



Mosquito feeding behavior and how it influences residual malaria transmission across Africa

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The antimalarial efficacy of the most important vector control interventions—long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS)—primarily protect against mosquitoes' biting people when they are in bed and indoors. Mosquito bites taken outside of these times contribute to residual transmission which determines the maximum effectiveness of current malaria prevention. The likelihood mosquitoes feed outside the time of day when LLINs and IRS can protect people is poorly understood, and the proportion of bites received outdoors may be higher after prolonged vector control. A systematic review of mosquito and human behavior is used to quantify and estimate the public health impact of outdoor biting across Africa. On average 79% of bites by the major malaria vectors occur during the time when people are in bed. This estimate is substantially lower than previous predictions, with results suggesting a nearly 10% lower proportion of bites taken at the time when people are beneath LLINs since the year 2000. Across Africa, this higher outdoor transmission is predicted to result in an estimated 10.6 million additional malaria cases annually if universal LLIN and IRS coverage was achieved. Higher outdoor biting diminishes the cases of malaria averted by vector control. This reduction in LLIN effectiveness appears to be exacerbated in areas where mosquito populations are resistant to insecticides used in bed nets, but no association was found between physiological resistance and outdoor biting. Substantial spatial heterogeneity in mosquito biting behavior between communities could contribute to differences in effectiveness of malaria control across Africa.

Plasmodium falciparum | malaria transmission | LLIN efficacy | vector interventions | *Anopheles*

Malaria control has proven immensely effective, with 663 million clinical cases predicted to have been averted from 2000 through 2015 (1). The key control interventions are long-lasting insecticidal bed nets (LLINs) and the indoor residual spraying of insecticides (IRS), which are estimated to have averted 68% and 10% of the clinical cases, respectively (1). However, it has become clear that in many areas transmission will persist even with universal LLIN use and IRS deployment. This “residual transmission” is defined in our analysis as ongoing transmission in populations where LLINs and IRS are both used at 100% (2).

The scale of residual transmission is unclear. As countries achieve near-universal coverage of nets the importance of residual transmission is likely to become evident. Residual transmission may be a contributing factor for the recent increase in the number of malaria cases and deaths reported in Africa in 2016 to 2017 (3). The constant pressure from chemical interventions increases the potential for mosquitoes to physiologically evolve resistance to insecticidal chemistries (4). In recent years there has been a substantial rise in the frequency of mosquitoes resistant to pyrethroids, the only insecticide recommended for

use on LLINs before 2017 (5). This year (2019), Interceptor G2 (BASF), a dual-action chlorfenapyr + pyrethroid LLIN, will be piloted in the field (6). Mosquito vectors also display a diverse set of behaviors that may diminish their exposure to insecticides (7), including outdoor resting, shifts toward crepuscular feeding, and wider foraging preferences (8–14). Indoor-focused vector control can alter species composition by reducing the proportion of endophilic species relative to exophilic ones (15–17). This makes quantifying residual transmission an ever more important goal as the epidemiological impact of these changes are poorly understood.

The proportion of bites taken on humans when they would be protected by LLINs and IRS can be estimated by the overlap time between mosquito biting behavior (in the absence of vector control) and whether people are in bed or indoors (18–22). Estimates for the percentage of bites taken on people when they are outdoors and out of bed in the absence of vector control (subsequently referred to as outdoor biting) can be generated and used to determine the proportion of people unprotected by current vector control activities. Previous transmission dynamics mathematical models have estimated

Significance

Malaria transmission persists even when mosquito control is used effectively. This “residual transmission” measures all forms of transmission that are beyond the reach of standard insecticidal nets and indoor residual spraying of insecticides when used optimally. The epidemiological importance of the time of day mosquitoes bite and how much this contributes to residual transmission is unclear. The scale of the problem must be understood to demonstrate the need for outdoor vector control tools. An additional 10.6 million clinical cases of malaria are predicted annually given the 10% higher level of outdoor biting observed here. Mosquito species and behavior data together with people's resting and sleeping patterns are needed to fully measure indoor intervention efficacy and accurately quantify residual transmission.

