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Predicting Future Disease Burden in a Rapidly Changing Climate

Amy Powell, Irina Tezaur, Warren Davis IV, Kara Peterson, Susan Rempe, Chuck Smallwood, Erika Roesler

Prepared by
Sandia National Laboratories
Albuquerque, New Mexico 87185
Livermore, California 94550

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ABSTRACT

The interplay of a rapidly changing climate and infectious disease occurrence is emerging as a critical topic, requiring investigation of possible direct, as well as indirect, connections between disease processes and climate-related variation and phenomena. First, we introduce and overview three infectious disease exemplars (dengue, influenza, valley fever) representing different transmission classes (insect-vectored, human-to-human, environmentally-transmitted) to illuminate the complex and significant interplay between climate disease processes, as well as to motivate discussion of how Sandia can transform the field, and change our understanding of climate-driven infectious disease spread. We also review state-of-the-art epidemiological and climate modeling approaches, together with data analytics and machine learning methods, potentially relevant to climate and infectious disease studies. We synthesize the modeling and disease exemplars information, suggesting initial avenues for research and development (R&D) in this area, and propose potential sponsors for this work. Whether directly or indirectly, it is certain that a rapidly changing climate will alter global disease burden. The trajectory of climate change is an important control on this burden, from local, to regional and global scales. The efforts proposed herein respond to the National Research Council's call for the creation of a multidisciplinary institute that would address critical aspects of these interlocking, cascading crises.

ACKNOWLEDGMENT

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1. INTRODUCTION

Global climate change is transforming the infectious disease landscape. Rising seas, increasing ocean and air surface temperatures, altered patterns of precipitation, humidity and radiative effects, polar ice sheet loss and deepening drought in arid regions are setting the stage for potentially significantly higher disease burdens for societies across the globe. That climate and weather contribute substantially to disease patterns and processes is ancient knowledge; Hippocrates, the "Father of Medicine" (5th century BCE), observed that epidemics were associated with natural climatic phenomena (seasonal and interannual variation, the hydrological cycle and atmosphere status):

> *"Whoever would study medicine aright must learn of the following subjects. First, he must consider the effect of the seasons of the year and the differences between them. Secondly, he must study the warm and the cold winds, both those which are in common to every country and those peculiar to a particular locality. Lastly, the effect of water on the health must not be forgotten."*
> – Airs, Waters, and Places, Hippocrates

Colloquialisms that persist in our language, such as "having a cold", and "feeling under the weather", reflect our innate understanding of the relationship between climate and disease; however, despite the National Research Council's urging in 2001 to create the highly-interdisciplinary institute for this purpose [28], integrated analytic predictive frameworks for studying this interplay do not exist at the present time. The growing tide of scientific reports documenting expanding geographic and temporal disease ranges, and more frequent, intense and novel outbreaks, both agricultural and human, highlight the obvious need for quantitative, predictive understanding of how a rapidly changing climate and concomitant environmental degradation drive and modulate contagion. Our own recent work in climate [105], coupled with expertise in vector-borne diseases, microbial pathogenesis, genome-based studies and ecosystem ecology, bring together a unique capability for addressing emerging, potentially high consequence-high probability, climate-infectious disease challenges.

The U.S. defense establishment views global climate change is a "threat multiplier[1]," a generally destabilizing force for societies and economies, with exploding risks and costs of strategic priorities and missions. Similarly, the changing climate-infectious disease nexus multiplies risks and costs to societies and economies, and will further magnify inequities and structural weaknesses in agricultural production and health care systems. In recent months, the rapid spread of SARS-Coronavirus-2 (a.k.a., COVID-19) has underscored both the devastation that unforeseen, novel pathogens can visit upon society, as well as the costs, human and otherwise. Comparable

[1] https://yaleclimateconnections.org/2019/07/a-brief-introduction-to-climate-change-and-national-security/.

pandemics, in terms of prevalence (proportion of people in a population with disease), incidence (number of new cases appearing in a time interval), and mortality, include the Black Death (14th century Europe) and the 1918 Spanish Flu. Both both of these pandemics profoundly reshaped societies and economies, and it has been argued that both were indirectly the result of altered modes of climate variation (Black Death [124]), and changing land use patterns (1918 Spanish Flu), respectively.

In this effort, we focus on human pathogens, and survey the state of climate and infectious disease research and development (R&D). We also outline Sandia's potential contribution to this important research domain. To motivate discussion of the interplay of climate and infectious disease, we will use exemplars representing key transmission categories: dengue virus for insect-vectored pathogens (positive strand RNA virus belonging to the Flavivirus genus); species of *Coccidioides*, the ascomycetous soil fungus that causes Valley Fever for environmentally transmitted infectious agents; and seasonal influenza (negative strand RNA viruses belonging to the Orthomyxoviridae genus) for human-to-human communicated disease with zoonotic potential and history.

The remainder of this report is organized as follows. In Chapter 2, we introduce three exemplars mentioned in the previous paragraph, and discuss briefly how each exemplar is influenced by natural climatic variation, and also responds to a rapidly warming climate. Chapter 3 provides a review of existing models for understanding the relationships between weather, climate and disease. Towards the end of this chapter, we identify some existing modeling and knowledge gaps hampering robust prediction of climate-driven spread of infectious disease. In Chapter 4, we discuss ideas for new modeling strategies for predictive modeling of climate and infectious disease, together with insights into how genome science and bioinformatics can advance this field, focusing on R&D that is well-suited to be undertaken at Sandia National Laboratories. Concluding remarks are offered in Chapter 5, in addition to a discussion of potential sponsors.

2. DISEASE EXEMPLARS

In this chapter, we introduce three exemplars, each one representing one of three key transmission categories of disease. Coccidiomycosis, also known as "Valley Fever" (Section 2.1), is caused by a species of *Coccidioides*, a soil fungus. It is representative of a wider class of diseases that are transmitted environmentally, such as wheat rust [106] and pollen-borne viruses [156, 34]. The dengue virus (Section 2.2) is a mosquito-borne viral infection that we take as an exemplar for a broader class of insect-vectored pathogens. Finally, seasonal influenza (Section 2.3), is meant to serve as an exemplar for a class of human-to-human communicated diseases, which include the recent COVID-19 virus. The diseases described in this chapter, and, more broadly, the classes of diseases they represent, are referenced later in Chapters 3 and 4 in the context of existing and new modeling approaches aimed at understanding and improving the study of climate-driven infectious disease spread.

2.1. Coccidiomycosis ("Valley Fever") in the Americas

2.1.1. Background

Coccidioides immitis and *C. posadasii* are the etiologic agents of "Valley Fever" (VF, also known as "San Joaquin Valley Fever", desert rheumatism, and Coccidioidomycosis) in New World arid lands (Figure 2-1). The disease, first described in the 1800s by Dr. Alejandro Posadas in Argentina, presents with a range of symptoms from mild pneumonia and flu-like symptoms, to potentially deadly pulmonary or meningoencephalitis syndromes when dissemination in a patient has occurred. The incidence of VF has dramatically increased in recent years [65, 50, 49, 53]. This increase is attributed in part to improved reporting, diagnosis and awareness, but also to climate-driven shifts resulting in higher incidence and prevalence in endemic regions, exacerbated by range expansion [50, 77]. Most human and animal infections occur as a result of inhaling infectious spores that are transferred from soil to the air in dust as a result of wind and other types of disturbance, including fires that remove plant cover.

Coccidioides endemism, the natural distribution of a species, is inferred from epidemiological data, i.e., confirmed diagnoses of Coccidioidomycosis [29, 50, 73, 148]. The majority of confirmed VF cases are in the American southwest, primarily Arizona and the Central Valley of California, with recent clusters occurring beyond historical disease centers in arid regions of Washington state in 2010 [77]. Most regions of New Mexico and portions of Utah and Texas are also in the known endemic region. New Mexico has many fewer cases a year than either California or Arizona, likely the result of a combination of factors, including lower human population density, different land use practices, and the ecology of species of *Coccidioides*. In the following sections, we summarize salient features of the biology of species of *Coccidioides*, pathogenesis, transmission

and interaction with a rapidly changing climate. Later, in Chapter 4, we discuss ways in which our climate-infectious disease team can help define and advance the field.

(a) U.S.A.

(b) Americas

Figure 2-1. Endemic regions for *Coccidioides* species in the U.S. and the Americas. *Coccidioides immitis* and *C. posadasii*, causative agents of Valley Fever, are present throughout arid lands in the Americas. Evidence suggests that climate change is contributing to significantly increased prevalence and incidence. Maps were adapted from the Centers for Disease Control resources [46].

2.1.2. Life cycle, ecology and transmission mode

Coccidioides immitis and *C. posadasii* are arid land, soil-dwelling, dimorphic ascomycetous fungi belonging to the order Onygenales. Onygenealan fungi are believed to have evolved as highly adapted animal pathogens $\sim$150 million years ago, and *Coccidioides* species are estimated to have diverged ca. 5.1 million years ago, well before human arrival in the New World [127]. These organisms are dimorphic in terms life cycle, growing saprobically as mycelia (multicellular filaments) on non-living organic matter (likely decaying animal carcasses), and upon inhalation of arthroconidia (asexual durable propagules, Figure 2-2) by an animal or human host, initiate the parasitic phase of growth in a yeast-like spherule stage [53]. Long and short-term temperature and moisture

conditions control the shift from saprobic growth to parasitism in the complex *Coccidioides* life cycle (Figure 2-3). When substrates become desiccated beyond a certain threshold, mycelia form arthroconidia, which can be inhaled by humans and other animals. Inhalation of arthroconidia promote lung infections that initiate the parasitic phase of the *Coccidioides* life cycle.

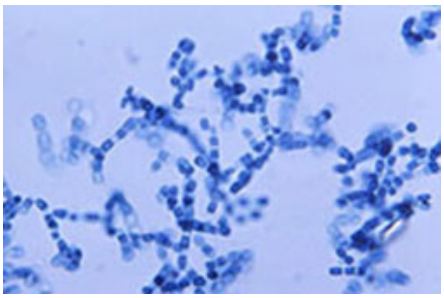


Figure 2-2. *Coccidioides* arthroconidia chains. When substrates become desiccated beyond critical thresholds, *Coccidioides* mycelia asexually differentiate into arthrocondia that are readily airborne upon soil disturbance. Human and animal hosts inhale arthroconidia, initiating pulmonary infection. Climate controls both the shift to parasitism and establishing environmental conditions that favor the atmospheric transport of arthroconidia. Image adapted from the Centers for Disease Control information about *Coccidioides* [44].

In addition to numerous potential climate-controlled points in the complex life cycle (Figure 3 2-3), there is a strong association between small-mammal burrows and soils testing positive for *Coccidioides*. Arid land rodents and other small mammals are hypothesized reservoirs, but definitive host delineations have not been made, nor has the potential role of animal reservoirs in outbreaks been made clear. A recent report provided a first molecular characterization of the small-mammal lung mycobiome (i.e., the commensal community of fungi in pulmonary tissues), and showed that potentially pathogenic members of the Onygenales were present [54], supporting the small mammals as reservoirs hypothesis. If small mammals and rodents are reservoirs for *Coccidioides*, then a rapidly changing climate will also affect the ecology of these animals, in turn, potentially changing the VF disease burden in human populations.

As mentioned above, spores of *Coccidioides* are transmitted in air, and climate substantially determines the environmental conditions that facilitate spore loads and movements. Human infections result from soil disturbance, in work-related activities (e.g., construction, agriculture, solar farms, archeological digs, etc.) and changing patterns of human settlement in arid lands. Weather events and natural disasters, such as wind and dust storms, fires and earthquakes are also important in promoting VF outbreaks [29, 65, 77, 132, 142, 148]. Additionally, prison populations and workers can have high rates of exposure and disease in regions with high endemicity [65]. Recent findings suggest a strong association between increasingly frequent dust storms and VF incidence and prevalence [142]. Coccidioidomycosis is not transmitted from human to human (the clinical aspects of Coccidioidomycosis are discussed in the "Therapeutics" section below).

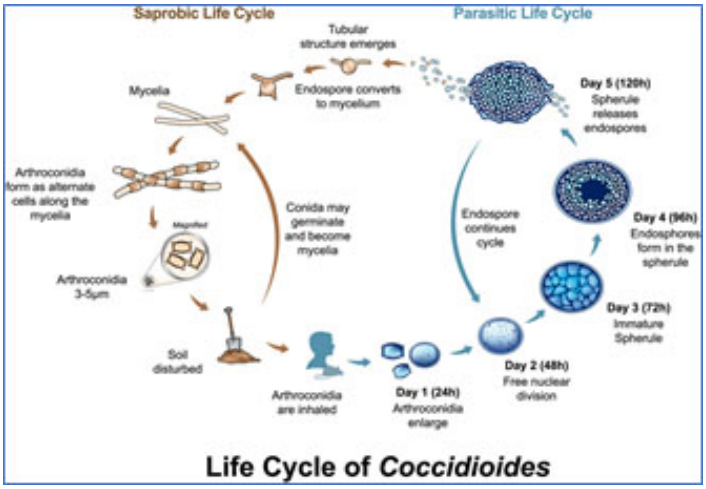


Figure 2-3. Complex lifecycle of *Coccidioides*, causative agent of Valley Fever. Species of *Coccidioides* have complex lifecycles comprised of two main modes of growth and development: saprobic and parasitic. In the saprobic mycelial mode of growth, these organisms reside in substrates (hypothesized to be decaying animals) in desert soils with suitable temperature and moisture profiles. When arid land soils become desiccated beyond a certain threshold, arthroconidia (durable, transportable infectious propagules) form, and can be inhaled by humans and other animals. Upon contact with airways, these propagules initiate the parasitic phase of the lifecycle. *In vivo*, arthroconidia form spherules, which in turn develop disease- disseminating endospores. If unchecked, disseminated endospores spread infection to other tissues, organs (spine, skin, brain), bones and joints. Figure adapted from Lewis *et al.* [73].

2.1.3. Biogeography, biodiversity and their potential impacts on disease

Populations of the two *Coccidioides* species causing VF show diversity among isolates, and also strong geographic structuring [50, 53]. A recent study based in the Four Corners region of northwestern New Mexico demonstrated the presence of *Coccidioides* in the state, with *C. posadasii* as the main infectious agent, and identified Native Americans in this area as an at-risk group. *C. immitis*, known as the "California species" was also associated with New Mexico VF cases in this study [53]. Other studies show similar magnitude of within-species diversity and geographic structuring of populations (Figure 2-4). How this genetic and phenotypic diversity in *Coccidioides* play out in a clinical setting is entirely unexplored, but accumulating evidence suggests this diversity is important in VF disease processes. Just as uncertain is how *Coccidioides* biological (genetic, phenotypic, etc.) diversity and geographic distribution will interact with a rapidly warming and drying climate; all reasonable estimates indicate expansion of the disease, both in space and time.

