Climate Change and Malaria: A Call for Robust Analytics

Daniel J Laydon[1,2,☯,*], David L Smith[3,☯,*], Kaustubh Chakradeo[4], Mark P Khurana[4], Jaffer Okiring[5], David A Duchene[4,☯], Samir Bhatt[1,4,☯]

1 MRC Centre for Global Infectious Disease Analysis, Department of Infectious Disease Epidemiology, School of Public Health, Imperial College London, London, UK
2 Centre for Health Economics & Policy Innovation, Department of Economics & Public Policy, Imperial College Business School, Imperial College London, London, UK
3 Department of Health Metrics Sciences, School of Medicine, University of Washington, Seattle, WA, USA
4 Section of Epidemiology, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
5 Clinical Epidemiology Unit, Makerere University College of Health Sciences, Kampala, Uganda

☯These authors contributed equally to this work
*Corresponding authors: d.laydon@imperial.ac.uk, smitdave@uw.edu

Abstract

Mosquito ecology and behavior and malaria parasite development display marked sensitivity to weather, in particular to temperature and precipitation. Therefore, climate change is expected to profoundly affect malaria epidemiology in its transmission, spatiotemporal distribution and consequent disease burden. However, malaria transmission is also complicated by other factors (e.g. urbanization, socioeconomic development, genetics, drug resistance) which together constitute a highly complex, dynamical system, where the influence of any single factor can be masked by others.

In this study, we therefore aim to re-evaluate the evidence underlying the widespread belief that climate change will increase worldwide malaria transmission. We review two broad types of study that have contributed to this evidence-base: i) studies that project changes in transmission due to inferred relationships between environmental and mosquito entomology, and ii) regression-based studies that look for associations between environmental variables and malaria prevalence. We then employ a simple statistical model to show that environmental variables alone do not account for the observed spatiotemporal variation in malaria prevalence.

Our review raises several concerns about the robustness of the analyses used for advocacy around climate change and malaria. We find that, while climate change's effect on malaria is highly plausible, empirical evidence is much less certain. Future research on climate change and malaria must become integrated into malaria control programs, and understood in context as one factor among many. Our work outlines gaps in modelling that we believe are priorities for future research.

Introduction

Malaria epidemiology, transmission, ecology and control are complex. The distribution of malaria, and its transmission intensity and seasonality have been shaped by a range of factors: climate [1–3], mosquito ecology and biogeography [4], malaria control [5], economic development [6], human genetics [7,8], and history [9]. Since the start of the 20th century, malaria incidence has declined over time, albeit unevenly [10, 11]. The geographical range of malaria has substantially contracted in recent times, and prevalence has dropped in places where it remains endemic [3].

While malaria has declined due to economic development and improved control strategies (e.g. elimination programs, improved healthcare, medical interventions), other factors push in the opposite direction. Malaria incidence has seen large changes caused by: drug resistance; changes in first-line therapies; healthcare system strengthening and degradation; economic development; efforts to scale up intervention coverage; resurgent outbreaks associated with the evolution of insecticide resistance; and pauses in malaria control [12–14]. These changes are often exacerbated by weather or land use changes. Therefore, how these factors aggregate to affect malaria incidence, and each factor's individual contribution, is far from straightforward.

Despite advances in control, malaria remains a major cause of mortality and morbidity, especially in sub-Saharan Africa. Because malaria parasites are transmitted by mosquitoes, and because mosquito ecology and behavior are affected by the environment, the interactions between weather, mosquito ecology, climate change, and malaria transmission have been of longstanding interest [1, 15, 16]. Here, we review and evaluate the evidence that has shaped science and advocacy concerning climate change and malaria. We focus on the broad sources of uncertainty underlying this evidence. We explain that statistical studies tend to find that environmental variables alone do not explain the total variation in malaria prevalence over space and time: environmental variables primarily define a population at risk, rather than the actual current transmission intensity. Taken together, we explain how the influence of climate change on future malaria transmission is far less certain than previously stated.

We consider two kinds of studies that have examined the relationship between climate change and malaria. First, we consider studies of potential malaria transmission, which project changes in malaria transmission based on the link between environmental variables and either mosquito behavior or mosquito ecology. These studies model malaria transmission using either the basic reproductive number, R_0, vector capacity [17, 18], or mathematical models of malaria transmission dynamics. In these studies, projections of malaria transmission under various climate change scenarios are based on observations of mosquitoes raised in a laboratory, in a semi-field environment, or in carefully controlled settings.

Second, we consider regression-based studies that look for associations between environmental variables and malaria prevalence. These studies have generally relied on large data sets curated by the Malaria Atlas Project [5]. We then use a simple regression to investigate the extent to which environmental variables can explain observed variation in malaria incidence by location over time.

While both types of analysis are valuable, they are incomplete. For example, a major limitation of studies of malaria and temperature over time is the lack of covariates describing treatment failure and anti-malarial drug resistance. The evolution of anti-malarial drug resistance in Africa in the 1990s is well-documented [19], but its effect on efficacy has proven difficult to measure. In this piece, we describe how these limitations weaken the evidence supporting a dominant link between climate change and malaria in Africa. Critically, highlighting

the risks of increased malaria due to climate change can be misleading, in that downstream consequences of climate change are important, but also multifaceted and nuanced.

