

SUPPLEMENTARY MATERIALS

“Climate change could shift disease burden from malaria to arboviruses in Africa”

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METHODS SUMMARY

Temperature-dependent R_0 models

In published work (1–3), we have estimated the relative temperature suitability for mosquito-borne disease transmission as temperature-dependent R_0 , the basic reproduction number. This metric, adapted from previously published models (4,5) to include effects of temperature on mosquito demography, biting, and transmission parameters, is expressed as:

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

where N is the human population size, r is the human recovery rate, and (T) indicates the temperature-sensitive mosquito or parasite traits: biting rate (a), vector transmission probability given infection (b), vector infection probability given parasite exposure (c), vector daily mortality rate (μ , estimated as 1/lifespan in days), parasite extrinsic incubation rate in the vector (PDR , in 1/days), eggs laid per female mosquito per day (EFD), and mosquito development rate from egg to adult (MDR , in 1/days). We estimated thermal performance curves for each temperature-sensitive trait from published laboratory studies that measured traits at three or more constant temperatures, both for *Anopheles* spp. mosquitoes and *Plasmodium falciparum* parasites (1,3) and for *Aedes aegypti* mosquitoes and dengue, chikungunya, and Zika viruses (2,6). We rescaled the resulting $R_0(T)$ models to range from zero to one as a metric of relative suitability based on temperature. This metric incorporates the multiple, nonlinear effects of temperature on transmission, but does not account for variation in human population size, susceptibility, vector habitat availability, vector control, or other factors that influence the absolute magnitude of R_0 . We validated the $R_0(T)$ models using field data on entomological inoculation rate—the number

of infectious mosquitoes per person per year—across Africa over 30 years for malaria (1) and on human dengue, chikungunya, and Zika infections across countries in the Americas (2). In both cases, the independent field data strongly supported the mechanistically predicted, nonlinear effects of temperature on transmission (Fig. 1 in the main text).

Arbovirus and vector surveys in Kenya

Arbovirus surveys

Children (less than 18 years of age) with undifferentiated febrile illness attending outpatient care in one of the four study locations (Mbaka Oromo Health Centre in Chulaimbo, Obama Children's Hospital in Kisumu, Msambweni District Hospital in Msambweni, and Ukunda/Diani Health Center in Ukunda) between 2014 and 2018 were enrolled in this study, as detailed elsewhere (7,8). Comprehensive clinical and demographic data were collected in addition to phlebotomy at the initial visit. Conventional PCR or targeted, multiplexed, rRT-PCR (9) (when available) was performed to evaluate for dengue and chikungunya viremia. Patients were treated based on Kenyan Ministry of Health algorithms by local health officers.

Vector surveys

Ovitrap were placed inside and outside approximately 20 houses per site per month for three to six days (mean = four days) each month between 2014 and 2018 as detailed elsewhere (10). Eggs laid in each ovitrap were taken to the lab and reared to adulthood for taxonomic identification. Mean *Aedes aegypti* eggs per house per month was calculated as the total number of eggs collected divided by the total number of houses sampled for each month and year, and then averaged by month across all years.

Maps of projected change in suitability for transmission

We created maps of current and future climate suitability for malaria and dengue transmission to illustrate one of many possible future scenarios of climate, human population change, and disease risk. The purpose of the maps is to show the consequences of increasing temperatures for transmission suitability across Africa, rather than to specifically predict future disease burden, which additionally depends on many other factors including rainfall, water storage practices, human population size, mobility, and prior exposure history.

The maps illustrate the predictions of mechanistic models (Fig. 1 in the main text) of temperature suitability for transmission under current and simulated future climates (Fig. 2 in the main text). These maps do not attempt to capture other social and environmental factors that affect transmission, although they do include an aridity mask and human population density, as described below. While there are many ecological niche models (ENMs) available to describe malaria (e.g., (11,12)) and dengue (e.g., (13,14)) suitability as a function of multiple environmental and human factors, these models rely on current distributions of disease to infer possible future responses to climate change. ENMs therefore may not accurately capture nonlinear thermal responses arising in novel temperature regimes, and may inaccurately describe temperature – transmission relationships because of strong geographic signatures of non-climate drivers such as economic development and the success of disease control programs (15,16). Our goal is to show the direct, nonlinear effects of temperature changes on transmission potential, not to predict all future changes in disease burden. For this reason, we focus on mechanistic model

predictions that accurately capture nonlinear temperature responses measured in the laboratory and observed in the field.

Climate data

Current mean monthly temperature data were derived from the WorldClim dataset (www.worldclim.org) (17), and clipped to the political boundaries of Africa, using GADM shapefiles (18). For the future climate scenarios, we selected a general circulation model (GCM) among the most commonly used by studies forecasting species distributional shifts: the Hadley GCM HadGEM2-ES. We chose the representative concentration pathway (RCP) 8.5, the worst-case, business-as-usual fossil fuel emissions scenario with no mitigation strategy in place. The scenarios are denoted by numbers (e.g., RCP 8.5) corresponding to increased radiation in W/m^2 by the year 2100. We chose the WorldClim data as our current temperature data because they have been downscaled and bias-corrected so that they are directly comparable to GCM outputs, ensuring that differences between current and future projections are due to predicted temperature changes rather than methodological differences.

