THE PENNSYLVANIA STATE UNIVERSITY
SCHREYER HONORS COLLEGE

DEPARTMENT OF GEOGRAPHY

SPATIAL SCALE AND MODELING DISEASE TRANSMISSION RISK: THE CASE OF MALARIA IN SUB-SAHARAN AFRICA AND THE KENYA HIGHLANDS

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SPRING 2019

A thesis
submitted in partial fulfillment
of the requirements
for a baccalaureate degree
in Biochemistry and Molecular Biology
with honors in Geography

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ABSTRACT

Students in introductory courses in plant pathology, public health, and immunology recognize the disease triangle and epidemiologic triad as conceptual models detailing the necessary components for presence of disease – a susceptible host, an infectious pathogen, and a conducive environment. A rich subset of the literature deals with "modifications" of these basic models, and, today, advanced spatial and mathematical models operate on the same principles as do the triad and triangle. As understanding of the precise mechanisms involved in the occurrence of multiple diseases improves, a challenge in the use of advanced models in predictive efforts has been the incorporation of the "complexity" of disease dynamics. Sub-Saharan Africa is a focal point in literature on studies of disease transmission. Moreover, as exemplified by recent "debates" in published work, the "re-emergence" of malaria in the previously "malaria-free" East African highlands is a prime example of the "complexity" of disease.

This thesis develops a conceptual model for understanding disease transmission risk through an expansion of Grulke's modification of the classic disease triangle model. This "modified Grulke model" (MGM) is applied to gain insight into malaria transmission risk for the region of sub-Saharan Africa (SSA), and, within the region of the Kenya highlands, for Kericho, a site of much discussion and debate in recent literature. Although questions still remain regarding malaria transmission risk in these areas, the MGM seeks a step forward in understanding the complex impacts and interactions of risk factors.

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ACKNOWLEDGEMENTS

To Dr. Downs, thank you for initially inspiring my interest in pursuing a thesis in Geography and serving as a mentor throughout this process. To Dr. Crane, thank you for guiding me and sharing your expertise.

Thank you also to my family and friends – your support has made this process possible.

Chapter 1

Introduction

During the summer after my junior year of high school, I had the privilege of traveling to Costa Rica. Knowing that I was to spend a few nights sleeping in cabins in areas of dense foliage, I wondered whether to pack a mosquito net. I, along with a few other members of my family, share the unfortunate trait of being particularly attractive to hungry mosquitoes. On my first night of the trip, I arrived at my designated sleeping room to find a cut-out window with no screen, and no hook on the ceiling from which to hang my net; my traveling companions had not brought nets themselves.

I awoke the next morning to find that my friends had been spared from mosquito bites, perhaps because the mosquitoes had found me instead. I took some comfort, however, in knowing that I was not alone in my annoyance. In a news feature for *Nature*, Janet Fang asks scientists for their thoughts on the ecological and human impacts of mosquito eradication. Fang highlights the words of Centers for Disease Control entomologist Janet McAllister: "'If there was a benefit to having them around, we would have found a way to exploit them. We haven't wanted anything from mosquitoes except for them to go away (Fang 2010).'" [1]

The "problem" of mosquitoes, however, is more than one of simple annoyance. Serving as an important biological vector of disease, mosquitoes enable transmission of diseases such as dengue, West Nile virus, Chikungunya virus, Zika virus, and, perhaps most famously, malaria.

[1] See Fang's article in *Nature*, "Ecology: A world without mosquitoes," at https://www.nature.com/news/2010/100721/full/466432a.html.

Malaria and the Modern "Question" of the East African Highlands

Few vector-borne diseases rival malaria in terms of morbidity, mortality, and a long history of responsibility for human suffering. Though malaria has been present in many regions of the world, unfortunately, African countries bear a large part of the "global malaria burden": of the 445,000 deaths due to malaria in 2016, 91% of these deaths fell in the World Health Organization's African Region (CDC, "Malaria's Impact Worldwide"). For many years, the miasmatic theory of disease played a large role in efforts at malaria prevention. European colonists arriving in Africa in the 1800s settled in highland areas in Kenya, Tanzania, Ethiopia, and Uganda, seeking to "escape" the "*mal'aria*, or bad air," thought to deliver malaria's characteristic cyclic chills and fever (Ferber and Epstein 2011). Today, it is known that the high rates of transmission of malaria in Africa are due not to bad air, but to infection of hosts by the "efficient" *Anopheles gambiae* complex mosquito as the malaria vector (CDC, "Malaria's Impact Worldwide"). These vectors deliver to hosts the malaria infectious agent, *Plasmodium* parasites, and the *Plasmodium falciparum* parasite, "predominant" in Africa, is described by the Centers for Disease Control (CDC) as the parasite "most likely to cause severe malaria and death" (CDC, "Malaria's Impact Worldwide"). Moreover, the CDC describes certain environmental factors as contributing to the presence of malaria in Africa, including "local weather conditions" allowing for malaria transmission throughout the year and control practices thwarted by "scarce resources and socio-economic instability" (CDC, "Malaria's Impact Worldwide"). However, for years, the colonialists' good fortune held, and the African highlands remained largely unburdened by the disease prominent in the neighboring lowlands. Several deadly malaria epidemics in the Kenya highlands were reported beginning around the 1940s (Tonui *et al.* 2013), and recent "return" (Cook *et al.* 2018) of a disease considered "eradicated"

from the Kenya highlands after epidemics in the 1960s (Alsop 2007) has prompted considerable study of this phenomenon. Cook and colleagues write,

"The population residing in the western highlands in Kenya has been subject to malaria epidemics since the 1930s,[9] despite traditional dogma dictating that the relatively high altitude should have been a barrier to malaria transmission. In more recent years, it appears that malaria in this region has become more stable with a reservoir of asymptomatic malaria infection.[10,11] The increase in prevalence in the region over the past few decades has generally been attributed to drug failure [9,12] and a change in mosquito behaviors. [13,14] In addition, intensification of agricultural production over the past 50 years has changed the entomological landscape of the area[1] resulting in renewed transmission in areas that were previously malaria-free" (Cook *et al.* 2018).

A Brief History of Malaria in the Kenya Highlands

Community elders in Kenya's Nandi Plateau attribute the first cases of malaria in the region to soldiers returning home from the Great War in 1918 and 1919 (Lindsay and Martens 1998), but large-scale malaria epidemics in highland areas were not recorded until 1940, 1958, and 1991 in Nairobi, Ethiopia, and western Kenya, respectively ((Lindsay and Martens 1998); Ferber and Epstein 2011). Known as highland and highland fringe malaria, these epidemics were concerning, as malaria has been thought to not often occur above 1500 meters (Malaria: Obstacles and Opportunities, 219).[2] As incidence of malaria in the highlands rose over the following years, researchers and policymakers attempted to find an explanation. For example, in 1998, Lindsay and Martens attributed the cases to agroforestry and a scarcity of "health resources," with outbreaks exacerbated by the lower levels of immunity among the previously unexposed highland residents (Lindsay and Martens 1998). They concluded that "outbreaks may be precipitated by certain climate and biological factors that favo[r] the growth and development

[2] However, as Baidjoe and colleagues have described, "The notion that malaria is largely absent in areas higher than 1500 m [40] has been challenged by findings of a large asymptomatic reservoir of malaria infections at altitudes [27] and an age-dependent acquisition of clinical immunity to malaria infections in highland communities [24]" (Baidjoe *et al.* 2018).

of mosquito vector and parasite" (Lindsay and Martens 1998). Moreover, they also discussed the importance of the interaction of factors in malaria incidence (see **Figure 1**) (Lindsay and Martens 1998). In particular, Lindsay and Martens emphasized the impacts of climate change on highland malaria transmission (Lindsay and Martens 1998), contributing to an area of study that would be further explored and even debated in later literature.

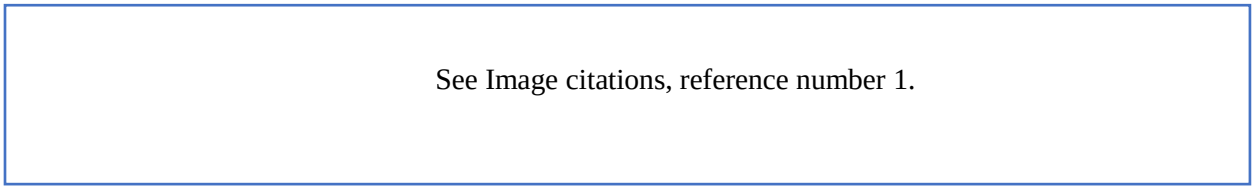


Figure 1. Organization of transmission factors with impact on highland malaria and their interactions (Lindsay and Martens 1998).

The severe burden that malaria imposes, along with the need for progress in understanding malaria transmission risk and the factors that influence it, has ensured an impressive output of research on the subject. [3] Such research has focused on understanding *why* malaria epidemics occur and have occurred in the Kenya highlands and includes the exploration of the relationships between malaria and "anomalous" weather events (UNDP 28), "population movements" and drug resistance (Shanks *et al.* 2005), certain "micro-climatic" changes (Tonui *et al.* 2013), and changes in land use (Himeidan and Kweka 2012; Chaves *et al.* 2011). Thus, the study of malaria, especially with emphasis on understanding the impact of environmental factors on transmission risk, has sparked continued scholarship. Now, with increasing knowledge of the scale of the processes of climate change and population growth in Africa and their implications

[3] See, for example, the PhD theses of Nicholas Ikol Adungo (1992) and C.J.M. Koenraadt (2003), *Factors Affecting Malaria Transmission by Vector Mosquito Populations in Western Kenya, with Special Reference to Altitude* (University of Nairobi Library) and "Mosquitoes, Men, and Malaria in Kenya: A Study on Ecological Factors Affecting Malaria Risk."

for disease, there is opportunity to advance understanding of malaria transmission risk through focus on these processes.

An Approach to Understanding Malaria Transmission Risk: Models for Understanding Disease Transmission

As an undergraduate student, my first exposures to the concepts of examining disease transmission and transmission risk came through two particular courses, one in immunology and one in human geography. My term paper in human geography examined the spread of the destructive Fusarium wilt of banana in Central America and the efforts of the United Fruit Company to contain the disease. Through it, I developed an interest in the geography of disease and medical geography, and I began to think and read about the transmission of plant, human, and animal diseases and the factors influencing this transmission. Later, in the first weeks of an immunology course, I learned of the epidemiologic triangle and its usefulness in understanding animal and human diseases as products of interactions among a susceptible host, an infectious agent, and a conducive environment. As I read more about diseases and disease transmission in the literature, I came across the foundations for what would become the two main parts of my thesis: first, the value of the disease triangle and the epidemiologic triad in advancing conceptual understanding of disease and the subsequent "modifications" of these classic models, and, second, the status of sub-Saharan Africa (SSA) as a focal point in studies on influences impacting transmission of disease.

The disease triangle (also described as the host-pathogen-environment triangle), I discovered, could be viewed as the plant-specific equivalent (see Francl 2001) of the

epidemiologic triad for human and animal disease, and many researchers had attempted to modify and expand the classic disease triangle model. Scholthof, in particular, had argued for the applicability of the disease triangle in understanding the human disease of malaria (Scholthof 2007; see Chapter Two of this work). One specific modification of the disease triangle that I had come across stood out to me – Grulke's modification of the disease triangle to emphasize the influence of "environmental change" on disease transmission (Grulke 2011). In her 2011 paper, "The Nexus of Host and Pathogen Phenology: Understanding the Disease Triangle with Climate Change," Grulke restructures the disease triangle to emphasize the role of environmental changes as influencing a plant pathogen-plant host relationship necessary for disease (Grulke 2011). Given the emphasis of recent research on understanding the impact of changing environmental conditions – especially climate change – on malaria transmission potential, Grulke's model seemed a valuable tool for enhancing conceptual understanding of these impacts. Thus, I arrived at the present thesis through a multitude of factors: my interest in Grulke's model, the relevance of environmental changes for sub-Saharan Africa, such as climate change and population growth, the importance of climatic conditions for the incidence of malaria, and the great interest among researchers in understanding highland epidemics.

The rest of this thesis is organized into two parts. Part I focuses on my first research interest in the use of models for understanding disease transmission. This part details an expansion of Grulke's disease model (the "modified Grulke model," or MGM) for examination of disease transmission in sub-Saharan Africa. The second part applies this MGM to malaria, specifically, where malaria transmission risk is studied at two spatial scales: first, at the "regional" level of sub-Saharan Africa, and, second to one highland site that has been a focus of much discussion – Kericho, Kenya. Ultimately, the goal of this work is to provide perspective to

the “questions” surrounding malaria in the Kenya highlands and to contribute to understanding of disease transmission risk for sub-Saharan Africa.

PART I. DEVELOPMENT OF A REGIONAL MODEL FOR DISEASE TRANSMISSION IN SUB-SAHARAN AFRICA (SSA)

Chapter 2

Choosing a Model for the Study of Disease Transmission

> *"All models are approximations. Essentially, all models are wrong, but some are useful. However, the approximate nature of the model must always be borne in mind."*
>
> -- George E. P. Box and Norman R. Draper in *Response Surfaces, Mixtures, and Ridge Analyses*

This chapter establishes a basis for a model for disease transmission risk. The chapter is somewhat of a non-exhaustive "history" of conceptual models for infectious disease, detailing two "traditional" models and the subsequent modifications of these models.

I. Traditional Conceptual Models for Infectious Disease

A Product of Multiple Disciplines

The study of disease transmission is one that has benefitted greatly not only from advancements in understanding through the "wet-lab" research often associated with the medical field, but also as a product of an "overlap" of knowledge through diverse studies in mathematical modelling of disease, medical geography, as well as spatial epidemiology, analyses of healthcare systems and their effectiveness in preventing and treating disease, and the impacts of relevant public policy and current events. For his explanation of cholera as a water-borne disease, Dr. John Snow, revered as "one of the founding fathers of modern epidemiology," famously drew from the geographer's toolbox in mapping the epidemic, realizing the proximity of cholera patients to London's Broad Street pump ((John Mack, "Mapping the 1854 London Cholera

Outbreak"). Since then, the "toolbox" for studying disease transmission has grown considerably, including the use of advanced statistics, surveys, and surveillance methods in epidemiology (Woodruff *et al.*, London School of Tropical Medicine, 2009)(Scholthof 2007), the development of mathematical models for understanding of transmission risk,[4] and the use of geographic information systems (GIS) to develop maps enabling a spatial sense of disease transmission potential.[5] One researcher, in particular, has advocated for application of a tool associated with plant pathology in efforts to improve human health. Karen-Beth G. Scholthof argues that the conceptual model of the disease triangle views disease as the product of "interactions" between a host, pathogen, and environment (**Figure 2**). The disease triangle, Scholthof maintains, "can be used to predict epidemiological outcomes in plant health and public health, both in local and global communities" (Scholthof 2007). Moreover, it "uses the temporal relationships between the environment, the host and an infectious (or abiotic) agent to develop new ideas to predict and control disease" (Scholthof 2007).

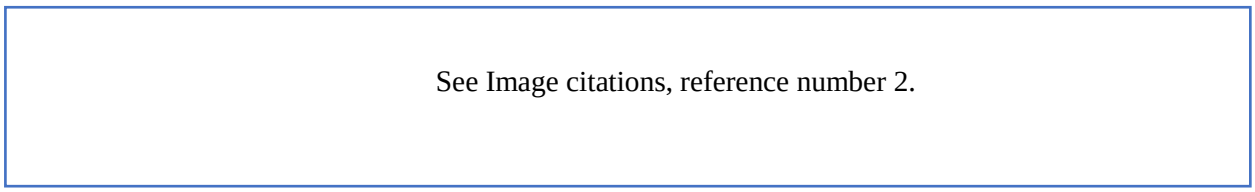


Figure 2. The disease triangle (Francl, 2001).

History of the Disease Triangle and its Fundamental Argument

The exact origins of the disease triangle model are unclear, although the model's original presentation seems to trace back to the 1960s. Francl and Grulke, for example, attribute the

[4] In terms of malaria, see Mandal *et al.* 2011, for example, discussed later in this thesis.
[5] Also in terms of malaria, see https://www.esri.com/news/arcnews/fall12articles/can-gis-help-fight-the-spread-of-malaria.html.

disease triangle (as depicted in their work) to Stevens' work, published in 1960 (Francl 2001, Grulke 2011). Scholthof describes a disease triangle "formalized" by George McNew in this decade (Scholthof 2007). Nevertheless, Francl contends that the principles displayed in the disease triangle were realized much earlier, recognizing "pioneering plant pathologists prior to Stevens" who described the incidence of disease in terms of "climatological factors" as well as a host and a pathogen, such as a parasite (Cohen and Shang 2015) (Francl 2001). The importance of the disease triangle lies in its structural interconnections: as Nelson writes, "if either the host is less susceptible, the pathogen is less virulent, or the environment is less favorable, diseases will either occur at a reduced level, or they will not occur at all" (Nelson 1994).

The Epidemiologic Triad as a Model for Understanding Human and Animal Diseases

If the exact origins of the disease triangle are complex, it seems that those of the epidemiologic triad (**Figure 3**) are equally so. The epidemiologic triad, although similar to the disease triangle, likely arose around the same time or earlier than the disease triangle – the triad has been attributed to Clark in a 1954 work (Cohen and Shang 2015). Used in descriptions of "disease causation" (CDC "Principles of Epidemiology," "Lesson 1, Section 8: "Concepts of Disease Occurrence") for human and animal diseases, the epidemiologic triad, like the disease triangle, describes disease as the result of interactions between a susceptible host, an "agent," which has been "broadened" to include not only biological pathogens, but also "chemical contaminants [. . .] as well as physical forces," and the environment as "extrinsic factors that affect the agent and the opportunity for exposure," including physical, biologic, and socioeconomic factors (CDC Lesson 1, Section 8: "Concepts of Disease Occurrence"). One important limitation of the epidemiologic triangle has been the problem of its application "for

many non-infectious diseases" due to the "multifactorial nature of causation" – for non-infectious diseases, models have arisen such as Rothman's Causal Pies, which describe how multiple "component causes" contribute to "sufficient cause," resulting in disease CDC Lesson 1, Section 8: "Concepts of Disease Occurrence").

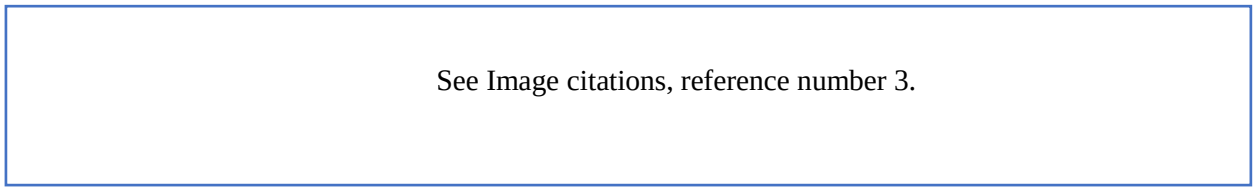


Figure 3. The epidemiologic triad, also called the epidemiologic triangle (CDC Lesson 1 Worksheet).

For all of their similarities, it is valuable to realize important differences between the epidemiologic triad and the disease triangle. Although Scholthof later argued for the capacity of the disease triangle to provide special insights on malaria, a human disease, for the triangle's emphasis on environmental impacts on "disease transmission and control" (Scholthof 2007), it is valuable to consider Francl's point for the basis of the disease triangle in plant pathology and its applicability specifically to plant diseases. Francl writes:

"This triangular relationship is unique to phytopathology in comparison to veterinary and medical sciences because terrestrial plants possess little thermal storage capacity and their immobility precludes escape from an inhospitable environment. The sophisticated immune system found in mammals is absent in plants, and this places an emphasis on the host's genetic constitution. Finally, the predominance in phytopathology of fungi, which are also highly dependent on the environment, may have contributed to the development of this paradigm" (Francl 2001).