Malaria is now a heavily managed disease, and if climate change is relevant for that management, then methods to attribute the effects of climate change, distinct from other factors, must be considered for future strategies. In this piece we argue that it is overall weather changes, rather than rising temperatures, that most influence vector density, and these pose a challenge for malaria control. Furthermore, malaria transmission has a changing baseline that varies with malaria control.

Despite this complex interplay of factors, the task of coping with climate change ultimately falls on malaria control programs. Therefore funding is needed to help develop surveillance, information systems, early warning systems, and capacity for effective outbreak responses. Regardless of the impact that climate change may have on malaria, it should not distract from the central task of reducing malaria burden, and research on climate change and malaria should serve those goals [20]. Future research on climate change and malaria must become integrated into malaria control programs, and understood in context as one factor among many.

Potential Transmission

Many studies of climate change and malaria are based on basic theory for malaria transmission dynamics and control. These include simulation studies that use mathematical models of transmission, and analyses of potential transmission based on Macdonald's formula for the basic reproductive number for malaria, R_0. Within malaria, R_0 describes the number of human malaria cases per human malaria case [17, 18, 21, 22]. Other studies of potential transmission use a formula for vectorial capacity (itself derived from the formula for R_0) [23].

Macdonald's formula was first developed in the 1950s in papers that synthesized the first decades of malaria epidemiology and medical entomology [17, 24–31]. A central question addressed by this mathematical model was the critical density of mosquitoes required to sustain transmission. Macdonald used the formula to understand endemic malaria, and he used the formula to weigh the relative importance of various parameters describing transmission [17]. The formula would serve as a threshold criterion in simple models of transmission: transmission would be sustained if $R_0 > 1$. Therefore, to eliminate malaria, mosquito population density would have to be reduced by factor that exceeds R_0.

In Macdonald's papers, the formula was derived from standard metrics (e.g. the human biting rate, sporozoite rate, and thus the entomological inoculation rate (EIR), to malaria prevalence and incidence) to measure transmission. Macdonald's analysis reframed the question of mosquito-borne transmission around key specific parameters, and drew attention to the important role played by mosquito survival [26].

To develop theory for vector control, Garrett-Jones isolated the purely entomological parameters in the formula for R_0 and called the new formula "vectorial capacity" (VC, see Box 1) [23]. VC, separated from the rest of the formula for R_0, computes transmission potential as if humans were perfectly infectious, avoiding the difficult issue of human infectiousness. In doing so, Garrett-Jones ignored differences among vector species in their ability to host the parasites (now referred to as "vector competence"). VC describes a daily reproductive number: the number of infective bites that arise from all mosquitoes that blood-feed on a single, perfectly infectious human per day [23]. Macdonald originally derived the formula for R_0 from the sporozoite rate and the human biting rate, the product of which is the daily entomological inoculation rate (dEIR), i.e. the number of infective bites received

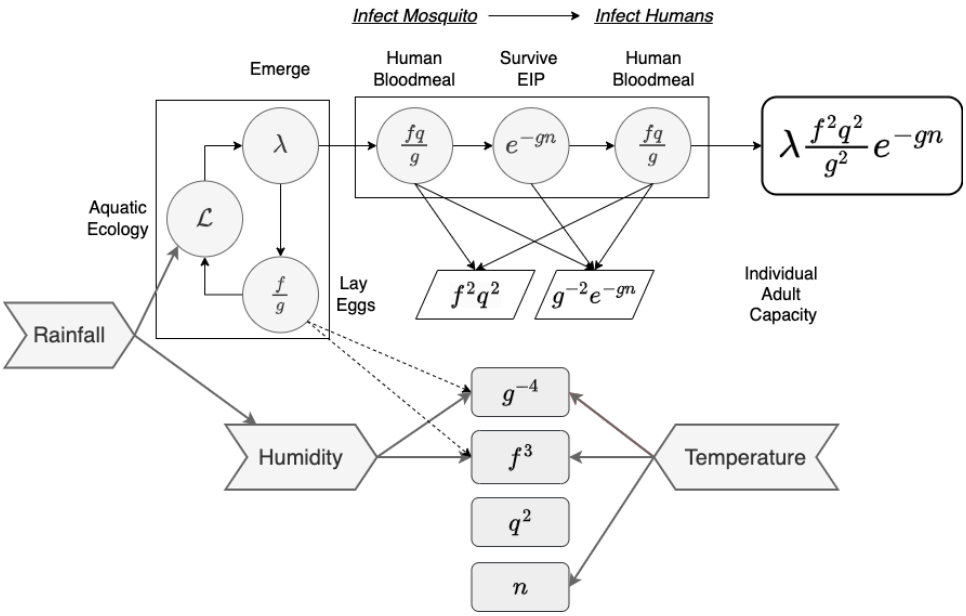

Fig 1. A diagram of 1) vectorial capacity as a summary of transmission potential (see Box #1) involving two parts: the emergence rate of mosquitoes, per human (λ); and the capacity of each individual mosquito to transmit parasites ($f^2q^2e^{-gn}/g^2$.), where f is the blood feeding rate, q is the fraction of human blood meals among all blood meals, and g is the instantaneous death rate 2) Some of the likely effects of weather; and 3) a ranking of parameters by the number of ways they affect transmission. The box around mosquito aquatic ecology ($\mathcal{L}$), including egg laying by adults and emergence, indicates an important source of variability in malaria transmission that is also affected by weather in ways that often depend on the local context.

per person per day [17,32]. This work suggested a basis for estimating VC from dEIR: the two main differences are the net infectiousness of humans (which could be extended to include vector competence), and mosquito superinfection [18,33].

