(4), 505–512. https://doi.org/10.1016/j.vaccine.2008.10.087

Institute of Medicine (US) Committee on a Strategy for Minimizing the Impact of Naturally Occurring Infectious Diseases of Military Importance: Vaccine Issues in the U.S. Military. (2002). Protecting Our Forces: Improving Vaccine Acquisition and Availability in the U.S. Military (S. M. Lemon, S. Thaul, S. Fisseha, & H. C. O'Maonaigh, Eds.). National Academies Press (US). http://www.ncbi.nlm.nih.gov/books/NBK220962/

International Federation of Red Cross and Red Crescent. (2014). Myanmar: Community health workers receive training about dengue fever, malaria, and diarrhoea. https://www.ifrc.org/en/news-and-media/news-stories/asia-pacific/myanmar/myanmar-community-health-workers-receive-training-about-dengue-fever-malaria-and-diarrhoea-65370/

Johnson, L. R., Ben-Horin, T., Lafferty, K. D., McNally, A., Mordecai, E., Paaijmans, K. P., Pawar, S., & Ryan, S. J. (2015). Understanding uncertainty in temperature effects on vector-borne disease: A Bayesian approach. *Ecology*, *96*(1), 203–213. https://doi.org/10.1890/13-1964.1

Kalayanarooj, S., Gibbons, R. V., Vaughn, D., Green, S., Nisalak, A., Jarman, R. G., Mammen, M. P., Jr, & Perng, G.C. (2007). Blood Group AB Is Associated with Increased Risk for Severe Dengue Disease in Secondary Infections. *The Journal of Infectious Diseases*, 195(7), 1014–1017. https://doi.org/10.1086/512244

Keeling, M. J., & Rohani, P. (2008). Modeling Infectious Diseases in Humans and Animals. Princeton University Press.

Keeling, M. J., Woolhouse, M. E. J., Shaw, D. J., Matthews, L., Chase-Topping, M., Haydon, D. T., Cornell, S. J., Kappey, J., Wilesmith, J., & Grenfell, B. T. (2001). Dynamics of the 2001 UK foot and mouth epidemic: stochastic dispersal in a heterogeneous landscape. *Science*, 294(5543), 813–817

Keesing, F., Belden, L. K., Daszak, P., Dobson, A., Harvell, C. D., Holt, R. D., Hudson, P., Jolles, A., Jones, K. E., Mitchell, C. E., Myers, S. S., Bogich, T., & Ostfeld, R. S. (2010). Impacts of biodiversity on the emergence and transmission of infectious diseases. *Nature, 468*(7324), 647–652. https://doi.org/10.1038/nature09575

Kelsey-Seybold Clinic. (2023). Travel Medicine Fee List. https://www.kelsey-seybold.com/medical-services-and-specialties/travel-clinic/price-list

Kitchener, S. J. (2010). The development of dengue vaccines and their military significance. *Australian Military Medicine,* Vol 9(2): 71-73.

Kitchener, S. J., Leggat, P. A., Brennan, L., & McCall, B. (2002). Importation of dengue by soldiers returning from East Timor to north Queensland, Australia. *Journal of Travel Medicine*, Jul-Aug;9(4):180-3. doi 10.2310/7060.2002.24234. PMID: 12962610

Kliks, S. C., Nimmanitya, S., Nisalak, A., & Burke, D. S. (1988). Evidence that maternal dengue antibodies are important in the development of dengue hemorrhagic fever in infants. *The American Journal of Tropical Medicine and Hygiene*, *38*(2), 411-419

Koenraadt, C. J. M., & Harrington, L. C. (2008). Flushing effect of rain on container-inhabiting mosquitoes *Aedes aegypti* and *Culex pipiens* (Diptera: Culicidae). *Journal of Medical Entomology*, 45(1), 28–35. https://doi.org/10.1603/0022-585(2008)45[28:feoroc]2.0.co;2

Kourí, G., Guzmán, M. G., Valdés, L., Carbonel, I., del Rosario, D., Vazquez, S., Laferté, J., Delgado, J., & Cabrera, M. V. (1998). Reemergence of dengue in Cuba: A 1997 epidemic in Santiago de Cuba. *Emerging Infectious Diseases*, 4(1), 89–92.

Kraemer, M. U., Sinka, M. E., Duda, K. A., Mylne, A. Q., Shearer, F. M., Barker, C. M., Moore, C. G., Carvalho, R. G., Coelho, G. E., Van Bortel, W., Hendrick, G., Schaffner, F., Elyazar, I. R., Teng, H. J., Brady, O. J., Messina, J. P., Pigott, D. M., Scott, T. W., Smith, D. L., … Hay, S. I. (2015). The global distribution of the arbovirus vectors *Aedes aegypti and Ae. Albopictus*. *ELife*, *4*, e08347. https://doi.org/10.7554/eLife.08347

Kraemer, M. U. G., Reiner, R. C., Brady, O. J., Messina, J. P., Gilbert, M., Pigott, D. M., Yi, D., Johnson, K., Earl, L., Marczak, L. B., Shirude, S., Davis Weaver, N., Bisanzio, D., Perkins, T. A., Lai, S., Lu, X., Jones, P., Coelho, G. E., Carvalho, R. G., … Golding, N. (2019). Past and future spread of the arbovirus vectors *Aedes aegypti* and *Aedes albopictus*. *Nature Microbiology*, 4(5), Article 5. https://doi.org/10.1038/s41564-019-0376-y

Lasluisa, D., Barrios, E., & Vasilieva, O. (2019). Optimal Strategies for Dengue Prevention and Control during Daily Commuting between Two Residential Areas. *Processes*, 7(4), 197. doi:10.3390/pr7040197

Laver, S. M., Wetzels, J., & Behrens, R. H. (2001). Knowledge of malaria, risk perception, and compliance with prophylaxis and personal and environmental preventive measures in travelers exiting Zimbabwe from Harare and Victoria Falls International airport. *Journal of Travel Medicine*, 8(6), 298–303. https://doi.org/10.2310/7060.2001.23975

Lavery, J. V., Scott, T. W., & Harrington, L. C. (2008). Ethical, Social, and Cultural Considerations for Site Selection for Research with Genetically Modified Mosquitoes. *The American Journal of Tropical Medicine and Hygiene*, 79(3), 312–318. https://doi.org/10.4269/ajtmh.2008.79.312

Leggat, P. A. (2006). Risk assessment in travel medicine. *Travel Medicine and Infectious Disease*, 4(3), 127–134. https://doi.org/10.1016/j.tmaid.2005.06.005

Le Gonidec, E., Maquart, M., Duron, S., Savini, H., Cazajous, G., Vidal, P.-O., Chenilleau, M.-C., Roseau, J. B., Benois, A., Dehan, C., Kugelman, J., Leparc-Goffart, I., & Védy, S. (2016). Clinical Survey of Dengue Virus Circulation in the Republic of Djibouti between 2011 and 2014 Identifies Serotype 3 Epidemic and Recommends Clinical Diagnosis Guidelines for Resource Limited Settings. *PLoS Neglected Tropical Diseases*, 10(6), e0004755. https://doi.org/10.1371/journal.pntd.0004755

Leta, S., Beyene, T. J., De Clercq, E. M., Amenu, K., Kraemer, M. U. G., & Revie, C. W. (2018). Global risk mapping for major diseases transmitted by *Aedes aegypti* and *Aedes albopictus*. *International Journal of Infectious Diseases*, 67(25-35).

