Integrating data from across insecticide resistance bioassay types using a mechanistic model incorporating mosquito genetic variation and behaviour

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Abstract

Malaria kills roughly 500,000 people each year, and our most effective intervention against the disease is insecticide treated nets (ITNs) which kill mosquitoes. Mosquito resistance to the most important class of insecticidal compound, pyrethroids, has unfortunately grown dramatically over the past few decades, but gauging the impact of resistance on public health remains difficult. Past work has shown how mortality data from cheap-to-conduct discriminating-dose bioassays can be used to predict mosquito mortality in more expensive and more true-to-life experimental hut trials. Here, we develop a new predictive approach to modelling these data which incorporates data from intensity-dose bioassays, which is a WHO-recommended test increasingly used in malarial regions that outputs a more nuanced measure of resistance. This new mechanistic model explicitly estimates epidemiologically important quantities that describe the interaction of mosquitoes with the insecticide. The model accounts for variation in the lethal dose in the mosquito population, for example, due to genetic variability in field populations. The utility of the model is illustrated by fitting it to data from a systematic review of experimental hut trials evaluating the efficacy of pyrethroid-only ITNs. This work represents a first step towards using intensity-dose bioassay data to determine the effects of mosquito insecticide resistance on public health.

Author summary

Bednets laden with insecticides that kill mosquitoes have been responsible for substantial reductions in the burden of malaria over the last few decades. Mosquito resistance to insecticides, however, threatens to halt further progress and potentially erode these gains. It is crucial to be able to gauge changes in insecticide resistance over time and how these changes affect the effectiveness of bednets. Important tools for quantifying these changes include intensity-dose bioassays, which expose mosquitoes to a range of insecticide doses and measure their mortality, and experimental hut trials, which are more expensive and aim to mimic how mosquitoes interact with insecticides on bednets in the field. Here, we develop a mathematical model which includes

mechanistic detail about how mosquitoes interact with insecticides in each of these types of experiment. We show how our models allow us to make accurate predictions of mosquito mortality in hut trials using data only from intensity-dose bioassays. Our models provide a more granular understanding of this important class of experiment and could be embedded into larger transmission dynamics models of malaria to predict the public health impact of measured changes to insecticide resistance.

Introduction

Malaria kills more than half a million people globally each year [1] and is vectored by mosquitoes of the Genus *Anopheles*. Insecticide treated bednets (ITNs) can protect the individuals sleeping under them from bloodfeeding mosquitoes but more importantly kill mosquitoes, which provides a community-level protection [2–7]. From 2000 until the mid 2010s, the number of deaths due to malaria fell dramatically, primarily due to the widespread use of ITNs [8]. However, emerging resistance in mosquitoes against the pyrethroid insecticides used in ITN formulations has led to a debate around the ongoing effectiveness of ITNs [9–16]. Large trials were conducted to assess the impact of pyrethroid resistance on the effectiveness of ITN-based malaria vector control [17, 18], but quantifying the impact of resistance by comparison across epidemiological settings is difficult due to many interfering factors [19] and thus the overall size of the resistance threat remains unclear [20].

Besides quantifying the malaria burden due to the loss of ITN effectiveness because of pyrethroid resistance spread, it is important to factor in resistance in localised malaria prevention planning. Stochastic models of malaria epidemiology [21–23] take into account many epidemiological factors and are increasingly used for fine-scale planning of intervention strategies. These modelling approaches require parameterising the differential ITN effects for a each considered ITN product and the specific epidemiological setting, including mosquito insecticide resistance. In particular, the decisions what ITN product to use in a specific setting depends on its resistance profile [24].

Experimental hut trials (EHT) are a standard procedure to evaluate ITN products under controlled field conditions [25] and are the primary data source for parameterising their effect in models of malaria epidemiology [13, 26–28]. An experimental hut mimics typical housing in the study area but is specially constructed to retain all entering mosquitoes, with three main hut designs used in sub-Saharan Africa – East African [29], West African [30] and Ifakara design [31] – that differ in catching efficiency [32]. During the EHT, a human volunteer sleeps inside the hut under either an untreated control net or an ITN and, after each study night, all dead and alive mosquitoes are collected from the hut and their blood-feeding status is recorded. From these detailed data, differential effects on mosquito survival and blood-feeding can be estimated [13, 26–28]. However, EHTs are relatively laborious and expensive and are thus only conducted in a limited number of locations.

Programs to monitor resistance occurrence across Sub-Saharan Africa, following either the WHO tube protocol [33] or the CDC bottle protocol [34], are in place and have already captured large amounts of data [35]. However, these susceptibility bioassays were designed to detect resistance to a pyrethroid insecticide in a geographical location [18, 33] and they are not designed to capture the impact of resistance on the efficacy of ITNs. In particular, these bioassays operate with a single dose to discriminate between fully susceptible and resistant mosquito populations and that 'discriminating dose' does not relate to insecticide exposure upon interaction with a ITN in the field. Consequently, statistical models predicting the impact of pyrethroid resistance on malaria transmission based on discriminating dose susceptibility bioassays

are forced to make extrapolations but nonetheless have some predictive power [13, 28].