The EIR and VC are vital determinants of malaria transmission intensity. The consequences of transmission are then explored in mathematical models that couple mosquito ecology, mosquito infection dynamics, and human malaria epidemiology, including infection and immunity. Such models have evolved substantially since Macdonald.

Early attempts to use the Ross-Macdonald model during field trials exposed its limitations [34]. Malaria models were subsequently extended to consider a variety of issues, including: immunity [35,36]; treatment with antimalarial drugs and chemoprotection [37]; heterogeneous transmission [38–40], and mosquito ecology [36]. Malaria models have become embedded in comprehensive individual-based simulation models [41,42]. These models have been used to guide malaria policies, including integrated malaria control.

Early studies on climate change and malaria employed computer simulation models, based on either simple extensions of the Ross-Macdonald model, or based on vectorial capacity (Fig 1, Box 1) [22,43–46], which itself is a great source of uncertainty [47].

Potential Transmission by Adults

If a given parameter is related to temperature over time, $T(t)$, then it can be written as a function of time and temperature. For example, the mosquito death rate g could be written as $g(T(t))$. Then a change in temperature would result in a change to the reproduction number R_0 by a factor Z_g, given by

$$Z_g = \frac{e^{-g(T(t))}}{g(T(t))^2} \times \frac{g(T(0))^2}{e^{-g(T(0))}}$$

We call Z_g the effect size on potential transmission associated with temperature-driven changes in mosquito survival. Using the formula for vectorial capacity, it is possible to compute additional changes in potential transmission associated with feeding rates, or the extrinsic incubation period (EIP, i.e. the mean time taken for malaria parasites to undergo development within the mosquito before they are infectious to humans), $n(T(t))$. The total effect size on potential transmission by adult mosquitoes would be a product of changes in each one of the bionomic parameters. Ideally, a total effect size would consider the effects of all changes caused by any relevant environmental variables. An advantage of these studies is that it is easy to communicate the results: an effect size of 1.5 can be reported as a 50% projected increase in potential transmission.

The estimated effects of environmental variables on mosquito entomological parameters are based on field studies or controlled experiments that have measured the effect of changes in bionomic parameters on adult mosquito behavior or demography, and parasite development rates while in the mosquito [48]. Temperature and humidity have been consistently identified as factors affecting malaria transmission by adult mosquito populations. When Macdonald wrote his synthesis in 1952, dozens of studies had already measured the EIP in relation to temperature [26, 49]. More recent data have looked in closer detail at the relationship between the EIP and temperature in *An. gambiae* and in *An. stephensi* [50]. Lab studies have examined effects of temperature and humidity on lab reared mosquitoes [51].

It is also useful to consider temperature through its interaction with humidity, and in particular relative humidity [51]. Relative humidity describes how much moisture the air holds relative to its maximum. The hotter the temperature, the more humidity the air can hold. There are strong associations between relative humidity and malaria transmission, and relative humidity also affects parasite and pathogen development within mosquitoes. Furthermore, relative humidity affects thermal performance curves of both mosquitoes and pathogens, leading to complex variation in the thermal optimum, limits, and operative range.

Despite disagreements on specific details, the studies agree on a set of core messages [52]: mosquito daily survival and blood feeding rates, as well as the EIP, all reach their optimum somewhere between 25 and 30 degrees. This optimum depends largely on relative humidity. Unlike temperature, mosquito survival and blood feeding rates tend to increase consistently with relative humidity. Later studies addressed the impact of other environmental variables on vectorial capacity [53].

Climate and Mosquito Populations

Since standing water serves as mosquito habitat, rainfall creates opportunities for (exponential) mosquito populations growth. Changing rainfall patterns may have large effects, but these are also highly unpredictable: short term rainfall is already unpredictable, and longer term climate projections for rainfall is even more so.

Further, the effects of rainfall on mosquito ecology are locally idiosyncratic, mediated by hydrology, terrestrial ecology, and many other factors. Therefore, the relationship between rainfall and transmission may be specific to each locality. And within a locality, rainfall can drive different patterns for each one of the local vector species populations.

The degree to which rainfall affects malaria transmission dynamics relates to the availability and quality of mosquito habitats. Any concavity that can be filled by rainfall or subterranean water flows can become a habitat for immature mosquitoes. However, increased rain will not necessarily lead to more habitat and thus more mosquitoes. First, the effects of rainfall are mediated by hydrology. Second, the effects of rainfall are affected by the temporal distribution, i.e. the times between successive rainfall events and their magnitude. Third, aquatic mosquito populations are affected by a large number of biotic interactions, including competition with other mosquitoes for resources. The effects of climate change are thus likely to be highly context dependent. In contrast to temperature, which varies smoothly between nearby locations, rainfall has high spatial variation between nearby localities [54].