Li, R., Xu, L., Bjørnstad, O. N., Liu, K., Song, T., Chen, A., Xu, B., Liu, Q., & Stenseth, N. C. (2019). Climate-driven variation in mosquito density predicts the spatiotemporal dynamics of dengue. *Proceedings of the National Academy of Sciences of the United States of America*, *116*(9), 3624–3629. https://doi.org/10.1073/pnas.1806094116

Libraty, D. H., Acosta, L. P., Tallo, V., Segubre-Mercado, E., Bautista, A., Potts, J. A., Jarman, R. G., Yoon, I.-K., Gibbons, R. V., Brion, J. D., & Capeding, R. Z. (2009). A prospective nested case-control study of Dengue in infants: Rethinking and refining the antibody-dependent enhancement dengue hemorrhagic fever model. *PLoS Medicine*, 6(10), e1000171. https://doi.org/10.1371/journal.pmed.1000171

Lim, S. K., Lee, Y., Namkung, S., Lim, J., & Yoon, I. K. (2016). Prospects for dengue vaccines for travelers. *Clinical and Experimental Vaccine Research*, 5, 89. https://doi.org/10.7774/cevr.2016.5.2.89

Lipsitch, M., Cohen, T., Cooper, B., Robins, J. M., Ma, S., James, L., Gopalakrishnan, G., Chew, S. K., Tan, C. C., Samore, M. H., Fisman, D., & Murray, M. (2003). Transmission dynamics and control of severe acute respiratory syndrome. *Science*, 300(5627), 1966–1970. https://doi.org/10.1126/science.1086616

Liu, Y., Lillepold, K., Semenza, J. C., Tozan, Y., Quam, M. B. M., & Rocklöv, J. (2020). Reviewing estimates of the basic reproduction number for dengue, Zika and chikungunya across global climate zones. *Environmental Research*, 182. 109114. https://doi.org/10.1016/j.envres.2020.109114

Louis, C. (2012). *Daily Newspaper View of Dengue Fever Epidemic, Athens, Greece, 1927–1931*—Volume 18, Number 1—January 2012—*Emerging Infectious Diseases, 18(1), 78.* https://doi.org/10.3201/eid1801.110191

Lounibos, L. P., Suárez, S., Menéndez, Z., Nishimura, N., Escher, R. L., O'Connell, S. M., & Rey, J. R. (2002). Does temperature affect the outcome of larval competition between *Aedes aegypti* and *Aedes albopictus*? *Journal of Vector Ecology*, 27(1), 86–95.

Lourenço, J., & Recker, M. (2014). The 2012 Madeira Dengue Outbreak: Epidemiological Determinants and Future Epidemic Potential. *PLoS Neglected Tropical Diseases*, *8*(8), e3083. https://doi.org/10.1371/journal.pntd.0003083

Luna, J. E., Chain, I., Hernandez, J., Clark, G. G., Bueno, A., Escalante, R., Angarita, S., & Martinez, A. (2004). Social Mobilization Using Strategies of Education and Communication to Prevent Dengue Fever in Bucarmanga, Colombia. *Dengue Bulletin*. 28;17-22

Mahmud, M. A. F., Abdul Mutalip, M. H., Lodz, N. A., Muhammad, E. N., Yoep, N., Hashim, M. H., Paiwai, F., Rajarethinam, J., Aik, J., & Muhammad, N. A. (2018). Environmental management for dengue control: a systematic review protocol. *British Medical Journal,* 9 doi: 10.1136/bmjopen-2018-026101

Mallhi, T. H., Khan, A. H., Sarriff, A., Adnan, A. S., & Khan, Y. H. (2017). Determinants of mortality and prolonged hospital stay among dengue patients attending tertiary care hospital: A cross-sectional retrospective analysis. *BMJ Open*, 7(7), e016805. https://doi.org/10.1136/bmjopen-2017-016805

Massad, E., Amaku, M., Coutinho, F. A. B., Struchiner, C. J., Burattini, M. N., Khan, K., Liu-Helmersson, J., Rocklöv, J., Kraemer, M. U. G., & Wilder-Smith, A. (2018). Estimating the probability of dengue virus introduction and secondary autochthonous cases in Europe. *Scientific Reports*, 8(1), 4629. https://doi.org/10.1038/s41598-018-22590-5

Mboera, L. E. G., Sindato, C., Mremi, I. R., Rumisha, S. F., George, J., Ngolongolo, R., Misinzo, G., Karimuribo, E. D., Rweyemamu, M. M., Haider, N., Hamid, M. A., & Kock, R. (2021). Socio-ecological Systems Analysis of the Prevention and Control of Dengue in two Districts of Dar es Salaam City, Tanzania [Preprint]. In Review. https://doi.org/10.21203/rs.3.rs-508043/v1

McCarthy, M. (2001). Should visits to relatives carry a health warning? *The Lancet*, *357*(9259), 862. https://doi.org/10.1016/S0140-6736(05)71796-7

McLeroy, K. R., Bibeau, D., Steckler, A., & Glanz, K. (1988). An ecological perspective on health promotion programs. *Health Education Quarterly*, 15(4), 351–377. https://doi.org/10.1177/109019818801500401

Melanson, V. R., Ryu, M., Gagnon, M., Hall, G., Mackey, K., Min, J., Turner, M., Burpo, F. J., & Barnhill, J. (2019). Combating Dengue: A US Military Perspective. *Virology & Retrovirology Journal,* 2(2):123

Mermin, J. H., Townes, J. M., Gerber, M., Dolan, N., Mintz, E. D., & Tauxe, R. V. (1998). Typhoid Fever in the United States, 1985-1994: Changing Risks of International Travel and Increasing Antimicrobial Resistance. *Archives Internal Medicine,* 158(6):633–638. doi:10.1001/archinte.158.6.633

Messina, J. P., Brady, O. J., & Golding, N. (2019). The current and future global distribution and population at risk of dengue. *Nature Microbiology* 4, 1508–1515 https://doi.org/10.1038/s41564-019-0476-8

Meynard, J. B., Chaudet, H., Texier, G., Ardillon, V., Ravachol, F., Deparis, X., Jefferson, H., Dussart, P., Morvan, J., & Boutin, J. P. (2008). Value of syndromic surveillance within the Armed Forces for early warning during a dengue fever outbreak in French Guiana in 2006. *BMC Medical Informatics and Decision Making*, 8, 29. https://doi.org/10.1186/1472-6947-8-29

