U.S. PRESIDENT'S MALARIA INITIATIVE

ANOPHELES STEPHENSI IN ETHIOPIA: POTENTIAL IMPACT AND MITIGATION

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EXECUTIVE SUMMARY

The invasion and establishment of *Anopheles stephensi* represents an imminent and potentially substantial threat to Ethiopia and the wider African region. Over the last 20 years, Ethiopia has seen substantial reduction in the burden of malaria. The addition of *An. stephensi* as a highly competent and adaptable vector could reverse this trend. To understand the potential magnitude of the problem we adapted a mechanistic model of malaria transmission and estimated the increase in vector densities required to explain the rise in malaria reported in Djibouti following the discovery and proliferation of *An. stephensi*. Assuming similar levels of *An. stephensi* invasion into areas of Ethiopia under 2000m and previously found suitable (Sinka et al., 2020), we predict the possible public health impact by incorporating local data on vector bionomics, pre-existing malaria prevalence, current use of vector control and drug treatment.

The possible increase in malaria is highly uncertain, but the impact could be considerable. In a conservative scenario the median relative increase in malaria prevalence is ~330% from current levels. Translating this to incidence in areas below 2000m, and that are estimated to be suitable for *An. stephensi* (Sinka et al., 2020), this could result in a 19-87% increase (95% CI 5-338%), corresponding to a crude increase of clinical cases of ~500,000 to 620,000 a year after establishment (with a possible plausible range from 140,000-2,406,000 additional cases). Subnationally, there is significant heterogeneity in expected public health impact dependent on pre-existing transmission, ongoing interventions and altitude (Figure 1). Models suggest that low altitude urban areas with current negligible malaria transmission risk seeing the highest increases in disease prevalence. In these areas the absence of existing vector control and low immunity indicates the possibility for substantial increases in transmission. High levels of pyrethroid resistance observed in *An. stephensi* captured in Ethiopia (Yared et al., 2020) suggest pyrethroid-only insecticide treated nets (ITNs) in use across the country will have a reduced efficacy for control of malaria transmitted by *An. stephensi*.

To combat the increase of malaria transmission following *An. stephensi* establishment, the deployment of a wide array of vector control interventions should be considered. Here we have modelled the impact of combinations of ITNs at various levels of use, indoor residual spraying (IRS) and reduction in adult emergence (through larvicide or breeding container management) once *An. stephensi* has invaded. It should be stressed that these estimates are highly speculative given that it is unclear how impacted the invading vector will be to these interventions. Subnationally, the impact of these interventions depends on what has already been implemented and current malaria transmission. Models indicate a multifaceted approach is needed to reduce the additional cases to a level that approaches transmission prior to *An. stephensi* introduction. Through combinations of high coverage of ITNs, IRS and larvicide, there is substantial potential to reduce the increase in annual malaria incidence from ~0.62 million cases, to ~0.27 million additional cases a year (Figure 2). Greater reductions maybe possible with more effective or targeted efforts, though they will need to be expanded to much of the population at a significant expected cost. The most comprehensive set of interventions investigated (80% use of ITNs, 80% of mosquito resting structures sprayed and a 40% reduction in adult emergence due to larviciding) it is estimated to cost ~$70 million dollars ($38-$101 million) per year, and $142 ($78- $204) per case averted. We do not currently attempt to quantify the economic burden of additional malaria cases, though it is likely to be substantial.

The establishment of *An. stephensi* as an additional malaria vector represents a significant change to malaria control strategies in Ethiopia and beyond. Predicting the public health impact is highly unclear, but its potential magnitude and the likelihood of it potentially reversing decades of hard-fought reductions necessitate it being a global health priority.

FIGURE 1. IMPACT OF *ANOPHELES STEPHENSI* ESTABLISHMENT ON PREVALENCE AND INCIDENCE OF MALARIA IN ETHIOPIA.

A) Illustrative malaria slide prevalence before and after the establishment of *An. stephensi* for example regions of existing high, medium and low disease prevalence. *An. stephensi* invasion is denoted to start by the left vertical dashed lines. B) Estimates of malaria prevalence increase across the different administrative units in Ethiopia by data source. Horizontal line show average increase whilst points denote the increase in different individual admin regions. C) Overall projected increase in annual incidence across Ethiopia for the different data sources. Individual points show uncertainty in the overall estimates individual LHC estimates.

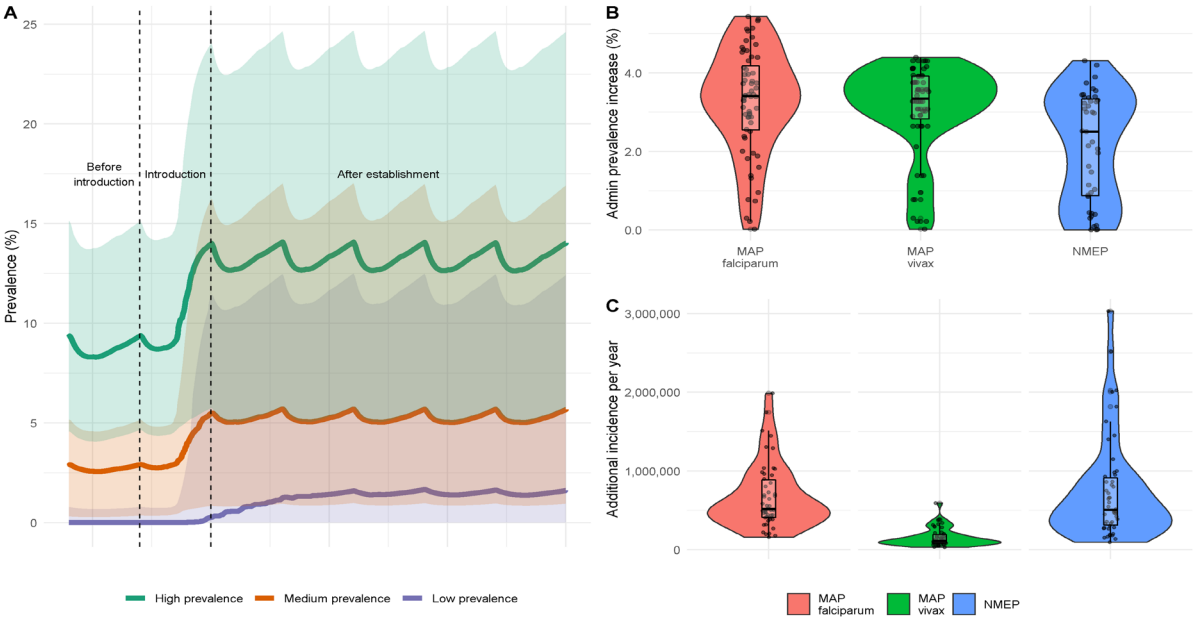
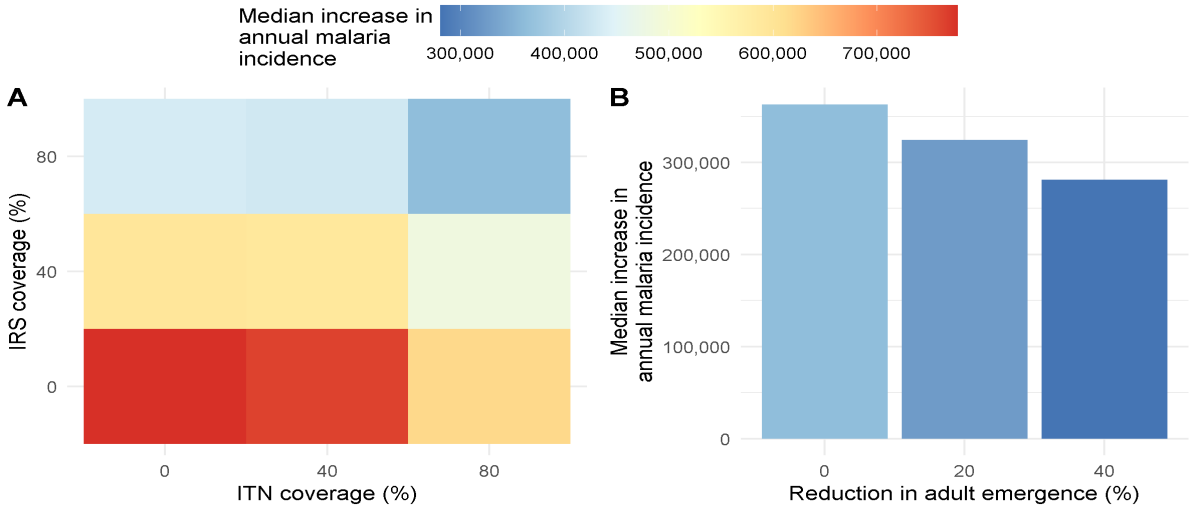


FIGURE 2. THE POTENTIAL IMPACT OF DIFFERENT COMBINATIONS OF CONTROL INTERVENTIONS ON MALARIA TRANSMISSION.

Here the MAP and NMEP data is combined to produce a median increase that is used to estimate A) The median increase of malaria under different ITN usage and IRS coverage started 3 years after the introduction of *An. stephensi*, B) the additional benefit from larvicide which achieves different percentage of reduced adult emergence when ITN usage and IRS coverage is at 80%.



LIMITATIONS

This body of work encompasses substantial assumptions and extrapolations on how malaria transmission will be affected by the establishment of *Anopheles stephensi* in Ethiopia. If, how and where it will invade and the impact it will have are currently all unknown. As a result, the report should be read as a possible scenario of what *could* happen, not as a prediction of what *will* happen. We have simulated different scenarios making explicit assumptions about how entomological and epidemiological factors may influence disease burden and all results should be interpreted in light of these assumptions. We have also included confidence interval estimates on many parameters to reflect their underlying uncertainty. This uncertainty should not be interpreted as the full range of future trajectories which will be substantially greater. We have additionally highlighted which of these parameters could be further refined to better parameterize the model.

Though there is a strong temporal correlation between malaria incidence increases in Djibouti and *An. stephensi* introduction (Seyfarth et al., 2019), there is no evidence to indicate that it is causative. Furthermore, we have assumed that *An. stephensi* is the sole vector responsible for malaria transmission when fitting the data in Djibouti. This is consistent with data presented by Naval Medical Research Unit-No. 3 in Djibouti, but is certainly an oversimplification of the transmission dynamics, given the presence of *An. arabiensis*, in Djibouti and could potentially inflate our results. However, malaria incidence in the early 2010's was almost negligible in Djibouti, but by 2019 they had an estimated ~50,000 cases per year, and so without additional data to the contrary, this was the most parsimonious approach.

Initially mosquito invasion dynamics have been simplified, assuming that all of Ethiopia is suitable for *An. stephensi* establishment and that human-to-mosquito densities universally reach the same level as observed in Djibouti. This is certainly unlikely to be the case but is currently the most parsimonious explanation in the absence of other information. Certain locations are likely to be more or less suitable due to local ecological and anthropological conditions, as well as inter-species competition with other mosquito species. This will likely change both the presence/absence of the species but also their relative abundance. While not accounting for these directly, we have tested the presence/absence assumption by only predicting increases into areas that have been previously estimated to be suitable for *An. stephensi* following an early geostatistical analyses (Sinka et al., 2020) and in those regions under 2000m (Figure 9). While this makes a substantial difference to the overall cases we still estimate an additional ~0.5-0.62 (0.14 – 2.4) million cases (compared to ~4.3-5.3 (1.1 – 22.2) million if the whole country is suitable). This different geographical spread will substantially affect the cost of scaling up interventions. The vector is may additionally be capable of establishing outside of areas previously predicted to be suitable, and by including the effect of a temperature dependent extrinsic incubation period (EIP), we can partially account for the effect of altitude on malaria transmission. This is shown by many of the regions at higher altitudes, with longer EIPs, have minor increases in prevalence (Figure 14). The model also assumes that invasion happens simultaneously everywhere in the country. This is again highly unlikely, though true rate of spread through the country is currently unknown. Our assumption allows the increase in cases to be observed across the region to be independent of the rate of geographical spread. A more realistic increase in burden would be staggered as establishment will likely vary, which has been seen in *An. stephensi* primarily being detected in Eastern Ethiopia, so far (Tadesse et al., 2021).