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Table 1. Summary of estimates for the proportion of mosquito bites taken when people are indoors or in bed

Parameter, definition	Mosquito species/complex (no. of data points)	Previous model estimates (21–23)	New estimate	
			Median	Range
ϕ_I , the proportion of mosquito bites indoors	All species (255)	0.97	0.87	0.13–1.00
	<i>An. gambiae</i> s.l. (167)	NA	0.89	0.23–1.00
	<i>An. gambiae</i> s.s. (8)	0.97	0.90	0.70–1.00
	<i>An. arabiensis</i> (13)	0.96	0.86	0.60–1.00
	<i>An. funestus</i> s.l. (41)	0.98	0.87	0.53–1.00
ϕ_B , the proportion of mosquito bites in bed	All species (255)	0.89	0.79	0.09–1.00
	<i>An. gambiae</i> s.l. (167)	NA	0.81	0.09–0.99
	<i>An. gambiae</i> s.s. (8)	0.89	0.85	0.53–0.98
	<i>An. arabiensis</i> (13)	0.90	0.80	0.50–0.92
	<i>An. funestus</i> s.l. (41)	0.90	0.78	0.38–0.98
Q_0 , anthropophagy, the proportion of bites on humans	<i>An. gambiae</i> s.s.	0.92		
	<i>An. arabiensis</i>	0.71		
	<i>An. funestus</i> s.l.	0.94		
Mean life expectancy, d (see references noted in ref. 23)	<i>An. gambiae</i> s.s.	7.6 (4.5–16.1) d		
	<i>An. arabiensis</i>	7.6 (4.1–16.1) d		
	<i>An. funestus</i> s.l.	8.9 (5.6–10.2) d		
Biting rate	All mosquitoes	1 bite every 3 d		

Values combined data from a systematic literature review and President's Malaria Initiative country reports. Most mosquitoes are classified as *An. gambiae* s.l. Adding information on mosquito species significantly improved statistical model fit (*SI Appendix, Table S1*), although there is considerable overlap between species and most data were collated from different sites. Additional mosquito species-specific related parameters, anthropophagy, background mortality, and mosquito biting rates used in the modeling are provided. NA, nonapplicable. The model in Griffin et al. (23) parameterizes mosquitoes with behaviors similar to *An. gambiae* s.s. rather than the complex more generally, although has the flexibility to do this. Therefore, no *An. gambiae* s.l.-like behavior is defined in Table 1.

in bed. This is on average 10% lower (for both estimates) than previous estimates used in transmission dynamics models (20, 23). There was substantial variability in estimates, the 95 percentiles ranged from 41.8 to 99.5% of bites received when people are indoors and from 33.9 to 97.2% for bites received when people are in bed. In the studies with all data available, the estimates for ϕ_I and ϕ_B ranged from 0.51 to 0.95 (median = 0.86) and from 0.42 to 0.87 (median = 0.80), respectively.

Statistical analyses indicate a weakly significant overall decline in the percentage of bites taken when people are protected by LLIN and IRS ($P = 0.071$ and $P = 0.011$ for ϕ_I and ϕ_B , respectively; *SI Appendix, Table S1*). Generalized linear mixed-effects models allowing estimates to vary between countries show that overall the proportion of mosquitoes that are biting indoors was predicted to have dropped by about 10 percentage points (Fig. 3A) and similarly for those in bed (Fig. 3B) from 2003 to 2018. There was some evidence for more outdoor biting for mosquito species that were not *An. gambiae* s.l. or *An. funestus* (*SI Appendix, Table S1*), although most datasets did not differentiate between species within the *An. gambiae* complex.

