Climate influences on the cost-effectiveness of vector-based interventions against malaria in elimination scenarios

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Despite the dependence of mosquito population dynamics on environmental conditions, the associated impact of climate and climate change on present and future malaria remains an area of ongoing debate and uncertainty. Here, we develop a novel integration of mosquito, transmission and economic modelling to assess whether the cost-effectiveness of indoor residual spraying (IRS) and long-lasting insecticidal nets (LLINs) against Plasmodium falciparum transmission by Anopheles gambiae s.s. mosquitoes depends on climatic conditions in low endemicity scenarios. We find that although temperature and rainfall affect the cost-effectiveness of IRS and/or LLIN scale-up, whether this is sufficient to influence policy depends on local endemicity, existing interventions, host immune response to infection and the emergence rate of insecticide resistance. For the scenarios considered, IRS is found to be more cost-effective than LLINs for the same level of scale-up, and both are more cost-effective at lower mean precipitation and higher variability in precipitation and temperature. We also find that the dependence of peak transmission on mean temperature translates into optimal temperatures for vector-based intervention cost-effectiveness. Further cost-effectiveness analysis that accounts for country-specific epidemiological and environmental heterogeneities is required to assess optimal intervention scale-up for elimination and better understand future transmission trends under climate change.

1. Background

Crucial to the development of mitigation policies against the potentially adverse effects of climate change on human health is the design, implementation and evaluation of public health intervention programmes that will remain both effective and cost-effective in offsetting additional mortality or morbidity. Health economic evaluation addresses this question by considering how best to allocate scarce healthcare resources from an economic perspective to maximize population health, and the use of decision analytical modelling to undertake this evaluation involves developing mathematical models to conceptualize and quantify policy decision problems while accounting for key uncertainties in epidemiological and economic factors [1–8]. Coupling such models with infectious disease models that facilitate epidemiological knowledge synthesis and offer mechanistic insights into observations of disease trends enables the effectiveness and cost-effectiveness of different interventions to be evaluated, and provides a valuable framework for assessing the robustness of public health decisions. In the case of modelling infectious, rather than chronic, diseases, integrating economic modelling with dynamic (rather than static) transmission models that incorporate nonlinearities in the underlying epidemiological processes is essential [9,10] and economic evaluations of interventions against infectious diseases such as HIV and influenza have been increasingly considered (e.g. [11–16]).

An important type of economic evaluation is cost-effectiveness analysis, in which alternative interventions are assessed in terms of associated changes in costs and health benefits [17]. In this case, the extra cost per extra health
benefit is quantified through the incremental cost-effectiveness ratio (ICER); if we define the cost and health effects of intervention $A$ as $C_A$ and $E_A$, respectively, together the associated cost and effects of an existing approach $C_0$ and $E_0$, then the ICER = $\Delta C/\Delta E = (C_A - C_0)/(E_A - E_0)$. Comparing resource allocation decisions across different diseases can only be undertaken if a single metric of health effect is defined, and two of the most common examples are the quality-adjusted life year (QALY) and disability-adjusted life year (DALY). The former captures the effects of an intervention on improving both life-expectancy and health-related quality of life, while the latter captures the difference between a population in perfect health (with a long life-expectancy and disease-free) and its current health state; the sum of all DALYs across a population is therefore used to quantify the burden of disease by accounting for both mortality and morbidity, and this is the chosen health metric in the Global Burden of Disease study [18]. In this case, calculation of ICERs involves calculating the cost per QALY gained or cost per DALY averted, and the latter is the preferred metric of the World Health Organization (WHO) as part of its ‘CHOosing Interventions that are Cost Effective’ (CHOICE) project [19]. Assessment of cost-effectiveness is typically determined by comparison of the ICER with an agreed threshold (or ceiling ratio) for how much the health-care provider is willing to pay per unit of health gain; in the UK, for example, this is set as £20 000/QALY by the National Institute for Health and Care Excellence for new treatments in the UK’s National Health Service, while the WHO’s CHOICE criteria deem interventions to be highly cost-effective if the incremental cost per DALY averted is less than the per capita gross domestic product (GDP) (and cost-effective if it is less than three times the GDP per capita) [19]. DALYs are given by the sum of the number of years of life lost (YLL) owing to disease-related mortality and the number of years lived with a disability (YLD) caused by the disease.

Climatic drivers have been shown to play an important role in the transmission of vector-borne diseases (VBDs) [20,21], although the exact magnitude, nature and direction of these influences given other ecological, epidemiological and socioeconomic factors known to drive transmission remain uncertain [22,23]. In the context of impacts on VBD transmission owing to climate change, malaria has undoubtedly attracted the most attention given its significant ongoing global disease burden [18]. Temperature, rainfall and humidity are thought to represent the strongest climatic drivers of malaria transmission [24] and examples of specific interactions include the temperature sensitivity of *Plasmodium* parasite development inside *Anopheles* vectors [25,26], the effect of diurnal temperature fluctuations on parasite development [27–29], the interaction between temperature and vector immune responses [30,31], and direct influences on vector life-history parameters [32,33]; a more comprehensive overview is given elsewhere [34].

Economic evaluations of the cost-effectiveness of malaria interventions have grown significantly over the past decade and figure 1 illustrates the results of combining the systematic review in [35] with economic evaluations in The Cochrane Library. These include vector-based strategies that seek to reduce the abundance of *Anopheles* mosquitoes responsible for transmission through the application of indoor residual spraying (IRS), distribution of insecticide-treated nets (ITNs), imposition of larval source management (LSM) and/or host-based antimalarial strategies such as chemoprophylaxis or intermittent preventative treatment (IPT). However, given the dependence of *Anopheles* population dynamics on climatic influences, it is also possible that the cost-effectiveness of vector-control interventions will be determined by local climate and that the long-term cost-effectiveness of existing interventions may be compromised by climate change in certain transmission settings, a hypothesis that, to the best of our knowledge, has not been considered to date. Here, we investigate this possibility in the context of imposing IRS and ITNs against *Plasmodium falciparum* malaria in humans through the development of an integrated approach that (i) includes stage-specific (and climate-driven) population-dynamic models of disease vectors, (ii) applies a climate-driven dynamic disease transmission model and (iii) undertakes an economic evaluation of stage-targeted vector-control strategies within a cost-effectiveness framework.

