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Indoor residual spray and insecticide-treated bednets for malaria control: theoretical synergisms and antagonisms

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Indoor residual spray (IRS) of insecticides and insecticide-treated bednets (ITNs) are the two most important malaria vector control tools in the tropical world. Application of both tools in the same locations is being implemented for malaria control in endemic and epidemic Africa. The two tools are assumed to have synergistic benefits in reducing malaria transmission because they both act at multiple stages of the transmission cycle. However, this assumption has not been rigorously examined, empirically or theoretically. Using mathematical modelling, we obtained the conditions for which a combination strategy can be expected to improve upon single control tools. Specifically, spraying of dichlorodiphenyltrichloroethane (DDT) in all houses where residents are not using ITNs can reduce transmission of malaria (R_0) by up to 10 times more than the reduction achieved through ITNs alone. Importantly, however, we also show how antagonism between control tools can arise via interference of their modes of action. Repellent IRS reduces the likelihood that ITNs are contacted within sprayed houses and ITNs reduce the rate at which blood-fed mosquitoes rest on sprayed walls. For example, 80 per cent coverage of ITNs and DDT used together at the household level resulted in an R_0 of 11.1 when compared with an R_0 of 0.1 achieved with 80 per cent ITN coverage without DDT. While this undesired effect can be avoided using low-repellence pyrethroid chemicals for IRS, the extent of the potential benefits is also attenuated. We discuss the impact that this result will likely have on future efforts in malaria control combination strategy.

Keywords: integrated vector management; insecticide; transmission dynamics

1. INTRODUCTION

Pyrethroid insecticide-treated nets (ITNs), particularly the long-lasting insecticidal nets, are the preferred tools for reducing malaria transmission and alleviating disease burden. Following numerous successful applications of ITNs, the WHO's Roll Back Malaria programme recently set the target of 80 per cent bednet coverage in malaria-endemic areas, and recent reports suggest that this target has already been actualized in many regions of Africa [1]. The next step to further reduce disease transmission is to assess alternative control tools that might be used in combination with ITNs. Indeed, integrated vector management (IVM) has rekindled hopes of malaria elimination [2]. Empirical evaluations of all possible control tool combinations would be costly, time consuming and potentially harmful in certain circumstances [3]. It would therefore

be prudent to theoretically assess possible control combinations before unnecessary risks and spending are undertaken. Here, we describe a mathematical model to assess the effects of combining indoor residual spray (IRS) of insecticides with ITNs, following the call for such an analysis in the recent Cochrane review [4].

Evidence for IRS efficacy in reducing malaria prevalence has been available for decades [5–7]. Because of their lower vertebrate toxicity and longer residual efficacy than organophosphates and carbamates, dichlorodiphenyltrichloroethane (DDT) and pyrethroids are particularly well-suited to endophagic mosquitoes such as *Anopheles gambiae* sensu stricto—the major African malaria vector [8]. IRS with pyrethroids kills mosquitoes that rest on sprayed walls after they have bloodfed. IRS with DDT has the additional function of deterring mosquito entry into sprayed houses (or promoting their rapid exit) [9,10]. ITNs primarily reduce mosquito bites on humans and cause additional mosquito mortality through contact. These tools are assumed to have synergistic benefits in reducing malaria transmission because they act at

multiple stages of the transmission cycle. In 2008, WHO issued a position statement [1] supporting IVM as set out in the Global Strategic Framework for Integrated Vector Management [11]. The feasibility of integrating IRS with ITNs is an important consideration in the President's Malaria Initiative [12]. However, Kleinschmidt *et al.* [13] present conflicting results of the relative benefits of integrating these approaches and describe the necessity of clear planning and sound implementation of randomized control trials (RCTs) to measure for any additive or multiplicative benefit. Before RCTs can be designed, clear strategy must be carefully examined [4,13]. Here, using a phenomenological approach, we derive the conditions under which integrating IRS with ITNs might be expected to be most effective. We examine the effects of a repellent insecticide versus a non-repellent insecticide used for house spraying both as a stand-alone tool and in conjunction with ITNs. Finally, the implications of our results are discussed in terms of malaria-control strategy in general.