The Purpose of the Disease Triangle and an Argument for its Applicability to Human Disease

Scholthof makes an important point about the original intentions of the disease triangle: the triangle "was intended as an empirical tool for use until research matured to provide new

methods to predict and control diseases" (Scholthof 2007). Nevertheless, the disease triangle is still acknowledged and discussed today. Francl describes its use in college courses as "a fundamental principle of the factors involved in disease transmission" (Francl 2001), and Scholthof argues for the increased use of the disease triangle as a "tool to discuss parameters that influence socioeconomic outcomes as a result of host-pathogen interactions involving plants and humans" (Scholthof 2007). Use of the disease triangle, Scholthof maintains, allows for a more thorough examination of the influence of the environment on disease transmission, a subject which has been "underestimated at times in the history of medicine" and in laboratory research exploring "host-pathogen interactions" (Scholthof 2007). Thus, in showing the applicability of the disease triangle both to the Irish Potato Famine, a disastrous consequence of the *Phytophthora infestans* pathogen, and to malaria, Scholthof's argues for the triangle's applicability in both the plant and human domains. Further, Scholthof clears a path for the application of the disease triangle to a host of other diseases in a crucial paragraph, noting again its emphasis on the impacts of environmental conditions:

" [. . .] Plant, animal, and human health outcomes are affected by local and global environmental conditions. These conditions might include economic or ecological factors, changes in host populations, trade and travel, technology and changes in microorganism populations. Several human diseases, such as HIV, tuberculosis, transmissible spongiform encephalopathies, plague, cholera, influenza, and malaria are clearly influenced by or more of these environmental conditions. Further environmental factors that influence disease outcome include famines, war, the use of biological weapons, and natural or man-made cataclysms such as hurricanes, deforestation, drought, air and water pollution; each of these factors demands flexible approaches to preventing disease and improving the social matrix" (Scholthof 2007).

A number of later publications have recognized Scholthof's work. Although many of these works remain grounded in the disease triangle's original "home domain" in plant pathology, there are a few articles on animal disease. For example, in a publication on the beliefs of "laypeople" on causes of H5N1 avian influenza, Liao and colleagues cite Scholthof's

explanations as a reminder of the principles of managing infections: "effective infection control requires separation of vector, agent and host" (Liao *et al.* 2009). Vander Wal and colleagues, writing on the importance of "evolutionary concepts" in wildlife disease ecology acknowledge both the epidemiological triangle's limits and its value as "a typical pedagogical framework":

> *"Albeit unrealistic, this basic framework begins as static. All three components, however, are involved in complex community interactions, including competition among multiple hosts (H_i), or among multiple pathogens (A_i) relying on the same host (Hudson et al., Fig. 2). These interactions are also affected by natural or anthropogenic environmental change (Wilcox and Gubler 2005), potentially leading to co- or eco-evolutionary dynamics (Duffy and Forde 2009)"* (Vander Wal *et al.* 2014).

As a final note on the value of the epidemiologic triad, there are two recent applications of the epidemiologic triad for understanding important human diseases. Mendez-Martinez and colleagues build a study of the "persistence" of human papillomavirus (HPV) in Mexican women through "identify[ing] epidemiologic triad-related factors," describing their identified factors as "important to consider in the diagnostic-therapeutic approach" (Méndez-Martínez *et al.* 2018). Similarly, Burke and colleagues described a "clarifying" of the factors of the epidemiologic triad as useful to "help guide preventive interventions for target populations, including vaccine development," in a study of "predictors of severe outcomes" in norovirus cases (Burke *et al.* 2018).

II. Modifications of Traditional Models

Variations on the Disease Triangle and Epidemiologic Triad

Although the disease triangle and epidemiologic triad have persisted in the literature in their "original" forms, since the publication of these models around the 1960s, numerous

researchers have attempted to modify and improve upon these models, in part because of the original models' acknowledged limitations. Francl describes a number of these. For example, the triangle may be extended into three dimensions through a fourth vertex representing time, humans, or a vector of disease (attributed to Agrios and Stevens); as a "disease cone" representing "expansion of disease intensity through time" (attributed to Browning); or as "triangles sequentially stacked to show development of plant disease through time" (Francl 2001). Along a similar vein, an "advanced epidemiology triangle for chronic diseases and behavioral disorders" includes a triangular relationship with the dimension of time in the middle of the triangle (see Figure 4). The triangle itself depicts a relationship between three vertices of the "environment," described as "behavior and culture, physiological factors, and ecological factors"; "causative factors' including biological, chemical, and physical factors; and a "group or population" further defined by characteristics such as "age, gender, ethnicity, religion, customs, occupation, heredity, marital status, family background, and previous diseases" (attributed to R.M. Merrill's *Introduction to Epidemiology*, 7e, 2017; depicted in Ping Johnson's presentation, "Epidemiology and Surveillance in Chronic Disease Prevention and Control").

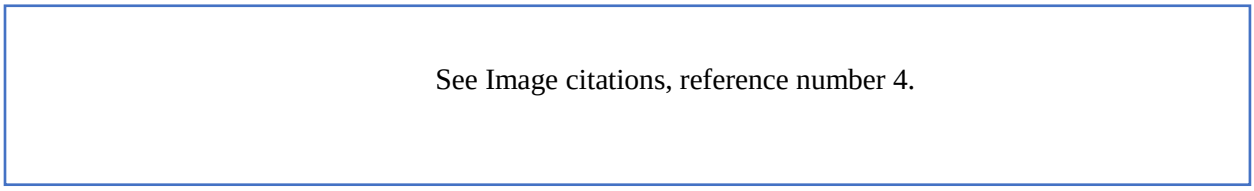


Figure 4. The advanced epidemiology triangle (attributed to R.M. Merrill's *Introduction to Epidemiology*, 7e, 2017, as depicted in Ping Johnson's presentation, "Epidemiology and Surveillance in Chronic Disease Prevention and Control").

Finally, a particularly interesting variation of the disease triangle is Marelli's "multidimensional disease triangle" depicted as a "'triangular disease prism.'" In it, Marelli argues for the

expansion of the disease triangle with addition of "cultures," "politics," and "economics" dimensions, arguing that the model "links a quantifiable concept (the interaction of host, pathogen, and environment) with a more qualitative representation of human intervention in disease epidemics (culture, politics, and economics)" (Marelli (2008), page 34).

As further variations, aside from depiction of the disease triangle in tandem with corresponding "diagnosis" and "management" triangles for combatting plant disease (Sanders, "Diagnosis and Management of Turfgrass Disease"), there have also been attempts to "quantify" the factors of the disease triangle. This has been accomplished through distortion of the length of the triangle's sides (Francl 2001) or including an internal axis showing "extent of damage to [the] host by disease" (Scholthof 2007, reproduced from McNew, 1960).

A particular interest of this thesis lies in "more radical" variations of the disease triangle which may depart visually from the "simple" triangular form of the original model. For example, Koenraadt (2003) employs a focus on malaria in highland regions and presents a model for understanding "factors that influence malaria transmission and risk," with intrinsic factors described as "characteristics belonging either to the parasite, mosquito or host and which are not part of the natural environment" (**Figure 5**) (Koenraadt 2003, pages 31-32).

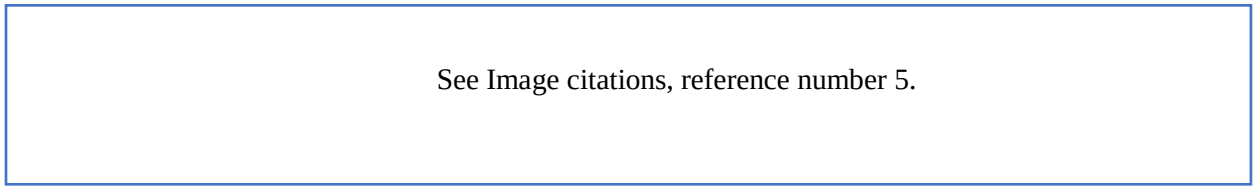


Figure 5. Factors influencing the transmission and "risk" of malaria. The figure and legend shown here appear as they do in Koenraadt's work (Koenraadt 2003, page 32).

Although Koenraadt does not specifically discuss the disease triangle or the epidemiologic triad, his figure shares important attributes with the "original" disease triangle and epidemiologic triad models. First, it depicts a triangular relationship between the vector, the

host, and the parasite; here, the environment could be thought of as a fourth "vertex," similar to the tetrahedron shapes that Francl attributes to researchers such as Agrios and Stevens (Francl 2001). Moreover, Koenraadt's addition of extrinsic and intrinsic risk factors allows for an opportunity to discuss and define what these factors might be in the context of the model.

Although Koenraadt's model is not defined as an explicit variation on the original disease triangle and epidemiologic triad models, Chappelka and Grulke do explicitly define a model as an "expansion of the disease triangle," arguing that this expansion allows them "to incorporate the complexities of the chemical and physical environment, as well as the effects on plant pathogens, including insect vectors of these pathogens" (Chappelka and Grulke 2015) (**Figure 6).**

See Image citations, reference number 6.

"Figure 2. Expansion of the disease triangle incorporating the influence of air chemistry and environmental variability on the health of the plant host and its susceptibility, the virulence of the pathogen, insect vectors (if part of the pathogen–plant system), and feedbacks between these components, soils and belowground processes critical for also understanding root pathogens (amended from Grulke 2011). NOy = ∑ of NOx+ compounds produced from oxidation of NOx" (Chappelka and Grulke 2015).

Figure 6. Chappelka and Grulke's expansion of the disease triangle showing the influence of the "chemical and physical environment." The figure and legend provided appear as they do in Chappelka and Grulke's work (Chappelka and Grulke 2015).

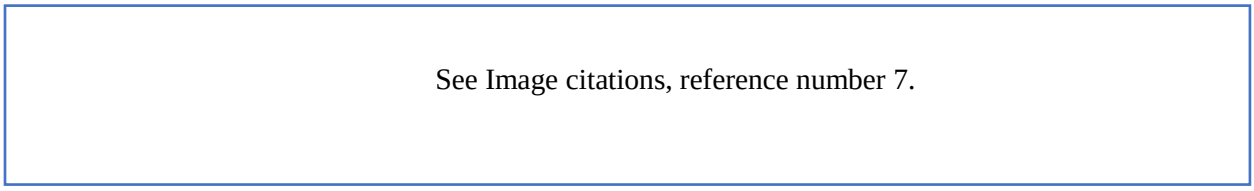
As with Koenraadt's model, the original elements of the disease triangle are visible and acknowledged within Chappelka and Grulke's variation. Here, the disease triangle elements of the pathogen and the plant host (and the vector element included in the tetrahedral variation) remain unchanged; instead, the disease triangle's usual third vertex of the environment is specified into three separate vertices of air pollutants, climate and variability, and soils and

belowground processes (Chappelka and Grulke 2015; **Figure 6**). Importantly, Chappelka and Grulke emphasize the benefits of developing and employing such a modification of the disease triangle. "Complex changes in air chemistry and subsequent physical changes in the environment have a profound effect on the disease triangle," they write, "and should be incorporated into research designs, their analyses, and in empirical modeling of the pathogen effects on forest ecosystems" (Chappelka and Grulke 2015). Thus, the expansion of what is sometimes described as a "simplistic" (Davies 2012) model can inform the more complex mathematical modeling approaches that were originally intended to replace it (see Scholthof 2007).

III. The Basis of the Model Expanded in This Work

Grulke's Modification of the Disease Triangle (2011)

One interesting aspect of the figure legend included with Chappelka and Grulke's 2015 model of disease triangle is the statement that it was "amended from Grulke 2011" (Chappelka and Grulke 2015). Grulke's modification of the disease triangle in 2011 (**Figure 7**) is structured to show a crucial aspect of the impact of the environment on disease transmission: the effects of environmental change.



"Figure 1. Modification of the environment–host–pathogen triangle (Stevens, 1960), indicating the importance of interactions between the physiology of the host and the capability of successful inoculation and growth of the pathogen under changing environmental conditions. Important components of environmental change include elevated temperature and greater duration of favorable conditions for plant and pathogen growth; change in atmospheric chemistry; and changes in precipitation patterns,

including higher frequency, duration and intensity of drought. Some of the attributes of the plant host that are relevant under changing environmental conditions include earlier onset of bud break and delayed onset of senescence; the potential for earlier and different magnitudes of peak growth; changes in tissue quantity and quality; and the potential for changes in the timing and type of responses to pathogens (plant capacity for resistance, tolerance, and mechanical and chemical defense). It is unclear for most species how environmental cues for phenology (e.g. degree days of warming, photoperiod) may limit the capacity of long-lived plants to synchronize plant growth with new environmental conditions in situ. Some of the attributes of the plant pathogen that are relevant under changing environmental conditions include the timing of optimal temperatures for growth relative to optimal moisture conditions, the nutritional status of the plant host (the 'media') and the changes in the cell structure that permit or slow pathogen growth" (Grulke 2011).

Figure 7. Grulke's modification of the disease triangle (2011) to emphasize the importance of environmental change as it impacts disease transmission. The figure and figure legend shown are presented as they appear in Grulke's 2011 work (Grulke 2011).

Importantly, a central point of Scholthof's argument for application of the disease triangle to human diseases was the need for an increased emphasis of the impacts of environmental factors on disease transmission (Scholthof, 2007). Thus, Grulke's model presents an opportunity to build upon and explore Scholthof's argument through an emphasis on the impacts of environmental *change* on human diseases. As Koenraadt maintained in 2003, the impact of environmental factors and changes on malaria transmission and transmission risk, and exactly which environmental changes and factors impact this transmission risk, was a central question in the literature, especially for vulnerable highland areas (Koenraadt 2003, pages 9; 20), and questions such as these are still being explored in more recent literature.[6] Now, given increasing knowledge and study of environmental changes such as climate change, urbanization, and deforestation and the great rates and impacts of these changes, it seems valuable to apply Grulke's model to aid in the study of malaria transmission as a method to interact with the scholars studying this problem and to explore how Grulke's model fits with those discussed in the literature.

[6] See, for example, Caminade and colleagues' "Impact of climate change on global malaria distribution" in *PNAS* (2014), https://doi.org/10.1073/pnas.1302089111.

Conclusion

The disease triangle and epidemiologic triad serve as valuable models for thinking about disease transmission, especially in their representation that a "break" in the triangular structure is used for "management" of disease ("Plant Disease Basics – The Disease Triangle"). Grulke's 2011 expansion of the plant-based disease triangle presents a model for focusing on the impacts of environmental change on disease, and Scholthof's argument for application of the disease triangle to the human disease of malaria emphasizes the need for study of the effects of environmental factors. Thus, Grulke's 2011 expansion is a valuable tool for efforts to integrate understanding of the impacts of environmental factors on malaria transmission risk. The next chapter presents a further "expansion" of Grulke's 2011 model in an effort to build upon Grulke's "environmental change" component, where this component will be used to explore changes in both the "physical" and "human" environments – this is "contextual change." In Chapter Three, this expansion of Grulke's work – called the "modified Grulke model" (hereafter, "MGM") – is applied to a study of disease transmission risk in sub-Saharan Africa (SSA), a focal point of literature in public health.

Chapter 3

The Modified Grulke Model (MGM) as a Definition of "Contextual Changes" Related to Disease Transmission

"This rapid economic growth, coupled with a young, growing population, wide uptake of technology, particularly mobile phone technology, and a burgeoning middle class, has led to a new view of Africa. Often referred to as 'Africa rising,' this new view sees Africa as becoming an increasingly important demographic and economic driver of global growth. This is beginning to change the standard view of the World Health Organization (WHO) African Region as a place plagued by poverty, interminable conflict, and incurable health problems"

- The World Health Organization's 2014 WHO African Region report, *The Health of the People*, page 5

This chapter builds upon Grulke's 2011 expansion of the disease triangle by creating a "modified Grulke model" (MGM) which will be used in conjunction with Grulke's original model to examine of malaria transmission risk in Part II. The MGM is defined as a tool for study of "contextual changes" – changes in the "physical" and "human" environments – that impact disease transmission. Trends are defined for sub-Saharan Africa, and these are compared to more "general" factors influencing disease transmission. Common diseases in the region are then described, the MGM is defined, and the MGM is applied to two of these diseases as examples of its applicability.

Sub-Saharan Africa: An Overview of Identified Trends and their Potential Impacts

The term "sub-Saharan Africa" (here abbreviated as SSA) seems to inspire some confusion in the literature. For the purposes of this work, Serdeczny and colleagues' definition

of the region will be followed, describing SSA as bounded by 15° north and 35° south latitude (Serdeczny *et al.* 2017) (see **Figure 8, page 27**). Countries included in this SSA region include those in the Central, East, West, and Southern African regions.[7]

As a vast region with striking differences between and within its component countries,[8] SSA presents a challenge for "generalization" of trends. However, researchers have written of several trends prevalent in the countries comprising SSA. The opening quote from a 2014 report by the World Health Organization describes a "young" African population (WHO, *The Health of the People*, page 5); as of September 2018, six out of every ten Africans is younger than twenty-five years old (McKay, *The Wall Street Journal,* September 18, 2018). A 2015 report by the PEW Research Center described "relatively high rates of economic growth in recent years" but spoke of "tremendous challenges [. . .] especially a lack of jobs" (PEW Research Center, 2015). Respondents to the Center's survey viewed access to health care and education as "top priorities" (PEW Research Center, 2015).

A main focus of attention in examination of trends and their impacts on SSA seems to be the region's enormous expected population growth, an increase of 1.3 billion people by the year 2050 (Devermont, CSIS, "The World Is Coming to SSA," 2018). As the Center for Strategic and International Studies reports, the opportunity presented by this "growing consumer base" has already begun to attract increased international attention from countries interested in trade and investment (Devermont, CSIS, 2018). However, the Office of the Director of National Intelligence maintains that this population growth "will strain food and water resources, health

[7] See the List of Sub-Saharan African Countries provided by the Library of Congress, https://www.loc.gov/rr/amed/guide/afr-countrylist.html.

[8] See, for example, Betsy McKay's "Extreme Poverty Concentrates in Sub-Saharan Africa," https://www.wsj.com/articles/extreme-poverty-concentrates-in-sub-saharan-africa-1537243201.

care capacity, education, and urban infrastructure" in addition to its ability to "generate increased migration outflows where economic growth is insufficient to support the population" (Office of the Director of National Intelligence, "Sub-Saharan Africa," 2017). This report also hints at the potential for conflicts and "complex security problems" in the region, writing, "a growing population of educated and urban youth will strengthen existing trends of religious affiliation and of protests fueled by dissatisfaction with corruption, rising inflation, high unemployment, and poor government performance" (Office of the Director of National Intelligence, "Sub-Saharan Africa," 2017).

In addition to these social and cultural trends, a focus of research over the last few decades has centered on attempts to understand the impacts of changes in the physical environment, especially desertification and climate change. In a 2017 piece for *The New York Times* on Niger, Thomas L. Friedman, through a conversation with the United Nations' Monique Barbut, captured the ability of a particular change in the physical environment to exert broad influences, interacting with other trends:

"Desertification is the trigger, and climate change and population explosions are the amplifiers. The result is a widening collapse of small-scale farming, the foundation of societies all over Africa. And that collapse is leading to a rising tide of 'economic migrants, interethnic conflicts and extremism,' Monique Barbut, who heads the United Nations Convention to Combat Desertification and guided me in Niger, explains" (Friedman 2017).

In a similar vein, Serdeczny and colleagues establish the broad influence of climate change and its impacts on trends in the region. Citing the previously established "connection between rainfall extremes and reduced GDP because of reduced agricultural yields," these researchers warn of a potential increase in the rate of rural-urban migration (urbanization) already ongoing in SSA (Serdeczny *et al.* 2017). Further, they discuss dual stresses on "water demand" through both expected rises in "irrigation and hydropower production" with population

growth and economic development as well as the "evaporative losses" associated with climate change (Serdeczny *et al.* 2017). However, perhaps most interesting for this work are Scholthof and colleagues' descriptions of the impacts of climate change on "human health," discussing the impacts of flooding, drought, and heat stress on such diseases as mosquito-borne Rift Valley fever, highland malaria, cholera, and other illnesses such as diarrheal disease, trachoma, and conjunctivitis (Serdeczny *et al.* 2017). It is in the context of both these "physical" and "human" factors and their impacts on other trends that I sought to establish the disease burden, or "disease profile," of sub-Saharan Africa.

