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A Malaria Ecology Index Predicted Spatial and Temporal Variation of Malaria Burden and Efficacy of Antimalarial Interventions Based on African Serological Data.

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A malaria ecology index predicted spatial and temporal variation of malaria burden and efficacy of antimalarial interventions based on African serological data

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Abstract

Reducing the global health burden of malaria is complicated by weak reporting systems for infectious diseases and a paucity of vital statistics registration. This limits our ability to predict changes in malaria health burden intensity, target antimalarial resources where needed, and identify malaria impacts in retrospective data. We refined and deployed a temporally and spatially varying Malaria Ecology Index (MEI) incorporating climatological and ecological data to estimate malaria transmission strength and validate it against cross-sectional serology data from 39,875 children from seven sub-Saharan African countries. The MEI is strongly associated with malaria burden; a one standard deviation higher MEI is associated with a 50-117% increase in malaria risk and a 3-5 g/dL lower level of Hg. Results show that the relationship between malaria ecology and disease burden is attenuated with sufficient coverage of insecticide treated nets (ITNs) or indoor residual spraying (IRS). Having both ITNs and IRS reduce the added risk from adverse malaria ecology conditions by half. Readily available climate and ecology data can be used to estimate the spatial and temporal variation in malaria disease burden, providing a feasible alternative to direct surveillance. This will help target resources for malaria programs in the absence of national coverage of active case detection systems, and facilitate malaria research using retrospective health data.

1. Introduction

Malaria remains the fourth leading cause of death for children under five in low income countries, and despite an aggressive increase in resources for malaria control still infects

approximately 200 million people every year, killing an estimated 438,000 in 2015.[1,2] In addition to the direct mortality and morbidity burden of malaria, recent research has broadened our understanding of malaria's full social and economic costs, including reduced adult productivity, higher poverty, and enduring effects on children's cognition, school absenteeism and literacy.[3-6]

Disease surveillance is the backbone of public health systems. Ideally, researchers and public health agencies would have precise measurements of malaria burden using case data; however, much of the developing world continues to have weak reporting systems for infectious disease and often lacks vital statistics registration.[7,8] This is particularly true in sub-Saharan Africa, which shoulders the largest malaria burden. At a global level only an estimated 10% of cases are detected, and different methods have led to large discrepancies in estimates of the global malaria burden.[2,7,9-12] Studies have begun using high spatial resolution data to model parasitaemia and the effects of malaria interventions, as well as to estimate placental and child infection risk in the absence of reliable case data.[13-15] Social scientists have proxied for malaria burden using the ecological suitability for disease transmission, while epidemiologists have employed these ecological models to quantify the effects of climate change on malaria transmission.[5,16-19]

This paper constructs and validates a new time-varying version of a Malaria Ecology Index (MEI) of transmission strength as an alternative measure based on readily observed variables that can be employed when direct disease counts are not feasible. Many of the places where surveillance is difficult are the same places where public health challenges are greatest. We evaluated the usefulness of this updated MEI in contexts without case data by testing its performance against children's serology from all available geolocated data from the Malaria

Indicator Survey (MIS) of the Demographic and Health Surveys (DHS), a sample of 39,875 children from 18 surveys taken in seven sub-Saharan African countries. Results demonstrate that the MEI is strongly associated with malaria infection and hemoglobin at time of survey. We leveraged the large sample size and variation in our data to show that this predictive relationship remains in place when comparing only sites within the same country, and even within the same subnational administrative region. We further show that the relationship between disease ecology and disease burden is attenuated by sufficient coverage of both insecticide treated nets (ITNs) and indoor residual spraying (IRS), highlighting how public health efforts can break the link between environment and disease.

2 Methods

2.1 Malaria Ecology Index

We refined a previously published Malaria Ecology Index (MEI) that combines retrospective climatological and ecological data with models of the disease's epidemiological dynamics, in particular the interaction of climate with the dominant properties of local *Anopheles* species determining vectorial capacity, to construct a spatially-and temporally-varying measure of the stability of malaria transmission.[20] The index was constructed for every month on a 0.5 degree spatial grid (around 50km at the equator), and has been shown to vary with malaria incidence and mortality in aggregate data.[17]

Previous work identified a dominant *Anopheles* species for each spatial zone, and for each month.[20] For vectors that breed mainly in temporary water, a minimum precipitation threshold of 10mm per month, lagged one month, was used to judge when the vector would be present in the site during a given month. The MEI formula incorporates the effects of ambient temperature on the force of transmission, as expressed through the length of the extrinsic

incubation period, excluding terms for mosquito abundance, vector competence, or recovery rate for infected people:

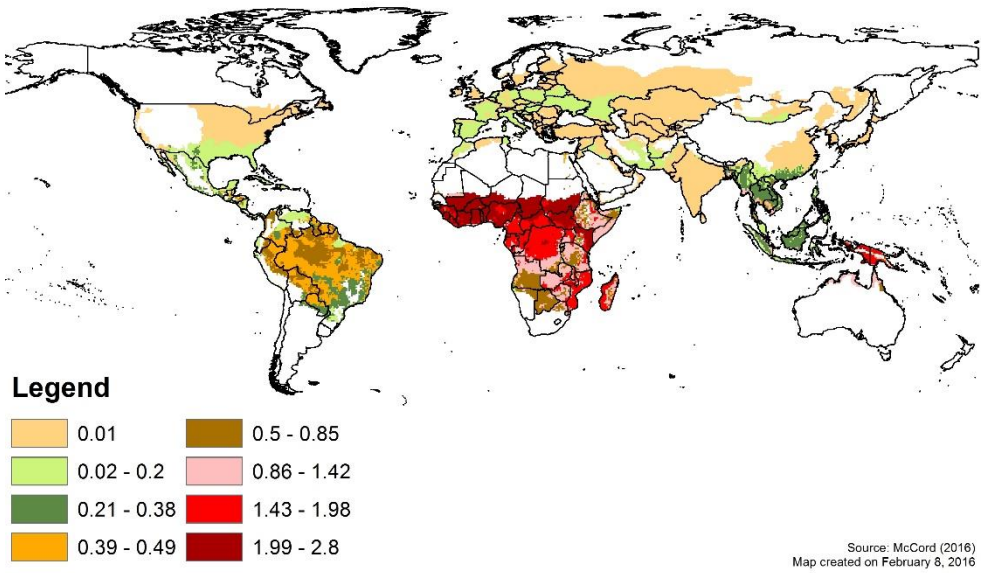
$$MEI_{i,m} = \frac{a_{i,m}^2 p_{i,m}^r}{-\ln p_{i,m}} \qquad (1)$$

In the equation above, the malaria ecology index in grid cell *i* in month *m* is a function of the proportion of bites *a* that the dominant vector in that location and month exacts on humans, the daily survival rate *p* of the vector, and the sporogony rate *r* in days. We modified the original index to incorporate pernicious effects of higher temperatures on parasite development.[17] The optimal rates of development for *P. falciparum* and *P. vivax* occur at 23-24ºC, whereas the development rates begin to decrease beyond 31ºC for *P. falciparum* and 29.8ºC for *P. vivax*. The new MEI differs from previous versions in that it uses the following equation for sporogony as a function of temperature:[21]

$$r = \frac{0.06044 \frac{T}{296.65} exp\left[\frac{17545}{1.987}\left(\frac{1}{296.65} - \frac{1}{T}\right)\right]}{1 + exp\left[\frac{-142843}{1.987}\left(\frac{1}{288.85} - \frac{1}{T}\right)\right] + exp\left[\frac{110980}{1.987}\left(\frac{1}{306.90} - \frac{1}{T}\right)\right]} \qquad (2)$$

The average MEI for 2006-2014 is mapped in Figure 1, constructed using monthly precipitation and temperature data from the University of Delaware.[22]

Figure 1:1980-2010 Average Malaria Ecology Index



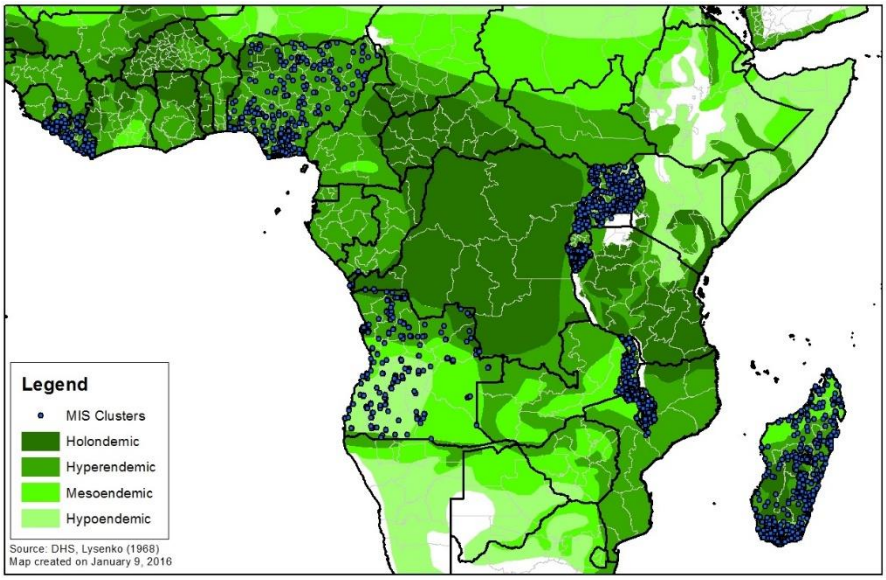
2.2 The Malaria Indicator Surveys

The MIS are implemented in a subset of malarious countries in the DHS.[i] Interview targets are women between the ages of 15 and 49 and their children, selected randomly using stratified sampling to be representative at the national level. The MIS collects malaria-relevant data such finger prick biomarker testing for children's malaria (using Rapid Diagnostic Testing in the field and microscopy in lab) and anemia (using the HemoCue analyzer), ownership and use of ITNs, and presence of IRS. In order to match each child to local malaria ecology, we limited our analysis to the MIS survey clusters that are geolocated, as mapped in Appendix Figure 2. Our data therefore include 18 surveys that cover Angola, Burundi, Liberia, Madagascar, Malawi, Nigeria and Uganda, with each country receiving between one and four surveys between 2006-2015. Excluding those not tested for malaria, our data includes 39,875 children in 1,943

[i] DHS data and documentation are available at http://www.dhsprogram.com/data

sampling clusters spread across 62 administrative units. Of these children, 28.8% tested positive for malaria and 57.7% had some level of anemia (Hb below 11.0 g/dL). 47.3% of the children were sleeping under an ITN, and 19·8% of the homes had been sprayed with IRS over the last 12 months.

