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Climate Change and the Crystal Ball of Vector-Borne Disease Forecasts

Aaron Bernstein [1,2]

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Abstract For decades, researchers have endeavored to better predict the incidence of vector-borne disease on a planet with a changing climate. Methods, though imperfect, have advanced considerably and led to the tantalizing prospect of forecasting the emergence of diseases such as malaria and dengue in new locations. This paper presents some of these recent advances and considers them in the context of their prospective aim: to prevent harm from vector-borne disease.

Keywords Climate change · Vector-borne disease · Malaria · Dengue · Daily temperature range · Anopheles · Aedes · El Niño southern oscillation

At various points in our species history, microbes have brought us to extinction's door, and despite major progress in combatting infectious diseases in recent decades, around 200 million people will fall sick with malaria, and nearly twice as many with dengue fever, this year. Millions more will contract other vector-borne diseases. No wonder, then, that much concern followed from initial suspicions [e.g., 1] and early research suggesting that climate change might foment conditions favorable to vector-borne disease transmission [e.g., 2, 3].

Yet, a look into the most current and scientifically informed crystal ball to discern the future of human vector-borne disease would at best yi\eld hazy results, even if much less hazy than in the past, owing to research over the past several decades that has deepened understanding about vectors, pathogens, and climate change itself. This paper explores recent advances in vector-borne disease modeling relevant to climate change and considers future directions for modeling vector-borne disease emergence as climate change unfolds.

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✉ Aaron Bernstein
aaron_bernstein@hms.harvard.edu

[1] Center for Health and the Global Environment, Harvard T.H. Chan School of Public Health, Boston, USA

[2] Hospitalist, Division of General Pediatrics, Boston Children's Hospital, Boston, USA

Better Knowledge of Bugs and Better Models of Disease

Models of future distributions of vector-borne disease endeavor to predict where and, often, when infections may occur. Over the past 20 years, these models have been honed based upon new knowledge of the many components that determine disease spread; whether this has come with increased accuracy remains unclear. However, many developments have given cause for optimism that disease incidence model accuracy is improving.

Consider models of malaria transmission and handling of temperature. Such models for a long time largely ignored temperature effects on mosquito development, this despite the knowledge that climate change was pushing temperatures upward and that adult mosquito populations depend strongly on juvenile (i.e., egg, larva, and pupa stage) survival. *Anopheles gambiae* larvae, for example, have shown that warmer aquatic larval temperature is associated with higher adult mortality [4]. Based upon this and other data obtained in a lab, Beck-Johnson et al. developed a malaria transmission model that incorporates all stages of the mosquito life cycle. Their model predicted peak abundance of infective mosquitoes at lower temperatures as compared to temperature-independent models, demonstrating the importance of factoring in temperature effects on mosquito development. The authors further compared their results to entomological inoculation rate data from 14 African countries to

demonstrate the better fit of their model output to field data as compared with traditional models of malaria transmission [5].

Discoveries about insects' and pathogens' biological responses to climate variables, such as temperature, have led to other refinements in model design. Early malaria transmission models relied on daily or, in some instances, monthly average temperatures to assign risk for disease incidence and spread [e.g., 2, 6, 7]. But average temperatures may belie important effects of daily temperature fluctuation.

A series of studies has investigated how temperature fluctuation—above and beyond mean temperature—affects parasites and vectors. Paaijmans and colleagues, for example, have shown that daily temperature variation influences determinants of malaria transmission intensity, such as parasite infectivity, parasite growth and development, as well as mosquito development and survival. *Anopheles stephensi*, an Asian malaria vector, grew to adulthood faster and was more likely to survive until adulthood when temperature fluctuated ±6 °C around a mean of 20 °C in contrast to those reared at constant temperature. However, at a mean temperature of 27 °C, temperature fluctuation resulted in longer development and fewer survivors into adulthood [8]. In this study, the authors also demonstrated that sporozoites of *Plasmodium chabaudi*, a rodent malarial parasite, were more likely to disseminate from mosquito vectors under varying temperatures at lower mean temperature (18 °C) and were not observed to disseminate from oocysts at all at higher mean temperature (26 °C). Whether these findings hold true for human malarial parasites is not yet known.