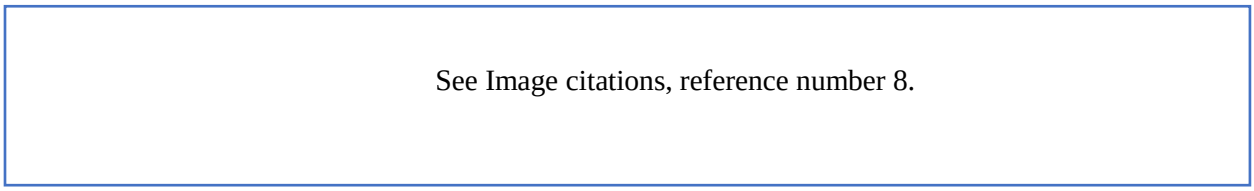


Figure 8. A political map of Africa (2012; Perry-Castaneda Library Map Collection, The University of Texas at Austin: University of Texas Libraries).

A General View of the Factors Influencing Disease Transmission

As a note before discussing the disease burden of the sub-Saharan African region, it is useful to again think along the lines of the disease triangle and basic epidemiological concepts in terms of the "general" factors influencing transmission of disease. In the 1996 edition of the text *Medical Microbiology*, Philip S. Brachman presents a table detailing the "general factors that influence the occurrence of infectious disease," reproduced here (**Figure 9**):

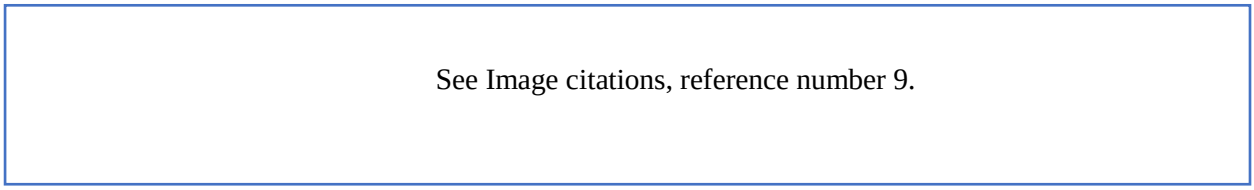


Figure 9. Philip S. Brachman's generalization of factors impacting transmission of infectious disease (as presented in *Medical Microbiology*, 4th ed. (1996), editor Samuel S. Baron).

Of the four categories of factors that Brachman details in the table, it is the "environment" component that is the shortest piece. Returning to Scholthof's argument for the application of the disease triangle to human disease as a method to further investigate the influence of the environment on disease transmission (Scholthof 2007), it seems that further "expansion" of this environmental component – through both use of the disease triangle and knowledge of the human and physical trends for SSA – would be a valuable contribution. Moreover, given the substantial impacts on disease transmission of the "human environment," rather than the environment in a physical sense alone, Brachman's "environment" piece can be expanded horizontally as well as vertically, as a "context" for disease.

A "Disease Profile" for Sub-Saharan Africa

The "disease burden" that SSA faces has been documented in detail by the World Health Organization (WHO). For example, the WHO reports an estimated 0.4% increase in economic growth with every 10% increase in life expectancy beginning at birth (WHO, *The Health of the People* 6)) and provides perspective on Africa's health challenges in terms of disability-adjusted-life-years (DALYs), that is, in terms of years lived, the number of years lost in addition to those years lived with a disability (WHO, *The Health of the People* 9). Of the 675.41 million DALYs lost for the WHO African Region[9] in 2011, for example, 36% were from "infectious and parasitic diseases," 26% from non-communicable diseases (NCDs), 13% from "neonatal conditions," 11% from infections of the respiratory system, 5% from deficiencies in nutrition, and 2% (each) from "maternal conditions" and "intentional injuries" (WHO, *The Health of the People* 9). When the WHO's regions are ranked for "leading causes of disease burden" measured in DALYs, the top five leading causes of disease burden in Africa, in order, are lower respiratory infections, HIV and AIDS, diarrheal diseases, malaria, and "preterm birth complications" (WHO, *The Health of the People* 10). As the World Health Organization emphasizes, overall health in its African Region "improved considerably" in the decade prior to the writing of its 2014 report (WHO, *The Health of the People* xx) – in the twelve years before 2014, mortality rates from malaria declined "by about 50%" (WHO, *The Health of the People* xviii) – however, the unique challenge of communicable diseases comprising two-thirds of the WHO African Region's total disease burden (WHO, *The Health of the People* xvii) demands special attention.

[9] Note that this WHO African Region is different than the "SSA" region defined in this thesis. A specification of the countries included in this region can be found here: https://www.who.int/choice/demography/african_region/en/

Given the disease landscape painted by the World Health Organization's report and the characteristic dependence of vector-borne diseases on environmental conditions and changes (see Vora 2008), it seemed appropriate to turn my focus to a vector-borne disease, and, specifically, one borne by mosquitoes. Malaria, in particular, has long been associated with Africa and discussed extensively in the literature, especially in terms of more recent concerns of the impact of climate change on malaria transmission potential and the "reach" of the disease into previously "malaria-free" highland areas (Balirane *et al.* 2010 in UNDP 25). By viewing this problem through a geographical lens, I seek perhaps a more complete conceptual understanding of the problem of changes in malaria transmission potential and the factors involved in this process, in the hope that it may inform future studies, policy, and prevention and treatment efforts."

Development of the Modified Grulke Model (MGM)

Investigation of "trends" in sub-Saharan Africa, "factors" influencing disease transmission, and the "disease burden" of sub-Saharan Africa itself formed the basis upon which the model used in this work, the MGM, was developed. Literature readings (from PubMed, Google, the Penn State Libraries) focused on some of the prominent diseases comprising SSA's disease burden and understanding the "factors" impacting their transmission. In particular, readings focused on infectious diseases: dengue fever, HIV/AIDS, malaria, cholera, schistosomiasis, Ebola, and Marburg Virus Disease among them. Environmental aspects discussed in relation to transmission of these diseases were noted, and a "system of systems" began to emerge as many of these environmental aspects seemed related to changes in both the "human" and "physical" environments – "contextual changes," as mentioned previously. The MGM

(**Figure 10**) was developed as a structure depicting these contextual aspects as they ultimately impacted disease transmission.

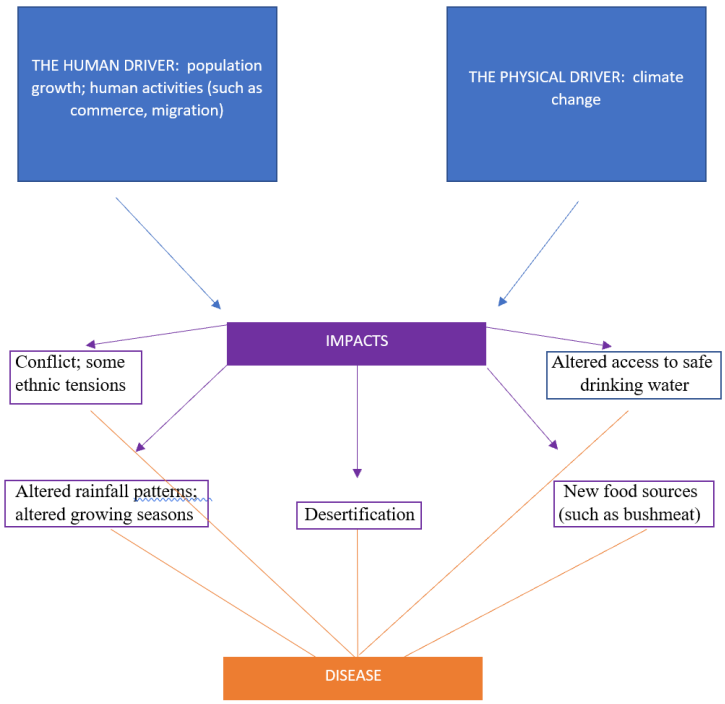


Figure 10. The modified Grulke model (MGM) as a broad view of "contextual" aspects relating to disease transmission in sub-Saharan Africa (SSA).[10]

Thus, as shown in **Figure 10**, the MGM identifies the "environmental aspects" discussed in the literature as "impacts" of broader contextual changes relating to the "human" and "physical" "drivers" of such impacts. The MGM is purposefully "broad" so as to allow for its "specification," or "tailoring," to a specific disease and/or region: the human and physical drivers, as well as the relevant impacts, can be specified for conceptualizing transmission risk for a particular disease for SSA as a whole or a smaller region. Thus, the above presentation of the "broad" version of the MGM describes common "impacts" relevant for transmission of a number of diseases of sub-Saharan Africa (**Figure 10**). Part II of this work will involve two such tailorings of the MGM, with the first being an MGM "specified" for viewing

[10] As a note, the MGM structure was inspired by conversations with Dr. Downs and his introducing me to the concept of systems thinking and views of climate as a system of systems. See Arnold and Wade 2015 for more on systems thinking (https://www.sciencedirect.com/science/article/pii/S1877050915002860).

malaria transmission risk in SSA and the second an MGM specified for malaria transmission risk specifically in Kericho, Kenya, in the Kenya highlands. Both of these "specifications" were accomplished through review of relevant literature on malaria in either SSA or in Kericho in order to define the "impacts" and scope of the human and physical drivers for each "tailored" MGM. Impacts of these contextual changes were then viewed in terms of Grulke's model to arrive at an understanding of how they might impact the host-pathogen interaction necessary for disease.

Conclusions (and set-up for Part II)

The goal of this chapter was to define the MGM as a model to be used in conjunction with Grulke's 2011 modification of the disease triangle. As a "standalone" piece, the MGM seeks to expand upon Grulke's depiction of "environmental change" and serve as a malleable method for conceptualizing relevant environmental aspects. When used in conjunction with Grulke's 2011 model, it links these contextual changes to the host-pathogen relationship, completing the host-pathogen-environment relationship necessary for the presence of disease.

Part II of this work turns from a general study of disease transmission to a focus on malaria, specifically, its transmission in SSA, and its recent "re-emergence" in the East African highlands.

PART II. A CONCEPTUAL VIEW OF MALARIA IN SUB-SAHARAN AFRICA

Chapter 4

Mosquitoes, *Plasmodium,* and Human Hosts: The Epidemiologic Triad for Malaria

"This day relenting God hath placed within my hand a wondrous thing; and God be praised. At His command, seeking His secret deeds with tears and toiling breath I find thy cunning seeds, O million-murdering Death. I know this little thing a myriad men will save. O Death, where is thy sting, thy victory, O Grave!'"

- From *In Exile, Reply – What Ails the Solitude*, Ronald Ross, 1897, upon discovering *Plasmodium* development stages in the mosquito[11]

As a set-up for discussions of malaria transmission risk in SSA (Chapter 5) and Kericho in the Kenya highlands (Chapter Six), this chapter seeks to describe malaria in the basic form of the epidemiologic triad and disease triangle: as a disease involving a human host, a *Plasmodium* parasite as a pathogen, and *Anopheles* mosquitoes as vectors. Several current strategies for treatment and prevention of malaria are also discussed in relation to the triad in that they "break" the link between the necessary conditions for disease (Gugino, "Plant Disease Basics" – The Disease Triangle").

A Disease with Long History

Malaria has left its mark on human history as immortalized in writing and culture – the disease was crowned "'king of diseases'" in Indian Vedic writings and mentioned in terms of its "periodic fevers" in cuneiform ("A Brief History of Malaria"). The Romans, too, plagued by malaria, prayed for respite from the goddess Febris (Shah 64). In *The Fever*, journalist Sonia Shah describes malaria as having "sculpted" ecological and cultural landscapes, working most

[11] As quoted by Baton and Ranford-Cartwright, in *Trends in Parasitology* (2005), https://doi.org/10.1016/j.pt.2005.09.012.

prolifically in Africa (Shah 34). Malaria, Shah writes, "has been plaguing humans in Africa for 500 years, with the first encounters between human, mosquito, and malaria parasite probably occurring around the time our ancestors discovered fire" (Shah 12). Of the seventy-member subset of mosquito species known to carry malaria (Shah 14-15), the emergence of *Anopheles gambiae* as a "human-adapted" malaria vector, spreading with Bantu migration, paved the way for emergence of malaria due to the *Plasmodium falciparum* parasite, described as "the most virulent and life-threatening" of the four *Plasmodium* species known to cause malaria in humans (Yé, Sankoh *et al.* 2).

An understanding of the implications of environmental change on malaria requires an understanding of the intricacies of the two other components of the epidemiologic triangle: the susceptible human host and the parasitic disease-causing agent. Here, the mosquito-parasite relationship is examined with an emphasis on human consequences.

The Mosquito as Vector

While the *Aedes* mosquito is responsible for transmission of the virus causing dengue fever (Baylor College of Medicine, "Mosquito-Borne Diseases"), it is *Anopheles* that carries the *Plasmodium* parasite. Specifically, many malaria-carrying mosquitoes in sub-Saharan Africa are part of an eight-member "complex of sibling species" that do not mate but have similar physical features, known as the *Anopheles gambiae* complex[12] (White and Kaufman, "Featured Creatures," University of Florida, citing White 1974; Fanello *et al.* 2002, and Coetzee *et al.*

[12] Note: *Anopheles* mosquitoes transmit malaria (see CDC – "About Malaria,"). *Anopheles gambiae* mosquitoes are an important malaria vector in Africa, but others are also important (for example, *Anopheles funestus* and *Anopheles arabiensis*, see Roche (https://entomologytoday.org/2015/04/24/anopheles-mosquitoes-as-vectors-of-malaria-in-east-africa-bed-nets-and-beyond/).

2013). Female mosquitoes bite human hosts to obtain blood meals with a proboscis as long as their palpus mouth appendages (White and Kaufman, citing Foster and Walker 2009) (**Figure 11**), enabling development of "several hundred" eggs from a single productive bite (Yé, Sankoh *et al.* 2). After two to three days (CDC, "About Malaria"), the female then deposits these eggs one-at-a-time onto the surface of stagnant water, with horizontally floating larvae hatching after one to two days, feeding on algae and surface microbes (CDC, "About Malaria," "*Anopheles* Mosquitoes"). Although female mosquitoes typically lay their eggs in stagnant water, in "exceptional" cases, eggs have been observed in soil and treeholes (Booth, *Advances in Parasitology*, 39-126).

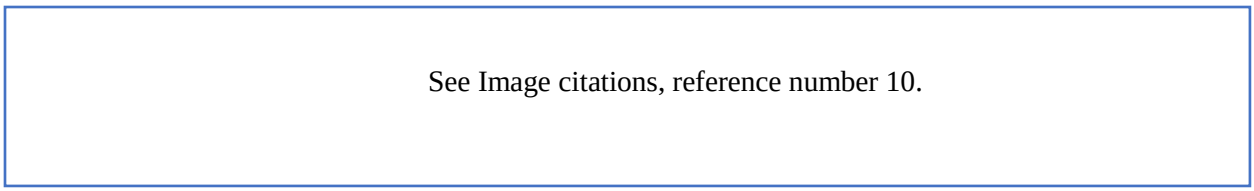


Figure 11. Female (top) and male (bottom) *Anopheles gambiae* mosquitoes (Mary F. Adams, MA, MS / CDC, 2010 – see Bibliography for source).

After four instar stages with molting, mosquito larvae undergo metamorphosis and enter a pupa stage before becoming nectar-feeding adults that sometimes mate in swarms (CDC, "*Anopheles* Mosquitoes"). Importantly, mosquito development is highly dependent on temperature (Yé, Sankoh *et al.* 2), lasting ten to fourteen days in tropical conditions, with adult male mosquitoes surviving for about a week. Female mosquitoes undergo multiple cycles of blood meal feeding and egg-laying throughout their adult lifespan, which is likely one to two weeks, but could be as long as one month (CDC, "*Anopheles* Mosquitoes").

Malaria transmission is best described with a view of these details of the mosquito life cycle. Importantly, the disease cannot be spread between mosquitoes or between human hosts,

aside from activities which transmit infected red blood cells, such as blood transfusions, organ transplants, sharing of contaminated needles, and vertical transmission during pregnancy (CDC, "Malaria," "Frequently Asked Questions"). Adult mosquitoes obtain the *Plasmodium* parasite in feeding from an infected human host, transmitting the parasite to another host through saliva after an incubation period in the mosquito of about a week (CDC, "Malaria," "Frequently Asked Questions"). Thus, the life cycle of the *Plasmodium* parasite occurs across two organisms in two stages: an asexual stage within the human host and a sexual stage within the mosquito vector (Takken, Martens, and Bogers 42).

The Parasite: Plasmodium falciparum

The origins of the infamous *Plasmodium falciparum* parasite have been the subject of much debate; recently, the parasite has been speculated to have originated from "a single gorilla-to-human cross-species transmission event" (Liu *et al.*, *Nature 467*). "Injected" into the human bloodstream as sporozoites, *Plasmodium* travels to the liver (**Figure 12**). There, sporozoites grow and divide as schizonts, which can release 2,000 to 4,000 merozoites in a period lasting six to sixteen days (Yé, Sankoh *et al.* 2). These merozoites can then return to the bloodstream to infect human red blood cells, or erythrocytes, in an erythrocytic stage (CDC, "DPDx," "Malaria"). Importantly, the rupture of red blood cells in this erythrocytic stage is linked to the length of time periods between which infected hosts experience malaria's characteristic cyclic fevers (Gilles and Warrell, 1993, as referenced by Yé, Sankoh *et al.*, page 2). A portion of the merozoites released with ruptured cells form male and female gametocytes, undergoing five

maturation stages before circulating in the bloodstream to allow uptake through a mosquito blood meal (Bousema and Drakeley, ASM *Clin. Microbiol. Rev.* 2011).

See Image citations, reference number 11.

Figure 12. A depiction of the life cycle of the *Plasmodium falciparum* parasite within the vector and the human host (Source: Bousema and Drakeley, *American Society of Microbiology Clinical Microbiology* Reviews, 2011).

Having completed the asexual portion of its life cycle within the human host, *P. falciparum* progresses through the sexual portion of its development in the mosquito (Takken, Martens, and Bogers 42). Male gametocyte (microgamete) exflagellation enables fertilization of female gametes and formation of a zygote. Twelve to forty-eight hours later (Yé, Sankoh *et al.* 2), this zygote becomes an ookinete, then an oocyst that releases the sporozoites to be injected into human hosts (Bousema and Drakeley, ASM *Clin. Microbiol. Rev.* 2011). As seen with mosquito development (Yé, Sankoh *et al.* 2), sporozoite formation, too, is highly influenced by temperature, with formation only occurring with ambient temperatures between 16 and 33°C (Yé, Sankoh *et al.* 3); the "optimal" temperature range for sporozoite formation occurs between 25 and 30°C (Snow and Omumbo, *Disease and Mortality in Sub-Saharan Africa*, 2nd Edition, Chapter 14). Thus, as both "within-vector parasite dynamics" and those of vector development are "weather-dependent" (Takken, Martens, and Bogers 44), slight changes in temperature have been observed to have great impact on malaria transmission. In a study described in Epstein's *Changing Planet, Changing Health,* KEMRI researcher Andrew Githeko underscores this temperature dependence: "at 18°C, malaria parasites reproduced too slowly to mature during the

lifetime of the mosquito, but at 20°C, they reproduced quickly and easily. 'That's why you might not think there's a big climate change, but, in the mosquito world, two degrees makes a big difference'" (Ferber and Epstein 2011).

Breaking the Epidemiologic Triad: Malaria Symptoms, Treatment, and Prevention Strategies

Symptoms

The incubation period seen with *falciparum* malaria lasts between a week and three months (WHO, "Disease information," "Malaria"), and hosts are often co-infected with multiple *P. falciparum* strains (Shah 31). After this period, malaria patients experience a host of symptoms, including fever and chills, headaches, muscle aches and weakness, abdominal pain, diarrhea, vomiting, and cough (WHO, "Disease information," "Malaria"). Organ failure and related symptoms can occur, such as dangerous pulmonary edema, convulsions, and, ultimately, a comatose state and death (WHO, "Disease information," "Malaria"). Thus, early treatment of malaria is essential, as delaying treatment beyond a day after the appearance of symptoms can be fatal (WHO, "Disease information," "Malaria"). Malaria cases can only be diagnosed through examination of drawn blood, and it is the toxic waste products of the erythrocytic stage (such as hemozoin and glucose phosphate isomerase) which influence the body's inflammatory response and the experienced symptoms (CDC, "About Malaria," "Disease").