In order to measure the resistance intensity in a mosquito population, intensity-dose susceptibility bioassays, which assess the mosquitoes' susceptibility for a range of insecticide doses, were recommended [33, 36] and are increasingly used [37]. A first framework for their analysis proposed fitting a generalised logistic function to the dose-response data and deriving the distribution of lethal doses in the population, from which the lethal dose with respect to any mortality level can be deducted [38]. However, these models are non-mechanistic, potentially limiting their practical use for characterising the impact of resistance on disease transmission. In addition, there is currently no method available to integrate data from discriminating dose and intensity-dose susceptibility bioassays for predicting effectiveness of ITN.

While much research effort focused on revealing resistance mechanisms and predicting the spread of resistance across time and space [39, 40], resistance of a given mosquito population is still usually characterised by a single value for the average mortality percentage in a specific resistance bioassay and the variability of insecticide tolerance in the population was largely overlooked.

We propose a simple, mechanistic model of insecticide-induced mortality in mosquito bioassays which incorporates stochasticity in insecticide exposure and tolerance. Our model provides a natural way to interpret dose-response relations in terms of the dose killing 50% of the mosquitoes (LD_{50}) and the variability of insecticide tolerance in the population. While purely statistical models of dose-response relations in insecticide-induced mosquito mortality impose essentially arbitrary functional relationships, our model requires only distributional assumptions on exposure and tolerance. More generally, our model provides a unified treatment of three types of experiments: discriminating dose bioassays, intensity-dose bioassays and experimental hut trials. Thus, our model relates susceptibility bioassays which provide a standardised insecticide susceptibility characterisation to EHTs which present a more realistic model system of how mosquitoes interact with insecticides in the field, and we obtain a predictive model for ITN effectiveness given resistance bioassay data.

Materials and methods

We analyse data from studies with the malaria transmitting female mosquitoes of the *Anopheles gambiae sensu lato* species complex, for simplicity referred to as 'mosquitoes' hereafter. In this instance, we do not consider differences between species within the species complex.

Mechanistic model for mortality in susceptibility bioassays

We represent the insecticide exposure of an individual mosquito i in a resistance bioassay by a positive random variable, X_i. We assume $X_i = V_i c$, where V_i is a positive random variable representing the volume of insecticidal material mosquito i comes into contact with and c is the fixed average insecticide concentration in a unit volume. Note that we use the term volume in a broad sense, including all uptake of insecticidal material during the bioassay, such as through surface contact and through contact with vaporised insecticide in the air. We further assume the concentration c grows sub-linearly with the dose d, i.e. $c = \alpha d^\beta$ for $\alpha > 0$ and $0 < \beta \leq 1$, and, without loss of generality, we can assume $c = d$ after possibly altering the exposure and volume measurement units. We model V_i as being log-normally distributed to account for the likely large variability in exposure of mosquitoes to insecticide. By appropriately re-scaling the volume measuring unit, along with the denominator of the concentration measuring unit, we can assume $\log(V_i)$ has zero mean without loss of generality. This

means that the exposure to insecticide also follows a log-normal distribution:

$$\log(X_i) \sim \mathcal{N}(\log(c), \sigma_V), \tag{1}$$

where $\sigma_V > 0$. The measuring unit for exposure is 'insecticide mass' but due to the possibly applied scale alterations it has the same scale as 'dose', measured as multiples of the discriminating dose defined by the World Health Organisation [33].

We represent the maximal insecticide tolerance (simply referred to as 'tolerance' hereafter) of mosquito i as a positive random variable T_i and assume mosquito i dies in the 24 hours post exposure (the holding time of mosquitoes in both the resistance bioassay and EHT for insecticides with a fast mode of action, such as the pyrethroid products considered here) if $X_i > T_i$. The indicator random variable $\mathbf{1}_{X_i > T_i}$ has a Bernoulli distribution with probability

$$\mathbb{P}(\text{death due to insecticide}) = \mathbb{P}(X_i > T_i). \tag{2}$$

However, mosquitoes can also die without insecticide contact during the holding time and we assume an additional, independent Bernoulli death process with probability p_0. By the law of total probability, the death of mosquito i is a Bernoulli random variable with probability

$$\mathbb{P}(\text{death}) = p_0 + (1 - p_0)\mathbb{P}(\text{death due to insecticide}). \tag{3}$$

Assuming the outcome of insecticide exposure is (conditionally) independent within the same assay, the total count of mosquitoes dying follows a binomial distribution with probability given by Eq 3.

Mechanistic model for insecticide-induced mortality of field-collected mosquitoes in susceptibility bioassays

Mosquitoes sampled from a wild population exhibit variable insecticide tolerance, due to both genetic variation and variation in environmental conditions during both juvenile and adult life stages. We assume the tolerance T_i of an individual mosquito i is independent of its exposure X_i and is distributed following a log-normal distribution

$$\log(T_i) \sim \mathcal{N}(\mu_T, \sigma_T), \tag{4}$$

where the mean μ_T and standard deviation σ_T characterise the tolerance distribution within a given population. By the monotonicity of the log function and the symmetry of the standard normal distribution, the insecticide-induced death probability can be computed as

$$\begin{aligned}
\mathbb{P}(\text{death due to insecticide}) &= \mathbb{P}(X_i > T_i) \\
&= \mathbb{P}(\log(T_i) - \log(X_i) < 0) \\
&= \mathbb{P}(\log(T_i) - \log(X_i) - (\mu_T - \log(c)) < \log(c) - \mu_T) \\
&= \Phi\left(\frac{\log(c) - \mu_T}{\sqrt{\sigma_V^2 + \sigma_T^2}}\right),
\end{aligned} \tag{5}$$

where Φ denotes the cumulative distribution function of the standard normal. Here we used the fact that the sum of two independent normal distributed random variables is normally distributed with mean equal to the sum of the two means and variance equal to the sum of the variances.

