Indoor residual spraying (IRS) is an important part of malaria control. There is a growing list of insecticide classes; pyrethroids remain the principal insecticide used in bednets but recently, novel non-pyrethroid IRS products, with contrasting impacts, have been introduced. There is an urgent need to better assess product efficacy to help decision makers choose effective and relevant tools for mosquito control. Here we use experimental hut trial data to characterise the entomological efficacy of widely-used, novel IRS insecticides. We quantify their impact against pyrethroid-resistant mosquitoes and use a Plasmodium falciparum transmission model to predict the public health impact of different IRS insecticides. We report that long-lasting IRS formulations substantially reduce malaria, though their benefit over cheaper, shorter-lived formulations depends on local factors including bednet use, seasonality, endemicity and pyrethroid resistance status of local mosquito populations. We provide a framework to help decision makers evaluate IRS product effectiveness.
The mass distribution of long-lasting insecticide treated nets (LLINs) and the spraying of residual insecticides on indoor surfaces (indoor residual spraying, IRS) are together estimated to have averted 517 million cases from 2000 to 2015. LLINs are attributed with the majority of this success, although bednets alone will be insufficient to push the parasite to elimination. LLINs, IRS and the use of prophylactic or curative drugs in areas of high endemicity are the only widely used tools for preventing malaria. Whilst these are proven technologies when used individually, their combined benefit is generally poorly understood. The few studies that have considered these tools in combination give seemingly contradictory results (likely due to location-specific factors that impact IRS and LLIN effectiveness) although the impact can be clear.

The substantial decade-long reduction in global malaria burden stalled in 2016 with an estimated increase of 5 million cases. Given the reliance of global malaria control on LLINs there are fears that recent advances in control are threatened by the proliferation of new IRS products, warrants its further investigation as conducting multiple RCTs for each product is financially challenging.

Here, experimental hut data are systematically assessed to characterise different IRS product efficacies against anopheline mosquitoes. We statistically assess IRS impact on mosquito mortality, blood-feeding and deterrence (whether mosquitoes preferentially enter unsprayed over sprayed structures) and how these impacts vary temporally. The impact of pyrethroid resistance on pyrethroid-IRS (approximated using the percentage of mosquitoes that survive during exposure to a diagnostic dose of a pyrethroid chemistry in 24-h WHO bioassay susceptibility tests) is also quantified statistically. A widely-used transmission dynamics mathematical model is then employed to predict the public health impact of IRS with varying insecticides in areas with different levels of LLIN coverage and pyrethroid resistance. The application of these models is demonstrated by comparing model predictions to a measured change in prevalence for a defined age-group, assessed by cross-sectional surveys in RCTs. A theoretical framework is provided to help decision makers evaluate IRS cost-effectiveness in specific settings.

Results

Initial efficacy. The meta-analyses (Supplementary Fig. 1) identified 98 individual experimental hut trials reporting an initial efficacy (against 24-h mosquito mortality, blood-feeding inhibition, exiting or deterrence) from 25 published studies and a further 3 unpublished datasets (Supplementary Table 1, Supplementary Data 1, analysis 1). The WHO recommends that Phase II studies reporting experimental hut trial data include 24-h
product-induced: mortality, blood-feeding inhibition, exophily and deterrence\textsuperscript{31} although more recently, some active ingredients may take longer to kill e.g. clothianidin. These key indicators are summarised at the earliest time point noted for each study (no more than 2 months since spraying) to minimise underestimating the effects of shorter-duration products (Table 1). Absolute values of mortality, blood-feeding and exophily are presented (instead of insecticide-induced estimates, corrected by untreated control huts) to allow different studies to be rigorously combined accounting for different covariates and weighted studies according to the number of mosquitoes caught.

There is substantial variation in the initial efficacy estimates for all IRS active ingredients. The binomial logistic regression model indicated that on average organophosphates killed a greater proportion of mosquitoes relative to all other active ingredients in the first 2 months after spraying (Fig. 1a). More mosquitoes were predicted to die in West African huts relative to East African huts and fewer mosquitoes were killed on mud substrate compared to cement (Fig. 1a, Supplementary Table 2). A greater proportion of mosquitoes exited from huts sprayed with carbamate or pyrethroid compared to organophosphates or neonicotinoids. Exit traps in East African huts had proportionally more

### Table 1 Summary data on IRS product entomological impact

| Insecticide chemical class | Indoor residual spraying IRS insecticide induced: |  |
|----------------------------|--------------------------------------------------|---|
|                            | N | Mean 24-h mortality %, (range) | Mean 24-h exiting %, (range) | Mean 24-h blood-feeding inhibition %, (range) | Mean 24-h deterrence %, (range) |
| Organophosphates           | 41 | 87.6 (39.8–100) | 15.9 (–175 to 96.3) | 7.1 (–18.0 to 49.4) | 42.3 (–106.9 to 94.9) |
| Neonicotinoids\textsuperscript{a} | 8 | 68.0 (44.5–100) | 9.5 (–37.6 to 49.6) | –4.2 (–22.9 to 20.4) | 18.0 (–59.1 to 70.0) |
| Carbamates                 | 7 | 77.8 (27.3–100) | 34.5 (0.3 to 100) | 11.9 (–29.4 to 84.7) | 30.9 (–12.6 to 90.9) |
| Pyrethroids                | 30 | 44.3 (5.0–92.8) | 43.7 (–5.1 to 96.4) | 18.2 (–29.7 to 82.6) | 5.6 (–151 to 77.4) |
| Organochlorines            | 5 | 53.8 (18.1–79.6) | 13.9 (–8.1 to 27.9) | 44.0 (6.0 to 81.3) | –18.3 (–77.0 to 39.6) |
| Pyrroles                   | 5 | 57.8 (49.4–71.0) | –12.3 (–100 to 59.2) | –11.0 (–58.4 to 39.9) | –46.2 (–237 to 51.9) |

Summary data for the initial efficacy (within 2 months since spraying) for 24-h insecticide-induced mortality, exiting, blood-feeding inhibition and deterrence for different indoor residual spray (IRS) chemical classes (Organophosphates: pirimiphos-methyl (Actellic® 300CS), fenitrothion; Neonicotinoids: clothianidin (SumiShield® 50WG); Carbamates: bendiocarb; Pyrethroids: alphacypermethrin, lambda-cyhalothrin, permethrin, deltamethrin; Organochlorines: DDT (dichloro-diphenyl-trichloroethane) and Pyrroles: chlorfenapyr) as evaluated in experimental hut trials. The full dataset is provided in Supplementary Data 1. *Adjusted 72-h mortality presented, see Methods.

**Fig. 1** Summary estimates for the level of mosquito mortality (a), exophily (b), blood-feeding (c) and insecticide-induced deterrence (d) as assessed in experimental hut trials with different indoor residual spray chemical classes measured within 2 months of spraying. Black box-plot show the binomial logistic model predictions (median (dark point), 25th and 75th uncertainty intervals indicated by box, 5th and 95th uncertainty intervals indicated by whiskers) which are weighted for the number of mosquitoes caught in experimental huts. The symbols show the raw data (also provided in Supplementary Data 1, analysis 1) and are classified according to the type of experimental hut (shape of symbol) and the hut substrate (symbol fill) as noted in the key in c. Point colour indicates the mosquito species complex, be it blue (A. funestus s.l.) or red (A. gambiae s.l.). Mosquitoes in the A. gambiae s.l. complex which were identified as A. arabiensis are shown in green. Supplementary Fig. 2–5 show the Bayesian posterior predictive fits against disaggregated data...
mosquitoes than West African huts, and both Anopheles funestus and Anopheles gambiae s.l. were predicted to be in exit traps more than Anopheles arabiensis (though there were only 5 data sets with A. arabiensis mosquitoes, Fig. 1b). Blood-feeding was greater in huts sprayed with carbamate relative to huts sprayed with other chemistries, A. gambiae s.l. was predicted to have blood-fed more than A. arabiensis and blood-feeding was greater in West African huts relative to East African huts (Fig. 1c). There were minimal differences in the degree to which products deterred mosquitoes (Fig. 1d). Further summary statistics of these initial impacts of IRS chemistries are provided in Supplementary Methods (Supplementary Table 2).