2. Material and methods

We consider the application of two vector-based interventions (IRS and ITNs; alone and in combination) against *Anopheles gambiae* s.s. mosquitoes (hereafter shorted to *An. gambiae*) in different transmission settings (characterized by disease prevalence PPR, the parasite rate of *P. falciparum* malaria in humans) and environmental conditions. *Anopheles gambiae* is one of the seven dominant vector species (DVS) of malaria in Africa, and it is considered to be one of the most efficient DVS, owing, in some part, to its relatively long longevity and short duration of the immature stages [59]. The bionomics of the seven DVS in Africa differ significantly in many respects, and these include the dependence of life-history parameters, such as survival and development, on temperature [60]; we focus on *An. gambiae* here. Breeding sites of the juvenile stages are typically small, clear, still (or stagnant), sunlit and shallow, and small pools,
puddles, ground depressions, hoof prints and wheel ruts are common locations, although larger habitats, such as marshes and rice fields, have also been reported and both natural and man-made sources are common. The distinction between M and S molecular forms is also sometimes made, with the former tending to reside in semi-permanent, often man-made sources, while the latter tend to prefer more temporary, rain-dependent habitats [59].

(a) Vector model development and parametrization

Despite the increasing number of economic evaluations shown in figure 1, only a limited number of these have assessed the cost-effectiveness of one or more malaria interventions using dynamic disease transmission models (e.g. [51, 61–63]). Here, we consider two *An. gambiae* population-dynamic, climate-driven, stage-structured models in order to assess the sensitivity of our results to structural uncertainty in the ecological modelling of climate–disease interactions. We adopt the models of Parham et al. [64] (hereafter referred to as the Parham model) and White et al. [65] (the White model) as the basis for our analysis given their simplicity, although more complex population- and individual-based models have also been developed [66–72]. Note that the Parham model is driven by temporal changes in temperature and rainfall, whereas the White model is driven solely by rainfall.

(ii) The Parham model

The Parham model is a discrete-time model fitted to 41 months of adult *An. gambiae* catch data from a rural community in northeast Tanzania (data described in [73]). The vector population is divided into four stages: the number of eggs *E*(t) at time *t*, larvae *L*(t), pupae *P*(t) and adults *A*(t), and the population dynamics described by the coupled difference equations

\[
\begin{align*}
E(t+1) = & P_1(T_w, \rho(t))E(t) + F_1(T_h, A(t)) \\
L(t+1) = & P_2(T_w, \rho(t))L(t) + G_1(T_w, \rho(t))E(t) \\
P(t+1) = & P_3(T_w, \rho(t))P(t) + G_2(T_w, \rho(t))L(t) \\
A(t+1) = & P_4(T_m, RH)A(t) + G_3(T_w, \rho(t))P(t)
\end{align*}
\]

(2.1)

where *P_1 = (1 - p_f T_1^2) / (1 - p_f T_2^2)*, *P_2 = p_f T_2 / (1 - p_f T_2^2)*, *G_1 = p_f T_1 / (1 - p_f T_2^2)*, *G_2 = p_f T_1 / (1 - p_f T_2^2)*, *F_1 = p_f T_2 / (1 - p_f T_2^2)*, and *F_2 = p_f T_2 / (1 - p_f T_2^2)* are, respectively, the probabilities of being in stage 1 at time *t* + 1 (given presence in stage 1 at time *t*) and the probability of moving from stage 1 at time *t* to stage 1 at time *t* + 1, while *F_2* is the average number of eggs laid per day per female. The stage-dependent daily survival probabilities *p_1* are assumed, for the juvenile stages, to be related to mean daily water temperature *T_w* (in °C), cumulative daily rainfall *ρ(t)* (mm), breeding site desiccation owing to prolonged periods without precipitation and density-dependent mortality (the magnitude of which depends on breeding site dimensions, daily evaporation and *ρ(t)*). Adult survival probability is assumed to be dependent on mean daily air temperature *T_m* and relative humidity, RH. However, although Parham et al. [64] demonstrate the dependence of adult mortality on RH, this does not vary significantly within RH = 60–100% for the temperature range of interest here. In this case, the population dynamics are far less dependent on RH than on temperature and rainfall; for this reason, and to ensure focus on the dependence of intervention cost-effectiveness on the dominant climatic drivers that (i) drive vector population dynamics and (ii) are expected to change under climate change (whereas globally averaged RH is expected to remain approximately constant, e.g. [74]), RH was fixed at 80%.

Stage-specific development rates for juveniles are assumed to depend only on *T_w*, while fecundity is related to *T_h*. Here, we adopt the same functional forms and best-fit parameter values as in [64]. In the original paper, the quantity *α_2 A(t)* is fitted to longitudinal field data and the scale parameter *α_2* inferred; here, *α_2* is left as a free parameter to allow different epidemiological scenarios to be considered.