From Eq 5 it follows that LD_{50}, the dose at which 50% of the mosquitoes die, is precisely $\exp(\mu_T)$ under our model, which equals the median of the tolerance. This is

due to the symmetry of the exposure and tolerance distributions on the log-scale and the monotonicity of the logarithm.

This model allows us to characterise the insecticide resistance of a mosquito population by location and scale parameters: LD_{50}, which equals $\exp(\mu_T)$, and the standard deviation of log-tolerance, σ_T, referred to as 'tolerance variability' hereafter.

Mechanistic model for mortality in experimental hut trials

For EHTs we use a similar model. We assume that mosquitoes from the local population enter the experimental hut randomly and independently of their individual insecticide tolerance. Note, this means that we assume there is no behavioural resistance to the insecticide, and each mosquito entering the hut has a tolerance T_i distributed as in Eq 4 with parameters μ_T and σ_T corresponding to the local population. We then assume each mosquito i in the hut experiences an exposure X_i which is independent of its tolerance T_i and distributed according to

$$\log(X_i) \sim \mathcal{N}(\mu_X, \sigma_x), \tag{6}$$

with fixed parameters μ_X and $\sigma_X > 0$ for a given EHT setup. Like in the resistance bioassay, we assume mosquito i dies if $X_i > T_i$ and by equation 2 the probability of death due to insecticide is

$$\begin{aligned}
\mathbb{P}(\text{death due to insecticide}) &= \mathbb{P}(X_i > T_i) \\
&= \mathbb{P}(\log(T_i) - \log(X_i) < 0) \\
&= \mathbb{P}(\log(T_i) - \log(X_i) - (\mu_T - \mu_X) < \mu_X - \mu_T) \\
&= \Phi\left(\frac{\mu_X - \mu_T}{\sqrt{\sigma_X^2 + \sigma_T^2}}\right).
\end{aligned} \tag{7}$$

Similarly to above we assume a independent background mortality process with probability q_0 of death for a given EHT experiment. Again, assuming the outcome for all mosquitoes is (conditionally) independent, then the count of mosquitoes dying follows a binomial distribution with probability

$$\mathbb{P}(\text{death}) = q_0 + (1 - q_0)\mathbb{P}(\text{death due to insecticide}), \tag{8}$$

and total count given by the number of mosquitoes entering the hut.

Joint model of mortality in dose-response bioassays and experimental hut trials

The aim of this study is to predict the killing effectiveness of insecticide-treated nets, as measured in EHT, in field settings with mosquito populations exhibiting a range of susceptibilities which were evaluated in both susceptibility bioassays and experimental hut trials. Here we define a mosquito population as all *Anopheles* mosquitoes, across all species, of a given village-sized geographical location and a given year; for details on the matching between bioassay and EHTs see the Data section. To this end, we combine the models for bioassays with wild-type mosquitoes and for EHTs in a joint model. The two sub-models are coupled via the common parameters μ_T and σ_T, which are specific per mosquito population setting. Thus, the exposure in EHT is defined with the same scale as the exposure in susceptibility bioassays. Here, we assume the parameter μ_V is the same across all susceptibility bioassay studies and the parameters μ_X and σ_X are the same across all EHT studies. We estimate the natural death probability in each EHT separately and independently, but we assume a fixed natural death probability across all susceptibility bioassays since for some studies no control data was available.