2. METHODS

In the absence of IRS, the probability that a mosquito contacts an ITN is simply the proportion of the human population that sleep under ITNs, c. Not even brand new ITNs are perfect in preventing a mosquito bite [14,15]. The level of protection provided by bednets is denoted κ (where $0 \leq \kappa \leq 1$). Therefore, the proportion of humans protected by ITNs is κc. Based on empirical reports of negligible spatio-repellency of pyrethroids [16], we assume the attraction to humans overrides any deterrent effect of ITNs, once a mosquito has entered the residence. Hence, blood-seeking mosquitoes will contact ITNs whether or not they successfully obtain a blood meal. The insecticidal properties of ITNs deplete over time and this can be modelled by allowing for κ to decay. Because insecticides decay over a timeframe of weeks and months, whereas the net materials may remain physically undamaged for several years, we also include a minimum level of protection that is equivalent to a non-impregnated bednet, ψ. Figure 1 illustrates an example of protective efficacy dynamics of ITNs over a simulated timeframe during which period the net material is expected to remain intact. An important future adaptation of the model would be incorporating the deterioration of the netting material for longer time periods.

The functionality of IRS, φ, also decays over time. Here, it is important to distinguish the functionalities of different types of spray. Specifically we want to compare the insecticides that have the greatest longevity— DDT and pyrethroids [8]. DDT is a strong repellent, deterring mosquito entry into a sprayed house [9,10], whereas pyrethroids have little repellence [16]. For simplicity, we assume the extent to which mosquito entry is deterred decays equivalently to the mosquito-killing efficacy of the insecticide, φ. The proportion of humans protected by IRS with DDT is the product of φ and the proportion of houses sprayed, γ. Following empirical evidence of the overwhelming percentage
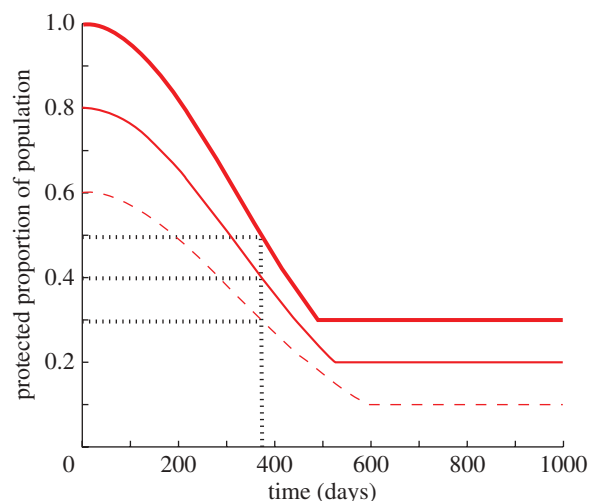

Figure 1. The temporal dynamics of the level of personal protection provided by insecticide-treated bednets (ITNs). The insecticidal property of ITNs decays over time, originating at the maximum level of efficacy (thick, thin and dashed lines correspond to κ values of 1.0, 0.8 and 0.6) and dropping to the minimum level of efficacy, ψ, as provided by the physical barrier of the netting alone (thick, thin and dashed lines correspond to ψ values of 0.3, 0.2 and 0.1). We calculate the decay rate as $\exp(-\tau^2 \times 0.000005)$ where τ is the time post-impregnation in days. The expression results in an insecticidal half-life of 1 year and a loss of more than 99% insecticidal properties within 3 years, irrespective of initial insecticidal efficacy.

($>90\%$) of indoor collected *A. gambiae* females being bloodfed [17], we assume that a mosquito comes into contact with IRS only if it has consumed a blood meal. The consequences of this assumption are discussed more completely following our analysis.