2.1.4. Therapeutics

Coccidioidomycosis typically presents as a pulmonary infection [53]. While the majority of infections progress asymptomatically, symptomatic VF cases present as mild flu-like symptoms,

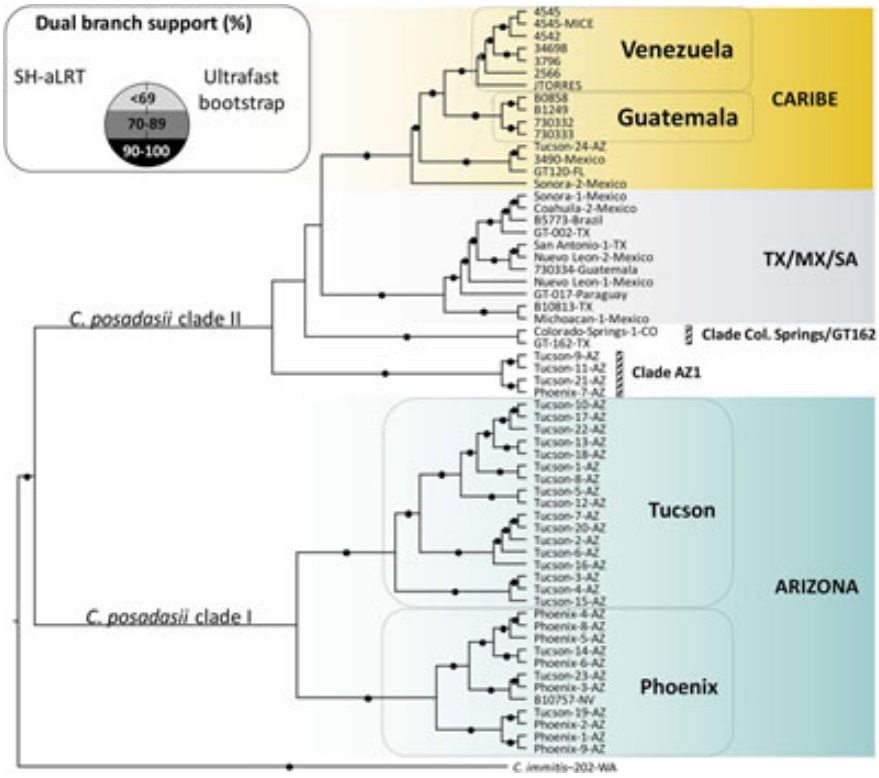


Figure 2-4. Species-Level Diversity in *Coccidioides posadasii* in the Americas. *C. posadasii* commonly causes Valley Fever (VF) outside of California. *C. posadasii* populations show strong geographical structuring, with isolates from a specific location being closely related. While evidence exists for interspecies hybridization and recombination at the population level, a sexual stage has not yet been described. The medical impact of genetic and phenotypic diversity is entirely unexplored, as are interactions with the rapidly changing climate. Panel adapted from [50].

with muscle and joint pain, rash and pulmonary symptoms [69]. Hypersensitivity skin testing (using the Coccidioidin antigen) suggest that large fractions of infected populations have few, if any symptoms. Similar to COVID-19 epidemiology, certain populations, including the immunocompromised or pharmaceutically immunosuppressed, African and Native Americans, and Filipinos are at much higher risk for severe, disseminated Coccidioidomycosis [53]. In a small percentage of cases, infection results in severe illness and death, even in immunocompetent hosts [69]. U.S. Cases of VF have increased steadily since the 1990s, with regular reporting by only 24 states and the District of Columbia (Figure 2-5). Most documented cases now occur in specific regions, e.g., southern Arizona and central California, showing high disease incidence and prevalence. States with confirmed and suspected elevated rates of endemism, such as Texas, Colorado, Oklahoma, Washington and Idaho do not report disease. Other countries in the endemic region do not systematically report Coccidioidomycosis, and therefore, the U.S. provides the only reliable, if incomplete, data for the disease [65].

Upon infection of human or animal lungs, arthroconidia form spherules, or parasitic structures

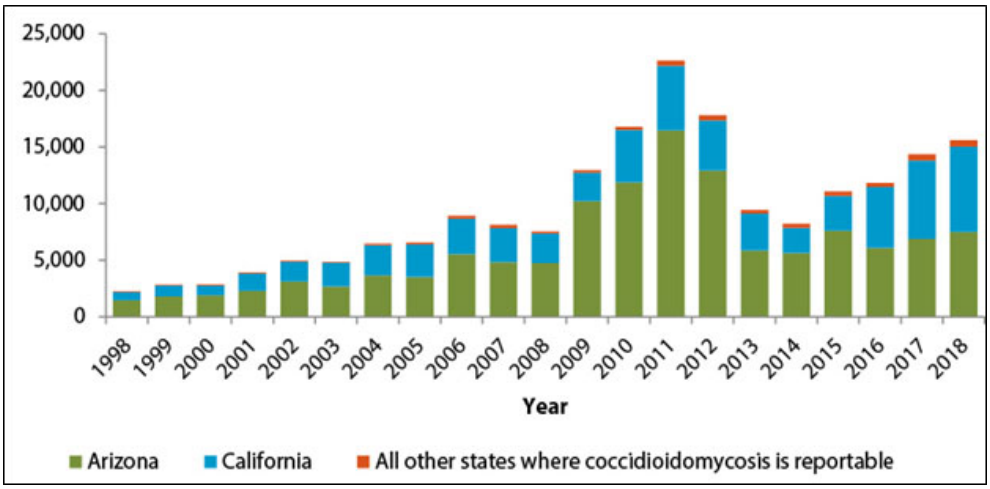


Figure 2-5. Cases of Coccidioidomycosis, or Valley Fever (VF) over time. The number Coccidioidomycosis cases have increased significantly in two decades, as indicated by confirmed diagnoses in reporting states. This dramatic increase is almost certainly an underrepresentation of the true number of cases, as many, if not most, cases are neither evaluated by, or reported to, medical authorities or state-level public health agencies. The increase in VF is attributed to better diagnostics, reporting and awareness of the medical community, but also changes in climate and human population pressures in arid lands. Chart adapted from the Centers for Disease Control Coccidioidomycosis Statistics resources [45].

that give rise to endospores, in pulmonary tissues (Figure 2-6) [93]. If severe infections remain unchecked by immune response and / pharmaceutical intervention, then spherules rupture, dispersing endospores to different tissues, organs (e.g., spleen, brain, spinal column, skin) bones and joints [65, 69]. Such severe cases can require life-long, harsh antifungal therapies, as no effective vaccine exists. The limited repertoire of antifungals slow or arrest fungal growth, but are not fungicidal. Resistance is prevalent among the main class of anti-fungals, the azoles.

2.1.5. Climate and Coccidioidomycosis

Temperature and moisture conditions are climatically controlled, and determine both *Coccidioides* endemicity and incidence. Recent reports point to endemicity in counties in the U.S. where annual mean surface temperature is at least 10°C and annual mean precipitation does not exceed 600 mm (Figure 2-7, [50, 65]). Regions such as the San Joaquin Valley of California and south-central Arizona are termed "highly endemic" with respect to VF disease incidence; highly endemic regions have at least 70 cases per 100,000 population, and an annual mean surface temperature of 16°C [65]. These same studies suggest that interannual moisture variation is a strong determinant of disease incidence, based on the life cycle of the fungus (Figure 2-3; [65]). When soil moisture is high, *Coccidioides* grows as a saprobic mycelium, but when soils become desiccated beyond a certain threshold, hyphal cells of mycelia differentiate into arthroconidia, the infectious propagule that is dispersed into the atmosphere by wind and dust (Figure 2-3). Epidemiological and climate

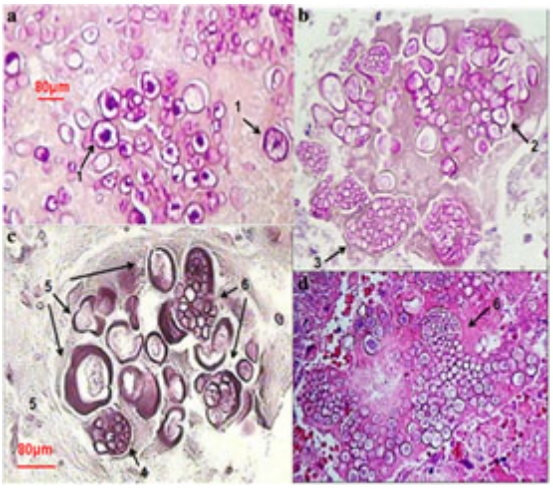


Figure 2-6. Spherule formation in pulmonary tissues initiates the parasitic phase of the *Coccidioides* life cycle in animal and human hosts. Inhalation of *Coccidioides* arthroconidia (associated with soil desiccation and disturbance in arid lands) leads to VF infection. Spherules are formed from inhaled arthroconidia, and give rise to endospores, which, if unchecked, lead to disseminated Coccidioidomycosis, invading different tissues, organs (including brain, spine and skin), bones and joints. In such severe cases, life-long treatments can be required. Panel adapted from Muñoz-Hernandez *et al.* [93].

data from Arizona show that when early summer precipitation is low, there is higher incidence of VF in the late summer. Conversely, with increased North American monsoonal activity in the early summer, the incidence of VF is lower in the late summer, ostensibly because soil conditions favor mycelial growth, versus arthroconidia development [65]. Kollath and others [65] also show an association between high winter and spring precipitation and increased VF incidence in the summer months. The explanation for this association: abundant winter and spring precipitation favoring fungal (mycelial) biomass proliferation, followed by the onset of higher temperatures in the summer that increase evaporative demand, resulting in the soil desiccation known to drive development of arthroconidia (Figures 2-2 and 2-3).

A rapidly warming climate is projected to increase VF disease burden significantly for the U.S. by 2100 [29, 50, 53, 65]. The landmark study from Gorris *et al.* [50] used a climate niche model to give county-level predictions for *Coccidioides* endemism for different time points in the 21st century with different climate trajectories: "Representative Concentration Pathway" (RCP) 4.5, an increase of 4.5°F in global mean annual temperature, and RCP 8.5, the "business as usual" pathway, with a projected increase of 8.5°F. Validated datasets from fully coupled climate models (in the "Coupled Model Intercomparison Project" (CMIP) [136, 40]), were used as inputs, as were human population projections from Shared Socioeconomic Pathways (SSP) data. Findings of this study suggest that on the "business as usual pathway" with invariant population, VF disease incidence will increase 12% by 2035, and 50% by 2095. Taking both climate change (RCP8.5) and population pressures (SSP2 and SSP5 population scenarios) into account, VF disease incidence is projected to skyrocket 72% (SSP2) or 80% (SSP5) by 2100. In both RCP scenarios, significantly expanded endemism is expected, with VF potentially ranging into the Great Plains and Canada

by 2100 under RCP8.5. Increased VF incidence and prevalence is predicted in regions where *Coccidioides* is already endemic (Figure 2-8; [50]).

While the majority of VF infections are believed to come from endemic populations, there has been some evidence that *Coccidioides* spores can be transported fairly long distances (across states) under the right atmospheric and wind conditions. In a 1979 paper by Flynn *et al.* [43], it was demonstrated that a 1977 high-velocity wind storm originating near Bakersfield, California led to the dispersion of the *C. immitis* fungi up to 700 km to the north, covering an area encompassing approximately 87,000 square kilometers.

Under all future climate scenarios, projected land use changes and demographic shifts indicate that U.S. arid lands will become hotter, drier and more populous, thus establishing environmental conditions for significantly increased VF disease burden. Given lack of reporting by states with existing endemism, together with the fact that large fractions of VF infections go undetected, undiagnosed and/or untreated in a clinical setting, the startling projections for disease burden reported by Gorris *et al.* [50] almost certainly represent underprediction (Figure 2-8).

2.1.6. Gaps

A myriad of gaps exist in all aspects of *Coccidioides* science, from the clinical and ecological, to the climatological. Here, we focus on gaps and uncertainties relevant to understanding VF endemism, range expansion and outbreaks in the context of hotter, drier arid lands in the Americas. Chief among these challenges is the dearth of longitudinal (both in time and space) epidemiological data for endemic regions. This lack of epidemiological data hampers the ability to develop climate-informed disease forecasting from year to year, and to estimate the likelihood of outbreaks in a warmer world. On the scientific side, there are no comprehensive temporally and geographically indexed collections of these organisms in a key microhabitat, desert soils, nor has there been systematic investigation of possible small mammal and rodent reservoirs, complicating interpretation of disease endemism, incidence, prevalence and outbreaks. Similarly, it is generally understood that various stages of the *Coccidioides* complex life cycle (e.g., the shift from mycelial growth to formation of infectious arthroconidia, arthroconidia dispersal by soil disturbance, fires, wind and increasing atmospheric instability, etc.) will interact with rapidly changing climate, but these presumed interactions have not been quantified on an annual basis for endemic regions, nor has arthroconidia viability been investigated under real-world conditions, such as desiccation, wide diurnal temperature variation, exposure to UV radiation, and long-range transport from point sources (animal burrows, carcasses, dust storms, etc.). Moving forward, comprehensive field, laboratory and standardized epidemiological data collection and reporting efforts, together with sophisticated climate and epidemiological modeling, will quantitatively address uncertainty in VF disease processes, seasonality, and range expansion to deliver robust disease burden forecasts for a warmer world.

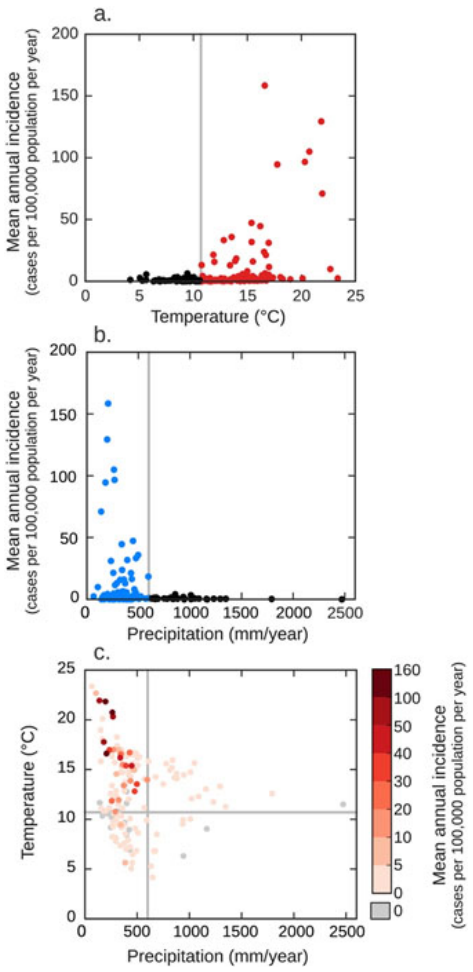


Figure 2-7. Coccidioidomycosis endemism is controlled by temperature and moisture. Valley Fever (VF) incidence for counties in the southwestern U.S. as a function of (a) mean annual temperature, (b) mean annual precipitation. Counties with endemic levels of VF (at least 10 cases per 100,000 population per year for 2000-2015) have a mean annual temperature of at least 10.7°C, and mean annual precipitation of not more than 600 mm/year. Higher VF disease incidence are observed in areas that are hotter and drier (c). Panels adapted from [50].

2.2. Dengue

2.2.1. Background

Dengue is a mosquito-borne viral infection that now affects 390 million people each year [13]. It is transmitted by the mosquitoes *Aedes aegypti* and *Aedes albopictus*. Forty percent of the world's population (3 billion people) live in areas with a risk of dengue. That area of risk is expected to expand due to climate change and urbanization [89]. Due to the high number of human infections worldwide, dengue is considered the most important of arthropod-borne viral disease in humans [28]. Dengue symptoms include fever, severe headaches, and muscle and bone pain that last 3-7

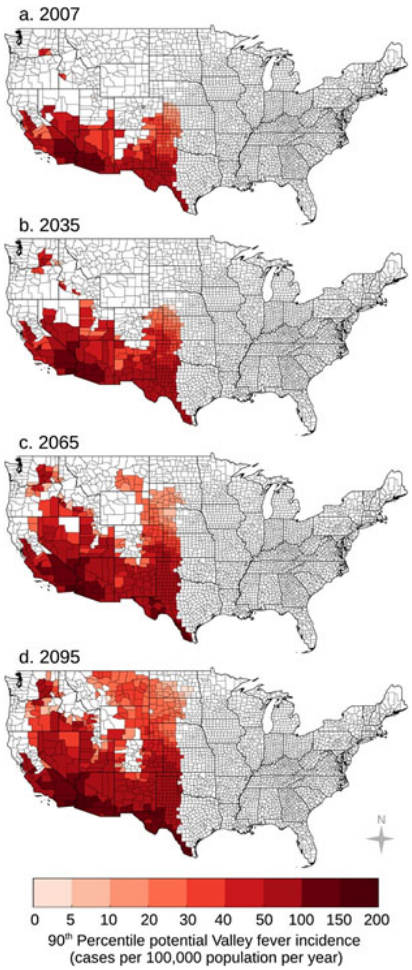


Figure 2-8. Upper bound projections for future Valley Fever (VF) incidence under the climate "business as usual" scenario. With respect to a 2007 baseline (a), projections for years up to 2095 show marked increase in VF incidence in the American west, ranging up into the Great Plains, and intensifying in regions where endemism is established. Taking only climate change into account, this increased disease burden will come with an estimated cost of $365M annually above current costs (in 2015 U.S. Dollars). Panel adapted from [50].

days after 3-14 day incubation period. Occasionally, shock and fatal hemorrhage occur. Fatality rates from dengue hemorrhagic fever is about 5 percent.