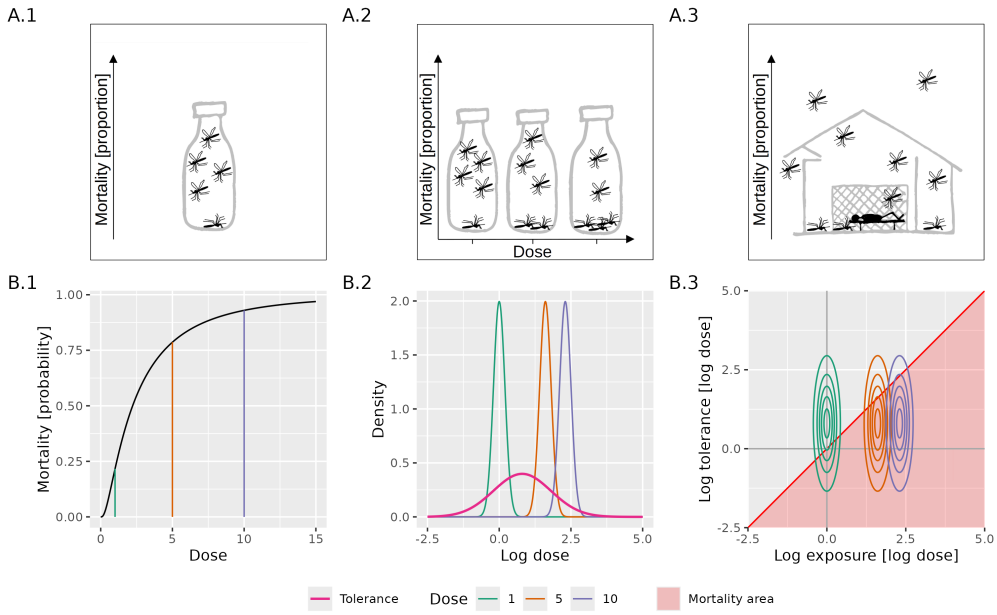


Fig 1. Illustration of bioassay types and mechanistic model. Panel **A** displays illustrations of the three bioassay types: **A.1** discriminating dose susceptibility bioassays (we depict the CDC bottle bioassay), **A.2** intensity-dose susceptibility bioassays and **A.3** experimental hut trials (here, we depict the East African hut type). Panel **B** explains how the mechanistic model of intensity-dose bioassays works. For a chosen mean tolerance (μ_T) of 0.8 and a tolerance standard deviation (σ_T) of 1 as well as an exposure standard deviation (σ_V) of 0.2, we display: **B.1** the modelled dose-response relationship (black curve) and mortality probabilities (vertical lines) for typical intensity-dose levels, **B.2** the univariate distributions of tolerance and exposure for typical intensity-dose levels, and **B.3** the corresponding joint bivariate normal distributions of exposure and tolerance, where the contour lines depict the amount of probability mass contained within them: the outermost contour has 90% of probability mass within it; the inner lines delineate regions containing 70%, 50%, 30% and 10% probability mass. The fraction of the probability mass lying in the mortality area (red) equals the mortality probability.

Predicting killing effectiveness of ITNs in experimental hut trials in a given setting from tolerance characteristics

After calibrating the parameters σ_V, μ_X and σ_X of the joint model with the present data, the same model can be employed to predict the killing effectiveness of ITNs in an entomological setting for which only resistance bioassay data for the corresponding insecticide are available. Specifically, the tolerance parameters μ_T and σ_T are estimated from the data by fitting the resistance bioassay model (Eq 3 and 5) and subsequently the ITN killing probability, with respect to experimental hut trial conditions, is predicted by Eq 7. Predictions are specific per pyrethroid-subclass if the subclass of the bioassay is known since the training data is matched per pyrethroid-subclass whenever possible (see Data section for exceptions).

Data

We extended an existing dataset of matched resistance bioassay studies and experimental hut trials (EHT) conducted on the same mosquito populations [28] with a recent study from Burkina Faso comprising intensity-dose susceptibility bioassays. Only resistance bioassay studies exposing field collected mosquitoes to single pyrethroids, and following either the WHO tube [33] or CDC botte [34] protocol, were included. Only EHTs on first generation, single active ingredient, pyrethroid ITNs that were unwashed were considered. Experiments with missing or inconsistent data in the variables needed for the model fit were excluded. For the EHT data analysis, we only analysed mortality and did not consider feeding or gravidity status. We pooled mortality recorded across all hut compartments and we did not include covariates hut or sleeper in our analysis. For both EHTs and resistance bioassay data, we pooled data for all *Anopheles* species if studies reported a finer species-breakdown, and we relied on mortality assessed 24h after the start of the study.

A resistance bioassay study and a EHT were considered a match, and thus included in the dataset, if they were conducted in the same, village-sized geographical location and in the same year. Within each match, the data were further grouped by insecticide if the pyrethroids tested in the bioassay study exactly matched the active ingredients of the net products tested in the EHT, or a single group across all insecticides and net products was defined otherwise. Within each group, net products with the same active ingredient were not differentiated. This procedure lead to a total of 41 groups of paired susceptibility bioassays and EHT arms. Control susceptibility bioassays, where available, and control arms of EHT were included and shared between groups, without replicating any data. Characteristics and sample sizes per group are listed in S1 Table, including references to the original studies. Overall, the dataset contains 23,624 mosquitoes observed in resistance bioassay studies and 114,730 mosquitoes observed in EHTs.

Bayesian Inference

The resistance bioassay model was fitted to the intensity-dose bioassay data and the joint model which couples that to the EHT model was fitted to the full dataset (S1 Table). We fitted the models using a Bayesian framework, and in S2 Table, we show our priors. These were generally weakly informative (S1 Fig shows prior predictive checks) with the exception of the prior for the daily background mortality probability (i.e. mosquito mortality in the presence of no insecticide) which we assumed had 65% prior probability mass below 10% mortality.

Both models were fitted using the probabilistic language Stan [41] and the posteriors were sampled using Stan's default NUTS algorithm [42] accessed through the rstan package v2.26.1 [43] in R 4.3.2 [44]. For the resistance bioassay model and the joint

model we run 4 chains with $4,000$ and $6,000$ iterations, respectively, and each time discarded half of the iterations as warm-up. To reduce the need for warm-up, we initialised the chains with point estimates obtained by optimisation; to obtain these point estimates, we used Stan's L-BFGS algorithm and used the set with the highest log-posterior across 10 optimisation runs. For all model fits, we diagnosed convergence with $\hat{R} < 1.01$ and bulk- and tail-effective sample sizes above 400 for all model parameters [45].

Results

The mechanistic model captures the wide variety of dose-response relationships observed across field settings

Our mechanistic model captures reasonably well the dose-response relations observed in bioassays across the range of locations and years and pyrethroid insecticides used in the studies within our dataset (Fig 2). Our model failed to fit data for Tengrela in 2020 involving the alphacypermethrin bioassay (panel 1 in Fig 2) as the data shows a drop in tolerance from dose 1 to dose 5 while our model only supports monotonically increasing dose-response relations. Except for this setting, the dose-response curves estimated with the joint model, which simultaneously fits the EHT data, were similar to those from the model fitting the resistance bioassay data only (Fig 2).