Malaria cases are distinguished as either uncomplicated or severe. In uncomplicated malaria, patients experience cold, hot, and sweating stages during a six-to-ten-hour attack. This

attack occurs every three days with three of the *Plasmodium* parasites infecting humans, *P. falciparum, P. ovale,* and *P. vivax* (CDC, "About Malaria," "Disease"). Severe malaria occurs in two percent of clinical malaria cases but results in ninety percent of malaria deaths worldwide (Shah 31), as it is accompanied by "serious organ failures or abnormalities in the patient's blood or metabolism" (CDC, "About Malaria," "Disease"). These severe symptoms can include severe anemia, metabolic acidosis, or the neurologic symptoms that accompany cerebral malaria (CDC, "About Malaria," "Disease").

Patients suffering multiple exposures to malaria obtain some immunity to the disease but serve as carriers from which other mosquitoes may obtain the parasite (Yé, Sankoh *et al.* 8). Unfortunately, this acquired immunity remains partial and "fleeting" at best, as, when a host is no longer "exposed to chronic infection . . . whatever immunity to the local parasite had been arduously acquired starts to fade away, canceled out by the new generation of the parasite[53]" (Shah 27-28). Therefore, malaria treatment and prevention strategies remain crucial.

Treatment"

In treatment of malaria, it is considered good practice to provide "parasitological confirmation" of a diagnosis of malaria based on clinical symptoms. This is done by either microscopy or rapid diagnostic test (RDT) prior to beginning treatment with antimalarials, which ideally occurs within a day of the appearance of fever (WHO, "Malaria Treatment"). According to the Mayo Clinic, chloroquine phosphate "is the preferred treatment for any parasite that is sensitive to the drug," but its efficacy has been limited by chloroquine resistance (Mayo Clinic, "Malaria: Diagnosis and Treatment"). Artemisinin-based combination therapies, or ACTs, are

thus often prescribed as "the first line treatment for malaria," serving as "a combination of two or more drugs that work against the malaria parasite in different ways" (Mayo Clinic, "Malaria: Diagnosis and Treatment"). In "low transmission areas," a dose of primaquine is given with ACTs to patients with malaria caused by *P. falciparum* "to reduce transmission" (WHO *Guidelines for the Treatment of Malaria* 9), and, in cases of severe malaria, artesunate, injected intramuscularly or intravenously, is used prior to treatment with ACTs (WHO, "Overview of Malaria Treatment"). Ultimately, treatment aims to successfully clear *Plasmodium* parasites from the host both for the good of the patient, in preventing "severe" outcomes and the "chronic infection that leads to malaria-related anemia," and "from a public health perspective," to act in "reducing the infectious reservoir, and to prevent the emergence and spread of resistance to antimalarial medicines" (WHO, "Malaria Treatment"). Thus, special care is given to patients at higher risk, as "several important patient sub-populations, including young children, pregnant women, and patients taking potent enzyme inducers [. . .] have altered pharmacokinetics, resulting in sub-optimal exposure to antimalarial drugs" (WHO, *Guidelines for the Treatment of Malaria* 48).

Prevention

Finally, preventive strategies are essential for reducing malaria morbidity and mortality. On a basic level, the Mayo Clinic recommends that those in areas with malaria parasite-carrying mosquitoes make special effort to prevent bites, such as sleeping under a net, using insect repellent, and covering exposed skin (Mayo Clinic, "Symptoms and Causes"). In addition to use of insecticide-treated nets (ITNs), indoor residual spraying (IRS) and larval source management (LSM), including vector "habitat modification," "habitat manipulation," "biological control"

with “natural enemies,” and “larviciding,” are established methods of “vector control” (Tizifa *et al.* 2018). Tizifa and colleagues also describe a number of “methods under development” for malaria prevention, including house improvement, use of attractive toxic sugar bait (ATSB) for mosquitoes, and even genetic modification of the vector “by making them unable to reproduce or genetically resistant to malaria followed by driving these to the population” (Tizifa *et al.* 2018). Finally, intermittent preventive therapy (IPT) may be used for pregnant women and in infancy (Tizifa *et al.* 2018), and in terms of prophylaxis, the Mayo Clinic explains that “in general, the drugs taken to prevent malaria are the same drugs used to treat the disease” (Mayo Clinic, “Symptoms and Causes”).

Conclusion

With knowledge of the mode of transmission of malaria, its characteristic symptoms, and treatment and prevention strategies, the next two chapters seek to examine those factors that influence the vertices of the epidemiologic triad – the host, the agent, and the environment -- in examining malaria transmission risk in SSA and in Kericho, Kenya.

Chapter 5

Approaches to Understanding Malaria Transmission Risk in Sub-Saharan Africa

"After almost two decades of substantial reductions in the global burden of malaria, progress has stagnated.[1] Global scientific and policy leaders agree that to achieve malaria eradication, interventions must focus not only on preventing malaria disease but also on decreasing malaria transmission.[2]"

- Lauren Cohee and Miriam Laufer, "Tackling Malaria Transmission in sub-Saharan Africa," *The Lancet Global Health,* 2018.

As discussed in Chapter Four, malaria is a disease highly dependent not only on the host-vector-parasite relationship that allows for its transmission, but also on the environmental conditions that influence this relationship. This chapter is organized into three sections. The first section discusses factors identified as influencing malaria transmission and transmission risk in sub-Saharan Africa. The second section provides several examples of models to study malaria transmission risk. Finally, the general form of the modified Grulke model (MGM) discussed in Part I is "specified" for understanding malaria transmission risk in sub-Saharan Africa as a whole.

I. An Examination of Factors Impacting Malaria Transmission Risk in SSA

Studies have implicated a variety of factors as influencing malaria transmission risk in SSA. This section details the factors identified in a literature review and their proposed impacts on transmission. Here, factors are discussed according to their impacts on the vector, the parasite, and/or the host and by their relationship to one another.

Impacts on the Vector and Parasite: Temperature, Rainfall, and Climate Change; Vegetation, Land Cover, and Topography

In Chapter Four, the importance of temperature to the life cycles and development of both the mosquito and the *Plasmodium* parasite was discussed, along with its implications for the transmission of malaria. While it is important to consider the implications of temperature for development and survival of the parasite within the vector, it is also necessary to consider the mosquitoes themselves. As Snow and Omumbo write, "extremely high temperatures are associated with the development of smaller and less fecund adult mosquitoes," and temperatures of 40 to 42 degrees Celsius bring about "thermal death" of the vectors (Snow and Omumbo, *Disease and Mortality in Sub-Saharan Africa*). Warmer conditions can also lead to "more frequent vector-host contacts," as "high temperatures increase the digestion rate of blood meals" (Yé, Sankoh *et al.*page 12). Further, as Booth writes, all stages in the *Anopheles* life cycle are poikilothermic (roughly, occurring in an insect in which internal temperature can vary significantly (*Cambridge Dictionary*)), so specific environmental conditions have great impact on an organism's "life history traits" beginning at the egg-laying stage. It is important to remember, however, that this life history, as Booth maintains, is highly influenced by "abiotic and biotic factors" – for example, the pH, flow, and algae levels in water have great impact on the larvae feeding, survival rates, and "population rates." [Importantly, however, Booth maintains that "understanding of these [life history] traits for individual species" is "necessary but not sufficient for modelling purposes," as competition between mosquito species and environmental conditions favoring a particular species are also significant (Booth, *Advances in Parasitology*, 29-126).]

One of these other abiotic factors influencing mosquito development, especially, is rainfall (and, through rainfall, "humidity and saturation deficit," as "adult vector longevity

increases with humidities over 60 percent" (Snow and Omumbo, *Disease and Mortality in Sub-Saharan Africa*)). While accumulated water is needed for mosquito egg-laying (Snow and Omumbo 2006) and larval stages (Yé, Sankoh *et al.*, page 14), excessive rainfall can "flush away" eggs and destroy crucial breeding sites (Yé, Sankoh *et al.*, page 13). The importance of temperature and rainfall to malaria transmission and transmission risk underscore the implications of climate change for SSA. As Serdeczny *et al.* write,

"Climate change projections for this region point to a warming trend, particularly in the inland subtropics; frequent occurrence of extreme heat events; increasing aridity; and changes in rainfall – with a particularly pronounced decline in southern Africa and an increase in East Africa. This region could experience as much as one meter of sea-level rise by the end of this century under a 4 degrees Celsius warming scenario." (Serdeczny *et al.* 2016).

It is this particular concern that forms the source of much of the "protracted debate" (Lyon *et al.* 2017) on the impacts of climate change on malaria in highland areas in East Africa, explored further in Chapter Five. However, other aspects of the physical environment are also important for their influence on malaria transmission, especially for their creation of "microclimatic conditions suitable for mosquitoes" (Yé, Sankoh *et al.*, page 14). For example, the presence of vegetation "provides a suitable environment for mosquito breeding" (Yé, Sankoh *et al.*, page 14) [additionally, "year-to-year vegetation dynamics are controlled primarily by changes in the frequency and timing of precipitation" (Amadi *et al.* 2018, citing source 13)]. Amadi and colleagues further state the importance of vegetation in considering malaria transmission risk, writing:

"Vegetation cover offers shade that potentially reduces evaporation, minimizes sub-canopy wind speed, and enhances near-ground humidity. Cumulatively, these factors enhance vector population and longevity, and malaria transmissions are likely to increase with increased vector survival. This has been demonstrated in previous studies which showed that mosquito vector populations are likely to be high when vegetation growth is at its peak." (Amadi *et al.* 2018). *(PLoS One.)*

Finally, topography has been identified as having an impact on malaria transmission risk through its influence on malaria breeding sites. In a study of highland areas in western Kenya, Wanjala and Kweka found differences in transmission between U-shaped and V-shaped valleys. "Environmental terrain conditions can modify the level of malaria transmission and the rate of development of immunity," the authors write (Wanjala and Kweka 2016); they find that U-shaped valleys and plateaus exhibited "higher parasite density" than did V-shaped valleys. Therefore, the residents of V-shaped valleys, with lower immunity to malaria than their U-shaped counterparts, were "at risk of having explosive malaria outbreaks during hyper-transmission periods" (Wanjala and Kweka 2016). Wanjala and Kweka provide an explanation for this difference in transmission risk with varying topography in terms of water drainage: "U-shaped valleys have poor drainage and this causes accumulation of water during rainy seasons creating excellent breeding habitats for malaria vectors; by contrast, there is no accumulation of water in the V-shaped valleys due to good drainage" (Wanjala and Kweka 2016).

Adaptation of the Vector: Urbanization, Insecticide Resistance

Along with the sensitivity of the malaria vector to climate variables, an important point in considering malaria transmission risk in SSA is the discussion of adaptations of the mosquito to changing environmental conditions. Among these, insecticide resistance is an often-discussed example of an adaptation of mosquitoes that poses a threat to current strategies of malaria control, and it has sparked concerns of a potential "increased malaria disease burden" as a result (Kleinschmidt *et al.* 2018). Insecticide-treated nets (ITNs) and indoor residual spraying (IRS), both forms of "insecticide-based vector control," have been credited with accounting for 79% of

the observed decrease in deaths from malaria from 2000 to 2015 (Alout *et al.* 2017). However, as Alout and colleagues argue, "insecticide-resistance frequency and intensity have increased dramatically in malaria vector populations" as the use of treatments selects for those mosquitoes with resistance to the pyrethroid insecticide (Alout *et al.* 2017). Ultimately, recent studies have recommended that insecticidal nets continue to be used as an effective form of malaria prevention despite vector resistance (Kleinschmidt *et al.* 2018), and, moreover, several important facts about the impact of resistance must be considered (Alout *et al.* 2017). Alout and colleagues write,

"There are at least 5 facts about the effect of insecticide resistance on malaria control: (1) the discrepancies between the entomological and epidemiological studies of malaria vector control efficacy in relation to insecticide resistance, (2) the overestimated phenotype of resistance in standard protocols compared to natural context (i.e., increased insecticide toxicity due to delayed insecticide effects or to age), (3) the fitness cost associated with insecticide resistance (on mosquito density, biting behavior, vector competence, and survival), (4) the increased parasite-induced mortality in insecticide-resistant mosquitoes (interactive cost between infection and resistance), and (5) the impact of insecticides on vector–parasite interactions (i.e., increased toxicity on infected/infectious vectors, reduced parasite development, and reduced transmission). In addition to these, other reasons for successful malaria control despite the selection of insecticide resistance exist, such as bed–net physical barrier and housing improvement (such as window screens and eave tubes). The local epidemiological, ecological, and entomological context (population structure, seasonality, multiple mechanisms of insecticide resistance, etc…) are thus crucial to consider to reach a more precise estimate of insecticide-resistance impact on vectorial capacity" (Alout *et al.* 2017).

(PLoS One)

Aside from the acquisition of resistance to insecticide treatments, another important "adaptation" of the malaria vector is to the changing "built environment"[13] with urbanization. In a review focusing on malaria transmission in urban contexts in SSA, De Silva and Marshall describe a number of aspects of the urbanization trend as having implications for transmission of malaria. A significant concept in De Silva and Marshall's work is the idea that "urbanization is

[13] Fellow Schreyer Scholar Sumit Pareek discusses this "built environment" as it relates to malaria transmission risk as the topic of his thesis, available at https://honors.libraries.psu.edu/files/final_submissions/5220.

generally expected to reduce malaria transmission; however, the disease still persists in African cities, in some cases at higher levels than in nearby rural areas" (De Silva and Marshall 2012). Thus, the authors discuss a number of "factors contributing to urban malaria" which may contribute to this phenomenon. "Improved infrastructure, better-quality 'mosquito-proof' housing, increased access to healthcare, and a reduction in vector breeding sites," along with polluted water and a higher human-to-mosquito ratio, are cited as factors associated with urbanization contributing to predictions of a lower level of malaria transmission in urban areas (De Silva and Marshall 2012, reference 5). However, the authors note a number of potential contributors to urban malaria transmission, discussing the presence of "artificial" vector breeding sites in urban areas (see **Figure 13**), some of which are associated with the growth of urban agriculture and construction and waste management. The authors also discuss the association of higher socioeconomic status with "factors that lead to reduced malaria transmission" (De Silva and Marshall 2012, references 50-52).

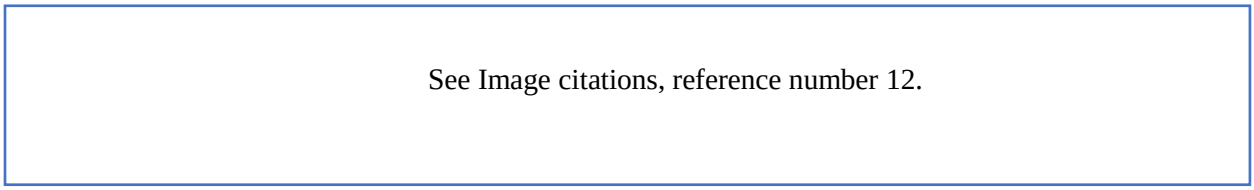


Figure 13. A figure provided by De Silva and Marshall, reproduced here as a representation of the diversity of potential mosquito breeding sites in urban areas (De Silva and Marshall 2012).

Finally, De Silva and Marshall also make reference to the impacts of "Vector Factors (Adaptation and Mutualism)" on urban malaria transmission in SSA. A particularly interesting discussion mentions a "mutually beneficial relationship" between the "nonmalaria vector" *Culex quinquefasciatus* and the malaria-transmitting *An. gambiae*, as the pollution-averse *An. gambiae*

has been observed to be able to inhabit and breed in artificial breeding sites previously inhabited by the *Culex* mosquito (De Silva and Marshall 2012, references 6, 32, and 46). Earlier in their review, De Silva and Marshall had discussed a finer division of the *An. gambiae* vector itself into two different "molecular forms" better suited to diverse geographies: an "M form" is "better adapted to urban and dry environments and tends to reproduce alongside irrigated fields and permanent or semipermanent swamps," and an S form remains "better adapted to rural and humid forest areas and prefers temporary pools and brick-made ravines" (De Silva and Marshall 2012, references 7, 15, 19, 20). Ultimately, De Silva and Marshall argue that a "universal trend" for malaria transmission in urban, periurban, and rural areas does not exist; "we should not combine our impression of urban malaria simply to urban centres, but we should also base it on an understanding of the underlying geography" (De Silva and Marshall 2012).

Adaptation of the Parasite: Evolution and Drug Resistance

While adaptation of the mosquito vector has been observed, especially in its resistance to insecticides used in efforts at malaria prevention, adaptation of the *Plasmodium* parasite itself has been observed as well. For example, Rono and colleagues find that *P. falciparum* "in low-transmission intensity areas have evolved to invest more in transmission to new hosts (reproduction) and less in within-host replication (growth) than parasites found in high-transmission areas," describing "increased production of reproductive forms (gametocytes) early in the infection at the expense of processes associated with multiplication inside red blood cells" and associated changes in parasite gene expression (Rono *et al.* 2018). On a related note, in describing adaptation of *P. falciparum* to New World anopheline mosquitoes, Molina-Cruz and Barillas-Mury note the parasite's development of ways to "evade" the mosquito's immune

system and establish infection (the authors cite Molina-Cruz, Garver *et al.* 2013, for example); they argue that this "evasion" is necessary for "adaptation of *P. falciparum* to new vectors" (Molina-Cruz and Barillas-Mury 2014). However, a highlighted concern in discussions about *Plasmodium* is the presence of and potential for the parasite's resistance to antimalarial drugs. According to the Centers for Disease Control, antimalarial resistance has been "confirmed" in both *P. falciparum* and *P. vivax* (CDC, "Malaria," "Drug Resistance"). *P. falciparum* resistance to the drug chloroquine is described as having "developed independently in three to four areas in Southeast Asia, Oceania, and South America in the late 1950s and early 1960s" and "spread to nearly all areas of the world where falciparum malaria is transmitted" (CDC, "Malaria," "Drug Resistance"). Additionally, parasite resistance (that "tends to be much less widespread geographically") has been observed for "nearly all of the other currently available antimalarial drugs, such as sulfadoxine/pyrimethamine, mefloquine, halofantrine, and quinine" (CDC, "Malaria," "Drug Resistance"), and resistance to "artemisinin and non-artemisinin components" of currently used artemisinin-based combination therapies has been observed in "parts of Southeast Asia" (CDC, "Malaria," "Drug Resistance"). The WHO's 2015 *Guidelines for the Treatment of Malaria* provides a useful discussion on antimalarial drug resistance:

"The development of resistance can be considered in two parts: the initial rare genetic event, which produces the resistant mutant, and the subsequent selection process, in which the survival advantage in the presence of the antimalarial drug leads to preferential transmission of resistant mutants, and, thus, to the spread of resistance. In the absence of the malarial drug, resistant mutants usually have a survival disadvantage" (WHO, Guidelines for the Treatment of Malaria (2015) 302-304).

The *Guidelines for the Treatment of Malaria* also identify a number "factors that determine a propensity for antimalarial drug resistance to develop," which include drug "pharmacokinetics and pharmacodynamics," the "intrinsic frequency" of genetic changes in the parasite, and,

relating to the human host, "the immunity profile of the community and the individual" (WHO, *Guidelines for the Treatment of Malaria* (2015) 303).

The Human Host: Biological Factors, Activities, and Socioeconomic Factors

Several aspects related to the human host have impacts on malaria transmission risk. First, as was mentioned in Chapter Three, patients with multiple malaria exposures do acquire some temporary immunity to malaria infection (Yé, Sankoh *et al.* 8) and are considered "'semi-immune'" (CDC, "About Malaria," "Human Factors and Malaria"). In areas with "lower transmission" of malaria caused by *P. falciparum*, this "protective immunity" is not as prevalent, so "malaria disease can be found in all age groups, and epidemics can occur" (CDC, "Human Factors and Malaria"). In contrast, "young children are a major risk group" for malaria in "areas with high *P. falciparum* transmission (most of Africa south of the Sahara)," since protective "maternal antibodies transferred to them through the placenta [. . .] decrease with time," and these children have not yet been exposed to "repeated infections" (CDC, "Human Factors and Malaria"). In addition, specific host characteristics may impact the treatment of malaria for some patients. The WHO's 2015 *Guidelines for the Treatment of Malaria* discuss a number of "special risk groups" for which special attention must be given in treating "uncomplicated *P. falciparum"* malaria, including women in the first trimester of pregnancy, infants weighing less than five kilograms, patients with HIV/AIDS, "non-immune travelers," and those with *P. falciparum hyperparasitaemia* (WHO, *Guidelines for the Treatment of Malaria (2015)* 5).