(b) Linking vector population dynamics to prevalence

In order to calculate the YLD component of DALYs averted, a means of relating *An. gambiae* population dynamics (predicted
by the Parham and White models) to malaria prevalence is required. While numerous transmission models have been developed [76], we adopt, for simplicity and parsimony, a climate-driven version of the consensus set of assumptions underpinning the suite of Ross–Macdonald models [77]. If \( x \) is the proportion of humans infected with \( P. falciparum \) in a population of size \( H \) (the parasite rate \( PPR \)) and \( y \) the proportion of infected mosquitoes in an adult female population of size \( A \), the version of the Ross–Macdonald model in [78] (with the addition of disease-induced mortality required to calculate the YLL component of DALYs averted) can be written as

\[
\begin{align*}
\frac{dx}{dt} &= m a b y (1 + x) - (\sigma + \mu) x, \\
\frac{dy}{dt} &= a c e (\epsilon r - y) - \mu_A y,
\end{align*}
\]

where \( m = A / H \) is the number of adult mosquitoes per human, \( a \) the human biting rate (the number of bites per host per anopheline per day), \( b \) the probability of transmission from infected anopheline to susceptible host, \( \sigma \) the rate at which infected humans recover, \( \mu \) the malaria-induced mortality rate in humans, \( \epsilon \) the probability of transmission from infected human to susceptible vector, \( \mu_A \) the mortality hazard rate for adult vectors and \( n \) the duration of parasite sporogony inside the mosquito.

The mathematical framework of the Ross–Macdonald models can also be used to define different transmission metrics that continue to be used to measure disease burden and guide control activities [79]; these include the \( P. falciparum \) entomological inoculation rate \( EIR = e = m a n y \) (the expected number of infectious bites per host per day) and the basic reproduction number \( \mathcal{R}_0 = m a b c e^{-\rho} \rho / \mu_A (\sigma + \mu) \) (the average number of secondary hosts that would become infected by a single infected host in an otherwise completely susceptible population in one generation of the parasite). At equilibrium, these transmission metrics are related by

\[
PPR = \frac{a e}{\sigma + \mu + be} = \frac{\mathcal{R}_0 - 1}{\mathcal{R}_0 + ac / \mu_A},
\]

and the implications of these relationships are discussed in more detail elsewhere [79]. This nonlinear link between vector abundance \( A \) and disease prevalence \( PPR \) therefore adopts many of the classical assumptions underpinning Ross–Macdonald models [76,77], but modifies the underpinning adult vector model from an immigration-death process to the stage-structured Parham and White models. We also note that the temperature-dependent relationship between \( A \) and \( PPR \) is not unique; multiple parameterizations of \( \mu_A \) [32], \( n(T_A) \) [25,68] and \( a(T_A) \) [26,68,80] exist for \( An. gambiae \) (and while we take \( b \) and \( c \) to be temperature-independent, this is not always assumed to be the case [80]). Here, we assume a human population size of 1 million, adult mosquito mortality based on the vector model selected (temperature-dependent for the Parham model, temperature-independent for the White model) and the temperature-dependent duration of parasite sporogony as per [68]; all other parameters will be varied as part of a sensitivity analysis (table 1).

(c) Vector controls

(i) Indoor residual spraying

IRS involves the spraying of surfaces within human habitations with either organochlorine-, organophosphate-, carbamate- or pyrethroid-based insecticides that significantly increase the mortality of adult mosquitoes that land or rest indoors, and repel vectors entering houses and surviving. IRS is currently recommended by malaria control programmes in 40 out of 43 countries with ongoing \( P. falciparum \) transmission in Africa, within which pyrethroid-based insecticides are primarily used and 10–12% of the population at risk were covered by IRS in Africa in 2012 [82]. IRS is clearly most effective (and cost-effective) against endophilic and endophagic mosquitoes (both characteristics of \( An. gambiae \) [59]). However, high-quality randomized control trials on the protective efficacy of different IRS insecticides in different transmission settings, particularly in regions of stable malaria, are currently limited [84].

The duration of IRS effectiveness depends on the insecticide employed, of which there are currently 12 WHO-approved compounds [85], and spraying typically needs to be undertaken one to three times per year (dependent also on the seasonality of transmission). Monitoring of insecticide resistance is currently undertaken in 37 out of 43 African countries with ongoing \( P. falciparum \) transmission [82] and resistance management (and the longer-term viability) of IRS is significantly aided by the wider range of insecticides available for IRS than ITNs. Long-term cost-effectiveness is driven by factors such as insecticide cost, the duration of residual efficacy (affecting the required number of spraying cycles per year), the seasonality of transmission and the emergence of resistance [85].

(ii) Insecticide-treated nets

ITNs act as both a physical barrier that reduces mosquito–human contact and a chemical barrier through the action of the pyrethroid that kills, severely disables or at least repels mosquitoes upon contact. Conventional ITNs require regular re-application of WHO-recommended insecticides (typically at least once a year or after three washes), while the fibres of long-lasting insecticidal nets (LLINs) are impregnated with the pyrethroid during the manufacturing process and most last 3–5 years; the WHO now strongly promotes their use in working towards the Millennium Development Goals [86]. Pyrethroids are currently the only insecticide class used in WHO-approved LLINs and thus resistance management is more difficult than with IRS (since strategies such as insecticide rotation cannot be employed) [87], although ITNs continue to work as physical barriers even after the insecticide becomes ineffective. ITNs are currently distributed free of charge in 39 out of 43 countries in Africa with ongoing \( P. falciparum \) transmission [82].

The relative efficacy, effectiveness and cost-effectiveness of ITNs versus IRS remain ongoing areas of interest and debate [35,54,55,88–90] and factors such as the cost, protective lifetime and net usage play an important role [88], while increasing pyrethroid resistance necessitates more spray rounds and hence decreases cost-effectiveness. LLINs are almost always more cost-effective than standard ITNs [86,88], particularly in regions of high endemicity, and have the additional benefit (compared to IRS) of enabling targeting to high-risk groups. However, neither LLINs nor IRS alone are likely to be sufficiently effective in regions of holoendemic transmission (\( e > 1 \) and \( PPR \) 60–70% in children aged under five years) [86], although there is little doubt that widespread use of ITNs has significantly reduced mortality in Africa [91]. High levels of ITN coverage have also been reported to have a useful community effect [86,91–93].