One mode of action of both ITNs and IRS with DDT is that they reduce the availability of the humans ($0 \leq \sigma \leq 1$), thereby extending the time required for the mosquito to seek and secure a blood meal. Assuming one bite per gonotrophic cycle, we calculate the resulting gonotrophic cycle duration in days, G, as follows:

$$G = 3 + \frac{1}{\sigma}. \tag{2.1}$$

Here, constant 3 is the number of days required for embryogenesis (including 0.5 days of post-meal resting), a value generated from empirical studies in western Kenya [18]. The insecticides also impose additional mortality on the mosquitoes that contact them. We assume that the imposed mortality of contacting both ITNs and IRS is additive rather than multiplicative. In this way, all potential synergies come about through extensions in the gonotrophic cycle delay. If $(1/\sigma)/G$ and $0.5/G$ denote the respective proportions of the gonotrophic cycle period that are involved in blood-seeking and resting, the probability of daily mosquito survival, p, can be calculated as

$$p = 0.85\left(1 - \left(\alpha \times c \times \frac{(1/\sigma)}{G} + z \times \gamma \times \frac{0.5}{G}\right)\right), \tag{2.2}$$

where 0.85 is the baseline mosquito survival rate [19]. The coverage levels of the control tools (c and γ) are

assumed not to change over time, whereas their functionality does (see calculations for α and z below). As the insecticidal potency of ITNs decays over time, so too does the induced additional mosquito mortality:

$$\alpha = \kappa \times \exp(-\tau^2 \times 0.000005), \qquad (2.3)$$

where α is the level of protection provided by bednets, allowing for insecticidal decay as a function of time, and τ the number of days since insecticide impregnation. The limited empirical evidence suggests that the insecticidal properties of pyrethroid-impregnated bednets do not decay substantially in the initial 3 months [16], but mosquito-killing potency is lost in most nets within 3 years [20]. Equation (2.3) describes an insecticidal half-life of 1 year and a loss of more than 99 per cent insecticidal properties within 3 years. The functionality of IRS (z) is also simulated to decay over time:

$$z = \varphi \times \exp(-\tau^2 \times 0.00005). \qquad (2.4)$$

IRS functionality is assumed to diminish substantially more rapidly than ITNs, with 12 months being the best longevity record for DDT and six months for pyrethroid spray [8]. We parametrize IRS decay with greater than 99 per cent loss of insecticidal potency within 1 year and 6 months for DDT and pyrethroid spray, respectively.

We examine the effects on malaria's transmission potential of three different combination strategies and compare them with ITNs or IRS used in isolation. These three strategies are (i) randomly distributing ITNs and IRS; (ii) preferentially distributing both together (i.e. IRS first goes to ITN-protected residences, and any surplus IRS goes to non-ITN houses); and (iii) preferentially distributing both apart. There are logical arguments for each of the three types of distribution policy, and each comes with their own operational difficulties, which will be discussed after the analysis. Calculating the probability of a mosquito contacting ITNs or IRS is dependent on which combination distribution strategy is used, the coverage proportions and the type of insecticidal spray (repellent or non-repellent, see table 1). The proportion of protected humans, n, is therefore also dependent on the control dissemination strategy, the levels of ITN and IRS coverage and the type of spray used (table 2).

As with most other studies, we model the impact of these three strategies on disease transmission using the basic reproductive number (R_0) of malaria. R_0 is calculated as follows:

$$R_0 = \frac{(m/(1-n))\mathrm{e}^{-\mu T}}{(r\mu)G^2}. \qquad (2.5)$$

Here, m is the ratio of mosquitoes per person ($10:1$), adjusted to allow for only unsuccessfully protected or unprotected humans ($1-n$) to provide blood meals; T is the extrinsic incubation period of malaria (14 days); r is the recovery rate which is calculated as the reciprocal of the average human infectious period (100 days); and μ is the force of mosquito mortality and calculated as $-\ln(p)$ [21]. Control efficacy is calculated for combined ITNs and IRS of all distribution

Table 1. Calculations used for determining the probability that a mosquito comes into contact with a lethal dose of insecticide via ITNs or IRS under the three different distribution strategies. The insecticides with repellent effect and without repellent effect (underlined) are modelled.

