Optimising the deployment of vector control tools against malaria: a data-informed modelling study

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Summary

Background **Concern that insecticide resistant mosquitoes are threatening malaria control has driven the development of new types of insecticide treated nets (ITNs) and indoor residual spraying (IRS) of insecticide. Malaria control programmes have a choice of vector control interventions although it is unclear which controls should be used to combat the disease. The study aimed at producing a framework to easily compare the public health impact and cost-effectiveness of different malaria prevention measures currently in widespread use.**

Methods **We used published data from experimental hut trials conducted across Africa to characterise the entomological effect of pyrethroid-only ITNs versus ITNs combining a pyrethroid insecticide with the synergist piperonyl butoxide (PBO). We use these estimates to parameterise a dynamic mathematical model of *Plasmodium falciparum* malaria which is validated for two sites by comparing simulated results to empirical data from randomised control trials (RCTs) in Tanzania and Uganda. We extrapolated model simulations for a series of potential scenarios likely across the sub-Saharan African region and include results in an online tool (Malaria INtervention Tool [MINT]) that aims to identify optimum vector control intervention packages for scenarios with varying budget, price, entomological and epidemiological factors.**

Findings **Our model indicates that switching from pyrethroid-only to pyrethroid-PBO ITNs could averted up to twice as many cases, although the additional benefit is highly variable and depends on the setting conditions. We project that annual delivery of long-lasting, non-pyrethroid IRS would prevent substantially more cases over 3-years, while pyrethroid-PBO ITNs tend to be the most cost-effective intervention per case averted. The model was able to predict prevalence and efficacy against prevalence in both RCTs for the intervention types tested. MINT is applicable to regions of sub-Saharan Africa with endemic malaria and provides users with a method of designing intervention packages given their setting and budget.**

Interpretation **The most cost-effective vector control package will vary locally. Models able to recreate results of RCTs can be used to extrapolate outcomes elsewhere to support evidence-based decision making for investment in vector control.**

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Introduction

The increased use of long-lasting insecticidal mosquito nets (LLINs) and indoor residual spraying (IRS) of insecticide is predicted to have prevented three quarters of malaria cases in Africa between 2000 and 2015.[1] Annual malaria case burden has shown no further decrease since 2017 despite wide-spread vector control and effective drug treatment.[2] Among many possible reasons for this stalling is the spread of mosquitoes resistant to pyrethroid insecticides with which the nets are treated.

Over 2 billion LLINs have been distributed globally yet there has been an acute lack of choice in net class, with all mass campaigns before 2019 distributing nets containing only pyrethroid insecticides. Mosquitoes displaying resistance to pyrethroids are increasingly widespread in Africa.[3] Entomological evidence indicates a declining ability of LLINs to kill mosquitoes entering experimental hut trials,[4] although the effect of pyrethroid resistance on malaria control is hard to measure directly, making the public health impact of resistance unclear.[5] The lack of choice of alternative mosquito nets (here referred to as ITNs) is being addressed. In 2018, following a Tanzanian cluster randomised controlled trial (RCT),[6] WHO conditionally recommended a new class of net treated with a pyrethroid and synergist piperonyl butoxide (pyrethroid-PBO ITN) for use in areas with pyrethroid resistant mosquitoes. The RCT showed that compared with pyrethroid-only LLINs, pyrethroid-PBO ITNs had substantially greater epidemiological effect 16 months after distribution.[6] A second RCT in Uganda[7] has recently corroborated the benefit, although the effect size varied. These trials indicate pyrethroid-only LLINs still protect against malaria but the epidemiological effect might be reduced by pyrethroid resistance, although other explanations are proposed.[8] The Alliance for

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For French translation of the abstract see Online for appendix 1

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For **Alliance for Malaria Prevention** see https://allianceformalariaprevention.com/

Research into context

Evidence before this study

Insecticide treated nets (ITNs) and the indoor residual spraying (IRS) of insecticide are the most effective method of preventing malaria. WHO currently recommends two types of ITN, pyrethroid-only and pyrethroid plus piperonyl butoxide (PBO) nets, as well as different IRS products. Cluster randomised controlled trials (RCTs) have shown that impact of these interventions vary substantially according to the type of net, whether IRS is also used, the epidemiological setting and the characteristics of the mosquitoes. Combining ITNs and IRS has shown epidemiological benefit, although cost-effectiveness is debated. An added challenge of recent years is that in some areas mosquitoes have developed intense resistance to pyrethroids, the only insecticide class currently used on WHO recommended ITNs. Resistance is thought to influence the effectiveness of pyrethroid and pyrethroid-PBO ITNs differently and they also vary in price. Previous modelling studies using experimental hut data found pyrethroid-PBO ITNs to be more cost-effective while both nets were likely to report some benefit even with resistant mosquitoes. National Malaria Control Programmes and decision makers could benefit from guidance about which vector control options they should deploy in different settings. The present work is based on four previously published systematic reviews on mosquito bionomics and the efficacy of the current first-line vector control tools recommended by WHO.

Added value of this study

We introduce a framework that can be used to identify the most cost-effective vector control interventions for a region according to local epidemiology, entomology, and budgets. The framework is validated for two settings by showing how the malaria transmission dynamic model—parameterised using entomological data from experimental hut studies—can broadly predict the outcomes of RCTs done in Tanzania and Uganda. Projections are compiled to inform an open-access online tool which aims to help policy makers identify the most cost-effective interventions for their setting.

Implications of all the available evidence

Models were able to capture the epidemiological benefit of different vector control interventions in two settings although further validation is needed to allow the results of trials to be extrapolated to other areas. Generally, results indicate that in regions where PBO synergises the killing of mosquitoes pyrethroid-PBO ITNs are likely to be more cost-effective (lower cost per case averted) than pyrethroid-only LLINs unless there is large difference in product price. Widespread use of effective IRS has the biggest public health effect depending on the level of intervention coverage assumed, resistance in mosquito populations and to a lesser extent, mosquito bionomics. Adding IRS to nets is predicted to have benefit, especially when IRS is deployed in the years following mass ITN campaigns, although this approach is likely to be less cost-effective than achieving high coverage of single interventions.