Figure 2: Malaria Indicator Survey Cluster Locations



Map shows distribution of MIS cluster locations in study sample, as well as the malaria endemicity level according to Lysenko (1968).

2.3 Study Design

We used the date of the DHS interview and the geolocation information of the sampling clusters to link the child data to the gridded malaria index for that month. Note that the DHS protects confidentiality by displacing geolocation information by 0-2 km in urban areas and 0-5 km in rural areas (with 1% of the data displaced 0-10 km).[23] However, the MEI is constructed at 50km resolution, assuaging concerns about misassignment bias due to geolocation displacement.

2.3.1 Ecology, Malaria Infection and Anemia

We tested the association between malaria outcomes (infection and hemoglobin levels) and MEI values by estimating the following model:

$$M_{ilmy} = \beta_0 + \beta_1 MEI_{lmy} + \gamma_l + \delta_y + \varepsilon_{ilmy} \qquad (3)$$

M is a binary variable coded as 1 if child *i* living in location *l* tests positive for malaria when the survey was conducted in month *m* of year *y*. In a second set of specifications, *M* represents the child's hemoglobin. β_1 measures the association of malaria ecology with these two measures of malaria outcomes.

Variables omitted from this specification could be correlated with both malaria outcomes and ecology, confounding our estimates of β_1. If, for example, public health systems are weaker in warmer countries for reasons unrelated to malaria, then the higher malaria incidence in warmer locations might be erroneously attributed to ecology. We addressed this problem by including indicator variables for each country (γ_l), thus only comparing clusters within the same country (or, in an even stricter specification, within the same subnational administrative region). Likewise, spurious correlation could occur if a trend in climate generated a trend in the MEI, and if financing for antimalarial programs increased over the period. We used indicator variables for each year (δ_y) to flexibly absorb global trends in the variables and attenuate any such spurious correlation.

We visually examined the relationship between MEI and malaria outcomes using locally smoothed polynomial plots, including a semiparametric version that partials out country indicator variables so that estimation only uses DHS clusters within the same country. We then used a logit regression model to estimate the association of MEI with malaria infection among children under 5, followed by ordinary least-squares regression to estimate the association between MEI and hemoglobin levels.

2.3.2 Estimating the Effect of Bednets and Indoor Residual Spraying Using the MEI

We tested whether the deployment of ITNs and IRS is associated with malaria incidence and whether it affects the relationship between malaria and the ambient ecology in the following equation:

$$M_{ilmy} = \beta_0 + \beta_1 MEI_{cy} + \beta_2 bednet_i + \beta_3\left(MEI_{lmy} * bednet_i\right) + \beta_4 IRS_i + \beta_5\left(MEI_{lmy} * IRS_i\right) + \beta_6\left(MEI_{lmy} * bednet_i * IRS_i\right) + \gamma_l + \delta_y + \varepsilon_{ily} \quad (4)$$

β_2 and β_4 measure the association between malaria burden and the bednet and IRS indicator variables. β_3 and β_5, meanwhile, estimate whether bednets or IRS alter the relationship between ambient ecology and malaria outcomes. β_6 measures the added effect of having both interventions.