Temporal characterisation. The public health impact of different insecticides will depend on how long they last relative to the length of the transmission season. Studies identified in the meta-analysis reporting the number of mosquitoes killed, blood-fed or exited at 3 different time-points or more were collated (Table 2, analysis reporting the number of mosquitoes killed, blood-fed or exited at 3 different time-points or more were collated (Table 2, analysis 2). There was no significant difference in the initial efficacy estimated for analysis 1 and those which provide sufficient temporal information to be used in analysis 2, for neither 24-h induced mortality, blood-feeding inhibition, exiting nor deterrence (generalised linear models $p > 0.1$ in all instances). This smaller dataset (number of studies $(N) = 12$ listed in Table 2, providing 28 sets of time series data) is used to characterise how mosquito mortality and blood-feeding changes over time for each IRS active ingredient assessed (Fig. 2). The change in the deterrent action of IRS over time cannot be rigorously evaluated in standard experimental hut trials (see Methods section) so here only the initial impact is assessed with the rate of decay following that observed with mosquito mortality (Fig. 2—row 3). The mean proportion of mosquitoes killed decreases with time since spraying, whilst the proportion of mosquitoes successfully blood-feeding increases. Efficacy varies substantially both within and between the different IRS active ingredients tested (Fig. 2, Supplementary Fig. 6). Generally, experimental hut data for both Actellic® 300CS and SumiShield® 50WG indicated these products induce high mortality over a prolonged period relative to the pyrethroids (given the average

| Study | Location | Type of hut | Wall surface | Where was the IRS applied? | Sleepers and nets | Mosquito species present | Insecticides tested |
|-------|----------|-------------|--------------|-----------------------------|-------------------|-------------------------|---------------------|
| 163   | Benin    | West African| Cement       | Walls (not ceiling)         | No nets           | A. gambiae s.l.         | Pyrethroids (lambda-cyhalothrin, Actellic® 300CS, Bendiocarb Pyrethroids (alphacypermethrin [2a], deltamethrin [14a], lambda-cyhalothrin[15a]), Pyrethroids (alphacypermethrin,films) |
| 254b  | Benin    | West African| Cement       | Walls (not ceiling)         | No nets           | A. gambiae s.l.         | Pyrethroids (lambda-cyhalothrin, Actellic® 300CS, Bendiocarb Pyrethroids (alphacypermethrin [2a], deltamethrin [14a], lambda-cyhalothrin[15a]), Pyrethroids (alphacypermethrin,films) |
| 217   | Benin    | West African| Cement       | Walls and ceiling           | No nets           | A. gambiae s.l. (A. coluzzi and gambiae ss) | Pyrethroids (lambda-cyhalothrin, Actellic® 300CS, Pyrethroids (lambda-cyhalothrin, Actellic® 300CS, Pyrethroids (deltamethrin [6a], alphacypermethrin [16a]), Bendiocarb [6a]) |
| 425b  | Benin    | West African| Cement [4a] and mud [13a] | Walls and ceiling         | No nets           | A. gambiae s.l.         | Pyrethroids (deltamethrin [6a], alphacypermethrin [16a]), Bendiocarb [6a]) |
| 565b  | Cote D’Ivoire | West African | Cement       | Walls and ceiling           | No nets           | A. gambiae s.l., A. funestus | Pyrethroids (lambda-cyhalothrin, Actellic® 300CS, Pyrethroids (deltamethrin [6a], alphacypermethrin [16a]), Bendiocarb [6a]) |
| 666b  | Benin    | West African| Cement       | Walls and ceiling           | Untreated nets    | A. gambiae s.l.         | Pyrethroids (deltamethrin [6a], alphacypermethrin [16a]), Bendiocarb [6a]) |
| 767b  | Benin    | West African| Cement [7], mud [17], plywood [18] | Walls and ceiling | No nets           | A. gambiae s.l.         | Pyrethroids (3 x deltamethrin [7 a, 17 a, 18a]), Clothianidin (200 mg m$^{-2}$) [7a]) |
| 839   | Burkina Faso | West African | Unknown    | Walls (not ceiling)         | Holed nets        | A. gambiae s.l.         | Bendiocarb |
| 926   | Tanzania | East African | Mud         | Walls and ceiling           | No nets           | A. arabiensis          | Actellic® 300CS |
| 1068  | Benin    | West African| Cement       | No nets                     | A. gambiae s.l.   | Pyrethroids (deltamethrin), Sumishield® 50WG |

Data available to assess temporal changes in IRS efficacy (against mortality, successful blood-feeding and deterrence) of mosquitoes in free-flying experimental hut trials of different indoor residual spray compounds.

*Number refers to the coded symbols in Figs. 2 and 3

*Multiple time series for an IRS product, see Supplementary Data 1, analysis 3b

Table 2 Data available to assess temporal changes in IRS efficacy
level of pyrethroid impact in experimental hut trials is estimated from studies in locations that may have pyrethroid resistance already) and bendiocarb. Bendiocarb initially induced high mortality (above 60%) but this declines rapidly. There is considerable variability in the temporal trends of the same product between studies, though it is unclear whether this specifically reflects differences between the local mosquito population, procedural or other factors. Using these data, the probability outcomes of a mosquito feeding attempt can be determined across time (Fig. 2—row 4). Parameter sets to describe these fits are provided in Supplementary Table 3.

**Pyrethroid resistance.** The impact of reduced susceptibility of local mosquitoes to pyrethroid insecticides on the efficacy of pyrethroid-IRS is summarised in Fig. 3 (Supplementary Data 1, analysis 3). Essentially, the initial efficacy of the pyrethroid-IRS is reduced and the active life-length of the insecticide is shorter as fewer mosquitoes are susceptible to a pyrethroid-IRS. Pyrethroid resistance is measured using a discriminatory dose bioassay test. There is a strong association between the level of resistance and 24-h mosquito mortality observed in the experimental hut trial (Fig. 3a), matching a similar trend seen with LLINs. For mosquitoes that enter the hut there is a clear increase in successful blood-feeding with increasing mosquito survivorship, as those that previously fed and then died, later survive (Fig. 3b). The level of deterrence initially observed in an experimental hut trial also decreases with increasing survivorship, though there is more uncertainty about this rate of decline (Fig. 3c). Insecticide resistance also diminishes the duration of the killing ability of the active ingredient for the pyrethroid-IRS. We represent this showing that the time taken to kill 50% of the mosquitoes (lethal time LT50) is reduced in experimental hut trials given increased mosquito survival during bioassay testing (Fig. 3d). The same is true for LT20 and LT80. A summary of the combined impact of resistance on the probability outcome of each mosquito feeding attempt is shown in Fig. 3e. Fewer mosquitoes are killed, more mosquitoes blood-feed and fewer are deterred from sprayed huts as pyrethroid resistance increases immediately after spraying. However, some mosquito mortality due to IRS is predicted even when all mosquitoes are surviving the discriminatory dose bioassay because there is measurable mortality in hut trials at \( t = 1 \) day at this level of resistance (Fig. 3a). Similar trends are also seen in resistant populations over time since spraying (Fig. 3f).