Moncayo, A. C., Baumblatt, J., Thomas, D., Harvey, K. A., Atrubin, D., Stanek, D., Sotir, M., Hunsperger, E., Muñoz-Jordan, J. L., Jentes, E. S., Sharp, T. M., & Arguello, D. F. (2015). Dengue among American Missionaries Returning from Jamaica, 2012. *The American Journal of Tropical Medicine and Hygiene*, *92*(1), 69–71. https://doi.org/10.4269/ajtmh.14-0341

Monge-Maillo, B., Norman, F. F., Pérez-Molina, J. A., Navarro, M., Díaz-Menéndez, M., & López-Vélez, R. (2014). Travelers visiting friends and relatives (VFR) and imported infectious disease: Travelers, immigrants, or both? A comparative analysis. *Travel Medicine and Infectious Disease*, 12(1), 88–94. https://doi.org/10.1016/j.tmaid.2013.07.004

Moore, J., Beeker, C., Harrison, J. S., Eng, T. R., & Doll, L. S. (1995). HIV risk behavior among Peace Corps Volunteers. *AIDS*, Jul;9(7):795-9. doi 10.1097/00002030-199507000-00018. PMID: 7546426

Mordecai, E. A., Cohen, J. M., Evans, M. V., Gudapati, P., Johnson, L. R., Lippi, C. A., Miazgowicz, K., Murdock, C. C., Rohr, J. R., Ryan, S. J., Savage, V., Shocket, M. S., Stewart Ibarra, A., Thomas, M. B., & Weikel, D. P. (2017). Detecting the impact of temperature on transmission of Zika, dengue, and chikungunya using mechanistic models. *PLOS Neglected Tropical Diseases*, 11(4), e0005568. https://doi.org/10.1371/journal.pntd.0005568

Morse, S. P. (1968). A Mathematical Model for the Analysis of Contour-Line Data. *Journal of the Association for Computing Machinery*, 15(2), 205-220. https://doi.org/10.1145/321450.321454

Mulligan, K., Dixon, J., Joanna Sinn, C.-L., & Elliott, S. J. (2015). Is dengue a disease of poverty? A systematic review. *Pathogens and Global Health*, 109(1), 10–18. https://doi.org/10.1179/2047773214Y.0000000168

Murray, C. K., & Horvath, L. L. (2007). An Approach to Prevention of Infectious Diseases during Military Deployments. *Clinical Infectious Diseases,* 44:424-30

Murray, K. O., Rodriguez, L. F., Herrington, E., Kharat, V., Vasilakis, N., Walker, C., Turner, C., Khuwaja, S., Arafat, R., Weaver, S. C., Martinez, D., Kilborn, C., Bueno, R., & Reyna, M. (2013). Identification of Dengue Fever Cases in Houston, Texas, with Evidence of Autochthonous Transmission Between 2003 and 2005. *Vector-Borne and Zoonotic Diseases,* 13(12), 835–845. https://doi.org/10.1089/vbz.2013.1413

Mushanyu, J., Chukwu, W., Nyabadza, F., & Muchatibaya, G. (2021). Modelling the potential role of super spreaders on COVID-19 transmission dynamics (p. 2021.08.30.21262341). *medRxiv*. https://doi.org/10.1101/2021.08.30.21262341

National Environment Agency. (2022). Dengue in Singapore. https://www.nea.gov.sg/dengue-zika/dengue/dengue-cases

National Institute of Meteorology (INMET). (2022). Brazil Weather, Conventional Stations (1961-2019). https://www.kaggle.com/datasets/saraivaufc/conventional-weather-stations-brazil?resource=download&select=weather_stations_codes.csv

Ndeffo-Mbah, M. L. (2021, August 31). *Lecture 1. Modeling the Dynamics of Infectious Diseases* [PowerPoint Slides]. Texas A&M University.

Ndeffo-Mbah, M. L., & Pandey, A. (2020). Global Risk and Elimination of Yellow Fever Epidemics. *The Journal of Infectious Diseases*, 221(12), 2026–2034. https://doi.org/10.1093/infdis/jiz375

Nelson, K. E., & Williams, C. M. (2007). *Infectious Disease Epidemiology: Theory and Practice*, Jones & Bartlett Learning.

Newton, E. A., & Reiter, P. (1992). A model of the transmission of dengue fever with an evaluation of the impact of ultra-low volume (ULV) insecticide applications on dengue epidemics. *American Journal of Tropical Medicine and Hygiene,* 47:709–720

Ngonghala, C. N., Ryan, S. J., Tesla, B., Demakovsky, L. R., Mordecai, E. A., Murdock, C. C., & Bonds, M. H. (2021). Effects of changes in temperature on Zika dynamics and control. *Journal of The Royal Society Interface*, 18(178), rsif.2021.0165, 20210165. https://doi.org/10.1098/rsif.2021.0165

Nii-Trebi, N. I. (2017). Emerging and Neglected Infectious Diseases: Insights, Advances, and Challenges. *BioMed Research International*, *2017*, 1–15. https://doi.org/10.1155/2017/5245021

Noble, L. M., Willcox, A., & Behrens, R. H. (2012). Travel Clinic Consultation and Risk Assessment. *Infectious Disease Clinics of North America*, 26(3), 575–593. https://doi.org/10.1016/j.idc.2012.05.007

Nordhaus, W., Azam, Q., Corderi, D., Hood, K., Victor, N. M., Mohammed, M., Milter, A., & Weiss, J. (2006). The G-Econ Database on Gridded Output: Methods and Data. Yale University Press

Ocasionez, R., Cortes, F. M., Villar, L. A., & Gomez, S. Y. (2006). Temporal distribution of dengue virus serotypes in Colombian endemic area and dengue incidence. Re-introduction of dengue3 associated to mild febrile illness and primary infection. *Memorias do Instituto Oswaldo Cruz,* 101:725–731

Oidtman, R. J., Lai, S., Huang, Z., Yang, J., Siraj, A. S., Reiner, R. C., Tatem, A. J., Perkins, T. A., & Yu, H. (2019). Inter-annual variation in seasonal dengue epidemics driven by multiple interacting factors in Guangzhou, China. *Nature Communications*, *10*(1), 1148. https://doi.org/10.1038/s41467-019-09035-x

O'Leary, D. R., Rigau-Pérez, J. G., Hayes, E. B., Vorndam, A. V., Clark, G. G., & Gubler, D. J. (2002). Assessment of dengue risk in relief workers in Puerto Rico after Hurricane Georges, 1998. *The American Journal of Tropical Medicine and Hygiene*, *66*(1), 35–39. https://doi.org/10.4269/ajtmh.2002.66.35