While we have made use of all available published and unpublished sources on *An. stephensi* bionomics in its endemic range (Manouchehri et al., 1976, Mehravaran et al., 2012, Vatandoost et al., 2006, Mojahedi et al., 2020, Basseri et al., 2010, Basseri et al., 2012, Maghsoodi et al., 2015, Thomas et al., 2017, Sinka et al., 2020, Herrel et al., 2004, Reisen and Boreham, 1982, Pramanik et al., 2006, Soleimani-Ahmadi et al., 2012), and in Africa (Tadesse et al., 2021, Seyfarth et al., 2019, The PMI VectorLink Project, 2020, Balkew et al., 2020) there is either insufficient data or substantial within species variability to simply ascribe a set of characteristics to how *An. stephensi* will interact with humans and control interventions in Ethiopia. In order to capture a range of possibilities in vector bionomics, we assumed a range of likely values for anthropophagy, daily mortality, endophily, the proportion of bites taken indoors and in bed and sampled

across this range during both the initial fitting to Djibouti data, and the forward extrapolation to Ethiopia. It should be stressed that these vector bionomics will influence the effectiveness of vector control interventions against the invading species, so these need to be verified as a matter of urgency.

Data Collection To Inform Mathematical Modelling

Improved understanding of the current entomological and epidemiological situation in regions where *An. stephensi* may invade will improve projections of its potential public health impact and how effective mitigation measures will be. This analyses has highlighted how the increase in malaria burden depends on current malaria endemicity, so more detailed knowledge of the heterogeneity in malaria prevalence and the existing use of vector control interventions in urban and peri-urban areas where the mosquito might invade will be key to understanding overall impact. Malaria burden is also heavily dependent on the abundance of the invading mosquito species and so an understanding of the carrying capacity of the species in the new environment (and how this varies between regions) will enable more tailored projections.

Uncertainty in vector bionomics and behaviours have necessitated several assumptions in this modelling framework. These unknowns, and the sampling structure designed to compensate for them, introduce substantial uncertainty into the results. While a level of uncertainty is expected, with further data on the vector and its role in transmission this can be substantially reduced. Some of the most important vector parameters and what they influence are listed below. We also list the important factors determining intervention effectiveness, many of which will depend on the level of effort deployed. An understanding of the price of these different levels of effort will allow further refinement of the cost-effectiveness analyses.

Parameter type	Parameter	What it informs
Vector bionomic/behaviour	Life-expectancy of An. stephensi in Africa	Disease endemicity and impact of interventions
	Anthropophagy (human blood index)	Disease endemicity and impact of interventions
	Endophily	Impact of IRS
	Proportion of mosquito bites taken when people indoors	Impact of IRS and ITN
	Proportion of mosquito bites taken when people in bed	Impact of IRS and ITN
	Sporozoite rate in different vector species	Estimate of the relative significance of the invading mosquito population in relation to other local species.
	Seasonality of An. stephensi abundance	Impact and requisite frequency of IRS
Intervention Efficacy	Level of pyrethroid resistance	Effectiveness of ITNs (both pyrethroid-only and pyrethroid-PBO nets)
	Percentage of mosquito resting sites accessible to IRS campaigns.	Impact and requisite frequency of IRS
	Durability of IRS in structures in the region (will vary between products)	Impact and requisite frequency of IRS
	Reduction in emergence of adult mosquitoes due to larval source management	Impact of larval source management

1. METHODS

1.1 HUMAN POPULATION SIZES

Administrative unit human population sizes were obtained by using WorldPop 2020 population raster, which provides population estimates at a 1/120 degree resolution (World Population Prospects). This was then standardised to the 2020 Ethiopia country level population estimate from the UN World Population prospects (United Nations, 2020). This raster was then applied to the administrative boundaries in order to estimate populations in each unit.

To estimate the population below a certain altitude or within areas found suitable by previous research (Sinka et al., 2020), we applied theses limits to the above standardised population raster using a suitability raster provided by Sinka et al., (2020) and altitude from WorldClim (Fick and Hijmans, 2017).

1.2 TEMPERATURE AND EIP DATA

Temperature data was accessed by WorldClim (Fick and Hijmans, 2017) which provided monthly temperature data at the maximum, mean and minimum for 2010-2018.

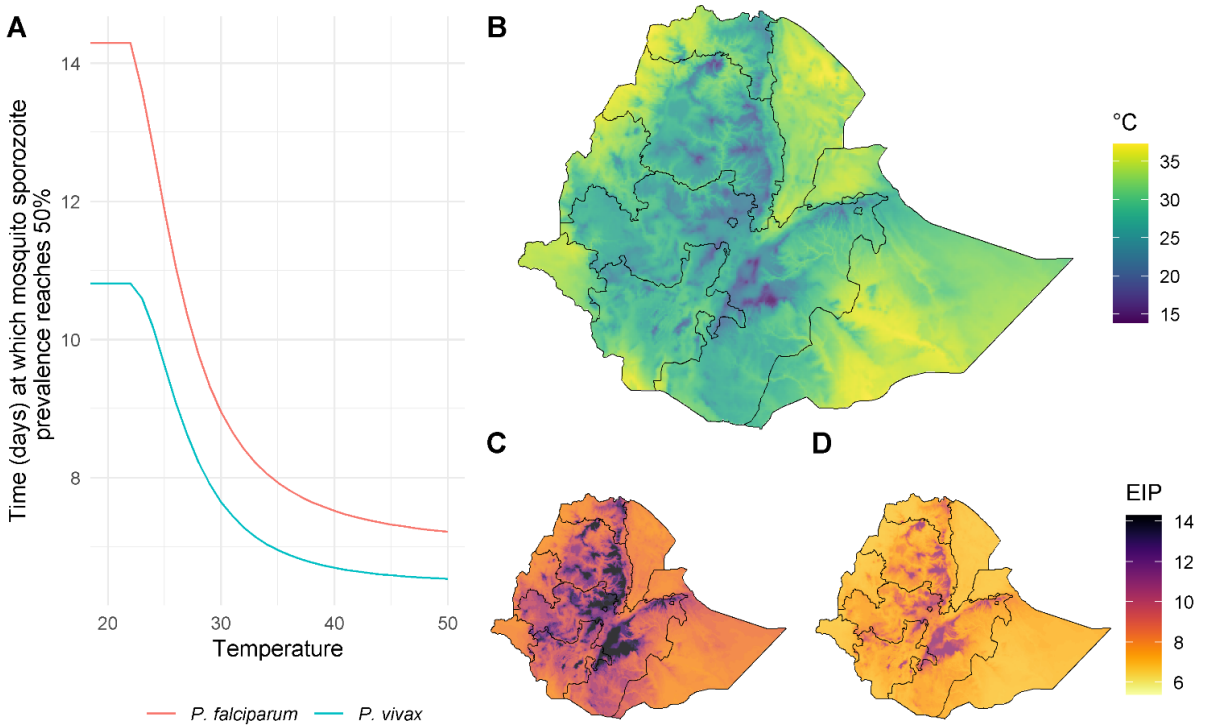
Highland regions of Ethiopia are predicted to be too cold to sustain malaria transmission throughout the year. As a result, here we have used the hottest months mean maximum temperature in the year, as it represents the "extreme" scenario – with the fastest EIP. While this may overestimate the value of EIP overall, the majority of malaria transmission occurs in relatively short "transmission seasons", and so it only takes a few months of heightened suitability in an otherwise less suitable temperature clime to have a substantial effect. Furthermore, additional sensitivity analysis found that taking the corresponding mean/minimum temperature had little impact on overall incidence (Figure 13). This was then averaged over the period to produce a single raster file of temperature at a resolution of 1/120 degrees.

This temperature was then converted into EIP based on a previous quantification by Stopard et al., (2021) which provided a description of the temperature dependent relationship of *Plasmodium falciparum* in *Anopheles stephensi* (Stopard et al., 2021) (Figure 3). As this temperature relationship was modelled on a limited set of temperatures (21-34 °C) it was necessary to extrapolate this further to capture the temperature range of Ethiopia. This necessitated applying the maximum EIP modelled for temperatures lower than 21 °C, for temperatures above 34 °C direct extrapolation was possible, and the relationship extended. In order to account for the persistence of *Plasmodium vivax* at lower temperatures, the fitted results of *P. falciparum* in *An. stephensi* was modulated by applying the ratio of EIP of *P. falciparum* to *P. vivax* estimated from the original Detinova degree day model (Detinova, 1962). For the NMEP data, due to the lack of species specific identifier, we default to the *Plasmodium falciparum* temperature dependent EIP as it is the most formally quantified.

This EIP estimate for each species was converted to the administrative level by taking the mean EIP in an area. All other mosquito bionomics and factors influencing transmission biology are assumed to be independent of temperature or altitude.

FIGURE 3. HOW PARASITE EXTRINSIC INCUBATION PERIOD IS ASSUMED TO VARY ACROSS ETHIOPIA.

A) Relationship between the extrinsic incubation period (days) and temperature for the development of *Plasmodium falciparum* and *vivax* in *Anopheles stephensi* in laboratory studies. B) The maximum monthly annual temperature across Ethiopia. C) Predicted EIP derived from the maximum temperature for *P. falciparum* and D) *P. vivax*.



1.2.1 *PLASMODIUM* PREVALENCE, INCIDENCE, IRS, TREATMENT, AND ITN COVERAGE

Prevalence and treatment (effective treatment with any antimalarial drug) in Ethiopia, were provided by the Malaria Atlas Project (MAP) through the R package, malariaAtlas (Pfeffer et al., 2018). The population-weighted mean value was then taken to provide the value at the 2nd administrative division.

Different estimates of the current level of malaria in Ethiopia exist. The MAP database was used to generate regional prevalence estimates aggregated to the administrative level by taking the population weighted mean (Figure 4). Predictions of the overall number of clinical cases were then generated by adjusting the transmission dynamics model (parameterised with malaria prevalence data) to the number of clinical cases to the values provided by the modelled estimates of malaria incidence in the World Malaria Report (WMR) 2020. This predicted a total of 2,614,852 cases (range 1,453,000 to 3,907,000). Incidence was also provided by the Ethiopian National Malaria Elimination Programme (NMEP) at the 1st administrative division. This source of data indicated a total of 712,021 cases in 2020 which is substantially less than the predicted cases reported in the WMR 2020. Both of these data sources are used independently to parameterise model runs in order to account for the uncertainty in the baseline assessments of malaria endemicity.

ITN coverage at the 1st administrative division, and IRS at the 2nd, was provided through a survey and shared through personal communication (National Malaria Control and Elimination Programme, 2020). In order to simplify the analysis and interpretation, we have assumed that coverage is the same as utilisation – while noting this is a limitation.