Intra- and inter-location variability in resistance profiles

Our characterisation of the insecticide resistance of a mosquito population by the mean (μ_T, equivalent to $\log(\mathrm{LD}_{50})$) and the standard deviation (σ_T) of its log tolerance to the insecticide allows for a detailed comparison of resistance across location, years and different pyrethroids. For the intensity-dose resistance bioassay data, the two parameters were identifiable with no or minor posterior correlation for the joint model fitted simultaneously to the EHT data (panel A in Fig 4).

With respect to inter-location variability in resistance profiles, Tiefora shows a significantly higher tolerance standard deviation than Tengrela, which is only 30 km away. In addition, LD_{50} estimates for alphacypermethrin were slightly higher in Tiefora than in Tengrela. With respect to intra-location resistance dynamics, our estimates suggest LD_{50} of alphacypermethrin dropped slightly between the year 2020 and 2021, both in Tengrela (labels 1 and 2 in panel A of Fig 4) and in Tiefora (labels 3 and 4 in panel A of Fig 4). With respect to differences in tolerance against different insecticides of the pyrethroid class, we estimated that for deltamethrin, both LD_{50} and tolerance standard deviation were significantly lower than for alphacypermethrin in Tiefora in the year 2020 (labels 3 and 7 in Fig 4).

The mechanistic model can integrating results from different bioassays

Fig 3 shows that the joint model fit simultaneously to both bioassay and experimental hut trial data recovers the mortality trends in both data sources, while for some entomological settings the predictions are not accurate. The model-based predictions are quite accurate even for the studies with single dose bioassays for which the resistance characterisation by LD_{50} and tolerance standard deviation is not identifiable. This is due to the similarity of the bioassay and experimental hut trial models: LD_{50} and tolerance standard deviation are correlated in the same way in both models. Not surprisingly, the model prediction is generally less accurate for the experimental hut

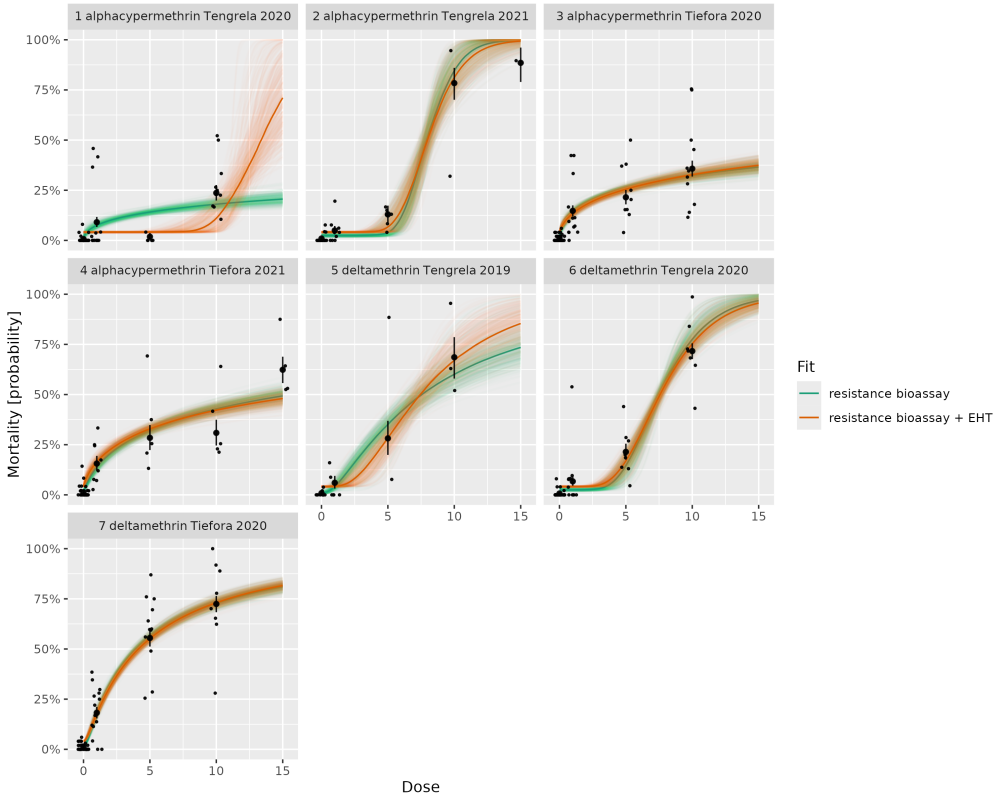


Fig 2. Model fits to intensity-dose resistance bioassay data from Burkina Faso. The panels show the data and estimates for the intensity-dose susceptibility bioassays from two near-by villages in Burkina Faso over up to 3 different years and with different pyrethroid insecticides. Each panel shows the data (black dots, plotted with jiter) and the estimates (posterior median) from either the model fitted to intensity-dose resistance bioassay data only or the joint model fitted simultaneously to the EHT data as well. Uncertainty bands for the model estimates are depicted by 500 curves that were randomly sampled from the posterior. The black vertical bars represent 95% credible intervals as estimated by a binomial model with a uniform prior for each panel and dose separately.