Climate model output data for the RCP 8.5 scenario were acquired from the research program on Climate Change, Agriculture, and Food Security (CCAFS) web portal (19), part of the Consultative Group for International Agricultural Research (CGIAR). We used the model outputs created using the delta downscaling method, from the IPCC AR5.

Population Data

To describe the human population at risk, comparable between current and future climate scenarios, we used population count data from the Gridded Population of the World, version 4 (GPW4) (20), predicted for the year 2015, following methods described in (21). This data product was interpolated from the most recently available census data at the smallest administrative unit globally but was otherwise minimally modeled. We used 30 arc-second gridded population data aggregated to match the climate scenarios (5-minute resolution), from the 2015 population count dataset. In analyses of future climate scenarios, we kept population data constant to ensure that mapped results were not affected by arbitrary assumptions about demographic projections into the future.

Aridity Mask

Following the methods described in (22), we excluded areas too arid for anopheline mosquito life-cycles, using long-term remotely sensed vegetation data. We used long term average monthly Normalized Difference Vegetation Index (NDVI) data to create an exclusion criterion as a function of the number of months below a threshold within a year (*sensu* (23)). We used the NDVI-based aridity mask derived in our previously published work for both the malaria and dengue maps (22). We did not develop a separate *Aedes* aridity mask because these mosquitoes are able to breed in water containers as small as a bottle cap, and are well adapted to urban environments, so their breeding habitat is disconnected from larger moisture patterns and more closely governed by human water use behavior around the domestic environment. Thus, we do not anticipate large scale predictive climate products to capture this relationship with breeding habitat, and rather assume it is better described by human population distributions, detailed in the previous section.

Mapping

The upper and lower bounds of the temperature range for relative $R_0 > 0.5$ on the median posterior probability curve for each of the malaria (3) and *Aedes aegypti* dengue (2) models was projected onto the climate data using the ‘raster’ package in R version 3.1.1 (24). The output of number of temperature-suitable months per year were rescaled to range from 0-1, multiplied by $\log(1 + \text{population density})$. The anopheline aridity mask was overlaid, and the resulting maps plotted in R (Fig. 2A-F in the main text).

Because we are working with relative R_0 rather than absolute R_0 —for which the magnitude varies according to many location-specific factors—we cannot directly specify the temperature at which $R_0 = 1$ as a threshold for transmission. Instead, we define high temperature suitability based on the (arbitrary) threshold of relative $R_0 > 0.5$, and count the number of months per year in which each location has average temperatures within this “high risk” range. Because the relationship between R_0 and incidence or prevalence is nonlinear, and saturates as absolute R_0 begins to greatly exceed 1 (25,26), we do not expect linear increases in relative R_0 between 0.5 and 1 to translate into linear increases in prevalence or incidence. To be conservative, we assume that the greatest effects of temperature on incidence will occur at marginal temperatures where absolute R_0 goes from near zero to just above 1, rather than at highly suitable temperatures near the optimum. Therefore, we arbitrarily set relative $R_0 = 0.5$ as a threshold for considering temperatures to be highly suitable, while acknowledging that in some settings where overall transmission potential is relatively low (i.e., maximum absolute $R_0 \sim 1$), small changes in temperature near the optimum could have a large effect on incidence. Similar approaches that

use $R_0 = 0$ as the critical threshold produce similar results (21,22), though this alternative assumption captures all locations in which transmission is theoretically possible, rather than locations where temperature suitability is high, as we aimed to capture here. Our aim was to qualitatively illustrate the type of temperature-driven shifts in disease transmission we might expect under climate change, rather than to make a specific quantitative and geospatial prediction.