Increased egg laying in a crowded habitat could delay development, and lower the number of adults emerging. While rainfall can increase the number and size of breeding sites, excess rainfall can wash out breeding sites [55]. Further, rainfall is a nonequilibrium relaxation process, in contrast to temperature.

Rainfall is a non-equilibrium relaxation process that is scale free and best described by a simple power law, characterizing the density and occurrence of rain events as well as drought periods. That is, rainfall events can be of enormous size in a very short period, followed by a prolonged drought, exhibiting complex and unpredictable fluctuations over time. Thus average rainfall is a misleading indicator of true dynamics. (Earthquakes are another example of a non-equilibrium relaxation process [56].)

In climate change, warmer oceans increase evaporation. Moisture-laden air moves over land or converges into a storm system, and intensifies precipitation. Rainfall is therefore expected to increase with climate change, but because precipitation dynamics are scale free (power-law distributed), increased rainfall is also expected to result in a larger incidence of both floods and droughts - each of which will reduce malaria. Furthermore, at a macroscopic scale, rainfall affects the availability of resources that mosquitoes need, making predictions based on climate change even more challenging.

Sensitivity, Variability, and Uncertainty

One approach to examining climate change's effects on adult mosquitoes and mosquito ecology has been mathematical – to examine the sensitivity or elasticity to parameters [57]. While many studies have emphasized the importance of adult mosquito survival and blood feeding, examination of the data suggests that most of the variability in malaria transmission intensity is related to mosquito ecology [58]. The primary data come from studies that have estimated the EIR. Notably, the EIR is computed as the product of two metrics: the human biting rate (HR), and the sporozoite rate (SR). The annual EIR ranges from practically zero to more than a thousand bites by infectious mosquitoes, per person, per year [59]. Most of the variability in the aEIR is attributed to differences in the HR, not the SR.

The mathematical approach that emphasizes sensitivity to parameters suggested that transmission should scale linearly with adult mosquito population density, but this does not account for mosquito ecology being highly non-linear. A single adult female mosquito can produce thousands of offspring over a few days, leading to

explosive bouts of malaria transmission.

Complexity, Scaling, and Malaria Metrics

To understand the effects of changes in potential transmission, mathematical models are needed to understand how malaria in humans responds to changes in malaria transmission intensity. Such models emphasize non-linearities and complexities in the relationship between exposure to the bites of infectious mosquitoes, the metrics used to measure parasite infections in populations, and malaria.

Rigorous studies have used models to compare patterns observed in studies of malaria, particularly those that have measured malaria in two or more ways at the same place and time. The relationship between the EIR and the average PR is strongly non-linear [60, 61]; the PR varies by age, sex, season, travel, and drug taking. While the EIR has been used as a measure of exposure, the association with the estimated force of infection (FoI), malaria incidence is also strongly non-linear and it also varies by age [62, 63]. Malaria immunity develops with age and exposure, and disease is concentrated in young children. Changing transmission intensity is expected to shift the burden to older ages, but the expected overall changes in burden are not simple linear responses to changing mosquito densities or to overall transmission intensity.

Such non-linearities give rise to great uncertainty regarding how one parameter affects another [63]. To put it another way, doubling the VC or EIR may not double mortality. Further, a second doubling of VC or EIR may not have the same effect as the first. These non-linearities also make it difficult to make credible projections about the changing burden of malaria, even in the ideal case where changes in expected transmission are certain and perfectly quantified.

Thresholds, Importations and Heterogeneity

Models and Macdonald's threshold condition have led to concerns that R_0 may increase above one due to climate change. While Macdonald's formula for R_0 was meant to describe a threshold condition for the establishment of endemic transmission, the predicted effect of crossing a threshold required for local transmission are dulled by malaria connectivity.

Malaria transmission can be sustained by malaria importation in mobile human populations. In models with spatial dynamics, threshold conditions are modified by heterogeneity, and transmission is dispersed widely by movement of humans and mosquitoes [64]. In most places where $R_0 < 1$, malaria is sustained through importation. Therefore crossing a threshold would not lead to a qualitative change.

Three important factors modifying threshold conditions are: i) the heterogeneous spatial distribution of mosquitoes; ii) the heterogeneous spatial distribution of humans, and iii) the heterogeneous temporal distribution of mosquito transmission potential. Consider a simple conceptual model for a time-varying reproduction number $R_0(t)$ that is piecewise constant (i.e. a step function), where seasonal endemic transmission is characterized by periods where $R_0(t) > 1$, and other periods where $R_0(t) \leq 1$. However, empirical malaria data is highly heterogeneous [58], and estimates of reproduction numbers exhibit roughness in their functional form over time [65] and space [3, 66].

Parasite populations are connected by movement of infected humans and mosquitoes [64]. So while Macdonald's formula $R_0 > 1$ is an important threshold for local malaria transmission in an isolated population, it

is best regarded as an informative pseudo-threshold condition [64, 67–70].

Predictions

Sub-Saharan Africa carries the majority of worldwide malaria burden, and so climate change's effects here are of particular interest. Despite uncertainty about the shape of $R_0(T)$, these effects are likely to be small, given that temperatures in Africa are already high enough to maximise spread. Indeed, the temperatures across much of sub-Saharan Africa are near optimum, where a change in temperature (T) has very little effect on potential transmission, insofar as rational guesses based on such extrapolations are even possible. Moreover, much of Africa is above the optimum, and so an increase in temperature would likely decrease malaria transmission.