| strategy (conditions)	contact IRS and ITN	contact only IRS	contact only ITN
(1) randomly distributing ITNs and IRS	$\gamma(1-z)c(1-\alpha)$, $\gamma c(1-\alpha)$	$\gamma(1-z)(1-c)$, $\underline{\gamma(1-c)}$	$(1-\gamma)c + \gamma(1-z)c\alpha$, $\underline{(1-\gamma)c + \gamma c\alpha}$
(2) preferentially distributing ITNs and IRS in combination			
when IRS coverage is higher than ITN coverage ($\gamma > c$)	$(1-z)c(1-\alpha)$, $\underline{c(1-\alpha)}$	$(\gamma - c)(1-z)$, $\underline{(\gamma - c)}$	$(1-z)c\alpha$, $c\alpha$
when IRS coverage is equal to or less than ITN coverage ($\gamma \le c$)	$\gamma(1-z)(1-\alpha)$, $\underline{\gamma(1-\alpha)}$	0, $\underline{0}$	$(c-\gamma) + \gamma(1-z)\alpha$, $\underline{(c-\gamma) + \gamma\alpha}$
(3) preferentially distributing ITNs and IRS apart			
when sum of IRS and ITN coverage rates is larger than 1 ($\gamma + c > 1$)	$((\gamma+c)-1)(1-z)(1-\alpha)$, $\underline{((\gamma+c)-1)(1-\alpha)}$	$(1-c)(1-z)$, $\underline{(1-c)}$	$(1-\gamma) + ((\gamma+c)-1)(1-z)\alpha$, $\underline{(1-\gamma) + ((\gamma+c)-1)\alpha}$
when sum of IRS and ITN coverage rates is equal or less than 1 ($\gamma + c \le 1$)	0, $\underline{0}$	$\gamma(1-z)$, γ	c, $\underline{c}$
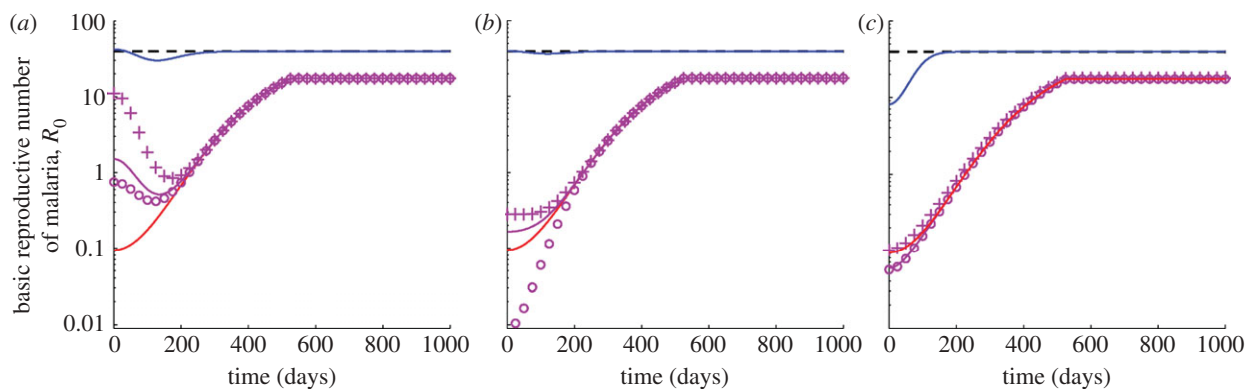
Figure 2. The distribution strategy for the combined control tools can have profound effects on their efficacy in reducing malaria transmission. (*a*) Both ITN and DDT coverage are at 80% with initial efficacies of 80%; (*b*) ITN coverage is at 80% and DDT coverage is at 20% with initial efficacies of 80% for each; and (*c*) both ITN and pyrethroid spray coverage are at 80% with initial efficacies of 80%. We parametrize corresponding decay rates of DDT and pyrethroid spray as $\exp(-\tau^2 \times 0.00005)$ and $\exp(-\tau^2 \times 0.00015)$ to ensure more than 99% loss of insecticidal potency within 12 and 6 months, respectively. ITN and IRS combination strategies: (1) randomly distributing ITNs and IRS; (2) preferentially distributing both together (i.e. IRS first goes to ITN-protected residences, and any surplus IRS goes to non-ITN houses); and (3) preferentially distributing both apart. The qualitative nature of this plot is representative of most parameter values of ITN and IRS combination. Combination 3 is always the most effective strategy followed by strategies 1 and 2, respectively. Dashed line, no control; red line, ITNs only; blue line, IRS only; pink line, combination 1; plus symbols, combination 2; circles, combination 3.