(d) Modelling the impact of vector-control interventions

The impact of IRS and ITNs on the adult mosquito population is modelled here using the approach of Griffin et al. [81] and White et al. [65] (an extension of the model in [94]), which assumes that these interventions increase adult mortality rate, increase gonotrophic cycle duration, affect the proportion of bites taken on protected and unprotected humans, and change the proportion of bites taken on humans relative to animals [81]. In the White model, the effect of implementing ITNs (assumed to be LLINs) and IRS on model parametrization is to modify the adult mortality rate from its baseline value of \( \mu_A(0) \) (when there is zero

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coverage) to \( \mu_A(\chi) \) for coverage level \( 0 \leq \chi \leq 1 \), whereupon manipulation of the equations in [81] gives

\[
\mu_A(\chi) = \frac{1 - z}{(1 + T_S)(1 - z)} \times \ln\left(\frac{1 - e^{(-\mu_A(\chi)T_S)}}{w}\right) + \mu_A(0)(1 + T_S).
\]

where \( z = Q \phi \delta \) is the probability of the mosquito resetting and beginning a new search and \( w = 1 - Q \phi(1 - s) \) the probability that the mosquito succeeds in feeding during a single attempt (and where (2.8) reduces to \( \mu_A(0) \), as required, when \( \chi = 0 \)). Here, \( Q \) is the proportion of blood meals taken on humans, \( T_S \) the time spent seeking a blood meal, \( T_c \) the time spent resting during the gonotrophic cycle and \( s \) the probability that the mosquito is successful during a feeding attempt. In the case of LLINs, \( T_{LLIN} \) is the probability of mosquito repellence by the LLIN, while for IRS, \( T_{IRS} \) is the probability that the mosquito is repelled by the sprayed insecticide. Similarly, \( \phi = \phi_{LLIN} \) is the proportion of bites taken on humans while sleeping under LLINs, while, for IRS, \( \phi = \phi_{IRS} \) is the proportion of bites taken on humans indoors. Likewise, \( s = s_{LLIN} \) is the probability that the mosquito recruits successfully despite the presence of LLINs, while \( s = s_{IRS} = (1 - T_{IRS})(1 - \phi) \) is the probability that the mosquito successfully feeds in the presence of IRS (where \( \phi \) is the probability that the mosquito rests indoors after feeding).

All model parameter values are for \( An. \ gambiae \) and taken from [81] (table 1). In the case of LLINs, \( \chi = \chi_{LLIN} \) is the proportion of individuals sleeping under nets, and we use coverage to refer to the combination of actual bednet distribution to households and occupant adherence; in general, the majority of individuals in Sub-Saharan Africa use the bednets available to them (with adherence, on average, of around 86% [82]). For IRS, \( \chi = \chi_{IRS} \) is the proportion of houses sprayed. For intervention programmes where both ITNs and IRS are employed, \( z = Q_{LLIN} (\phi_{LLIN} + \phi_{IRS} \delta_{IRS}) \), while \( w = 1 - Q_{LLIN} (\phi_{LLIN} (1 - s_{LLIN}) + \phi_{IRS} \delta_{IRS} (1 - s_{IRS})) \).

The impact of LLINs and IRS is analogously implemented in the Parham model by writing the adult daily survival probability (denoted \( p_A(T_A, RH) \) in [64]) as \( \mu_A(\chi) = e^{-\mu_A(\chi)} \) and substituting (2.8) with \( \mu_A(0) = (\beta_2 T_A + \beta_1 + \beta_0) \) (with the RH-dependent parameters \( \beta_2, \beta_1, \) and \( \beta_0 \) as per [64]). Strictly, \( \lambda_1 \) and \( \lambda_2 \) are also temperature-dependent, and at least three different parametrizations of the duration of the gonotrophic cycle \( G_c = 1/(\lambda_1 + \lambda_2) \) have been developed [26,32,80]. Thus, one important limitation of the intervention model adopted here is the assumed temperature-independence of \( G_c \), and with the assumed values in [65,81], this underestimates \( G_c \) at lower temperatures. However, given the mathematical form of (2.8), \( \lambda_1 \) and \( \lambda_2 \) do not, unfortunately, always appear in the form \( \lambda_1 + \lambda_2 \); if this were the case, we could implement one of the temperature-dependent forms of \( G_c \) in [26,32,80]. Hence, as there is also currently no reliable parametrization of the separate temperature-dependences of \( \lambda_1 \) and \( \lambda_2 \), we adopt the original temperature-independent parametrization of Griffin et al. [81] and White et al. [65], noting that this is, at least, consistently assumed for the intervention model applied to both the Parham and White models (enabling comparable results). This temperature-dependence is also relatively weak compared with other parameters, such as adult mortality, that more strongly affect temperature-dependent transmission [80]).

### (e) Insecticide efficacy waning and resistance

Insecticides used in IRS and LLINs naturally wane in efficacy over relatively short timescales, while the emergence of insecticide-resistance is likely to become an important factor affecting longer-term cost-effectiveness. Let, \( T_T \) and \( T_N \) be the average durations before a house needs to be re-sprayed and LLINs need to be replaced, respectively (where \( T_T \) is taken to be variable and \( T_N \) fixed at five years [65]). Following the model of Griffin et al. [81], the natural waning in efficacy of insecticides used in IRS, as quantified by the decay rate \( \gamma_0 \), is modelled by

\[
r_{IRS} = r_{S0} e^{-\gamma_0 t},
\]

where, for dichlorodiphenyltrichloroethane (DDT), \( r_{S0} = 0.60 \) and \( \gamma_0 = 3.80 \times 10^{-5} \text{d}^{-1} \), while, for lambda-cyhalothrin, \( r_{S0} = 0.207 \) and \( \gamma_0 = 0.015 \text{d}^{-1} \) [81]. For LLINs, the probability of mosquito repellence, given an efficacy decay rate \( \gamma_0 \), is given by

\[
r_{LLIN} = (N_B - N_{MM}) e^{-\gamma_0 t} + N_{MM},
\]

where \( r_{S0} = 0.56, r_{SMM} = 0.24 \) and \( N_B = 7.19 \times 10^{-4} \text{d}^{-1} \), while the probability of successful mosquito feeding despite the presence of a LLIN is