2.2.2. Lifecycle, Ecology, and Transmission Mode

Dengue virus belongs to the genus Flavivirus in the family Flaviviridae. Other members of the genus include West Nile virus, tick-borne encephalitis virus, yellow fever virus, and Zika virus. Shared features of flavivurses include size (50-65 nm), symmetry (enveloped, icosahedral nucleocapsid), nucleic acid (positive-sense single-stranded RNA), and appearance. Dengue, like zika

and yellow fever viruses, require mosquito vectors and are also replicated to high enough titers in humans to reinfect the bugs needed to continue the virus lifecycle. In other words, humans are not a dead-end host to dengue virus (Figure 2-9).

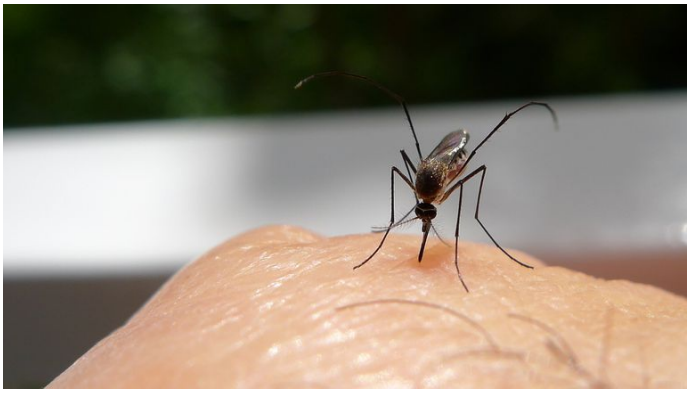


Figure 2-9. Dengue, zika, and yellow fever viruses require mosquito vectors for transmission. Humans reinfect the bugs because the virus accumulates to sufficiently high titers inside the human host. Direct interactions between mosquitoes and humans continue the virus lifecycle. Image adapted from `https://www.treehugger.com/reason-mosquitoes-bite-some-people-more-others-4858811`.

Dengue virus evolved into four serotypes (1-4), based on analysis of the envelope protein. A Bayesian analysis of all four serotypes estimated that their most recent common ancestor existed around 340 AD. The rate of nucleotide substitution is similar to other RNA viruses (6.5×10^{-4} per nucleotide per year). The American-African genotype is thought to have evolved between 1907 and 1949, spanning both world wars. The consequent movement of large populations and environmental disturbance are factors known to promote the evolution of new vector-borne viral species.

The life cycle of dengue virus starts with entry into the host cell via attachment of the viral envelope protein (E) to host receptors, which mediates endocytosis. The exact nature of the cellular receptor is unknown. Endocytosis is triggered by acidification of the endosome, which causes a conformational change to the envelope protein (E), exposing a fusion peptide that facilitates fusion of the envelope with the endosomal membrane. Molecular details of E protein binding to host cells and the membrane-membrane fusion process, and how both depend on lipid composition in the host cell membrane, are active areas of investigation pursued at Sandia [118, 68, 149] (Figure 2-10). After fusion, the virion capsid is released into the cytoplasm. Replication and transcription follow the positive-stranded RNA virus models and occurs in the cytoplasm of the host cells. Viral particles are released via exocytosis.

Transmission of dengue originally proceeded between mosquitoes of the genus *Aedes* and non-human primates in Africa, Southeast Asia, and South Asia. The global spread of dengue virus followed the shift from transmission through mosquitoes and wild animals (sylvatic cycles) to direct transmission between humans and *Aedes* mosquitoes. In fact, mosquitoes prefer to bite people, both indoors and outdoors, during the day and night (Figure 2-9) [66].

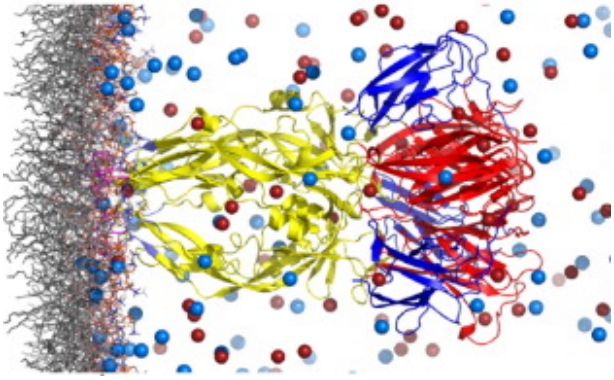


Figure 2-10. A snapshot from molecular dynamics simulations of the envelope protein of dengue virus (serotype 2, molecule colored in yellow, red, and blue and surrounded by aqueous solution of sodium chloride electrolytes, depicted as blue and red circles) inserting into lipid membranes representing a target human cell. Insertion of the envelope protein into the target membrane serves to anchor the envelope protein prior to fusion of the viral and target membranes. Molecular studies, such as these and others carried out at Sandia [118, 68, 149], focus on understanding the detailed mechanism of viral infection since fusion of the viral and target membranes are essential for infectivity. Membrane fusion is a target for therapeutic development. Figure adapted from [118].

Infection stimulates host homeostatic processes such as autophagy (orderly cell degradation and recycling) and ER (endoplasmic reticulum) stress response that stimulates the unfolding of proteins, and apoptosis, depending on infected cell type. Activation of autophagy and ER stress during infection enhances virus reproduction [33, 88].

2.2.3. Biogeography, biodiversity potential impacts on disease processes

The current distribution of dengue, based on data from 2015 (Figure 2-11), shows that the probability of dengue infection occurs in tropical and sub-tropical zones, especially in South America, Southeast Asia, and central Africa. This distribution is consistent with the historical spread of *Aedes* mosquitoes, which have driven the expansion of dengue around the world.

The four dengue serotypes occur together in the same geographical regions. An interesting characteristic of dengue is that each serotype can cause disease independently of prior infection by another serotype. When infected with dengue virus, the immune system produces cross-reactive antibodies that provide immunity to that particular serotype. Those antibodies do not neutralize other serotypes upon reinfection, but instead increase viral replication. This occurs because the virus can replicate within macrophages that consume the so-called neutralized virus, inducing more severe disease (hemorrhagic fever and shock syndrome). This effect is called antibody-dependent enhancement.

Models of the global distribution of *Aedes* mosquitoes and the geographical determinants of their ranges were developed by Kraemer, et al. [66] (Figure 2-12). The authors used a probabilistic

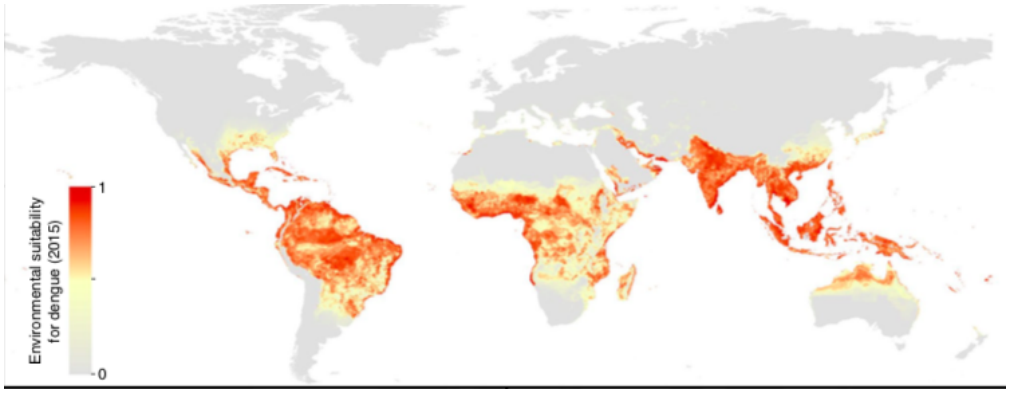


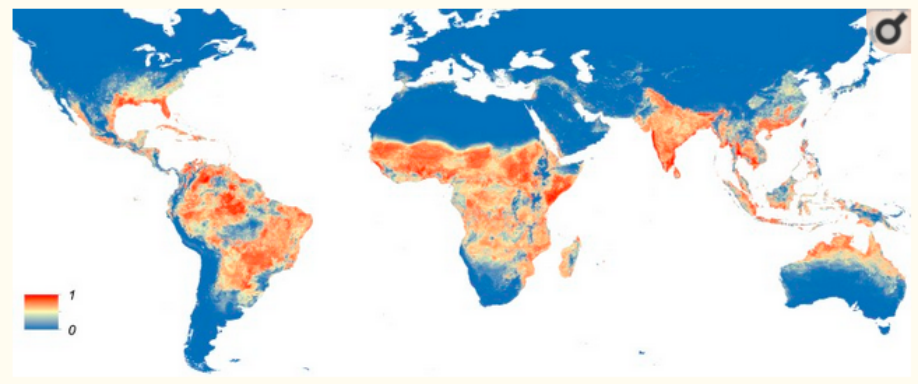
Figure 2-11. Data in a 5x5-km resolution map showing the probability of occurrence of dengue in 2015 due to suitability of the environment (red, suitable environment, gray, unsuitable environment). Environmental suitability for dengue transmission measured in terms of (a) temperature, (b) cumulative annual precipitation, (c) minimum relative humidity, (d) gross domestic product per capita, (e) human population density, (f) environmental suitability for mosquitoes *Aedes aegypti* and *Aedes albopictus*. Figure adapted from [89].

species distribution model, with boosted regression trees for each mosquito vector. The models combined both environmental, and, for the first time, land-cover variables to predict the global distribution of both mosquito species at high resolution. The results show that the *Aedes* mosquitoes have expanded their ranges and are now found all around the world. As of 2015, most *Aedes* mosquitoes occur in Asia (more than 60% of *Aedes aegypti* and 75% of *Aedes albopictus*). The distributions have expanded in both space and time, but most studies to date have focused on spatial distributions. These mosquitoes are predicted to occur primarily in the tropics and sub-tropics, with *Ae. aegypti* showing a wider geographic distribution than *Ae. albopictus*. This difference in geographic distribution is attributed to the well-established ability of *Ae. albopictus* to tolerate lower temperatures [144, 82, 138, 16]. The most important predictor of mosquito occurrence, for both *Aedes* species, was found to be temperature. This work lays an important foundation for understanding the relationship between the vectors for dengue and climate, but further work is needed to understand which factors are contributing to the rapid expansion of both mosquitoes' ranges.

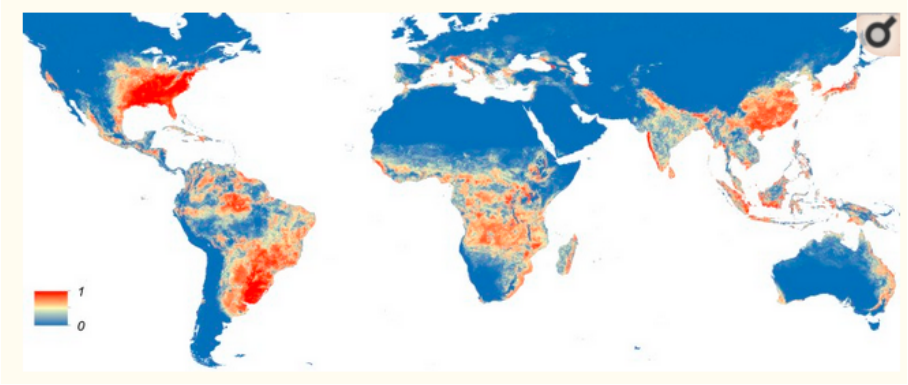
2.2.4. Therapeutics

Direct treatments for dengue fever do not exist. Most drug research for dengue infections has focused on inhibition of the NS2B/NS3 protease or NS5 proteins. NS denotes nonstructural protein. In 2013 and 2014, studies of the drug Balapiravir, an NS5 polymerase inhibitor used for hepatitis C infections, progressed to a Phase II clinical trial before being stopped due to lack of efficacy [97, 25]. Prevention consists of avoiding mosquito bites.

Currently, one vaccine is approved for dengue in eleven countries. Several vaccines are under development. The challenge to vaccine development is that it must immunize against all four serotypes to be effective. Vaccination against only one serotype could lead to severe disease when



(a)



(b)

Figure 2-12. Predicted geographical distribution of *Aedes aegypti* (a) and *Aedes albopictus* mosquitoes at a spatial resolution of 5 km x 5 km based on a probabilistic species distribution model [66]. *Aedes* mosquitoes are the primary transmission vector for dengue. Figure adapted from [66]

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infected with another serotype due to antibody-dependent enhancement, as described above. Similarly, offspring of mothers infected with dengue carry immunity to particular serotypes, but are susceptible to hemorrhagic fever if infected with any of the other serotypes.

2.2.5. Climate and Dengue Virus

The abundance of dengue vectors (mosquitoes) depends on the availability of water-filled breeding sites, such as water storage containers. The survival of eggs and adults depends on both temperature and relative humidity, taken into account as saturation deficit. Desiccation destroys eggs, high humidity destroys adult mosquitoes, but these conditions are rarely encountered in humid tropical locations [28]. Atmospheric moisture influences the rate of water loss from containers, thus affecting the abundance of dengue vectors (mosquitoes).

Temperature affects each stage of the mosquito life cycle, thus affecting potential spread of dengue virus. *A. aegypti* are tough. They can survive a broad range of temperatures (5°C to 42°C). Nev-

ertheless, temperatures below 20°C inhibit the hatching of mosquito eggs. Temperature influences the time for each stage of mosquito life cycle (embryonic, larval, pupal). Temperature plays a major role in the frequency of biting. Temperature even alters the time between mosquito bite and infection, introducing seasonality into transmission dynamics [28].

Effects of climate change on the dengue virus may be mixed. On the one hand, increased temperature by 1°C are projected to increase infection rates by as much as 47 percent, which translates into more people with multiple infections and thus serious dengue illness. On the other hand, higher temperatures may lower atmospheric moisture levels, which could reduce dengue transmission [28].

Messina and colleagues performed statistical modeling to predict the influence of the environment on future global distribution of dengue infection [89]. This work differs from prior modeling efforts by being the first to restrict the models to make predictions only within areas that correspond to the occurrence and future potential spread of relevant mosquito populations (*Ae. aegypti* and *Ae. albopictus*). Those researchers fit a boosted regression tree statistical model based on more than 13,000 locations of dengue infection between 1960 and 2015. In their model, they also included a set of environmental covariates to characterize the distribution of dengue: temperature suitable for dengue transmission, cumulative annual precipitation, minimum relative humidity, and environmental suitability for mosquitoes that transmit dengue (*Aedes aegypti* and *Aedes albopictus*) from the work of Kraemer [66]. In addition to environmental covariates, the models also included socioeconomic covariates of gross domestic product per capita and human population density.

The resulting predictions (Figure 2-13) show increasing probability that dengue will occur in certain regions, and declining probability in other regions. Notably, those models predict that the suitability of dengue is particularly influenced by the environmental variables of temperature, precipitation, and relative humidity, contributing 68, 13, and 6 percent to the variation in the ensemble of models. Much of the southeastern USA is predicted to become suitable to dengue by 2050, and the risk of dengue infection is predicted to extend to higher altitudes in central Mexico, northern areas of Argentina and inland areas of Australia. The largest increases in suitability are predicted in southern Africa and West Africa, due to more favorable temperatures and increased rainfall. Globally, the models predict about 2.25 billion more people will be at risk of dengue in 2080 compared to 2015, mainly due to changes in temperature. That scenario would bring the total population at risk to over 6 billion people, or 60% of the world's population.