**Comparing model predictions and randomised control trials.** Transmission dynamics models provide a means of converting entomological measures of IRS efficacy into a prediction of their impacts on public health. To illustrate the utility of the IRS characterisation, a transmission dynamics model is used to predict the outcome of two recent IRS RCTs. Standard pyrethroid...
LLINs were distributed to participants of all arms of the trial analysed here so their efficacy was adjusted for the impact of pyrethroid resistance. Overall best fit model predictions broadly match observed data for a single round of Actellic® 300CS® (Fig. 4a) or bendiocarb® (Fig. 4b). The uncertainty in Actellic® 300CS efficacy has a relatively minor impact on the uncertainty of public health predictions for the first 10 months after application but substantial variation after this point. A similar pattern is seen in the bendiocarb data though the uncertainty manifests itself earlier due to its shorter residual activity. Predictions of the impact of IRS from each of the individual studies (Supplementary Fig. 6) are shown as thin lines demonstrating the contrasting predictions that are determined from these independent parameter sets (individual study parameters are provided in Supplementary Table 4). Interestingly, the Actellic® 300CS data on *A. gambiae s.l.*, the most prolific mosquito present in Muleba district® more closely predict the observed change in prevalence during the trial. Both mud and cement are used as wall substrate for houses in Muleba and the experimental hut data for these surfaces® most closely reflects the measured impact. There is less uncertainty in the predicted impact of bendiocarb (Fig. 4b) though the efficacy model was parameterised with fewer experimental hut studies which had less variability (i.e. they were all from West African design, *A. gambiae s.l.* mosquitoes and probably cement substrate, though this was unknown for one study®).

**Predicting the public health impact of IRS.** The public health benefit of IRS with different compounds is then predicted using the model for a wider range of settings and LLIN use. Long-lasting products (Actellic® 300CS and SumiShield® 50WG grouped together) used at 80% coverage, are estimated to avert up to 500 clinical cases per 1000 people per year in perennial settings with moderate endemicity, when the level of pyrethroid resistance is very high and bednet use is low (Fig. 5a–c). The uncertainty in these estimates is illustrated in Supplementary Fig. 7 which show predictions using parameters that define the best-
worst-performing experimental hut trials. In highly seasonal settings, short-lasting IRS products (such as bendiocarb sprayed once at an optimal time prior to the transmission season) can span the duration of relatively short transmission seasons and avert similar numbers of cases as long-lasting products over the course of a single short season (Fig. 5d–f). Bendiocarb is often sprayed biannually so we also predicted the cases averted for the biannual scenario for this insecticide which demonstrates bendiocarb can be as effective as long-lasting IRS. This would need to be considered for cost-effectiveness estimates, although the product cost per unit may be low, the logistical costs of implementing an additional spray campaign remain high. The cases averted from using IRS is greater at higher levels of resistance and lower net coverage levels because the IRS is then able to mitigate lost impact from the pyrethroid-LLINs (Fig. 5). Ultimately, the benefits of adding IRS will be location specific and dependent on multiple factors including the local level of endemicity, mosquito species, house wall substrate, length of the transmission season and existing LLIN coverage and use.

To provide a framework for decision makers, the relative efficacy (relative reduction in clinical cases due to using IRS at 80% coverage vs no change in historic IRS use in a scenario with a pre-defined level of resistance ranging from 0 to 100%) is estimated (Supplementary Data 2). Each administration subunit 1 across sub-Saharan Africa is predicted given assumptions that are made about the proportion of local mosquitoes of different species, local bednet coverage and historic net use (as estimated up to 2015). To give an idea of the uncertainty in these estimates, Supplementary Data 2 also show the estimated cases averted if we use parameter estimates describing the experimental studies with the least or most impact on mosquito behaviours for each IRS active ingredient. In places already using high net coverage the additional benefit of IRS is relatively low whereas where bednets are not implemented or used at lower coverage, IRS is predicted to have a big impact. Short-lasting bendiocarb IRS estimates are provided for either annual or biannual application of the active ingredient in Supplementary Data 2. This will enable local decision makers to take cost data and predict the most cost-effective option in their location depending on available funds and programme goals.

Discussion

The use of IRS to supplement LLINs for malaria control and elimination is increasing in part due to concerns of pyrethroid resistant mosquitoes impeding bednet efficacy and the drive for malaria elimination. This modelling exercise highlights that the added public health benefit of the WHO policy to add IRS to LLINs can be substantial in areas where bednet usage is low and pyrethroid resistance is a concern. However, the scale of the impact varies according to the type of insecticide sprayed and where it is used. These results are in broad agreement with a recent epidemiological literature review on combining IRS and LLIN interventions in Zambesia, Mozambique and Bioko, Equatorial Guinea. A further study in Burundi found no additional impact on prevalence when LLINs were combined with pyrethroid-IRS. An RCT in Southern Benin also showed no additional epidemiological benefit of annual bendiocarb-IRS over LLINs alone although our analyses show that the residual half-life of bendiocarb is relatively short (less than 2 months) compared to the long transmission season in Benin which may partially explain this lack of additional benefit. A key consideration for trial design is the timing of bednet re-distributions. Nets are generally very effective during the first year when LLIN usage is high, nets are un torn, and the active ingredient is most effective. Therefore, fewer mosquitoes blood feed and rest on the wall and have less contact with insecticide-sprayed surfaces. This can mask the impact of IRS (or other interventions) used on top of nets and may explain some of the discontinuities in IRS and LLIN RCT results.

The recent registration of Actellic® 300CS and SumiShield® 50WG means that for the first-time multiple long-lasting IRS products are available with different modes of action that achieve broadly equivalent reductions in malaria burden across Africa. It is therefore imperative that pre-emptive rotation of products or their use in mosaics is implemented to maintain the efficacy of both insecticides. The decline in the efficacy and public health effectiveness of pyrethroid-IRS highlights the dangers of the use of interventions with single modes of action, especially given the ubiquity of pyrethroid-based LLINs across Africa. This work focuses on the impact of resistance as measured in experimental hut trials. Pyrethroid-IRS might still provide protection against mosquito populations no longer killed by the insecticide (and therefore not detected in a standard hut trial) as it may reduce their fecundity or elicit other sub-lethal effects but such impacts may be minimal given the impacts seen when resistant areas switch to alternative IRS products. Similarly the transmission model employed here assumes that mosquito biting times remain constant throughout the simulations and between
cases though short-lasting products perform substantially better in highly seasonal settings. In all panels IRS is applied, untargeted, to 80% of the population using either a long-lasting IRS product (for example Actellic®) (a, d), a short-acting IRS product (for example bendiocarb, applied annually) (b, e) or a pyrethroid-IRS product (for example deltamethrin (c, f)). Long-lasting products avert more cases though short-lasting products perform substantially better in highly seasonal settings.