\[
s_{LLIN} = 1 - r_{LLIN} - ds_{LLIN} e^{-\gamma_0 t},
\]

with \( d_{S0} = 0.41 \) [81]. The expressions (2.9), \( s_{LLIN} = (1 - r_{IRS}) (1 - \phi) \) (2.10) and (2.11) hold for \( kT_S \leq t \leq (k + 1)T_S \) (where \( k = 1, 2, \ldots \)), but represent discontinuous, periodic functions arising from the regular re-application of insecticide required to overcome waning efficacy. In order to represent these parameters in continuous-time, we approximate each function by its corresponding
(trigonometric) Fourier series, so that, for example,

$$r_{IRS} = r_{SIRS}(1 - e^{-\gamma_{TS}t}) \times \left( \frac{1}{\gamma_{TS}} + \sum_{j=1}^{2} \frac{g_j T_j \cos(2\pi j/T_j) + 2\pi j \sin(2\pi j/T_j)}{4\pi^2 j^2 + \gamma_{TS}^2} \right).$$  (2.12)

(see the electronic supplementary material). We implement these functions with $j = 10$ such that over a 5-year period (the assumed lifetime of LLINs), the difference between the function and its Fourier representation is, in each case, $\approx 5\%$.

In the case of IRS insecticide resistance, we assume that the probability of mosquito repellence (defined by (2.12)) further decays exponentially at a rate proportional to the coverage level $x_{IRS}$, so that

$$r_{IRS} = r_{SIRS} e^{-\gamma_{IR} x_{IRS}} \times (1 - e^{-\gamma_{TS}t}) \times \left( \frac{1}{\gamma_{TS}} + \sum_{j=1}^{2} \frac{g_j T_j \cos(2\pi j/T_j) + 2\pi j \sin(2\pi j/T_j)}{4\pi^2 j^2 + \gamma_{Ts}^2} \right),$$  (2.13)

where we define the resistance half-life $t_{1/2}^{IRS}$ (not currently known precisely [87]) to be the time taken for the baseline insecticide efficacy (in the absence of natural waning) to halve at perfect coverage ($y_{IRS} = 1$); thus, $t_{1/2}^{IRS} = \ln 2/\gamma_{IR}$. Similarly, for LLINs, we find that

$$r_{LLIN} = r_{SLLIN} e^{-\gamma_{IR} x_{LLIN}} \times (1 - e^{-\gamma_{LLIN} t}) \times \left( \frac{1}{\gamma_{LLIN}} + \sum_{j=1}^{2} \frac{g_j T_j \cos(2\pi j/T_j) + 2\pi j \sin(2\pi j/T_j)}{4\pi^2 j^2 + \gamma_{LLIN}^2} \right),$$  (2.14)

with associated half-life $t_{1/2}^{LLIN} = \ln 2/\gamma_{LLIN}$, while the probability of successful mosquito feeding becomes

$$s_{LLIN} = 1 - r_{LLIN} - d_{LLIN}(1 - e^{-\gamma_{LLIN} t}) \times \left( \frac{1}{\gamma_{LLIN}} + \sum_{n=1}^{N} \frac{g_n T_n \cos(2\pi n t/T_n) + 2\pi n \sin(2\pi n t/T_n)}{4\pi^2 n^2 + \gamma_{LLIN}^2} \right).$$  (2.15)

(f) Model parameters for economic analysis

An economic analysis of different vector-control programmes is undertaken from the perspective of the provider (costs incurred by the public health system). Financial costs, which reflect the total monetary expenditure (incorporating the intervention unit cost, together with all other costs associated with implementation such as storage, transport and personnel), rather than economic costs (that account for all opportunity costs, monetary or otherwise), are considered. Standardized Africa-specific cost data (in 2009 US dollars, $2009) on IRS and LLINs are taken from the systematic review in [35] (also consistent with more recent cost data in [56,57,88,95–97]), and reflect the financial cost per person (of any age) per year of protection by IRS and LLINs. The five studies on IRS usage and 19 studies on ITN usage identified in [35] are used as part of one-way deterministic sensitivity analyses (DSA) to assess the dependency of ICERs on entomological, epidemiological and economic parameter uncertainty. Point estimates of unit cost data are taken to be the median costs estimated from the transmission model (2.6). As per the assumptions of Yuktich et al. [88] (and following [83]), we assign a value of 33 YLL per death, while YLD values are calculated as the product of $\beta$ and a disability weight associated with infection (taken as 0.191, with range 0.172–0.211 for the DSA, based on [83]). Costs and benefits are discounted at 3% per annum [19] and this is varied between 0 and 6% in the DSA (assumed identical for both).

3. Results

Both vector models were initiated in 2005 and run for five years prior to the application of interventions to remove any effects of model transients on estimates of cost-effectiveness. Four intervention strategies (representative of existing programmes in Africa [82]) were imposed from 2010 to 2015 to form comparators for the cost-effectiveness analysis: no IRS, but 25% LLIN coverage (representative, for example, of Congo and Nigeria in 2012; Scenario 1); as per Scenario 1, but with 5% IRS coverage (typical of recent programmes in Angola, Ghana, Senegal and Uganda; Scenario 2); IRS and LLIN coverages at 5% and 60%, respectively (similar to recent data from household surveys on the proportion of individuals sleeping under ITNs in Madagascar, Mali, Rwanda and the United Republic of Tanzania; Scenario 3) and IRS and LLIN coverages of 10% and 25%, respectively (typical of recent coverage levels in Ghana and Malawi; Scenario 4). In 2015, existing interventions were either continued until 2020 or subjected to three scale-up programmes: increasing IRS coverage by 5%, increasing LLIN coverage by 5% or increasing both IRS and LLIN coverage by 2.5%.