2.3. Influenza

2.3.1. Introduction/background

Influenza virus is a pathogen of global health significance, but human-to-human transmission remains poorly understood. In particular, the relative importance of the different modes of transmission (direct and indirect contact, large droplet, and aerosols (airborne droplet nuclei)) remains uncertain during symptomatic and asymptomatic infection [17, 64, 135]. Concerns about the likely occurrence of an influenza pandemic in the near future are increasing. The highly pathogenic strains of influenza A (H5N1) virus circulating in Asia, Europe, and Africa have become the most

Figure 2-13. Changes in the environmental suitability for dengue occurrence predicted for years 2020-2050 by the modeling presented in [89]. Areas of expansion denoted in red, areas of contraction denoted in blue. Declines in suitability occur as geographical areas become hotter and drier, while expansion of suitability occurs with temperatures and increased rainfalls that favor mosquito breeding, survival, and biting activity. Figure adapted from [89].

feared candidates for giving rise to a pandemic strain. The evidence base for influenza transmission is derived from studies that have assessed virus deposition and survival in the environment, the epidemiology of disease; pharmaceutical and non-pharmaceutical interventions, animal models and mathematical models of transmission. Those approaches have yet to produce conclusive data quantifying the relative importance of human-human transmission modes.

In temperate regions, wintertime influenza epidemics are responsible for considerable morbidity and mortality. These seasonal epidemics are maintained by the gradual antigenic drift of surface antigens, which enables the influenza virus to evade host immune response. Recent influenza epidemics have resulted from the cocirculation of three virus (sub)types, A/H1N1, A/H3N2, and B, with one generally predominant locally in a given winter. In contrast, influenza pandemic activity can occur any time of year, including during spring or summer months, in the rare instances when a novel virus to which humans have little or no immunity jumps from avian or mammalian hosts into the human population, as in the on-going H1N1v pandemic. Despite numerous reports describing wintertime transmission of epidemic influenza in temperate regions, our understanding of the mechanisms underlying influenza seasonal variation remains very limited.

Despite 70 years of research since the influenza virus A was discovered, there continues to be a vocal debate about the modes of influenza transmission, specifically whether influenza is transmitted via the airborne route, via the droplet or contact route, or a combination of these routes [67]. Establishing how influenza is transmitted under different circumstances, and whether transmission requires close contact, is of great importance because the results will have a major influence on the choice of infection control measures in health-care settings. Infection control guidance for pandemic and seasonal influenza assumes that most transmission occurs during symptomatic infection, predominantly via large droplet spread at short range (1-2m). Thus, social distancing measures are often proposed to mitigate the spread and impact of a pandemic. Hand washing, and respiratory etiquette are also promoted to reduce transmission.

During the past 100 years, four pandemics of human influenza have occurred, with the 1918 pandemic caused by an influenza A H1N1 virus being the most devastating, as it was associated with more than 40 million deaths. Influenza A H2N2, H3N2 and H1N1 viruses caused the 1957, 1968 and 2009 pandemics, respectively. In 1977, influenza A H1N1 restarted circulation in humans without causing a pandemic, as the strain was similar to that which preceded the 1957 influenza A H2N2 pandemic. In contrast, the 2009 pandemic influenza A H1N1 virus was antigenically very different to the previous seasonal influenza A H1N1 viruses and replaced them as the circulating influenza A H1N1 strain. Examples of the spreading of human influenza A viruses in the world are shown for pandemic 1918 and 1957 viruses and for seasonal H3N2 viruses (Figure 2-14). For pandemic virus outbreaks, the arrows in the figure indicate the first and second waves of transmission. For seasonal influenza A H3N2 spread, the arrows indicate the seeding hierarchy of seasonal influenza A (H3N2) viruses over a 5-year period, starting from a network of major cities in east and southeast Asia; the hierarchy within the city network is unknown. Seasonal influenza B viruses (not shown) are co-circulating in humans with influenza A viruses.

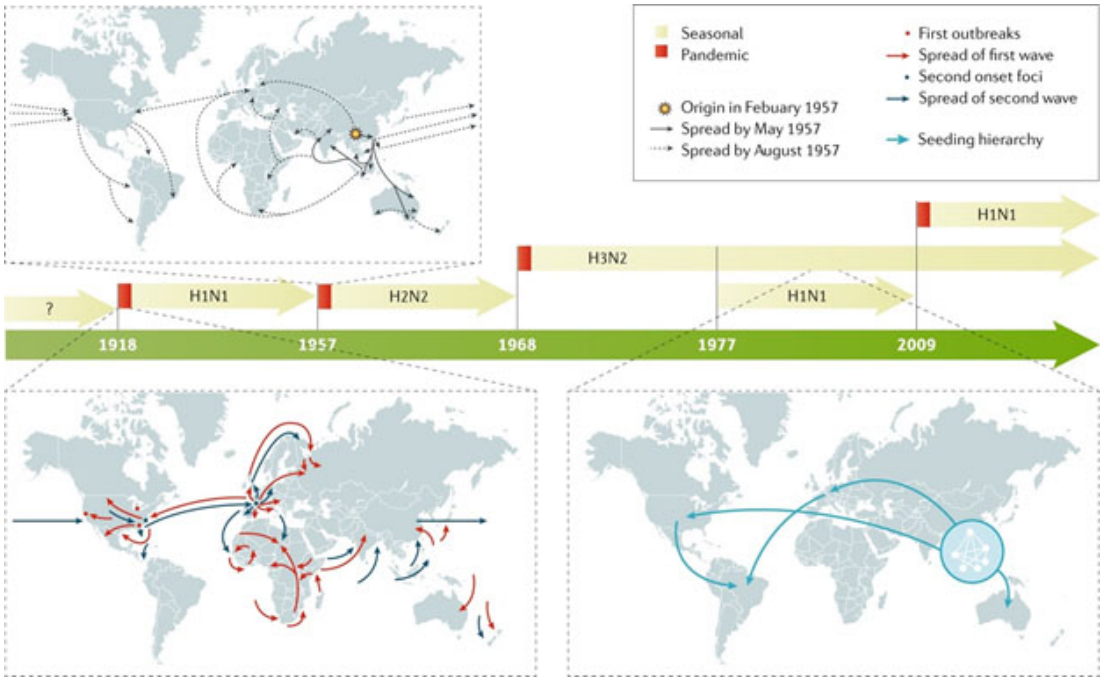


Figure 2-14. Timeline of influenza geographical spread (from [67])

2.3.2. Influenza epidemiology and ecology

The influenza virus, like all of its viral cousins, is a shell of protein and lipid protecting a nucleic acid core. In, addition to these general features, it has characteristics typical to the orthomyxoviridae family to which it belongs, including a complicated structure of plasma membrane derived from the host cell enveloping sequential protein shells and, finally the virus' RNA genome. Like HIV and the smallpox virus, the influenza virus recognizes particular receptor molecules on the outside of a human cell. In this case, the appropriate receptors are usually found in the cells of the

respiratory tract such as the epithelial cell lining of the throat, bronchial tubes, and trachea. The availability and identity of the receptors accounts for why some viruses infect particular species better than others. For example, a chicken has different receptor molecules on the surface of its cells than a human, and the viral HA proteins usually stick more strongly to the receptor of one species than another. The cases of avian flu in which the virus jumped from birds to humans can be explained by viral mutations in the composition of the virus' outer coat, resulting in "stickier" virions that now bind to human cells (Figure 2-15). There has also been evidence that the avian flu virus is more difficult to transmit between humans because only human cells deep within the respiratory tract have the necessary receptors to the stick to the virus.

In theory, influenza viruses can be transmitted through aerosols, large droplets, or direct contact with secretions (or fomites) [135]. These three modes are not mutually exclusive. Humans acutely infected with influenza A virus have a high virus titer in their respiratory secretions, which will be aerosolized when the patient sneezes or coughs. The viral titer measured in nasopharyngeal washes culminates on approximately day two or three after infection and can reach up to 10^7 50% tissue culture infective dose (TCID50)/mL [94]. The persistence of the infectivity of influenza virus in aerosols has been studied in the laboratory. In experiments that used homogeneous aerosolized influenza virus suspensions (mean diameter 6 μm), virus infectivity (assessed by in vitro culture) at a fixed relative humidity undergoes an exponential decay; this decay is characterized by very low death rate constants, provided that the relative humidity was in the low range of 15%–40%. In all these studies, the decay of virus infectivity increased rapidly at relative humidity $> 40\%$. The increased survival of influenza virus in aerosols at low relative humidity has been suggested as a factor that accounts for the seasonality of influenza.

Influenza virus enters the cell by endosomal uptake and release, and its negative-sense genetic material in the form of viral ribonucleoproteins (vRNPs) is imported to the nucleus for transcription of mRNA and replication through a positive-sense complementary ribonucleoprotein (cRNP) intermediate. Viral mRNA is translated into viral proteins in the cytoplasm, and these are assembled into new virions together with the newly synthesized vRNPs (Figure 2-16). In the case of influenza virus, constant mutation via antigenic shift and drift, and a wide, shifting host range also add an additional layer of complexity to the interpretation of the existing data: different strains of influenza clearly behave differently, and this also depends on the species infected. For example, avian influenza strains are generally transmitted between birds via the faecal-oral route, yet transmission of avian strains to human beings is believed to occur mostly via direct contact between infected bird secretions and human respiratory mucosa. Therefore, we do not believe that the results of animal transmission studies can necessarily be extrapolated to human beings, but rather, should provide guidance in developing appropriate human-based studies.

Influenza A viruses have been found in multiple species all seemingly derived from viral ancestors in wild birds, with the possible exception of bat influenza-like virus, which is of still uncertain origin. Influenza viruses from wild birds can spill over through water or fomites to marine mammals and to domestic free-range ducks. Transmissions to other avian species (for example, poultry) from domestic ducks or directly from wild birds can also occur from contaminated water. Transmission from ducks to other species occurs through 'backyard' farming, whereby the animals are raised together, and in live poultry and/or animal markets. Transmission from backyard to commercial farms can occur via lack of biosecurity and via spread through live markets (Figure 2-17). Humans

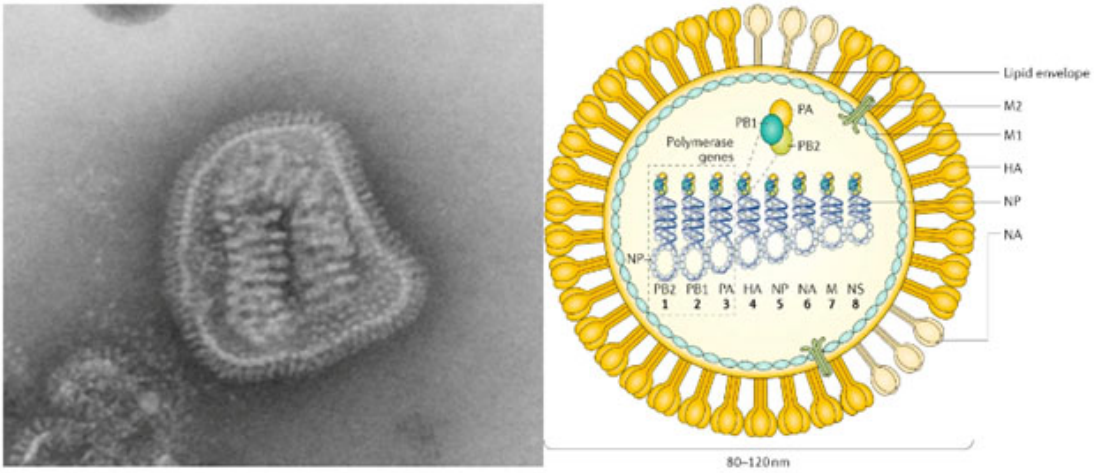


Figure 2-15. Influenza A virus particle or virion. The figure represents an influenza A virus particle or virion. Both influenza A and influenza B viruses are enveloped negative-sense RNA viruses with genomes comprising eight single-stranded RNA segments located inside the virus particle. Although antigenically different, the viral proteins encoded by the viral genome of influenza A and influenza B viruses have similar functions: the three largest RNA segments encode the three subunits of the viral RNA-dependent RNA polymerases (PB1, PB2 and PA) that are responsible for RNA synthesis and replication in infected cells; two RNA segments encode the viral glycoproteins haemagglutinin (HA, which has a 'stalk' domain and a 'head' domain), which mediates binding to sialic acid-containing receptors and viral entry, and neuraminidase (NA), which is responsible for releasing viruses bound to non-functional receptors and helping viral spread. The RNA genome is bound by the viral nucleoprotein (NP), which is encoded by RNA segment 5. RNA segments 6 and 8 encode more than one protein, namely, the matrix protein (M1) and membrane protein (M2) – BM2 in the case of influenza B – and the nonstructural protein NS1 (not shown) and nuclear export protein (NEP). The M1 protein is thought to provide a scaffold that helps the structure of the virion and that, together with NEP, regulates the trafficking of the viral RNA segments in the cell; the M2 protein is a proton ion channel that is required for viral entry and exit and that, together with the HA and NA glycoproteins, is located on the surface of the virus anchored in a lipid membrane derived from the infected cell. Finally, the NS1 protein is a virulence factor that inhibits host antiviral responses in infected cells. The influenza viruses can also express additional accessory viral proteins in infected cells, such as PB1-F2 and PA-x (influenza A), that participate in preventing host innate antiviral responses together with the NS1 protein or NB (influenza B), the function of which is unknown. NS1, NEP, PB1-F2 and PA-x are not present in the virus particle or are present in only very small amounts. NB is a unique influenza B virus surface protein anchored in the lipid membrane of the virus particles. Figure adapted from [146] and [67].

can be infected with poultry and swine influenza viruses through aerosols, fomites or contaminated water. However, in most instances these infections do not result in subsequent human-to-human transmission. Human-to-human transmission of seasonal or pandemic human viruses can be medi-

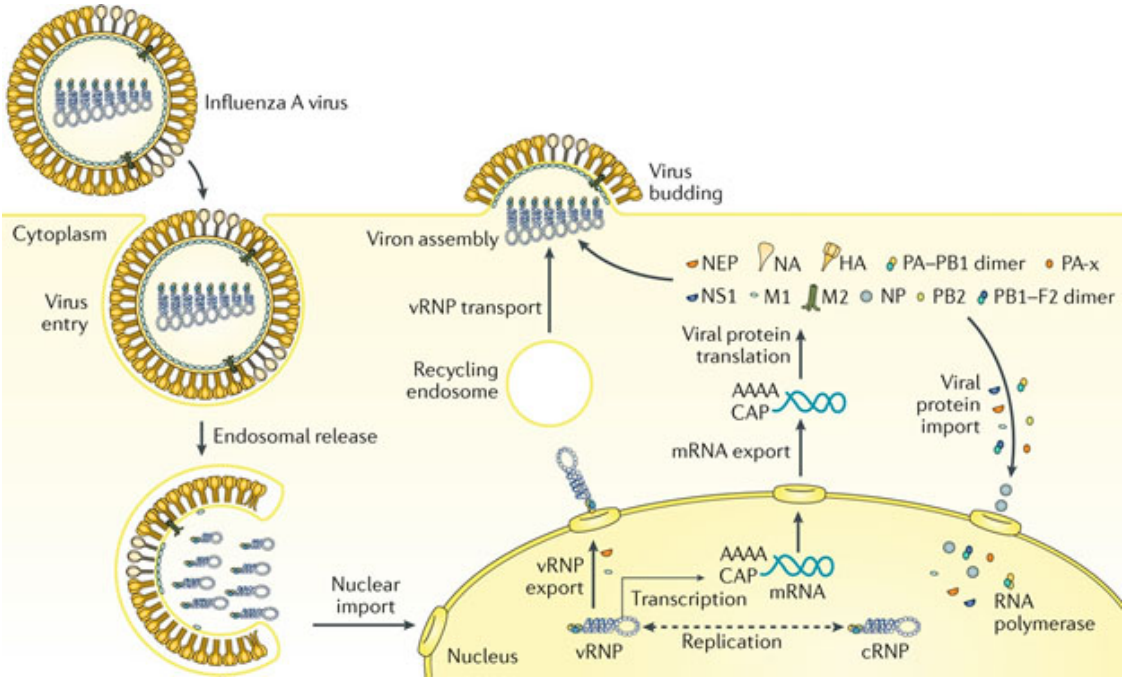


Figure 2-16. Influenza viral life cycle (from [67]). PB1–F2 is shown here as a dimer, but can also be multimeric. HA, haemagglutinin; M1, matrix protein; M2, membrane protein; NA, neuraminidase; NEP, nuclear export protein; NP, nucleoprotein; NS1, nonstructural protein; PB1, PB2 and PA, viral RNA polymerases.

ated by respiratory droplets, aerosols or self-inoculation after touching of fomites. Additional virus adaptations would be required for sustainable human-to-human transmission of animal influenza viruses. Other domestic animals known to be susceptible to influenza virus infections are dogs and cats. Dashed lines represent transmission that bypasses a domestic duck intermediate.