Fig. 5 The additional impact of adding IRS to bed nets. The predicted number of malaria cases averted by annual application of IRS to a population with an existing level of bednet use (0–100% cover, y-axes) and a defined level of pyrethroid resistance (measured as percentage survival in a standard pyrethroid discriminating dose bioassay, x-axes). Clinical cases averted are measured per 1000 people per year, following standard LLIN distribution in a moderate endemicity area (30% prevalence in 2-10-year olds in the absence of interventions) with perennial transmission (a–c), highly seasonal transmission (d–f).

There are some key limitations to the presented analyses. First, we have minimal data on how different malaria vectors will be affected by IRS and have consequently assumed the same probability outcomes for each mosquito species. The substrate of local housing also impacts IRS efficacy. There were too few experimental hut studies on each insecticide to reliably differentiate these effects for specific scenarios. Currently, to the best of our knowledge there are no published studies where experimental hut trials were conducted in the same location as an RCT. This will be important to ensure the efficacy of the interventions are being assessed against the same mosquito populations although we can broadly recreate RCT outcomes with the meta-analysis approach.
outlined here (although there can be considerable uncertainty). Experimental hut data are often aggregated which means that assumptions that the proportion of mosquitoes that are feeding and surviving during the trials need to be made. Deterrence is notoriously challenging to measure and the assumption is made that the waning effect for deterrence mirrors that for mortality, although this needs to be verified. The discriminating dose bioassay test has inherent limitations for measuring the level of pyrethroid resistance in wild mosquito populations that are outlined above and previously. Finally, we do not consider behavioural resistance in mosquito species that may render indoor vector control less effective. The proportion of mosquito bites received indoors is assumed to be consistent across different settings here.

Here we provide a comprehensive method to assess IRS products using experimental hut data and extrapolate their impact for public health outcomes. Model simulations indicate that the lost impact of pyrethroid-IRS and pyrethroid-LLINs in the presence of pyrethroid resistant mosquitoes can be mitigated using IRS products with different modes of action and that new long-lasting products such as Actellic® 300CS and SumiShield® 50WG can have substantial public health benefit especially in areas with perennial malaria transmission. A full cost-effectiveness analysis is beyond the scope of this study and is needed to help inform policy. The price of different IRS and LLIN products are continually changing making it hard for programme managers to justify procurement decisions. Here we provide estimates for the number of cases averted per 1000 people per year at increasing levels of pyrethroid resistance for every administrative 1 unit in Africa considering local seasonality and LLIN coverage (Supplementary Data 2). These estimates are determined using IRS at 80% cover which may not be financially achievable everywhere or with all products. Different insecticides and formulations have different effects on different wall surfaces as well as contrasting smells or propensity to leave stains which affects acceptability. The present analysis assessing the potential impact of IRS at different levels of pyrethroid resistance can contribute to decision making. From these predictions, the greatest added value to LLIN is in areas where LLIN usage is low and pyrethroid resistance is high. NMCPs can combine these data with local, up-to-date cost information to generate broad cost-effectiveness estimates for implementing different IRS campaigns on top of existing LLIN programmes given their unique entomological and epidemiological settings. As the number of novel malaria control interventions increases these locally tailored strategies can help to achieve local goals and push for malaria elimination.

Methods

Data collation. A meta-analysis of IRS experimental hut trials is used to summarise measures of IRS efficacy. Whilst experimental hut trials cannot account for all of the effects of IRS alone they provide a relatively standardised method to assess IRS efficacy and are considered the entomological equivalent of a Phase II trial. They are also a pivotal part of the testing of new products and are required by WHO Prequalification which enables products to be bought by international procurers for low-income countries.

Data extrapolation and exclusion criteria. The meta-analysis was conducted based on the PRISMA guidelines which highlight how best to perform systematic reviews for clinical trial data. Here, we are interested in count data for mosquitoes in Phase II studies over a time series of multiple months. Four search engines were used (Web of Knowledge, PubMed, JSTOR and Google Scholar) to identify relevant data sources. Policy teams and authors’ regularly conducting these studies were also contacted to access unpublished resources. A schematic of the process (Supplementary Fig. 1) and table noting the reasons for excluding studies are included in Supplementary Table 1. To the authors’ knowledge, there has been no previous published systematic meta-analysis on IRS compounds tested in experimental hut trials. Studies are limited to trials conducted in Africa (where the biggest burden of falciparum malaria is found) and to mosquito species belonging to the Anophelinae family (vectors of the disease).

Summary statistics. Experimental hut studies typically report 24-h product-induced: mortality, blood-feeding inhibition, exophily and deterrence. Here we also report values of mosquitoes feeding, blood-feeding and exophily as measured in the treated huts. This is to allow the results of different studies to be appropriately statistically combined, though each are presented individually, and insecticide-induced estimates can be calculated from Supplementary Data 1, analysis 1. There is relatively little variation in the level of mortality, blood-feeding and exophily observed in the control (unsprayed) huts in the studies examined here and this method is consistent with previous modelling efforts. Summaries of each are described below.

(i) Mortality: The number of female mosquitoes found in the hut which are dead on collection or die within the next 24-h is denoted . In the following equations, the subscript denotes whether the number dead (or other characteristic) was measured in the control (unsprayed hut = C) or the sprayed hut (T). If is the total number of female mosquitoes that were found in the hut or exit traps then,

\[
\text{Mortality(False Positive Rate)} = \frac{D_{T}}{N_{T}} \times 100
\]

(ii) Exophily: Exophily is the propensity for mosquitoes to rest outdoors after feeding which can diminish the impact of IRS. It is calculated as the number of female mosquitoes in exit traps (E) compared to the sum of the number collected in the hut and exit traps (N),

\[
\text{Exophily(False Positive Rate)} = \frac{E_{T}}{N_{T}} \times 100
\]

(iii) Blood feeding: The number of mosquitoes that are blood fed which were collected in the hut and exit traps is denoted B so the percentage blood fed in a sprayed hut is given by,

\[
\text{Blood fed(False Positive Rate)} = \frac{B_{T}}{N_{T}} \times 100
\]

(iv) Deterrence: Deterrence induced by IRS is defined as the reduction in the entry rate of mosquitoes into experimental huts with or without IRS,

\[
\text{Deterrence(False Negative Rate)} = \frac{(N_{T} - N_{C})}{N_{C}} \times 100
\]

Comparison of the initial impact of IRS. The first analysis summarises and compares the initial impact of different IRS products. Data were restricted to initial timepoints collected within 2 months of IRS application as the active ingredient decays with time, so that averaging across the whole dataset may mis-represent the initial potency of IRS as studies had different durations. Statistical models were fit to generate overall estimates of the chemical class. These explanatory factors included the mosquito vectors (classified at the species complex level and species level where possible, e.g. A. arabiensis, A. funestus s.l. and A. gambiae s.l.), experimental hut type (West or East African design) and hut wall substrate (cement or mud) alongside the chemical class used for the IRS (carbamate, clothianidin, organophosphate and pyrethroid). Preliminary data exploration revealed that there were too few data to perform an extensive statistical test on all covariates. To overcome this a subset of the full database was generated by removing Ifakara hut studies, wall substrates that were not mud or cement and chemistries other than pyrethrins, organophosphates, carbamates or neonicotinoids. Binomial logistic regression models were fitted to the remaining count data (N = 78) to estimate the number of mosquitoes that were dead in 24-h, had exited, blood-fed or been deterred by the IRS product. The predicted value for the proportion of mosquitoes being killed, exiting, blood-fed or deterred is calculated as:

\[
\pi_i = \logit^{-1}(\text{ln}(1/1 - \pi)) = \exp(\beta_0 + \sum \beta_i X_i) / (1 + \exp(\beta_0 + \sum \beta_i X_i))
\]

where is the estimated proportion for the ith data (e.g. the proportion of mosquitoes killed), is the intercept, the subscript denotes the covariate of interest (taking number of 1 to 3) and is a matrix of explanatory factors (mosquito species, hut type, substrate and chemistry sprayed) with coefficients . Bayesian models were fitted using Hamiltonian Monte Carlo sampling methods. Four chains were initialised to assess the convergence of 2000 iterations, the first 1000 of each were discarded as burn in. The posterior distributions of parameters (4000 iterations) and 90% Bayesian credible intervals were estimated, posterior checks were performed using ShinyStan (version 1.0.0) and visually confirmed to fit the data (Supplementary Fig. 2–5).