Table 2. Calculations used for determining the proportion of humans that are protected by either ITN or IRS or both under the three different distribution strategies. The insecticides with repellent effect and without repellent effect (underlined) are modelled.

strategy (conditions)	proportion of humans that are protected
(1) randomly distributing ITNs and IRS	$\gamma z + \gamma(1-z)c\alpha + (1-\gamma)c\alpha$, $\underline{c\alpha}$
(2) preferentially distributing ITNs and IRS in combination	
$\quad(\gamma > c)$	$\gamma z + (1-z)c\alpha$, $\underline{c\alpha}$
$\quad(\gamma \le c)$	$\gamma z + (1-z)c\alpha + (c-\gamma)\alpha$, $\underline{c\alpha}$
(3) preferentially distributing ITNs and IRS apart	
$\quad(\gamma + c > 1)$	$z(1-c) + (\gamma - (1-c))(z + (1-z)\alpha) + (1-\gamma)\alpha$, $\underline{c\alpha}$
$\quad(\gamma + c \le 1)$	$\gamma z + c\alpha$, $\underline{c\alpha}$

strategies as well as for both control tools used in isolation. 'Antagonism' refers to a control combination that yields lower efficacy than ITNs used as a stand-alone strategy. 'Synergism' refers to a control combination that yields higher efficacy than the additive effects of both control tools used in isolation. Monte Carlo analysis is performed to determine the sensitivity of R_0 to the variables pertaining to control (i.e. control tool coverage proportions, protective efficacy, mosquito killing efficacies, repellence and insecticide depletion rates). Each control variable is set to vary by 10 per cent randomly within a uniform distribution for 1000 runs of a Monte Carlo simulation.

3. RESULTS

In the absence of control and using the parameter values described in §2, R_0 is calculated to be 39.5. When equivalent initial values for insecticidal properties of ITNs and IRS are assumed ($\varphi = \kappa$), ITNs as a stand-alone strategy are a more effective tool in reducing R_0 than IRS (figure 2). The lowest basic reproductive number achieved by stand-alone strategies

at 80 per cent coverage and 80 per cent initial efficacy is 0.1 (ITNs), 8.1 (pyrethroid IRS) and 30.1 (DDT IRS). In the case of DDT alone, R_0 remains relatively unchanged because the repellent effect reduces the rate at which blood meals are taken in sprayed houses and bites are simply deflected onto residents of non-sprayed houses (figure 2*a,b*). IRS with pyrethroids has a more substantial effect on R_0 than with DDT, but it is still inferior to ITNs when an equivalent coverage level is attained (figure 2*c*). The superior capacity of ITNs as a stand-alone tool in reducing transmission potential stems from multiple factors working in unison. Not only do the insecticidal properties of bednets last longer, but the physical barrier that they provide also does not diminish over our simulated timeframe. Additionally, on entry into a residence, the mosquito will contact ITNs whether or not a blood meal is secured. However, the mosquito will only contact the IRS if it manages to secure a blood meal [17]. This is a subtle but important difference in the modes of action of these two control tools.

Irrespective of the distribution strategies, combined use of IRS with ITNs (both at high coverage of 80%)
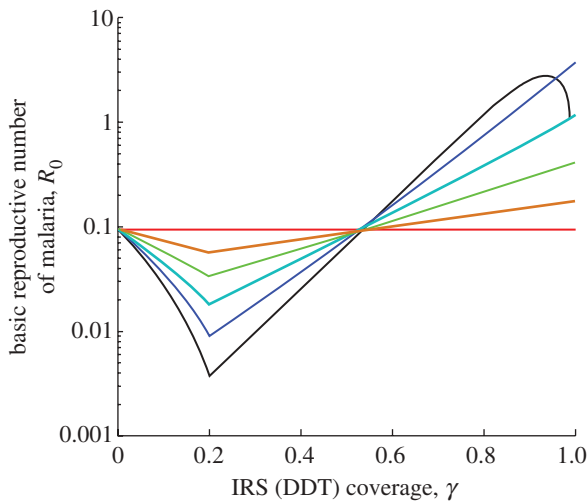
Figure 3. The optimum DDT coverage for minimizing the R_0 of malaria when used in conjunction with ITNs. Greatest reduction in R_0 results from strategy 3 (preferentially distributing ITN and IRS apart) and $\gamma = (1 - c)$, irrespective of the initial repellence level and toxicity of the DDT (φ). Results for 80% ITN coverage ($c = 0.8$) and 80% initial ITN efficacy ($\kappa = 0.8$) are presented (other values are shown in the electronic supplementary material, figure S1). Values of φ are as follows: red line, 0; orange line, 0.2; light green line, 0.4; blue line, 0.6; dark blue line, 0.8; black line, 1.0.