To summarize, many studies of climate change and malaria have come to similar conclusions. First, since large fractions of Africa are already at or near optimal temperatures required for transmission, global warming will only sometimes increase and often decrease malaria. Second, the predicted effect sizes on potential transmission are small compared with the natural variability in malaria transmission. Third, the predicted effect sizes of climate on potential transmission are much smaller than the potential reductions in transmission that can be achieved through vector control. Fourth, the greatest changes in malaria transmission are likely to come through changes in rainfall [2].

Regression

A common approach to climate change and malaria has come through regression analyses [3,5,71,72]. Previous studies have used regression analyses to interpolate data across space and time to understand the drivers of change [5]. In this section, we perform a simple regression analysis. Using detailed satellite imagery from a range of different satellites, data can be collected on temperature and precipitation etc.Ċrucially, these data can be matched to the location and time (month) of the malaria observations, which we denote as y. Note these malaria observations were adjusted for age (2-10 years of age) and diagnostic type [73]. Let the resulting basis matrix of covariates be given by X. Loosely, a statistical model can be expressed using the following linear equation

$$y \sim \beta X^T + Z(x, y, t) \tag{1}$$

where β is a vector of coefficients and Z is a zero-mean Gaussian process with a space-time covariance function denoting the residuals.

Intuitively, this model attempts to explain *Pf*PR (*Plasmodium falciparum* parasite rate) as a function of environmental covariates X. A question then is how much of the data can be explained as a linear function of these environmental covariates? If the predictive power of this linear function is high, then an argument can be made that a simple relationship between temperature and rainfall and malaria prevalence exists. The Z term accounts for residual patterns that cannot be explained by the covariates, but it is structured and not simply random noise. Z does not tell us what causes this unobserved structure; it could be a wide range of factors, including nutrition, culture, mosquito ecology and dispersal, or human mobility and travel. We fit this model using Approximate Bayesian inference (the Laplace approximation [74]) such that the resultant model balances over and under fitting.

For a simple illustration, we consider two major climate factors: temperature suitability and average rainfall. Temperature suitability [75, 76] is a dynamic biological mathematical model that incorporates temperature dependency in the malaria transmission cycle, and then uses satellite data on temperature to estimate a suitability index. Rainfall is measured using CHIRPS (Climate Hazards Group InfraRed Precipitation with Station data), which estimates the average rainfall per month from rain gauge and satellite observations. It is then possible to match this temperature suitability index to the month and year of malaria observations, and to match rainfall to the month (averaged over years) to account for minor aspects of seasonality.

Outliers such as heatwaves, droughts and floods are not adequately captured using these data, but major variations in the spatial and temporal distribution of the environment factors relevant to the mosquito are. Using the large Malaria Atlas Project dataset on malaria parasite rate surveys, where each data point is a sample of the number of parasite positive individuals out of the total, it is possible to match temperature suitability to the specific latitude, longitude, rainfall, month and year (2001-2022) to the specific latitude, longitude, month, with years averaged due to data paucity. For consistency, data on parasite rates are adjusted for age [77] and diagnostic time [73].

Malaria parasite rate data are proportions, thus bounded between zero to one. To simplify regression, we transformed these data via the empirical logit into a Gaussian scale. Once again, we call these observations y. Consider three simple models, explaining parasite rate observations by: (i) a constant model $y_{x,y,t} \sim I$; (ii) a linear model with temperature suitability and rainfall $y \sim I + \beta^T X_{x,y,t}$, where $X_{x,y,t}$ is the temperature suitability index and rainfall at the matched locations and times of the malaria parasite rate observations; and (iii) a Gaussian process model $y \sim I + \beta^T X_{x,y,t} + Z(x, y, t)$, where again Z is a space-time random field that captures structure in the data. We evaluate model performance by computing the mean absolute percentage error and the correlation on the original untransformed parasite rate scale.

The mean absolute error of the first model that simply fitting a constant intercept to the data is 17% with a correlation of zero. The second model with temperature suitability does explain variation with a mean absolute error of 16.5% and a correlation of 0.2. The third Gaussian process model with temperature suitability yields a mean absolute error of 9% and a correlation of 0.8. This difference is substantial, and while this example is simplistic, and by no means rigorous, it reveals that the overwhelming bulk of the spatial distribution of malaria and its change in time over the past 2 decades is negligibly explained by temperature and its biological effect on the mosquito.

Figure 2 shows the predictions for the linear and Gaussian process model (i.e. the second and third models) alongside the raw data. We see that the model with just temperature suitability and rainfall is unable to capture the large variations in parasite rate, and creates predictions within a narrow band (Figure 2 top right) and the fine grained spatial variation only predicts a limited variation in $PfPr$ (Figure 2 bottom left). In contrast, the Gaussian process (Figure 2 bottom right) is an excellent fit to the data, both in terms of spatial pattern but also in predicting the full range of variation in $PfPr$. These results reinforce that, while climate plays a pivotal role in defining the population at risk, simple relationships are not the primary driver in the dynamic changes of infection.