Temporal characterisation of different active ingredients. Four insecticide active ingredients, pyrethroids (including deltamethrin, lambda-cyhalothrin and aldrin), carbamates (permethrin, bendiocarb and clothianidin) and organophosphates (methyl parathion) were further characterised from data identified in the meta-analysis. These four groups of active ingredients were chosen as they are likely to be the main insecticides used by NMCPs for IRS in the next few years (prior to 2020) where sufficient published and unpublished data were available (Table 2). For simplicity insecticides containing the appropriate concentration of permethrin methyl and clothianidin are subsequently referred to by their product names Actellic®300CS and SumiShield®50WG, respectively. The impact of IRS depends on its initial efficacy and how this changes
over time. Studies with 3 or more experimental hut trial time-points were con-
sidered sufficient to characterise temporal changes. Reasons for excluding studies are
noted in Supplementary Table 1.
Altogether 8 published and 1 unpublished studies (providing 21 time series)
were found that reported experimental hut trials on pyrethroid IRSs.27,25,63–68 (Table 2).
Three published studies and a further unpublished dataset were iden-
tified for bendiocarb.69,70,76. Four published and 1 unpublished study
provided 6 time series data for Alphacypermethrin 50CS.25,63,65,66
and 1 published and 2 unpublished datasets were available for SumiShield®50WG.67,68. This
new formulation was tested at different concentrations and we include concentrations of 300 g m\(^{-2}\) and above in the present analyses.

**Delayed mortality.** The mode of action of the neonicotinoid insecticide clothi-
adin has also been shown to act over multiple days on the insect’s nervous system so
the 24-h mosquito mortality measured in a SumiShield®50WG experimental hut trial is
unlikely to fully represent the efficacy of this chemistry.69. To generate comparable products of insecticides with different modes of action a simple
conversion is used to convert 72-h experimental hut trial mortality rates into 24-h
mortality rates that can be used in the transmission dynamics model. This is
possible if it is assumed that SumiShield®50WG exposed mosquitoes have no
epidemiological impact between 24 and 72-h following exposure, which, given the
frequency of blood-feeding, appears the most parsimonious assumption. If mos-
quitoes caught in the other arms of the trial (untreated huts and those with fast
acting chemistries) die at a constant rate between 24 and 72-h, then the back-
ground mosquito death rate for a mosquito in captivity following a hut trial can be
estimated using the exponential function. If \(l_{\text{c}}(t)\) denotes the proportion of mosqui-
toes that are dead in captivity \(t\) days after the start of the hut, then the background
mortality rate (\(\mu_b\)) can be estimated as:
\[
l_{\text{c}}(t) = 1 - \exp(-\mu_b t).
\]
Fitting this function to all datasets where 72-h (\(t = 3\) days) mortality were
recorded gave \(\mu_b = 0.035\). This value was then used to adjust the mortality
observed 72-h after the start of the SumiShield®50WG trials to generate estimates of
24-h mortality comparable to the other insecticides.

**Successful blood-feeding.** Data were not always disaggregated by the mosquitoes
that had fed and survived or fed and died. Therefore, it was not possible to directly infer which mosquitoes were successfully feeding. Instead, before fitting the time series data, we adjusted the number of mosquitoes that were blood feeding (\(N_{\text{dead}}\)) to provide an estimate for the successful blood-feeding mosquitoes \(N_{\text{successfully fed}}\). Those that feed and survive, as follows:
\[
N_{\text{successfully fed}} = N_{\text{dead}} \cdot \left(1 - \frac{N_{\text{dead}}}{N_{\text{total}}}\right)
\]
\(N_{\text{dead}}\) and \(N_{\text{total}}\) denote the total number of mosquitoes sampled and the total number recorded as dead for each time series.

**Model fitting.** Logistic binomial models were fitted to the count data to determine the relationship between the probable outcome of a mosquito feeding attempt (the mosquito is deterred, killed, successfully feeds or exits without feeding) and how this
change over time. Briefly, to determine, for example, the relationship for the
proportion of mosquitoes that are killed \(l_k\) in the presence of an IRS product over
time \(t\), we fit:
\[
l_k = \logit^{-1}(\rho) = \frac{1}{1 + \exp(\logit^{-1}(\rho) - \logit^{-1}(\theta))}
\]
\(N_{\text{dead}} \sim \text{binomial}(\logit^{-1}(\rho), N_{\text{total}})\)

The proportion of mosquitoes dying following entering a hut is denoted \(l_k\) and is dependent on a parameter that determines initial efficacy \(l_{k0}\) and how this changes over time, denoted by the depreciation parameter \(l_{k1}\). The mosquitoes that are successfully feeding or delivering a standard dose and exit in the same way (Supplementary Methods). These different probable outcomes of a feeding attempt are then translated into the probability of a mosquito being killed, successfully feeding or being repelled as detailed in Supplementary Methods. To determine uncertainty, the maximum and minimum data for each unique time point were fitted in the same way. The results for the probability of mosquitoes successfully feeding, exiting or being killed at each feeding attempt in the presence of each IRS product could then be distinguished (Supplementary Fig. 8). As previously, Bayesian models were fitted using Hamiltonian Monte Carlo sampling
methods.65,66,69 The fits were visually confirmed to fit the data (Fig. 2).

**Transmission dynamics mathematical model.** A widely used transmission
dynamics model of malaria17–22 is used to investigate the public health impact of
different IRS compounds. In this model, people are born susceptible to Plasmo-
dium falciparum infection and are exposed to infectious mosquito bites at a rate
dependent on local mosquito density and infectivity. Maternal immunity is
acquired for new born infants and this decays in the initial 6 months of life.
Infants (and a susceptible population) were included in the model to reflect the varying impact of the new chemistries and how these change over time. These changes unify the way LLINs and IRS are represented in the model (and are parameterised with experimental hut trials) and provide greater flexibility to capture the impact of different insecticides. The transmission model is used to simulate the parameterisation (Supplementary
Table 3) to explore the minimal and maximal entomological impact of a given
product and the knock-on predicted impact on cases (Supplementary Data 2).