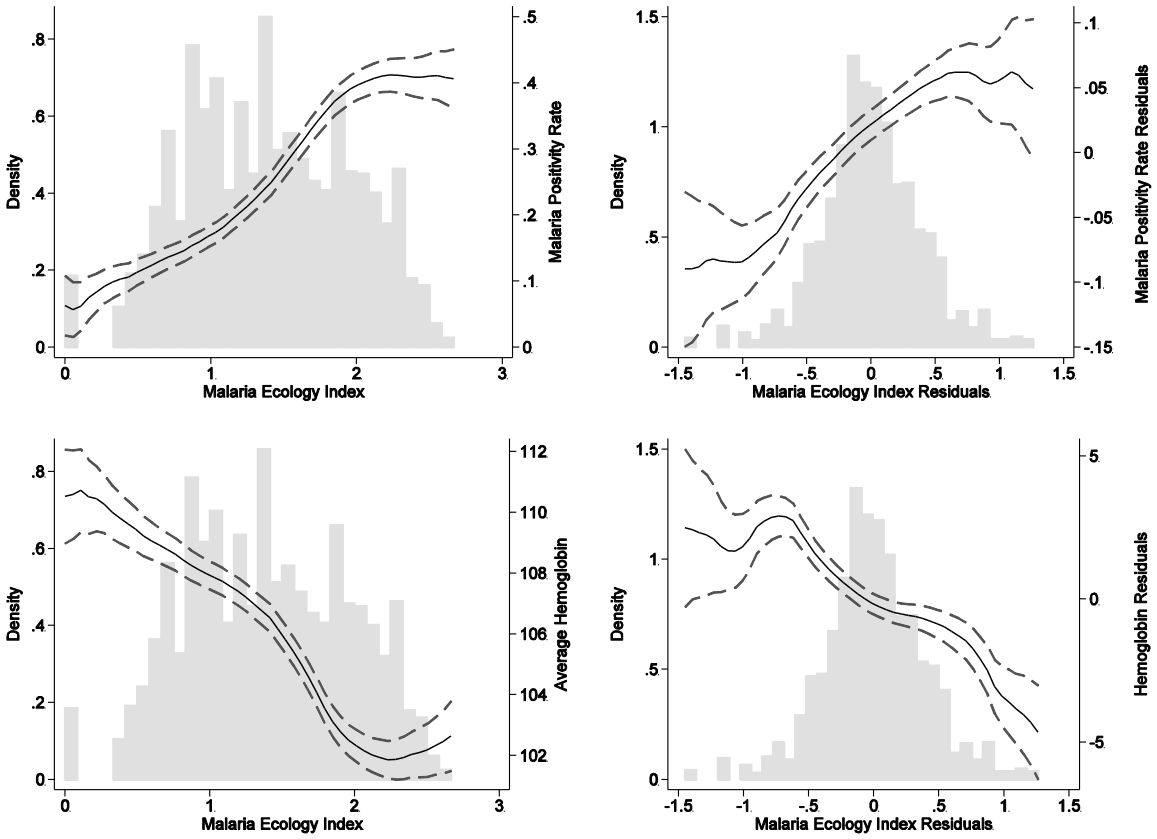
3 Results

3.1 Malaria Ecology and Infections

The top panels of Figure 3 plot the average malaria positivity rate in each cluster against the Malaria Ecology Index, showing a clear positive relationship between malaria outcomes and the MEI spanning the domain of the data. The top panel of Table 1 presents results from logistic regressions, providing odds ratios of a child having malaria as a function of the MEI. Column (I) presents the association across all of the data, showing that children in places with a 1-unit higher MEI index (1·7σ) face a 3-fold increase in malaria risk (p<0·01). Column (II) adds the year and country indicator variables to assuage concerns of spurious correlation across countries or trends in variables over time, thus only comparing children in the same country and in the same year. Column (III) uses subnational administrative-level indicator variables instead, so that only children within the same subnational region are being compared. Given that urban areas

provide less hospitable habitats for the *Anopheles* vector, columns (IV) and (VI) confirm that variation in malaria ecology is predictive of malaria risk in areas designated by the DHS as rural, while column (V) shows that malaria in urban areas is less dependent on ecology.

Figure 3: Malaria Outcomes and Malaria Ecology



Plots show local smooth polynomial plots with 95% confidence intervals. Histograms represent density of child-level observations by Malaria Ecology Index at time of survey. Top panel plots the proportion of children in the cluster testing positive for malaria against the MEI, while the bottom panel plots the average hemoglobin level in the cluster against the MEI. Right column plots represent within-country comparisons by first regressing all variables on country indicator variables and plotting residuals.

172

173 Table 1: Regression estimates of association of Malaria Positivity and Hemoglobin Levels with

174 Malaria Ecology Index

Dependent Variable	(I)	(II)	(III)	(IV)	(V)	(VI)
OR on Child Positive for Malaria	3·10***	2·25***	1·89***	2·68***	1·55	2·15***
	(2·12-4·54)	(1·60-3·16)	(1·49-2·38)	(1·87-3·85)	(0·75-3·24)	(1·44-3·21)
N	39,875	39,875	39,776	32,072	7,803	31,912
Pseudo R-squared	0·06	0·15	0·18	0·16	0·20	0·19
Hemoglobin	-4·80***	-3·18***	-2·65***	-3·77***	-2·29***	-3·04***
	(-6·35 - -3·24)	(-4·35 - -2·00)	(-3·54 - -1·76)	(-5·11 - -2·42)	(-3·89 - -0·70)	(-4·59 - -1·50)
N	39,739	39,739	39,739	31,947	7,792	31,947
Adjusted R-squared	0·03	0·05	0·07	0·06	0·06	0·08
Year Fixed Effects		Y	Y	Y	Y	Y
Country Fixed Effects		Y		Y	Y	
Administrative Region FE			Y			Y
Sample	All	All	All	Rural	Urban	Rural
Countries	7					
Subnational Admin Regions	62			60	55	60
DHS Clusters	1,943			1,461	482	1,461

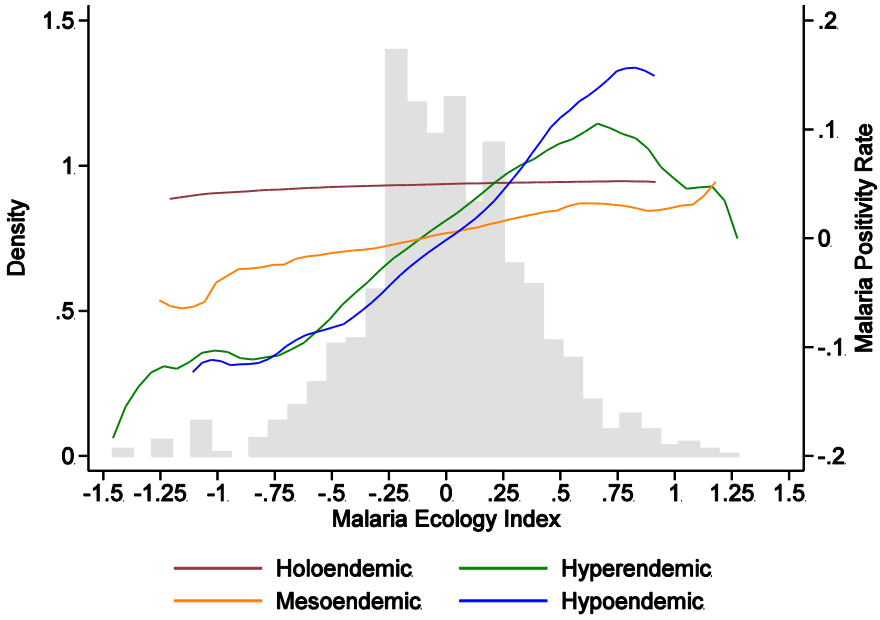
Independent variable is Malaria Ecology Index. 95% confidence intervals in parentheses. Standard errors clustered by admin 1 level to account for spatial and serial autocorrelation. *** significant to 99% levels.