2.3.3. Influenza biodiversity and evolutionary relationships

The substantial increase in the number of publicly available IAV sequences in recent years has given researchers and the public health community new opportunities to study the biology and evolutionary dynamics of this globally significant virus. Most of these studies focused specifically on one of several subtypes of primary concern for humans (H1N1, H3N2, H5N1, and H7N9) or for companion animals, including dogs and horses (H3N8). Influenza A viruses (IAVs) are found throughout the world and cause frequent epidemics in humans and domestic animal species, including poultry, pigs, and horses.

The IAV genome consists of eight segments of negative-stranded RNA which code for at least 10 proteins. IAVs are classified on the basis of two highly variable glycoproteins, hemagglutinin (HA) and neuraminidase (NA), expressed inside the host cell and assembled on the surface of the virus particles. Avian IAVs are further classified based on their pathogenicity in poultry, with high-pathogenicity avian influenza (HPAI) virus strains causing severe and often fatal disease and

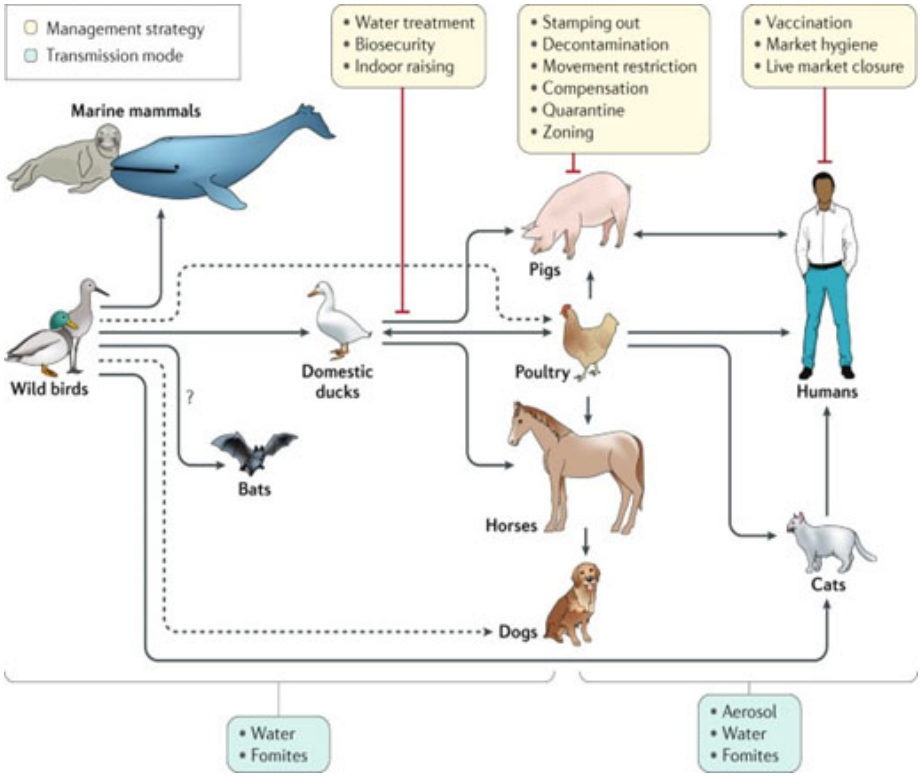


Figure 2-17. Emergence of influenza A virus from aquatic wild bird reservoirs (from [67])

low-pathogenicity avian influenza (LPAI) virus strains causing mild disease in domestic fowl. To date, 18 HA and 11 NA antigenic subtypes of IAV have been identified [79, 143]. Over 120 unique HA and NA combinations (e.g., H3N2, H5N1, and H10N8) have been documented. Variation among IAVs is further enhanced by their high mutation rates (due to the presence of an RNA polymerase that lacks proofreading ability) and the ability of coinfecting viruses to exchange segments (reassortment), producing novel strains. Therefore, understanding the long-distance movement of wild migratory birds between breeding and wintering grounds is critical in explaining the circulation of avian influenza virus (AIV). Upon arrival at their breeding and wintering sites, migratory birds are thought to introduce AIV into native populations facilitating exchange and reassortment of AIV subtypes.

Evolutionary analysis of 14 high-priority subtypes showed that nucleotide substitution rates for all subtypes except H5N3, H7N3, and H7N7 were higher in East Asian countries, including China, Hong Kong, Japan, Mongolia, South Korea, and Taiwan, than in Canada and the United States. However, we did not observe consistently high nucleotide substitution rates across all the subtypes in any single East Asian country, indicating that there was not a specific focal point or evolutionary 'hot spot' for all the IAVs analyzed. A regional analysis of nucleotide substitution rates further demonstrated that evolutionary rates for several subtypes, including H5N1, H5N2, and H6N2, were significantly greater in East Asia than in North America. These findings suggested that, among the majority of high-priority subtypes analyzed, novel, potentially pathogenic IAV strains may be more likely to evolve in East Asia. In fact, the majority of emerging IAV strains that have

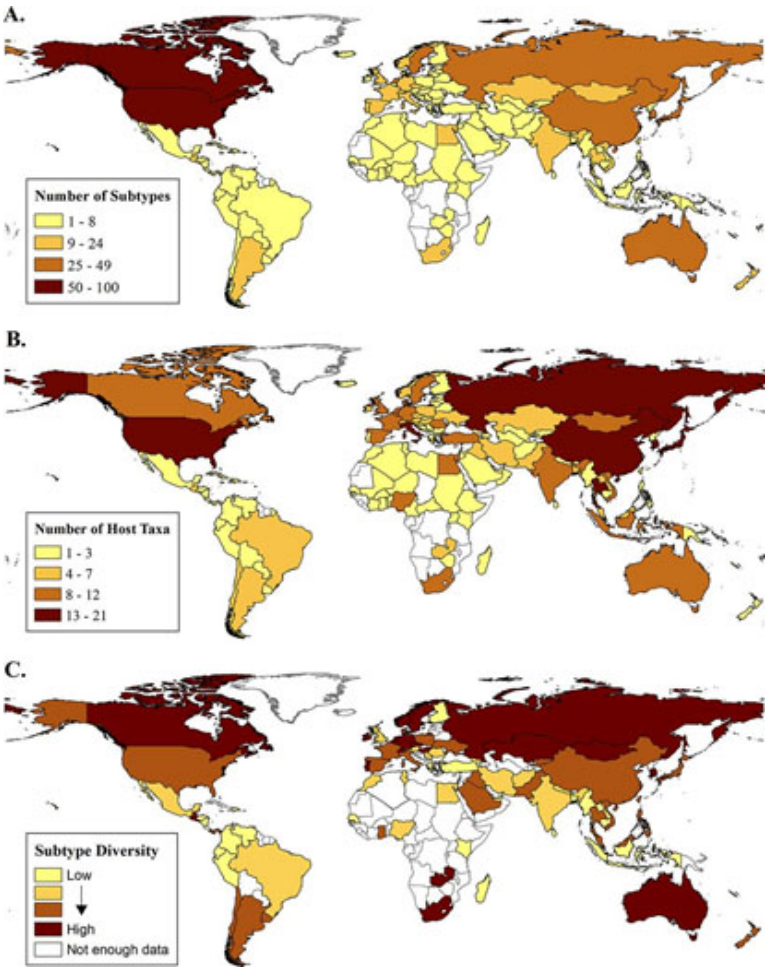


Figure 2-18. Global distribution of influenza A virus subtypes. (A) Number of unique IAV subtypes (subtype diversity) per country. (B) Number of unique IAV animal host groups with reported IAV sequences per country (see Table S1 in the supplemental material for host group designations). (C) IAV subtype diversity, controlling for reporting effort. Data are presented as the log-normalized proportion of subtype diversity over the number of reported IAV strains per country. Data are based on GenBank and Influenza Resource Database (IRD) submissions as of April 2013. (Maps were created by Kate Thomas with ArcGIS version 10.2 software.) Figure adapted from [115].

caused disease and mortality in humans in recent years, including those belonging to subtypes H5N1, H7N9, H9N2, and H10N8, were first detected in China and Hong Kong.

The growing number of unique subtypes detected in humans and poultry in recent years suggests that subtype diversity might be an important factor associated with the emergence of pathogenic IAV strains. While not all subtypes likely exist in all countries or regions, current strategies of targeted testing for specific influenza virus subtypes such as H5N1 severely limit our understanding of the total diversity of subtypes present and circulating in many countries. These strategies, in turn, limit our ability to monitor the evolution and diversity of influenza virus subtypes circulating globally. As such, there is a great need to encourage all countries currently conducting only tar-

geted IAV testing to perform broader testing that includes protocols to detect all subtypes, followed by sequencing and subtyping procedures, in at least a subset of surveillance samples.

2.3.4. Influenza in clinical practices

Many are familiar with flu vaccines (i.e. "the flu shot"). There are several different strategies for preventing infection with the influenza virus (many of which are similar to those discussed in the HIV/AIDS module): (1) vaccines with live virus (most common form), (2) vaccines using chemically "killed" viruses, (3) vaccines using only a select portion of the viral coat, such as the NA or HA proteins, and (4) vaccines partially live, but inactive forms of the virus. While this last strategy has proven effective in clinical research, the live virus vaccine is still the standard treatment except for children. The main problem is that the inactive virus must be prepared in a very pure form before it is approved as a vaccine, a procedure that can take up to two years to develop. However, influenza vaccine production is a seasonal game. Unlike a DNA virus (like the smallpox virus) whose careful genetic proofreading minimizes mistakes upon replication, an RNA virus' use of the error-prone RNA polymerase allows mutations to propagate from generation to generation. The surface proteins (HA and NA) are almost always changed, allowing viral strains to elude detection by the immune system. Antibodies generated for last year's flu strain may offer no protection against this year's variation. Similarly, a drug or vaccine that takes two years to develop will already be a year too late – by the time it is available, the influenza virus will have already mutated from the original strain on which the vaccine was based.

Year-round surveillance for human influenza is conducted by > 100 designated national influenza centers around the world. The laboratories send isolated viruses for genetic and antigenic characterization to five World Health Organization (WHO) Collaborating Centers for Reference and Research on Influenza, which are located in the United States, the United Kingdom, Australia, Japan and China. A WHO committee reviews the results of surveillance and laboratory studies twice per year and makes recommendations on the composition of the influenza vaccine on the basis of the use of antigenically matched viruses with those that are expected to be highly prevalent in the next season. Each country then makes their own decision about which viruses should be included in influenza vaccines licensed in their country. Despite the availability of seasonal and pandemic influenza vaccines, debate is ongoing as to the efficacy (as measured by randomized controlled trials) and effectiveness (as measured by observational studies involving vaccinated and unvaccinated individuals) of these vaccines.

In addition to vaccines and antiviral drugs, non-pharmaceutical interventions can help to slow the spread of influenza illness. These interventions include personal measures, such as hand washing and using alcohol-based sanitizers, covering coughs and/or the nose and mouth when sick and staying at home when sick. Additionally, social distancing by closures of schools and places of gathering, quarantine measures and frequent cleaning of potentially virus-contaminated surfaces, such as doorknobs, can also slow the spread. Mathematical modeling studies suggest that non-pharmaceutical interventions have a substantial effect on lowering the attack rate of pandemic influenza before vaccines are available.

2.3.5. Climate and influenza

The origin of seasonality in influenza transmission is both of palpable public health importance and basic scientific interest. Though influenzas are thought to mostly spread in the northern hemisphere, it does spread yearly in the tropics. Additional influenza outbreaks have been reported to occur outside of the traditional flu season, but the climate related spread is currently still undetermined. Strong evidence for population crowding correlate with start of school or peak during winter holidays. However, studies in mice show that influenza transmission, under simulated crowding, is influenced by a strong seasonal component. Potential climate related influences could be related to humidity effects on increased survival rate in aerosolized droplets that increase spread or decreased temperatures. However, the high interannual variability of influenza cases clouds the interpretation of these data. Therefore, understanding the diverse range of influenza strains related to geographic regions and their associated weather patterns may reveal underlying linkages that will enable precise models for emergence and transmission.

Influenza A incidence peaks during winter in temperate regions. The basis for this pronounced seasonality is not understood, nor is it well documented how influenza A transmission principally occurs. Previous studies indicate that relative humidity (RH) affects both influenza virus transmission (IVT) and influenza virus survival (IVS) [125]. Many pathogens, however, are very sensitive to fluctuations of the environment. For instance, the fluctuations of the temperature and humidity have been shown to have a huge impact on the infectivity of many viral pathogens like influenza [125] and a diversity of other infectious diseases [6, 84].

Seasonal influenza epidemics have been shown to have a meteorological component. Many of focused on the association of absolute humidity. However, in a recent study, a time series analysis of daily influenza infection data and found that even when absolute humidity is decreasing, the number of influenzas cases showed significant increases [128]. Therefore, there are other seasonal factors driving influenza spread across populations.

3. REVIEW OF EXISTING MODELS FOR UNDERSTANDING RELATIONSHIPS AMONG WEATHER, CLIMATE AND DISEASE

In this chapter, we briefly review the existing models relevant to quantifying and understanding the complex relationship between weather, climate and disease. These include epidemiological models, climate/weather models, and empirical-statistical as well as mechanistic approaches for coupling these two classes of models or informing one class of models with output from the other class. We also overview some of the key climatic variables influencing disease spread in a rapidly changing climate. The discussion in this chapter enables us to identify some modeling gaps, which are summarized in Section 3.5.

3.1. Epidemiological models

Epidemiological models are one key ingredient relevant to studying the impact of climate change on disease spread.