Malaria Prevention reports that pyrethroid-PBO ITNs are increasingly recommended by the national malaria control programmes (NMCPs), with over 43 million nets delivered in 2020.

Insecticides with prolonged activity against vector mosquitoes are available for IRS.[9] IRS campaigns remain logistically more challenging than net distributions due to product cost and annual application that can be expensive and disruptive to communities.[10] The extra choice of vector control products makes decisions on resource allocation challenging. Historically, WHO recommended universal coverage of pyrethroid-only LLINs for all regions. Now NMCP decisions on which nets to procure might depend on price, as budgets are constrained and pyrethroid-PBO ITNs might be more expensive (although this might change over time and volume procured). Additional cases might be averted in areas with mostly susceptible mosquitoes by distributing pyrethroid-only rather than pyrethroid-PBO ITNs at a lower population coverage. Pyrethroid-PBO ITN deployment is recommended at sites showing entomological evidence of PBO synergism[11] but these nets might have use elsewhere. The optimum interventions will depend on the NMCPs' strategy, budgets, product price, disease endemicity, historical malaria control and characteristics of local mosquitoes—including the intensity and prevalence of pyrethroid resistance. These factors continually change so there is urgent need for guidance. Mathematical models can provide a framework to help investigate the most cost-effective vector control package for a setting.

The goal of this work is to support local decisions on the most cost-effective vector control package. To do this we (i) combine entomological data from experimental hut trials with a mechanistic model of *Plasmodium falciparum* malaria to estimate intervention impact; (ii) compare model predictions to epidemiological data from two recent RCTs; (iii) extrapolate model simulations across different scenarios reflecting ecology and disease endemicity observed across Africa; and (iv) introduce an online tool (Malaria INtervention Tool [MINT]) to help decision makers to access modelling results and investigate setting-specific, cost-effective vector control.

Methods

Choice of control

Mosquito nets and IRS are core vector control tools recommended by WHO for malaria prevention. Currently net choice is limited to either pyrethroid-only LLINs or pyrethroid-PBO ITNs.[12] Multiple IRS products with different insecticides are pre-qualified by WHO and

should be rotated as part of an insecticide resistance management plan.[13] We consider general long-lasting IRS active-ingredients (eg, organophosphates [pirimiphos methyl] or neonicotinoids [clothianidin]),[14] to which local mosquitoes are assumed susceptible. Here we consider net choice and IRS implemented alone or jointly within an area. Care should be taken when interpreting results combining interventions as it is assumed that net and IRS use is random (ie, having a house sprayed does not influence net use), and entomological effects of the two interventions are independent and sequential,[15] both of which require verification.

ITN and IRS efficacy

Experimental hut trials are the standard tests for assessing nets and IRS product efficacy against local mosquitoes.[16,17] Hut trials assess the probability that a blood-seeking mosquito will (i) be deterred from entering (measured by the number of mosquitoes caught in a hut with an intervention compared with a control hut), or (ii) enter the hut and either exit without feeding, (iii) die, or (iv) successfully blood-feed.

The efficacy of pyrethroid-only LLINs and pyrethroid-PBO ITNs vary with pyrethroid resistance and is assumed to be determined by the level of pyrethroid resistance as measured by a WHO discriminatory dose susceptibility bioassay (resistance is defined as the percentage of mosquitoes surviving 24-hours following exposure).[4] Statistical models describing the added advantage of pyrethroid-PBO ITNs over pyrethroid-only LLINs are fitted to data from systematic reviews of published and unpublished experimental hut trials (appendix 2 p 2). IRS is parameterised as previously (appendix 2 p 9).[14] An individual-based transmission model of *P falciparum* malaria incorporating human immunity, age structure, and larval and adult mosquito dynamics is used to predict vector control efficacy from these entomological efficacy estimates (appendix 2 p 12) and site characteristics.[15,18] Full details of the transmission model are provided in appendix 2 (p 15).

Mosquito bionomics

Multiple mosquito characteristics influence endemicity and disease control including the propensity of mosquitoes to bite humans (human blood index),[19] seasonality of transmission and likelihood of mosquitoes biting people indoors when there is potentially greater protection from nets and IRS. Variables used in the analyses and justification for the ranges adopted are provided (appendix 2 p 12).

Site characteristics

Intervention impact will vary with seasonality (appendix 2 p 13), disease endemicity and history of control. We consider seven current endemicities, ranging from 5% to 60% malaria prevalence in children younger than 5 years, to broadly reflect endemicities observed across sub-Saharan Africa. The mathematical model is calibrated to the specified endemicity given historical levels of vector control use and efficacy (itself determined by mosquito bionomics and human activity).

To instil confidence in the mathematical model approach, we compare predictions to gold-standard field data (appendix 2 p 30). Two RCTs have compared epidemiological efficacy of pyrethroid-PBO ITNs and long-lasting IRS in areas with pyrethroid resistant mosquitoes. The Tanzania study[6] empirically compared pyrethroid-only and pyrethroid-PBO ITN with and without a single round of organophosphate IRS. The dominant vector was *Anopheles gambiae s l* (92% *An gambiae*, 4·6% *Anopheles arabiensis*) which exhibited on average 91% pyrethroid resistance as measured by WHO bioassay.[6] The Ugandan study[7] compared prevalence in children aged 2–10 years across two products within the pyrethroid-PBO net class to two products within the pyrethroid-only LLIN class.[7] Vectors consisted of *An gambiae* (71%), *Anopheles funestus* (24%) and *An arabiensis* (4·6%),[20] pyrethroid resistance varied considerably across clusters and between mosquito species;[21] we investigated an estimate for pyrethroid resistance of 53% (95% CI 49–55) survival at bioassay. The model is parameterised using local site characteristics and adjusted to match malaria prevalence at study initiation. Forward predictions are made given net use measured during trials. Results are compared with observed malaria prevalence over subsequent months (appendix 2 p 30).