Osorio, J. E., Wallace, D., & Stinchcomb, D. T. (2016). A recombinant, chimeric tetravalent dengue vaccine candidate based on a dengue virus serotype 2 backbone. *Expert Review of Vaccines*, 15(4), 497–508. https://doi.org/10.1586/14760584.2016.1128328

Paaijmans, K. P., Wandago, M. O., Githeko, A. K., & Takken, W. (2007). Unexpected High Losses of Anopheles gambiae Larvae Due to Rainfall. *PLoS ONE*, 2(11), e1146. https://doi.org/10.1371/journal.pone.0001146

Pan American Health Organization. (2013). Pueblo Pitanga. http://www.pueblopitanga.com/

Pancharoen, C., Mekmullica, J., & Thisyakorn, U. (2001). Primary dengue infection: what are the clinical distinctions from secondary infection? *Southeast Asian Journal Tropical Medicine and Public Health* 32:476–480

Pasco County. (2022). Mosquito Control. Resources: Mosquito Biology. https://www.pascomosquito.org/resources/mosquito-biology/

Patz, J. A., Campbell-Lendrum, D., Holloway, T., & Foley, J. A. (2005). Impact of regional climate change on human health. *Nature*, 438(7066), 310–317. https://doi.org/10.1038/nature04188

Peace Corps. (2022). Fast Facts. https://www.peacecorps.gov/news/fast-facts

Peace Corps. (2023). Explore Get to Know Us. https://www.peacecorps.gov/

Peace Corps Medical Care. (2022). Medical Care During Service. https://www.peacecorps.gov/volunteer/health-and-safety/medical-care-during-service/

Peeling, R. W., Artsob, H., Pelegrino, J. L., Buchy, P., Cardosa, M. J., Devi, S., Enria, D. A., Farrar, J., Gubler, D. J., Guzman, M. G., Halstead, S. B., Hunsperger, E., Kliks, S., Margolis, H. S., Nathanson, C. M., Nguyen, V. C., Rizzo, N., Vázquez, S., & Yoksan, S. (2010). Evaluation of diagnostic tests: Dengue. *Nature Reviews Microbiology*, 8(12), Article 12. https://doi.org/10.1038/nrmicro2459

Peragallo, M. S., Nicoletti, L., Lista, F., & D'Amelio, R. (2003). East Timor Dengue Study Group. Probable dengue virus infection among Italian troops, East Timor, 1999-2000. *Emerging Infectious Diseases*, Jul;9(7):876-80. doi 0.3201/eid0907.020496. PMID: 12890333; PMCID: PMC3023449

Perkins, T. A., Siraj, A. S., Ruktanonchai, C. W., Kraemer, M. U. G., & Tatem, A. J. (2016). Model-based projections of Zika virus infections in childbearing women in the Americas. *Nature Microbiology*, 1(9), 1–7. https://doi.org/10.1038/nmicrobiol.2016.126

Pliego Pliego, E., Velázquez-Castro, J., Eichhorn, M. P., & Fraguela Collar, A. (2018). Increased efficiency in the second-hand tire trade provides opportunity for dengue control. *Journal of Theoretical Biology*, 437, 126–136. https://doi.org/10.1016/j.jtbi.2017.10.025

Pollett, S., Kuklis, C. H., Barvir, D. A., Jarman, R. G., Romaine, R. M., Forshey, B. M., & Gromowski, G. D. (2022). The seroepidemiology of dengue in a US military population based in Puerto Rico during the early phase of the Zika pandemic. *PLoS Neglected Tropical Diseases*, 16(1), e0009986. https://doi.org/10.1371/journal.pntd.0009986

Porter, K. R., Beckett, C. G., Kosasih, H., Tan, R. I., Alisjahbana, B., Rudiman, P. I., Widjaja, S., Listiyaningsih, E., Ma'roef, C. N., McArdle, J. L., Parwati, I., Sudjana, P., Jusuf, H., Yuwono, D., & Wuryadi, S. (2005). Epidemiology of dengue and dengue hemorrhagic fever in a cohort of adults living in Bandung, West Java, Indonesia. *American Journal of Tropical Medicine and Hygiene,* 72:60–66

Poulos, C., Boeri, M., Coulter, J., Huang, L., Schley, K., & Pugh, S. J. (2022). Travelers' preferences for tick-borne encephalitis vaccination. *Expert Review of Vaccines*, 21(10), 1495–1504. https://doi.org/10.1080/14760584.2022.2108798

Prattay, K. M. R., Sarkar, M. R., Shafiullah, A. Z. M., Islam, M. S., Raihan, S. Z., & Sharmin, N. (2022). A retrospective study on the socio-demographic factors and clinical parameters of dengue disease and their effects on the clinical course and recovery of the patients in a tertiary care hospital of Bangladesh. *PLoS Neglected Tropical Diseases,* 16(4), e0010297. https://doi.org/10.1371/journal.pntd.0010297

Promprou, S., Jaroensutasinee, M., & Jaroensutasinee, K. (2005). *Climatic Factors Affecting Dengue Haemorrhagic Fever Incidence in Southern Thailand*. *29*, 8.

Rapid Sigma Solutions LLP. (2022). Sigma Magic Analysis Software. Contour and Surface Plot Blog. https://www.sigmamagic.com/blogs/contour-plot/

Reiner, R. C., Jr., Achee, N., Barrera, R., Burkot, T. R., Chadee, D. D., Devine, G. J., Endy, T., Gubler, D., Hombach, J., Kleinschmidt, I., Lenhart, A., Lindsay, S. W., Longini, I., Mondy, M., Morrison, A. C., Perkins, T. A., Vazquez-Prokopec, G., Reiter, P., Ritchie, S. A., … Scott, T. W. (2016). Quantifying the Epidemiological Impact of Vector Control on Dengue. *PLoS Neglected Tropical Diseases*, 10(5), e0004588. https://doi.org/10.1371/journal.pntd.0004588

Reiter, P. (1998). *Aedes alpobictus* and the world trade in used tires, 1988-1995: The shape of things to come? *Journal of the American Mosquito Control Association*; 14: 83–94

Reiter, P., Lathrop, S., Bunning, M., Biggerstaff, B., Singer, D., Tiwari, T., Baber, L., Amador, M., Thirion, J., Hayes, J., Seca, C., Mendez, J., Ramirez, B., Robinson, J., Rawlings, J., Vorndam, V., Waterman, S., Gubler, D., Clark, G., & Hayes, E. (2003). Texas Lifestyle Limits Transmission of Dengue Virus. *Emerging Infectious Diseases*, 9(1), 86–89. https://doi.org/10.3201/eid0901.020220