**Pyrethroid resistance.** Discriminating dose bioassays (WHO tube assay, WHO
cone assay, CDC bottle assay) are a practical option for control programmes to
assess the proportion of the mosquito population that are killed by a standard dose.
The assumption is made that the inverse of this proportion, i.e. those mosquitoes
surviving in the presence of the standard dose of insecticide, is representative of the
level of resistance in the mosquito population. The location-specific seasonal pro-
fi cacy (as described by the percentage of mosquitoes that feed and survive, as follows:
\[
l_k = \logit^{-1}(\rho) = \frac{1}{1 + \exp(\logit^{-1}(\rho) - \logit^{-1}(\theta))}
\]
\(N_{\text{dead}} \sim \text{binomial}(\logit^{-1}(\rho), N_{\text{total}})\)

The proportion of mosquitoes dying following entering a hut is denoted \(l_k\) and is dependent on a parameter that determines initial efficacy \(l_{k0}\) and how this changes over time, denoted by the depreciation parameter \(l_{k1}\). The mosquitoes that are successfully feeding or delivering a standard dose and exit in the same way (Supplementary Methods). These different probable outcomes of a feeding attempt are then translated into the probability of a mosquito being killed, successfully feeding or being repelled as detailed in Supplementary Methods. To determine uncertainty, the maximum and minimum data for each unique time point were fitted in the same way. The results for the probability of mosquitoes successfully feeding, exiting or being killed at each feeding attempt in the presence of each IRS product could then be distinguished (Supplementary Fig. 8). As previously, Bayesian models were fitted using Hamiltonian Monte Carlo sampling
methods.65,66,69 The fits were visually confirmed to fit the data (Fig. 2).

**Transmission dynamics mathematical model.** A widely used transmission
dynamics model of malaria17–22 is used to investigate the public health impact of
different IRS compounds. In this model, people are born susceptible to Plasmo-
dium falciparum infection and are exposed to infectious mosquito bites at a rate
dependent on local mosquito density and infectivity. Maternal immunity is
acquired for new born infants and this decays in the initial 6 months of life.
Infants (and a susceptible population) were included in the model to reflect the varying impact of the new chemistries and how these change over time. These changes unify the way LLINs and IRS are represented in the model (and are parameterised with experimental hut trials) and provide greater flexibility to capture the impact of different insecticides. The transmission model is used to simulate the parameterisation (Supplementary
Table 3) to explore the minimal and maximal entomological impact of a given
product and the knock-on predicted impact on cases (Supplementary Data 2).

**Utility of the model.** RCTs are the gold standard for assessing intervention efficacy and effectiveness in the field. Results from two RCTs testing the additional benefit of Actellic®300CS® or bendiocarb68 IRS in combination with standard LLINs over local transmission species present and the level of pyrethroid resistance are taken from the relevant publications and discussions with study authors (see Table 3 for a summary of input parameters). Predictions were made for all RCT data combined without differentiating between clusters. Absolute mosquito abundance is varied to ensure model predictions at baseline match the average malaria prevalence for the age cohort examined. Future predictions are then made using the model and the parameters estimated from our study and the study authors (see Supplementary Methods). These changes are demonstrated in Supplementary Fig. 9. The code for analyses 1–3 are provided in Supplementary Methods.

**Model simulations.** IRS and LLINs are used concurrently (i.e. the same people receive IRS and LLIN) in many malaria endemic communities.27 The efficacy of IRS on top of LLINs will depend on LLIN coverage, the level of pyrethroid resistance and the seasonality of malaria transmission. To illustrate how these factors influence disease control, the transmission model is parameterised for a theoretical perennial and a highly seasonal setting. For simplicity all simulations are initially run in an area with moderate transmission (slide prevalence of 30% without intervention or treatment) in an area with no history of malaria control. At the start of year 0, LLINs are distributed at a pre-determined coverage level (the percentage of people who use them) ranging from 0 to 100%. IRS net usage remains at this level for the whole simulation. Pyrethroid resistance is simulated to arrive overnight at a defined level (as described by the percentage of mosquitoes
surviving a 24-h discriminating dose bioassay test, 0–100%) with the introduction of nets at year 0. At the start of year 3, IRS is introduced, be it a long-lasting product (e.g. Actellic® or SumiShield®), a short-lasting product (e.g. bendiocarb) or a pyrethroid performing at the defined level of resistance. SumiShield® produced broadly similar results to Actellic® and is not represented in Fig. 5. Eighty percent of the people are protected by the IRS. The households are sprayed just prior to the peak in the transmission season each year. A 3-yearly reporting cycle is adopted to coincide with the redistribution of LLINs (generally every 3 years). The disease cases averted per 1000 people per year by the respective IRS chemistries are calculated between years 3 and 6 relative to a scenario for the same level of pyrethroid resistance where no IRS is implemented.

Every area of Africa has a different malaria seasonality and history of control interventions so the impact of adding different types of IRS will vary locally. To facilitate assessment of the public health and economic benefit of adding different IRS options their impact is simulated at each administration unit 1 across sub-Saharan Africa and at increasing levels of pyrethroid resistance. Location-specific seasonal profiles9 and historic scale-up of IRS and LLIN interventions from 2000 to 2013 are used (Malaria Atlas Project, MAP) as per2. The mosquito density is adjusted for each location to capture the underlying transmission intensity and ensure model predictions match MAP estimates for S. falciparum prevalence in 2–10-year olds. Mosquito densities are then scaled up for each country so that the total cases estimated is equal to the WHO estimate for 2015 for that location whilst also capturing administration-level heterogeneity in transmission6. Pyrethroid resistance is switched on overnight in 2018, whilst maintaining 2015 net coverage levels. A 3-yearly reporting cycle is once again adopted to coincide with the redistribution of LLINs (generally every 3 years). IRS is introduced at 80% coverage in 2021 using either long-lasting (Actellic® or SumiShield®), short-lasting (bendiocarb, with annual or biannual application) or pyrethroid-IRS for distinct levels of pyrethroid resistance (ranging from 0 to 100%) (Supplementary Data 2). The IRS product parameterisations are the mean fits for the temporal data (Supplementary Table 3), with the exception of pyrethroid IRS, which is complicated by the presence of resistance in local mosquito populations. To provide some indication of the uncertainty in these product impacts, the transmission model is also used to simulate the predicted maximum and minimum impact of non-pyrethroid IRS products as estimated from the temporal analysis (Supplementary Data 1, analysis 2). Bendiocarb was modelled annually and biannually because it is usually sprayed twice a year if used for IRS programmes. The mean number of cases averted per 1000 people per year across the following 3 years, 2021–2024, was then calculated relative to a scenario where no IRS was used.

Data availability

The authors declare that all published data collated during the systematic review supporting the findings of this study are available within the paper and its supplementary information files. The unpublished data that support the findings of this study are available from the corresponding author upon reasonable request and in agreement with the data owners. The transmission model parameters that are used to define specific administration units across Africa can be provided upon request.

**Table 3 Site-specific factors used to parameterise the transmission dynamics model**

| Study                              | West8 | Protopopoff8 |
|------------------------------------|-------|--------------|
| Year                               | 2011–2012 | 2015–2017 |
| Malaria prevalence diagnostic     | Rapid diagnostic tests | Rapid diagnostic tests |
| Cohort survey age range            | 0.5–14 years | 0.5–15 years |
| Baseline malaria prevalence       | 24% LLIN only arm | 68% |
| Percentage of mosquitoes A. gambiae s.s. & | 80% | 91.6% |
| Percentage of mosquitoes A. arabiensis & | 20% | 4.6% |
| Percentage of mosquitoes A. funestus & | 0 | 3.8% |
| Bioassay mortality (A. gambiae s.s.) & | - | 7.8% |
| IRS insecticide                    | Bendiocarb | Pirimiphos methyl |
| IRS coverage (%)                   | 5% (LLIN only arm) | 94% |
| IRS timing                        | December 2011 and May 2012 | February 2015 |
| LLIN coverage (%)                  | 53% LLIN arm | 78% |
| Average duration of LLIN use (bednet usage assumed to decline at a constant rate) | 3.636 years | 2.813 years |

Site-specific factors used to parameterise the transmission dynamics model and investigate its ability to predict the impact of IRS in the two randomised control trial (RCT). The efficacy of standard LLINs and pyrethroid IRS is adjusted according to the mosquito mortality in the discriminating dose bioassay using the adjustments noted in Supplementary Methods and methods presented in Churcher et al.8,2. All other parameters are consistent with Griffin et al.5, White et al.6. Griffin et al.5,6,7,8 (for seasonality profiles, historical intervention coverage, drug treatment information). There is insufficient data to characterise whether the mosquito species distribution or the level of pyrethroid resistance changed over time, so these are assumed to have remained constant throughout in all intervention arms. Systematic non-compliance is assumed in arms where both LLINs and IRS were distributed.