A total of 403 200 scenarios were run varying intervention net type (pyrethroid or pyrethroid-PBO) coverage (past and future intervention use), transmission seasonality (seasonal or perennial) and endemicity (prevalence in children younger than 5 years ranging from 5% to 60%), mosquito bionomics (degree of indoor or human biting) and pyrethroid resistance among local mosquitoes. In each scenario, we assume the level of pyrethroid resistance was constant throughout. Results are shown for a 3-year period chosen to reflect the expected regularity of mosquito net mass campaigns (with IRS assumed to be repeated once annually and distributed at the optimal time in the year before the transmission season). The counterfactual scenario considered simulates no future use of vector control and we compare this with vector control use (5 scenarios: pyrethroid-only LLINs or pyrethroid-PBO ITNs and IRS alone or in combination with each net). Uncertainty is incorporated by simulating outputs using the maximum and minimum parameter estimates of entomological efficacy for each intervention (appendix 2 pp 2–12). All possible parameter combinations to determine effect of nets and spraying are summarised (appendix 2 p 38).

See Online for appendix 2

Mosquito net costs are differentiated between the product cost per person and the delivery cost per person per 3-year mass distribution campaign (assumed equivalent across net types, appendix 2 p 40). IRS cost per person is calculated from the per unit cost (assuming

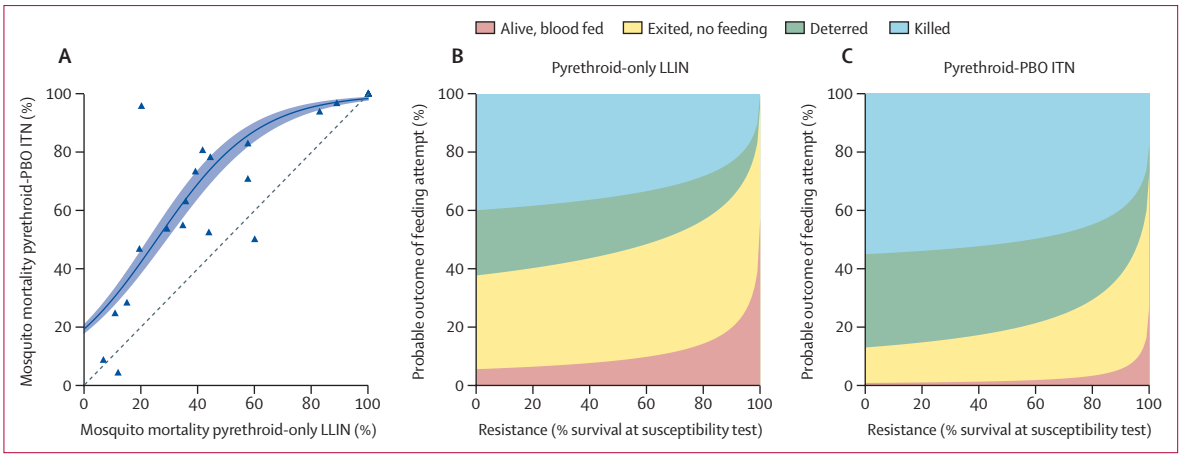

Figure 1: **Efficacy of different insecticide treated mosquito nets against mosquitoes with different levels of pyrethroid resistance**
(A) Pyrethroid-PBO ITNs do better at killing mosquitoes than pyrethroid-only LLINs in experimental hut trials directly comparing induced mosquito mortality. (B–C) The average estimated outcome changes given the level of resistance in mosquitoes approximated as the proportion of mosquitoes surviving in a discriminatory dose bioassay. We assume that for any feeding attempt, a mosquito is either deterred from entering a hut (green), enters and is killed (blue), enters and then exits again without feeding (yellow) or successfully blood-feeds (red). As the pyrethroid-PBO ITN is shown to induce more mortality than the pyrethroid-only LLIN (A), the contrasting outcomes differ for pyrethroid-only LLINs (B) or for pyrethroid-PBO ITNs (C) with the latter maintaining protective effects (killing and deterring) for longer as mosquito populations become increasingly pyrethroid resistant. IRS=indoor residual spraying. LLIN=long-lasting insecticidal mosquito net. PBO ITNs=piperonyl butoxide insecticide treated nets

this is standardised to treat 250 m² of wall surface) and the remaining cost of storing, transporting, and recycling or disposing of containers in different settings[10] accounting for three deployments across the 3 years to standardise comparisons with nets. Hypothetical costs are illustrated and understood to be broadly representative of the current market.

For **MINT tool** see https://mint.dide.ic.ac.uk/

Our MINT tool has a user-friendly interface and is provided to enable exploration of vector control interventions.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Pyrethroid-PBO ITNs kill significantly more (P450-mediated) resistant mosquitoes than pyrethroid-only LLINs with benefit varying according to level of pyrethroid resistance (figure 1A). The absolute difference between ITN types is greatest at intermediate prevalence levels of pyrethroid resistance (~60% survival at susceptibility bioassay testing) where, on average a pyrethroid-PBO ITN is predicted to increase mosquito mortality at the population level by 30%. Induced deterrence, and the relationship between mosquito survival and blood-feeding are highly variable between studies but could be considered consistent across all net types (appendix 2 p 5). These statistical models[4] summarise efficacy of different net types by showing how the probability that a mosquito dies, is deterred, exits without blood-feeding, or successfully feeds varies per feeding attempt at different levels of pyrethroid resistance (figure 1B–C)

A mathematical model parameterised with entomological data is broadly able to recreate results of the Tanzanian (figure 2A, nets, and figure 2C, nets and IRS) and Ugandan (figure 2B) RCTs of pyrethroid-only LLINs, pyrethroid-PBO ITNs, and organophosphate IRS. Model projections broadly match the average malaria prevalence observed in the trials (linear regression: R^2=0·95, gradient=0·86, p<0·001; figure 2D). There is some difference in observations and predictions at 18 months in the Tanzanian study, but relative difference between study arms is approximately consistent. The observed overall effect size (average difference between trial arms) varies for pyrethroid-PBO ITNs between studies (observed estimates for Tanzania 32·0 [range 17·5–43·8%], Uganda 20·1% [range 15·7–26·2%]) as predicted by the model (model estimates for Tanzania 18·2% [range 10·7–28·2%], and Uganda 29·7% [range 11·1– 47·7%]; figure 2E).