FIGURE 4. PARAMETERS INCLUDED FOR EACH ADMINISTRATIVE GROUPING

A) IRS coverage (percent), B) ITN coverage (percent),, C) treatment coverage (percent),, D) EIP for *P. falciparum* (days), E) EIP for *P. vivax* (days)

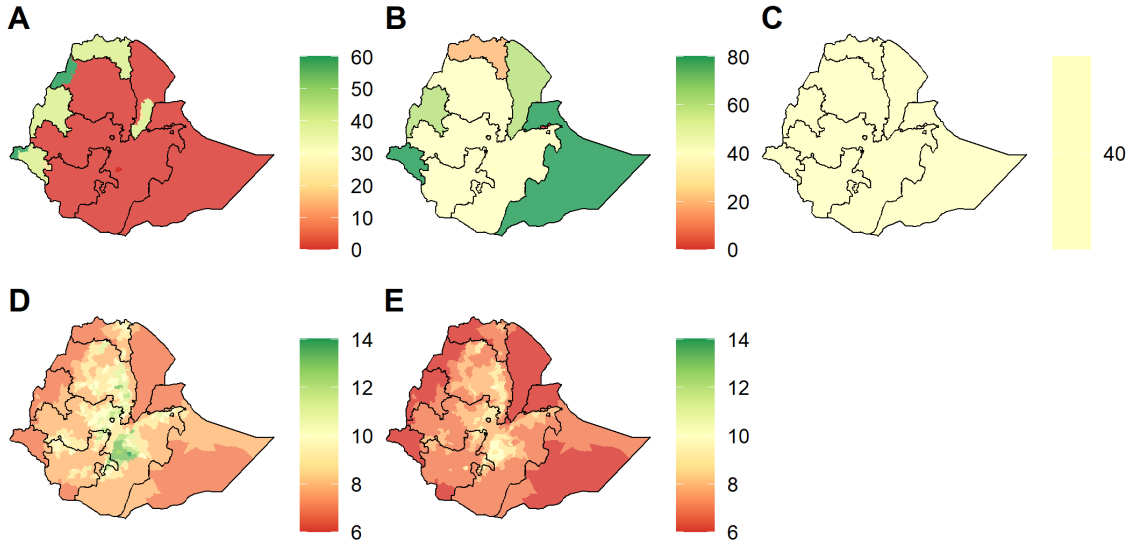
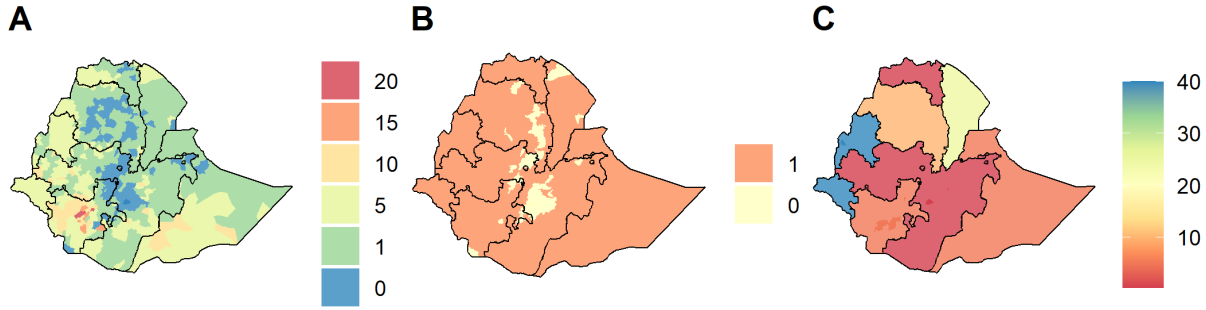


FIGURE 5. CURRENT MALARIA PREVALENCE ASSESSED BY MAP AND INCIDENCE BY THE NMEP.

A) MAP prevalence (2-10 years old) for *P. falciparum*, B) MAP prevalence (all ages) for *P. vivax*, and C) NMEP annual incidence per 1000, for malaria (all ages and species).



1.3 SHAPEFILES AND GROUPING ADMINISTRATIVE UNITS

Shapefiles were provided through the humanitarian data exchange (https://data.humdata.org/dataset/ethiopia-cod-ab) at the country, 1st, 2nd and 3rd administrative unit level.

Administrative units at the 3rd level were grouped based on their pre-existing transmission, interventions and EIP. Here we round prevalence to the nearest 5%, with an additional value of 1% as to capture areas with low but not negligible levels of transmission which account for much of Ethiopia. Interventions and treatment coverages were rounded to the nearest 20% and EIP to the nearest integer. This rounding allows us to substantially reduce the number of runs required, and by using approximate rather than "exact" values from the data we aim to not overstate the accuracy of our findings.

By then grouping administrative locations by their combination of parameters, we can reduce the number of simulations required from 690 (each individual adm3 location) to 64 for those utilising the MAP prevalence data, and 43 for the NMEP incidence data. A full list of locations and values is available in the Appendix (Table 4).

1.4 Vector Bionomics and Latin Hypercube Sampling

A rapid literature search was undertaken aimed at finding *An. stephensi* specific bionomics in order to parameterise the mechanistic model. Data on *An. stephensi*' s behaviour within Africa was sparse, and so most of the information available comes from studies in Iran, India and Pakistan, with limited data from Ethiopia.

Due to the relatively low number of studies, 20, from which the data was collected, and large uncertainty around how the vector would behave, we incorporated parameter sampling in the modelling fitting and extrapolation stage. This was done through taking the median value from the data, and sampling from values 25% smaller and 25% larger than this Table 1. Except for the proportion of blood meals taken on humans, which was ranged from 0.1 to 0.4 given the variations seen across its endemic range, and the importance of the parameter on the model. There is no clear picture of how *An. stephensi* abundance changes with rainfall in Asia, and so mosquito density in Ethiopia is assumed to remain consistent throughout the year.

From this we undertake Latin hypercube sampling (LHS) which is a statistical method for generating near-random samples of parameter values from a multidimensional distribution. This allows us to efficiently sample different parameter combinations in order to generate uncertainty in predictions (Iman, 2014).

Resistance to pyrethroids was taken from, unpublished estimates of *An. stephensi* resistance in Ethiopia from work carried out by the PMI VectorLink Project and estimated at a 57% survival in a discriminating dose bioassay (Yared et al., 2020). This value was assumed throughout the country given the absence of data from most regions.

Table 1. Parameters and Values Used in Latin Hypercube Sampling

Parameter	*Values*
Daily mortality	0.093 – 0.154
Proportion of blood meals taken on humans	0.1 – 0.4
Anthropophilly	0.375 – 0.625
Bites taken indoors	0.358 – 0.597
Bites taken in bed	0.391 – 0.652

1.5 Cost of Interventions Per Person

Approximate estimates of the cost of intervention (purchasing, delivering, and applying) were provided from literature and from the PMI through personal communication. We have assumed 1.8 people per ITN, which were assumed to be standard pyrethroid nets.

Table 2. Approximate Estimated Costs Per Person Per Year for the Different Vector Control Interventions Considered

Intervention	*Costing estimate per year per person*		
	Low	Medium	High
ITN-pyrethroid	$0.43	$0.45	$0.49
IRS	$3.35	$6.19	$8.9
Larvicide	$1.00	$2.00	$3.00

1.6 Mechanistic Model

Here we use a deterministic version of a well-established and highly utilised compartmental model of *Plasmodium falciparum* malaria transmission (Griffin et al., 2014, Challenger et al., 2021, Griffin et al., 2010, White et al., 2011, Griffin et al., 2016), which models transmission within humans at various stages of infection, and the vectors themselves. We account for heterogeneity in transmission as well as age-

dependent biting rates and the acquisition of natural immunity. The model has previously been described fully in the aforementioned publications, but we summarise it briefly below (Figure 6).

When Susceptible (S) individuals become infected, they progress to either an asymptomatic (A) state or clinical disease, dependent on the force of infection, Λ, and the probability of acquiring clinical disease, φ, which is dependent on natural immunity. Dependent on infection, those progressing to clinical disease either enter the treated (T) or clinical disease (D) compartment dependent on the probability of treatment (f_T). Treated individuals progress through to a period of protection through prophylaxis (P), at rate r_T, and return to the susceptible compartment at rate r_P.

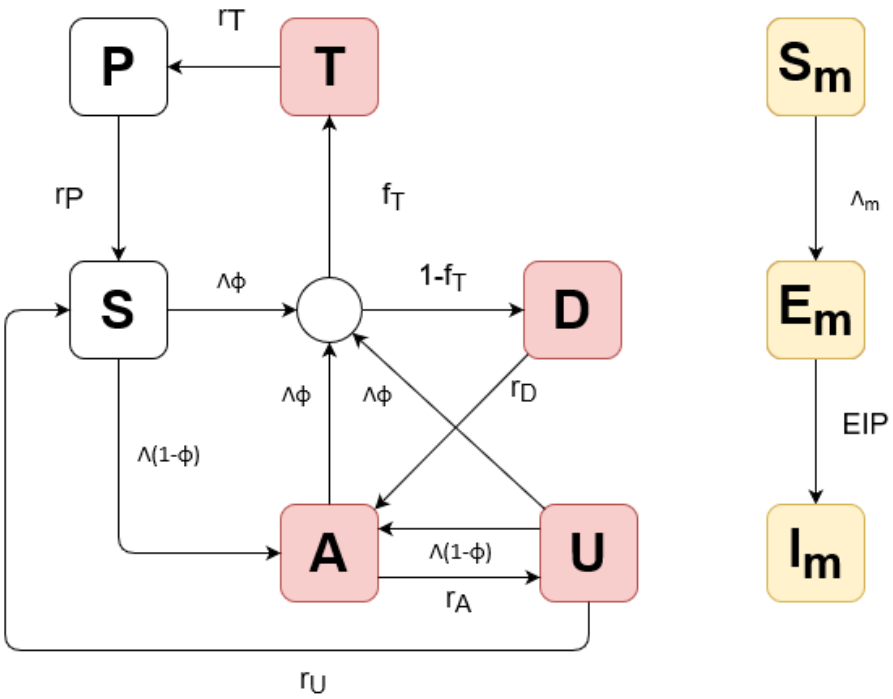
Individuals in clinical disease (D) remain symptomatic for the duration of the disease course, r_D, then move to an asymptomatic state (A), which is detectable through microscopy, before the infection becomes submicroscopic and so undetectable through microscopy (U) at rate r_A. Asymptomatic individuals (in either the A or U compartment) can develop clinical disease, but if they do not, they clear the infection and return to the symptomatic compartment at rate r_U. Adult mosquito populations are modelled through a susceptible (S_m) and progress to the exposed (E_m) state at rate Λ_m, and onto the infectious (I_m) after the extrinsic incubation period (EIP) has been completed. Mosquitoes are exposed to human infection through feeding through the treated (T), clinical disease (D), asymptomatic (A) and submicroscopic (U) infection states.

To simulate the invasion of *An. stephensi*, the vector density is increased in a sigmoidal fashion over 3 years so that malaria clinical incidence best fits that reported in the Djibouti data (Figure 8).

The package required to run the model and a version of the model code is found at https://github.com/mrc-ide/deterministic-malaria-model.

FIGURE 6. MODEL DIAGRAM SHOWING THE PROGRESSION BETWEEN HUMAN AND VECTOR STATES

S = susceptible, A = asymptomatic, T = treated, D = clinical disease, U = submicroscopic infection, S_m = Susceptible mosquitoes, E_m = exposed mosquitoes, I_m = infectious mosquitoes. The arrows shown transitions between compartments and the circle represents treatment. Red compartments indicate states that can expose susceptible mosquitoes to infection and yellow the mosquito compartments. The life-cycle of the pre-adult life-stages of the mosquito are omitted for simplicity though see (White et al., 2011) for full details.



The model outlined in Figure 5 is for *falciparum* malaria. As both *falciparum* and *vivax* malaria are present in Ethiopia, an approximation of the impact on *vivax* malaria was generated by rerunning the *falciparum* model for regions with *P. vivax* assuming a *vivax* malaria EIP. This necessary simplification given the timescale enables estimates of *P. vivax* burden, but results should be treated with caution due to the absence of species-specific parameterisation and the lack of a hypnozoite stage in the model structure. The model will therefore be more appropriate for assessing the spread of *vivax* malaria rather than the decline following control interventions as this is likely to be overly optimistic.

There are three types of existing anti-malaria interventions assumed to be present prior to the invasion of *An. stephensi*; treatment of clinical disease, insecticide treated nets (ITNs) and indoor residual spraying (IRS). Treatment influences the probability of transition through compartments once infected as detailed in Figure 6. Generally, IRS and ITNs alter transmission through two aspects:

1. Altering vector behaviour
    a. Increasing the daily mortality rate
    b. Lengthening the time between bloodmeals
    c. Reducing the human blood index (HBI)
2. Protecting human populations
    a. Reducing the number of infectious bites taken on protected people and unprotected people

For ITNs, the impact of their use depends on which the type of ITN used, insecticide resistance in the mosquito, and the duration of net use, as efficacy decays over time. The framework for including the entomological impact of pyrethroid resistant mosquitoes as described by the discriminating dose bioassay follows methods derived by (Churcher et al., 2016) but updated in December 2020. IRS accounts for similar characteristics, with the additional consideration of the anthropophily, the propensity for the vector to associate with areas of human habitation (and so be rest on treated surfaces) as a modifier for mortality. Full details can be found elsewhere (Sherrard-Smith et al., 2018).