These findings and others have prompted updated assessments of malarial spread across Africa under climate change, as previous models did not account for daily temperature range (DTR). Blanford et al. estimated external incubation period (EIP) for *Plasmodium falciparum* using a model that includes DTR. Consistent with the studies described, they found that at low mean temperatures excluding variability in temperature underestimates parasite development. The converse also held: models based on high mean temperature overestimate parasite development when they omit DTR. In their analysis across the African continent using hourly, rather than monthly, average temperatures, the extrinsic incubation period for the malarial parasite was 100 % or more different in many areas with malaria endemicity [9]. As many mosquitos spend some time indoors, the authors also assessed indoor DTR by modeling indoor temperatures based upon available research on the relationship between outdoor and indoor temperatures. (Outdoor temperatures were obtained from the National Climate Data Center's Global Surface Summary of the Day Database http://www.ncdc.noaa.gov/). Modeled indoor temperatures had reduced DTRs and a higher mean, but the relationship between DTR and EIP remained present though was attenuated.

Other research on the influence of temperature variability on mosquito development has shown that all malarial mosquitoes are (unsurprisingly) not created equally, limiting the potential generalizability of Blanford et al.'s findings. Research on three other malarial vectors, *Anopheles arabiensis*, *Anopheles funestus*, and *An. gambiae*, found that all species differed in the optimal temperature for maximum developmental rate at the larval and adult, but not pupal, stages in their life cycles. *An. gambiae* develops best at cooler temperatures, *An. arabiensis* at warmer temperatures, and *An. funestus* somewhere in between. In addition, development rate and survival of *An. funestus* did worse with fluctuating temperatures whereas *An. arabiensis* either did the same or better as temperatures varied [10].

Temperature variation also may influence the likelihood of dengue virus spread. Lambrechts et al. showed that captive *Aedes aegypti* mosquitoes infected with one of two different dengue serotypes died sooner when exposed to higher DTRs [11]. They also found that DTR effects on mosquito infection and human transmission were dependent on mean temperature in a thermodynamic model of dengue. At a mean temperature of 18 °C, DTR had little or no effect on infection or transmission. At mean temperatures below 18 °C, larger DTRs were associated with greater probability of transmission; at mean temperatures above 18 °C, larger DTRs had the opposite effect, presumably due to temperatures exceeding the upward temperature limits of dengue virus reproduction.

In addition to these findings related to DTR bring to modeling future disease transmission under climate change, they call out the still largely uncertain consequences of climate change for DTR. The most recent IPCC report expressed medium confidence that the DTR is shrinking worldwide but enough uncertainty remains, including recent evidence that DTR to render interpretation of the above findings on disease transmission difficult.

There have been two studies adding further ripples to malaria modeling in recent years. The first addresses how best to account for malarial parasites and their mosquito vectors altering their development and biting rates, respectively, in response to temperature. The timing of an *Anopheles* first blood meal after emergence changes with temperature, ranging from a few days to 2 weeks [e.g., 11] [12]. The joint modeled effect of this finding, along with temperature effects on mosquito feeding frequency and EIP of the parasite, results in a 20–60 % decrease vectorial capacity as compared to conventional models. Interactions between time to sporozoite maturity and waiting for the next blood meal may also reduce odds of transmission across all viable temperatures, though the signal is noisier as duration of EIP and feeding interval move in and out of phase [13].

The second comes from a study by Garske et al. that modeled air temperatures based upon the better quantified (both temporally and spatially) land surface temperatures, as air temperatures are more likely to accurately predict parasite and mosquito parameters relevant to malaria transmission. They found substantial differences between land and air day

and night temperatures, which translate into markedly different values for determinants of malaria transmission, including mosquito lifespan, EIP, biting rate, and temperature suitability index [14]. These findings are consistent with previous research on *Culex* mosquitos showing that assessing temperature in the places mosquitos inhabit at various points of day matters to accuracy of EIP [15].

All Over the Map?

Even as more knowledge about fundamental drivers of disease transmission grows, ways of incorporating that knowledge into models varies. Consider recent papers that model the future distribution of *Aedes albopictus*, a vector for dengue fever and chikungunya.

Proestos et al. sought to project regional and global *A. albopictus* distribution in 2050 using the ECHAM5/MESSy2 atmospheric chemistry (EMAC) general circulation model at high spatial and temporal resolution. Fuzzy logic was used to meld a series of predictors into a composite habitat suitability index. Predictors included average rainfall, average annual temperature, minimum winter temperature, maximum summer temperature, and relative humidity.[1] Using the SRES A2 scenario, they compared a baseline 2000–2009 distribution to a modeled distribution for 2045–2054 and found that by 2050, approximately 2.4 billion individuals will potentially be exposed to *A. albopictus* using a habitat suitability index threshold of 70 % [16].