Figure 3-1. Flow diagram for SIR compartmental model

One of the most common approaches for studying the spread of infectious disease that falls into the former class of models is to use so-called epidemic compartmental models. These models separate individuals within a given closed population into mutually exclusive "compartments", based on their disease status. The most basic compartmental model is the Susceptible-Infected-Recovered (SIR) model [55, 11]. This model aims to predict the number of individuals who are susceptible to infection, are actively infected, or have recovered from infection at any given time using ordinary differential equations (ODEs). Let the variables $S(t)$, $I(t)$ and $R(t)$ denote the number of susceptible, infectious and recovered individuals respectively at time t. The SIR model assumes that each member of the population typically progresses from susceptible to infected to

recovered according to the following evolution equations, as depicted graphically in Figure 3-1:

$$\begin{cases} \frac{dS}{dt} &= -\frac{\beta IS}{N} \\ \frac{dI}{dt} &= \frac{\beta IS}{N} - \gamma I \\ \frac{dR}{dt} &= \gamma I. \end{cases} \tag{3.1}$$

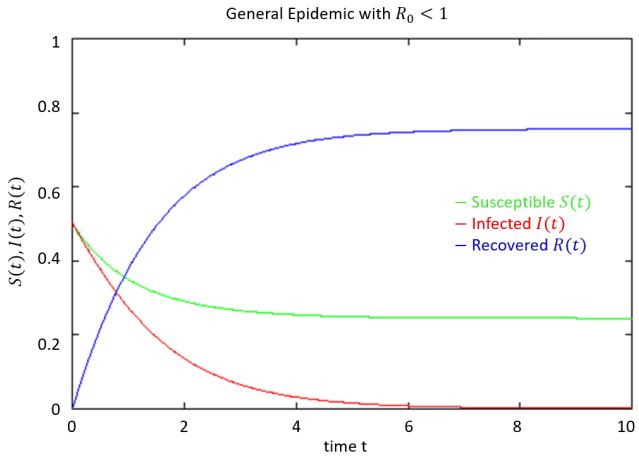
In equation (3.1), N denotes the total population size, and β is the average number of contacts per person per time multiplied by the probability of disease transmission in a contact between a susceptible and infectious subject. The variable γ is defined as $\gamma = 1/D$, where D is the average time period during which a particular individual is infectious. A critical parameter in SIR and related models is the so-called basic reproduction number R_0, defined as the following ratio:

$$R_0 \equiv \frac{\beta}{\gamma} \tag{3.2}$$

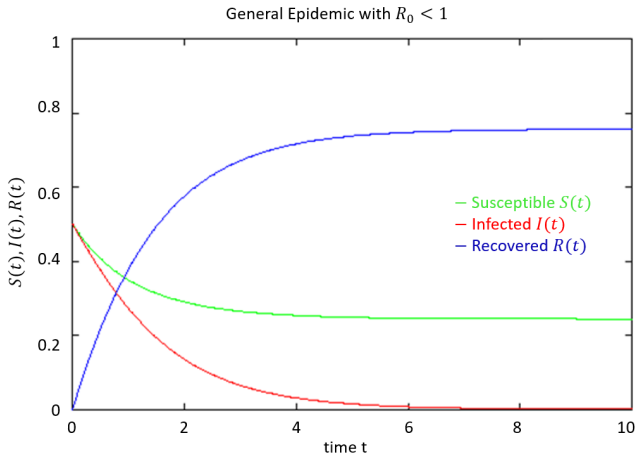
The basic reproduction number (3.2) is effectively the expected number of new infections from a single infection in a population where all subjects are susceptible [8, 51]. Under certain conditions, the nonlinear system of ODEs (3.1) has an exact analytical solution [55]. In general, it can be solved numerically on a computer following discretization in time. The extent of an epidemic can be determined by studying the local stability of the ODE system (3.1) to determine the endemic equilibrium (EE). In general, if $R_0 \leq 1$, a disease will eventually go extinct. In contrast, if $R_0 > 1$, the disease will remain permanently endemic within a given population [51]. Figure 3-2 shows two possible equilibrium scenarios encompassed within the SIR model: one with $R_0 < 1$ and one with $R_0 > 1$. The latter situation is possible only in the unlikely case where no individuals are able to recover from a given disease.

A number of variations of the SIR (3.1) model exist. These include the following:

- **The Susceptible-Infectious-Susceptible (SIS) Model** [78]: This model is relevant when attempting to model infections that do not produce immunity upon recovery. It is commonly used to model diseases such as the common cold and influenza.
- **The Susceptible-Infectious-Recovered-Deceased (SIRD) Model** [86]: This model is similar to the SIR model but takes into account the fact that a particular disease may lead to death. In addition to the rate of infection β and the rate of recovery γ, the SIRD model takes in an auxiliary parameter μ, the mortality rate.
- **The Susceptible-Exposed-Infectious-Recovered (SEIR) Model** [28]: This model takes into account the fact that, with some diseases, there is a significant incubation period during which individuals have been infected but are not yet infectious themselves. This is known as the “Exposed" period within the context of the SEIR model.
- **The Susceptible-Exposed-Infectious-Susceptible (SEIS) Model** [41]: This model is similar to the SEIR model, with the exception that no immunity is acquired at the end.
- **The Susceptible-Exposed-Infectious-Recovered-Deceased (SEIRD) Model**: This model is effectively a combination of the SIRD and SEIRD models. In recent months, the SEIRD model has become a popular model for quantifying the spread of the COVID-19 [110].



(a) $R_0 < 1$



(b) $R_0 > 1$

Figure 3-2. Sample output from an SIR epidemiological model

The list of models itemized above is not exhaustive, and each of the aforementioned models can be modified to include additional variations or disease-specific factors. For instance, the models can be modified to include vaccination [48] or humidity-based forcing [126]. In addition, efforts have been made to formulate stochastic versions of the SIR and related models (e.g., [21, 72]) towards enabling uncertainty quantification (UQ) using these models. For a more detailed overview of compartmental models, the reader is referred to [57], [51] and the references therein. The choice of model of what model or combination of models to employ for a particular disease/epidemic is a critical part in the mathematical modeling of infectious disease spread.

The primary advantage of the SIR and related models is that they are easy to compute and can be modified for a variety of diseases. Such models have been used to study a variety of diseases (e.g., Ebola, malaria, dengue, HIV/AIDS, etc.), including COVID-19 (see [22, 4, 32, 24, 110] and numerous other references). Compartmental models also have some disadvantages, stemming

largely from the fact that they make several simplifying assumptions about the population (e.g., assuming homogeneous mixing of a population, not accounting for social structures). In addition, the parameters in compartmental models such as the SIR model are not always easy to estimate for a given population [140].

It is important to recognize that compartmental models are often combined with empirical-statistical approaches (described in more detail in Section 3.4.1). For instance, statistical methods can be used to estimate the parameters in models where transmission data are incomplete or highly correlated [51], e.g., [10]. Additionally, the use of Bayesian inference methods, designed to incorporate uncertainty, for estimating epidemiological parameters like R_0 have been considered by several researchers [98, 12]. Recently, researchers have turned to machine learning (ML) and artificial intelligence (AI) approaches, using these methods to calibrate more traditional compartmental models such as the SEIR model [155]. Purely data-driven approaches for real-time characterizations of partially observed epidemics are also possible, e.g., [120].

3.2. Climate and weather models

Climate and/or weather models are the second ingredient relevant to studying the impact of climate change on disease spread. First and foremost, it is important to differentiate between climate models and weather models. The primary difference between climate and weather models has to do with the spatial and temporal scales which the models are intended to capture and simulate. Whereas weather models are intended to make short-term predictions (hours-days) over a specific area, climate models are broader and developed to analyze longer timespans (years-decades-centuries). Moreover, climate models are often used to simulate average conditions over time (e.g., several decades), rather than precise instantaneous conditions. Climate and weather models are in general both mechanistic models at the heart of which are partial differential equations (PDEs) describing the physics and dynamics of the underlying physical processes (e.g., atmospheric transport, ocean circulation, etc.). These equations are discretized (or represented approximately using discrete quantities) on the sphere, and advanced forward in time using sophisticated mathematical techniques that ensure conservation of relevant quantities (e.g., water). Once this is done, one can extract relevant temporal and spatial data from the climate or weather simulation, such as temperature, winds and current, ocean salinity and atmospheric pressure. The numerical solution of the equations underlying these models can be computationally demanding and usually requires the use of supercomputers. In this report, we focus our attention primarily on climate models, as our interest is primarily the effect of long-term climate change on disease dynamics; however, it is important to recognize that it may be interesting and useful to study the spread of disease at a smaller and more localized scale using weather models.

In the past two decades, efforts have been put forth to develop global climate models known as Earth System Models (ESMs), sometimes known also as Global Circulation Models (GCMs). ESMs and GCMs are aimed at projecting and quantifying the effects of global climate change during the twenty-first century and beyond. ESMs combine the interactions of atmosphere, ocean, land, ice and biosphere into a single model that allows the estimation of the state of regional as well as global climate scenarios under a wide variety of conditions (e.g., different emissions scenarios).

The individual components comprising an ESM are typically developed separately according to the relevant physics and dynamics, and subsequently synthesized into the ESM, which passes relevant data between the various components through what is known as the "flux coupler". A number of ESMs exist worldwide. Chief among them are the two U.S. models: the Community Earth System Model (CESM) [59], a fully-coupled community global climate model developed primarily at the National Center for Atmospheric Research (NCAR), and the Energy Exascale Earth System Model (E3SM) [20], a state-of-the-art ESM funded by the U.S. Department of Energy (DOE). For a review of the history of ESM development during the past century, the reader is referred to [109].

3.3. Key climatic variables influencing disease spread

In attempting to link climate change with the spread of infectious disease, one must first and foremost identify the climatic variables that can lead to changes in disease transmission. Although many climatic variables may be influential in disease transmission, the most influential variables are in general believed to be temperature, precipitation, humidity (relative or absolute), sunshine and wind [101, 153, 100]. All five of these variables are strongly affected by global climate change. We briefly discuss the impacts of each of these variables in the following subsections.

3.3.1. Temperature

The importance of ambient temperature on disease spread can be explained by the fact that this variable has in general a strong effect on the life cycle of disease vectors (e.g., mosquitoes, fleas, ticks, flies). Vectors typically need a certain temperature range to survive and develop. Rising temperatures can influence the reproduction period of vectors. Extended periods of hot weather can raise the average temperature of bodies of water, which may promote vector breeding. Little work has been done to date in understanding the effect of temperature extremes on disease dynamics [101]. It is expected that regional increases in mean temperatures will cause non-linear changes in disease incidence, due to the relationship between temperature and other factors relevant to disease transmission. Temperature change can actually restrict the distribution of some disease vectors. For example, excessive heat can increase the mortality rates for certain pathogens, e.g., mosquitos, which cannot survive in prolonged temperatures greater than 40°C [26]. As global temperatures rise, it is therefore likely that diseases transmitted by mosquitos (e.g., malaria) will begin to appear in higher latitude locations.

3.3.2. Precipitation

Precipitation plays an important role in the development of water-borne disease pathogens: there is in general an increased likelihood of water-borne parasitic, bacterial and viral diseases following severe rainfall events [101]. Precipitation also plays a role in the proliferation of vector hosts. While the population of vectors can decline during an extreme rainfall event, increased precipitation almost always increases vector abundance as it creates additional vector breeding sights.

According to the Intergovernmental Panel for Climate Change's (IPCC's) Fourth Assessment Report [2], increases in precipitation appears to be almost independent of the emissions scenario during the next few decades, but displays significant variability thereafter. Increases in the intensity of rainfall extremes is expected to be greater than changes in mean precipitation worldwide [101].

3.3.3. Humidity

Humidity is a particularly important variable that impacts the pathogens of infectious diseases. Absolute humidity and temperature have been found to affect influenza virus transmission and survival in a number of studies [126, 154]. Humidity changes also affect viruses of water-borne and vector-borne diseases. Studies have suggested that increased relative humidity (RH) increases vector abundance of *Anopheles gambiae* mosquitoes, known to transmit malaria [62]. It is expected that globally averaged RH will remain approximately constant under climate change [5], but considerable regional structural and temporal variability remains [152]. According to [152], additional research is needed to better understand RH trends and anomalies in areas most severely affected by diseases such as malaria.

3.3.4. Sunshine

It has been demonstrated by Islam *et al.* [60] that sunshine hours and temperature act synergistically during cholera periods, thereby creating favorable conditions for the multiplication of the *Vibrio cholerae* bacteria in aquatic environments. More specifically, high temperature and medium sunshine hours tend to provide the most agreeable conditions for a cholera outbreak. Cholera can spread in relatively low temperatures provided sunshine is available [153]. A study reported on a recent U.S. White House briefing suggested that increased sunlight, together with increased temperature and humidity, is detrimental to SARS-Coronavirus-2 (a.k.a., COVID-19) in saliva droplets and in the air[1].

3.3.5. Wind

As one may expect, wind is a key factor that can spread air-borne diseases. Global and local wind patterns affect the spread of infectious disease in the following ways [101]:

- they affect the dispersal ability and behavior of disease vectors;
- they change hydrological processes (e.g., evaporation) that have a correlation with vector abundance;
- they can affect human susceptibility to diseases.

[1] See: `https://justthenews.com/sites/default/files/2020-04/Coronavirus%20Half-Life-Department%20of%20Homeland%20Security.pdf`.

Additionally, it has been reported that the presence of desert dust in the atmosphere is associated with increased concentrations of cultivable bacteria, fungi and fungal spores [153, 43]. According to [101], little research to data has looked at the potential impact of changes in wind patters on diseases. The IPCC's Fourth Assessment Report [2] suggests that peak wind intensities will likely increase in future tropical cyclones.

3.3.6. Accounting for seasonal and interannual climate variability

It is important to recognize that seasonal and interannual cycles of climate variability play an important role in determining if/when an epidemic will occur. Such relationships can be studied using empirical-statistical and/or mechanistic methods (described below in Sections 3.4.1 and 3.4.2), though the bulk of past work has focused on approaches of the former flavor. Some recent work in this area is reviewed succinctly below.

Within the field of epidemiology, seasonal variation in disease transmission is known as seasonal forcing [119]. Certain diseases[2], such as influenza, measles, malaria, cholera and have a clear seasonal cycle [84]. Influenza typically arrives in colder winter months (Figure 3-3). Measles cases typically drop in summer months in temperate climates, while peaking in the dry season in tropical regions. Seasonal patterns for cholera vary by region, but peak in the spring/summer months in many locations [38]. Recently, there has been much speculation about the effect of seasons on the transmission of the novel COVID-19 virus [7, 9]. While some authors have suggested humidity and temperature play a significant role in the seasonal spread of coronaviruses [122, 151], the effects of seasonality on COVID-19 are difficult to predict without long time series [108].

The persistence of extreme temperature and/or precipitation conditions is thought to have a strong effect on virus transmission patterns and seasonality [131, 145, 76]. Despite evidence for correlation between seasonality and disease spread for these and other notable examples, the mechanisms driving disease seasonality have yet to be systematically characterized for most infections [84]. When interpreting correlations between seasonal changes and disease prevalence, it is important to incorporate domain knowledge, so as not to confuse correlation with causation (see [90] and Section 3.4.1 above). For example, in the specific case of influenza, while it is reasonable to assume that the disease transmission cycle is influenced by climate, studies have demonstrated that annual influenza outbreaks do not appear to correlate with mean winter temperature [70]. It is likely that the cause of increased influenza cases in winter is an increase in indoor crowding, which leads to greater disease transmission. For diseases spread by mosquito vectors, such as malaria, seasonality can be explained by changes in the relevant vectors' extrinsic incubation periods (EIPs) [100, 129, 18, 56]. Again, researchers are warned about interpreting the results of correlative studies of malaria prevalence and seasonal climate fluctuations: "the distribution of malaria cases ia complex and poorly understood consequence of ecological, socio-economic and other factors, such that causal relationships are frequently obscured" [100].

In addition to seasonal correlations between climate and infectious disease spread, interannual climate fluctuations can also be important to investigate. In particular, it has been suggested in numerous references, including in three recent assessment reports [1, 28, 147], that the El Niño/Southern

[2]Tables 1-3 in [84] summarize the hypothesized seasonal drivers for a number of human infectious diseases.