175

176

Figure 4 plots the same relationship according to endemicity levels.[24] The flat slope of holoendemic zones comports with residents gaining some level of functional immunity when continuously exposed, while the steepest slopes in hyper- and hypoendemic zones suggest populations where exposure to the disease is occasional were more severely affected during periods of transmission.[25]

Figure 4: Malaria Positivity and Malaria Ecology, by Endemicity Level



Plots show local smooth polynomial regression of average malaria positivity in the DHS cluster and the Malaria Ecology Index. Comparisons are only made across clusters in the same country and endemicity level by partialing out from both variables the country and endemicity indicator variables and plotting residuals. Histogram represents density of malaria ecology values.

3.2 Malaria Ecology and Anemia

The bottom panel of Figure 3 plots the relationship between hemoglobin levels and the MEI, and the bottom panel of Table 1 presents regression results. A one standard deviation increase in the MEI (0·6) is associated with a 3-5 g/dL lower level of Hg (0·2-0·3 standard

193 deviations). Results across specifications are consistent with the top panel using malaria
194 infection.

195 **3.3 The Effect of Anti-Malaria Interventions**

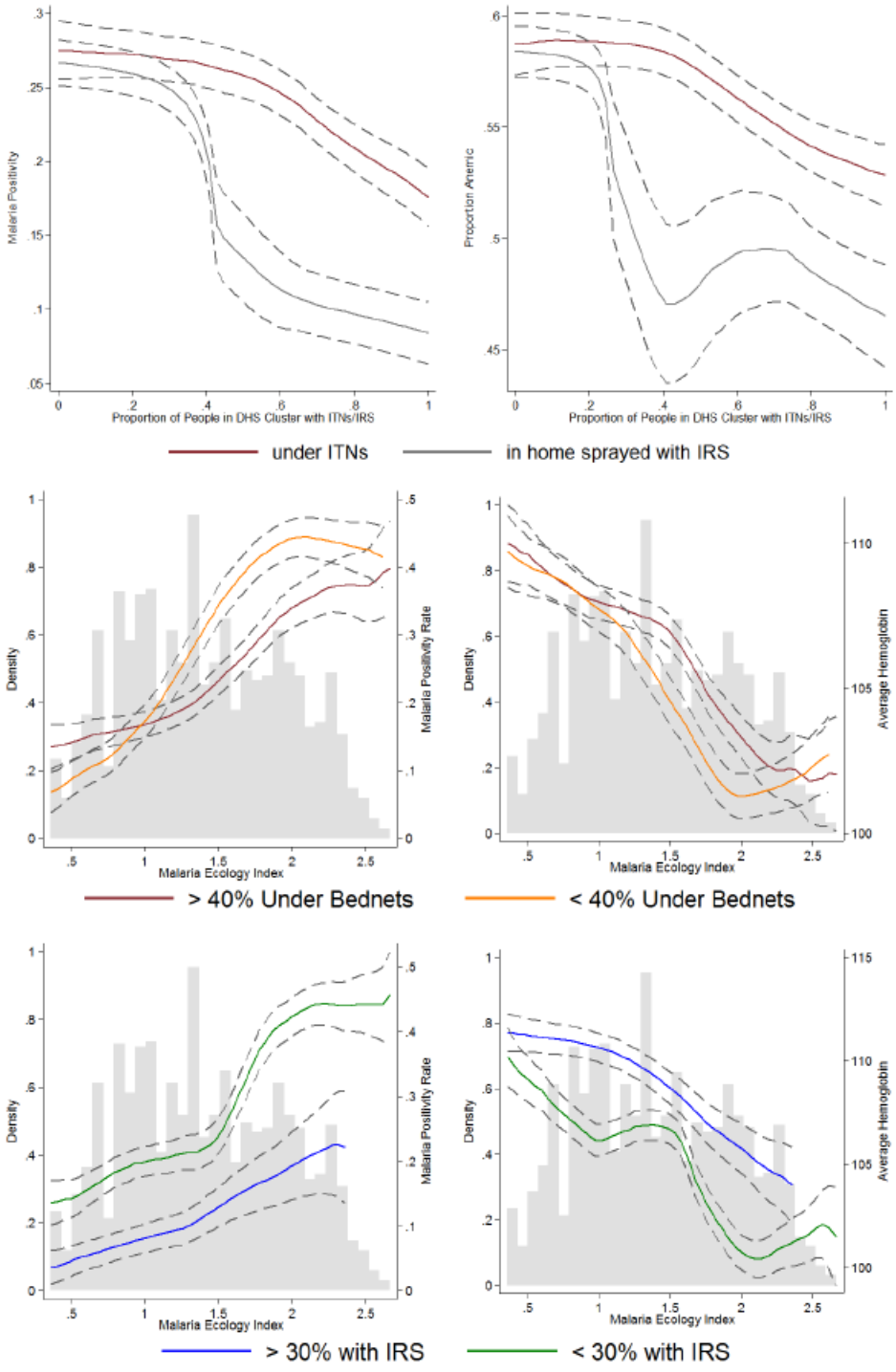
196 We collapsed the individual-level data to the cluster level, and plot in the top panel of
197 Figure 5 the percent of children having malaria and the percent of children having anemia (Hg <
198 11·0 g/dL) against the percentage of children in the cluster sleeping under bednets and the
199 percentage of homes sprayed with IRS. Both outcomes showed a sharp decrease in the
200 prevalence of malaria and anemia at around 40% bednet coverage, perhaps suggestive of herd
201 immunity at this threshold of ownership. This is consistent with evidence of limited association
202 between bednet use and infection rates among children living in areas of near-universal ITN
203 coverage.[26] We used a 40% cutoff in the second panel of Figure 5 to show the relationship MEI,
204 the likelihood of malaria infection, and hemoglobin levels, but differentiating by high vs. low
205 ownership of ITNs.[ii] These graphs clearly show that higher levels of malaria ecology are
206 associated with a higher likelihood of malaria infection and lower hemoglobin levels. In clusters
207 where over 40% of households use ITNs, malaria prevalence was lower and hemoglobin levels
208 were higher at MEI levels between 1-2.5.