Impact of outdoor biting on public health and residual transmission. A transmission model for malaria (23, 26, 30) was used to investigate the potential public health significance of different levels of outdoor biting. Residual transmission is a theoretical concept which assumes LLINs and IRS are used at capacity (i.e., 100% LLIN coverage which does not decline over time since the mass campaign and 100% IRS coverage). In real-life situations LLIN usage is very unlikely to reach these levels and remain so high. Nevertheless, to conceptualize residual transmission within the model we assume 100% coverage and use, and no decline in

use, although insecticide concentration declines over time since LLIN distribution (every 3 y) or IRS application (annually).

It is initially assumed that LLINs and IRS are working optimally and there are no pyrethroid-resistant mosquitoes. For example, in a perennial setting with a mixture of mosquito species and a baseline malaria prevalence of ~75%, introducing LLINs and IRS at 100% coverage is predicted to have reduced malaria prevalence by 96% 5 y later when 98% of bites are taken when people are indoors, but only by 52% when 58% of bites are taken when people are inside (Fig. 4A). The increase in malaria resulting from a rise in outdoor biting will vary between locations and depend on endemicity, mosquito species, seasonality of transmission, and history of malaria control interventions. This is broadly illustrated across Africa using a theoretical example assuming all regions increase indoor intervention cover in 2015 to achieve 100% nightly LLIN use and IRS coverage (100% of people sleep within structures sprayed with Actellic300CS from Syngenta). There are substantial differences in the epidemiological impact of residual transmission (Fig. 4B). Despite maximal use of current vector control going forward from 2016, some communities are expected to still receive on average up to 0.11 (median 0.001) infectious bites per person per year with some areas experiencing up to 6.08 infectious bites per person per year (Mopti Region, Mali; Fig. 4B). Care should be taken interpreting the maps presented in Fig. 4 B–D as malaria endemicity has been averaged over a wide geographical distribution (the administrative 1 unit) and there is expected to be substantial variation within these areas. Nevertheless, this theoretical example illustrates that a 10% higher percentage of mosquito bites taken when people are outdoors could result in an increase in the entomological inoculation rate