References Cited in Supplementary Materials

1. Mordecai EA, Paaijmans KP, Johnson LR, Balzer C, Ben-Horin T, de Moor E, et al. Optimal temperature for malaria transmission is dramatically lower than previously predicted. *Ecol Lett.* 2013;16(1):22–30.
2. Mordecai EA, Cohen JM, Evans MV, Gudapati P, Johnson LR, Lippi CA, et al. Detecting the impact of temperature on transmission of Zika, dengue, and chikungunya using mechanistic models. *PLoS Negl Trop Dis.* 2017 Apr 27;11(4):e0005568.
3. Johnson LR, Ben-Horin T, Lafferty KD, McNally A, Mordecai E, Paaijmans KP, et al. Understanding uncertainty in temperature effects on vector-borne disease: a Bayesian approach. *Ecology.* 2015 Jan 1;96(1):203–13.
4. Parham P, Michael E. Modeling the Effects of Weather and Climate Change on Malaria Transmission. *Environ Health Perspect.* 2010;118(5):620–6.
5. Dietz K. The estimation of the basic reproduction number for infectious diseases. *Stat Methods Med Res.* 1993 Mar 1;2(1):23–41.
6. Tesla B, Demakovskiy LR, Mordecai EA, Ryan SJ, Bonds MH, Ngonghala CN, et al. Temperature drives Zika virus transmission: evidence from empirical and mathematical models. *Proc R Soc B.* 2018 Aug 15;285(1884):20180795.
7. Vu DM, Mutai N, Heath CJ, Vulule JM, Mutuku FM, Ndenga BA, et al. Unrecognized Dengue Virus Infections in Children, Western Kenya, 2014–2015. *Emerg Infect Dis.* 2017 Nov;23(11):1915–7.
8. Hortion J, Mutuku FM, Eyherabide AL, Vu DM, Boothroyd DB, Grossi-Soyster EN, et al. Acute Flavivirus and Alphavirus Infections among Children in Two Different Areas of Kenya, 2015. *Am J Trop Med Hyg.* 2019 Jan 9;100(1):170–3.
9. Waggoner JJ, Gresh L, Mohamed-Hadley A, Ballesteros G, Davila MJV, Tellez Y, et al. Single-Reaction Multiplex Reverse Transcription PCR for Detection of Zika, Chikungunya, and Dengue Viruses. *Emerg Infect Dis.* 2016 Jul;22(7):1295–7.
10. Ngugi HN, Mutuku FM, Ndenga BA, Musunzaji PS, Mbakaya JO, Aswani P, et al. Characterization and productivity profiles of *Aedes aegypti* (L.) breeding habitats across rural and urban landscapes in western and coastal Kenya. *Parasit Vectors.* 2017 Jul 12;10(1):331.
11. Foley DH, Linton Y-M, Ruiz-Lopez JF, Conn JE, Sallum MAM, Póvoa MM, et al. Geographic distribution, evolution, and disease importance of species within the Neotropical *Anopheles albitarsis* Group (Diptera, Culicidae). *J Vector Ecol.* 2014;39(1):168–81.

12. Hundessa S, Williams G, Li S, Liu DL, Cao W, Ren H, et al. Projecting potential spatial and temporal changes in the distribution of *Plasmodium vivax* and *Plasmodium falciparum* malaria in China with climate change. *Sci Total Environ*. 2018 Jun 15;627:1285–93.
13. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. *Nature*. 2013 Apr 25;496(7446):504–7.
14. Mweya CN, Kimera SI, Stanley G, Misinzo G, Mboera LEG. Climate Change Influences Potential Distribution of Infected *Aedes aegypti* Co-Occurrence with Dengue Epidemics Risk Areas in Tanzania. *PLOS ONE*. 2016 Sep 28;11(9):e0162649.
15. Gething PW, Smith DL, Patil AP, Tatem AJ, Snow RW, Hay SI. Climate change and the global malaria recession. *Nature*. 2010 May 20;465(7296):342–5.
16. Bhatt S, Weiss DJ, Cameron E, Bisanzio D, Mappin B, Dalrymple U, et al. The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015. *Nature*. 2015 Sep 16;526:207–11.
17. Hijmans RJ, Cameron SE, Parra JL, Jones PG, Jarvis A. Very high resolution interpolated climate surfaces for global land areas. *Int J Climatol*. 2005;25(15):1965–78.
18. Global Administrative Areas. GADM database of Global Administrative Areas [Internet]. 2015 [cited 2019 Mar 9]. Available from: <https://gadm.org/>
19. CCAFS. Spatial Downscaling Data [Internet]. [cited 2019 Mar 13]. Available from: http://ccafs-climate.org/data_spatial_downscaling/
20. Center for International Earth Science Information Network (CIESIN). Gridded Population of the World, Version 4 (GPWv4): Population Count Adjusted to Match 2015 Revision of UN WPP Country Totals [Internet]. Palisades, NY: NASA Socioeconomic Data and Applications Center (SEDAC); 2016. Available from: <https://doi.org/10.7927/H4SF2T42>
21. Ryan SJ, Carlson CJ, Mordecai EA, Johnson LR. Global expansion and redistribution of *Aedes*-borne virus transmission risk with climate change. *PLoS Negl Trop Dis*. 2019;in press.
22. Ryan SJ, McNally A, Johnson LR, Mordecai EA, Ben-Horin T, Paaijmans K, et al. Mapping Physiological Suitability Limits for Malaria in Africa Under Climate Change. *Vector-Borne Zoonotic Dis*. 2015 Nov 18;15(12):718–25.
23. Suzuki R, Xu J, Motoya K. Global analyses of satellite-derived vegetation index related to climatological wetness and warmth. *Int J Climatol*. 2006;26(4):425–38.
24. Hijmans RJ, Etten J van, Sumner M, Cheng J, Bevan A, Bivand R, et al. raster: Geographic Data Analysis and Modeling [Internet]. 2019 [cited 2019 Mar 9]. Available from: <https://CRAN.R-project.org/package=raster>

25. Huber JH, Childs ML, Caldwell JM, Mordecai EA. Seasonal temperature variation influences climate suitability for dengue, chikungunya, and Zika transmission. *PLoS Negl Trop Dis*. 2018 May 10;12(5):e0006451.
26. Smith DL, McKenzie FE, Snow RW, Hay SI. Revisiting the basic reproductive number for malaria and its implications for malaria control. *PLoS Biol*. 2007;5(3):e42.