Cost-effectiveness was determined by tracking the total costs and DALYs accrued under existing intervention programmes and potential scale-up options from 2015 to 2020, and calculating the cost per DALY averted. Four representative African climate profiles were considered by analysing air temperature and rainfall data for 1990–2009 (from the Climate Change Knowledge Portal run by the World Bank; see http://sdwebx.worldbank.org/climateportal/) and fitting the functions

$$T_A(t) = T_0(1 + T_1 \sin(\omega_0 t + \phi_1)),$$  (3.1)

and (2.3), respectively, for the 43 countries in Africa with ongoing transmission, and analysing the cost-effectiveness in each temperature–rainfall combination. ICERs were compared with World Bank classifications of GDP per capita, namely $<\$1045$, $1046–$4125, $4126–$12745 and $>$$12746 for low, lower-middle, upper-middle and high income economies, respectively. Representative, rather than country-specific, values of $T_0$, $T_1$, $\rho_0$ and $\rho_1$ were considered in order to obtain more general insights into the role of climatic variables on scale-up options and because there is frequently considerable spatial heterogeneity in weather patterns, microclimatic effects and epidemiological settings within countries (and hence deviation from country-level aggregates). The values of $\lambda$ (in the White model) and $c_2$ (in the Parham model) were varied in order to assess the health outcomes of different intervention programmes when endemicity is around 5% (typical of many regions in eastern and southern Africa) in a human population size of 1 million.

The effectiveness and cost-effectiveness of interventions in the Parham and White models were compared for a wide range of temperature and rainfall scenarios, existing combinations of interventions, and IRS and LLN scale-up options, and were found to closely match across the scenarios considered, particularly as endemicity increases; selected comparisons for a 5% increase in IRS coverage are shown in figure 2. In this case, IRS scale-up decreases cumulative incidence by 55–80% dependent on climate characteristics.
and the existing combination of interventions; scale-up is typically more effective at lower mean temperatures. The White model generally predicts slightly higher incidence than the Parham model, but the proportional reduction in the number of cases owing to IRS scale-up is nearly identical. Temperature variability has less impact on the effectiveness of these interventions than mean temperature in both models.

The similarity of these models in predicting the impact of interventions on reducing incidence also translates into comparable predictions of cost-effectiveness and policy implications. More specific conclusions about cost-effectiveness follow shortly. Differences between the models increase only as prevalence becomes very low; in this case, the deterministic nature of both models becomes an inherent limitation and small changes in small numbers of cases can lead to large changes in the incremental cost per DALY averted. Overall, temperature and rainfall are found to affect cost-effectiveness, but the extent to which this affects policy decisions about scale-up depends on current endemicity, existing interventions and the rate at which insecticide resistance emerges. We also find, in both models, that a 4°C increase in mean temperature has far less influence on reducing incidence than a 5% increase in IRS coverage. Such insights have important implications for the ongoing debate around the magnitude of climate and climate change effects on future transmission compared to other epidemiological and socioeconomic drivers [34]: the effect of insecticide resistance (and its interaction with climate) will be considered shortly. For the scenarios considered in figure 2, increasing IRS coverage becomes increasingly cost-effective as prevalence increases and it is highly cost-effective in all African countries with ongoing transmission when endemicity is high.

Figure 3 compares the prevalence time-series for the Parham model from 2015 to 2020 under Scenarios 1 to 4 when 

$T_0 = 21°C$, $T_1 = 0.05°C$, $\rho_0 = 3$ mm and $\rho_1 = 0.5$ mm; all other parameters are set to the baseline values in table 1. The three scale-up programmes are contrasted with the ‘business as usual’ comparator (and where the conclusions for the White model are identical). Despite each Scenario arising from the same average prevalence in 2010–2015, the effects of different combinations of interventions on progress towards elimination are very different. The effectiveness of intervention scale-up on prevalence (and its seasonality) is found to depend on existing vector-control strategies. In Scenarios 2 and 4 when LLIN coverage is 25% (and IRS coverage is 5% and 10%, respectively), all existing and scale-up interventions are effective (but not necessarily cost-effective) in overcoming resistance, the influence of climatic drivers, and reducing prevalence towards elimination. By contrast, in Scenario 1, maintaining bednet usage at 25%, or further increasing to 30%, is insufficient to overcome the effects of resistance; thus, despite decreases from 2010 to 2015, prevalence subsequently begins to increase from around 2017 onwards and with increasing domination by climatic drivers, causing increasing seasonality in transmission. In this case, implementation of IRS is essential and we find that even very low coverage levels are sufficient to continue elimination progress. Similarly, in Scenario 3, even with very high levels of bednet usage, further coverage increases in the presence of such resistance are neither effective nor cost-effective and resistance again dominates, causing prevalence to increase in magnitude and seasonality.

The cost per DALY averted of different scale-up options in different epidemiological and climatic settings is shown in table 2. IRS alone is found to be more cost-effective than...
LLINs alone, or in combination, in all the scenarios considered, independent of existing vector controls or climatic conditions, and this is particularly true when IRS is either absent or coverage is poor. Implementation of the scale-up programmes considered is more cost-effective at lower mean rainfall and higher rainfall variability, a result that holds independent of temperature. For fixed rainfall variability, lower mean rainfall reduces the carrying capacity of mosquito breeding sites and hence the number of emerging adults; thus, targeting adult mosquitoes through IRS or LLINs achieves greater reductions in the proportion of the adult population eliminated and able to pass on infection. For rainfall patterns with a given annual mean, increasing variability means that breeding site capacity will be low at certain times of the year and thus, by the same reasoning, vector-based interventions will be particularly effective at reducing prevalence at these times; the same interventions will therefore be more effective and cost-effective when rainfall variability is high. We also find that cost-effectiveness improves when temperature variability is greater. Significantly, while cost-effectiveness also depends on mean temperature, it does not do so in a linear manner. Work elsewhere (e.g. [80,98]) has illustrated the nonlinear dependence of transmission (e.g. as quantified by $P/R_o$) on mean air temperature; in [80], transmission is shown to peak at around 25°C and we find that this unimodal peak in transmission also translates into effectiveness and cost-effectiveness peaks when applying vector-based interventions.