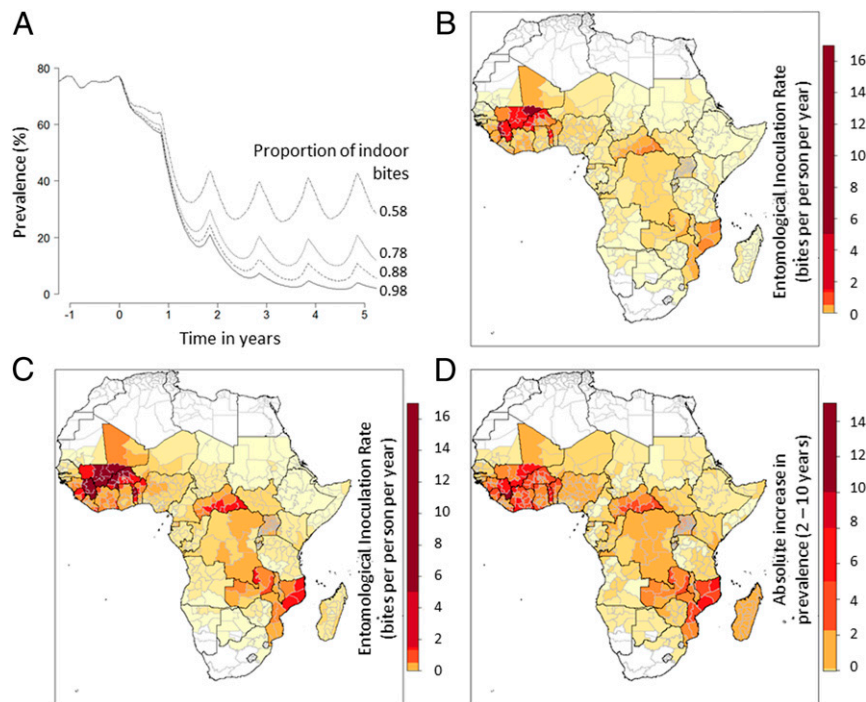


Fig. 4. Estimated impact of outdoor biting on the prevalence of malaria and residual transmission. (A) Illustration of the public health impact of LLINs and IRS when used at 100% coverage and how this depends on the proportion of bites taken when people are indoors. Lines show malaria prevalence in 2- to 10-year-old children in a high-transmission, perennial setting with a mixed mosquito species population (50% *An. gambiae* s.s., 25% *An. arabiensis*, 25% *An. funestus*). Universal use of LLIN and IRS at time 0 is shown for communities where a different percentage of mosquito bites is taken when people are indoors, be it 98% (historical value, solid line), 88% (approximate current estimation, dotted line; Table 1), 78% (dashed line), or 58% (dotted-dashed line). (B) Estimates of residual transmission if high proportions of mosquito bites were taken when people are indoors. Shaded region indicates the annual entomological inoculation rate (EIR) measured 3 y after the introduction of LLIN and IRS at 100% coverage (see color scale). (C) Residual transmission (EIR) if 10% fewer bites were taken when people are indoors (comparable to the drop estimated between 2003 and 2018; Fig. 3A). Such a difference in outdoor biting is predicted to have a substantial impact on malaria prevalence. (D) The absolute increase in malaria prevalence (in 2- to 10-y-old children) estimated from the higher outdoor biting (malaria prevalence resulting from the difference between B and C). Note that the level of residual transmission and malaria prevalence in B–D is intended to be illustrative of the variance seen across Africa. Results should not be overinterpreted as transmission is averaged at an administrative unit-1 scale and there will be substantial variability within these units.

season (*SI Appendix*, Fig. S3). There was considerable variation in biting patterns between countries (Fig. 3C and D and *SI Appendix*, Table S1). The analysis identified Burkina Faso, Eritrea, Ethiopia, Gabon, and Tanzania to have relatively low proportions of mosquitoes feeding when people were indoors (Fig. 3C) and in bed (Fig. 3D).

The Malaria Atlas Project (MAP) has estimated the efficacy of bed nets to reduce malaria prevalence across Africa and identified areas where LLINs seem to be underperforming (i.e., locations where the MAP statistical model predicts larger reductions in prevalence should be seen than was observed in survey data). It was hypothesized that the proportion of mosquitoes feeding when people are in bed could potentially explain some of the variation in the estimated performance of bed nets across Africa (1). Results indicate the relative efficacy (that is, what the reduction in parasite rate as a function of the starting parasite rate and insecticide-treated net coverage is) of LLINs across Africa increases with an increasing proportion of biting occurring in bed (*SI Appendix*, Fig. S5), although the data were noisy and the statistical association between bed net performance and the proportion of bites taken outside is not statistically significant (linear regression $P = 0.82$; *SI Appendix*, Fig. S5, *Inset*).

Relationship between Outdoor Biting and Physiological Resistance. A recent randomized control trial has provided the strongest evidence that pyrethroid-resistant mosquitoes are reducing the public health impact of pyrethroid-only LLINs (35). The level of

physiological resistance in a mosquito population against pyrethroid insecticide can be approximated using discriminatory dose susceptibility bioassay tests. Similarly, the proportion of mosquito bites taken indoors is an expression of how effective vector control interventions might be. Bioassays and mosquito activity data were recorded for matched locations by PMI ($n = 67$ data points for deltamethrin bioassays and $n = 28$ data points for permethrin bioassays). Regression analysis found no association between these two measurements, which appear to be independent (deltamethrin resistance $P = 0.93$ and permethrin resistance $P = 0.44$) (Fig. 5A).

The Predicted Public Health Impact of Outdoor Biting and Physiological Resistance. The effectiveness of LLINs and IRS depends on both the level of outdoor biting and physiological resistance. Estimates of the percentage of mosquito bites taken when people are indoors varies from ~40 to 100% (Fig. 5A). This difference in outdoor biting is predicted to reduce LLIN efficacy (at 100% coverage) from 66 to 54% (a 12% drop) in the site simulated in Fig. 5B. Conversely, the level of physiological resistance (survivorship measured in a discriminating dose bioassay) is seen to vary in the same dataset from 0 to 85% (Fig. 5A). This is predicted to have 3 times the public health impact, reducing LLIN efficacy by 36% (Fig. 5C).