We assume a 3-year mass distribution of ITNs. IRS is conducted annually with a long-lasting product which the local mosquito population is fully susceptible to. The efficacy of ITNs and IRS decay over the product lifespan of 3 and 1 years respectively. Widespread usage of larval control is assumed to be constant and at a level to reduce adult emergence by the coverage stated.

1.7 Modelling Framework

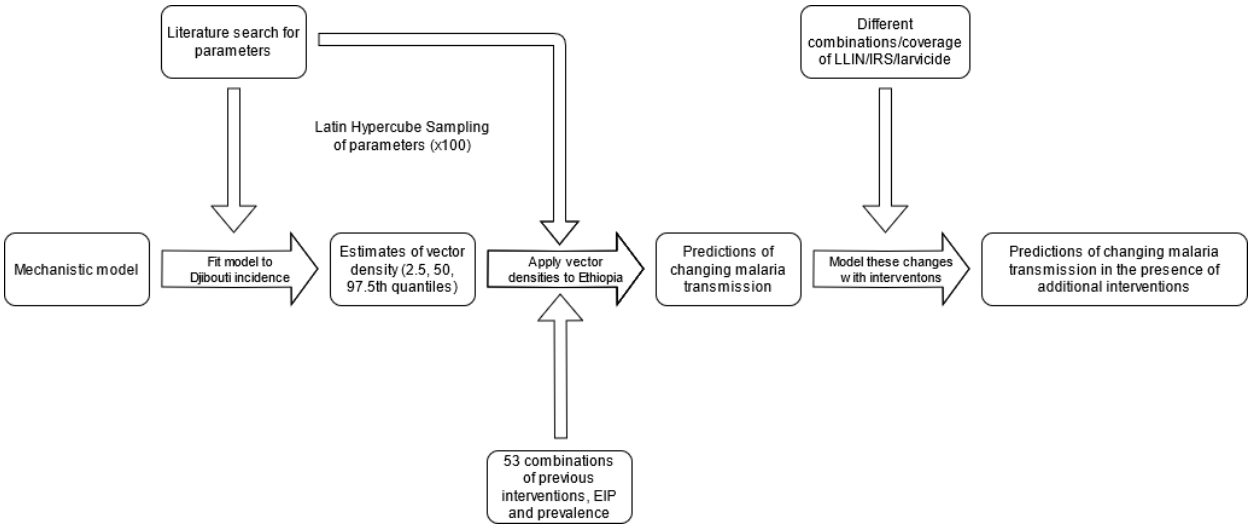
Initially the mechanistic model is fit to malaria incidence data in Djibouti using 200 draws of Latin Hypercube Sampling of vector bionomics and EIP derived from Djibouti temperature data. In order to fit to the data, the vector density is varied – producing estimates of the required vector density increase to reach the incidence observed. From these fits, we discard LHC combinations that are biologically implausible, or unable to be fit adequately to the data and take the 50 best fitting draws of the LHC. We then re-assess the remaining draws and confirm they continue to represent the range and non-correlation of the original draws.

The 2.5, 50 and 97.5th quantiles of these fit vector densities are then applied to the 64 combinations of previous interventions, EIP and prevalence for the MAP data and the 43 for the NMEP data, for a total of 192 and runs respectively. These combinations of previous interventions, EIP and prevalence are then used to calibrate the model, so that starting conditions pre-*stephensi* accurately replicate the current malaria context and environment. These are then run for each of the 50 draws of the Latin Hypercube for a total of 9600 for each *falciparum* and *vivax* MAP runs, and 6450 for the NMEP runs to produce predictions of changing malaria transmission.

From this, different combinations of coverage of ITN/IRS/larvicide are run to produce estimates of how these changes in malaria will occur in the presence of additional interventions. Individual model runs are

calibrated to the expected number of malaria cases pre-introduction of *An. stephensi* in order to replicate current conditions.

FIGURE 7. THE MODELLING FRAMEWORK USED FOR THE ANALYSIS.



1.8 COMBINING MODEL PREDICTIONS

In order to utilise all available data sources (MAP and NMEP) in our predictions of the impact of interventions, we have taken the median of the MAP (*falciparum* + *vivax*) and NMEP predictions for each intervention combination. By doing so we hope to compensate for some of the intrinsic surveillance or data assumption issues that are found in either dataset.

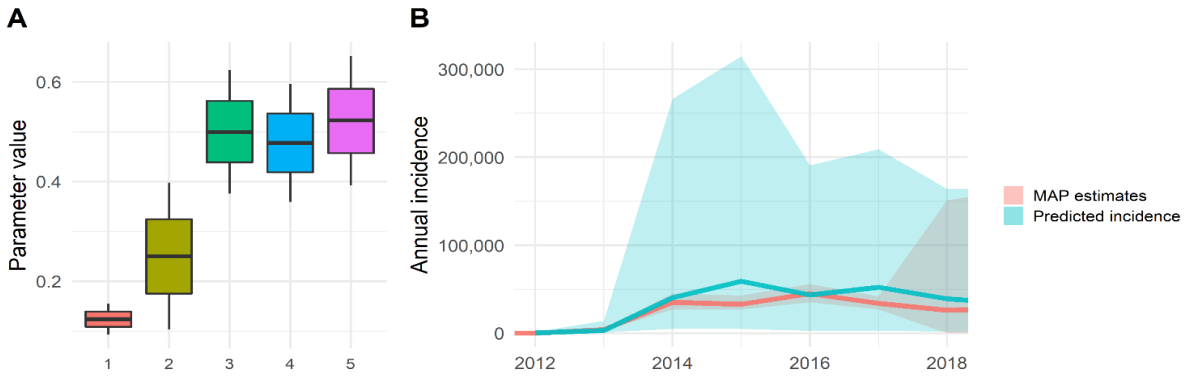
2. Additional Results

2.1 Parameter Ranges Sampled in the Latin Hypercube Sampling and Fitting to Djibouti Malaria Incidence Data

In order to account for the substantial uncertainty around vector bionomics, we used LHS of vector bionomics in order to parameterise the vector component of the model (Figure 8A). Due to the wide array of parameters sampled, and that some of these will over- or underestimate incidence, we find large estimates vary substantially across parameterisations. However, the median predicted incidence closely follows the MAP estimates the model is fit to.

Figure 8. Parameter Ranges Sampled Using LHS and Model Fits to Djibouti Incidence Data

A) Boxplots of mosquito bionomics sampled. 1 = Daily mortality, 2 = Anthropophagy, 3 = Endophily, 4 = Bites taken indoors, 5 = Bites taken in bed. B) Model fit to Djibouti incidence provided by the Malaria Atlas Project. Red line, and shaded area shows median MAP estimates and confidence intervals around these. The blue line and the shaded area depict the median and 50% credible intervals of model predicted incidence.



2.2 Impact of *Anopheles stephensi* under Different Assumptions of Populations Exposed

Here we have varied where *An. stephensi* is predicted to increase based on pre-existing estimates of regional suitability for *An. stephensi* as estimated using the geostatistical models of (Sinka et al., 2020). This particularly highlights urban areas, though many people reside in these regions meaning the epidemiological impact could be substantial (Figure 9). Another method of generating alternative metrics of the population suitable for ongoing malaria transmission is to only include communities under 2000m, as estimate of an altitude above which malaria transmission is less suitable. This assumption means that a much wider geographical region is suitable but excludes some large cities so the population at risk is substantially lower (Table 3). If *An. stephensi* is confined to areas previously demarked as suitable then we project an additional ~0.7-0.9 million malaria cases a year with a plausible range of (0.19–3.6) million cases, or a 26-120% (7–500%) increase in cases per year. This compared to ~4.3-5.3 (1.1–22.2) million if the whole country is equally suitable, 165-744% (42-3117%), and ~2.5-3.1 (0.7-12.7) million, 96-435% (26–1784%) if we only consider areas under 2000m.

The combination of these estimates leads to ~0.50-0.62 (0.14–2.4) million cases (Figure 9 and Table 3), a 19-87% increase (95% CI 5-338%). Estimates vary substantially according to the assumed malaria burden, be it NMEP or MAP. Both are presented for completeness in Figure 9 and Table 3.

Figure 9. Sensitivity Analyses Given Uncertainty of the Range of Environments Suitable for *An. stephensi* Malaria Transmission and Different Sources of Data for Parameterisation

A) Comparison of different population denominators on the estimates of increases to malaria incidence, B) Ethiopian areas over/under 2000m and C) Sinka et al., (2020) estimates of suitability normalised to a 0-1 scale, the cut-off assumed was 0.5. Coloured points in panel A, indicate the calculated annual incidence increase for individual LHC runs.

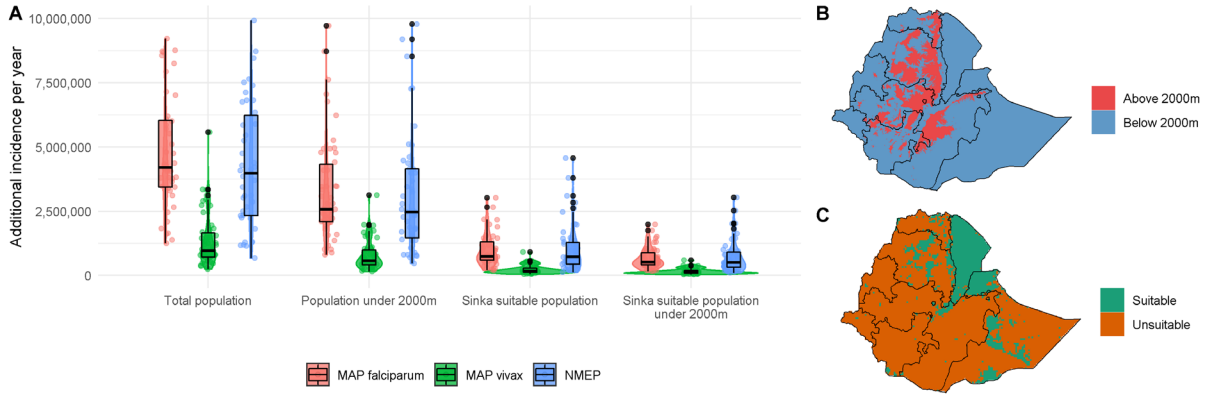


Table 3. Populations and Increase in Annual Incidence from Pre-Stephensi to After Establishment for Different Scenarios and by Data Sources

Cases prior to the invasion of *An. stephensi* were assumed to be 2,614,852 (MAP) and 712,021 (NMEP) per year all species combined. MAP estimates are divided into estimates of falciparum and vivax malaria whilst NMEP estimates are combined.