Interestingly, a number of host "genetic factors" (CDC, "Human Factors and Malaria") are relevant for malaria transmission. Perhaps most famously, those heterozygous for the sickle cell trait experience some "protective effect" against malaria (see Gong *et al.* 2013). However, multiple other genetic variations have been associated with malaria, some of which are reviewed in a table by Kwiatkowski, reproduced here (**Figure 14**):

See Image citations, reference number 13.

Figure 14. Kwiatkowski's review of multiple genetic variations (here, relating to erythrocytes) associated with some protection against malaria infection (Kwiatkowski 2005).

In addition to host genetic characteristics and immunity, the activities and related socioeconomic characteristics of human hosts also have implications for malaria transmission. In its discussion of "Human Factors and Malaria," the CDC names a number of "behavioral factors" influencing malaria transmission risk (CDC, "Human Factors and Malaria"), some of which also relate to the section on urbanization and insecticide resistance above. These include the creation of new vector breeding sites with "irrigation ditches" and "burrow pits" and lack of use of recommended malaria prevention and treatment methods as due to inability to afford proper housing and bed nets, lack of knowledge of effective methods, or preference for "traditional, ineffective methods of treatment" due to "cultural beliefs" (CDC, "Human Factors and Malaria"). Other "behavioral factors" relate to changes in exposure to malaria, such as "increased nighttime exposure to mosquito bites" with "agricultural work," exposure of "non-immune individuals" from "war, migrations (voluntary or forced) and tourism," and the fact that "raising domestic animals near the household may provide alternate sources of blood meals for *Anopheles* mosquitoes and thus decrease human exposure" (CDC, "Human Factors and Malaria").

As discussed in this section, a variety of factors influence malaria transmission risk, with implications for the host, vector, and parasite. By influencing the relationships among the host, vector, and parasite, these factors, by extension, influence malaria transmission itself, whether they include "physical" environment factors such as temperature and rainfall, factors of the "human" environment such as urbanization, socioeconomic status, and host genetic characteristics, or the characteristics of the mosquito vectors themselves.

II. Examples of Malaria Models

This section discusses examples of models proposed for the study of malaria. Of course, it does not attempt to be comprehensive; the models discussed were chosen for their importance (frequency) in the published literature and/or their contribution to development of the MGM for malaria in sub-Saharan Africa.

Models with Relation to the Epidemiologic Triad

As discussed in Part I, the classic epidemiologic triad model has been applied to a variety of human and animal diseases (see **Figure 15**), including malaria. Often, for vector-borne diseases such as malaria, a fourth "vector" vertex to the agent-host-environment triad is added or described.

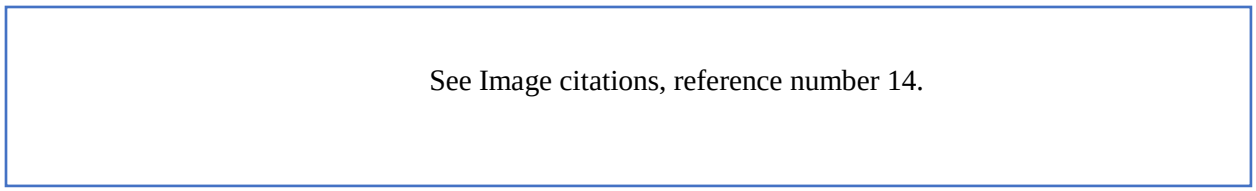


Figure 15. A representation of the epidemiologic triad (or "epi-triangle," as described here) for diseases relating to mosquito and sand fly vectors (Marfin 2009).

Another representation of the epidemiologic triad for malaria and other infectious diseases focuses on the "interactions" and "interplay" of factors in the triad, as shown in a series of slides from a presentation by G.C. Sahu (**Figure 16**) (Sahu 2010). Sahu provides a depiction of the classic epidemiologic triad in the upper left panel, then shows the "interactions" of triad components as they influence triad relationships.

See Image citations, reference numbers 15-16.

Figure 16. A representation of the "interactions" of factors in the epidemiologic triad relevant for transmission of infectious diseases (Sahu 2010).

Sahu then expands upon this discussion with a representation of the "environmental determinants of malaria," introducing also the crucial question of the impact of climate (**Figure 17)** (Sahu 2010).

See Image citations, reference number 17.

Figure 17. Sahu's representation of environmental factors influencing malaria transmission, with special reference to the impact of climate on transmission (Sahu 2010).

Finally, the model of Teboh-Ewungkem, Ngwa, and Ngonghala for "interacting components in the transmission dynamics of malaria" is of interest for its displayed three-component relationship between the host, vector, and pathogen (see also Koenraadt's model, Figure 3, Part I of this work) and the implications for control based on this model (**Figure 18**) (Teboh-Ewungkem *et al.* 2013). Teboh-Ewungkem and colleagues note not only the host, vector, and parasite "components" enabling malaria transmission, but also specific malaria "control" methods relevant for each component. Importantly, as the parasite component is relevant for both the human host and the mosquito, "control" of this component is described separately for the host and for the vector.

See Image citations, reference number 19.

Figure 18. Teboh- Ewungkem and colleagues' three-component model for examining malaria transmission, with special implications for malaria control. The authors' figure legend traces the concept for this model to a reading of Kakkilaya's Malaria Site in 2009 (Teboh-Ewungkem *et al.* 2013).

In addition to those conceptual models with a clear visual resemblance to the triangular structure of the epidemiologic triad, other conceptual models have employed unique structures that may incorporate or expand upon the ideas communicated by the epidemiologic triad. One such model was published in a United Nations Development Programme (UNDP) report (**Figure 19**), especially relevant here for its development as part of a study on the impact of "climate and non-climate factors" on malaria transmission in the Western Kenyan highlands (UNDP 2013).

See Image citations, reference number 20.

"Figure 7 presents a framework of linkages between climate and malaria in the western Kenyan highlands. It is based on a detailed review of the literature and was validated by key national stakeholders. It shows how different drivers influence malaria parameters, which in turn impact the key characteristics of malaria epidemics. The framework especially highlights how climate drivers are only one type of driver among others. In addition to other biophysical and environmental drivers, consideration needs to be given to socio-economic, policy, and cultural and behavioural drivers, some of which have been largely ignored in previous studies. These drivers include social relations, inequalities and gender, which influence how natural resources are managed and determine differing levels of risks and health behaviours (Plaen et al., 2004). The figure also points out the importance of understanding how climate drivers may interact with, and therefore influence, other drivers (and vice versa). For example, climatic events may change food and water quantity and quality and indirectly affect sensitivity to malaria risk due to reduced ability to fight infections and disease. Most drivers influence the transmission and diffusion of malaria epidemics indirectly by modifying parasite and/or vector development and human vulnerability to malaria epidemics. Policies (e.g., control efforts such as distribution of bed nets) can directly influence the transmission and diffusion of malaria" (UNDP, 2013).

Figure 19. A conceptual model for studying malaria transmission in the Western Kenya highlands as part of a 2013 UNDP (UNDP 27). The original description accompanying this model is reprinted above.

Figure 20, developed by Yé, Sankoh *et al.* in a study of the impact of environmental factors on malaria transmission risk in Burkina Faso, is a conceptual model which incorporates "the human host and vector host models [. . .] linked by the mosquito blood meal" (Yé, Sankoh *et al.* 27). Along with this necessary host-vector interaction for malaria transmission, the model also includes the "environment" component as influencing this interaction.

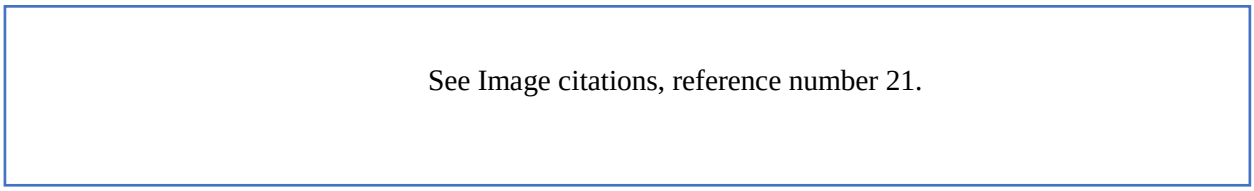


Figure 20. A conceptual model developed for studying malaria transmission in "a holoendemic area of Burkina Faso" (Ye, Sankoh *et al.* 27).

Finally, it is useful to consider Sumit Pareek's grouping of "source factors," or "variables that result in the spread of malaria" (Pareek 14). Pareek describes these factors as "attributed to triggers that can be influenced by three main disciplinary sectors: the built environment, public health, and climate change" (Pareek 15; 14-16) (Figure 21). In the context of the epidemiologic triad, Pareek's work is a valuable characterization of components of the environment influencing malaria transmission, especially in its perspective on the built environment.

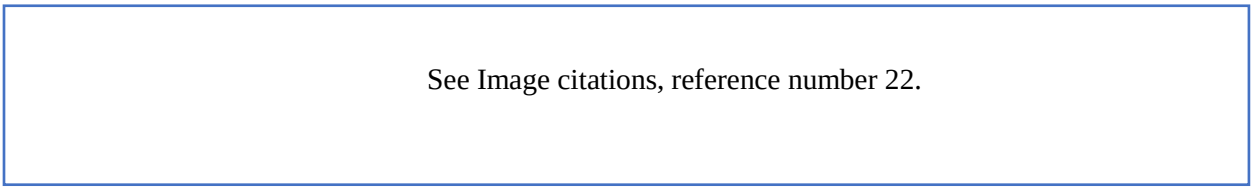


Figure 21. Pareek's identification of source factors describing malaria transmission risk as grouped by three crucial environmental aspects, or "disciplinary sectors" (Pareek 15-16).

As shown previously in **Figure 18**, an advantage of the model proposed by Teboh-Ewungkem was its grouping of malaria control methods by their relation to the vector, parasite, or host. In a similar manner, Pareek proposes a grouping of "intervention methods" by their impact on the "sectors" identified (**Figure 22**).

See Image citations, reference number 23.

Figure 22. Pareek's grouping of identified malaria control, or "intervention," strategies by "disciplinary sectors" (Pareek 15-16).

Thus, the above models each provide readers with valuable methods of conceptualizing malaria transmission risk, influences on this risk, and, in the case of Teboh-Ewungkem's model and Pareek's table, how this risk might be reduced. The next section considers models that are "spatially explicit."

Models with Spatial Emphasis

Hay and Snow summarize the value of mapping malaria: "Malaria parasite transmission intensity is spatially heterogeneous [6, 22-24]. This heterogeneity has important implications for risks and age patterns of progression from malaria infection to disease, disability, and death [5, 25]" (Hay and Snow 2006). Moreover, they note the importance of viewing malaria transmission in a spatial sense for control efforts: "Global maps of malaria endemicity should therefore be essential in every step, from selecting appropriate intervention options and identifying requirements and budgeting, to planning, implementing, and monitoring at subnational, national, and regional scales" (Hay and Snow 2006). The following section will discuss models of malaria transmission which have clear spatial components.

The "Fuzzy Climate-Suitability Map" (Hay and Snow 2006)

Hay and Snow describe the fuzzy climate-suitability map as "a milestone in the mapping of malaria in Africa [10]" for its description of "the likelihood that stable transmission can occur" at the "continental scale" for the *P. falciparum* parasite (Hay and Snow 2006). In developing this model, Craig, Snow, and le Sueur employed fuzzy logic to define the limits, or "edges," of malaria transmission through use of the expected impacts of rainfall and temperature on sporogony (development of the *P. falciparum* parasite within the mosquito) and survival of the mosquito (Craig *et al.* 1999; Omumbo *et al.* 2004). Thus, the importance of this "climate-based distribution model" was its "numerical basis for further refinement and prediction of the impact of climate change on transmission" (Craig *et al.* 1999) (**Figure 23**).

See Image citations, reference number 24.

Figure 23. Snow and Omumbo's modification of Craig, Snow, and le Sueur's 1999 model of the likelihood of stable malaria transmission using fuzzy climate suitability (FCS) values (Snow and Omumbo, *Disease and Mortality in sub-Saharan Africa*).

As Snow and Omumbo describe, realization of the need for future mapping efforts grew out of analysis of the fuzzy climate-suitability map and other mapping efforts. In 2006, Snow and Omumbo wrote that "current distribution maps of *P. falciparum* depend entirely on the biotic effects of climate and transmission. They fail to capture the more localized yet marked effects, such as urbanization and localized control" (Snow and Omumbo, *Disease and Mortality in sub-Saharan Africa*). Moreover, they emphasized the need for "climate-driven models" to include "other important factors that determine localized transmission intensity," such as

"widespread use of insecticide-treated bednets," "population displacement due to conflict or resettlement," "man-made ecological changes, such as deforestation; and agricultural practices" (Snow and Omumbo, *Disease and Mortality in sub-Saharan Africa*). Importantly, for those models incorporating population data, Snow and Omumbo argued for analysis of the impact of population distribution on malaria risk at a smaller scale: "more refined microcensus data or models are required for future mapping of disease burdens" (Snow and Omumbo, *Disease and Mortality in sub-Saharan Africa*). Importantly, from an analysis of Craig, Snow, and le Sueur's 1999 work came the ongoing Malaria Atlas Project, focused on sharing data on *P. falciparum* and *P. vivax* in order to map malaria "on a global scale" (Hay and Snow 2006). **Figure 24** presents data from the project on the change in malaria rates in children between the ages of two and ten from 2000 to 2015.

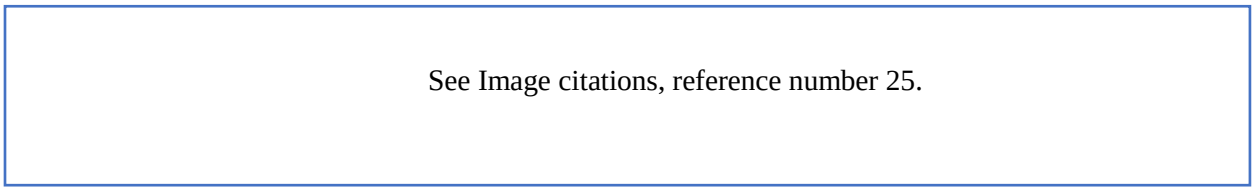


Figure 24. A reproduction of an analysis of Malaria Atlas Project data. The change in malaria rates in children between the ages of two and ten from 2000 to 2015 is shown, with larger changes shown in warmer (lighter orange) colors and smaller changes shown in cooler (blue) colors (Cappelli (*ArcUser*, Fall 2018) 54 – see the note in the citations).

More Recent Spatially Explicit Models

Okami and Kohtake provide a useful description of more recent spatial approaches to mapping malaria risk. These include "a world map of *Plasmodium falciparum* malaria endemicity," identification of "hotspots" through remote sensing approaches, and Cohen and colleagues' "fine-scale risk maps of both high endemic and low endemic seasons in Swaziland from routinely collected individual case data combined with environment-related indices calculated from remote sensing data" (Okami and Kohtake 2016). Of special interest with

regards to the focus of this thesis on Kenya, however, is a study by Paaijmans and colleagues using downscaled General Circulation Models (GCMs) "to derive site-specific predictions for the effects of climate warming on the potential for mosquitoes to transmit malaria in Kenya" (Paaijmans *et al.* 2014). In particular, the authors discuss the importance of considering scale in predicting the effects of warming on malaria transmission: "More generally, a growing number of studies now highlight the need to evaluate the impacts of climate change from the perspective of microclimate rather than macroclimate (De Frenne *et al.* 2012; Potter *et al.* 2013; Bakken and Angilletta 2014). Similarly, our results caution against the use of raw GCMs to explore impacts of climate change on biophysical processes that, like malaria transmission, exhibit considerable spatial heterogeneity and a dependence on high temporal variability in temperature" (Paaijmans *et al.* 2014).

A Note on Mathematical Modeling of Malaria

Mathematical approaches to modeling disease have become increasingly common in recent years, especially with increased efforts to understand "complexity" in disease transmission and to create a "global surveillance network" for pandemics (Siettos and Russo 2013). For diseases in which mosquitoes act as vectors, an important 1911 work by Ross focused on malaria "time-dynamics," and this work is widely regarded as having "establishe[d] modern mathematical epidemiology" (Siettos and Russo 2013; Smith, Battle, *et al.*). Many of the factors described in mathematical models can be conceptualized by the visuals of the disease triangle and epidemiologic triangle, including "numerous variables ranging from the micro host-pathogen level to host-to-host interactions, as well as prevailing ecological, social, economic, and demographic factors" (Siettos and Russo 2013).

Mandal and colleagues provide an informative review of multiple mathematical models developed for the study of malaria, focusing on those models using the epidemiological compartment approach (identifying the population susceptible (S) to infection, exposed (E) but not yet infectious (I), and those recovered (R) from infection (Mandal *et al.* 2011). Mandal and colleagues describe multiple models descended from that of Ronald Ross (see **Figure 25**). For example, Macdonald was the first to include latency with respect to parasite development in the mosquito, introducing an "exposed" mosquito "class" (Mandal *et al.* 2011, citing reference 40), and Anderson and May introduced an exposed human class reflecting parasite latency in human hosts (Mandal *et al.* 2011, citing reference 12); "next-generation mathematical models" have included such "factors as "age and immunity, host-pathogen variability and resistant strains, environmental factors, social and economic factors, and migration and visitation" (Mandal *et al.* 2011). However, Mandal and colleagues emphasize their perspective that, at least at the time of writing of their work, no true "consensus model" for malaria existed: "Because of the overwhelming complexity of the disease system and its nonlinear interdependence on the environmental and socioeconomic factors, there has not been one consensus model where all factors are included" (Mandal *et al.* 2011).

The multiple models discussed here contribute to understanding of malaria transmission risk and represent only a subset of the rich literature on this subject. These models, along with the factors impacting transmission risk discussed in the previous section, inform construction of an MGM in the following section.

See Image citations, reference number 21.

Figure 25. A reproduction of a figure used in Mandal and colleagues' review of mathematical models used for the study of malaria (Mandal *et al.* 2011).

III. A Regional MGM for Understanding Malaria Transmission Risk in SSA

Taking into account those factors identified as impacting malaria transmission risk in SSA, as well as the implications of other models, one can attempt to "specify" for malaria transmission the general model for disease transmission in SSA discussed previously. In the figure legend provided with Grulke's original model (Grulke 2011; **Figure 9**), she identifies not only "important components of environmental change," but "attributes" of the plant host and plant pathogen "relevant under changing environmental conditions" (Grulke 2011). Taking the "drivers" and "impacts" describing "contextual change" (**Figure 9**) as an expansion of Grulke's original "environmental change" piece, both the host-pathogen (and, by extension, host-pathogen-vector) relationship in Grulke's original model and the "contextual change" piece are developed for malaria here.

Contextual Change

The MGM (**Figure 10**) identified a number of potential "impacts" relevant under the human and physical drivers for disease transmission in SSA, including conflict, altered rainfall patterns, desertification, altered access to safe drinking water, and new food sources. In the context of malaria transmission risk in SSA, important impacts of the physical driver of climate

change can be identified as changes in humidity, temperature, and rainfall. In terms of the human drivers, impacts such as deforestation, urbanization, changing agricultural practices, and changing socioeconomic conditions should be considered. Thus, one might consider the MGM as presented in **Figure 26**.