There is an interesting 3D relationship between the 2 ways a mosquito can reduce the insecticidal actions of LLINs (Fig. 5D). If there is no physiological resistance, then small increases in mosquito outdoor biting elicit a relatively small public health impact because mosquitoes are still likely to have contact with an

interventions in the global battle against malaria, although in some locations they will need to be augmented by interventions that target the mosquito and the parasite outside of the home.

Methods

Systematic Review. Dataset 1 reports a literature review conducted following PRISMA guidelines (CRD42016047459) and undertaken to specify biologically realistic parameters for *Anopheles* vectors feeding on people indoors or in bed. Additional data were provided by Eritrea courtesy of the National Malaria Control Program. In some cases, mosquito activity is estimated from figures in published papers (noted in Dataset S1). The systematic review is presented in Fig. 1 and the included data are provided in Dataset S1.

The PMI has rolled out IRS vector control campaigns in 22 African countries since 2007. Dataset 2 is comprised from PMI country-level reports. In some cases, these reports provide data on the proportion or numbers of mosquitoes feeding indoors or outdoors throughout the night. In most cases, discriminatory dose bioassay tests are also conducted at these sentinel sites to test for physiological resistance to insecticides used in nets or sprays. There are no data on human activity in these reports. Therefore, it is assumed that human behavior is consistent between sites and throughout the year and represented by the studies included in the systematic review. Using the PMI mosquito activity data from Nigeria and Liberia, it was possible to calculate monthly estimates for the proportion of mosquito bites taken indoors or in bed for specific sentinel sites (SI Appendix, Fig. S3). Mosquito studies with fewer than 30 mosquitoes across all sampling nights were not included in the analyses.

Estimating the proportion of mosquito bites indoors and in bed. Mosquito feeding attempts can be measured using indoor or outdoor light traps (27) or using human landing catches (55). The number of mosquitoes caught in a trap during an hourly period is assumed to represent the number of mosquitoes attempting to feed on humans for the same period. In the absence of data, no bites are assumed to occur during the hours for which mosquito bites were not sampled. Raw data are converted into the proportion of all mosquito bites during a 24-h period that were taken indoors [denoted $\lambda_i(t)$] or outside [denoted $\lambda_o(t)$] at hour (t) using

$$\lambda_h(t) = \frac{\text{Sum of Bites at hour}(t)\text{for location (inside or outside)}}{\text{Sum of bites for all hours for both locations}}, \quad [1]$$

where subscript h indicates whether bites are taken indoors ($h = 1$) or outdoors ($h = 0$) (23).

The proportion of mosquito bites taken on humans indoors (ϕ_i) and the proportion of mosquito bites taken on humans in bed (ϕ_B) are calculated as follows (23):

$$\phi_i = \frac{\sum_t p_i(t)\lambda_i(t)}{\sum_t ((1-p_i(t))\lambda_o(t) + p_i(t)\lambda_i(t))}, \quad [2]$$

where, $p_i(t)$ is the proportion of people inside at hour (t), $\lambda_i(t)$ is the biting rate indoors at hour (t), and $\lambda_o(t)$ is the biting rate outdoors at hour (t). Similarly,

$$\phi_B = \frac{\sum_t p_B(t)\lambda_i(t)}{\sum_t ((1-p_i(t))\lambda_o(t) + p_i(t)\lambda_i(t))}, \quad [3]$$

where $p_B(t)$ denotes the proportion of people in bed at hour (t). These measures are collected on volunteers (or traps) without personal vector control and so represent the maximum proportion of bites preventable by LLINs or IRS. The overall proportion of bites taken when people are indoors is calculated by the model according to intervention coverage and the level of insecticide resistance.