Model code is available at https://github.com/dlaydon/MalariaClimateRegression.

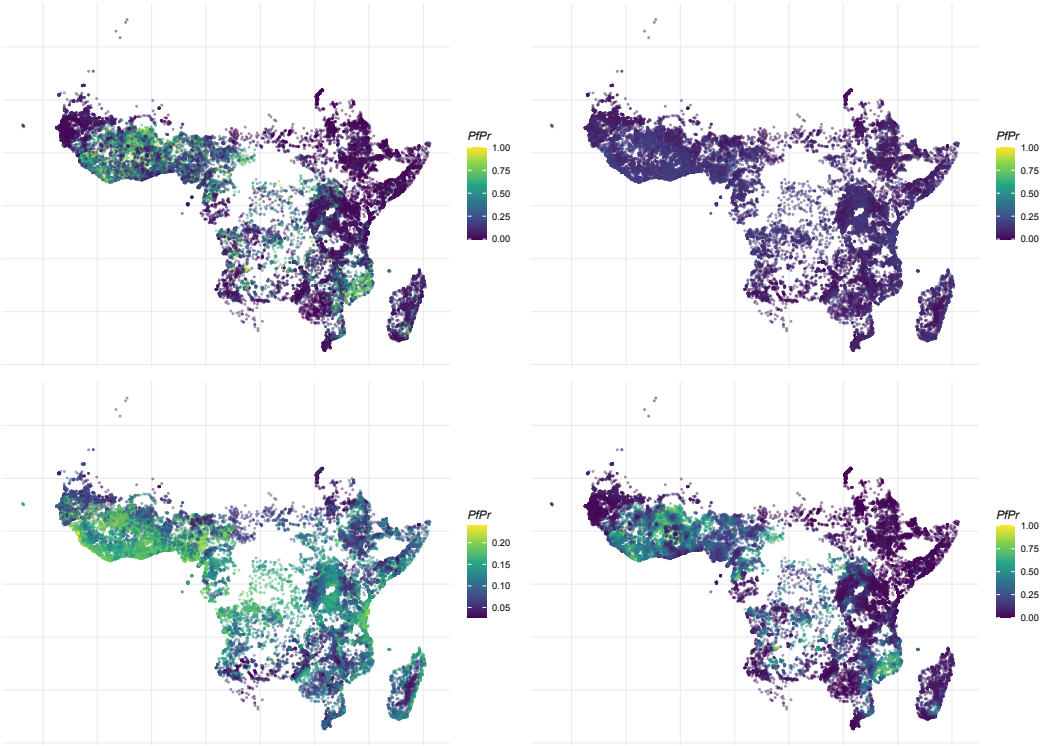

Fig 2. *P. falciparum* prevalence or parasite rate (*Pf*PR) as a function of environmental covariates. (top left) *Pf*PR from the Malaria Atlas Project Database. (top right) Linear model with temperature and rainfall with the colour scale ranging from 0-1 (bottom left) Linear model with temperature and rainfall with a restricted colour scale to show variation (bottom right) Gaussian process process with linear mean function of temperature and rainfall

Gaps in modelling

While substantial efforts have been made to model malaria dynamics over time [41], important gaps remain. In most places, malaria transmission must be understood as a changing baseline that has been modified by malaria control. While many studies have looked at climate and its effects on baseline malaria, and many others have examined vector control and malaria, few have examined both climate and vector control and their interactions.

In developing a research agenda for climate and malaria, it is thus critical to develop an understanding of climate and malaria that does not ignore the role of malaria control and other exogeneous variables affecting the baseline and confound efforts to understand malaria in context. While many of these factors are easy to list, such as demography, changing housing quality, evolution of drug and insecticide resistance, economics, politics and logistics, any analysis including these from the past is hampered by a lack of consistently available data.

Since 2000, malaria has been profoundly changed by mass distribution of long-lasting insecticide treated nets, widespread access to artemisinin combination therapies (ACTs), and local indoor residual spraying [5]. Understanding the effects of vector control is hindered by a lack of knowledge of local vector species mixes, vector ecology, and insecticide resistance. Understanding the effects of malaria control from health systems must consider antimalarial drugs, evolution of drug resistance, and changing drug policies.

Data on socio-economic factors, climate, local environmental conditions are needed to understand the effects of landscape and topography on malaria transmission within any given region. Human mobility patterns, land

use changes, migration effects as well as exposure to malaria vectors are usually used in malaria modelling. However, data for all of these factors is difficult to acquire.

For example, military conflicts can drastically and quickly change population numbers, but acquiring exact estimates is almost impossible. Even in periods of relative stability, limited infrastructure can mean that population numbers are still difficult to extrapolate. For example, the last official census in the Democratic Republic of Congo was held in 1984. Methods for estimating census data will continue to improve and contribute greatly in this field.

Drug resistance

Drug resistance profoundly influences malaria, independently of climate change. The low cost, high demand, and widespread use of antimalarial drugs have led to strong selection for drug resistant parasite strains. Further, drug resistance can arise with relatively modest molecular change. One example is the small amount of change needed for chloroquine resistance; four amino acid substitutions, in a single gene called *pfcrt* (*P. falciparum* chloroquine resistance transporter) confer resistance to chloroquine-based antimalarial drugs [78].