In regions where IRS is not currently implemented and LLIN use is around 25%, the scaling up of IRS alone, LLINs alone, or IRS and LLINs in combination is highly cost-effective in all low, middle and high income countries in Africa with ongoing transmission. In this case, regional rainfall and temperature play no role in influencing policy about scale-up, and continuation of existing policies does not lead to elimination within five years. Moreover, while prevalence is reduced to very low levels (figure 3), LLIN scale-up is not sufficient to overcome the effects of insecticide resistance under certain climatic conditions. Nonetheless, it is both effective and cost-effective to adopt any of these three scale-up programmes.

Similarly, in settings where bednet usage is unchanged, but existing IRS coverage is around 5%, IRS scale-up alone is almost always highly cost-effective or cost-effective (with the only exception in the very poorest low income countries) for all rainfall scenarios considered (and when mean temperature is low and/or annual temperature variability is small). In this case, climatic conditions only play a role in very low income countries. An important observation is that while increasing LLIN usage is also highly cost-effective, far less progress is made towards elimination than with the same scale-up in IRS, highlighting an important difference between assessing effectiveness and cost-effectiveness; the latter only refers to conclusions reached about policy through comparing the ICER with an accepted threshold (in this case, GDP per capita), while the amount by which the ICER is

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**Figure 3.** Prevalence predicted by the Parham model in Scenarios 1–4 (a–d, respectively) and different IRS/LLIN scale-up options when $T_0 = 21°C$, $T_1 = 0.05°C$, $\rho_0 = 3$ mm and $\rho_1 = 0.5$ mm. All other parameters are as per table 1. (Online version in colour.)
Table 2. Incremental cost per DALY averted (in $2010) in four different temperature and rainfall settings; temperature scenarios correspond to TS1: $T_0 = 21.8$°C and $T_1 = 0.05$°C; TS2: $T_0 = 21.8$°C and $T_1 = 0.15$°C; TS3: $T_0 = 25.8$°C and $T_1 = 0.05$°C; and TS4: $T_0 = 25.8$°C and $T_1 = 0.15$°C, while rainfall scenarios correspond to RS1: $r_0 = 3$ mm and $r_1 = 0.5$ mm; RS2: $r_0 = 3$ mm and $r_1 = 0.9$ mm; RS3: $r_0 = 6$ mm and $r_1 = 0.5$ mm; and RS4: $r_0 = 6$ mm and $r_1 = 0.9$ mm. All other model parameters are set to the baseline values in table 1.

<table>
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above or below this threshold is of considerable importance in targeting elimination. For example, in Scenario 1 (and climatic conditions TS1 and RS1), maintaining existing interventions leads to a cumulative incidence over five years of approximately 142,000; increasing IRS coverage by 5% causes this figure to drop by around 82%, but the same increase in LLIN coverage only makes a 24% drop in incidence. In this case, both options are cost-effective, but the former makes far greater progress towards elimination.

Results from undertaking a one-way DSA of Scenario 2 are shown in figure 4. Cost-effectiveness is found to be most sensitive to the average duration of host infectiousness by a factor of approximately five times greater than the next strongest determinant. The range of recovery rates $\sigma$ in table 1 reflects ongoing uncertainty (and variability) in human immune response to malaria infection, with parameters considered as part of the DSA ranging from the order of weeks to years (based on [69]). Another important finding is that, after host immunity, uncertainty in both the mosquito to host and, to a lesser extent, host to mosquito transmission probabilities can influence estimates of cost-effectiveness with sufficient magnitude to affect policy decisions in many low and middle income countries in Africa. In fact, for the range of resistance emergence rates considered here (albeit very uncertain [87]), uncertainty in these three quantities more significantly affects ICERS than resistance. Other entomological parameters such as vector endophilicity and anthropophily, plus economic parameters such as cost and benefit discounting rates, are found to be far less influential on policy decisions based on cost-effectiveness. Repeating this DSA for a wider range of climate scenarios shows that these results on the role of parameter uncertainty are independent of the climate regime considered (figure 4a,c,d). Interestingly, we also find that the second strongest driver of cost-effectiveness, the mosquito to human transmission probability $b$, is the strongest determinant of intervention effectiveness; uncertainty in $b$ compared to $\sigma$ leads to variation in the cumulative number of cases from 2015 to 2020 of 1.4 m compared with 0.2 m (table 3).

In the case of low transmission despite 5% and 60% IRS and LLIN coverage, respectively, further scale-up of LLINs by 5% is almost never cost-effective, even in high income countries, and it is clear that, in this case, investment is better spent on increasing IRS coverage (independent of the environmental conditions). Indeed, increasing IRS coverage by 5% is likely to be highly cost-effective or cost-effective even in low income countries, although this decreases at higher temperatures (and greater temperature variability); for example, when $T_0 = 25^\circ$C and $T_1 = 0.15^\circ$C, it is only cost-effective in middle and high income countries, which account for 19 of the 43 African countries with ongoing transmission. If logistical or other constraints do not allow an increase in IRS by 5%, we find that increasing both IRS and LLIN coverage by 2.5% would, for the majority of affected African countries, represent a cost-effective alternative.