The public health effect of different nets and IRS is substantial. Illustrating this in an area with perennial transmission, moderate disease prevalence (30% prevalence in children younger than 5 years) and high pyrethroid resistance (60% mosquito survival in a bioassay), increasing use of pyrethroid-only LLINs from 40% to 80% (figure 3A, blue line) still provides substantial protection compared with halting vector control (figure 3A, grey line) averting an average 395 (307–454) cases per 1000 people annually over 3 years (figure 3B). Switching to a pyrethroid-PBO ITN at 80% use (80% of people are using mosquito nets across the community) is predicted to avert 482 (464–541) cases per 1000 people per year over the same period (a 22% increase in the number of cases averted). The effect of different ITNs is projected to be relatively consistent the first year after a mass campaign, although differences increase as usage drops and resistant

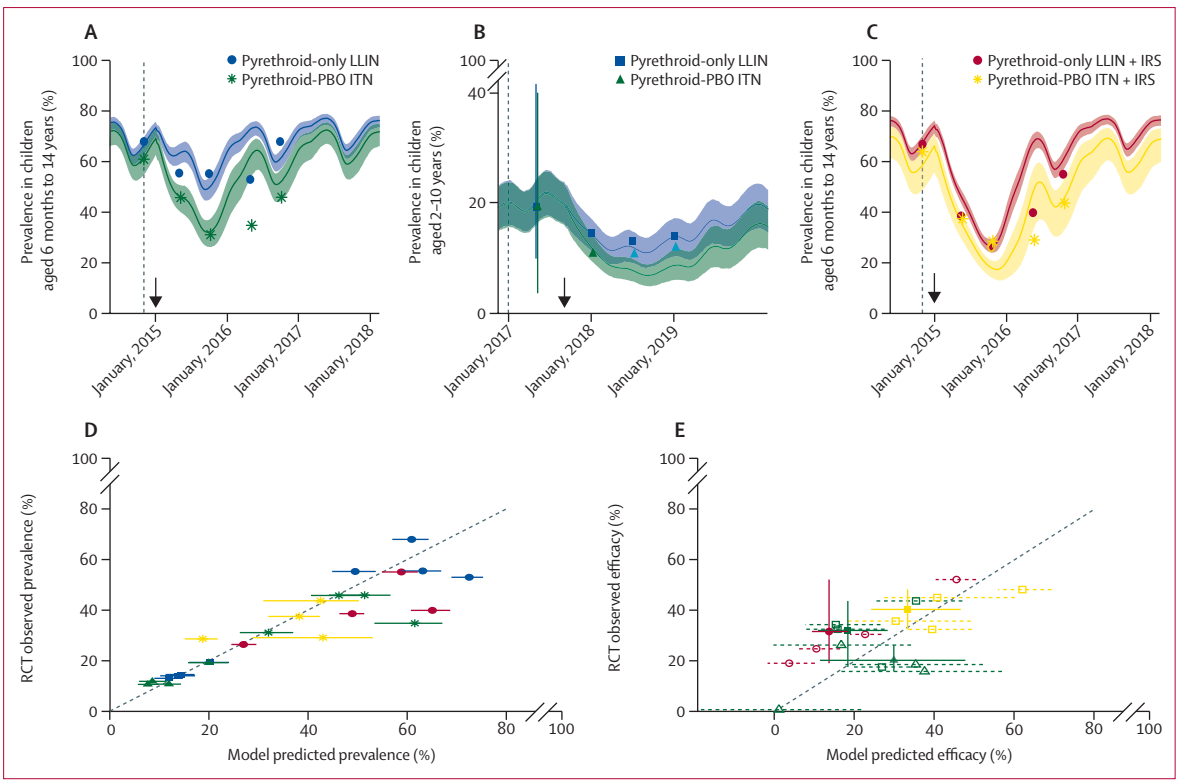

Figure 2: **Ability of a transmission model of malaria parameterised with experimental hut entomological data to predict the epidemiological results of two cluster RCTs**

The RCT results for mosquito nets in (A) Tanzania,[6] and (B) Uganda.[7] Changes in malaria prevalence (in children aged 6 months to 14 years in Tanzania,[6] and those aged 2–10 years in Uganda),[7] measured by rapid diagnostic test, over time following the introduction of different mosquito nets—pyrethroid-only LLIN (in both A and B blue lines and polygons show model predictions and 95% uncertainty intervals; symbols show mean point estimates for trial arms observed during the trials), and pyrethroid-PBO ITN (green). Arrows indicate when the nets were distributed in the respective trials. (C) The net + IRS RCT results for Tanzania[6] where pyrethroid-only LLIN were supported by a single year deployment of long-lasting IRS (red) and compared with pyrethroid-PBO ITN with IRS (yellow). IRS was sprayed once at the beginning of the study (February 2015, marked by the arrow). Vertical dashed line denotes start of trial in panels (A–C). (D) Model predictions (x-axis) of prevalence for the respective age cohort of each trial used to estimate the observed data (y-axis). Colours and symbols correspond to the respective groups of the trials as shown in panels (A–C; Tanzania [A, C]: pyrethroid-only LLIN blue circles, pyrethroid-PBO ITN green asterisks, pyrethroid-only LLIN + IRS red circles, and pyrethroid-PBO ITN + IRS yellow asterisks; Uganda [B]: pyrethroid-only LLIN blue squares and pyrethroid-PBO ITN green triangles). (E) The relative efficacy against prevalence in the respective age cohort of the different intervention packages compared with the continued use of pyrethroid-only LLIN as predicted by the model (x-axis) and compared with the observed data (y-axis). Open shapes show the point estimates of each RCT (Tanzania: pyrethroid-PBO ITN green squares, pyrethroid-only LLIN plus IRS red circles, and pyrethroid-PBO ITN plus IRS yellow squares; Uganda: pyrethroid-PBO ITN green triangles) over time as noted in (A–C), colours correspond to the trial arms in (A–C), and solid shapes indicate the average impact across time points. Black dashed lines in (D–E) show perfect agreement between the observed and model predicted data. IRS=indoor residual spraying. LLIN=long-lasting insecticidal mosquito net. PBO ITNs=piperonyl butoxide insecticide treated nets. RCT=randomised controlled trial.