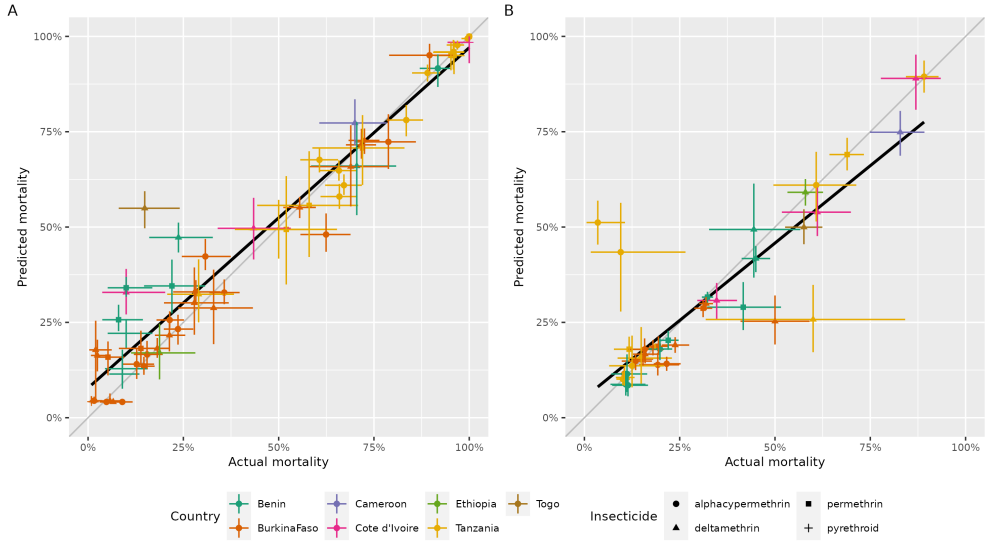


Fig 3. Model-based predictions ('predicted') and empirical estimates ('actual') of mortality in susceptibility bioassays and experimental hut trials. Mortality in **A** susceptibility bioassays and **B** EHTs, for 41 different settings defined by geographical location, year and insecticide. Point estimates correspond to the posterior median and interval estimates to 95% credible intervals, as estimated by an effect-free binomial model with uniform prior ('actual') and by the joint mechanistic model fitted to both resistance bioassay and EHT data ('predicted'), respectively.

trials than for the bioassays since in the latter conditions are more controlled. Note that for two entomological settings for which the model predictions are far from the empirical estimates (both from Tanzania), the uncertainty of the empirical estimates is very large.

Varying the mean level of tolerance in the population has an impact in ITN killing quite distinct from varying the tolerance variability

In Fig 4 we predict the ITN killing effect for a a range of possible resistance characterisations as estimated by the joint model fitted to discriminating dose and intensity-dose resistance bioassay as well as EHT data. As expected, the killing effect decreases with increasing LD_{50}, with a rate of decrease depending on the standard deviation of the tolerance in the population (panel B in Fig 4). Irrespective of the tolerance standard deviation, 50% killing is attained if the mean tolerance ($\log(LD_{50})$) matches the median exposure in the experimental hut trial. Varying the tolerance standard deviation σ_T shows a more nuanced effect on EHT mortality (panel C in Fig 4). Small σ_T values accentuate extremes in EHT mortality for low and high mean tolerance ($\log(LD_{50})$) and lead to high uncertainty if the mean tolerance is close to the mean EHT exposure. Large σ_T values push the mortality to 50%. The convergence of the mortality estimate to 50% for increasing σ_T is due to the symmetry in the exposure model and not an instance of falling back to the prior (the prior mortality has a median of 50% as well but coverage of the full mortality range). Overall, across the range of locations and years and pyrethroid insecticides covered by the studies in our dataset which provide intensity-dose resistance bioassay data, the ITN killing effect in EHTs is

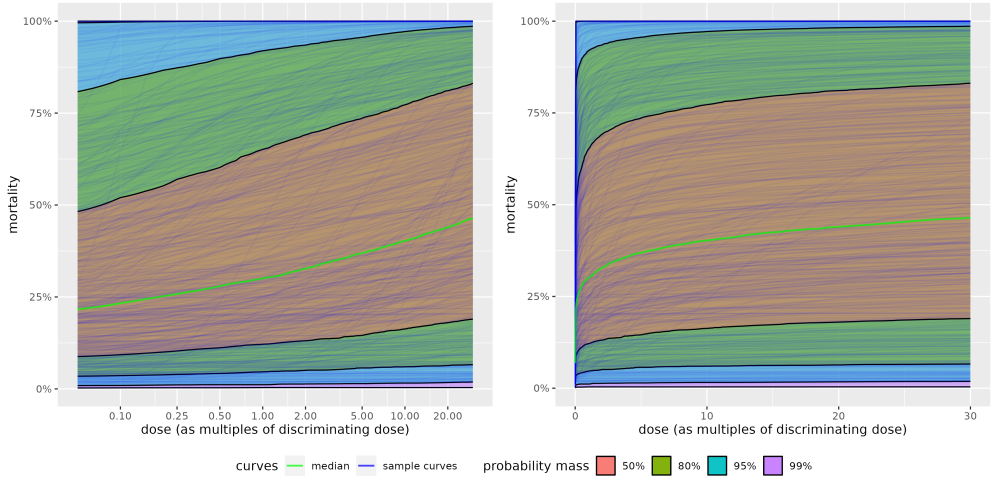
estimated to be very low, despite significantly different resistance characterisations.