Finally, in the case of IRS and LLIN coverage at 10% and 25%, respectively, the steady decline in incidence means that further increases in IRS scale-up by 5% are not cost-effective in low income countries and, in some climate regimes (namely, as mean rainfall increases and variability in rainfall and temperature decreases), may not even be cost-effective in lower-middle income economies. Scale-up of LLINs alone is rarely cost-effective for most African countries, particularly as mean temperature and temperature variability increase.
4. Discussion

Although we have presented a useful and novel framework for integrating vector, epidemiological and economic modelling in the context of assessing the cost-effectiveness of interventions against climatically driven VBDs, as with all modelling studies, it is important to acknowledge the inherent limitations. We have necessarily considered only a limited set of representative scenarios around existing intervention coverages, scale-up options and climatic settings to contain our analysis. Nonetheless, an important aspect of such studies is the issue of model validation and although different types exist [8], assessment of validity must always be undertaken within the context for which a model is intended. Both the Parham and White models have been independently and externally validated against An. gambiae field data in Africa, while the Ross–Macdonald model was selected as a parsimonious, widely applied set of assumptions [77]. Validation of the health economic modelling, however, differs to the sense in which validation of mathematical models of infectious diseases is typically interpreted; the purpose of economic modelling (generally) is to inform decisions and, in particular, an improved understanding of future vector-based intervention programmes in order to overcome increasing levels of pyrethroid, and other insecticide, resistance [99,100]. Likewise, dynamic or mosaic implementation of LLINs and IRS as a further means of overcoming resistance (as recommended by [99]) is not considered here, but is also likely to become increasingly important. Incorporating more dynamic intervention programmes such as these into current epidemiological, intervention and economic models represents a complex, but necessary, challenge for future modelling efforts and is likely to have implications for cost-effectiveness. Avoiding donor fatigue is also vital in maintaining progress towards elimination [101]. Continued development of African economies may also increase future capability of national malaria programmes to invest in intervention scale-up activities, although this is arguably more a question of affordability than cost-effectiveness.

Modelling studies are only as reliable as the data used to parametrize them and our work is no exception; epidemiological, entomological and economic uncertainties exist throughout. Here, we have focused on P. falciparum transmission by An. gambiae s.s. mosquitoes, but further exploration of other parasite–vector systems is certainly required. As noted earlier, for example, the ecology of the seven DVS of malaria in Africa differ significantly, yet despite some recent experimental studies (e.g. [60]), there are currently limited data on the dependence of these vectors’ life-history traits on environmental variables; without this, it is difficult to extrapolate our results on cost-effectiveness to such systems and evaluate the impact of such heterogeneities on intervention scale-up in different settings. Uncertainties in several key epidemiological parameters have also been shown here to potentially affect economic decisions and, in particular, an improved understanding of host immune response to infection and data on the transmission probability between infectious mosquitoes and susceptible hosts are found to be influential on cost-effectiveness estimates, independent of climatic conditions. Such parameter uncertainties are accounted for here using a one-way DSA to quantify the robustness of our conclusions to these uncertainties, but this approach is itself limited in several respects, particularly when parameters may not be independent (e.g. [1,19]). Multi-way sensitivity analysis of deterministic models should ideally also be undertaken and a range of methods now exists for doing so [102]. Given our interest in addressing transmission and control dynamics in regions with low endemicity, it may be argued that stochastic approaches to disease modelling may be more appropriate and, in this case, probabilistic sensitivity analysis may be undertaken and used to form cost-effectiveness acceptability curves and cost-effectiveness acceptability frontiers (e.g. [1]).
This study uses two models of the mosquito population (and couples each with the simple Ross-Macdonald assumptions) to address the issue of cross-validation; examining different modelling approaches to the same problem (and comparing results) represents an important means of dealing with structural uncertainty. The close agreement between the Parham and White models in their qualitative (and often quantitative) predictions, despite having very different mathematical structures and formulations, adds confidence and robustness to the results within the scope of our study. The importance of structural uncertainty on the conclusions reached cannot be assessed by varying model parameters, but robust policy decisions, despite these unavoidable uncertainties, are required. It should be noted, however, that even disagreement between models would also be insightful, as this would indicate potential sensitivity to key structural assumptions underpinning model development. Numerous models of Anopheles mosquito population dynamics, ranging in complexity, have been developed [66–72], as have a range of malaria models [76]; an ensemble-based approach may therefore be valuable and, in the context of cost-effectiveness analyses, this has already begun for other infectious diseases (e.g. [104]). More general methods for dealing with the different types of uncertainties that occur in such integrated health economic studies have also recently been reassessed (e.g. [104]). Moreover, in addition to more fully quantifying the different types of uncertainties that arise when applying our integrated framework to country-specific scenarios under changing epidemiological and climatic conditions, an improved understanding and quantification of the emergence of insecticide resistance is undoubtedly required and this represents an important priority for the field.

5. Conclusion

The effectiveness and cost-effectiveness of vector-based interventions against malaria depend on a region’s climatic profile, which, in some cases, may be important for the economic viability of scale-up programmes in countries likely to experience significant changes in rainfall and/or temperature owing to global warming. In the context of elimination, a ‘one size fits all’ approach in regions with low endemicity is unlikely to be optimal. For the range of epidemiological and environmental conditions considered, in regions of low endemicity, we find that IRS alone is more cost-effective than LLINs at the same levels of scale-up, particularly when existing IRS coverage is low or absent. Implementation of IRS and LLIN scale-up is more cost-effective at lower mean precipitation and higher variability in both precipitation and temperature. We also find that the unimodal peak in transmission as a function of mean air temperature reported elsewhere [80,98] translates into the cost-effectiveness of vector-based interventions required to interrupt transmission and this nonlinear dependence of cost-effectiveness on temperature is an important finding in the context of the potential effects of climate change on malaria transmission and control. Although temperature and rainfall are found to affect the effectiveness, cost-effectiveness and, in some cases, public health policy decisions of the interventions considered, our results do nonetheless suggest that these climatic variables may play a less dominant role than interventions in driving transmission. Our results are consistent with the message that continued investment in intervention scale-up, monitoring and surveillance of insecticide resistance, implementation of resistance management programmes and improved entomological and epidemiological knowledge on key parameters driving spatio-temporal spread are likely to be more important in driving future trends than climate change. Nonetheless, further cost-effectiveness analysis accounting for country-specific current and future epidemiological and environmental changes, and quantifying the range of uncertainties therein, is required to assess options for regional intervention scale-up moving forwards and the relative importance of different factors likely to drive future transmission trends under climate change.

References