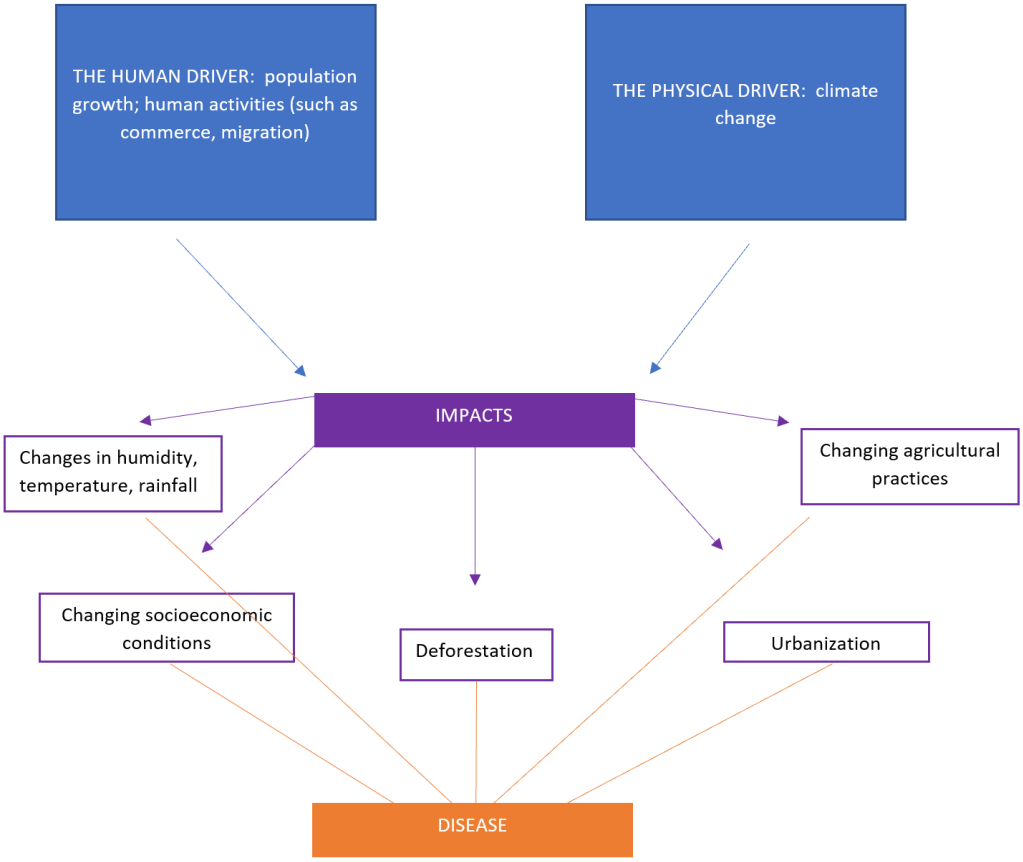


Figure 26. The MGM "specified" for the contextual changes relevant for malaria transmission in SSA.

As a reminder, **Figure 26** represents a tool to be used in consideration of what particular contextual factors *might* be relevant for studying malaria transmission risk in SSA; the factors

listed in **Figure 26** are not comprehensive, impact malaria transmission risk in varying ways, and interact with one another in addition to factors relevant to the host, vector, and pathogen.[14]

Specification of the Host-Pathogen Relationship

Following Grulke's original concept, several "attributes" of the host and pathogen "relevant" under the contextual changes defined in **Figure 26** emerge. Important, too, to the host-pathogen relationship is the presence of the vector. Here, relevant attributes are defined for the vector, host, and pathogen.

The Vector

In terms of the mosquito vector, the availability of breeding sites and favorable climatic conditions for mosquito development can be conceptualized as relating to all of the "impacts" shown in **Figure 26.** Relevant, too, under these contextual changes, are the vector's access to blood meals and the use of vector management, or vector control, approaches.

The Host

As discussed previously, the "built environment," or housing conditions, are relevant in terms of the human host for the impact on vector access to blood meals as part of the vector-host relationship necessary for transmission. Further, the location of the home with regards to topography, the presence of nearby livestock, socioeconomic status, "genetic factors," and access to preventive measures and treatment influence malaria transmission risk.

[14] Put another way, the MGM prompts readers to consider the capacity of the MGM to be "modified" as relevant factors are explored (see the study by Cook *et al*. 2018). For example, additional factors relevant to the "built environment," as Pareek discusses (Pareek 2018), could be explored as impacts related to the human driver.

The Parasite

Finally, climatic conditions, especially temperature, are relevant for the *Plasmodium* both for development of the parasite within the vector and for vector survival (see "The Fuzzy Climate Suitability Map"). For the parasite, the vector's access to blood meals is important as a source of new human hosts, and the presence or lack of malaria preventive efforts and treatment measures (and their effectiveness in terms of the development and spread of drug resistance) remains crucial.

Thus, use of **Figure 26** and identification of its relevance for the malaria host-vector-pathogen relationship provides a method of conceptualizing malaria transmission risk in SSA and provides opportunities for future malaria study and prevention efforts.

A Note on Spatial Scale

Some hints at the importance of spatial scale in studying malaria transmission risk already appeared in discussions in the "Examples of Previously Published Malaria Models" section of this chapter. While viewing malaria transmission risk for SSA, a view at a "regional" scale is valuable for the opportunity to discuss "overall" or "broad" trends, crucial information on the specific interactions of the drivers' "impacts" and transmission risk "factors" demands study on a smaller, more local scale. Koenraadt makes scale a focal point in the design of his research: "Since large variations in malaria transmission intensity exist on a relative small spatial scale, we designed a study that investigated mosquito population dynamics and malaria prevalence in relation to local environmental conditions. Ultimately, the data would be used for the validation and refinement of existing models on environmental change and malaria risk"

(Koenraadt 22). Consideration of spatial scale in this work is also significant for the idea of "emergent properties" seen on different spatial scales: different transmission factors may hold varying degrees of relevance at different spatial scales. Therefore, the focus of the next chapter will be on "localizing" the MGM specified for malaria transmission risk in the sub-Saharan African region to the substantially smaller region of the East African highlands, and, ultimately, to Kericho, Kenya.

Chapter 6

Kericho, Kenya: A Tailoring of the MGM for Examining Highland Malaria in East Africa

"For over a decade, the highlands of malaria endemic countries have been considered areas of special concern for the impacts of climate change.[12] Lindsay and Martens suggested in 1998 that, with all other factors remaining equal, global warming may result in the geographic spread of malaria transmission into previously malaria-free highland areas.[13] Since then, the discussion around the evidence for this has raised a heated and highly polarized debate. Multiple peer-reviewed publications,[14, 15, 16, 17] newspaper articles, editorials and blogs have been written and yet, to date, the debate continues to smolder."

- Omumbo *et al.*, "Raised Temperatures over the Kericho Tea Estates: Revisiting the Climate in the East African Highlands Malaria Debate," *Malaria Journal* 2011.

This chapter examines malaria transmission risk at a smaller spatial scale: in the region of the East African highlands, and, ultimately, for the site of Kericho, Kenya. Following a discussion of highland malaria, an MGM is defined for Kericho based on an examination of those factors influencing malaria transmission risk identified in the literature. It is through this MGM that understanding of the complexity of highland malaria transmission is sought.

I. The Problem of the Highlands

Highland Malaria

"Altitude is one of the oldest defences against malaria," Lindsay and Martens write (Lindsay and Martens 1998), and the apparent deterioration of this defense in the face of recent (since the 1980s, roughly (Waweru *et al.* 2011)) epidemics in the East African highlands has led to a robust discussion on the occurrence of highland, or "highland fringe," malaria. In these

highland areas, where populations have "little or no immunity to malarial parasites," the disease strikes not only children and "primigravidae" (Lindsay and Martens 1998), as it does in lowland areas where exposed adults have acquired a "partial" immunity (Mayo Clinic, "Malaria: Symptoms and Causes"), but also adults, resulting in "high morbidity and mortality" among highland populations (Lindsay and Martens 1998). "The highlands are thus areas of unstable malaria patterns primarily because of the low and fluctuating levels of transmission experienced by local communities," Lindsay and Martens write; "Consequently many of these semi-immune populations experience severe outbreaks every few years" (Lindsay and Martens 1998).

According to Waweru and colleagues, Lindsay and Martens' 1998 suggestion of the idea that "global warming may trigger geographic spread of malaria transmission into the previously malaria-free highland areas" (Waweru *et al.* 2011) predated a rich literature "written without resolving the debate," and the tea estates in Kericho, Kenya, have remained a focal point of study in this debate (Waweru *et al.* 2011). In a 1998 study, Malakooti and colleagues sought to determine the "local risk factors for malaria infection" through examination of the health records of workers for a tea company. The authors describe epidemics as occurring "during May to July, after the long rains and before the temperature drops in July" (Malakooti *et al.* 1998). Significantly, Malakooti *et al.* write,

"Several pertinent factors have remained stable and do not appear to explain the increase in malaria in this area. Firstly, climate data from the Kericho area show no obvious change in average temperature or rainfall over the last 10 to 20 years that would explain the present almost annual epidemics in the highlands. Although the climate data used in this study may not be sensitive enough to detect small changes in environmental temperature, global warming would also not explain the epidemics seen in the 1940s to 1950s. Deforestation may be relevant, providing more breeding sites for vector mosquitoes in sunlit pools and perhaps leading to localized changes in weather patterns and increased microenvironmental temperatures (1)" (Malakooti *et al.* 1998).

The authors then explain that "the increase in malaria does not seem to be explained by an increase in the number of nonimmune to semiimmune/immune persons nor simply by an increase in the total population," and they cite "degradation of the health-care infrastructure" as a "a third factor that could lead to an impression of increasing malaria" (Malakooti *et al.* 1998). Ultimately, the authors offer a "hypothesis" of drug resistance as an explanation for the observed increase malaria rates (Malakooti *et al.* 1998). "The period during which epidemic malaria was absent from the highlands corresponds to the time when pyrimethamine and chloroquine were still effective malaria treatments," they write (Malakooti *et al.* 1998). Further,

"the failure to cure falciparum malaria infections leads to an increase in the human gametocyte-carrier pool, resulting in the spread of epidemic malaria among the largely nonimmune highland population [. . .] while increased drug resistance may be the major factor in the documented increase of epidemic malaria, the causes are undoubtedly multifactorial and include vector, host, and environmental components" (Malakooti *et al.* 1998).

A later study by Shanks and colleagues also upheld this view of chloroquine resistance as an aspect that "may be key in the increase of highland malaria" in the Kenyan highlands. The study also referenced an absence of a "warming trend or increase in temperature records that extend back over a century" and described that "extensive comparison of temperature, rainfall, and malaria records in Kericho after 1965 has not indicated any convincing multiple-year link between either rainfall or temperature and malaria" (Shanks *et al.* 2005). Referencing both the work of Malakooti and colleagues and a 2002 study by Shanks and colleagues, Waweru *et al.* argue that the limitations of these studies led to their disagreement with the "long-term warming trend at Kericho" found by Omumbo and colleagues in a 2011 study making use of "a time series of quality-controlled daily temperature and rainfall data from the Kenya Meteorological Department observing station at Kericho" (Waweru *et al.* 2011). Waweru and colleagues write,

"*The reason that previous studies disagree is that researchers had limited access to quality data from Kericho or meteorological stations. Studies relied heavily on short-term series of station data, with inadequate quality control, or ignored local ground observations completely in favour of interpolated data that are intended for regional or global-scale analyses, and use only a fraction of the stations maintained by National Meteorological and Hydrological Services. As a result, analysts relied on the interpolated temperature surfaces, a poor choice for local-level analyses. These limitations have been clearly stated by the producers of these data (5)"* (Waweru *et al.* 2011).

Moreover, on the argument for the existence of a warming trend for Kericho, Waweru and colleagues are similarly confident:

"An adjusted monthly time series of maximum, minimum, and mean temperatures was examined for statistically significant temporal trends between 1977 and 2009. Upward trends on the order of +0.2 degrees Celsius per decade were found for all three of the temperature variables. While local factors may contribute to the upward trend at Kericho, it was found to be consistent with trends in the global tropics. This indicates that both local and large-sale climate variations are likely at work and gives additional validity to the finding of an increasing trend in temperatures at this site" (Waweru *et al.* 2011).

Despite these assertions, however, the "debate" over the impact of climate change on malaria still continues. Although others have asserted that "temperature is widely accepted as a fundamentally important environmental factor constraining its [malaria] transmission," (Lyon *et al.* 2017), Siraj and colleagues describe hesitations on the impact of climate change:

"Despite the expectation that global warming should lead to an increase in the altitudinal range of malaria, empirical evidence for this phenomenon is lacking, and the attribution of trends to specific factors remains difficult because of multiple drivers, including drug resistance, land-use change, human migrations, and access to health facilities (9, 10)" (Siraj *et al.* 2014).

Moreover, as the UNDP report for the western Kenya highlands describes,

"Today, the debate over climate and malaria linkages in East African highlands has focused on four main questions: whether malaria is increasing and re-emerging in the region; whether temperatures are increasing in the region; if yes to the latter, what might be the exact causes (e.g., land-use change, climate change); and finally, whether there is a causal relationship between trends in temperature and malaria incidence (Omumbo *et al.*, 2011)" (UNDP 26).

This chapter explores the impacts of the multiple "drivers" on highland malaria transmission in East Africa, with special emphasis on Kericho, Kenya, as it is a focal point in the malaria literature. Here, again, it is useful to remember the complexity of the drivers and impacts themselves as well as the idea that multiple interacting impacts influence malaria transmission risk.

A View of Kenya, Kericho, and Malaria

Kenya: Geography, Climate, and Population

Kenya lies in Eastern Africa, bordering Ethiopia, Somalia, South Sudan, Uganda, and Tanzania, as well as the Indian Ocean (**Figure 28**). Its size is "slightly more" than twice that of the U.S. state of Nevada, and its terrain is described as "low plains [that] rise to central highlands bisected by [the] Great Rift Valley," with a "fertile plateau in [the] west" (CIA, "Africa :: Kenya"). Several "geographic regions" have been described for Kenya: "the Lake Victoria basin, the Rift Valley and associated highlands, the eastern plateau forelands, the semiarid and areas of the north and south, and the coast" (Ingham *et al.*, "Kenya"). **Figure 29** shows the diversity of Kenya's vegetation along with some of its major cultivated crops. In terms of climate, Kenya experiences a rainy season from the end of March until May, and precipitation and average temperatures vary for the geographic regions (Ingham *et al.*, "Kenya"). The highlands "adjacent" to the Rift Valley, for example, experience over thirty inches of rain annually and see average temperatures between 13 and 18 degrees Celsius (Ingham *et al.*, "Kenya"). In terms of population and demographics, "accelerating population growth" was seen beginning in the early 1960s until the early 1980s due to "a sharp fall in mortality rates – especially infant mortality – and the traditional preference for large families," and slowed

population growth rates beginning in the mid-1980s have been attributed to lower fertility and birth rates as well as increasing AIDS mortality (Ingham *et al.*, "Kenya"). Today, Kenya's population remains young (see **Figure 27**), with population "heavily concentrated" on the shores of Lake Victoria and with "high density" in Nairobi and on the coast of the Indian Ocean (CIA, "Africa :: Kenya").

See Image citations, reference number 27.

Figure 27. A population pyramid for Kenya in 2016 (CIA, "Africa :: Kenya").

See Image citations, reference number 28.

Figure 28. A "shaded relief" map of Kenya (1988) (from the Perry-Castañeda Library Map Collection, University of Texas Libraries).

See Image citations, reference number 29.

Figure 29. A map showing vegetation and agricultural cash crops in Kenya (1974) (from the Perry-Castañeda Library Map Collection, University of Texas Libraries).

Kericho

According to the Central Intelligence Agency's World Factbook, "the Kenya Highlands comprise one of the most successful agricultural production regions in Africa" (CIA, "Africa ::

Kenya"). One of these highland areas includes Kericho County (with its capital of Kericho), an area with a population of approximately 752,000 and that hosts large tea companies such as Unilever, Finlays, Williamson Tea, and Kenya Tea Packers Limited (Ketepa) ("Kericho County"). The Climate Information Platform provides useful data on "historical seasonality" for Kericho, displaying monthly averages for rainfall and maximum and minimum temperature from 1979 to 2000 (**Figure 30**). The elevation of Kericho as displayed in the Climate Information Platform is 2184 meters (Climate Information Platform).

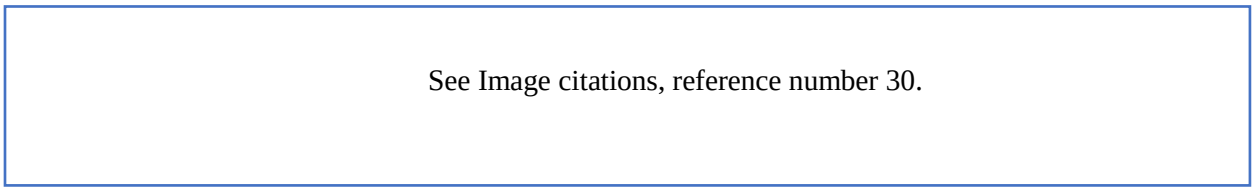


Figure 30. "Historical seasonality" (average monthly rainfall, maximum temperature, and minimum temperature) for Kericho as displayed by the Climate Information Platform (CIP, "Historical Seasonality").

Kericho and the western highlands of Kenya are considered to be "malaria epidemic-prone areas" with "seasonal transmission"; the UNDP report (focusing on the impact of climate) describes malaria in these areas as with a "level of transmission generally low, but can be very high during epidemics, which occur when climatic conditions are favourable" (UNDP 25). Such favorable conditions, the report described, might be "abnormal temperatures followed by rainfall exceeding certain thresholds [. . .] depending on topography (Githeko, 2010)," and "peak transmission generally occurs in June-July-August [. . .] (DOMC/MOPHS, 2011)" (UNDP 27). To convey the importance of "the link between unusual climate variables (temperature, precipitation, and humidity) and malaria" (UNDP 27), the authors reprint a table shown here (**Figure 31**), writing that the table "shows that the combination of unusually high temperature,

rainfall, and humidity has led to major epidemics in Nandi District" (UNDP 27). [15] As a caution, however, the authors do note that "given the high complexity associated with emergence of malaria epidemics, drawing a direct correlation between temperature and malaria risk is unwise" (UNDP 28). They note the value of us "diurnal temperature fluctuations" rather than "mean monthly temperatures" in models (Paaijmans *et al.* 2009 in UNDP 28) and of considering water temperature as well as air temperature in studying the impacts of temperature on vector development (Paaijmans *et al.* 2010, Githeko *et al.* 2000 in UNDP 28).

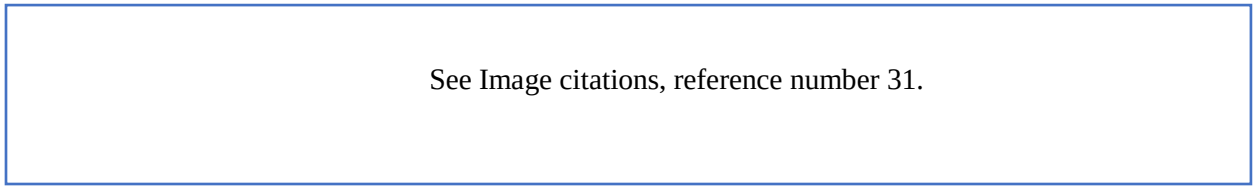


Figure 31. A reprinted work in the UNDP report on the impacts of climate change on malaria in the western Kenya highlands examining the link between "anomalous" weather conditions and malaria in Nandi District, an area in Kenya's Rift Valley region (UNDP 28).

The following section turns specifically to examining malaria in Kenya's western highlands.

A History of Malaria in the Western Kenya Highlands

As mentioned in the introductory chapter, the emergence of malaria in the Kenya highlands is a relatively recent phenomenon, as areas in Kenya above 1,500 meters in elevation were considered "malaria-free before the 1910s" (Balirane *et al.* 2010 in UNDP 25). Malakooti and colleagues describe various human activities as contributing to the spread of malaria to the Kenya highlands, including the 1901 "completion of a railway from the Kenya coast to the

[15] Note that the UNDP report discusses not just Kericho, but other areas in Kenya's western highlands, as well, such as Nandi. Table 6 of this report (Figure 31) describes malaria in Nandi District, specifically.

highlands from the low-lying hyperendemic disease areas (5)," "the development of tea estates and agriculture in the highlands with concomitant clearing of the forests," contributing to emergence of "suitable mosquito breeding grounds," and the "importation of infected laborers" (Malakooti *et al.* 1998). Shanks *et al.* also attribute the spread of malaria to the Kenya highlands to human activity, writing,

"Movement of people associated with the opening of civil and military posts probably introduced malaria into the highlands. During World War I, soldiers from Kericho were recruited to fight against the German forces in Tanganyika. With troop demobilization and resettlement in 1918 and 1919, a malaria epidemic followed the influenza pandemic (15). Further development in this region, including the completion of the Ugandan railway from the Mau escarpment to the malaria-endemic Lake Victoria region, increased movement of people and parasites" (Shanks *et al.* 2005).