Discussion

We presented a new mechanistic model of insecticide-induced mosquito mortality in bioassays which explicitly describes the interaction of the mosquitoes with the insecticide. By fitting to data from multiple countries in sub-Saharan Africa since 2000, we have shown that the model applies to discriminating dose, intensity-dose and experimental hut trial bioassays and yields meaningful, interpretable estimates of insecticide exposure in these different assays as well as insecticide resistance in the mosquito population. Our model can be used to predict ITN effectiveness for transmission settings in which no EHTs but cheaper intensity-dose susceptibility bioassays, which are WHO-recommended and increasingly used, can be conducted. Such predictions can also be generated from discriminating dose bioassay data, but with limited accuracy. Further, our insecticide resistance characterisation of a mosquito population including an estimate of heterogeneity may help to better understand resistance spread. There is a need for a fuller exportation of historical EHT data in order to parameterise transmission dynamics mathematical models to improve reliability of the epidemiological benefit of these important global health tools.

Supporting information

S1 Fig. Prior predictive check for bioassay model. The specified priors support a sufficiently wide variety of dose-response curves for doses up to 30 times the discriminating dose. Due to the log-transformation the priors are non-informative on the log-scale, but weakly informative on the actual dose-scale.



S2 Fig. Posteriors of exposure parameters for the joint model. Pairwise scatter plots and histograms of the posterior samples for the exposure parameters.

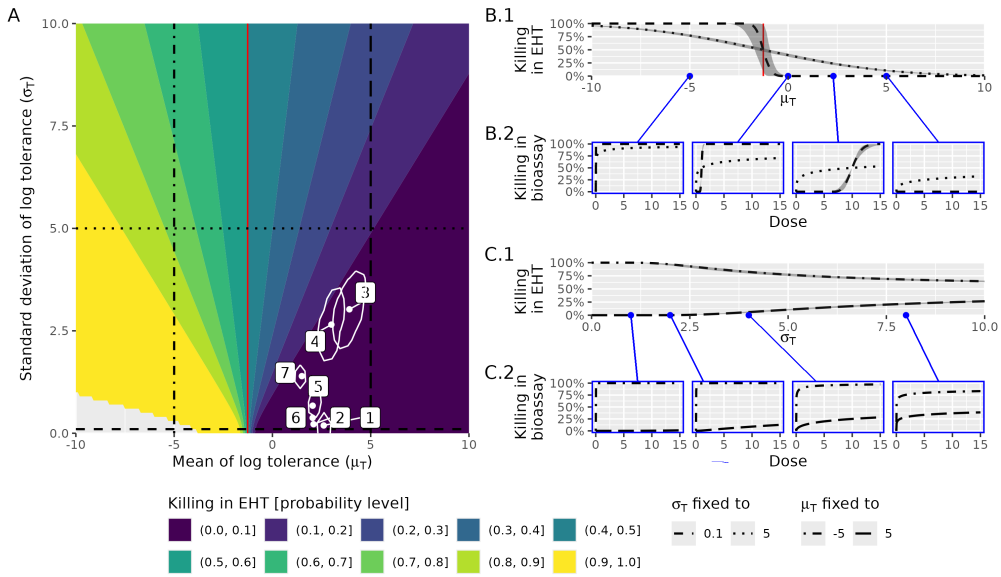
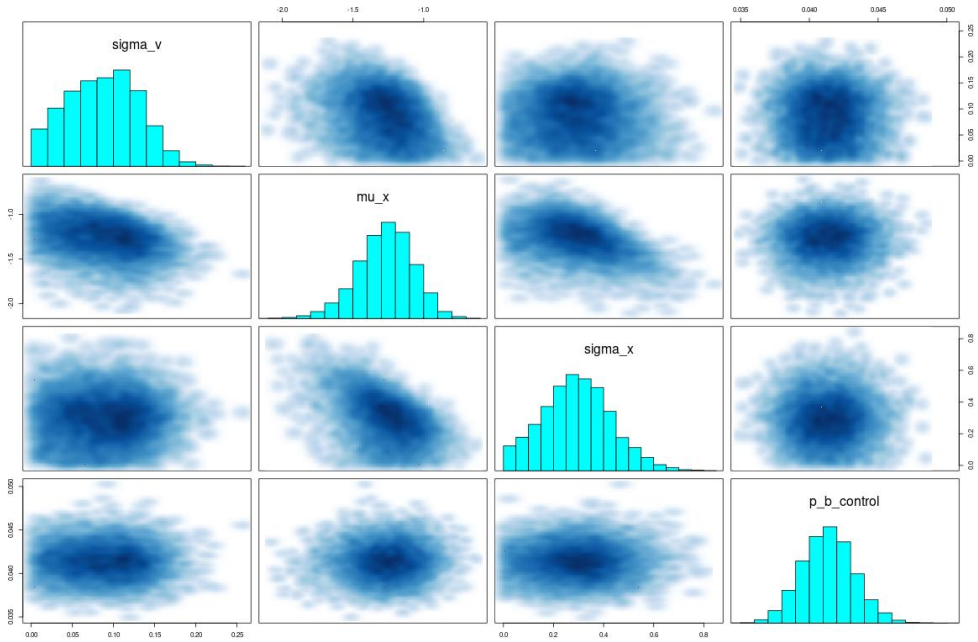