Three studies had sufficient human and mosquito data collected at the same time in the same location to be able to estimate ϕ_i and ϕ_B (19, 27, 28). To capture the uncertainty across studies where data are not matched, for each of the 132 datasets on mosquito behavior from the systematic review and the 128 datasets on mosquito behavior from PMI reports, ϕ_i and ϕ_B are calculated

for all possible combinations of human indoor p_i and in bed p_B data. The median ϕ_i and ϕ_B are estimated from these ranges (Table 1). Only 2 locations in the meta-analysis recorded estimates at successive time points: Tokoli and Lokohoué in Benin had data for the years 2008, 2009, and 2011 (12, 34).

Statistical analysis. Logistic regression models were fitted to explore temporal trends in the mean (and median) proportion of mosquito bites taken indoors (ϕ_i) and in bed (ϕ_B). Only data where more than 30 mosquitoes (total across all sampling nights) had been recorded in the sampling effort were included. Country was included as a random effect to account for possible large-scale spatial heterogeneity (SI Appendix, Table S1, Model A). Standard linear regression was used to 1) explain variation in the time when people went to bed or rose in the morning using data from Beale et al. (29), 2) identify countries with significantly different estimates of ϕ_i and ϕ_B (SI Appendix, Table S1, Model B), and 3) investigate the association between the level of physiological pyrethroid resistance [measured using World Health Organization or Centers for Disease Control and Prevention discriminating dose bioassay tests (4)] and a measure for mosquito activity indoors (ϕ_i). In all analyses, mosquito species *Anopheles hancocki*, *Anopheles melas*, and *Anopheles nili* were grouped together under one species name, "other," as there were few data on these species. Visual inspection of model residual plots did not indicate any deviance from homoscedasticity or normality. Significance (P values) was calculated using likelihood ratio tests and is reported in SI Appendix, Tables S1 and S2. All analysis was conducted using R statistical software (56) using the package lme4 (57).

A Bayesian approach was used to test for an association between the MAP net performance residual and the proportion of mosquito bites taken indoors by fitting a regression with a gamma distribution. All functions were fitted using Hamiltonian Monte Carlo sampling methods (58–60). Four chains were initialized to assess the convergence of 1,000 iterations, the first 500 of each were discarded as burn in. The posterior distribution of parameters was then derived from the 2,000 iterations and posterior checks were performed using shinystan (version 1.0.0, ref. 61) and visually confirmed to overlay the data (Dataset S1).

Relationship between relative LLIN effectiveness and mosquito biting when people are in bed (ϕ_B). Relative bed-net effectiveness was estimated from the mean residual plots of LLIN efficacy estimated between the years 2000 and 2015 across Africa by the MAP (for full details see ref. 1). These plots show the difference between the estimated LLIN effectiveness (given covariates such as LLIN coverage and baseline endemicity present in the geostatistical model) and the observed malaria prevalence. Values <1 indicate in that location LLIN are less effective than was predicted; values >1 denote areas where greater reductions in prevalence were seen than were predicted. Raw data are presented in SI Appendix, Fig. S5 and estimates for the effectiveness score were generated for the individual mosquito studies by taking the average estimate around predictions of the study coordinates (assuming a 10-km radius, 5 km and 50 km were also explored and gave similar patterns). Estimates for the proportion of bites received in bed were regressed assuming a gamma distribution to explain the residual for net effectiveness (number of data = 108). The model was fit using a Hamiltonian Monte Carlo method (58–60), warm-up was 500 iterations, and the subsequent 500 samples were collected from each of the 4 chains. The mean linear predictor was estimated as 1.80 and variance parameter as 0.72.

Estimating public health impact. An established malaria transmission dynamics model (23, 26, 30) is used to investigate the impact of changing ϕ_i and ϕ_B on predictions of EIR, malaria prevalence (measured in 2- to 10-y-old children), and clinical incidence. The model structure has been published comprehensively elsewhere (e.g., see supplementary information of refs. 47 and 62). For clarity, we outline the important assumptions and model structure specifically associated with LLIN and IRS implementation in this model (SI Appendix).

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