209

[ii] Note that for these graphs we dropped clusters with the lowest MEI values, since plotting the joint distribution of bednets and malaria ecology in Appendix Figure A.1 revealed data sparsity at MEI levels below 5% of the maximum value (1.3% of the clusters).

210

211 Figure 5: Malaria Outcomes & Malaria Ecology, by Bednet and IRS Coverage



Plots show local smooth polynomial plots with 95% confidence intervals. Histograms represent density of child-level observations by Malaria Ecology Index at time of survey. Left column plots the percentage of children in the cluster testing positive with malaria against the MEI, while the right column plots the proportion of children anemic (top panel) or the average hemoglobin the cluster (middle and bottom panel) against the MEI.

The first panel of Figure 5 shows a nonlinear decrease in malaria infection rates and anemia when 30-40% of households in a cluster have been sprayed with IRS. The bottom panel shows that clusters with high IRS use had lower infection rates and higher average hemoglobin at all levels of malaria ecology. Moreover, the effect size of MEI on infection rates, captured by the slope of the curves, appears smaller for high IRS clusters. This suggests that IRS not only decreased infection rates and anemia but also attenuated the effect of adverse malaria ecology.

Table 2 examines these relationships in a regression framework. Given problems with interpreting coefficients on interactions terms in nonlinear models, the table replaces odds ratios in column (I) with coefficients from a linear probability model for ease of interpretation.[27] The coefficient in column (I) on the MEI (representing the role of ecology in the absence of both bednets and IRS) continues to be strongly significant and implies an 11% increase in probability of having malaria at a 1-unit higher level of MEI. Having a bednet is associated with reduced malaria risk (p=0.07). Homes benefiting from both ITNs and IRS have a net coefficient on MEI of 0.06, indicating that the interventions halve the effects of perniciously adverse ecological conditions for malaria transmission. Column (II) corroborates these results using hemoglobin. In summary, these results provide evidence that LLINs and IRS not only decreased infection rates, but also reduced the extent to which variation in the ecology of malaria translated into variation in infection rates and in hemoglobin levels.

232

233 Table 2: Regression estimates testing attenuation of malaria ecology effect on malaria positivity

234 and hemoglobin levels in the presence of ITNs and IRS

	Dependent Variable	
	Malaria Infection	Hemoglobin
Independent Variable	(I)	(II)
Malaria Ecology Index	0·11***	-2·35**
	(0·03-0·20)	(-4·28 - -0·41)
Slept w/ Treated Net	-0·07*	2·03*
	(-0·13-0·01)	(-0·22 - 4·28)
Indoor Residual Spray	-0·001	3·29*
	(-0·12 - 0·12)	(-0·36 - 6·94)
Net*IRS	0·12**	-4·01*
	(0·03-0·21)	(-8·30 - 0·29)
MEI*Net	0·04*	-1·49**
	(-0·004-0·08)	(-2·92 - -0·06)
MEI*IRS	0·12	-0·98
	(0·03-0·21)	(-4·32 - 2·36)
MEI*Net*IRS	-0·09**	2·87*
	(-1·16 - -0·18)	(-0·57 - 6·31)
constant	-1·39***	108·81***
	(-2·45 - -0·34)	(105·89 - 111·73)
Country FE	Y	Y
Year Fixed Effects	Y	Y
Sample	Rural	Rural
N	22,487	22,350
Within-country R-squared	0.20	0.08
Countries	7	7
Subnat Adm Regions	51	51
DHS Clusters	1,943	1,943

Note: 95% confidence intervals in parentheses. Standard errors clustered by admin 1 level to account for spatial and serial autocorrelation.