Ogden et al. likewise sought to model regional *A. albopictus* distribution by mid-century, but used a different set of habitat suitability criteria than did Proestos et al. and a different modeling strategy. The first they term overwintering that is on a 0-3 ordinal scale based on January temperature and annual precipitation.[2] The second they named overwintering combined with annual air temperature which includes an overwintering score ≥1 with different thresholds of mean annual temperature (T_{ann}).[3] The third criterion, which they named "SIG" because it employed a sigmoidal transformation of temperature data, combined summer temperatures, January average temperatures and annual precipitation.[4]

Each criterion had sensitivity and specificity for *A. albopictus* distribution of over 90 % for the current mosquito presence in the USA, though specificity declined substantially in areas of the USA east of 100 °W where mosquito prevalence is high but mosquito surveys are rarer. When projected out to 2041–2070 using nine regional climate models with representative concentration pathways taken from IPCC AR5 and the A2 SRES scenario, these criteria resulted in substantially different geographic distributions. The SIG criterion, in contrast to the other two, predicted suitability ranging up to 1000 km into Canada and a marked contraction of habitat in the southeast, with the latter owing to decreased rainfall and higher temperatures. This may be explained by SIG's lack of absolute cutoff for mosquito survival at cold temperatures [17].

The recent paper from Rochlin et al. made use of yet another modeling approach and set of predictors. They chose a set of six environmental variables,[5] pared down from an original group of 22, based upon collinearity, prior research, and ultimately those that led to the best fit with current mosquito distribution and had high Akaike information criterion scores. They employed a maximum entropy (MaxENT) model and the SRES B2 and A2 scenarios to assess future distribution of *A. albopictus* in the northeastern USA. In their model, mean winter temperature fared better than minimum January temperature in predicting mosquito distribution, but January precipitation outperformed overall winter precipitation. The latter result may reflect precipitation falling as rain or sleet outside the coldest months. The former result may owe to the insulating effects of snowfall. Overall, they found that suitable habitat would increase from 5 to 16 % of the entire northeastern land area by mid-century [18].

These three studies employ valid approaches to determining future geographic spread of a disease vector, even if they relied upon different sets of climate variables and models to determine vector habitat suitability. In the case of *A. albopictus*, and perhaps other disease vectors establishing populations in new areas, the invasive populations may have different sensitivities to climate in their new habitats [19]. This implies that a single set of climate criteria may not accurately predict mosquito presence if applied globally.

Perhaps in light of this, or due to better ability to do local long-term climate modeling, an increasing number of studies

[1] Average annual rainfall of 200 mm per year; average annual temperature above 8 °C; minimum winter temperature above −4 °C; summer maximum temperature below 40 °C; at least 60 days each year with 1 mm or more of rain; average summer relative humidity of at least 30 %; average winter relative humidity of more than 50 %.

[2] Overwintering scale: (0) very unsuitable if January temperature (T_{Jan}) is lower than 0 °C and annual precipitation (P_{ann}) is below 500 mm; (1) 0 °C≤T_{Jan}<1 °C and 500 mm≤P_{ann}<600 mm; (2) high when 1 °C≤T_{Jan}< 2 °C and 600 mm≤P_{ann} <700 mm; and (3) very high when T_{Jan}≥2 °C and P_{ann} ≥700 mm.

[3] Overwintering with average temperature provided five-point ordinal scale: (0) very unsuitable conditions when T_{ann} is below 9 °C, (1) low risk when 9 °C≤T_{ann}<10 °C, (2) moderate risk if 10 °C≤T_{ann}<11 °C, (3) high risk if 11 °C≤T_{ann}<12 °C, and (4) totally suitable conditions if T_{ann}≥ 12 °C.

[4] Habitat suitability for the third criteria was based upon annual precipitation, (suitability was zero for annual precipitation <450 mm and maximum when precipitation was >800 mm): summer temperatures (suitability was zero for temperatures <15 or >30 °C and maximum when temperatures were between 20 and 25 °C) and January temperatures (suitability was zero when temperatures were <2 °C, and maximum when temperatures were >3 °C).

[5] Mean temperature of coldest quarter, precipitation of wettest quarter, precipitation of driest quarter, January precipitation, and land use/cover.

have done regional projections of vector-borne disease transmission. To examine the consequences of using downscaled versus global climate models on predictions of future malarial incidence, Paaijmans et al. compared results from raw global circulation models to downscaled models and found that the raw models may underestimate transmission of *P. falciparum* by as much as threefold in hot and 12-fold in cold extremes [20].