mosquitoes are more able to overcome insecticide on older nets (figure 3B) making the residual effect of the synergist especially important. In this scenario, annual IRS, covering 60% of people, is projected to prevent 527 (399–579) cases per 1000 people per year. The added benefit of both nets is projected to diminish in areas with more resistant mosquito populations with the additional cases averted by pyrethroid-PBO ITNs being relatively consistent across resistance levels (figure 3C). A reduced effect is predicted for ITNs and IRS when fewer mosquitoes blood-feed indoors (figure 3C).

Adding a non-pyrethroid, long-lasting IRS to areas with high ITN coverage is projected to have substantial benefit, especially in the third year after net distribution—when net campaign efficacy diminishes due to net attrition and aging nets. Adding ITNs to areas with high IRS coverage is projected to have less benefit in moderate transmission areas (figure 3B), although greater effect is projected in areas with higher transmission (appendix 2 p 44).

Malaria control budgets are restricted, so implementing the most impactful interventions everywhere is infeasible. The most cost-effective intervention package will depend on product price and goals of the NMCP. Given the heterogeneity in setting, entomology, and epidemiology we provide a tool by which policy makers can explore the most cost-effective option for differing budgets. The tool indicates that in a high resistance scenario assuming nets are procured at US$2 (1·48–2·64) for pyrethroid-only LLIN and $2·30 (1·80–4·00) for pyrethroid-PBO, mass distribution of pyrethroid-PBO ITNs is predicted to be marginally more cost-effective within a $2 per person campaign (3 years) budget

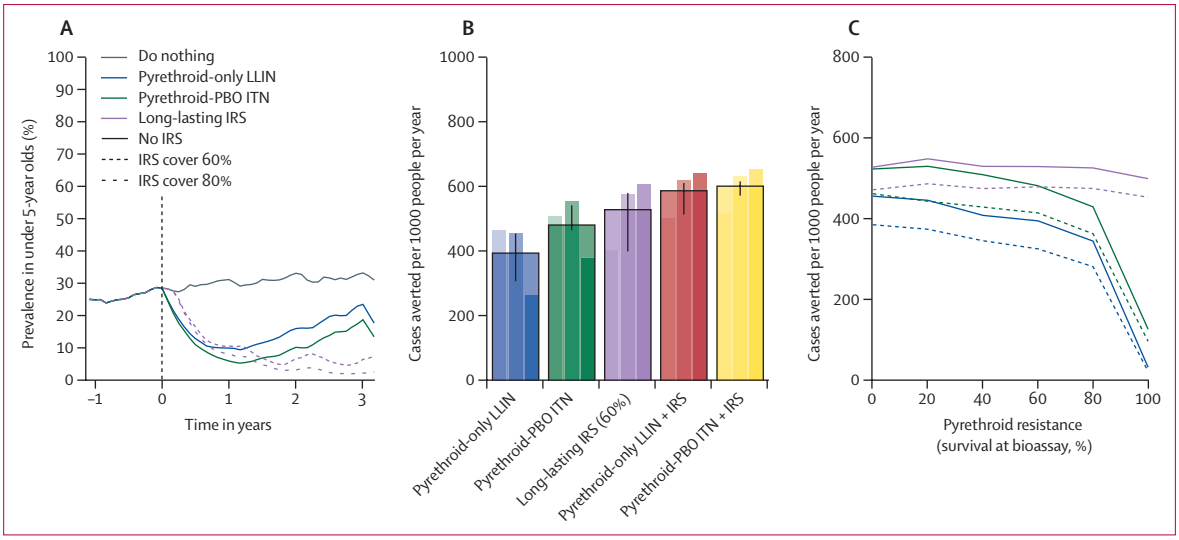

Figure 3: **Efficacy of different intervention packages for vector control as estimated for a scenario with moderate perennial transmission (30% prevalence in children younger than 5 years), and highly anthropophilic (92% human biting) and endophilic (97% indoor-biting in the absence of interventions) mosquitoes with 60% pyrethroid resistance**

(A) The prevalence in children younger than 5 years is reduced in the resistance scenario with no historic spraying by increasing the use of pyrethroid-only LLINs (blue) from 40% to 80% across the population or using pyrethroid-PBO ITNs (green) at the same 80% usage. Mosquito nets are simulated to be distributed on mass in year 0 and not replaced for 3-years. Long lasting IRS is implemented annually from year 0 to cover 60% (dashed line) or 80% (dash-dotted line) of households (purple). (B) In a scenario with the same baseline description as (A), comparing the intervention impacts relative to the do nothing scenario indicates that pyrethroid-only LLINs can still avert 395 (307–454) clinical cases per 1000 people per year, averting most in year 1 and 2 (paler bands indicate annual impact, solid bands show 3-year average impact) post increasing net cover and redistributing nets. Pyrethroid-PBO ITNs are predicted to be better, averting 482 (464–541) clinical cases per 1000 people per year in the scenario (green bars), again averting most cases in year one. Annual application of long-lasting IRS at 60% use using a chemistry assumed to elicit no resistance in local mosquitoes achieves an overall better result (averting 528 [399–579] clinical cases per 1000 people per year) making most gains in the later years (purple line in A and bars in B). Together pyrethroid LLINs plus IRS at 60% cover can avert 586 (512–610) clinical cases per 1000 people per year in this pyrethroid resistance scenario (red bars), whereas pyrethroid-PBO ITN plus IRS avert 600 (571–615) clinical cases per 1 000 people per year (yellow bars). (C) In a perennial example with 30% prevalence in children younger than 5 years, the relative efficacy of each intervention package against clinical cases per 1000 people per year decreases for both nets with resistance, but does so most dramatically after 80% or more mosquitoes survive exposure to pyrethroid insecticides (due to the association between mosquito mortality in the experimental huts and susceptibility bioassay, appendix 2 p 5). In contrast, the average effect over 3-years remains the same each year if IRS is annually applied when pyrethroid resistance increases (assuming no resistance to organophosphates or neonicotinoids). Of note, when mosquitoes are highly endophilic (97% biting indoors, solid lines), indoor interventions are predicted to result in greater protection than when mosquitoes are less endophilic (78% biting indoors, dashed lines). IRS=indoor residual spraying. LLIN=long-lasting insecticidal mosquito net. PBO ITNs=piperonyl butoxide insecticide treated nets.