Perhaps counterintuitively, drug resistant strains are inferior in their natural environment, given that they involve relatively rare combinations of molecular changes [79]. This inferiority of drug resistant strains means that reduced use of antimalarial drugs leads to the loss of drug resistance after selection for resistance by drug use declines.

Since drug resistance is a crucial factor in driving malaria prevalence, limiting antimalarial drugs to symptomatic cases will maximize their efficacy [80]. The misuse of low-cost antimalarial drugs will, conversely, increase the risk of drug resistance. Whereas development of new drugs can decrease prevalence in the medium term. The major impact of drug development and resistance on prevalence has been evident for both chloroquine in the second half of the 20th century and artemisinin-based combination therapies in the last two decades [81].

There is a hypothetical link between antimalarial drug use, evolution of resistance, and climate change, where the climate mediates the logistics and accessibility for drug administration [82]. Alternatively, novel climatic conditions might tend to disproportionately benefit the emergence of drug resistant strains, although the biological mechanism of this has not been described. Genetic surveillance will ellucidate the immunological and environmental conditions that benefit drug resistant strains. More immediately, genomic surveillance can play an important role for optimising drug administration, by helping map the emergence and spread of drug resistant strains [80].

Conclusion

Our work raises several concerns about climate change and malaria research, regarding its accuracy, strength of evidence, and at times insufficient consideration of the complexity of the processes involved. Effect sizes due to temperature are easily mimed or masked by other environmental factors, vector control, anti-malarial drug use, healthcare systems, land use changes, economic development, and drug and insecticide resistance. Given the complexity of malaria epidemiology and transmission, concerns about global warming and climate change must be evaluated in context, as part of multi-factorial studies that provide accurate assessments of causation and estimates of effect sizes. Decades after concerns were first raised about the effects of climate and malaria, the

questions to be addressed today are: how much should research on climate change and malaria be prioritized, and to what end?

First, our analysis suggests that the risks posed by climate change on malaria incidence have been overstated [3]. While compelling analyses demonstrate that temperature affects several aspects of transmission, a focus on sensitivity to parameters has diverted attention away from effect sizes and other factors affecting malaria. If, instead, effect sizes are computed by propagating the expected changes in temperature, they are much smaller compared the observed variability in transmission intensity across Africa. Given current ambient temperatures in Africa, increasing temperatures are as likely to reduce transmission as increase it.

Empirical data emphasize the importance of rainfall on both malaria, and on interactions between temperature and humidity, and not merely temperature alone. Analyses of the long-term longitudinal studies from Africa have so far not found strong evidence for large effects of temperature on malaria. While analysis of long time series describing malaria and climate in some settings could help, the few studies that have been done came to different conclusions, and were ultimately undermined by the failure to consider the evolution of chloroquine resistance in sub-Saharan Africa during the 1990s and resulting changes in drug policies.

Advocacy around climate and malaria has motivated studies that attribute changing malaria mortality to changing climate. The basis for making projections about climate and malaria, and thus likely changes in malaria mortality, has largely focused on climate without considering other potential causes. This basic methodological flaw undermines the validity of the studies. The robustness of the conclusion that climate change will increase malaria transmission is challenged by the dramatic differences between the projections given differing scenarios, as well as the vastly different effect sizes reported between studies.

While some changes in transmission due to changing temperatures are probable, the changes attributable to climate change are highly spatially heterogeneous, with malaria likely to increase in some locations and decline in others. The evidence suggests that studies of climate change and malaria must be understood through its effects on mosquito ecology.

In sub-Saharan Africa, malaria remains a leading cause of death and suffering, stifling economic development. Malaria is often called a disease of poverty because is highly prevalent in poor, rural African populations. Wealthy individuals, who tend to also be better educated, can afford to protect themselves against malaria, but those same interventions are not affordable or accessible to the poor. Meanwhile, the same populations who are at greatest risk of malaria are also most likely to be affected by climate change in other ways. Enhanced malaria control would stimulate economic growth in Africa and make the most vulnerable populations resilient to the effects of climate change.

While climate could worsen malaria, we are not hapless victims of a changing climate. Effective ways of managing the effects of climate change on malaria are already available, and existing methods of malaria control could be the most effective way of protecting poor populations.

Box 1: Vectorial Capacity

Macdonald's R_0 formula was based on the sporozoite rate (SR) and the human biting rate (HR) [17, 32], which is now called the entomological inoculation rate (EIR).

Vectorial capacity (VC) includes three parameters: the blood feeding rate (f); the fraction of all blood meals that are human blood meals (q); and instantaneous death rate (g). Together, these terms describe the expected number of human bloodmeals a mosquito would take over its lifetime ($S = fq/g$). A single parameter describes parasites in mosquitoes, called the extrinsic incubation period (EIP, n days), defined as the number of days required for malaria parasites to develop. To transmit, a mosquito must survive through the EIP (with probability $P = e^{-gn}$). The formula for VC includes one parameter describing mosquito ecology: the emergence rate of mosquitoes from aquatic habitats, per human (λ). These parameters are combined into a formula for vectorial capacity.

$$V = \lambda \frac{f^2 q^2}{g^2} e^{-gn} = \lambda S^2 P$$

The right hand side denotes parasite transmission by mosquitoes: after emerging (λ), a mosquito must blood feed on a human to become infected (S), then survive through the EIP (with probability P); and then bite other humans to transmit (S). This is equivalent to Macdonald's formula, after a change in notation [58]. The formula has been used to understand parameters that could have the greatest influence on transmission [32, 47].