References

1. Bhatt, S. et al. The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015. Nature 526, 207–211 (2015).
2. Griffin, J. T. et al. Reducing Plasmodium falciparum malaria transmission in Africa: a model-based evaluation of intervention strategies. PLoS Med. 7, e1000324 (2010).
3. Ferguson, H. M. et al. Ecology: a prerequisite for malaria elimination and eradication. PLoS Med. 7, e1000303 (2010).
4. World Health Organization. Review of Current Evidence on Combining Indoor Residual Spraying and Long-Lasting Insecticidal Nets (2014).
5. World Health Organization. WHO Guidance for Countries on Combining Indoor Residual Spraying and Long-Lasting Insecticidal Nets (World Health Organization, 2014).
6. Corbel, V. et al. Combination of malaria vector control interventions in pyrethroid resistance area in Benin: a cluster randomised controlled trial. Lancet Infect. Dis. 12, 617–626 (2012).
7. Protopopoff, N. et al. Combination of insecticide treated nets and indoor residual spraying in Northern Tanzania provides additional reduction in vector population density and malaria transmission rates compared to insecticide treated nets alone: a randomised control trial. PLoS ONE 10, e0142671 (2015).
8. Protopopoff, N. et al. Effectiveness of a long-lasting piperonyl butoxide-treated insecticidal net and indoor residual spray interventions, separately and together, against malaria transmitted by pyrethroid-resistant mosquitoes: a cluster, randomised controlled, two-by-two fact. Lancet 391, 1577–1588 (2018).
9. WHO. World Malaria Report 2017 (World Health Organization, 2017).
10. Hemingway, J. The role of vector control in stopping the transmission of malaria: threats and opportunities. Philos. Trans. R. Soc. B Biol. Sci. 369, 20130431 (2014).
11. Hemingway, J. The way forward for vector control. Science 358, 998–999 (2017).
12. Ranson, H. Current and future prospects for preventing malaria transmission via the use of insecticides. Cold Spring Harb. Perspect. Med. 7, a026823 (2017).
13. Kleinschmidt, I. et al. Design of a study to determine the impact of insecticide resistance on malaria vector control: a multi-country investigation. Malar. J. 14, 282 (2015).
14. Kleinschmidt, I. et al. Implications of insecticide resistance for malaria vector control with long-lasting insecticidal nets: a WHO-coordinated, prospective, international, observational cohort study. Lancet Infect. Dis. 3099, 1–10 (2018).
15. Ranson, H. & Lissenden, N. Insecticide resistance in African Anopheles mosquitoes: a worsening situation that needs urgent action to maintain malaria control. *Trends Parasitol.* **32**, 187–196 (2016).

16. World Health Organization. *Conditions for Deployment of Mosquito Nets Treated With a Pyrethroid and Piperonyl Butoxide* (2017).

17. Ngufor, C. et al. Chlorfenapyr (A Pyrrole Insecticide) applied alone or as a mixture with alpha-cypermethrin for indoor residual spraying against pyrethroid-resistant Anopheles gambiae s.l.: an experimental hut study in Cove, Benin. *PLoS One* **11**, e0162210 (2016).

18. N’Guessan, R., Odjo, A., Ngufor, C., Malone, D. & Rowland, M. A Chlorfenapyr Mixture Interceptor® G2 shows high efficiency and wash durability against resistant mosquitoes in West Africa. *PLoS One* **11**, e0165923 (2016).

19. Darrieu, F. et al. Impact of the résistance aux pyréthrinoïdes sur l’efficacité des moustiquaires imprégnées dans la prévention du paludisme: résultats des essais en cases expérimentales avec la deltaméthrine SC. *Bull. Soc. Pathol. Exot.* **93**, 131–134 (2000).

20. Churcher, T. S., Lissenden, N., Griffin, J. T., Worral, E. & Ranson, H. The impact of pyrethroid resistance on the efficacy and effectiveness of bednets for malaria control in Africa. *elife* **5**, e16990 (2016).

21. van den Berg, H. et al. Global trends in the use of insecticides to control malaria vectors. *Environ. Health Perspect.* **120**, 577–582 (2012).

22. Wageman, J. et al. An observational analysis of the impact of indoor residual spraying with non-pyrethroid insecticides on the incidence of malaria in Senegal, 2012–2015. *Malar. J.* **17**, 19 (2018).

23. Pluess, R., Tanser, F. C., Lengeler, C. & Sharp, B. L. Indoor residual spraying for preventing malaria. *Cochrane Database Syst. Rev.* https://doi.org/10.1002/14651858.CD006657.pub2 (2010).

24. World Health Organization. *Global Plan for Insecticide Resistance Management in Malaria Vectors* (World Health Organization, 2012).

25. Rowland, M. et al. A new long-lasting indoor residual formulation of the organophosphate insecticide pirimiphos methyl for prolonged control of pyrethroid-resistant mosquitoes: an experimental hut trial in Benin. *PLoS One* **8**, e69516 (2013).

26. Oxborough, R. M. et al. Long-lasting control of Anopheles arabiensis by a single spray application of micro-encapsulated pirimiphos-methyl (Actellic® 300 CS). *Malar. J.* **13**, 37 (2014).

27. World Health Organization. *The Evaluation Process for Vector Control Products* (World Health Organization, 2018).

28. Oxborough, R. M. Trends in US President’s Malaria Initiative-funded indoor residual spray coverage and insecticide choice in sub-Saharan Africa (2008–2015): urgent need for affordable, long-lasting insecticides. *Malar. J.* **15**, 146 (2016).

29. World Health Organization. *The Evaluation Process for Vector Control Products* (2017).

30. World Health Organization. *Malaria Vector Control Policy Recommendations and Their Applicability to Product Evaluation* (2017).

31. World Health Organization. *Guidelines for Testing Mosquito Adulticides for Indoor Residual Spraying and Treatment of Mosquito Nets Control of Neglected Tropical Diseases*. WHO Pesticide Evaluation Scheme (2006).

32. Huho, B. et al. Consistently high estimates for the proportion of human exposure to malaria vector populations occurring indoors in rural Africa. *Int. J. Epidemiol.* **42**, 235–247 (2013).

33. Briët, O. J., Smith, T. A. & Chitnis, N. Measurement of overall insecticidal effectiveness of insecticidal nets against malaria transmission in rural Tanzania. *BMC Infect. Dis.* **6**, 161 (2006).

34. Shcherbacheva, A., Haario, H. & Killeen, G. F. Modeling host-seeking behavior of African malaria vector mosquitoes in the presence of long-lasting insecticidal nets. *Math. Biosci.* **295**, 36–47 (2017).