Evolution Happens

As the research described above attests, the nuances of temperature effects on vector-borne disease transmission raise hurdles to accurate models. But temperature effects are but one of many areas of investigation that have added to the concerns of disease modelers.

Vectors and pathogens may evolve—in some instances rapidly—to changing temperature regimes that can alter their responsiveness, for example, to absolute or relative temperatures [21]. Sternberg and Thomas have summarized available evidence and theory on the topic of local adaptations of arthropods to climate variation [22].

Aedes japonicus, a possible vector for chikungunya and dengue based upon laboratory assessment, [23] and native to Japan and the Korean peninsula, has in the past decade invaded the USA and Europe in locations with similar climates to its native territory. It has also established populations in Hawaii and the southeastern USA in climate regimes far different from its origins. This new geographic and climatological spread enabled a genetic comparison of populations to assess for the ability of the mosquito to evolve tolerance to warmer regimes. Populations that survived in warmer temperatures lost genetic diversity suggesting that selection occurred for tolerance to warmer temperatures (though genetic drift cannot be entirely excluded). Furthermore, comparisons of populations at high temperatures in Hawaii had fewer rare alleles than those at low temperatures, suggesting genetic bottlenecks beyond initial founder effects. In both Hawaii and Virginia, specimens sampled at 7 and 10 years post-arrival demonstrate a gradient of decreasing diversity from low-lying, warmer habitats to cooler, mountainside locales [24].

Among the vector traits that have been shown to evolve in the face of novel environments has been the critical photoperiod.[6] Diapause in mosquitoes, which is a period of hormonally induced dormancy during development triggered by environmental cues such as hours of sunlight, is a strategy to cope with adverse conditions, such as temperatures that are too high or low for mosquito survival. Researchers characterized the critical photoperiod and diapause incidence across latitudes in populations of *A. albopictus* from Japan and the USA, first in the late 1980s and then again in the late 2000s. When comparing specimens collected in the 1980s from the native Japanese populations to the invasive US populations, higher latitude produced a smaller increment in critical photoperiod in the US as compared to Japanese populations. By the late 2000s, however, this difference waned: the US mosquito's response to latitude became nearly identical to Japanese populations. By 2008, US mosquitoes were also more likely to enter diapause at lower latitudes. Of note, other traits of these mosquitoes, including body size, wing length, or egg volume, did not change [25].

Evolution happens and inserts uncertainty—and possibly surprise—into how disease will respond to changing climate. Assessing this uncertainty remains an open field of investigation.

Simpler Systems

As with any scientific inquiry, reductionist approaches have their benefits and drawbacks, so too with models of infectious disease transmission under climate change. Though evidence has suggested, for instance, that climate change has spurred the move of malaria into populations in the highlands of east Africa [26], fully excluding the influence of human actions is difficult. Human intervention for human disease is the norm, and while humans do intervene in wild animal disease ecosystems, the same cannot be said for many diseases of wild animals. This affords an opportunity to study these diseases as a potentially less biased subject to understand how climate change may affect vector-borne disease.

Elevational gradients provide a natural setting to investigate the effects of temperature change on disease prevalence. In a study from North Queensland, Australia, 403 birds were tested for the presence of four parasites across an elevational gradient. Temperature predicted parasite prevalence independent of elevation with a 1 °C increase in temperature associated with a 10 % increase in parasite prevalence. The authors of this study speculate that birds could respond to more pathogen pressure in one of three ways: (1) stronger immunity, (2) higher mortality and resulting lower populations, or (3) move to higher elevations [27].

If the example of avian malaria on Hawaii, one of the better-studied disease introductions, is representative, birds have largely either succumbed to parasites or had their lowland habitats destroyed. Hawaiian birds were naïve to avian malaria having been isolated some 3–4 million years ago [28]. Although the avian malarial parasite was likely introduced by exotic bird introductions on numerous occasions, epizootics

[6] The critical photoperiod is often measured as the number of hours of light needed to induce egg diapause in 50 % of a population, excluding eggs that do not enter diapause when exposed to very short-day lengths.

did not occur until the arrival of *Culex quinquefasciatus* as early as 1826 [29]. Atkinson et al. conducted surveys of parasite prevalence in eight native and eight non-native bird species in three locations on Kauai's Alaka'i Plateau, where many of Kauai's remaining endemic and endangered birds reside, in 1994–1997 and 2007–2013. Overall, the prevalence of infection doubled from 8.6 to 19.6 %. The steepest increase in prevalence occurred at the highest elevation (~1350 ft). These changes were also associated with rising temperature at each site and decreased precipitation and streamflow, all of which facilitate mosquito survival. The authors also documented malarial incidence in a sedentary bird, the 'elepaio, which increased from 17.2 to 27 % across the nearly 20 years of study indicating that local malaria transmission was responsible for at least part of the observed increased prevalence. Other research has shown that remaining populations of honeycreepers, as well as other endemic birds, which have been decimated by avian malaria, survive at an elevation of 1500 ft or higher, which coincides with lab and field observations of the thermal limits of parasite sporogony [30].