Malaria epidemics are described as having occurred in the highlands from the mid-1920s to the 1940s (UNDP 25), with the return of "parasitemic soldiers" from Ethiopia during World War II leading to parasite infection of mosquitoes and "the now indigenous malaria transmission" in Kericho (Shanks *et al.* 2005, citing references 17 and 18). In the late 1940s and early 1950s, attempts at malaria control with use of the "chemoprophylactic" proguanil and DDT spraying of houses achieved success, despite a challenge from a 1952 "prolonged rainy season [that] shifted the epidemic period from July to January" (Shanks *et al.* 2005). Shanks and colleagues state that malaria in the Kericho tea estates "ceased to be a major problem from 1960 to 1980, which roughly coincides with the period during which chloroquine was fully effective against *P. falciparum* malaria" (Shanks *et al.* 2005). Subsequently, the 1980s and 1990s brought a "resurgence of malaria in the East African highlands" (Paaijmans *et al.* 2010 in UNDP 25) and the beginnings of the rich literary output on possible causes of this increase that still grows today.

II. Factors Identified as Potentially Impacting Malaria Transmission Risk in Kericho

In their study of malaria epidemics in Kericho, Shanks and colleagues proposed a number of "possible factors" contributing to the "reemergence of mid-year malaria epidemics in the western Kenya highlands," citing "changes in climate variability, population movements, decrease in quality of health services, changes in mosquito vectors, and antimalarial drug resistance" (Shanks *et al.* 2005). In the following section, the impacts of several of these possible factors are examined for another tailoring of the MGM, including the impact of climate change, drug resistance, El Niño Southern Oscillation (ENSO), elevation and topography, and changes in land use. Here, again, the importance of spatial scale is relevant. As is written in the UNDP report for the western Kenya highlands, "exposure to malaria risk is not homogeneous, due to the topography of the highlands and population dynamics between the highlands and lowlands" (UNDP 31). Thus, although studies of the impacts of factors examined on a larger spatial scale will be referenced, this section emphasizes the "factors" specific to Kericho itself.

Climate Change

Many of the debated impacts of climatic change on malaria were already discussed in this chapter and earlier: for example, the importance of the use of downscaled data (Paaijmans *et al.* 2014) and the significance of temperature increases for malaria transmission risk (Waweru *et al.* 2011), along with the literature's "debate" in this area, especially for the Kericho site. However, a few points merit additional discussion. For example, considering malaria transmission on the

scale of the western Kenya highlands, the UNDP report provides a list of "climate hazards" and their impacts on malaria epidemics (**Figure 32**) (UNDP 30). Thus, climate here is seen in the context of the "contextual changes" as discussed in the MGM model. Additionally, "human"-relevant access to health care is considered (UNDP 30).

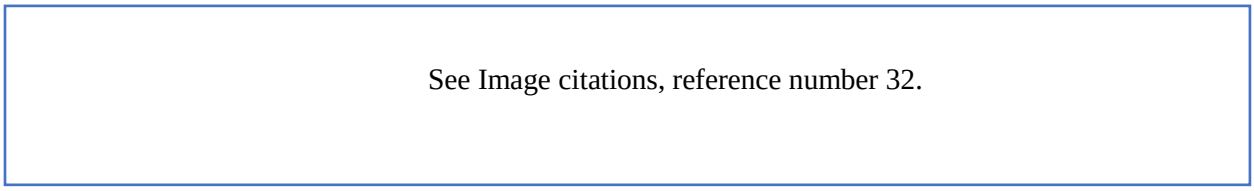


Figure 32. An identification of "main climate hazards" in the western Kenya highlands and their impacts on livelihoods and malaria epidemics, as published in the UNDP report on the impacts of climatic change on malaria transmission in the western Kenya highlands (UNDP 30).

Also relevant is the distinction of "micro-climate change" and the importance of "local environmental factors" discussed by Tonui and colleagues (Tonui *et al.* 2013). In their study of malaria epidemics in Kericho, Tonui *et al.* assert.

"An important demonstration of this study is that temperature and rainfall have not significantly changed over the last 17-20 years in the study area (Tonui, 2008) to influence malaria transmission as an indicator of climate change. This observation indicates that other factors such as micro-climate change due to deforestation, people mobility (to and from malaria holoendemic areas[)], socio-economic changes, deterioration of environmental sanitation, resistance phenomenon of Plasmodia and A. mosquitoes and inefficiency in the district health delivery systems may have contributed to upsurge in malaria transmission in the district hence increase in malaria morbidity burdens [. . .] Effective malaria control programmes need to address local environmental factors that lead to the reduction of malaria transmission in the district" (Tonui *et al.* 2013).

Thus, it seems that study of both the impacts of climate change processes happening on larger scales and of more "micro"-scale processes is relevant in understanding malaria transmission.

Finally, in considering the potential impacts of climate change on malaria transmission risk in Kericho, it is useful to consider downscaled future climate projections from the Climate Information

Platform (CIP) for several "malaria-relevant" factors (see "Map" citations). For example, **Figure 33**[16] provides a view of "anomalies" in total monthly rainfall in Kericho expected from 2040 to 2060.

See Image citations, reference number 33.

Figure 33. Expected "anomalies" in total monthly rainfall for Kericho for the period from 2040 to 2060, created using downscaled CMPI5 GCMs for the RCP 8.5 pathway (Climate Information Platform).

Among the other projections provided by the CIP are data on projected counts of wet days, dry spells, frost days, and heat spell duration. Here, projections for "anomalies" in the number of "hot days" (where the maximum temperature is over 32 degrees Celsius) per month from 2040 to 2060 is provided (**Figure 34**).

See Image citations, reference number 34.

Figure 34. Expected "anomalies" in hot days (where the maximum temperature is over 32 degrees Celsius) for Kericho for the period from 2040 to 2060, created using downscaled CMIP5 GCMs for the RCP 8.5 pathway (Climate Information Platform).

Drug Resistance

According to Shanks and colleagues, 1979 marked the first documentation of chloroquine resistance in Kenya in a visiting tourist (Shanks *et al.* 2005), and, "after resistance became

[16] Note that, in Figure 33, "RCP 8.5" refers to the Representative Concentration Pathway (RCP) 8.5, "the pathway with the highest greenhouse gas emissions" (see Riahi *et al.* 2011, https://link.springer.com/article/10.1007/s10584-011-0149-y). The colored red and blue bars show 10th to 90th percentile ranges of projected values for ten downscaled models (Crane; see http://cip.csag.uct.ac.za/webclient2/datasets/africa-merged-cmip5/ and "Map" citations).

widespread (11), chloroquine continued to be used as the first-line antimalarial drug for another 19 years" (Shanks *et al.* 2005). In their study of malaria epidemics on Kericho tea plantations, Shanks *et al.* maintain that "drug resistance, specifically chloroquine resistance, may be key in the increase of highland malaria" (Shanks *et al.* 2005), citing a "period without major malaria epidemics" from the introduction of chloroquine treatment until the status of resistance became "widespread," "the increase in death rates of hospitalized malaria patients since 1990," and "the absence of an epidemic on plantation 1 after use of more effective antimalarial drugs" (Shanks *et al.* 2005). However, the authors also specify that "drug resistance is not a universal explanation for epidemic malaria in the highlands of East Africa, especially given the highly controlled nature of the tea estates, which is atypical of rural Africa" (Shanks *et al.* 2005).

Although the role of drug resistance in the recent malaria epidemics in Kericho also has sparked "debate" (Stern *et al.* 2011), several studies have sought to contribute to understanding of drug resistance at the site. Zhong and colleagues, for example, analyzed malaria parasites from the highlands and lowlands of western Kenya for genetic mutations associated with drug resistance, finding that, in both highland and lowland samples, over 70% of samples had mutations in the chloroquine resistance transporter gene (*pfcrt*), and more than 80% of samples had resistance-associated "quintuple mutations" in dihydrofolate reductase and dihydropteroate synthetase (Zhong *et al.* 2008). Importantly, the authors note the absence of a "significant difference in the frequencies of these mutations between symptomatic and asymptomatic malaria volunteers, and between highland and lowland samples" (Zhong *et al.* 2008) and that a previous study by Mbaisi *et al.* did see differences in the prevalence of some mutations between the Kisumu lowland region and Kericho, Magadi, and Entosopia highland regions (Zhong *et al.* 2008).

More recently, there have also been efforts to study the potential emergence of resistance to artemisinin-based combination therapy (ACTs) in sub-Saharan Africa (SSA) and Kenya (Muiruri *et al.* 2018), especially given the presence of artemisinin-resistant parasites in Southeast Asia (Muiruri *et al.* 2018; De Laurent *et al.* 2018). Muiruri and colleagues discuss differences in genetic variations ("prevalence of *pfmdr 1* alleles" associated with drug resistance) between parasite populations in western Kenya as compared to coastal regions (see Muiruri *et al.* 2018). Importantly, they write in the conclusion to their work,

"Further, evidence of soft sweeps of pfmdr1 has been shown, but the direction of the selection for the pfmdr1 haplotypes is different from one region [of Kenya] to another, which can be explained by factors such as difference in parasite genetic diversity, drug pressure and much more. This finding poses further challenges for malaria control programmes in malaria endemic countries because transmission rates might change differently in the same country, which might require different malaria control strategies. It would be worthwhile to use this type of data as an additional molecular surveillance tool for guiding decisions for effective malaria control policies based on the region and not at a country wide level" (Muiruri *et al.* 2018).

Finally, in considering the impact of drug resistance on highland malaria, it is useful to consider the argument of Zhou and colleagues about the significance of this factor:

"Drug resistance can only aggravate malaria-induced morbidity and mortality; it cannot initiate an epidemic. In addition, drug resistance could not explain the sporadic malaria epidemics in the Kenyan highlands in the 1920s and 1950s, when the problem of drug resistance was insignificant (18). The reemergence of epidemic malaria is likely due to local malaria transmission in the highlands (10)" (Zhou *et al.* 2004).

El Niño Southern Oscillation (ENSO)

The United Nations Development Program (UNDP) report, *Climate Risk Management for Malaria Control in Kenya: The Case of the Western Highlands*, discusses El Niño Southern Oscillation (ENSO) as one of the "processes [. . .] that affect Africa's current climatic drivers" (UNDP 22) and an event "linked to malaria epidemics in Africa, Asia, and South America (Githeko *et al.* 2000) because it can seasonally increase the local temperature and rainfall

(Githeko 2009)." In particular, ENSO and its associated "short-term increases in temperature and rainfall" has been linked with malaria epidemics in the Kenya highlands in 1998 and 1999 (DOMC/MOPHS 2011 and Githeko *et al.* 2000 in UNDP 31). Further, in a study of malaria "time series" from five sites in West Kenya, Chaves and colleagues report that "ENSO significantly led the time series of Kisii and Kericho" (Chaves *et al.* 2011).

Elevation and Topography

As discussed with Wanjala and Kweka's study in Chapter Five, topography has an observed impact on malaria transmission in the highlands, with a "higher parasite density" observed in U-shaped over V-shaped valleys (Wanjala and Kweka 2016). However, elevation as it relates to temperature (in terms of adiabatic lapse rate) is also significant given the "temperature limitations" on malaria previously discussed, as atmospheric temperature declines with altitude. With regards to this discussion of elevation, Chaves and colleagues make an additional important point. Differentiating between sites below 1600 meters, where "malaria trends began to decrease in the late 1980s," and altitudes above 1600 meters, where increases in malaria were observed in the mid and late 1990s (Chaves *et al.* 2011) Chaves *et al.* propose explanations for observed increases and decreases in "malaria trends" (Chaves *et al.* 2011). For epidemics above 1600 meters, Chaves and colleagues write, "we consider that finely grained landscape transformation, in synergy with increased rainfall associated with IOD (Hashizume *et al.* 2009), probably were major drivers" (Chaves *et al.* 2011). For those "decreasing malaria trends," Chaves *et al.* argue,

"*the mechanism driving changes at low and high altitudes seems to be different. At low altitude, below 1600 m, malaria trends began to decrease before the 1990s, and could likely reflect self-regulation of transmission, either by immunity development (Hay et al. 2000; Pascual et al. 2008), or the more general reduced inflow of susceptible individuals, i.e., immune adults and well protected children, as observed outside Africa (Chaves et al. 2008, 2009, 2011; Kaneko et al. 1998, 2000). At high altitude (>1600 m), large-scale malaria control interventions with insecticide-treated bednets could have driven both the reduction of malaria transmission and mosquito population size (Lindblade et al. 2004) and a shift of dominant vector species, from An. gambiae to An. arabiensis (Bayoh et al. 2010). In fact, the interruption of malaria transmission has been documented in highland sites near the locations we studied (John et al. 2009; Zhou et al. 2011). More, generally differences in malaria incidence trends can reflect a myriad of historic changes in East Africa. From demographic changes to land use changes (Lindblade et al. 2000; Lindsay and Martens, 1998), drug resistance (Shanks et al. 2005), and global warming (Alonso et al. 2011) differences in malaria trends ultimately link the sensitivity of malaria transmission to its context (Chaves and Koenraadt, 2010)"* (Chaves *et al.* 2011).

Changes in Land Use

Changes in land use as they relate to human activities have the potential to impact malaria transmission risk. In their review of the impacts of environmental changes on malaria in the East African highlands, Himeidan and Kweka describe the relevance of both "land cover change" and "land use change" for malaria transmission (Himeidan and Kweka 2012). "Land cover change," they discuss, deals with "population pressure" in the highlands and associated deforestation that "can lead to changes in microclimate of both adult and larval [mosquito] habitats, hence increase larvae survival, population density, and gametocytes development in adult mosquitoes (Afrane *et al.* 2006; Munga *et al.* 2006, 2007; Kweka *et al.* 2011)" (Himedian and Kweka 2012); Himeidan and Kweka discuss the associations between deforestation and increased larval habitat water temperatures (citing Tuno *et al.* 2005 and Munga *et al.* 2007) and impacts for the mosquito with higher mean indoor temperatures found for "houses located in the deforested area of [the] western Kenya highlands" (Himeidan and Kweka 2012). In terms of "land use change," Himeidan and Kweka again discuss "population pressure" as leading to

"expanded and intensified agricultural activities and pastoral land use systems" (citing Bolwing 2006) (Himeidan and Kweka 2012), with changes in land use "reported to create and spread habitats for malaria vectors breeding as well as changing microclimate by altering temperature to that more suitable for larval development and adult survival (Lindblade *et al.* 2000b)" (Himeidan and Kweka 2012). Similarly, for the western Kenya highlands, Chaves and colleagues write of clearing of highland forests especially for "self-subsistence agriculture," and they place special emphasis on the impacts of "a long history unequal access to land," (Chaves *et al.* 2011), writing,

"*In addition, population growth in this region, with a long history of unequal access to land derived from colonial plundering (Prothero, 1965; Chaves and Koenraadt, 2010), also forces locals to migrate to valley bottoms where they are likely exposed to a large number of vectors and high malaria transmission (Munyekenye et al. 2015). Thus, the indirect impacts of population growth, which are ultimately expressed in diverse degrees of land transformation and human movement, make our analysis robust to the lack of explicit consideration of population growth data"* (Chaves *et al.* 2011).

Chaves and colleagues also discuss the significance of population growth for malaria transmission in the highlands, writing,

"*Moreover, regulation of malaria transmission, which is best described by frequency dependent models (Hay et al. 2000; Pascual et al. 2008; Chaves et al. 2009; Alonso et al. 2011), implies that population growth plays a relatively minor role on the dynamics of transmission (McCallum et al. 2001). In fact, several studies have shown that there is not a direct mapping between population growth and trends in malaria transmission, both in this area (Hay et al. 2002a,b; Pascual et al. 2008; Alonso et al. 2011) and outside Africa (Chaves et al. 2009). On the other hand, frequency dependent transmission models are sensitive to conditions of population immunity, which is indeed reduced in highland populations, when compared to low-land populations (John et al. 2002), as product of a decreased exposure to malaria infection (Drakeley et al. 2005)"* (Chaves *et al.* 2011).

As a final note, it is useful to consider Lindsay and Martens's discussion of "human activities" as they influence malaria transmission in the African highlands (Lindsay and Martens 1998). Lindsay and Martens argue that "once malaria is introduced into a highland area, it tends to become a growing problem largely as a consequence of agroforestry development, as

suggested by Garnham (15) and Mason (14)" (Lindsay and Martens 1998). They cite a "reason" for this as the relationship between vector ecology and human activities (Lindsay and Martens 1998). Among these many activities, the authors discuss the prevalence of new mosquito breeding sites in "expanding communities," "passive dispersal" of the vector "by car, truck, train, or ox wagon" as a likely explanation for how the vector "colonized the highlands," deforestation, including clearing of swamps and creation of "suitable breeding sites," especially in the absence of some of the breeding restrictions that papyrus imposes (see Lindsay and Martens 1998), irrigation, travel and migration of parasite-carrying hosts, and "deteriorating health systems" (Lindsay and Martens 1998).

A variety of factors have been identified as impacting malaria transmission risk in Kericho, and complexity exists not only in the nature of the exact impacts of these factors, but also in the multiple interactions and "interplay" among these factors. By defining the MGM for Kericho, we can attempt to capture and understand this complexity.

III. A Model for Understanding Malaria Transmission Risk in Kericho

This section closely parallels the third section in Chapter Five in that it generates an MGM specialized for viewing malaria transmission risk not at the "regional" level of sub-Saharan Africa, but at the level of Kericho. The model is not exhaustive, but it seeks to capture contextual change factors relevant for malaria transmission risk in Kericho and provide a basis on which to develop future approaches.

A Note: Zhou and Colleagues' Conceptual Model for Highland Malaria Transmission

Prior to tailoring the MGM for malaria transmission risk in Kericho, it is worth considering a "conceptual model to illustrate the pathways leading to epidemic malaria in the East African highlands" proposed by Zhou and colleagues (Zhou *et al.* 2004), as the description of the model allows for appreciation of the complexity of factors impacting malaria transmission at an "intermediate scale" between the larger scale of sub-Saharan Africa and the smaller scale of Kericho itself. Zhou and colleagues' description is reproduced here:

"This study demonstrates the important role of climate variability in malaria dynamics in some highland sites. However, malaria transmission involves complex interactions between Plasmodium parasites, anopheline mosquitoes, and humans. What pathways are being affected by climate variability and cause frequent epidemic malaria in the highlands? We propose the following conceptual model to illustrate the pathways leading to epidemic malaria in the East African highlands. The East African highland region contains numerous valleys and basin-like depressions in a plateau where malaria transmission intensity ranges from low to a level as high as the lowland (9). Human settlers in these foci are the main malaria reservoir, and they develop some degree of immunity to the severe consequences of malaria infection, whereas the human population uphill is not exposed to malaria infection regularly and generally lacks immunity to malaria. The valleys and basin-like depressions were recognized as less desirable areas to live; the human density in these foci was relatively lower. As a result of rapid human population increases over the past four decades in the East African highlands (http://grid2.cr.usgs.gov/globalpop/africa/app-2.php3), however, there have been unprecedented human settling pattern and land-use changes (45, 46). More families have settled in these less desirable areas and thus have dramatically increased malaria reservoir size. Land-use changes have created more mosquito breeding sites and have changed the water chemistry and temperature of mosquito larval habitats so that mosquito larval development is accelerated and survivorship increased (25, 47). They have also altered the microclimate of the adult mosquitoes and accelerated malaria parasite development (25). When the ambient temperature and rainfall is suitable for a short period, mosquito population size and parasite sporogonic development rates, and thus, mosquito vectorial capacity (48), increase rapidly. People living in the valleys receive more infective bites under such ambient conditions, but only a small proportion of residents, particularly young children, develop symptomatic malaria because of their functional immunity. An epidemic arises when people living uphill are being infected by malaria parasites through locally bred mosquitoes or mosquito dispersal; because they lack functional immunity, they are very vulnerable to malaria infection and often develop symptomatic or even severe malaria. Human mortality is increased when drug resistance, inadequate administration of drugs, failure to seek treatment or delayed treatment of malaria patients, and HIV infections in the human population become increasingly prevalent (9, 15, 22, 49, 50)."