35. Reddy, M. R. et al. Outdoor host seeking behaviour of Anopheles gambiae mosquitoes following initiation of malaria vector control on Bioko Island, Equatorial Guinea. *Malar. J.* **10**, 184 (2011).

36. Braimah, N. et al. Tests of bednet traps (Mbita traps) for monitoring mosquito populations and time of biting in Tanzania and possible impact of prolonged insecticide treated net use. *Int. J. Trop. Infect. Dis.* **25**, 208–213 (2005).

37. Moïse, E. et al. Challenges in Anopheles funestus biting behaviour following universal coverage of long-lasting insecticidal nets in Benin. *Malar. J.* **12**, 1622–1629 (2012).

38. Tirados, I., Costantini, C., Gibson, G. & Torr, S. J. Blood-feeding behaviour of the malarial mosquito Anopheles arabiensis: implications for vector control. *Med. Vet. Entomol.* **20**, 423–437 (2006).

39. Ibrahim, K. T., Popoola, K. O. & Akure, K. O. Laboratory evaluation of residual efficacy of Actellic 300 CS (Pirimiphos-Methyl) and K-Othrine WG 250 (Deltamethrin) on different indoor surfaces. *Int. J. Infect. Sci.* **9**, 11795431773298 (2017).

40. Onedo, B. M. et al. Current status of insecticide resistance among malaria vectors in Kenya. *Parasit. Vectors* **10**, 429 (2017).

41. Massue, D. I. et al. Comparative performance of three experimental hut designs for measuring malaria vector responses to insecticides in Tanzania. *Malar. J.* **15**, 165 (2016).

42. Oumoukou, W. A., Fongnikin, A., Soukou, K. B., Moore, S. J. & N’Guessan, R. Relative performance of indoor vector control interventions in the Ifakara and the West African experimental huts. *Parasit. Vectors* **10**, 432 (2017).

43. World Health Organization. *Meeting Report of the WHO Evidence Review Group on Assessing Comparative Effectiveness of New Vector Control Tools* (2017).

44. Kaufman, M. R., Rweyemamu, D., Koender, H. & Macha, J. “My children and I will no longer suffer from malaria”: a qualitative study of the acceptance and rejection of indoor residual spraying to prevent malaria in Tanzania. *Malar. J.* **11**, 220 (2012).

45. Killeen, G. F. et al. Preventing childhood malaria in Africa by protecting adults from mosquitoes with insecticide-treated nets. *PLoS Med.* **4**, e229 (2007).

46. Smithson, M., Davies, M. & Aminola Davies, A. M. Exploiting test structure: case series, case-control comparison, and dissociation. *Cogn. Neuropsychol.* **28**, 44–64 (2011).

47. Papapliopoulou, O., Roberts, G. O. & Skold, M. A general framework for the parameterization of hierarchical models. *Stat. Sci.* **22**, 59–73 (2007).

48. Betancourt, M. & Girolami, M. *Current Trends in Bayesian Methodology with Applications* (eds Upadhyay, S. K. et al.) 79–102 (Chapman and Hall CRC Press Taylor & Francis Group, 2015).

49. Team, S. D. *Stan modeling language. User’s Guide Reference Manual 1–488* (2015).

50. Agossa, F. R. et al. Efficacy of various insecticides recommended for indoor residual spraying: pirimiphos methyl, potential alternative to bendiocar for pyrethroid resistance management in Benin, West Africa. *Trans. R. Soc. Trop. Med. Hyg.* **107**, 84–91 (2013).

51. Agossa, F. R., Ganguenon, V., Anagonou, R. & Azondekon, R. Impact of insecticide resistance on the effectiveness of pyrethroid-based malaria vector control tools in Benin: decreased toxicity and repellent effect. *PLoS ONE* **10**, 1–15 (2015).

52. Tchiaya, E. S. et al. Micro-encapsulated pirimiphos-methyl shows high insecticidal efficacy and long residual activity against pyrethroid-resistant malaria vectors in central Côte d’Ivoire. *Malar. J.* **13**, 332 (2014).

53. Agkóbeto, M. C., Padonou, G. G., Gbènou, D., Irish, S. & Yadouleton, A. Bendiocar, a potential alternative against pyrethroid resistant Anopheles gambiae s.s. in Benin, West Africa. *Malar. J.* **9**, 204 (2010).

54. Ngufor, C., Fongnikin, A., Rowland, M. & N’Guessan, R. Indoor residual spraying with a mixture of clothianidin (a neonicotinoid insecticide) and...
deltamethrin provides improved control and long residual activity against pyrethroid resistant Anopheles gambiae s.l in Southern Benin. PLoS ONE 12, e0189575 (2017).

68. Agossa, F. R. et al. Efficacy of a novel mode of action of an indoor residual spraying product, SumiShield® 50WG against susceptible and resistant populations of Anopheles gambiae (s.l.) in Benin, West Africa. Parasit. Vectors 11, 293 (2018).

69. Tomizawa, M. & Casida, J. E. Neonicotinoid insecticide toxicology: mechanisms of selective action. Annu. Rev. Pharmacol. Toxicol. 45, 247–268 (2005).

70. White, M. T. et al. Modelling the impact of vector control interventions on Anopheles gambiae population dynamics. Parasit. Vectors 4, 153 (2011).

71. Griffin, J. T., Ferguson, N. M. & Ghani, A. C. Estimates of the changing age-burden of Plasmodium falciparum malaria disease in sub-Saharan Africa. Nat. Commun. 5, 1–10 (2014).

72. Griffin, J. T. et al. Gradual acquisition of immunity to severe malaria with increasing exposure. Proc. R. Soc. B Biol. Sci. 282, 20142657 (2015).

73. Hancock, P. A. et al. Associated patterns of insecticide resistance in field populations of malaria vectors across Africa. Proc. Natl. Acad. Sci. U.S.A. 115, 5938–5943 (2018).

74. National Weather Service. Climate Prediction Center (2016). Available at: http://www.cpc.ncep.noaa.gov/products/international/. Accessed 24th March 2016.

75. Okumu, F. O. & Moore, S. J. Combining indoor residual spraying and insecticide-treated nets for malaria control in Africa: a review of possible outcomes and an outline of suggestions for the future. Malar. J. 10, 208 (2011).

76. Protopopoff, N. et al. High level of resistance in the mosquito Anopheles gambiae to pyrethroid insecticides and reduced susceptibility to bendiocarb in north-western Tanzania. Malar. J. 12, 149 (2013).

Acknowledgements

The work was supported by the Innovative Vector Control Consortium (IVCC), the Wellcome Trust [200222/Z/15/Z] MiRA and the UK Medical Research Council (MRC)/UK Department for International Development (DFID) under the MRC/DFID Concordat agreement. Thank you to all who conducted the experimental hut trials.

Author contributions

T.S.C., J.H.R. and E.S.-S. designed the project. V.C., C.P., A.D., S.M., P.M., C.E., N.P., R.O., F.A., R.N. and M.R. collected data, performed experimental hut trials and randomised control trials. E.S.-S., T.S.C., J.T.G. and P.W. analysed the data and produced all the figures. T.S.C. supervised all aspects of the project. E.S.-S. and T.S.C. wrote the paper. All authors discussed results, commented on and approved the final manuscript.

Additional information

Supplementary Information accompanies this paper at https://doi.org/10.1038/s41467-018-07357-w.

Competing interests: The authors declare no competing interests.

Reprints and permission information is available online at http://npg.nature.com/reprintsandpermissions/

Publisher’s note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.