Population Type	Population Size	Malaria Data Source	Increase In Annual Incidence (95% Ci)	Increase In Annual Incidence All Malaria (95% Ci)
Total Population	114,139,000	MAP *falciparum*	4,352,000 (1,434,000-15,170,000)	
Total Population	114,139,000	MAP *vivax*	955,000 (307,000-3,348,000)	5,307,000 (1,741,000-18,518,000)
Total Population	114,139,000	NMEP	4,328,000 (1,151,000-22,185,000)	
Population Under 2000m	63,564,000	MAP *falciparum*	2,572,000 (913,000-8,474,000)	
Population Under 2000m	63,564,000	MAP *vivax*	563,000 (188,000-1,968,000)	3,135,000 (1,101,000-10,442,000)
Population Under 2000m	63,564,000	NMEP	2,529,000 (711,000-12,730,000)	
Sinka Suitable Population	18,757,000	MAP *falciparum*	737,000 (239,000-2,548,000)	
Sinka Suitable Population	18,757,000	MAP *vivax*	158,000 (52,000-563,000)	895,000 (291,000-3,111,000)
Sinka Suitable Population	18,757,000	NMEP	729,000 (193,000-3,634,000)	
Sinka Suitable Population Under 2000m	12,410,000	MAP *falciparum*	515,000 (181,000-1,692,000)	
Sinka Suitable Population Under 2000m	12,410,000	MAP *vivax*	109,000 (38,000-384,000)	624,000 (219,000-2,076,000)
Sinka Suitable Population Under 2000m	12,410,000	NMEP	504,000 (140,000-2,406,000)	

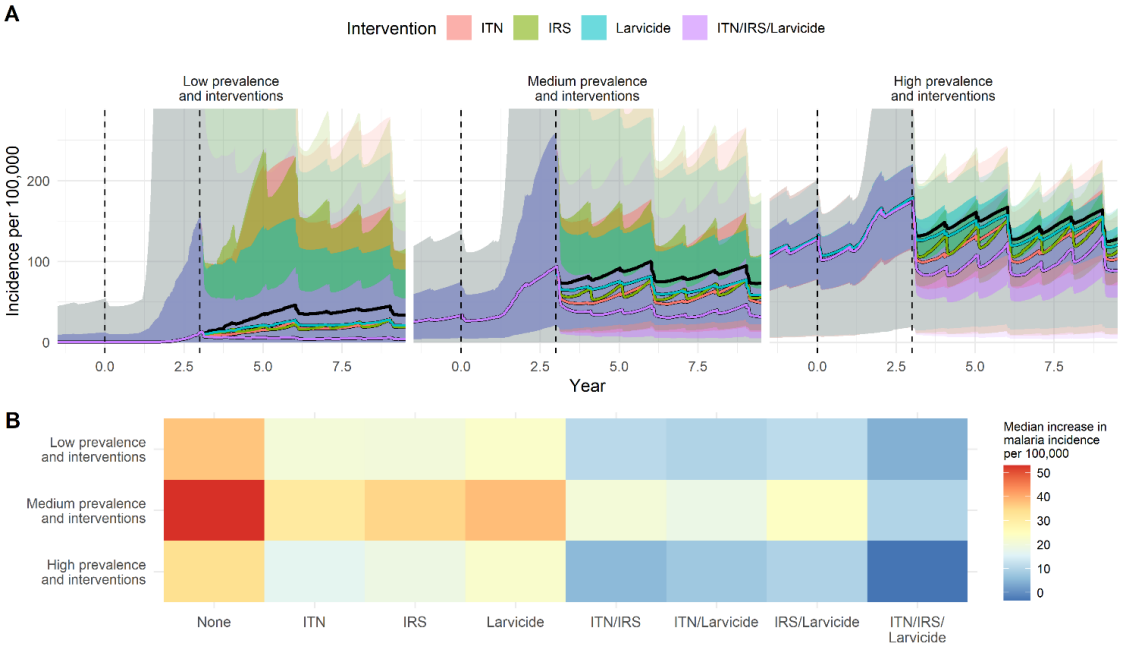
2.3 Potential Intervention Combinations

In the absence of any scaleup of interventions, proportionally, areas without current transmission or interventions may see the largest increases in incidence, with corresponding high levels of uncertainty (Figure 10A). In absolute terms, it is areas with intermediate levels of transmission (for example, ~5%) and interventions that see the most additional malaria cases (Figure 10B).

In areas without high levels of pre-existing interventions, scaling up a single control measure may lead to relatively minor decreases in incidence following establishment. However, in areas where existing interventions are already at an intermediate level of transmission and higher coverage, a single intervention has minimal effect, and combinations of interventions are required in order to mitigate impact. At higher levels of transmission and intervention, though due to the non-linear relationship of prevalence and vector density, additional invading vectors have a relatively minimal increase to transmission, and already high levels of interventions mean that the effects are not as dramatic as in intermediate settings. The largest decreases in incidence across prevalence and intervention are seen by combining all three modelled interventions. Care should be taken interpreting these findings as the effectiveness of existing control interventions on the invading vector are unknown.

Figure 10. The Effect of Control Measures on Mitigating the Impact of *An. stephensi* Introduction for Different Regions

A) The relationship of *An. stephensi* introduction and incidence in three locations, with low (~0.1%), medium (~5%) and high prevalence (~25%), with the impact of control measures. The solid line indicates the median value, dark coloured shapes show the 50% CIs and light the 95% CIs, plot is cropped to 50% CIs for ease of interpretation, black line shows the no intervention scenario. Year 0 refers to the introduction of *An. stephensi*, which occurs between the dashed lines and is fully established by year 3. B) The median increase in malaria incidence per 100,000 comparing before and after scenarios for each of the locations across a range of intervention combinations. The increase here refers to the difference in the median incidence of the 3 years prior to the introduction of *An. stephensi*, and the median incidence across years 6 to 9 after the introduction and establishment of *An. stephensi*. We assume pre-existing interventions (Table 4) and scale up of ITN/IRS to a minimum of 80% (if prior coverage was higher, this is maintained) and a reduction in the emergence of adult mosquitoes by 40% for larviciding.



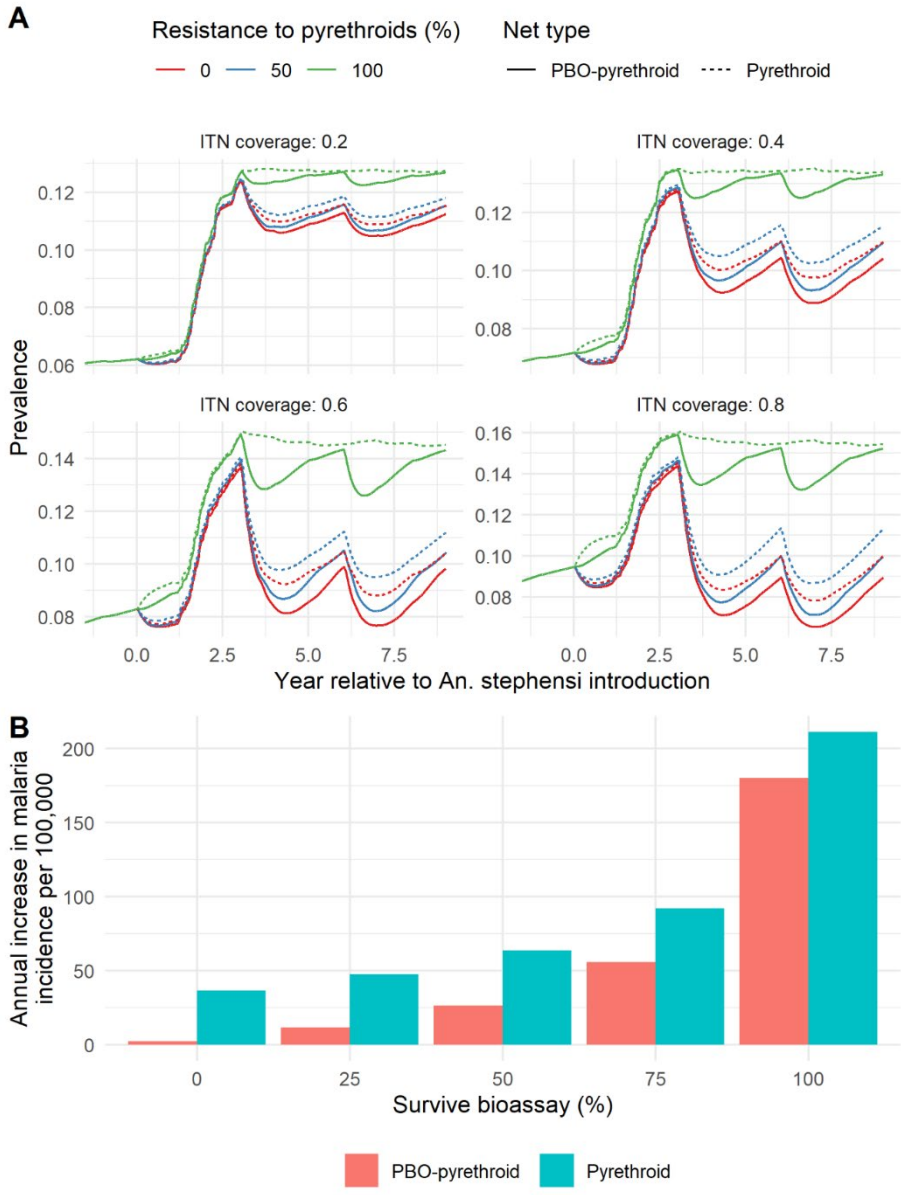
2.4 Additional Impact of PBO-pyrethroid ITN

In the presence of significant levels of pyrethroid resistance, the utilisation of PBO-pyrethroid ITNs over standard pyrethroid ITNs can offer an additional reduction in *An. stephensi* malaria transmission (Figure 11).

At low levels of resistance, and low levels of ITN coverage, there is minimal effect of resistance. However, as both coverage and resistance increase the benefits of PBO-pyrethroid nets become substantial. Given the current level of resistance documented among *An. stephensi* in Ethiopia (~57%), the scenario of 50% resistance is most comparable, and at 80% ITN coverage this offers an additional 1-2% reduction in prevalence. In terms of annual incidence, there are substantial gains made even at lower levels of pyrethroid resistance, at 50% bioassay survival we estimate that the use of PBO-pyrethroid nets will reduce the annual increase in malaria by ~60% compared to using standard nets.

Figure 11. The Potential Impact of PBO-pyrethroid and Pyrethroid-only Nets on an Example Population of Differing ITN Coverage and Pyrethroid Resistance

A) The impact of different net type coverages of ITN and resistance to pyrethroids on the prevalence of malaria and B) the annual incidence increase in malaria per 100,000 across different bioassay survival rates for net types at 60% ITN coverage.



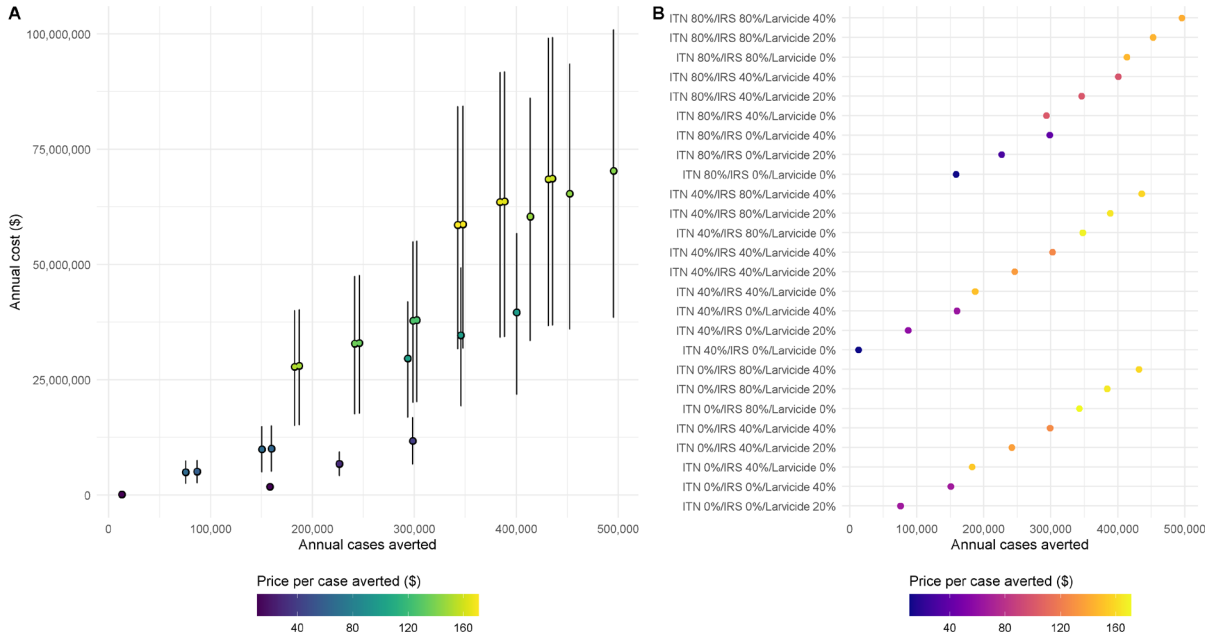
2.5 Economic Impact of Establishment, and the Costs Associated with Intervention Strategies

Here, using the median malaria increase, a combination of MAP and NMEP model estimates, we estimate the cost of different intervention strategies and their epidemiological impacts. Different strategies are going to have different costs depending on the size of the population at risk. If *An. stephensi* invades areas of Ethiopia under 2000m, and previously found to be suitable for *An. stephensi*, (Sinka et al., 2020), the most intensive intervention scenario of 80% ITN/IRS coverage and 40% larvicide coverage estimated at a total cost of ~$70 million dollars ($38-$101 million) per year, and $142 ($78- $204) per case averted.