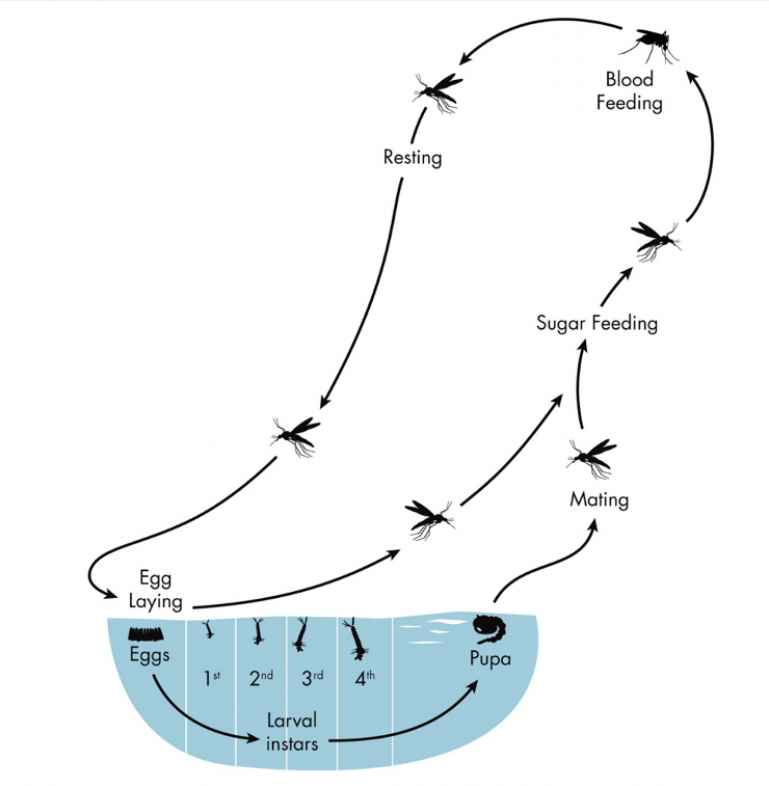

Fig 3. The mosquito life cycle includes immature aquatic stages and a volant adult. Female mosquitoes lay eggs in water bodies. Eggs hatch within a few days to months. Larvae live in water and develop into pupae in as few as 5 days. Pupae continue to live in water and develop into flying adult mosquitoes that leave the water in 2-3 days. Adult mosquitoes meanwhile fly in search of resources, including vertebrate hosts to blood feed, sugar sources for sugar, and aquatic habitats to lay eggs.

Box 2: Mosquito Ecology

Mosquitoes have seven distinct life stages: eggs, four larval instars, pupae, and adults (Figure 3). Adults lay eggs in aquatic habitats. After hatching and developing in water through pupation, adults emerge as adults that mate and sugar feed. Female mosquitoes (but not males) also blood feed; the protein and nutrients in blood are used to make eggs. It is the cycle of blood feeding, egg laying, and sugar feeding by adult females that is of greatest interest sets the stage for mosquito ecology and malaria parasite transmission. Mosquitoes, like most insects, are poikilothermic – their internal temperature depends on the surrounding environment. Mosquito activities and many of the resources they require to complete their life cycle are also affected by weather and climate, including vertebrate animals for blood, sugar, vegetation and resting habitats, and aquatic habitats.

Acknowledgments

DJL acknowledges funding from the Wellcome Trust for the Vaccine Impact Modelling Consortium (VIMC) Climate Change Research Programme (grant ID: 226727_Z_22_Z), as well as funding from the European Commission Horizon Europe OBCT project (No. 101080250). DJL, SB acknowledge funding from the MRC Centre for Global Infectious Disease Analysis (reference MR/X020258/1), funded by the UK Medical Research Council (MRC). This UK funded award is carried out in the frame of the Global Health EDCTP3 Joint Undertaking. DLS and JO acknowledge funding from a grant from the Bill and Melinda Gates Foundation (INV 030600). DLS was also supported by a grant from the National Institute of Allergies and Infectious Diseases (R01 AI163398). SB is funded by the National Institute for Health and Care Research (NIHR) Health Protection Research Unit in Modelling and Health Economics, a partnership between the UK Health Security Agency, Imperial College London and LSHTM (grant code NIHR200908). Disclaimer: 'The views expressed are those of the author(s) and not necessarily those of the NIHR, UK Health Security Agency or the Department of Health and Social Care.'. DAD acknowledges support from the Novo Nordisk Foundation via the Emerging Data Science Investigator award (NNF23OC0084647). SB acknowledges support from the Novo Nordisk Foundation via The Novo Nordisk Young Investigator Award (NNF20OC0059309), which also funds KC. SB acknowledges the Danish National Research Foundation (DNRF160) through the chair grant which also supports MPK. SB acknowledges support from The Eric and Wendy Schmidt Fund For Strategic Innovation via the Schmidt Polymath Award (G-22-63345).

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