El Niño

The El Niño Southern Oscillation (ENSO) refers to periodic changes in water temperature in the eastern Pacific Ocean that occur roughly every 5 years. ENSO cycles have dramatic effects on weather around the globe. Warmer than average water temperatures in the eastern Pacific define El Niño events, whereas cooler than average temperatures define La Niña periods.

Because of the dramatic shifts in weather they produce around the world, El Niño events have been used as a model to understand how climate change-associated extreme weather events, such as droughts, floods, and heat waves, may alter infectious disease epidemiology as climate change unfolds. Recently, however, some evidence has suggested that climate change itself may be driving more severe El Niño events, raising the possibility that El Niños may be more than just a natural experiment to understand the infectious disease consequences of climate change [31–33].

Associations of El Niño with outbreaks of Rift Valley fever, a vector-borne viral illness that affects both livestock and humans in East and Southern Africa, have been known since the 1950s [34]. El Niño favors wet conditions favorable to the insect vectors of the disease in these regions, and models based upon Pacific and Indian Ocean sea surface temperature and the normalized difference vegetation index (a measure of green land cover, consistent with rainfall in arid regions) have successfully predicted Rift Valley fever epidemics in humans and animals months in advance. In the 2006–2007 El Niño season, for example, outbreaks of Rift Valley fever were accurately predicted 2 to 6 weeks prior to epidemics in Somalia, Kenya, and Tanzania [35].

Links between El Niño events and vector-borne disease beyond Rift Valley fever are weaker. El Niño has had inconsistent associations with malarial incidence in African countries. Some of the strongest associations between El Niño and malaria have been identified in South Africa and Swaziland where available data on incidence are relatively robust though even in this instance the observed increased risk did not reach statistical significance. A stronger, though still variable, link to El Niño has been found in several studies done in South America. [e.g., 36]. In Venezuela, a periodic analysis of climate variables and malarial incidence found that sea surface temperature, the marker for El Niño, was associated with malarial outbreaks on a 2- to 6-year cycle. The period of the cycle and the strength of association varied by location and the parasite species (*Plasmodium vivax* vs. *P. falciparum*) [37]. The influence of El Niño on malarial incidence may be detectable but is highly variable.

In the case of dengue, El Niño signals are similarly mixed though evidence suggests it may be driving disease in many parts of the world. In Thailand, for instance, 15–22 % of the variance in monthly dengue disease incidence is attributable to El Nino [38].

Several studies in Central and South America have suggested that El Niño periods may elevate risk for dengue. A recent small study in Risaralda, Columbia, found that oscillation Nino index was, along with rainfall, the strongest predictors of dengue incidence [39]. Similar findings have come out of Venezuela and Honduras [40, 41]. Given the small-scale and limited data available in each of these studies, their conclusions must be viewed with caution.

Conclusion

Research as described in this paper is a worthy, if imperfect, activity given that at least one objective of disease modeling is to anticipate disease outbreaks and thereby afford an opportunity to prevent harm. But even if the crystal ball for vector-borne disease has gotten clearer, the question remains as to whether the models for diseases like malaria and dengue will ever be good enough to achieve this end [42]. The advances described here suggest that focusing attention at smaller scales may be a way to sharpen focus, even if available data to base forecasts on are limited. They also speak to the need for a greater investment in understanding fundamental aspects of vector and pathogen biology, especially as relate to expected changes in climate including changes in temperature and precipitation.

Climate change constitutes only a part of the equation that determines the future incidence of vector-borne disease worldwide. On a planet with nearly one billion people

undernourished, another billion lacking access to clean water, and two billion living on less than US$2 a day, what influence climate change may have on disease incidence could easily be dwarfed by other, more powerful, forces. Nonetheless, climate change may undermine recent progress in reducing major burdens of disease, and so understanding its affects on health in general and to the spread of vector-borne disease in particular is vital to ensuring the healthiest possible future.

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