For a full breakdown of interventions and costs by population targeted see Table 6.

Figure 12. Costs of Different Vector Control Interventions in Combination to Mitigate the Impact of *An. stephensi* Invasion

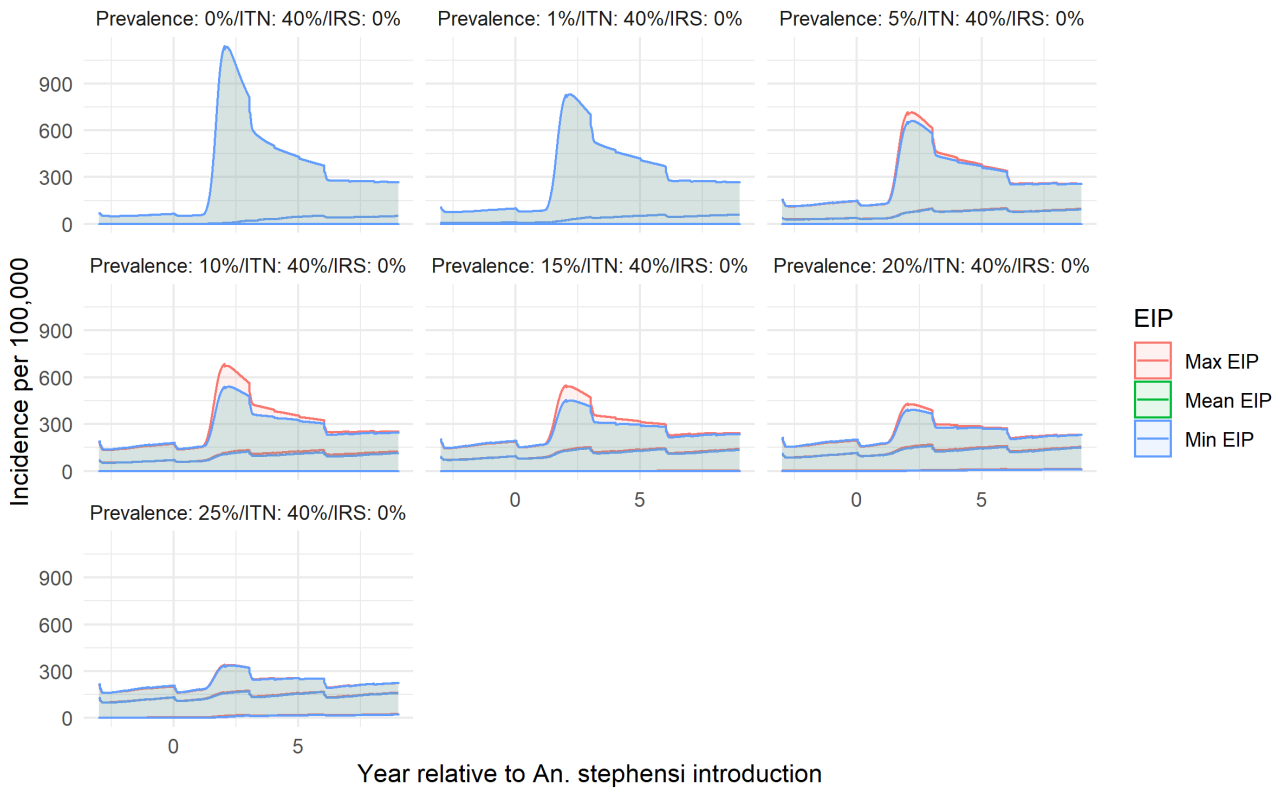
A) The number of cases averted and the annual cost, coloured by the cost per case averted across all interventions considered, illustration to show range in overall costs and impacts. B) The total cases averted for all intervention combinations considered coloured the price per case averted. For ease of interpretation the median annual cases averted is used.



2.6 Differing Values of EIP

In our baseline scenarios we have utilised the maximum temperature in an area in order to calculate the EIP (max EIP). While this is an extreme scenario, given the potential seasonal nature of malaria where the majority of transmission can occur in a few months, we believe this is a permissible assumption. Furthermore, when utilising different temperature values (mean and minimum) there is only a minor effect on the predicted incidence (Figure 13).

FIGURE 13. IMPACT OF DIFFERENT EIP ASSUMPTIONS ON THE INCIDENCE PER 100,000 FOR 7 DIFFERENT LOCATIONS WITH DIFFERENT PRE-EXISTING *FALCIPARUM* PREVALENCE (2-10 YEAR OLDS) AND INTERVENTIONS.

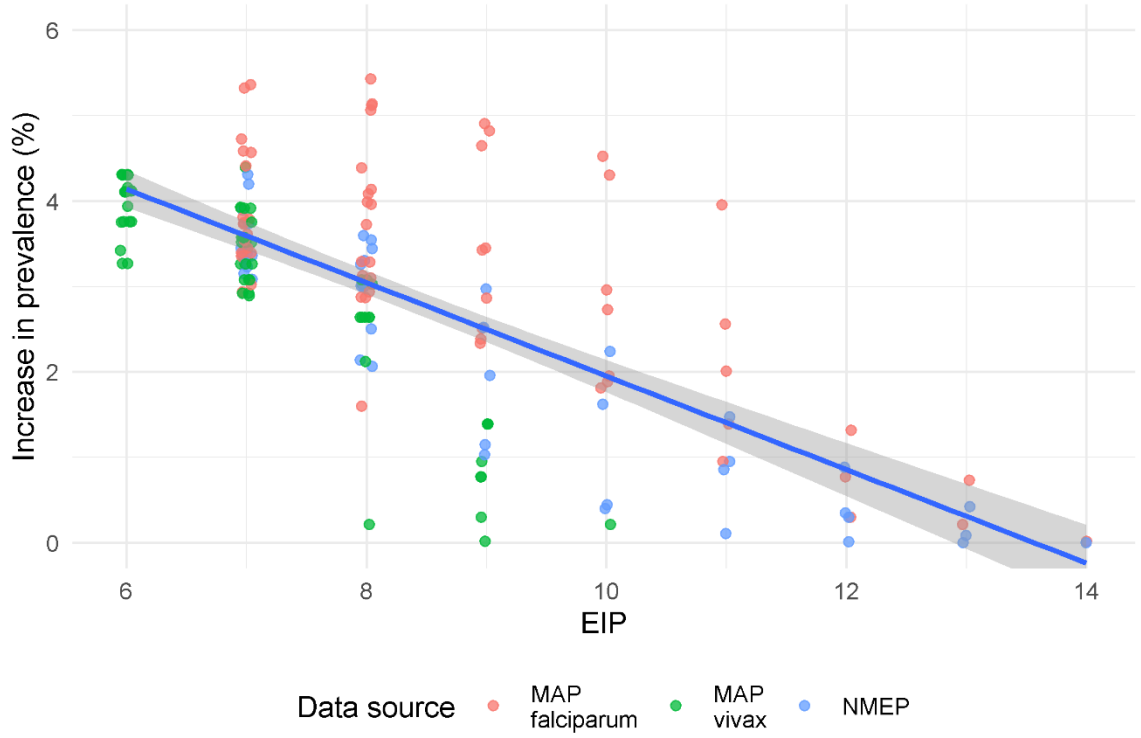


2.6.1 RELATIONSHIP OF EIP AND INCREASES IN PREVALENCE

Areas at higher altitude have lower values of temperature dependent EIP. Following the establishment of *An. stephensi*, there is predicted to be minimal increase in malaria prevalence in areas with high EIPs, those at higher altitudes, compared to those at lower altitudes, and so lower EIPs. This is because the average time for a mosquito to acquire *Plasmodium* infection and then develop infectiousness begins to eclipse the expected lifespan of the mosquito. In these areas even if *An. stephensi* was to establish, it would have a minimal contribution to malaria transmission.

FIGURE 14. RELATIONSHIP OF ABSOLUTE PREVALENCE INCREASE FOLLOWING *AN. STEPHENSI* INTRODUCTION AND EIP ACROSS DATA SOURCES

Points are jittered on the x-axis to aid interpretation, but are integer values in the data. Line represents a linear regression of the relationship of increase in prevalence and EIP.



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Appendix

Table 4. MAP grouping of administrative units and the number of admin units per category (total 650), by *P. falciparum* prevalence, IRS/ITN coverage and *P. falciparum* EIP with corresponding EIP of *P. vivax* and *P. vivax* prevalence.

ID	No. admin units	Falciparum prevalence (2-10 years)	Vivax prevalence (All ages)	IRS	ITN	EIP falciparum	EIP vivax
1	1	0	0	0	0.4	14	9
2	11	0	0	0	0.4	13	10
3	2	0	0	0	0	12	10
4	22	0	0	0	0.4	12	9
5	4	0	0	0	0	11	9
6	28	0	0	0	0.4	11	9
7	1	0	0.01	0.4	0.2	10	8
8	26	0	0.01	0	0.4	10	8
9	3	0	0.01	0.4	0.2	9	7
10	31	0	0.01	0	0.4	9	8
11	1	0	0.01	0.4	0.2	8	7
12	15	0	0.01	0	0.4	8	7
13	1	0	0.01	0	0.8	8	7
14	1	0	0	0	0.4	7	6
15	3	0	0.01	0	0.6	7	6
16	2	0.01	0	0	0.4	13	10
17	3	0.01	0	0	0.4	12	9
18	11	0.01	0	0	0.4	11	9
19	3	0.01	0.01	0.4	0.2	10	8
20	50	0.01	0.01	0	0.4	10	8
21	5	0.01	0.01	0.4	0.2	9	7
22	68	0.01	0.01	0	0.4	9	8
23	2	0.01	0.01	0	0.8	9	7
24	2	0.01	0.01	0	0	8	7
25	11	0.01	0.01	0.4	0.2	8	7
26	117	0.01	0.01	0	0.4	8	7
27	3	0.01	0.01	0.4	0.6	8	7
28	13	0.01	0.01	0	0.8	8	7
29	3	0.01	0.01	0.4	0.2	7	6
30	4	0.01	0.01	0	0.4	7	6
31	2	0.01	0.01	0.6	0.4	7	6
32	19	0.01	0.01	0	0.6	7	6
33	1	0.01	0.01	0.2	0.6	7	6
34	8	0.01	0.01	0.4	0.6	7	6
35	12	0.01	0.01	0	0.8	7	6

ID	No. admin units	Falciparum prevalence (2-10 years)	Vivax prevalence (All ages)	IRS	ITN	EIP falciparum	EIP vivax
36	6	0.05	0	0	0.4	11	9
37	2	0.05	0.01	0	0.4	10	8
38	1	0.05	0.01	0.4	0.2	9	7
39	28	0.05	0.01	0	0.4	9	7
40	1	0.05	0.01	0.4	0.2	8	7
41	59	0.05	0.01	0	0.4	8	7
42	2	0.05	0.01	0	0.6	8	7
43	6	0.05	0.01	0.4	0.6	8	7
44	4	0.05	0.01	0	0.8	8	7
45	2	0.05	0.01	0.2	0.8	8	7
46	5	0.05	0.01	0.4	0.2	7	6
47	3	0.05	0.01	0	0.4	7	6
48	1	0.05	0.01	0.6	0.4	7	6
49	2	0.05	0.01	0	0.6	7	6
50	8	0.05	0.01	0.4	0.6	7	6
51	16	0.05	0.01	0	0.8	7	6
52	7	0.05	0.01	0.4	0.8	7	6
53	4	0.05	0.01	0.6	0.8	7	6
54	1	0.1	0.01	0	0.4	11	8
55	2	0.1	0.01	0	0.4	10	8
56	6	0.1	0.01	0	0.4	9	7
57	21	0.1	0.01	0	0.4	8	7
58	1	0.1	0.01	0	0.8	8	7
59	1	0.1	0.01	0	0.4	7	6
60	4	0.1	0.01	0	0.8	7	6
61	1	0.15	0.01	0	0.4	10	8
62	1	0.15	0.01	0	0.4	9	7
63	4	0.15	0.01	0	0.4	8	7
64	2	0.2	0.01	0	0.4	8	7

TABLE 5. NMEP GROUPING OF ADMINISTRATIVE UNITS AND THE NUMBER OF ADMIN UNITS PER CATEGORY (TOTAL 650), BY INCIDENCE, IRS/ITN COVERAGE AND EIP.