Fig 4. Predicted ITN killing effect in EHT across a range of resistance characterisations and estimated resistance characterisations from intensity-dose bioassays. In panel **A**, ITN killing effect predictions are displayed by contour lines for a range of resistance characterisations given by a combination of μ_T (mean of log tolerance, $\log(\mathrm{LD}_{50})$) and σ_T (standard deviation of log tolerance). All predictions are with respect to the fitted joint model integrating both susceptibility bioassays and EHT. Resistance characterisations estimated from the intensity-dose susceptibility bioassays studies (with numerical labels corresponding to Fig 2) are displayed as point estimates (white dots) and 95% credible regions (white contour lines). The red vertical line marks the estimated mean EHT exposure (posterior median). Black horizontal lines represent transects through the resistance characterisation at σ_T values 0.1 and 5, and black vertical lines transects at μ_T values -5 and 5. Corresponding to the horizontal transects, panel **B.1** details the impact of varying the mean log tolerance (μ_T) on the ITN killing effect, while fixing the standard deviation of the log tolerance (σ_T) to either 0.1 or 5. The red vertical line marks the estimated mean EHT exposure (posterior median). Panel **B.2** shows corresponding dose-response curves for the selected μ_T values $-5, 0, \log(10)$ and 5. Dose is measured as multiples of the discriminating dose defined by the World Health Organisation. Corresponding to the vertical transects, panel **C.1** details the impact of varying the standard deviation of the log tolerance (σ_T) on the ITN killing effect, while fixing the mean log tolerance (μ_T) to either -5 or 5. Panel **C.2** shows corresponding dose-response curves for the selected σ_T values $1, 2, 4$ and 8. The 95% credibility bands of the EHT mortality predictions are displayed in grey, but do only account for uncertainty of the exposure parameters and not the tolerance parameters and are thus much narrower than the bands in Fig 2.



S1 Table. Data sources, characteristics and summarised data.

Group	Reference	Country	Site	Year	Assay type	Hut type	Assay insecticides	Net insecticides	Net products	# treated assays	# control assays	# treated huts	# control huts
1	[46]	Benin	Malanville	2010	WHO	West	deltamethrin	deltamethrin	LifeNet	97	0	676	911
2	[46]	Benin	Akron	2010	WHO	West	deltamethrin	deltamethrin	LifeNet	61	0	63	144
3	[47]	Ethiopia	GGDam	2011	WHO	East	deltamethrin	deltamethrin	PermaNet2	80	0	426	511
4	[48]	Cameroon	Pitoa	2008	WHO	West	deltamethrin	deltamethrin	PermaNet2	100	0	105	401
5	[49]	Togo	Kolokope	2013	WHO	West	deltamethrin	deltamethrin	Yorkool	74	0	389	465
6	[50]	Cote d'Ivoire	Yaokoffikro	2009	WHO	West	deltamethrin	deltamethrin	PermaNet2	50	0	317	796
7	[51]	Tanzania	LowerMoshi	2013	WHO	East	deltamethrin	deltamethrin	PermaNet2	100	0	10	75
8	[52]	Tanzania	Zeneti	2006	WHO	East	alphacypermethrin	alphacypermethrin	Interceptor	752	0	202	252
9	[53]	Tanzania	Zeneti	2005	WHO	East	permethrin	permethrin	Olyset	393	0	399	854
10	[54]	Tanzania	Mabogini	2005	WHO	East	permethrin	permethrin	Olyset	100	0	196	716
11	[55]	Cote d'Ivoire	Tiassale	2012	WHO	West	deltamethrin	deltamethrin	PermaNet2	99	0	108	130
12	[56]	Benin	Cove	2010	WHO	West	permethrin	permethrin	Olyset	100	0	3804	2874
13	[57]	Burkina Faso	VDK	2011	WHO	West	deltamethrin	deltamethrin	PermaNet2	100	0	114	336
14	[58]	Tanzania	Lupiro	2010	WHO	Ifakara	deltamethrin	deltamethrin	PermaNet2, Icon Life	96	0	30431	11777
15	[58]	Tanzania	Lupiro	2010	WHO	Ifakara	permethrin	permethrin	Olyset	125	0	15836	11777
16	[59]	Benin	Malanville	2011	WHO	West	permethrin	permethrin	Olyset	100	0	96	69
17	[60]	Burkina Faso	Tengrela	2014	WHO	West	deltamethrin	deltamethrin	DawaPlus2, PermaNet2	85	0	1485	482
18	[60]	Burkina Faso	Tengrela	2014	WHO	West	permethrin	permethrin	Olyset	101	0	922	482
19	[60]	Burkina Faso	VK5	2014	WHO	West	deltamethrin	deltamethrin	DawaPlus2, PermaNet2	163	0	2532	1095
20	[60]	Burkina Faso	VK5	2014	WHO	West	permethrin	permethrin	Olyset	153	0	1458	1095
21	[61]	Benin	Cove	2012	WHO	West	deltamethrin, permethrin	alphacypermethrin	Interceptor	100	0	631	673
22	[62]	Benin	Cove	2015	WHO	West	deltamethrin, permethrin	alphacypermethrin	Interceptor	200	0	175	310
23	[63]	Cote d'Ivoire	Yaokoffikro	2000	pre2000	West	pyrethroid	deltamethrin	PermaNet	50	0	69	84
24	[64]	Burkina Faso	VDK	2014	WHO	West	deltamethrin, permethrin	alphacypermethrin	Interceptor	227	0	519	853

S2 Table. Prior specifications.

Parameter	Prior distribution
μ_T	$\mathcal{N}(5, 10)$
σ_T	half-normal$(0, 5)$
σ_V	half-normal$(0, 5)$
μ_X	$\mathcal{N}(0, 5)$
σ_X	half-normal$(0, 5)$
p_0	Beta$(1, 10)$
q_0	Beta$(1, 10)$

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