does not necessarily improve upon ITNs alone, and, in the case of DDT, can be two orders of magnitude less effective (R_0 of 11.1 for IRS preferentially targeting ITN houses versus 0.1 for ITNs alone; figure 2a). When ITNs and DDT are used together in the same residence, they act antagonistically: ITNs are less likely to be contacted when the mosquito is repelled by DDT and DDT is less likely to be contacted when the mosquito fails to secure a blood meal inside a residence with ITNs. However, when DDT is used exclusively in non-ITN houses, the combination can be an order of magnitude more effective than ITNs alone (R_0 of 0.009 and 0.094, respectively)—and the effects of this combination are markedly more substantial than the additive effect of both tools in isolation (figure 2b). Irrespective of the distribution strategy, IRS/ITN combination cannot substantially improve upon ITNs alone, when pyrethroid spray is used (figure 2c). Preferential distribution of ITNs and IRS apart (combination strategy 3) is always the most effective strategy, followed by random distribution of ITN and IRS (strategy 1) and preferential distribution of ITN and IRS together (strategy 2), respectively.

Figure 3 illustrates the effects of ITNs with DDT using combination strategy 3, for the full range of DDT coverage and initial functionality levels. Optimal suppression of R_0 is achieved when DDT is provided only to houses without ITNs (the obvious exception is when complete coverage is attained with IRS of perfect repellent and mosquito-killing efficacy). Sensitivity analysis found that the qualitative nature of this result is insensitive to assumed ITN coverage levels (electronic supplementary material, figure S1).

Given the notably diminished efficacy of both tools over time (figure 2) and having ascertained that

strategy 3 (IRS preferentially implemented in non-ITN houses) is the most effective combination strategy for both pyrethroids and DDT, we simulated the temporal dynamics of the basic reproductive number of malaria following regular re-spraying and re-impregnation of bednets (figure 4a,b). We simulated biannual re-spraying and re-treatment regimes as per the WHO [8] recommendations. When ITNs and IRS are applied simultaneously at biannual intervals, the resulting transmission dynamics exhibited cycles of high amplitude: transmission intensity gradually increases as the insecticide deteriorates over time, and then plummets following combined re-treatment and re-spraying (figure 4a,b). When re-impregnation of bednets and re-spraying are alternated (e.g. ITNs are re-treated on months 0, 6, 12, etc., while IRS is re-sprayed on months 3, 9, 15, etc.), cycle amplitude is diminished and transmission potential peaks immediately before ITN re-impregnation and is at its lowest just after re-spraying (figure 4a,b). Figure 4c,d shows the temporal dynamics of the protected proportion of the population resulting from the different re-spraying/re-treatment regimes, and for the different classes of insecticidal spray. While maintaining the lowest levels of R_0, the mutually exclusive application of DDT (20% coverage) with ITNs (80% coverage) also protected a greater proportion of the population than any other strategy, including combination strategy 3 using 80 per cent pyrethroid spray coverage with 80 per cent ITN coverage.

Figure 5 displays the general insensitivity of model output to variability in the parameters governing control. Ranking of the distribution strategies is consistent irrespective of whether the temporally alternating or combined approach is implemented. Control through combination strategy 2 (preferentially together) using temporally alternating DDT spray (80% coverage) with ITN re-impregnation (80% coverage) was both the least-effective measure and the most sensitive to variations in the control parameters (figure 5a). A low transmission potential was maintained most effectively through alternating DDT spray with ITN re-impregnation with mutually exclusive coverage and this optimized approach was least sensitive to control parameter variability.