Reñosa, M. D. C., Wachinger, J., Bärnighausen, K., Aligato, M. F., Landicho-Guevarra, J., Endoma, V., Landicho, J., Bravo, T. A., Demonteverde, M. P., Guevarra, J. R., de Claro, N., III, Inobaya, M., Adam, M., Chase, R. P., & McMahon, S. A. (2021). How can human-centered design build a story-based video intervention that addresses vaccine hesitancy and bolsters vaccine confidence in the Philippines? A mixed method protocol for project SALUBONG. *BMJ Open*, 11(6), e046814. https://doi.org/10.1136/bmjopen-2020-046814

Rivera, L., Biswal, S., Sáez-Llorens, X., Reynales, H., López-Medina, E., Borja-Tabora, C., Bravo, L., Sirivichayakul, C., Kosalaraksa, P., Martinez Vargas, L., Yu, D., Watanaveeradej, V., Espinoza, F., Dietze, R., Fernando, L., Wickramasinghe, P., Duarte Moreira, E., Jr., Fernando, A. D., Gunasekera, D., … Borkowski, A. (2021). Three-year Efficacy and Safety of Takeda's Dengue Vaccine Candidate (TAK-003). Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 75(1), 107–117. https://doi.org/10.1093/cid/ciab864

Rogers, D. J., & Randolph, S. E. (2006). Climate Change and Vector-Borne Diseases. *Advances in Parasitology*, Vol 62, 345-381

Rothman, A. L., & Ennis, F. A. (1999). Immunopathogenesis of Dengue Hemorrhagic Fever, *Virology*, Volume 257:1; 1-6 ISSN 0042-6822, https://doi.org/10.1006/viro.1999.9656. https://www.sciencedirect.com/science/article/pii/S0042682299996563

Rowe, K., Chaves, N., & Leder, K. (2017). Challenges to providing pre-travel care for travellers visiting friends and relatives: An audit of a specialist travel medicine clinic. *Journal of Travel Medicine*, *24*(5), tax038. https://doi.org/10.1093/jtm/tax038

Ruche, G. L., Souarès, Y., Armengaud, A., Peloux-Petiot, F., Delaunay, P., Desprès, P., Lenglet, A., Jourdain, F., Leparc-Goffart, I., Charlet, F., Ollier, L., Mantey, K., Mollet, T., Fournier, J. P., Torrents, R., Leitmeyer, K., Hilairet, P., Zeller, H., Bortel, W. V., … Gastellu-Etchegorry, M. (2010). First two autochthonous dengue virus infections in metropolitan France, September 2010. *Eurosurveillance*, *15*(39), 19676. https://doi.org/10.2807/ese.15.39.19676-en

Rückert, C., Weger-Lucarelli, J., Garcia-Luna, S. M., Young, M. C., Byas, A. D., Murrieta, R. A., Fauver, J. R., & Ebel, G. D. (2017). Impact of simultaneous exposure to arboviruses on infection and transmission by *Aedes aegypti* mosquitoes. *Nature Communications*, 8(1), Article 1. https://doi.org/10.1038/ncomms15412

Ryan, S. J., Carlson, C. J., Tesla, B., Bonds, M. H., Ngonghala, C. N., Mordecai, E. A., Johnson, L. R., & Murdock, C. C. (2021). Warming temperatures could expose more than 1.3 billion new people to Zika virus risk by 2050. *Global Change Biology*, *27*(1), 84–93. https://doi.org/10.1111/gcb.15384

Salje, H., Alera, M. T., Chua, M. N., Hunsawong, T., Ellison, D., Srikiatkhachorn, A., Jarman, R. G., Gromowski, G. D., Rodriguez-Barraquer, I., Cauchemez, S., Cummings, D. A. T., Macareo, L., Yoon, I.-K., Fernandez, S., & Rothman, A. L. (2021). Evaluation of the extended efficacy of the Dengvaxia vaccine against symptomatic and subclinical dengue infection. *Nature Medicine*, 27(8), Article 8. https://doi.org/10.1038/s41591-021-01392-9

Salmon, D. A., & Dudley, M. Z. (2020). It is time to get serious about vaccine confidence. *The Lancet*, 396(10255), 870–871. https://doi.org/10.1016/S0140-6736(20)31603-2

Sánchez-González, L., Venuto, M., Poe, S., Major, C. G., Baskara, L., Abdiyeva, S., Murphy, D., Munoz-Jordan, J. L., Medina, F. A., Paz-Bailey, G., Petersen, K., Becker, K., & Sharp, T. M. (2021). Dengue Virus Infections among Peace Corps Volunteers in Timor-Leste, 2018–2019. *The American Journal of Tropical Medicine and Hygiene*, 104(6), 2202–2209. https://doi.org/10.4269/ajtmh.21-0020

Sangkawibha, N., Rojanasuphot, S., Ahandrik, S., Viriyapongse, S., Jatanasen, S., Salitul, V., Phanthumachinda, B., & Halstead, S. B. (1984). Risk Factors in Dengue Shock Syndrome: a prospective epidemiologic study in Rayong, Thailand: I. The 1980 Outbreak. *American Journal of Epidemiology*, 120(5), 653–669. https://doi.org/10.1093/oxfordjournals.aje.a113932

Schaffner, F., & Mathis, A. (2014). Dengue and dengue vectors in the WHO European region: Past, present, and scenarios for the future. *The Lancet Infectious Diseases*, *14*(12), 1271–1280 https://doi.org/10.1016/S1473-3099(14)70834-5

Schwartz, E. (2012). Prophylaxis of Malaria. *Mediterranean Journal of Hematology and Infectious Diseases*, 4(1): e201245

Senda, A., Sakuntabhai, A., Inaida, S., Teissier, Y., Matsuda, F., & Paul, R. E. (2018). Estimating Frequency of Probable Autochthonous Cases of Dengue, Japan. *Emerging Infectious Diseases*, 24(9), 1705–1708. https://doi.org/10.3201/eid2409.170408

Sequeira, M., Espinoza, H., Amador, J. J., Domingo, G., Quintanilla, M., & de los Santos T. (2010). Dengue in Nicaragua. Seattle, Washington: PATH; 2010.

Shekhar, K. C., & Huat, O. L. (1992a). Epidemiology of dengue/dengue hemorrhagic fever in Malaysia--a retrospective epidemiological study 1973-1987. Part I: Dengue hemorrhagic fever (DHF). Asia-Pacific Journal of Public Health, 6(2), 15–25. https://doi.org/10.1177/101053959300600203

Shekhar, K. C., & Huat, O. L. (1992b). Epidemiology of dengue/dengue hemorrhagic fever in Malaysia--a retrospective epidemiological study. 1973-1987. Part II: Dengue fever (DF). Asia-Pacific Journal of Public Health, 6(3), 126–133. https://doi.org/10.1177/101053959200600302

Shen, C., Luo, L., Li, L., Jing, Q. L., Ou, C. Q., Yang, Z. C., & Chen, X. G. (2015). The Impacts of Mosquito Density and Meteorological Factors on Dengue Fever Epidemics in Guangzhou, China, 2006–2014: A Time-series Analysis. *Biomedical and Environmental Sciences*, 2015; 28:321–329. doi 10.3967/bes2015.046.