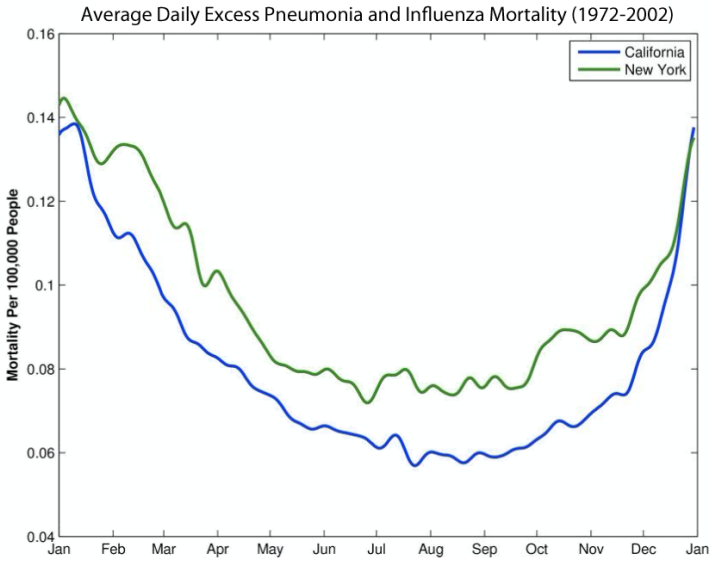


Figure 3-3. Figure from Shaman *et al.* [125, 126] showing average daily excess pneumonia and influenza mortality during the years 1972–2002 in the states of New York and California. One can see that the mortality peaks in the winter season.

Oscillations (ENSO) cycle (an irregular cycling back and forth between warm El Niño and cold La Niña phases) has been at least partially responsible for major outbreaks of diseases such as cholera and dengue [28, 131]. El Niño events are characterized by abnormally heavy rainfall over the warm Pacific waters off the coast of Ecuador and Peru, together with drought conditions in Australia, Malaysia, Indonesia, Micronesia, Africa, northeast Brazil, Central America and tropical Africa [28]. Higher temperatures in northern Pakistan resulting from El Niño events have correlated with increased malaria incidence [15]. Similar conclusions have been drawn from studies correlating El Niño with outbreaks of malaria in India, Sri Lanka, Venezuela and Colombia [28]. Associations have been found between warmer water temperatures during El Niño years and cholera cases in various locations, e.g., Peru [85] and Bangladesh [27], as well as chikungunya, hantavirus, Rift Valley fever, cholera, plague and Zika [131]. Other recurring interannual events shown to correlate with disease transmission include La Niña, the Quasi-Biennial Oscillation (QBO), and extreme weather events such as droughts, heatwaves and floods [153][3]. These associations can be extrapolated to infer the potential impact of longer-term climate change on infectious disease spread. More specifically, there has been some speculation that a climate warming trend is likely to affect the occurrence and intensity of El Niño events (floods, droughts, storms/hurricanes, etc.); however, more observational data are needed to corroborate this hypothesis [1].

[3]For specific details, the author is referred to Table 1 of [153], which summarizes the relationship between different interannual extreme weather events and disease types.

3.4. Methodologies for modeling the impact of climate change on disease spread

In recent years, researchers have developed various mathematical modeling approaches aimed at studying the relationship between weather/climate and infectious disease. Existing modeling approaches fall into roughly two categories: empirical-statistical models and mechanistic (or process-based) models [28, 101, 90]. Both approaches are useful in certain contexts, with each one having its own set of strengths and weaknesses. It is important to emphasize that empirical-statistical modeling approaches are not mutually exclusive: a potentially powerful approach is to harness statistical methods within a mechanistic modeling framework.

3.4.1. Empirical-statistical models

Empirical-statistical models aim to correlate climate and disease-related variables that have been estimated from observational and/or simulated data in time and/or space. These models typically derive relationships between relevant variables (e.g., disease transmission and climate factors) from a purely descriptive perspective and do not attempt to incorporate known mechanistic relationships between these variables [100]. Prime examples of statistical modeling approaches are traditional time-series and regression methods, e.g., autoregressive integrated moving average (ARIMA) models [90]. Such methods have been used to study the relationship between key climatic variables such as precipitation, temperature, and humidity and various diseases (e.g., water-borne diseases within the U.S. [31], cutaneous leishmaniasis in Brazil [74]). More recently, an autoregressive model known as a generalized additive model (GAM) was developed and used to calculate relationships between temperature data and the number of cumulative total confirmed cases of COVID-19 in Brazil [107]. In [124], a permutation test was used to calculate whether plague-relevant climate fluctuations in Asian climate proxies preceded reintroductions of plague into Europe between the fourteenth and nineteenth centuries. An early statistical model based on "fuzzy logic" was used to quantify disease transmission in different regions in sub-Saharan Africa given local temperature and rainfall data in [30]. Statistical approaches have been used to study the expected global malaria distribution change by 2050 [117], as well as correlate relative risk maps (estimations of the spatial distribution of human risk of infection) with future malaria risk in Africa [91]. Examples of other statistical models for the effect of climate change on the spread of vector-borne diseases such as malaria are provided in Section 3(i) of [100].

In recent years, researchers have begun to look at combining traditional time series models with machine-learning (ML) algorithms using epidemiological (e.g. malaria, dengue) and meteorological data [150, 52, 23]. A machine-learning approach known as MaxEnt (short for "maximum entropy") [36] is gaining popularity within epidemiological modeling communities. The approach enables the prediction of species distributions based on environmental variables and is capable of accounting for interactions between variables. The approach is used to study the effects of global climate change on Chikungunya transmission in the twenty-first century in [139]. In [50], Gorris *et al.* use MaxEnt to perform a sensitivity analysis using an ecological niche model forced with bias-corrected spatially downscaled Coupled Model Intercomparison Project (CMIP5) [136] climate projections under several possible emissions scenarios.

The main advantage of empirical-statistical models lies in their simplicity: these models are in general far simpler to develop and use than mechanistic models. They are also in general far less computationally expensive than mechanistic models [100]. As discussed in [63] and [100], when carefully trained, evaluated and tested, non-mechanistic autoregressive models can make reliable predictions over short time-horizons.

Empirical-statistical models have several deficiencies. Generally speaking, empirical-statistical models are not explanatory in nature, since they do not incorporate the underlying mechanisms driving climate change and disease spread [28]. One must therefore be careful in interpreting results from such models as well as extrapolating the results beyond the data from which the models were derived: inference using empirical-statistical models is in general correlative rather than causative, so simple correlations and statistical associations between climatic variables and disease outbreaks cannot in general be used to infer the underlying causal mechanisms [90]. According to [100], statistical models aiming to correlate climate change with the distribution of recorded cases of diseases such as malaria "are fraught with problems of interpretation and should be interpreted carefully". Another limitation comes from the fact that there are often limited data points to calibrate model projections. This makes predictions made by the models difficult to validate [28]. Additionally, empirical-statistical approached, in particular, ML-based approaches, typically require a large amount of data. Unfortunately, high-quality epidemiological data on disease incidence is lacking in many locations, and the data that are available can be highly uncertain [101]. A final challenge faced by statistical models stems from discrepancies between the spatial and temporal scales in the available data: for most epidemics, disease incidence data are available at smaller spatial and temporal scales than those typically employed in and relevant to climate modeling [100].

3.4.2. Mechanistic (process-based) models

In contrast to empirical-statistical models, mechanistic, or process-based, models are based on theoretical knowledge of the underlying biophysical, epidemiological and/or environmental processes describing the relationships between weather/climate and infectious disease [28, 101]. These processes are modeled using mathematical equations that represent the relevant mechanisms involved. The resulting models are dynamic: future states of the underlying system are evolved in time given an initial state using discretizations of fundamental laws that are known to drive the relevant mechanisms and processes. Hence, mechanistic models offer explanatory and forecasting power.

3.4.2.1. Epidemiological models driven by climate data

One approach in developing predictive mechanistic models for climate-driven disease spread is to take observational and/or simulation data from climate drivers and these data to drive a dynamic model for the spread of an infectious disease (e.g., the SEIR model, or one of the other models described in Section 3.1). Numerous researchers have explored this approach. In [125], Shaman *et al.* develop a dynamic SIRS (Susceptible Infectious Recovered Susceptible) epidemiological model for the spread of influenza in the U.S. which incorporates observed absolute humidity conditions. The resulting model was used to simulate the seasonal cycle of observed influenza-related

mortality. Similar approaches were taken in [35] and [83], where epidemiological models forced with observational and/or experimental data were used to examine associations between precipitation and cholera in Haiti and temperature and dengue in Europe, respectively. For an in-depth overview of other relevant mechanistic modeling approaches, the reader is referred to Section 3.2.2 of [101] and Section 3(ii) of [100].

With the advancement of regional and global climate modeling in recent years, a number of researchers have turned their attention to integrating readily-available data from these models into their epidemiological models. In [39], the Liverpool Malaria Model (LMM) was used to simulate and project the spread of malaria under past and future weather conditions using daily temperature and rainfall data from the high-resolution regional climate model REMO. A similar approach was taken in [71], which also employs the LMM but forces it with seasonal forecasts of meteorological variables (e.g., rainfall) from a state-of-the-art operational coupled ocean-atmosphere forecast model developed at the European Center for Medium-Range Weather Forecasts (ECMWF). A number of recent works have looked at integrating into epidemiological models climate change data from ESMs that participated in CMIP5 [136]. Many of these studies considered various emission scenarios. In [92], Monaghan *et al.* used monthly near-surface air temperature and precipitation fields from fifteen members of the CESM [59] ensemble generated under CMIP5 to study diseases spread by the *Aedes aegypti* mosquito (dengue, chikungunya, Zika, yellow fever). Two emissions scenarios were considered: Representative Concentration Pathway (RCP) 4.5 and 8.5, the latter of which corresponds to the "business as usual" scenario, and the former to reduced emissions. Human population growth was incorporated into the model. It was demonstrated that there are statistically significant changes to expected human exposure to the relevant diseases under the RCP8.5 emissions scenario. In a recent study, Tomkins and Caporaso [141] assessed the potential for land use change (LUC) with low-end and high-end emissions scenarios (RCP2.6 and RCP8.5 respectively) to impact malaria transmission in Africa. These authors incorporated into a gridded mathematical malaria model known as VECTRI (vector-borne disease community model of the International Center for Theoretical Physics in Trieste, Italy) daily precipitation and temperature output from the four ESMs that participated in the LUC experiment under CMIP5.

3.4.2.2. Fully coupled epidemiological and weather/climate models

A second approach for studying the impact of climate change on disease is one in which an epidemiological model is coupled or integrated into a regional or global weather or climate model. To the authors' knowledge, there exist few models of this sort in the climate/epidemiology literature [101]. Approximately a decade ago, two notable references came out, namely [123] and [14]. In [123], Schaeffer *et al.* develop a matrix model for viruses transmissible by mosquitos that integrates climate variables evolved as a part of the model. In [14] *et al.* present a fully-coupled hydrology and entomology model.

The aforementioned fully coupled models are simplistic in their treatment of the climate evolution. Recently, several interesting approaches aimed at integrating epidemiological models into modern fully coupled ESMs have appeared in the literature. These works are aimed at studying the emission and long-range transport of molecules that can lead to the spread of disease. In [106],

the CESM [59] was adapted to include modules for modeling the emission and long-range transport of fungal spores, the most relevant vector for the spread of certain crop diseases, e.g. wheat stem rust. In [156], Zhang *et al.* integrate the STaMPS (Simulator of Timing and Magnitude of Pollen Season) [34] pollen transport model into the WRF (Weather Research Forecasting) [130] and CMAQ (Community Multiscale Air Quality) [19] regional air-quality modeling system to simulation the variation of temporal-spatial patterns for different species of pollen under several key meteorological variables (wind speed/direction, temperature, precipitation, relative humidity and dew point temperature). Similar to the model in [106], the pollen grains were treated as passive tracers in CMAQ. Although seemingly irrelevant, a number of studies have demonstrated a correlation between pollen transport and the seasonality of flu-like illnesses, including COVID-19 [58].

3.5. Modeling gaps

The literature review performed while compiling this report has led us to identify a number of research gaps within the field of climate-driven epidemiologically. There are summarized succinctly below.

- **Research is needed to move beyond identifying simple correlations between climatic variables and disease spread to identifying the underlying causal mechanisms [90, 28].** In order to accomplish this, focus must shift from traditional statistical methods to more mechanistic or joint statistical-mechanistic modeling approaches [90]. In addition, tight interdisciplinary work between climate scientists and epidemiologists is needed in order to make appropriate conclusions based on the relevant mathematical models [90, 28].

- **Additional epidemiological surveillance data should be collected to allow model calibration/validation [28, 100].** Unfortunately, there is in general a lack of high-quality epidemiological data for most diseases at the present time. This situation is a serious obstacle when it comes to studies aimed at linking disease incidence with climate change. A concerted effort to collect long-term spatially-resolved disease surveillance data worldwide would go a long way towards remedying the present data dearth problem [28]. Additionally, it may be possible to use remote-sensing data to study the relationship between disease outbreaks and climate variables, *cf.* [80].

- **Improvement of "first-principle" disease transmission models (including systematic data integration into these models) is needed [28].** This is especially true in the case where there is insufficient observational/surveillance data on disease incidence/transmission, as empirical-statistical models (in particular, models based on ML and AI principles) typically require very large data sets to be useful predictive tools. It is also true when longer-term forecasts are of interest. First-principle mechanistic models are preferable in these situations, but should incorporate any available observational data to maximize the value in their predictions. The models can be used to uncover and derive improved parametrization of computationally cheaper empirical/statistical disease transmission models.

- **There is a need to develop models that take account of multiple co-occurring diseases and examine how climate change affects co-transmission patterns of diseases [100].** This can be accomplished through a more direct coupling of climate variables with things like vector/host population dynamics and geographical factors (e.g., land use change). According to [100], a study of this sort has yet to be undertaken systematically.
- **There is a need to study systematically the health consequences of climate change and co-benefits actions [42].** "Co-benefits" are defined by the IPCC as positive benefits related to the reduction of greenhouse gases, e.g., improved energy efficiency, a shift away from the consumption of animal products, etc. This research gap can be addressed through the integration of existing longitudinal data on population health into joint climate-epidemiological models [42].
- **The mismatch of spatial and temporal scales between climate prediction and relevant epidemiological as well as socio-economic data must be addressed [100].** At the heart of this challenge is the fact that climate and epidemiological data and models are in general targeting very different spatial and temporal scales. Some ideas for addressing this challenge are suggested in [100], and include the use of regional climate models rather than global climate models, where necessary.
- **There is a need to provide uncertainty bounds in forecasts from joint climate-epidemiological models [28, 100, 153, 101].** There are numerous uncertainties inherent in empirical-statistical as well as mechanistic models of climate change as well as disease transmission, which should be studied in a systematic way using formal methods for uncertainty quantification (UQ) in order to provide projections equipped with uncertainty bounds. While statistical uncertainty has been considered by a few authors [95, 120, 99], these works have only scratched the surface of formal UQ within the field of climate-disease modeling [101].
- **Data from climate-disease models should be synthesized with relevant socio-economic variables, towards informing public policy decisions [28].** This information can be used to develop early warning systems for epidemics and assist with community planning. Currently there is an important research gap concerning the scientific evaluation of the health implication of adaptation measures at community and national levels for people from varied demographics and income brackets [3, 42]. There is also a need to better understand the effectiveness of interventions aimed to protect health, and health implications of various adaptation/mitigation decisions and strategies [42].
- **A systematic study of how climate change may affect the evolution and emergence of infectious diseases [28] has yet to be performed.** There is a need to characterize pathogen biodiversity and biogeography so as to understand how climate change influences evolutionary patterns and processes, including adaptations relevant to altered virulence, drug resistance and shifting spatiotemporal ranges.

4. NEW MODELING STRATEGIES FOR PREDICTIVE MODELING OF CLIMATE & INFECTIOUS DISEASE PATTERNS AND PROCESSES

In this chapter, we outline succinctly several ideas for novel modeling approaches aimed at improved understanding and prediction of the complex relationship between climate change and infectious disease transmission/spread that Sandia is well-positioned to pursue. These approaches are attempts at addressing some of the known research gaps within this field (see Section 3.5).