(figure 4A). With these prices, and in the context of the setting presented (seasonality, endemicity, mosquito behaviour, historic interventions), pyrethroid-PBO ITNs appear to be marginally more cost-effective across areas where resistance has been detected (table), as approximated using discriminatory dose bioassays. To show how cost effectiveness is setting specific, transmission endemicities of less than 30% prevalence in children younger than 5 years in the otherwise matched scenario suggest the cost of nets will alter which option is cost-effective given differences in indoor biting preference and approximate resistance profiles of mosquitoes (figure 4B). Other mosquito or community characteristics are also shown to have an effect, including the propensity of vectors to blood-feed on other animals, endemicity, or population net use achieved (figure 4C).

Annual deployment of IRS alone or in combination with nets is highly effective but its implementation might be restricted by budgets unless very high levels of resistance exist, and IRS costs were to drop substantially (appendix 2 p 42). Nevertheless, mosquito net use alone when distributed through mass campaigns is unlikely to eliminate malaria in areas with moderate to high transmission so additional strategies require consideration.

Cost-effectiveness of interventions depends on population usage per delivered product. High population coverage with ITNs is difficult, and more nets might need to be distributed per person to achieve universal coverage due to system inefficiencies.[22] The incremental epidemiological impact, combining individual and community effects, of increasing ITN coverage declines with overall increasing coverage (ie, going from 60% to 70% usage averts more cases than going from 70% to 80%, figure 4C). Improving net use is always beneficial, with the greatest benefit of achieving high coverage seen in areas of moderate disease endemicity (appendix 2 p 47). Nevertheless, the high cost-effectiveness of pyrethroid-PBO ITNs means that increasing ITN allocation from 0·5 to 0·8 nets per person (2·0 to 1·25 people per net) to achieve high ITN usage is still likely to result in a cost of less than $10 per case averted per campaign (figure 4C). Achieving high usage of pyrethroid-PBO ITNs appear to remain the most cost-effective option across most