*** significant to 99% levels, ** 95%, * 90%.

235

236

4 Discussion

The paucity of data on malaria burden is one of the greatest challenges for public health systems in malarious countries; ecology-based models can complement existing data to aid in research and public health programming.[8,13-15] These results demonstrate the predictive power of an ecology-based index of malaria transmission using nationally representative geolocated serology data from seven countries, showing results that comport with many features of malaria epidemiology. National Malaria Control Programs can employ the MEI to gauge average malaria burden in places lacking outcome data, as well as to locally calibrate models in order to estimate changes in infection rates given weather variation and weather forecasts. An integrated geospatial framework linking weather data, the MEI, and malaria outcomes (measured and predicted) can produce easy-to-use outputs that would serve malaria program coordination and help evaluate program efficacy. In addition to serving health systems, these tools are useful given that understanding the effects of climate change on health has been recognized as important, in particular in the case of infectious diseases and vector-borne diseases specifically.[28-31]

Our analysis used cross-country large-N surveys with random sampling to document patterns in malaria incidence and deployment of ITNs and IRS. Consistent with other studies, these antimalarial interventions were strongly associated with lower malaria incidence and higher hemoglobin levels in children, conditional on the prevailing disease ecology.[13,32] More novel is the fact that households using both ITNs and IRS gained a protective effect from variation in malaria ecology. Indeed, public health efforts can help break the link between environment and disease burden.

While these associations complement the treatment effect estimates from randomized controlled trials, our results are not valid causal estimates of ITN or IRS deployment (there is evidence, for example, of limited compliance among owners of ITNs, as well as evolving vector resistance to pyrethroids).[33,34] Population-level associations are a reminder that as interventions are scaled up, estimated treatment effects from randomized trials might become increasingly poor approximations in different social and ecological contexts.

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References

1 Ravishankar N, Gubbins P, Cooley RJ, Leach-Kemon K, Michaud CM, Jamison DT, et al. Financing of global health: tracking development assistance for health from 1990 to 2007. *Lancet*. 2012;379:413_431.

2 World Health Organization. *World Malaria Report 2015*. Geneva: World Health Organization; 2015.

3 Sachs JD, Malaney P. The Economic and Social Burden of Malaria. *Nature*. 2002;415(6872):680-685.

4 Bleakley H. Malaria Eradication in the Americas: A Retrospective Analysis of Childhood Exposure. *American Economic Journal: Applied Economics*. 2010;2(2):1-45.

5 Barreca AI. The Long-Term Economic Impact of In Utero and Postnatal Exposure to Malaria. *Journal of Human Resources*. 2010;45(4):865-892.

6 Lucas AM. Malaria Eradication and Educational Attainment: Evidence from Paraguay and Sri Lanka. *American Economic Journal: Applied Economics*. 2010;2(2):46-71.

7 Murray CJL, Lopez AD. Measuring the Global Burden of Disease. *New England Journal of Medicine*. 2013;369(5):448-457.

8 Alonso PL, Tanner M. Public health challenges and prospects for malaria control and elimination. *Nature Medicine*. 2013;19(2):150-155.

9 World Health Organization. *World Malaria Report 2012*. Geneva: World Health Organization; 2012.

10 Murray CJL, Rosenfeld LC, Lim SS, Andrews KG, Foreman KJ, Haring D, et al. Global malaria mortality between 1980 and 2010: a systematic analysis. *Lancet*. 2012;379:413-431.

11 Hay SI, Okiro EA, Gething PW, Patil AP, Tatem AJ, Guerra CA, et al. Estimating the Global Clinical Burden of Plasmodium falciparum Malaria in 2007. *PLOS Medicine*. 2010;7(6):1-14.

12 Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI. The global distribution of clinical episodes of Plasmodium falciparum malaria. *Nature*. 2005;434:214-217.

13 Giardina F, Kasasa S, Sié A, Utzinger J, Tanner M, Vounatsou P. Effects of vector-control interventions on changes in risk of malaria parasitaemia in sub-Saharan Africa: a spatial and temporal analysis. *Lancet Global Health*. 2014;2:e601-15.

14 van Eijk AM, Hill J, Noor AM, Snow RW, ter Kuile FO. Prevalence of malaria infection in pregnant women compared with children for tracking malaria transmission in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Global Health*. 2015;3:e617-28.

15 Walker PG, ter Kuile FO, Garske T, Menendez C, Ghani AC. Estimated risk of placental infection and low birthweight attributable to Plasmodium falciparum malaria in Africa in 2010: a modelling study. *Lancet Global Health*. 2014;2:460-67.

16 Carstensen K, Gundlach E. The primacy of institutions reconsidered: Direct income effects of malaria prevalence. *The World Bank Economic Review*. 2006;20(3):309-339.

17 McCord GC. Malaria Ecology and Climate Change. *European Physics Journal*. 2016;225:459-470.

18 Caminade C, Kovats S, Rocklov J, Tompkins AM, Morse AP, Colon-Gonzales FJ, et al. Impact of climate change on global malaria transmission. *PNAS*. 2014;111(9):3286_3291.

19 Tanser FC, Sharp B, le Sueur D. Potential effect of climate change on malaria transmission in Africa. *Lancet*. 2003;362:17921798.

20 Kiszewski A, Mellinger A, Spielman A, Malaney P, Sachs SE, Sachs J. A global index representing the stability of malaria transmission. *American Journal of Tropical Medicine and Hygiene*. 2004;70(5):486-498.

21 Ikemoto T. Tropical Malaria Does Not Mean Hot Environments. *Journal of Medical Entomology*. 2008;45(6):963-969.

22 Matsuura K, Willmott CJ. Terrestrial air temperature: 1900-2012 Gridded Monthly Time Series. Center for Climatic Research, Dep Of Geography, University of Delaware, Newark. 2012;.

23 Perez-Heydrich C, Warren JL, Burgert CR, Emch ME. *Guidelines on the Use of DHS Spatial Data*. DHS Spatial Analysis Reports 8. Calverton, Maryland, USA; 2013.