4. DISCUSSION

We examined the strategies of combining ITNs and IRS, the two most important malaria vector control tools. Significantly, we have shown that maximizing coverage of both tools is not necessarily the best mechanism for reducing malaria-transmission potential. ITNs and IRS can either act antagonistically or synergistically, depending on the distribution policy and the insecticide classes used. We tested distributing both pyrethroid spray and DDT with ITNs randomly, preferentially together and preferentially apart and showed that ensuring every household is protected by either ITNs or DDT (but not both) maximizes the synergism of these control tools. When there is overlap of both control methods, IRS with strongly repellent insecticides (such as DDT) reduces the probability
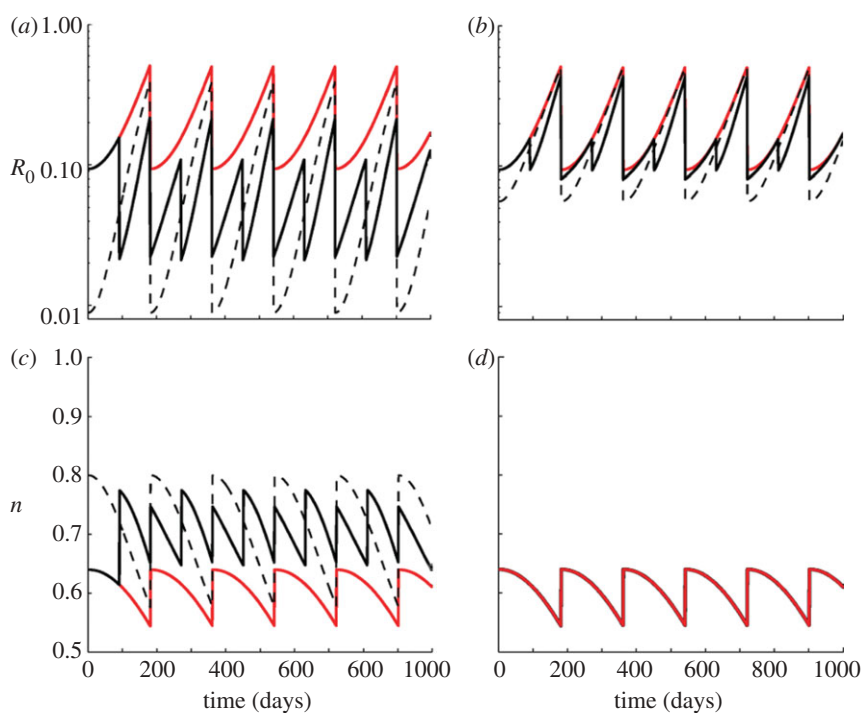
Figure 4. The effects of biannual retreatment of IRS and ITN on the transmission potential of malaria (R_0) and the protected proportion of humans (n) when IRS and ITN are preferentially distributed apart (combination strategy 3). (a) R_0 dynamics with 20% DDT coverage; (b) R_0 dynamics with 80% pyrethroid spray coverage; (c) dynamics of protected proportion of humans (n) with 20% DDT coverage; (d) dynamics of protected proportion of humans (n) with 80% pyrethroid spray coverage. The dashed line refers to ITNs and IRS applied together at months 0, 6, 12, etc., and the black line refers to ITNs applied on months 0, 6, 12, etc., and IRS on months 3, 9, 15, etc. The red line refers to ITNs only.
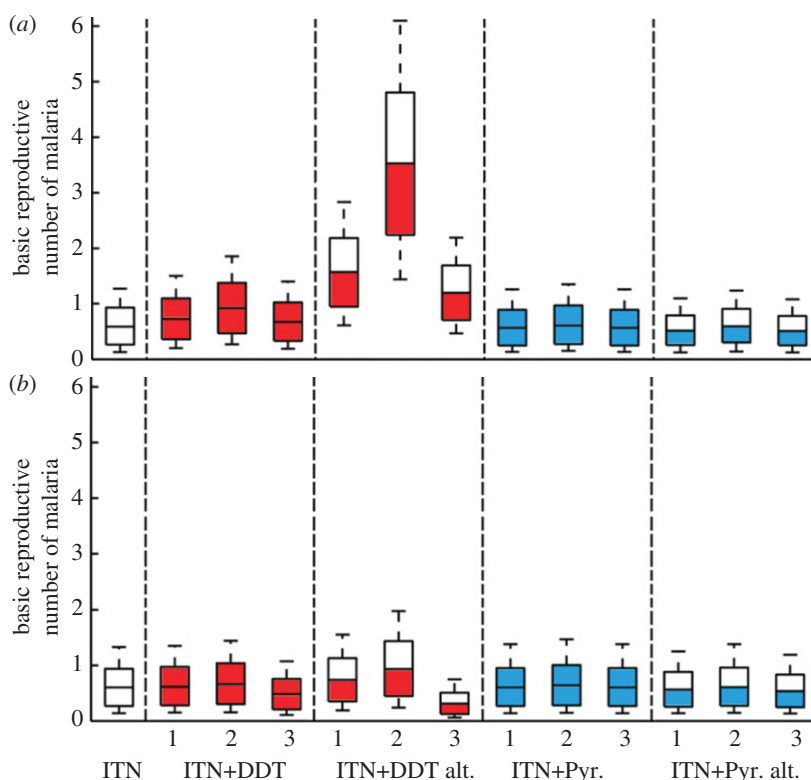