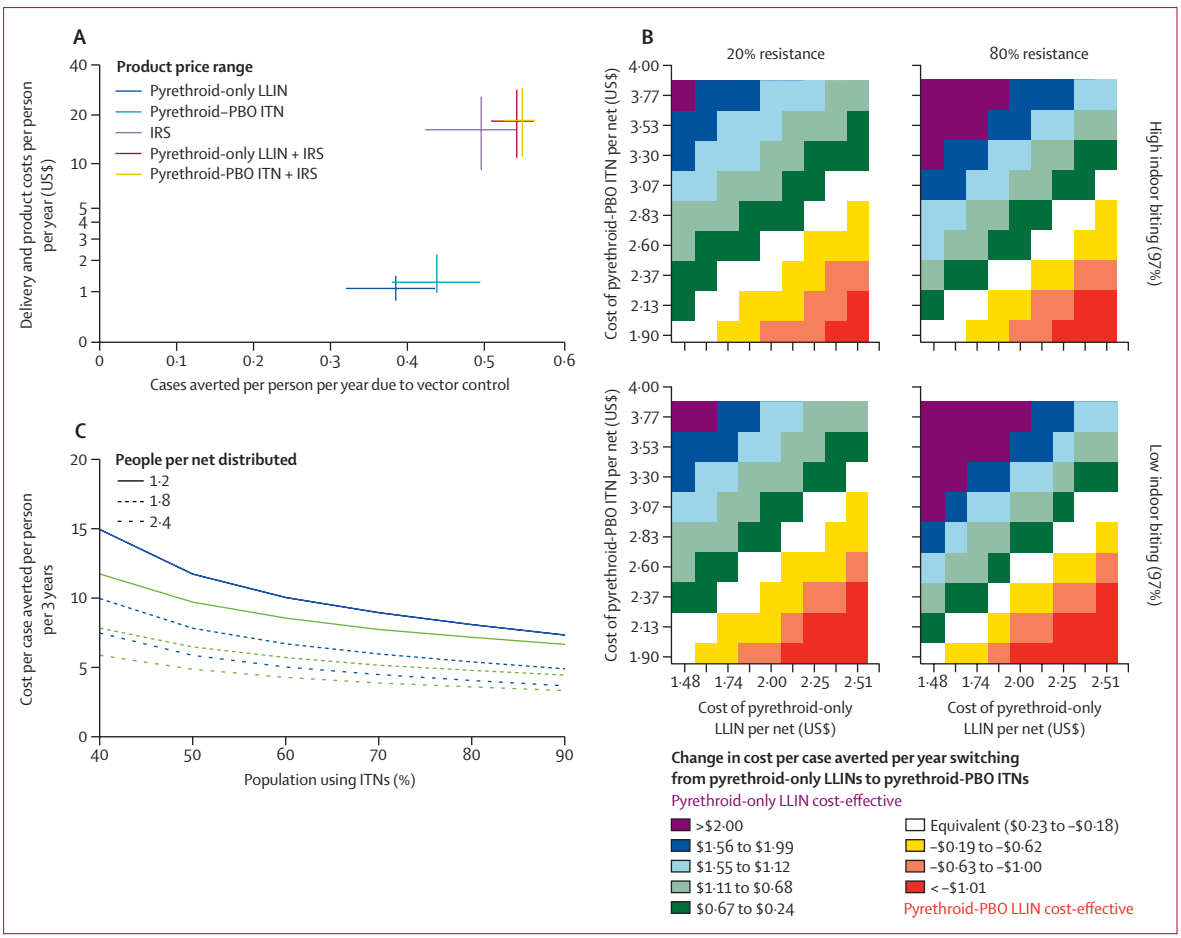

Figure 4: **Cost-effectiveness of indoor vector control interventions**
Costs are illustrative in this example, but to show the importance of considering local ecology we show how cost-effectiveness varies with the potential intervention packages (dark blue=pyrethroid-only LLIN alone, green=pyrethroid-PBO ITN, purple=IRS, red=pyrethroid LLIN plus IRS, yellow=pyrethroid-PBO plus IRS) (A). Cost-effectiveness plane across the total 3-year mass campaign cycle, in a scenario with perennial transmission, a baseline prevalence of 30% in children younger than 5 years, historic LLIN use of 40% without IRS, high indoor biting (97% of *Anopheles* bites are received indoors in the absence of interventions), high human blood index (92% of bloodmeals are taken on people), and 60% pyrethroid resistance. New nets are distributed which achieve 80% use with 80% of people covered by IRS. Pyrethroid-only LLINs in this scenario are priced at US$2·00 per LLIN (vertical coloured line indicating range $1·48–2·64), pyrethroid-PBO ITNs at $2·30 (1·80–4·00) and $1·50 per person for the distribution campaign assuming 1·8 people per net with 7% buffer (107% of the total required nets are procured to cover any discrepancies in census data). IRS is priced at $5·73 per person protected with range $3·35–8·90. In (B) the two nets are contrasted to identify the most cost-effective strategy if implemented alone given different net prices (green-purple price region=pyrethroid-only LLINs more cost effective, red-yellow region=pyrethroid-PBO ITNs are more effective). Different plots are shown for different levels of resistance (left panels 20% or right panels 80% survival at bioassay), and at either high 97% (top panels) or low 78% (bottom panels) indoor blood-feeding behaviours for female mosquitoes. Each plot otherwise assumes the epidemiological and entomological scenario outlined in panel (A) and results will change in different epidemiological and entomological settings. Colour of the plots indicate whether or not switching to pyrethroid-PBO ITNs is a cost-effective option given the difference in price of the two nets. For example, red area shows cost region where switching to pyrethroid-PBO ITNs is highly cost-effective, reducing cost per case averted by over $1 per case per year. The cost region where both nets have an equivalent cost-effectiveness are shown in white whilst positive values (green-blue colours) indicate where switching to pyrethroid-PBO is not cost-effective (ie, cost per case averted increases). (C) For the same scenario as (A), projections of the cost-effectiveness of different net campaigns which achieve different levels of usage following a mass campaign given the net allocation (dotted-dashed lines represent 2·4 people per net, dotted 1·8, and dashed and solid 1·2). Cost per case averted across the 3-year campaign is lowest when campaigns achieve greater use following mass campaigns for both pyrethroid-only LLINs (blue) and pyrethroid-PBO ITNs (green). Figures are intended to be illustrative and ignore challenges of insecticide resistance management, net caps, and logistical challenges for the delivery of IRS (eg, deployment taking multiple months) that are important in the decision-making process. IRS=indoor residual spraying. LLIN=long-lasting insecticidal mosquito net. PBO ITN=piperonyl butoxide insecticide treated net.

resistance levels given approximate current prices (appendix 2 p 48) although there might be reasons why this is not possible.[23] More realistic net allocation scenarios where numbers of nets distributed per person might need to increase to achieve high usage, could make IRS more cost-effective (appendix 2 p 49).

Discussion

New vector control strategies are needed to improve malaria control. There is an increasing diversity of ITNs (with combinations of active ingredients),[24–26] and other types of interventions are under epidemiological evaluation; selecting the most appropriate intervention is likely

	Pyrethroid LLIN (US$)	Pyrethroid-PBO ITN (US$)	IRS (US$)
5%	$6·27 (5·34–7·41)	$6·61 (5·74–9·57)	$51·64 (30·19–80·20)
10%	$2·74 (2·33–3·24)	$2·79 (2·42–4·04)	$20·83 (12·18–32·35)
20%	$1·93 (1·64–2·28)	$1·89 (1·64–2·73)	$12·89 (7·53–20·02)
30%	$1·75 (1·49–2·08)	$1·72 (1·49–2·49)	$11·04 (6·45–17·14)
40%	$1·73 (1·47–2·04)	$1·67 (1·45–2·42)	$9·60 (5·61–14·91)
50%	$1·76 (1·50–2·08)	$1·68 (1·46–2·44)	$9·05 (5·29–14·06)
60%	$1·88 (1·60–2·22)	$1·81 (1·57–2·62)	$9·03 (5·28–14·03)

Data are mean annual cost per case averted during 3-year campaign, including distribution costs; ranges are shown in parentheses. Scenario represented: perennial transmission, historic LLIN use of 40% without IRS, high indoor biting (97% of *Anopheles* bites are received indoors in the absence of interventions), high human blood index (92% of bloodmeals are taken on people). We vary baseline prevalence from 5% to 60% in children under age 5 years (transmission) and explore a resistance scenario where 60% of mosquitoes survive a discriminating dose bioassay. New nets are distributed which achieve 80% use in the absence of IRS or 80% of people covered by IRS in the absence of a net campaign. Nets in these scenarios are priced at US$2 (1·48–2·64) for pyrethroid-only LLINs and $2·30 (1·80–4·00) for pyrethroid-PBO ITNs. The mean cost of IRS is $5·73 (3·35–8·90). We contrast costs per case averted to ensure estimates are comparable across intervention types. IRS=indoor residual spraying. LLIN=long-lasting insecticidal mosquito net. PBO ITNs=piperonyl butoxide insecticide treated nets.