4.1. Proposed new modeling methodologies

4.1.1. Development of novel epidemiological models driven by climate data

As discussed in Section 3.4.2.1, a promising approach for advancing the modeling of epidemics driven by climate change is to create epidemiological models driven or forced with data from climate models. Previous efforts to do this are have some acknowledged shortcomings [92, 139, 141, 50, 39], including:

- a limited focus on environmental/climate drivers (e.g., considering only temperature and precipitation, when additional climatological variables can be important as well; see Section 3.3);
- focusing on one particular disease (e.g., malaria, dengue, Coccidioidomycosis) rather than a set of co-occurring diseases;
- focusing on a limited set of emissions scenarios (e.g., RCP4.5 and RCP8.5 only);
- a limited (or outright missing) incorporation of expected land use change (LUC), a major driver of emerging infectious diseases;
- the use of ESM/GCM data at too coarse of a spatial and/or temporal scale;
- failure to incorporate more recent climate model ensemble data, e.g., data from CMIP6 [40];
- failure to provide uncertainty bounds on model projections.

As a key player in the development of the Energy Exascale Earth System Model (E3SM) [20], Sandia is well-positioned to address these limitations. High-resolution output from the E3SM can be used to derive improved climate forcings to drive epidemiological models. This model has pushed the envelope in terms of model resolution, and features a unique capability of regional refinement for all of its component models in a multi-resolution modeling settings. Additionally, the E3SM

includes new ocean, sea ice and land-ice models, and contains a state-of-the-art dynamic vegetation model known as ELM-FATES [96] that integrates *in situ* observations, remote sensing output and integrated assessments. Ongoing improvements to the E3SM Land Model (ELM) include new implementations for land disturbances including wildfire[1].

4.1.2. Development of fully-coupled mechanistic climate-epidemiology models

As a key player in the development of the E3SM, Sandia is also well-positioned to explore methodologies of the flavor described in Section 3.4.2.2 by incorporating epidemiological models or disease-related diagnostic variables into relevant E3SM components to yield a fully-coupled mechanistic climate-epidemiology framework. Several ideas worth exploring are:

- The introduction of tracers into the E3SM Atmosphere Model (EAM) [111] as general proxies for infectious disease transport. This approach is viable for diseases that are transmitted across long distances environmentally. These include diseases caused by fungi such as wheat stem rust [106], *Aspergilli* and *Coccidioides* [133, 43], and pollen-borne viruses [156, 34], among others. Tracer transport methods combined with models that predict prevalence of infectious agents on land and how environmental impacts lead to atmospheric transport could provide important insights on disease spread. In particular, dust storms and wildfire are known to drive regional valley fever outbreaks [102]. Developing a *Coccidioides* model within E3SM that includes environmental drivers like drought, wind, and fire, would provide future projections of incidence within a coupled modeling system. Modeling with regionally refined grids in E3SM could enable development of disease burden projections for Southwestern cites (Phoenix, Albuquerque) and the Central Valley in California.

- Addition of SIR-type epidemiology models that incorporate effects of climate variables into E3SM to investigate seasonal and interannual cycles of climate variability on disease spread. Machine learning or data-modeling approaches could be used to develop parameterizations for the epidemiological models based on available data. Influenza would be an exemplar for this type of approach, which would enable research into average seasonal variability as well as impacts associated with longer-term climate oscillations such as ENSO.

- Combining models for the spread of animal and insect vectors of disease with E3SM. Models that predict the spread of disease vectors, such as the *Aedes Aegypti* mosquito, based on temperature, humidity, precipitation, and land use changes could be used to generate long-term projections for human exposure. Incorporation of these models into E3SM would also enable investigation of the disease response to seasonal and longer-term climate variability.

- Modernizing the representation of biological processes in sophisticated full coupled earth system models such as the E3SM. Existing ESMs, including the E3SM, fail to include any of the last three decades' advances in the molecular biological realm, such as the ability to parameterize climate models with genome-based information, or with diverse bioinformatics and computational biology inputs, such as microbial community composition or keystone

[1] `https://e3sm.org/about/organization/ngd-sub-projects/ngd-land-and-energy/`

species' genotypes in specific ecological zones (e.g., grasslands, boreal forests, different photic zones of the oceans, etc.).

4.1.3. Application/development/integration of advanced ML/AI data-driven techniques

As discussed in Section 3.4.1, a popular class of methods in characterizing disease transmission are empirical-statistical methods. The vast majority of work in developing this class of methods up to now has focussed on simple time-series and/or regression models, e.g., ARIMA models. We hypothesize that empirical-statistical models of epidemics can be improved by sophisticated ML and AI methodologies that are currently being pioneered at Sandia.

Early research utilizing machine learning includes using neural networks to make short term predictions in stochastic geophysical time series data [37]. This particular machine learning technique was also used to extract temperature profiles from NOAA-16 Advanced Microwave Sounding Unit-A (AMSU-A) measurements. The results were better or comparable to those from using the International Advanced TOVS (ATOVS) Processing Package (IAPP), the state of the art for temperature retrieval at the time [157]. Other machine learning techniques, such as support vector machines, have been used to classify cloud types from Multi-angle Imaging SpectroRadiometer data in [87].

Climate and weather modeling often require heavy tuning of parameters, sometimes based on structural assumptions. Researchers in [47] were able to train generative adversarial networks, a class of algorithms that use deep neural networks to generate new data from previously observed data, to create stochastic parameterizations for subgrid forcings in the Lorenz 96 model [81] to develop more accurate forecastings. Anomaly detection techniques were used in [75] to detect the presence of cyclones in climate simulation data. The techniques developed in this research are not specific to cyclones but, rather, to extreme or rare events in general.

Future areas of machine learning and climate research include:

- combining ML/AI-based empirical-statistical models with mechanistic models, e.g., by using ML techniques to calibrate and inform mechanistic models using available epidemiological and/or climate data;
- using ML for data compression (e.g., through the use of autoencoders);
- using ML to detect/predict extreme weather and climate events and correlate them with disease outbreaks.

Recently, researchers have begun to apply forecasting modeling techniques, popular in climate studies, to the study of the spread of infectious diseases [103, 114]. These models attempt to predict the spread of diseases like influenza using mathematical humidity-drive SIRS (susceptible-infected-recovered-susceptible) models and ensemble approaches. Some research [112] attempts to create ensembles approaches such as the seasonal autoregressive integrated moving average (SARIMA) [134] approach, an approach that blurs the line between statistical techniques and machine learning. However, the inclusion of more popular machine learning approaches, such as deep

neural networks, for this type of forecasting is still in its beginning stages. Moreover, the study of approaches that not only borrow methodology from climate studies for the study of diseases, but instead actually integrates climate and disease models together utilizing machine learning, is largely unexplored.

4.1.4. Integration/development of UQ methodologies into climate-epidemiology models

Sandia is also paving the way in advancing methods to enable sensitivity analysis [137] and the characterization of parametric uncertainties in various E3SM components [116, 61], and developing Bayesian frameworks for introducing uncertainty quantification into epidemic forecasts (including COVID-19 forecasts) [121, 113, 120]. These efforts can be leveraged by equipping epidemiological models driven by climate data as well as fully-coupled climate-epidemiological models with uncertainty propagation and global sensitivity analysis (GSA) capabilities.

An idea to explore within the realm of UQ is the use of adjoint-based inversion/optimization methods together with Bayesian approaches. Rigorous optimization-based approaches, e.g., adjoint-based inversion, can be used to invert for unknown/uncertain parameters in mechanistic models for disease spread using available data. This approach has been shown to deliver robust and accurate initial conditions for climate simulations that are far less noisy and give rise to better agreement with observational data than traditional "spin-up" approaches [104]. In order to provide uncertainty bounds in predictions made by mechanistic models, one can inform this inversion or inference in a Bayesian framework to obtain uncertainty bounds on the model parameters, given some known uncertainty in the available observational epidemiological data. This step is known as "Bayesian calibration". The uncertainties in the parameters can then be propagated through the forward model to obtain uncertainties on the model quantities of interest (QOIs). Figure 4-1 shows a schematic that demonstrates the proposed workflow. This workflow is similar in flavor to the approach presented in [61] for land ice models.

4.1.5. Collection and fusion of genome-based biological data as a foundation for climate change-infectious disease studies and climate model parameterizations

A high fidelity, climate-informed disease forecasting capability will require the development of a scalable, automated "wet lab" and bioinformatics workflows for rapidly and cheaply sequencing, annotating and functionally characterizing the genomes of pathogens from various transmission classes. This capability should be tied to directed (i.e., focusing on specific pathogens, such as dengue, influenza and valley fever) and undirected (not focusing on a specific pathogen, but rather collection of background biota as a moving baseline) surveillance efforts in key locations in all climatic zones. Such long-term, genome-based, widely-deployed biological surveillance activities have a precedent in the BioWatch program[2], whose stated goal is atmospheric monitoring of biologicals to minimize the risk of biological attacks, a low probability, potentially high consequence

[2] `https://www.dhs.gov/biowatch-program`.

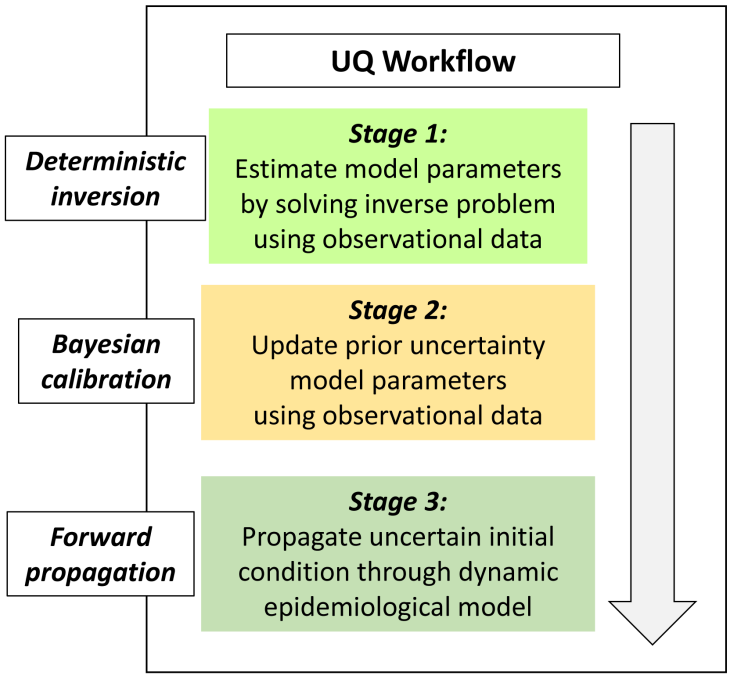


Figure 4-1. Proposed uncertainty quantification workflow for epidemiological models comprised of three steps: (1) determininstic inversion, (2) Bayesian calibration, and (3) forward propagation of uncertainty

scenario. Sandia has made sporadic, yet significant investments in biosecurity-oriented, genome-based technologies, such as Microscale Immune Studies Laboratory (MISL), Rapid Threat Organism Recognition System (RapTOR), and more recently CRISR-Cas9 programs, but to the best of our knowledge, none of these have been adopted and scaled by commercial or government partners. However, the knowledge and experience from these efforts are potentially valuable for developing the heavily biological components of a climate-infectious disease forecasting capability. The importance of sustained investment for building a scientific critical mass of knowledge and expertise at the intersection of computational biology/bioinformatics and climate science cannot be overstated.

Climate change-infectious disease studies require large-scale, continual biological monitoring and analyses to ensure global health. There is an opportunity to create tools to collect and process these genome-based data, as well as to use these data to develop standard knowledge products useful for the intelligence and military communities, decision makers and public health authorities, among others. To accelerate development of new theraputics that will be required for future disease burden, these genome-based knowledge products can be used as inputs to Molecular Dynamics (MD) modeling for comparative studies of early infection events. MD-based comparisons of early infection steps are important because these first steps are informative not only for identifying potential new drug targets, but also because initial steps can illuminate how infections lead to outbreaks and epidemics. Ancillary benefits will also include: shoring up basic epidemiologically-relevant

data collection, which are typically uneven, sparse, spatiotemporally mismatched for large-scale modeling or simply unavailable; deepening our understanding of climate-change signatures in the genomes of ecosystem inhabitants; discerning possible relationships between pathogenesis and climate change.

5. CONCLUDING REMARKS

> *"Observational, experimental, and modeling activities are all highly interdependent and must progress in a coordinated fashion. Experimental and observational studies provide data necessary for the development and testing of models; and in turn, models can provide guidance on what types of data are most needed to further understanding. The committee encourages the establishment of research centers dedicated to fostering meaningful interaction among the scientists involved in these different research activities through long-term collaborative studies, short term information-sharing projects, and interdisciplinary training programs. The National Center for Ecological Analysis and Synthesis* `https://www.nceas.ucsb.edu/` *provides a good model for the type of institution that would be most useful in this context."*
> –National Research Council (NRC). 2001. Under the Weather: Climate, Ecosystems, and Infectious Disease. Washington, DC: The National Academies Press (`https://doi.org/10.17226/10025`)

Infectious disease processes have complex webs of causation, and climate is an important, if poorly understood, component of this web. Climate change and the attendant environmental degradation, are putting unprecedented pressure on ecosystems and their organisms, including hosts and pathogens, forcing selection and adaptation at time scales vastly different from those under which they evolved. This results in a destabilized biosphere and climate, as the two are strongly coupled. In the previous chapters, we have detailed the interaction of climate with representative examples of different transmission categories of infectious diseases: insect-vectored, human-to-human and environmentally-transmitted diseases. We have also reviewed the current state-of-the-art in climate-informed epidemiological modeling/forecasting, identified significant knowledge gaps in this field, and proposed a number of ideas for advancing this field.

Sandia is ideally suited for leading the proposed R&D, and developing the multidisciplinary climate-infectious disease effort highlighted in the NRC quote above. Just within our team, we have demonstrated highly productive multidisciplinary collaboration in the natural sciences, and computational and mathematical modeling. Our approach will be multi-pronged, as scientific bridges robustly linking modern disease biology with mathematical and climate modeling must be built. This multi-pronged approach accepts of the reality of increased future disease burden accompanying a rapidly changing climate, and the need for robust, immediate scientific responses to meet these challenges, from design of novel therapeutics, to development of new climate-infectious disease forecasting frameworks. We intend to tackle thematic, high-likelihood, potentially high-consequence problems, including:

1. Understanding how interannual climate and seasonal variation interact with infectious disease.

2. Quantifying impacts of major and multiyear climate phenomena (e.g., El Niño Southern Oscillation, Pacific Decadal Oscillation, Asian and American Monsoons, teleconnections, large-scale storms, etc.) on infectious disease burden over space and time.

3. Ascertaining how altered land-use patterns, together with a rapidly changing climate, promote outbreaks and epidemics.

4. Discovering how early steps in the infection process can profoundly affect disease progression, in both individual hosts and also at the population/epidemiological levels.

5. Characterizing pathogen biodiversity and biogeography to understand how climate change influences evolutionary patterns and processes, including adaptations relevant to altered virulence, drug resistance and shifting spatiotemporal ranges.

Potential external public sponsors for establishing this capability include U.S. Department of Energy (DOE) Biological and Environmental Research (BER), Advanced Scientific Computing Research (ASCR), Scientific Discovery through Advanced Computing (SciDAC), the National Institutes of Health (NIH), the U.S. Department of Defense and Homeland Security, among others. Private entities whose missions align with our vision include the Moore[1] and the Gates[2] Foundations. Our near term goal is to secure BER funding to establish key pillars of the climate-informed disease forecasting capability. Our vision for a multi-disciplinary institute to tackle potentially civilization-altering climate change-infectious disease challenges, offers the opportunity for funding agencies to co-invest in areas that do not fit neatly within traditional funding boundaries. In addition to external resources, our aim is to try to procure Laboratory Directed Research and Development (LDRD) funding to further our literacy in climate change and infectious disease, to grow our R&D community, and to develop initial climate-informed infectious disease forecasting capability using the E3SM, epidemiological modeling frameworks and diverse biological data.

[1] https://www.moore.org/.

[2] https://www.gatesfoundation.org/.

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