ID	No. admin units	Malaria incidence	IRS	ITN	EIP
1	4	0.0003	0	0	11
2	41	0.0003	0	0.4	10
3	2	0.0003	0	0	12
4	20	0.0003	0	0.4	11
5	24	0.025	0	0.6	7
6	2	0.025	0	0.6	8
7	4	0.025	0.4	0.6	7
8	1	0.025	0.4	0.6	8
9	1	0.025	0.2	0.6	7

ID	No. admin units	Malaria incidence	IRS	ITN	EIP
10	35	0.01	0	0.4	9
11	20	0.01	0	0.4	10
12	47	0.01	0	0.4	8
13	4	0.01	0	0.4	7
14	18	0.01	0	0.4	11
15	1	0.01	0	0.4	13
16	1	0.01	0	0.4	12
17	3	0.01	0.6	0.4	7
18	12	0.04	0.4	0.6	7
19	8	0.04	0.4	0.6	8
20	2	0.0003	0	0	8
21	7	0.04	0.4	0.8	7
22	2	0.04	0.2	0.8	8
23	4	0.04	0.6	0.8	7
24	66	0.0003	0	0.4	9
25	10	0.0003	0	0.4	13
26	16	0.0003	0	0.4	12
27	109	0.0003	0	0.4	8
28	1	0.0003	0	0.4	14
29	2	0.0003	0	0.4	7
30	32	0.005	0	0.8	7
31	19	0.005	0	0.8	8
32	2	0.005	0	0.8	9
33	62	0.005	0	0.4	8
34	33	0.005	0	0.4	9
35	3	0.005	0	0.4	7
36	20	0.005	0	0.4	10
37	8	0.005	0	0.4	11
38	8	0.005	0	0.4	12
39	2	0.005	0	0.4	13
40	9	0.0003	0.4	0.2	9
41	13	0.0003	0.4	0.2	8
42	4	0.0003	0.4	0.2	10
43	8	0.0003	0.4	0.2	7

TABLE 6. DIFFERENT INTERVENTION BREAKDOWNS BY POPULATION SCENARIO, THE POPULATION NUMBER TARGETED, THE MEDIAN CASES AVERTED AND THE TOTAL COST AND COST PER CASE.

Intervention	Scenario	Population Targeted (ITN/IRS/Reduction)	Median Cases Averted	Total Cost ($)	Cost Per Case Averted ($)
ITN 0%/IRS 0%/LARVICIDE 0%	Total	0/0/0	0	0 (0-0)	0 (0-0)
ITN 0%/IRS 0%/LARVICIDE 0%	Under 2000m	0/0/0	0	0 (0-0)	0 (0-0)
ITN 0%/IRS 0%/LARVICIDE 0%	Sinka	0/0/0	0	0 (0-0)	0 (0-0)
ITN 0%/IRS 0%/LARVICIDE 0%	Sinka under 2000m	0/0/0	0	0 (0-0)	NaN (NaN-NaN)
ITN 0%/IRS 0%/LARVICIDE 20%	Total	0/0/22,828,000	692,000	45,656,000 (22,828,000-68,484,000)	8 (4-12)
ITN 0%/IRS 0%/LARVICIDE 20%	Under 2000m	0/0/12,713,000	382,000	7,503,000 (3,751,000-11,254,000)	2 (1-3)
ITN 0%/IRS 0%/LARVICIDE 20%	Sinka	0/0/3,751,000	118,000	25,426,000 (12,713,000-38,138,000)	74 (37-110)
ITN 0%/IRS 0%/LARVICIDE 20%	Sinka under 2000m	0/0/2,482,000	75,000	4,964,000 (2,482,000-7,446,000)	66 (33-99)
ITN 0%/IRS 0%/LARVICIDE 40%	Total	0/0/45,656,000	1,358,000	91,312,000 (45,656,000-136,967,000)	16 (8-24)
ITN 0%/IRS 0%/LARVICIDE 40%	Under 2000m	0/0/25,426,000	758,000	15,006,000 (7,503,000-22,509,000)	5 (2-7)
ITN 0%/IRS 0%/LARVICIDE 40%	Sinka	0/0/7,503,000	234,000	50,851,000 (25,426,000-76,277,000)	121 (60-181)
ITN 0%/IRS 0%/LARVICIDE 40%	Sinka under 2000m	0/0/4,964,000	150,000	9,928,000 (4,964,000-14,892,000)	66 (33-99)
ITN 0%/IRS 40%/LARVICIDE 0%	Total	0/42,021,000/0	1,457,000	260,107,000 (140,769,000-373,983,000)	46 (25-66)
ITN 0%/IRS 40%/LARVICIDE 0%	Under 2000m	0/23,077,000/0	876,000	41,363,000 (22,385,000-59,471,000)	12 (7-18)
ITN 0%/IRS 40%/LARVICIDE 0%	Sinka	0/6,682,000/0	253,000	142,846,000 (77,307,000-205,384,000)	316 (171-454)
ITN 0%/IRS 40%/LARVICIDE 0%	Sinka under 2000m	0/4,497,000/0	182,000	27,836,000 (15,065,000-40,023,000)	153 (83-219)
ITN 0%/IRS 40%/LARVICIDE 20%	Total	0/42,021,000/22,828,000	2,008,000	305,763,000 (163,597,000-442,467,000)	54 (29-78)
ITN 0%/IRS 40%/LARVICIDE 20%	Under 2000m	0/23,077,000/12,713,000	1,183,000	48,865,000 (26,137,000-70,725,000)	14 (8-21)
ITN 0%/IRS 40%/LARVICIDE 20%	Sinka	0/6,682,000/3,751,000	344,000	168,271,000 (90,020,000-243,522,000)	329 (176-476)
ITN 0%/IRS 40%/LARVICIDE 20%	Sinka under 2000m	0/4,497,000/2,482,000	242,000	32,800,000 (17,547,000-47,469,000)	136 (73-196)
ITN 0%/IRS 40%/LARVICIDE 40%	Total	0/42,021,000/45,656,000	2,505,000	351,419,000 (186,425,000-510,950,000)	61 (32-89)
ITN 0%/IRS 40%/LARVICIDE 40%	Under 2000m	0/23,077,000/25,426,000	1,468,000	56,368,000 (29,888,000-81,980,000)	16 (9-24)
ITN 0%/IRS 40%/LARVICIDE 40%	Sinka	0/6,682,000/7,503,000	431,000	193,697,000 (102,733,000-281,660,000)	340 (181-495)
ITN 0%/IRS 40%/LARVICIDE 40%	Sinka under 2000m	0/4,497,000/4,964,000	299,000	37,764,000 (20,029,000-54,915,000)	126 (67-184)

Intervention	Scenario	Population Targeted (ITN/IRS/Reduction)	Median Cases Averted	Total Cost ($)	Cost Per Case Averted ($)
ITN 0%/IRS 80%/LARVICIDE 0%	Total	0/87,563,000/0	2,839,000	542,015,000 (293,336,000-779,311,000)	94 (51-135)
ITN 0%/IRS 80%/LARVICIDE 0%	Under 2000m	0/48,389,000/0	1,704,000	87,799,000 (47,516,000-126,238,000)	25 (14-36)
ITN 0%/IRS 80%/LARVICIDE 0%	Sinka	0/14,184,000/0	483,000	299,529,000 (162,104,000-430,664,000)	489 (265-703)
ITN 0%/IRS 80%/LARVICIDE 0%	Sinka under 2000m	0/9,460,000/0	343,000	58,557,000 (31,691,000-84,194,000)	171 (92-246)
ITN 0%/IRS 80%/LARVICIDE 20%	Total	0/87,563,000/22,828,000	3,208,000	587,671,000 (316,164,000-847,795,000)	101 (54-145)
ITN 0%/IRS 80%/LARVICIDE 20%	Under 2000m	0/48,389,000/12,713,000	1,910,000	95,302,000 (51,268,000-137,492,000)	27 (14-39)
ITN 0%/IRS 80%/LARVICIDE 20%	Sinka	0/14,184,000/3,751,000	547,000	324,955,000 (174,817,000-468,802,000)	497 (267-717)
ITN 0%/IRS 80%/LARVICIDE 20%	Sinka under 2000m	0/9,460,000/2,482,000	384,000	63,521,000 (34,173,000-91,640,000)	165 (89-239)
ITN 0%/IRS 80%/LARVICIDE 40%	Total	0/87,563,000/45,656,000	3,602,000	633,327,000 (338,992,000-916,279,000)	108 (58-156)
ITN 0%/IRS 80%/LARVICIDE 40%	Under 2000m	0/48,389,000/25,426,000	2,147,000	102,805,000 (55,019,000-148,746,000)	29 (15-41)
ITN 0%/IRS 80%/LARVICIDE 40%	Sinka	0/14,184,000/7,503,000	615,000	350,380,000 (187,529,000-506,941,000)	499 (267-723)
ITN 0%/IRS 80%/LARVICIDE 40%	Sinka under 2000m	0/9,460,000/4,964,000	431,000	68,485,000 (36,655,000-99,086,000)	159 (85-230)
ITN 40%/IRS 0%/LARVICIDE 0%	Total	2,362,000/0/0	98,000	1,076,000 (1,023,000-1,150,000)	0 (0-0)
ITN 40%/IRS 0%/LARVICIDE 0%	Under 2000m	898,000/0/0	51,000	543,000 (517,000-581,000)	0 (0-0)
ITN 40%/IRS 0%/LARVICIDE 0%	Sinka	1,193,000/0/0	31,000	409,000 (389,000-437,000)	1 (1-2)
ITN 40%/IRS 0%/LARVICIDE 0%	Sinka under 2000m	307,000/0/0	13,000	140,000 (133,000-150,000)	11 (10-12)
ITN 40%/IRS 0%/LARVICIDE 20%	Total	2,362,000/0/22,828,000	780,000	46,732,000 (23,851,000-69,634,000)	8 (4-13)
ITN 40%/IRS 0%/LARVICIDE 20%	Under 2000m	898,000/0/12,713,000	429,000	8,046,000 (4,268,000-11,835,000)	2 (1-4)
ITN 40%/IRS 0%/LARVICIDE 20%	Sinka	1,193,000/0/3,751,000	145,000	25,834,000 (13,102,000-38,575,000)	72 (37-108)
ITN 40%/IRS 0%/LARVICIDE 20%	Sinka under 2000m	307,000/0/2,482,000	87,000	5,104,000 (2,615,000-7,596,000)	59 (30-87)
ITN 40%/IRS 0%/LARVICIDE 40%	Total	2,362,000/0/45,656,000	1,432,000	92,387,000 (46,679,000-138,118,000)	16 (8-25)
ITN 40%/IRS 0%/LARVICIDE 40%	Under 2000m	898,000/0/25,426,000	799,000	15,549,000 (8,020,000-23,090,000)	5 (2-7)
ITN 40%/IRS 0%/LARVICIDE 40%	Sinka	1,193,000/0/7,503,000	254,000	51,260,000 (25,815,000-76,714,000)	119 (60-178)
ITN 40%/IRS 0%/LARVICIDE 40%	Sinka under 2000m	307,000/0/4,964,000	160,000	10,068,000 (5,097,000-15,042,000)	63 (32-94)
ITN 40%/IRS 40%/LARVICIDE 0%	Total	2,362,000/42,021,000/0	1,505,000	261,183,000 (141,792,000-375,133,000)	46 (25-67)
ITN 40%/IRS 40%/LARVICIDE 0%	Under 2000m	898,000/23,077,000/0	896,000	41,906,000 (22,902,000-60,052,000)	12 (7-18)
ITN 40%/IRS 40%/LARVICIDE 0%	Sinka	1,193,000/6,682,000/0	272,000	143,254,000 (77,696,000-205,821,000)	313 (170-450)