Silva, N. M., Santos, N. C., & Martins, I. C. (2020). Dengue and Zika Viruses: Epidemiological History, Potential Therapies, and Promising Vaccines. *Tropical Medicine and Infectious Disease*, 5(4), 150. https://doi.org/10.3390/tropicalmed5040150

Simo, F. B. N., Bigna, J. J., Kenmoe, S., Ndangang, M. S., Temfack, E., Moundipa, P. F., & Demanou, M. (2019). Dengue virus infection in people residing in Africa: A systematic review and meta-analysis of prevalence studies. *Scientific Reports*, 9(1), Article 1. https://doi.org/10.1038/s41598-019-50135-x

Siraj, A. S., Santos-Vega, M., Bouma, M. J., Yadeta, D., Carrascal, D. R., & Pascual, M. (2014). Altitudinal Changes in Malaria Incidence in Highlands of Ethiopia and Colombia. *Science*, 343(6175), 1154–1158. https://doi.org/10.1126/science.1244325

Smallman-Raynor, M. R., & Cliff, A. D. (2004). Impact of infectious diseases on war. *Infectious Disease Clinics of North America*, 18(2), 341–368. https://doi.org/10.1016/j.idc.2004.01.009

Smith, D. L., Perkins, T. A., Tusting, L. S., Scott, T. W., & Lindsay, S. W. (2013). Mosquito Population Regulation and Larval Source Management in Heterogeneous Environments. *PLoS ONE*, 8(8), e71247. https://doi.org/10.1371/journal.pone.0071247

Soda, K. J., Moore, S. M., España, G., Bloedow, J., Raybaud, B., Althouse, B., Johansson, M. A., Wenger, E., Welkhoff, P., Perkins, T. A., Perkins, T. A., & ten Bosch, Q. A. (2018). DTK-Dengue: A new agent-based model of dengue virus transmission dynamics [Preprint]. *Epidemiology*, https://doi.org/10.1101/376533

Stalidzans, E., Zanin, M., Tieri, P., Castiglione, F., Polster, A., Scheiner, S., Pahle, J., Stres, B., List, M., Baumbach, J., Lautizi, M., Van Steen, K., & Schmidt, H. H. H. W. (2020). Mechanistic Modeling and Multiscale Applications for Precision Medicine: Theory and Practice. *Network and Systems Medicine*, 3(1), 36–56. https://doi.org/10.1089/nsm.2020.0002

Takeda. (2022). Takeda's Qdenga (Dengue Tetravalent Vaccine [Live, Attenuated]) Approved for use in European Union. Press Release. https://www.takeda.com/newsroom/newsreleases/2022/takedas-qdenga-dengue-tetravalent-vaccine-live-attenuated-approved-for-use-in-european-union/

Tantracheewathorn, T., & Tantracheewathorn, S. (2007). Risk factors of dengue shock syndrome in children. *Journal Medical Association of Thailand,* 90:272–277

Tesla, B., Demakovsky, L. R., Mordecai, E. A., Ryan, S. J., Bonds, M. H., Ngonghala, C. N., Brindley, M. A., & Murdock, C. C. (2018). Temperature drives Zika virus transmission: Evidence from empirical and mathematical models. *Proceedings of Royal Society Biological Sciences*, Aug 15;285(1884):20180795. doi 10.1098/rspb.2018.0795. PMID: 30111605; PMCID: PMC6111177.

Thomas, L., Verlaeten, O., Cabie, A., Kaidomar, S., Moravie, V., Martial, J., Najioullah, F., Plumelle, Y., Fonteau, C., Dussart, P., & Cesaire, R. (2008). Influence of the dengue serotype, previous dengue infection, and plasma viral load on clinical presentation and outcome during a dengue-2 and dengue-4 co-epidemic. *American Journal of Tropical Medicine and Hygiene,* 78:990–998

Torres, J. (2019). Philippine parishes told to clean churches to fight dengue. Union of Catholic Asian News. https://www.ucanews.com/news/philippine-parishes-told-to-clean-churches-to-fight-dengue/85645#

Travel & Immunization Clinic of Portland. (2015). Resources: Appointments and Services. https://travelhealthnw.com/resources/

Trayers, F. J., Simon, J., Praske, S. P., & Christopher, K. L. (2008). Fever, Headache, and Myalgias after Deployment to the Philippines. *Military Medicine*, Volume 173 (12) 1188-1193, https://doi.org/10.7205/MILMED.173.12.1188

Trofa, A. F., DeFraites, R. F., & Smoak, B. L. (1997). Dengue fever in US military personnel in Haiti. *Journal of American Medical Association,* 277:1546–8.

Tsuda, Y., & Takagi, M. (2001). Survival and Development of *Aedes aegypti* and *Aedes albopictus* (Diptera: Culicidae) Larvae Under a Seasonally Changing Environment in Nagasaki, Japan. *Environmental Entomology*, 30(5), 855–860. https://doi.org/10.1603/0046-225X-30.5.855

Tully, D., & Griffiths, C. L. (2021). Dengvaxia: The world's first vaccine for prevention of secondary dengue. *Therapeutic Advances in Vaccines and Immunotherapy*, 9, 25151355211015840. https://doi.org/10.1177/25151355211015839

United Nations. (2021). Intergovernmental Panel on Climate Change Climate Change in 2021 The Physical Science Basis. Contribution of Working Group I to the Sixth Assessment Report of the Intergovernmental Panel on Climate Change [Masson-Delmotte, V., P. Zhai, A. Pirani, S. L. Connors, C. Péan, S. Berger, N. Caud, Y. Chen, L. Goldfarb, M. I. Gomis, M. Huang, K. Leitzell, E. Lonnoy, J.B.R. Matthews, T. K. Maycock, T. Waterfield, O. Yelekçi, R. Yu and B. Zhou (eds.)]. Cambridge University Press. In Press.