24 Lysenko AJ, Semashko IN. Geography of malaria. A medico-geographic profile of an ancient disease. In: Lebedew AW, editor. *Itogi Nauki: Medicinskaja Geografija*. Moscow, USSR: Academy of Sciences; 1968. p. 25-146.

25 Marsh K, Snow RW. Malaria transmission and morbidity. *Parassitologia*. 1999;41:241-246.

26 Eisele TP, Miller JM, Moonga HB, Hamainza B, Hutchinson P, Keating J. Malaria Infection and Anemia Prevalence in Zambia's Luangwa District: An Area of Near-Universal Insecticide-Treated Mosquito Net Coverage. *American Journal of Tropical Medicine and Hygiene*. 2011;84(1):152-157.

27 Ai C, Norton E. Interaction terms in logit and probit models. *Economics Letters*. 2003;80(1):123-129.

28 Watts N, Adger WN, Agnolucci P, Blackstock J, Byass P, Cai W, et al. Health and climate change: policy responses to protect public health. *The Lancet*. 2015;386(10006):1861-1914.

29 Rodo X, Pascual M, Doblas-Reyes FJ, Gershunov A, Ston DA, Giorgi F, et al. Climate change and infectious diseases: Can we meet the needs for better prediction? *Climatic Change*. 2013;118:625-640.

30 Shuman EK. Global Climate Change and Infectious Diseases. *New England Journal of Medicine*. 2010;362(12):1061-1063.

31 Campbell-Lendrum D, Manga L, Bagayoko M, Sommerfeld J. Climate change and vector-borne diseases: what are the implications for public health research and policy? *Philosophical Transactions of the Royal Society of London B: Biological Sciences*. 2015;370(1665):20130552.

32 Gonçalves BP, Huang CY, Morrison R, Holte S, Kabyemela E, Prevots R, et al. Parasite Burden and Severity of Malaria in Tanzanian Children. *New England Journal of Medicine*. 2014;370(19):1799-1808.

33 Atieli HE, Zhou G, Afrane Y, Lee MC, Mwanzo I, Githeko AK, et al. Insecticide-treated net (ITN) ownership, usage, and malaria transmission in the highlands of western Kenya. *Parasites & Vectors*. 2011;4(113).

34 N'Guessan R, Corbel V, Akogbeto M, Rowland M. Reduced Efficacy of Insecticide-treated Nets and Indoor Residual Spraying for Malaria Control in Pyrethroid Resistance Area, Benin. *Emerging Infectious Diseases*. 2011;84(1):152-157.

Appendix

Figure A.1: Joint Distribution of Bednet Use and Malaria Ecology Index

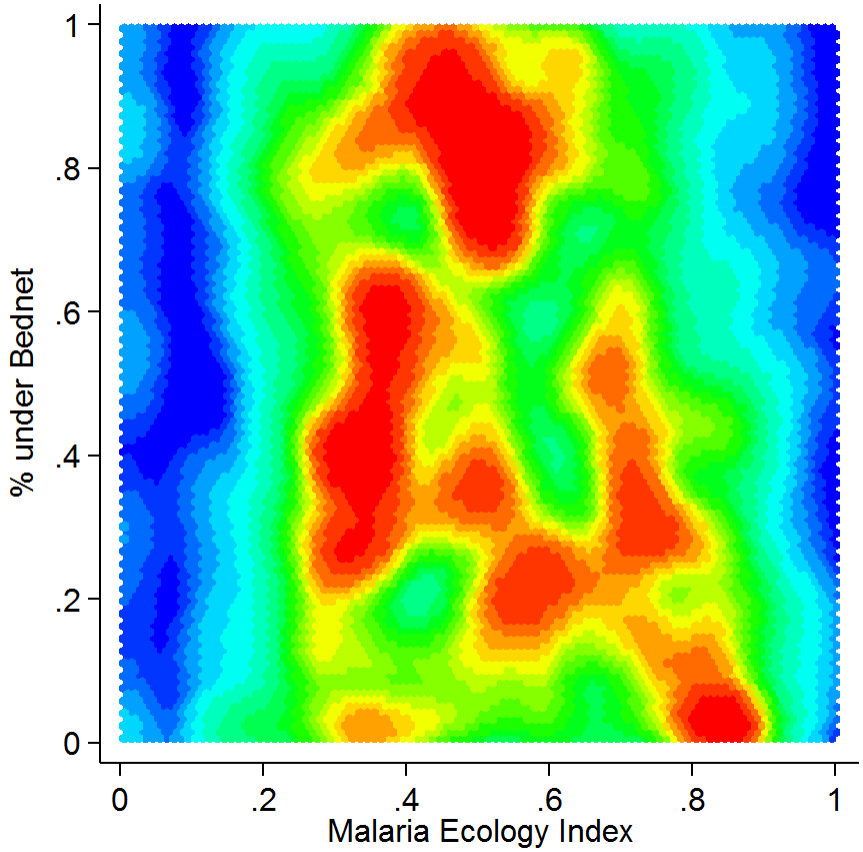

Figure A.1 plots the joint distribution of the Malaria Ecology Index (rescaled to be between 0-1) and the % of the cluster population sleeping under a bednet. Blue indicates sparse data, while red indicates highest data density in that domain of the two variables. We observed that very few clusters have MEI values below 5% of the maximum for all values of the bednet variable, which is why clusters at these very low MEI levels were excluded (1.3% of all clusters).