Intervention	Scenario	Population Targeted (ITN/IRS/Reduction)	Median Cases Averted	Total Cost ($)	Cost Per Case Averted ($)
ITN 40%/IRS 40%/LARVICIDE 0%	Sinka under 2000m	307,000/4,497,000/0	187,000	27,976,000 (15,198,000-40,172,000)	149 (81-215)
ITN 40%/IRS 40%/LARVICIDE 20%	Total	2,362,000/42,021,000/22,828,000	2,052,000	306,839,000 (164,654,000-443,568,000)	54 (29-78)
ITN 40%/IRS 40%/LARVICIDE 20%	Under 2000m	898,000/23,077,000/12,713,000	1,202,000	49,409,000 (26,671,000-71,282,000)	14 (8-21)
ITN 40%/IRS 40%/LARVICIDE 20%	Sinka	1,193,000/6,682,000/3,751,000	361,000	168,680,000 (90,422,000-243,941,000)	327 (175-473)
ITN 40%/IRS 40%/LARVICIDE 20%	Sinka under 2000m	307,000/4,497,000/2,482,000	246,000	32,940,000 (17,684,000-47,612,000)	134 (72-194)
ITN 40%/IRS 40%/LARVICIDE 40%	Total	2,362,000/42,021,000/45,656,000	2,542,000	352,495,000 (187,482,000-512,052,000)	61 (33-89)
ITN 40%/IRS 40%/LARVICIDE 40%	Under 2000m	898,000/23,077,000/25,426,000	1,485,000	56,912,000 (30,422,000-82,536,000)	16 (9-24)
ITN 40%/IRS 40%/LARVICIDE 40%	Sinka	1,193,000/6,682,000/7,503,000	444,000	194,106,000 (103,135,000-282,079,000)	339 (180-493)
ITN 40%/IRS 40%/LARVICIDE 40%	Sinka under 2000m	307,000/4,497,000/4,964,000	302,000	37,904,000 (20,166,000-55,058,000)	125 (67-182)
ITN 40%/IRS 80%/LARVICIDE 0%	Total	2,362,000/87,563,000/0	2,886,000	543,091,000 (294,360,000-780,461,000)	94 (51-135)
ITN 40%/IRS 80%/LARVICIDE 0%	Under 2000m	898,000/48,389,000/0	1,728,000	88,343,000 (48,033,000-126,819,000)	25 (14-36)
ITN 40%/IRS 80%/LARVICIDE 0%	Sinka	1,193,000/14,184,000/0	499,000	299,938,000 (162,493,000-431,101,000)	485 (263-698)
ITN 40%/IRS 80%/LARVICIDE 0%	Sinka under 2000m	307,000/9,460,000/0	348,000	58,697,000 (31,824,000-84,343,000)	169 (91-242)
ITN 40%/IRS 80%/LARVICIDE 20%	Total	2,362,000/87,563,000/22,828,000	3,250,000	588,747,000 (317,222,000-848,897,000)	101 (54-145)
ITN 40%/IRS 80%/LARVICIDE 20%	Under 2000m	898,000/48,389,000/12,713,000	1,931,000	95,845,000 (51,802,000-138,049,000)	27 (15-39)
ITN 40%/IRS 80%/LARVICIDE 20%	Sinka	1,193,000/14,184,000/3,751,000	560,000	325,364,000 (175,219,000-469,221,000)	494 (266-712)
ITN 40%/IRS 80%/LARVICIDE 20%	Sinka under 2000m	307,000/9,460,000/2,482,000	389,000	63,661,000 (34,310,000-91,783,000)	164 (88-236)
ITN 40%/IRS 80%/LARVICIDE 40%	Total	2,362,000/87,563,000/45,656,000	3,638,000	634,403,000 (340,050,000-917,380,000)	108 (58-156)
ITN 40%/IRS 80%/LARVICIDE 40%	Under 2000m	898,000/48,389,000/25,426,000	2,166,000	103,348,000 (55,553,000-149,303,000)	29 (15-41)
ITN 40%/IRS 80%/LARVICIDE 40%	Sinka	1,193,000/14,184,000/7,503,000	626,000	350,789,000 (187,931,000-507,359,000)	497 (266-719)
ITN 40%/IRS 80%/LARVICIDE 40%	Sinka under 2000m	307,000/9,460,000/4,964,000	435,000	68,625,000 (36,792,000-99,229,000)	158 (84-228)
ITN 80%/IRS 0%/LARVICIDE 0%	Total	44,344,000/0/0	1,717,000	20,201,000 (19,216,000-21,597,000)	4 (3-4)
ITN 80%/IRS 0%/LARVICIDE 0%	Under 2000m	22,671,000/0/0	926,000	3,368,000 (3,203,000-3,600,000)	1 (1-1)
ITN 80%/IRS 0%/LARVICIDE 0%	Sinka	7,392,000/0/0	265,000	10,328,000 (9,824,000-11,042,000)	24 (23-26)
ITN 80%/IRS 0%/LARVICIDE 0%	Sinka under 2000m	3,970,000/0/0	158,000	1,809,000 (1,720,000-1,934,000)	11 (11-12)
ITN 80%/IRS 0%/LARVICIDE 20%	Total	44,344,000/0/22,828,000	2,299,000	65,857,000 (42,044,000-90,081,000)	12 (7-16)
ITN 80%/IRS 0%/LARVICIDE 20%	Under 2000m	22,671,000/0/12,713,000	1,261,000	10,871,000 (6,955,000-14,855,000)	3 (2-4)

Intervention	Scenario	Population Targeted (ITN/IRS/Reduction)	Median Cases Averted	Total Cost ($)	Cost Per Case Averted ($)
ITN 80%/IRS 0%/LARVICIDE 20%	Sinka	7,392,000/0/3,751,000	364,000	35,754,000 (22,537,000-49,180,000)	72 (45-99)
ITN 80%/IRS 0%/LARVICIDE 20%	Sinka under 2000m	3,970,000/0/2,482,000	226,000	6,773,000 (4,202,000-9,380,000)	30 (19-41)
ITN 80%/IRS 0%/LARVICIDE 40%	Total	44,344,000/0/45,656,000	2,910,000	111,513,000 (64,872,000-158,564,000)	19 (11-28)
ITN 80%/IRS 0%/LARVICIDE 40%	Under 2000m	22,671,000/0/25,426,000	1,626,000	18,373,000 (10,706,000-26,109,000)	5 (3-8)
ITN 80%/IRS 0%/LARVICIDE 40%	Sinka	7,392,000/0/7,503,000	467,000	61,179,000 (35,250,000-87,318,000)	108 (62-154)
ITN 80%/IRS 0%/LARVICIDE 40%	Sinka under 2000m	3,970,000/0/4,964,000	298,000	11,737,000 (6,684,000-16,826,000)	39 (22-56)
ITN 80%/IRS 40%/LARVICIDE 0%	Total	44,344,000/42,021,000/0	2,670,000	280,308,000 (159,985,000-395,580,000)	49 (28-69)
ITN 80%/IRS 40%/LARVICIDE 0%	Under 2000m	22,671,000/23,077,000/0	1,532,000	44,730,000 (25,589,000-63,072,000)	13 (7-18)
ITN 80%/IRS 40%/LARVICIDE 0%	Sinka	7,392,000/6,682,000/0	442,000	153,174,000 (87,132,000-216,426,000)	272 (155-384)
ITN 80%/IRS 40%/LARVICIDE 0%	Sinka under 2000m	3,970,000/4,497,000/0	293,000	29,645,000 (16,785,000-41,956,000)	101 (57-143)
ITN 80%/IRS 40%/LARVICIDE 20%	Total	44,344,000/42,021,000/22,828,000	3,125,000	325,964,000 (183,453,000-463,156,000)	56 (32-80)
ITN 80%/IRS 40%/LARVICIDE 20%	Under 2000m	22,671,000/23,077,000/12,713,000	1,798,000	52,233,000 (29,447,000-74,175,000)	15 (8-21)
ITN 80%/IRS 40%/LARVICIDE 20%	Sinka	7,392,000/6,682,000/3,751,000	517,000	178,599,000 (100,172,000-254,100,000)	290 (163-413)
ITN 80%/IRS 40%/LARVICIDE 20%	Sinka under 2000m	3,970,000/4,497,000/2,482,000	346,000	34,609,000 (19,324,000-49,321,000)	100 (56-143)
ITN 80%/IRS 40%/LARVICIDE 40%	Total	44,344,000/42,021,000/45,656,000	3,578,000	371,620,000 (206,281,000-531,640,000)	64 (35-91)
ITN 80%/IRS 40%/LARVICIDE 40%	Under 2000m	22,671,000/23,077,000/25,426,000	2,074,000	59,736,000 (33,198,000-85,429,000)	17 (9-24)
ITN 80%/IRS 40%/LARVICIDE 40%	Sinka	7,392,000/6,682,000/7,503,000	594,000	204,025,000 (112,885,000-292,238,000)	304 (168-436)
ITN 80%/IRS 40%/LARVICIDE 40%	Sinka under 2000m	3,970,000/4,497,000/4,964,000	400,000	39,573,000 (21,806,000-56,767,000)	99 (54-142)
ITN 80%/IRS 80%/LARVICIDE 0%	Total	44,344,000/87,563,000/0	3,594,000	562,217,000 (312,552,000-800,908,000)	96 (53-137)
ITN 80%/IRS 80%/LARVICIDE 0%	Under 2000m	22,671,000/48,389,000/0	2,120,000	91,167,000 (50,720,000-129,838,000)	25 (14-36)
ITN 80%/IRS 80%/LARVICIDE 0%	Sinka	7,392,000/14,184,000/0	601,000	309,857,000 (171,928,000-441,706,000)	453 (251-646)
ITN 80%/IRS 80%/LARVICIDE 0%	Sinka under 2000m	3,970,000/9,460,000/0	414,000	60,366,000 (33,411,000-86,127,000)	146 (81-208)
ITN 80%/IRS 80%/LARVICIDE 20%	Total	44,344,000/87,563,000/22,828,000	3,930,000	607,872,000 (336,020,000-868,485,000)	103 (57-147)
ITN 80%/IRS 80%/LARVICIDE 20%	Under 2000m	22,671,000/48,389,000/12,713,000	2,323,000	98,670,000 (54,578,000-140,941,000)	27 (15-39)
ITN 80%/IRS 80%/LARVICIDE 20%	Sinka	7,392,000/14,184,000/3,751,000	656,000	335,283,000 (184,968,000-479,380,000)	464 (256-663)
ITN 80%/IRS 80%/LARVICIDE 20%	Sinka under 2000m	3,970,000/9,460,000/2,482,000	452,000	65,330,000 (35,951,000-93,492,000)	144 (79-207)
ITN 80%/IRS 80%/LARVICIDE 40%	Total	44,344,000/87,563,000/45,656,000	4,268,000	653,528,000 (358,848,000-936,968,000)	110 (60-158)

Intervention	Scenario	Population Targeted (ITN/IRS/Reduction)	Median Cases Averted	Total Cost ($)	Cost Per Case Averted ($)
ITN 80%/IRS 80%/LARVICIDE 40%	Under 2000m	22,671,000/48,389,000/25,426,000	2,532,000	106,172,000 (58,329,000-152,195,000)	29 (16-41)
ITN 80%/IRS 80%/LARVICIDE 40%	Sinka	7,392,000/14,184,000/7,503,000	715,000	360,708,000 (197,681,000-517,519,000)	471 (258-676)
ITN 80%/IRS 80%/LARVICIDE 40%	Sinka under 2000m	3,970,000/9,460,000/4,964,000	496,000	70,294,000 (38,433,000-100,938,000)	142 (78-204)