Valdez, L. D., Sibona, G. J., & Condat, C. A. (2018). Impact of rainfall on *Aedes aegypti* populations. *Ecological Modelling*, 385, 96–105. https://doi.org/10.1016/j.ecolmodel.2018.07.003

Van Herck, K., Van Damme, P., Castelli, F., Zuckerman, J., Nothdurft, H., Dahlgren, A. L., Gisler, S., Steffen, R., Gargalianos, P., Lopéz-Vélez, R., Overbosch, D., Caumes, E., & Walker, E. (2004). Knowledge, attitudes and practices in travel-related infectious diseases: The European airport survey. *Journal of Travel Medicine*, 11(1), 3–8. https://doi.org/10.2310/7060.2004.13609

Vaughn, D. W., Green, S., Kalayanarooj, S., Innis, B. L., Nimmannitya, S., Suntayakorn, S., Endy, T. P., Raengsakulrach, B., Rothman, A. L., Ennis, F. A., & Nisalak, A. (2000). Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity. *Journal of Infectious Diseases,* 181:2–9

Veregin, H. (2022). How Big is a Degree? State Cartographer's Office. https://www.sco.wisc.edu/2022/01/21/how-big-is-a-degree/

Visser, J. T., & Edwards, C. A. (2013). Dengue Fever, Tuberculosis, Human Immunodeficiency Virus, and Hepatitis C Virus Conversion in a Group of Long-Term Development Aid Workers. *Journal of Travel Medicine*, *20*(6), 361–367. https://doi.org/10.1111/jtm.12072

Wang, X., Tang, S., & Cheke, R. A. (2016). A stage structured mosquito model incorporating effects of precipitation and daily temperature fluctuations. *Journal of Theoretical Biology*, *411*, 27–36. https://doi.org/10.1016/j.jtbi.2016.09.015

Watanaveeradej, V., Simasathien, S., Mammen, M. P., Nisalak, A., Tournay, E., Kerdpanich, P., Samakoses, R., Putnak, R. J., Gibbons, R. V., Yoon, I.-K., Jarman, R. G., De La Barrera, R., Moris, P., Eckels, K. H., Thomas, S. J., & Innis, B. L. (2016). Long-Term Safety and Immunogenicity of a Tetravalent Live-Attenuated Dengue Vaccine and Evaluation of a Booster Dose Administered to Healthy Thai Children. *Am J Trop Med Hyg*, 94(6), 1348–1358. https://doi.org/10.4269/ajtmh.15-0659

Weger-Lucarelli, J., Rückert, C., Chotiwan, N., Nguyen, C., Garcia Luna, S. M., Fauver, J. R., Foy, B. D., Perera, R., Black, W. C., Kading, R. C., & Ebel, G. D. (2016). Vector Competence of American Mosquitoes for Three Strains of Zika Virus. *PLoS Neglected Tropical Diseases*, 10(10), e0005101. https://doi.org/10.1371/journal.pntd.0005101

Whitehead, S. S. (2016). Development of TV003/TV005, a single dose, highly immunogenic live attenuated dengue vaccine; what makes this vaccine different from the Sanofi-Pasteur CYDTM vaccine? *Expert Review of Vaccines*, 15(4), 509–517. https://doi.org/10.1586/14760584.2016.1115727

Wilder-Smith, A. (2018). Risk of Dengue in Travelers: Implications for Dengue Vaccination. *Current Infectious Disease Reports*, 20(12), 50. https://doi.org/10.1007/s11908-018-0656-3

Wilder-Smith, A., & Deen, J. L. (2008). Dengue vaccines for travelers. *Expert Review of Vaccines*; 7:569-78.

World Health Organization. (1997). Dengue Haemorrhagic Fever: Diagnosis, Treatment, Prevention and Control. Second Edition. World Health Organization

World Health Organization. (2008). The World Health Report 2008: Primary Health Care Now More than Ever. *Rapport Sur La Santé Dans Le Monde 2008* : Les Soins de Santé Primaires - Maintenant plus Que Jamais, 119.

World Health Organization. (2009). Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. New Edition. World Health Organization. https://apps.who.int/iris/handle/10665/41988

World Health Organization. (2014). Ebola Virus Disease in West Africa—The First 9 Months of the Epidemic and Forward Projections. *New England Journal of Medicine*, *371*(16), 1481–1495. https://doi.org/10.1056/NEJMoa1411100

World Health Organization. (2018). Vaccines and Immunization: Dengue. https://www.who.int/news-room/questions-and-answers/item/dengue-vaccines

World Health Organization. (2019). Dengue and Severe Dengue https://www.who.int/multi-media/details/dengue-and-severe-dengue

World Health Organization. (2019b). Ten threats to global health in 2019. https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019

World Health Organization. (2020). Vector-borne Diseases. https://www.who.int/news-room/fact-sheets/detail/vector-borne-diseases

World Health Organization. (2021). Dengue and Dengue Hemorrhagic Fever: Fact Sheet. http://who.int/mediacentre/factsheets/fs117/en/print.html

World Health Organization. (2022). Neglected Tropical Diseases. Fact Sheets Dengue and Severe Dengue. https://www.who.int/health-topics/neglected-tropical-diseases#tab=tab_1

WorldPop.org. (2018). School of Geography and Environmental Science, University of Southampton; Department of Geography and Geosciences, University of Louisville; Departement de Geographie, Universite de Namur) and Center for International Earth Science Information Network (CIESIN), Columbia University. Global High Resolution Population Denominators Project - Funded by The Bill and Melinda Gates Foundation (OPP1134076). www.worldpop.org

Wright, W. F., & Pritt, B. S. (2012). Update: The diagnosis and management of dengue virus infection in North America. *Diagnostic Microbiology and Infectious Disease*, 73(3), 215–220. https://doi.org/10.1016/j.diagmicrobio.2012.03.021

Zemke, J. N., Sanchez, J. L., Pang, J., & Gray, G. C. (2019). The Double-Edged Sword of Military Response to Societal Disruptions: A Systematic Review of the Evidence for Military Personnel as Pathogen Transmitters, *The Journal of Infectious Diseases*, 220(12): 1873-1884, https://doi.org/10.1093/infdis/jiz400

Zhang, M., Liu, Z., He, H., Luo, L., Wang, S., Bu, H., & Zhou, X. (2011). Knowledge, attitudes, and practices on malaria prevention among Chinese international travelers. *Journal of Travel Medicine*, 18(3), 173–177. https://doi.org/10.1111/j.1708-8305.2011.00512.x

Zhang, Q., Sun, K., Chinazzi, M., Pastore y Piontti, A., Dean, N. E., Rojas, D. P., Merler, S., Mistry, D., Poletti, P., Rossi, L., Bray, M., Halloran, M. E., Longini, I. M., & Vespignani, A. (2017). Spread of Zika virus in the Americas. *Proceedings of the National Academy of Sciences*, *114* (22), E4334–E4343. https://doi.org/10.1073/pnas.1620161114

APPENDICES

Appendix A: R_0 Functional Equations

This section holds the R_0 functional equations used as the basis for building the models depicted in this study. Each equation is labeled by the authors, and the variables are defined below. The specific values for the equations from Mordecai et al. 2017; Ngonghala et al., 2021; and Caldwell et al., 2021 utilized within the paper are defined in the tables within the text.