"Our model postulates that climatic condition is one crucial factor in initiating an epidemic, but topography, human settlement pattern, land use, and drug resistance are also important. Climate conditions influence the development, reproduction, and survivorship of anopheline mosquitoes and malaria parasites. Topography and human settlement patterns affect the spatial distribution of mosquitoes and susceptible and immune human populations. Land-use changes can cause the environmental conditions to be more favorable for the development and reproduction of mosquitoes and parasites. Drug resistance aggravates malaria case fatality after an epidemic is initiated. Our model predicts that, in the highlands, most severe malaria cases during an epidemic come from uphill human populations that have not been regularly exposed to malaria infection. The model, if validated by epidemiological and entomological data, suggests several potential approaches for preventing or controlling malaria epidemics in the highlands. For example, targeted control of malaria vectors, using larvicides at the larval stage and using adulticides at the adult stage, in the valleys and basin-like depressions in a plateau may be a cost-effective approach to reduce malaria transmission. Malaria transmission in the valley can be further reduced if insecticide-based mosquito control is combined with elimination of larval habitats through appropriate land-use management" (Zhou *et al.* 2004).

Contextual Change in the Kericho Region

As was the case for the regional MGM for malaria transmission in sub-Saharan Africa, by considering the "factors" impacting malaria transmission discussed in Section II of this chapter, the "impacts" of the physical driver of climate change and the human drivers of human activities can be "specified" for malaria transmission in Kericho. Here, the human driver includes population growth and such human changes as migration, although, as discussed in Section II, it is important to remember that the significance and "role" of population growth and migration deserve further consideration. The role and consequences of the "impacts" that one might consider, also deserves further consideration especially given the debates discussed. Thinking specifically of Kericho, one might consider impacts such as changes in temperature and rainfall, deforestation, changing agricultural practices, urbanization in terms of the "expanding communities" (Lindsay and Martens 1998) discussed. Additionally, changes in control interventions and their use in terms of changing treatment and prevention practices are relevant (see **Figure 35**). Thus, many of the impacts identified at the level of Kericho remain similar or

identical to those identified on the regional level (see **Figure 28**), but with unique application and interaction at the Kericho site.

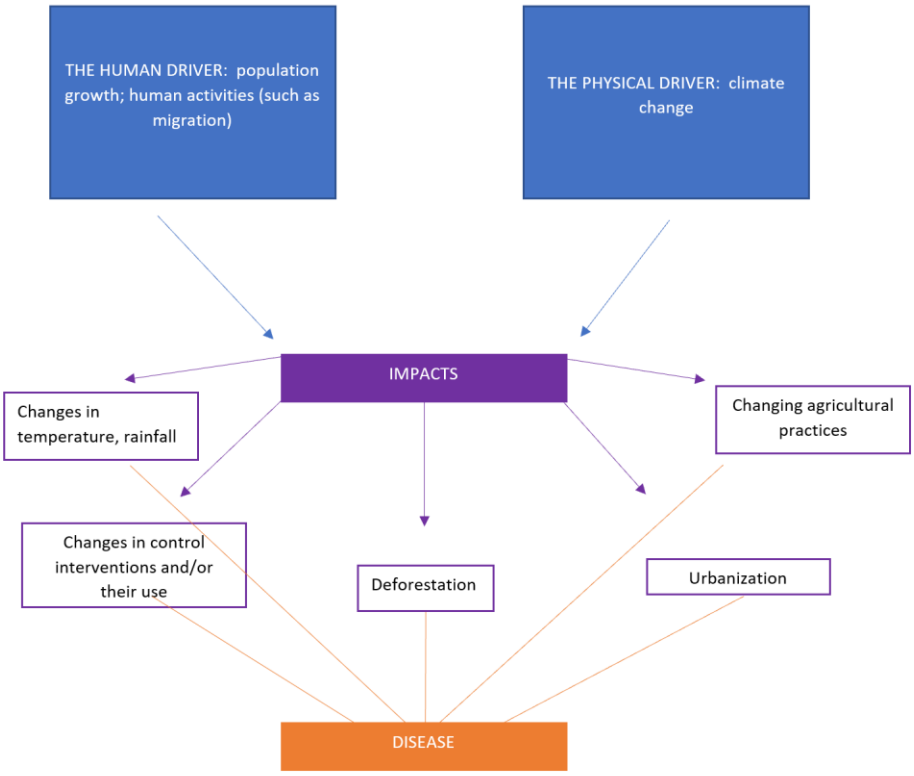


Figure 35. The MGM "specified" for contextual changes relevant for malaria transmission risk in Kericho, Kenya.

Specification of the Host-Pathogen Relationship for Malarial Transmission Risks in Kericho

Unfortunately, as discussed in this chapter, the exact nature of many of the "impacts" identified here remains unclear, and the specific interactions of impacts can lead to unique results for malaria transmission at the local scale. Perhaps this idea is best represented through

consideration of the debated impacts of climatic factors and climate change, especially as they relate to vector-borne diseases impacting humans. As Altizer and colleagues maintain,

"Climate change has already increased the occurrence of disease in some natural and agricultural systems, but in many cases, outcomes depend on the form of climate change and details of the host-pathogen system [. . .] for human diseases, vector-control, antimicrobial treatments, and infrastructure changes can dampen or mask climate change effects. Wildlife and plant diseases are generally less influenced by these control measures, making the climate signal easier to detect (4)" (Altizer *et al.* 2013).

Further, as Altizer and colleagues describe,

"Warming-driven increases in vector and pathogen development coupled with greater vector-biting rates under warmer temperatures create the potential for increased transmission of human vector-borne diseases such as malaria and dengue (but see Box S2 for important nonlinearities). However, this potential might not be realized in areas where economic conditions support adequate vector control, surveillance, health care, housing, or water management, leading some researchers to consider climatic factors relatively unimportant in predicting future human health risks (78, 79). Only recently have models simultaneously addressed both climate-driven and human-driven forces operating on mosquito-borne diseases" [e.g. (79)]" (Altizer *et al.* 2013).

For the highlands, specifically, Lafferty describes this complexity in terms of "logical alternative explanations" (Lafferty 2009):

"Malaria in highland regions since the 1980s has been linked to global warming (Epstein et al. 1998, Epstein 2001a). Altitudinal expansion of malaria exposes populations with little resistance, leading to substantial mortality in humans (Lindsay and Martens 1998). A widely cited example is an increase in malaria in Rwanda in the warm, wet year of 1987 (Loevinsohn 1994). Analysis of a longer time series suggests that climate has warmed at four highland sites to temperatures suitable for increased mosquito abundance (Pascual et al. 2006). This is not necessarily a distributional change; some have argued that none of the 'new' reports are above the historical altitudinal limits for malaria (Reiter 2001). For most examples of climate-induced increases in highland malaria, logical external explanations exist. Control efforts, clearing for agriculture (Lindblade et al, 2000), drug resistance (Ndymugyengi and Magnussen 2004), and changes in surveillance (Reiter 2001) also correspond with the changes in malaria, making it difficult to determine the contribution of climate change. Season, epidemiology, and interannual climate variation all contribute to variation in the number of malaria cases reported at highland sites, with climate explaining 12-63% of the variation in malaria, suggesting that, at some high-altitude locations, recent small increases in temperature may explain some of the increase in malaria (Zhou et al. 2004)" (Lafferty 2009).

Given these arguments and those discussed earlier in the chapter, this specification of the MGM is viewed as a "middle ground": even though the exact impacts of climate change on malaria transmission in Kericho are unclear, they are included for their potential to influence malaria transmission risk. Moreover, despite debate about the existence of a warming trend or trends relating to temperature and rainfall, changes in temperature are included as impacts in the MGM as prompts to consider these trends as factors – for example, the "changes in temperature" term allows for consideration of these changes in terms of *microclimates* and the relationship of these changes to other impacts such as deforestation, changing agricultural practices, "people mobility," and health interventions (Tonui *et al.* 2013).

Thus, as described for the regional MGM for malaria transmission risk in sub-Saharan Africa in Chapter Five, the "attributes" of the host, vector, and pathogen interpreted "relevant" under the contextual changes identified in Figure 35 are discussed here.

The Vector

Attributes of the vector relevant under contextual changes in Kericho are very similar to those discussed with development of the MGM at the regional level of SSA: availability of breeding sites has great impact on vector abundance, and agricultural practices and changing land uses can impact the availability of these sites. Climatic conditions, especially those that are "anomalous**" (**such as conditions of "unusually high temperature," "unusual rainfall," or "unusual humidity") (UNDP 28), are also relevant as potentially impacting vector survival and behavior. As a note, any efforts at the "vector-control" measures that Altizer and colleagues describe (Altizer *et al.* 2013) are relevant impacts on the vector here that could be traced to "human activities" with the human driver.

The Host

As discussed in the context of the malaria vector, changes in human activities (agricultural practices, land use, migration, and deforestation) are also relevant in the context of the host with regards to host exposure to infected mosquitoes. These are also significant in terms of host immunity, which has been discussed as especially relevant for highland epidemics where residents have been described as lacking the immunity present in their lowland counterparts (see Zhou *et al.* 2004). As discussed by Chaves and colleagues, population growth may also impact malaria transmission risk (Chaves *et al.* 2011).

The Parasite

The factor most discussed as relevant in terms of the *P. falciparum* parasite has been parasite drug resistance and the "debate" on its relevance for Kericho, as Shanks and colleagues noted that a "period without major malaria epidemics" in Kericho corresponded with the period from the first uses of chloroquine to what they describe as "widespread" chloroquine resistance (see Shanks *et al. 2005*, Stern *et al. 2011*). However, on a somewhat larger spatial scale, also relevant are the possible genetic differences between parasites from the highland and lowland areas in Kenya discussed by Muiruri and colleagues (Muiruri *et al.* 2018) and the contrasting presence of similarities between highland and lowland parasites (Zhong *et al.* 2008, see page 91 of this work). Potential differences in the prevalence of parasite resistance may also be relevant with respect to host travel and settlement patterns.

In conclusion, then, the MGM developed for Kericho specifically points to many of the same general "impacts" as seen in the MGM developed for SSA. However, analysis of these

contextual changes in terms of Grulke's model points to "Kericho-specific" attributes relevant for the host, pathogen, and vector. The MGM, thus, prompts readers to consider the debates discussed for Kericho and the implications of uncertain impacts and their interactions for malaria transmission on a local scale.

Chapter 7

Conclusions and Future Implications

"*In the highlands, small differences in altitude may lead to contrasting suitability and availability of vector breeding habitats and consequently divergent risks of malaria transmission and intervention.*[9, 10] *In Tanzania, for example, altitude alone accurately predicted whether a resident had splenomegaly in 73% of households.*[11] *The success of malaria control in the complex highland eco-epidemiological systems will depend on a systematic understanding of the micro-geographic risk of malaria transmission that would enable identification of high risk spots."*

- Balirane *et al.*, "High Prevalence of Asymptomatic *Plasmodium falciparum* Infections in a Highland Area of Western Kenya: A Cohort Study," *J. Infect. Dis.* 2009

The Scope of this Work

The goal of this work was to apply Grulke's model and its expansion (the MGM) to aid in understanding malaria transmission risk in a conceptual sense on two different spatial scales: for the larger region of SSA and for the smaller region of the East African highlands, (specifically, to Kericho). As the MGM was originally developed through readings about multiple infectious diseases in SSA (see Chapter Three), the decision to apply the MGM to the study of malaria transmission risk is a case study of application of the MGM to a particular disease. Ultimately, malaria was chosen not only for its relative importance to the disease burden in SSA, but also for the rich discussions in the literature on factors impacting malaria transmission risk, the complexity of the interactions of these factors, and, at times, the ambiguity surrounding the importance of certain factors and their exact impacts, especially with regards to highland malaria. Acknowledgement of this rich literature, complexity, and ambiguity is, in fact, crucial for understanding the limits of the scope of this work. The East African and Kenya highlands as well as Kericho have been areas of focus in the literature, and, inevitably, only a subset of the literature on these topics and the relevant work of others are reviewed in this work. Although my discussion of relevant factors impacting malaria transmission risk attempted to consider those "major" factors discussed in the literature, the impacts of additional factors are worth considering in greater depth: for example, the

impacts of "sea surface temperature anomalies" and their use in predicting malaria epidemics (see Githeko *et al.* 2018), discussions of "population gametocytes" in human hosts and the impact of travel between highland and lowland regions (Shanks *et al.* 2005; Lindsay and Martens 1998; Shanks *et al.* 2002), discussions related to the impacts of vector management and control (see Thomas and Read 2016 on insecticide resistance, for example), and discussions of the impacts of access to health care (see Altizer *et al.* 2013 and the UNDP report, for example). Relevant, too, is that the MGM was used in an effort to understand the complexity and ambiguity of malaria transmission risk, rather than as an attempt at predicting malaria transmission risk. The predictive capabilities of spatial and mathematical malaria models as well as malaria early warning systems[17] merit further consideration. As Githeko and colleagues describe,

"From the late 1900s until mid-2000s severe malaria epidemics occurred in the East African Highlands, often catching the health authorities by surprise (10-12). Many of the epidemics occurred during the short rainy season when they were unexpected. Later, the epidemics were associated with the El Niño weather phenomenon (13-15). It was critically important to develop early warning systems so that the transmission risks could be identified before the epidemics evolved (16-18). While the anomalous weather initiated the hyper-transmission, drug resistance and lack of vector control failed to prevent the evolution of malaria epidemics (6, 19-21). Later, the use of effective chemotherapy and vector control reduced the incidence of the epidemics although the climate risk remained. Afterwards, the 1997/8 El Niño event studies were initiated to develop a model for the western Kenya highlands. A model was developed for a site in the highlands and with a potential for application in other sites. The model showed that the epidemics were driven by anomalous temperatures and rainfall (13)" (Githeko *et al.* 2018).

Additionally, as Githeko *et al.* describe, efforts at prediction of malaria epidemics have been contested:

"Traditionally, most malaria transmission models are either statistical or dynamical. These two approaches have not been very successful as predictive tools for malaria epidemics and this has led to a degree of skepticism as to whether malaria epidemics are predictable in the modelling community (30). The problem in the models has been the failure to include environmental attributes that modify vector breeding habitats such as topography and hydrology (7). Our models were developed to address the different ecosystems (22, 3)" (Githeko *et al.* 2018).

Thus, although the MGM itself does not allow for specific predictions of malaria transmission risk, it seeks to understand the factors underpinning this risk. Understanding derived from use of conceptual

[17] See the "climate based malaria epidemic early warning system for the western Kenya highlands" developed by Githeko *et al.* 2018, for example, https://spg.ltd/wp-content/uploads/2018/12/020-SPG-2.pdf.

models such as Grulke's model and the MGM has the potential to inform or improve more complex models with predictive capabilities, as acknowledged in Chappelka and Grulke's expansion of the disease triangle (Chappelka and Grulke 2015; see pages 18-19 of this work). Finally, in developing the MGM through consideration of disease transmission risk in SSA, it was acknowledged that many of the ideas for the "drivers" and "impacts" of the MGM for SSA (see Chapter Three) came from reading about diseases in the region which were mainly infectious in nature as opposed to noncommunicable ones. Further consideration of additional relevant diseases, both infectious and noncommunicable, will improve the impacts considered with the MGM by expanding the scope of potential impacts considered.

Future Efforts

In the manner discussed by Chappelka and Grulke (see Chappelka and Grulke 2015; pages 18-19 of this work), it is my hope that this work will inform current understanding of malaria transmission risk and inspire future studies, especially with regards to the continued "debate" on the impacts of climate change on malaria transmission.[18] With regards to the MGM itself, several avenues for future work are clear. For example, in this work, the MGM was not formally validated in the context of malaria or applied to additional infectious or noncommunicable diseases. Further, the MGMs as defined for malaria transmission risk in SSA and Kericho appear quite similar on the surface, with finer similarities and differences. Additionally, there are interactions between the "impacts," discussed verbally with application of the contextual changes of the MGM to Grulke's host-pathogen relationship. Thus, future work with the MGM may consider methods of visual representations of interactions between MGM impacts. Future efforts might also consider if the "scale," or "relevance," of particular impacts or drivers

[18] Consider, for example, discussions of Kericho as a "cool" site and discussions of increased malaria "incidence" in "cooler, marginal transmission environments" as opposed to decrease in "warmer" regions with "endemic transmission" (Murdock *et al.* 2016; Blanford *et al.* 2013; Paaijmans *et al.* 2014).

could be represented in a qualitative or semi-quantitative manner (see McNew's figure in Scholthof 2007, for example).

Future work may consider expansion of areas studied on smaller spatial scales beyond the site of Kericho, Kenya. For the purposes of this work, Kericho, Kenya, was chosen for its prevalence in literature written in the Kenya highlands and the complexity and "debates" surrounding recent epidemics there. However, recent literature has extended study to additional sites within Kenya (such as Kisumu, Kitale, and Garissa (see Blanford *et al.* 2013 and Paaijmans *et al.* 2014). Sites outside of Kenya have been studied as well (for example, the Burundi highlands, for which a conceptual model describing "human related factors," "environmental factors," and "biological factors" as they affect "malaria presence" has been developed (Protopopoff *et al.* 2009)).[19] Thus, though Kericho was chosen deliberately as a case study, study of additional sites is an area of great interest and value.[20]

Ultimately, although the factors influencing malaria transmission risk and their exact impacts still remain complex and questions surrounding the "ambiguity" of factors and impacts remain, this thesis attempts a step forward in recognizing the relevance of contextual changes. Moreover, this approach emphasizes the importance of scale in analyzing malaria transmission risk. The MGM and its capacity to be "tailored" presents a step toward meeting Balirane and colleagues' call for "a systematic understanding of the micro-geographic risk of malaria transmission" (Balirane *et al.* 2009).

[19] Additionally, Onyango and colleagues discuss develop a "systems conceptual model detailing the causal relationships between variables in the malaria transmission system" for the East African systems that is worth considering for its detail and implications, along with their "integrated assessment framework to guide studies of climate change and malaria risk and vulnerability" (Onyango *et al.* 2016, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5105305/). See also the work of Ernst *et al.* (2011) (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3109621/).

[20] See also the comments in Chaves *et al.* 2011 about the focus of many time series analyses on data from Kericho (Chaves *et al.* 2011).

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34. "KERICHO (altitude 2184 m), Hot days (tmax > 32) RCP 8.5." Snapshot from the Climate Information Platform, "Map." n.d. (Climate Information Platform). Accessed April 7, 2019a. http://cip.csag.uct.ac.za/webclient2/datasets/africa-merged-cmip5/#nodes/observed-cmip5?folder_id=33&extent=99790.

ACADEMIC VITA

Laura M. Elliott

EDUCATION

The Pennsylvania State University, Schreyer Honors College — **University Park, PA**
Bachelor of Science in Biochemistry and Molecular Biology — August 2015 – May 2019
Smeal College Business Fundamentals Certificate

The Pennsylvania State University, Smeal College of Business — **University Park, PA**
M.P.S. in Management and Organizational Leadership — August 2019 – May 2020

ADDITIONAL EXPERIENCE

Summer Intern — **King of Prussia, PA**
Theodore Presser Company — Summer 2018

Schreyer MD/PhD Summer Exposure Program Intern — **Hershey, PA**
Penn State College of Medicine, Milton S. Hershey Medical Center — Summer 2016

Research in Molecular Biology — **University Park, PA**
Penn State Center for Eukaryotic Gene Regulation — 2016 - 2017

Learning Assistant — **University Park, PA**
Penn State Department of Physics (Physics 251) — 2017 - 2019

HORT 499H: Schreyer Signature Travel Program — **University Park, PA | Ireland**
"Walking in the Footsteps of the Irish During the Irish Potato Famine" — May 2018

SELECTED COURSEWORK

- Human Geography (GEOG 020U)
- STEM Learning (SC 220, as part of the Learning Assistant Program)
- Introduction to Bioinformatics, with Course Project (BMB 497)
- Coursework for the Smeal Certificate: Financial and Managerial Accounting (ACCTG 211), Microeconomics, Finance, Marketing, Management and Organization, Supply Chains, Business Law (BLAW 243)
- Honors coursework in Chemistry, Microbiology, Molecular and Cellular Biology, and Biochemistry