Table: **Comparison of the annual cost per case averted for singular interventions across multiple baseline endemicities ranging from 5% to 60% malaria prevalence in children under the age of 5 years (first column)**

to become more complex. The most appropriate tools to use depend on many factors including mosquito characteristics, net use, and costs. Epidemiological trials add critical value over entomological data by showing impact on malaria transmission.[27] RCTs are a lengthy process, requiring specialist expertise, can only be conducted in a limited number of settings, and cannot inform the diversity of effect that nets and IRS will have in different ecologies. Although they are no substitute for good epidemiological data, mathematical models can provide a useful tool to support the decision making process if they can reliably recreate real-world results. Here we show for two RCTs[6,7] that entomological data, combined with existing models, can reasonably predict epidemiological effect of pyrethroid-PBO ITNs and long-lasting IRS over pyrethroid-only LLINs. Only two RCTs have investigated the effect of mass pyrethroid-PBO ITNs distribution on malaria so their wider benefit remains untested. The mechanistic model broadly captures the effect size of these three different interventions affording some confidence that the framework could reasonably predict impact elsewhere. Nevertheless, this needs to be tested as mosquito populations can vary substantially so projections should be treated with caution until their accuracy can be verified across the range of settings where they might be used.

The analysis highlights the added benefit of IRS to nets, particularly as the impact from nets wanes toward the third year after the campaign. The Tanzanian study used IRS during the first year which showed significant benefit[6] and our simulations indicate repeated annual IRS would have been substantially more impactful in later years as ITN benefits decline. The addition of IRS to LLIN or ITNs has been debated,[28] generally finding the combination is beneficial from a health perspective,[28] although single interventions are most cost-effective.[29] Our model shows similar trends to other modelling work, though the scale of intervention effects differ minimally given assumed parameters and subtle differences in underlying assumptions.[30] Ideally results from multiple mathematical models could be presented within the online tool to illustrate this uncertainty in projections.

Disease control decisions must be made in a context of limited budgets, so interventions are compared by cost per case averted across matched time periods. Careful interpretation is needed for the economic analyses as the most impactful interventions might not be most cost-effective, and goals of NMCPs should be prioritised. The online tool shows how cost per case averted varies substantially between sites and shows the need of bespoke cost-effectiveness analyses. Some broad trends emerge when comparing between similar interventions, for example, compared with pyrethroid-only LLINs, pyrethroid-PBO ITNs are likely to be cost-effective unless there is low resistance or a substantial difference in price. Decisions about switching between nets and IRS or improving coverage are likely to be more nuanced—eg, increasing net numbers allocated per person might not linearly increase net use[31] and similar inefficiencies probably exist for IRS campaigns. The online tool is flexible enough to explore these options, although collecting appropriate empirical data to do this might be challenging.

There are multiple limitations to our approach. Substantial uncertainty exists about the entomological effect of interventions as the discriminatory dose susceptibility bioassay data is notably variable.[32] The assay is thought to be relatively poor at differentiating between moderate and highly resistant mosquito populations where most mosquitoes survive the discriminating dose, meaning estimates in high resistance areas require cautious interpretation. Further work is needed to parameterise the model with alternative phenotypic or genotypic measures of mosquito susceptibility once sufficient data are available. Uncertainty exists about how novel nets age under field conditions[17,23] and whether entomological effects of pyrethroid-PBO ITNs can be fully characterised in the outcomes routinely recorded in experimental hut trials. Some of this between-study variability might be explained by factors such as mosquito species, seasonal and climatic factors, or experimental hut trials design, which are not currently considered here. We restrict IRS simulations to long-lasting products as variability of effects from different products are within a similar range.[14] Appropriate resistance management would require rotating products with potentially different costs, which we do not account for in the MINT tool currently. The transmission model does not predict the rate of selection of resistance to new classes of insecticide, or synergists, nor the evolutionary lifespan of a chemical class, so integrated vector management, including

community engagement, is always valuable. Net usage was assumed equivalent between the different classes; however, the effective life of a net depends on physical integrity and active ingredient durability and differences between brands exist[23] with consequences for adherence to use. We are yet to consider alternative net distribution channels to mass campaigns, which could have a different effect and expense.[33] We do not consider nets distributed through continuous routine distribution channels, which might make up a significant contribution to vector control locally. We have used a simplistic economic analysis, which needs to be extended to include greater detail of the factors influencing vector control procurement and delivery costs.

The online tool provided aims to support strategy teams making decisions on the most cost-effective vector control products to deploy. The tool currently only includes information on a limited set of scenarios and vector control commodities, though more intervention strategies can be added as further options become available. The user can define a region characterising the local heterogeneity in seasonality, entomological and epidemiological factors, and the scale at which interventions are deployed. Care should be taken as parameters such as the level of resistance are thought to be highly uncertain, so users should investigate a range of plausible values and different geographical scales to determine whether this changes the optimal intervention package for the region.

New vector control tools or more locally driven and sustainable management strategies[34] are needed to meet disease reduction and elimination targets. The framework presented here can be expanded to bring in new malaria control interventions once shown to be effective. This together with good quality local entomological and epidemiological data can support NMCPs and donors with evidence-based decision making and improved targeting.

Contributors

TSC, ES-S, and PW conceptualised the work. TSC was principal investigator. ES-S did the analysis, designed the online tool, produced tables and appendix. ES-S produced figures. AHa, and PW provided additional coding expertise. AHa, AHi, ELR, MW, TSC, and ES-S developed the online tool MINT, with critical insight and guidance from MWG and AS. ELR, MW and AHi were the programmers of MINT. ES-S, PW, AS, MWG, NP, MR, CN, JHR, CF, and TM provided critical insight for operational logistics and for the MINT interface. CN, NP, MR, RN, PT, MJD, SS, and SG provided key data and accept responsibility for RCT data. CN, AS, MWG, provided experimental hut data, RKN and ES-S analysed experimental hut data, TSC checked data for verification, all these authors accept responsibility for these data. AS, MWG, and MDK provided French translations for the online user guide. ES-S and TSC drafted the manuscript and all authors provided comments and approved the final submission.

Declaration of interests

We declare no competing interests.

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