Model 1: Mordecai et al., 2017

$$R_0(T) = \left(\frac{a(T)^2 \, b(T) \, c(T) \, e^{-\mu(T)/PDR(T)} \, EFD(T) \, p_{EA}(T) \, MDR(T)}{N \, r \, \mu(T)^3} \right)^{1/2}$$

R_0 = # of secondary infections that would originate from a single infected individual introduced to a fully susceptible population

T= trait is a function of temperature

a = per-mosquito biting rate

b = proportion of infectious bites that infect susceptible humans

c = proportion of bites on infected humans that infect susceptible humans

(b*c) = vector competence

μ = adult mosquito mortality rate

lf= lifespan (1/ μ)

PDR = parasite development rate = inverse of the extrinsic incubation period (time required between a mosquito biting an infected host and becoming infectious)

EFD = # of eggs produced per female per day

ρEA = mosquito egg-to-adult survival probability

MDR = mosquito immature development rate (inverse of egg-to-adult development time)

N=density of humans

r = human recovery rate

Model 1 Continued

Each temperature sensitive trait was fit with symmetric (Quadratic, $=c(T-T_0)(T-T_m)$ or asymmetric (Briere, $cT(T-T_0)(T_m-T)^{1/2}$)

T_0 = Minimum temperature for transmission

T_m = maximum temperature for transmission

Model 2: Ngonghala et al., 2021

*Main difference in this model vs. Ross-Macdonald is the probability that the mosquito survives the latent period.

$$R_0 = \sqrt{\frac{b_v^2 \beta_{vh} \beta_{hv} \sigma_v}{\gamma_h \mu_v (\sigma_v + \mu_v)} \frac{N_v^*}{N_h}}.$$

Dynamics of total human population and mosquito populations

$$\dot{N}_h = 0 \quad \text{and} \quad \dot{N}_v = \left(\alpha_v \left(1 - \frac{N_v}{\kappa_v} \right) - \mu_v \right) N_v.$$

Mosquito recruitment at per capita rate (input in Sv compartment)

$$f(I_v) = \alpha_v (1 - (N_v / \kappa_v))$$

Mosquito Constant

$$\alpha_v = \theta_v \nu_v \phi_v / \mu_v$$

Mosquito population rate

$$N_v^* = \kappa_v (1 - (\mu_v / \alpha_v))$$

R_0 = Basic reproduction number

b_v = (b) # of human bites per mosquito per unit of time

β_{vh} = (beta_vh) probability that an infectious mosquito successfully transmits the virus while taking a blood meal from a susceptible human (i.e., transmission rate)

β_{hv} = (beta_hv) probability that an infectious human successfully transmits the virus to a biting susceptible mosquito (i.e., infection rate)

σ_v = (sigma_v) rate at which vectors become infectious

σ_h = (sigma_h) rate at which humans become infectious

γ_h = (gamma_h) per capita human recovery rate

γ_v = (gamma_v) per capita vector recovery rate

μ = (mu) natural mosquito death rate ($1/\mu$ = average lifespan of mosquitos)

N_h = Human population

N_v = Mosquito population

κ_v = (kappa) carrying capacity (maximum # of mosquitos a breeding site can support)

Θ_v = (theta) # of eggs a female mosquito produces per day

v_v = (nu) the probability of surviving from egg to adult

φ_v = (phi) rate at which an egg develops into an adult mosquito

α_v = (alpha) constant representing mosquito egg laying rate/egg survival rate/egg development rate

f = mosquito recruitment at a per capita rate

Model 3: Caldwell et al., 2021

Adult Mosquito Carrying Capacity Model

$$K(T,H,R) = \frac{\mathrm{EFD}(T_0) * pEA(T_0) * \mathrm{MDR}(T_0) * \mu(T_0,H_0)^{-1} - \mu(T_0,H_0)}{\mathrm{EFD}(T_0) * pEA(T_0) * \mathrm{MDR}(T_0) * \mu(T_0,H_0)^{-1}} * N_{m.\max} * e^{\frac{-E_A*(T-T_0)^2}{K_B*(T+273)*(T_0+273)}} * f(R)$$

EFD = # of eggs produced per female per day

ρEA = probability of mosquito egg-to-adult survival

MDR = mosquito immature development rate (inverse of egg-to-adult development time)

μ = adult mosquito mortality rate

lf= lifespan (1/ μ)

α = biting rate

pMI = probability of mosquito infection per bite on an infectious host

PDR = parasite development rate

b = probability of mosquito infectiousness given an infectious bite

H_0 = Humidity when the carrying capacity is greatest (optimal physiological conditions from laboratory experiments 29°C and 6kPA)

T_0 = Temperature where carrying capacity is greatest (see above)

$N_{m.max}$ = maximum mosquito abundance in a population (twice the human population)

K_B = Boltzmann constant (8.617 x10^{-5} eV/K)

E_A= Activation energy (0.05)

Modeling Rainfall (R)

$$f(R_{\mathrm{Briere}}) = c * R * (R - R_{\min}) * \sqrt{(R_{\max} - R)} * z$$

$$f(R_{\mathrm{Quadratic}}) = c * (R - R_{\min}) * (R - R_{\max}) * z$$

$$f(R_{\mathrm{Inverse}}) = \frac{1}{R} * z$$

R_{min} = 1 mm

R_{max} = 123 mm (based on the high probability of flushing)

Appendix B: Key Definitions

This section contains key critical to understanding the text.

Table B.1

Key Definitions for Epidemiologic Characteristics of Infectious Diseases

Term	Definition
Autochthonous transmission	Disease spread from one individual and is acquired in another in the same place; local transmission.
Ectotherm	An animal that is dependent on external sources of body heat (Mordecai et al., 2017)
Extrinsic incubation period	For vector-borne infections, the time it takes for the pathogen to develop within a mosquito and become transmissible; the viral incubation period between the time the mosquito takes a viremic bloodmeal and the time when said mosquito becomes infectious (Chan et al., 2012)
Fecundity	The ability to produce an abundance of offspring or new growth; fertility
Flushing	Washing away of larva habitats after a rainstorm
Intrinsic incubation period	The time between a human becoming infected and the onset of symptoms due to the infection. (Chan et al., 2012)
Latent period	The period between infection and onset of infectiousness (Chan et al., 2012)
Mathematical modeling	Mathematical models are simplified descriptions of a system or process used to assist in calculations and predictions, whereas infectious disease models are a set of equations describing the transmission of a pathogen in a population with an attempt to capture key processes while ignoring unnecessary details (Ndeffo-Mbah, 2021)
Mechanistic modeling	A mathematical description of the components that form a system, their interactions with each other and interactions with the environment. (Stalidzans et al., 2020)
R-naught (R_0)	The value calculated for communicable diseases representing the total, on average, number of people that a single infected person can be expected to transmit that disease to in a susceptible population; a calculation of the *spreadability* of the disease (Mordecai et al., 2017)
Secondary Infection	A serial/subsequent infection with another Dengue virus serotype; recovery from dengue infection confer lifelong immunity to that particular strain but an individual could still get another dengue infection from one of the other strains
Sequence of Infection	The order of dengue infections; a specific virus infection and then a second infection with another virus serotype (i.e., DENV1 → DENV3; DENV2 → DENV4; DENV2 → DENV3; etc.)