Figure 5. Analysis of R_0 sensitivity to control tool-coverage proportions, protective efficacy, mosquito killing efficacies, repellence and insecticide depletion rates. The four scenarios include: ITN re-treatment with either pyrethroid or DDT spray, temporally coinciding or alternating. '1', '2' and '3' refer to random, preferentially together and preferentially separate distributions, respectively. Each control tool value was allowed to vary randomly by 10% within a uniform distribution centred on the standard values. The box corresponds to the 25%, mean and 75% values (whiskers to the 5% and 95% values) of the probability distribution resulting from 1000 runs of a Monte Carlo simulation. (a) IRS and ITN coverage both at 80% and (b) IRS at 20% coverage with ITNs at 80% coverage.

that mosquitoes contact ITNs within the treated residence. Similarly, ITNs within the IRS residence reduce the probability that a blood meal is ingested, thereby reducing resting on the sprayed walls. In our model, we assume that *A. gambiae* mosquitoes rest on the walls of houses where they imbibe a blood meal, and that they tend not to rest on walls sprayed with repellent insecticide unless they are burdened with the weight of a recent blood meal [17]. The high rates of blood-fed status (approx. 80%) of *A. gambiae* collected from experimental huts sprayed with DDT [22] corroborate this assumption. If notable numbers of recently fed females were recorded vacating houses without contacting the walls sprayed with DDT, we would have to relax our assumption, and the antagonism of using both tools together would be attenuated.

We modelled three strategies of combining ITNs and IRS in malaria control, and assessed potential pitfalls and opportunities in producing synergistic effects. Our aim was to assess mechanistically the optimal combined implementation of these tools as a generalized starting point for field-testing. Simulations suggest that judicious use of DDT with ITNs can have more than additive efficacy in reducing malaria-transmission potential. Exclusively mutual distribution of these control tools improves upon ITNs alone by an order of magnitude. Importantly, we show that simply maximizing coverage of the control tools might not only be sub-optimal, but can hamper the efficacy of ITNs as a stand-alone strategy.

Caution must be taken in interpreting the results that we have presented in this analysis based on the basic reproductive number. R_0 is not synonymous with human infection prevalence. It is the transmission potential to an unprotected individual. We select R_0 instead of entomological inoculation rate or projected human prevalence of infection because we feel that it is a more transparent metric for describing community-level benefits of control. It is undisputed that somebody sleeping under a recently impregnated ITN will benefit, to a certain extent, from its protection. While community-wide benefits have been recorded from ITN implementation [23–25], there is a trade-off between reducing transmission via increasing mosquito mortality and enhancing transmission in the unprotected subgroup via deflected bites. Concern for enhancing transmission through bite rate heterogeneities has been raised in numerous studies [3,26,27]. Measuring the overall incidence or prevalence of human infection within a community will miss this heterogeneity.

There are justifications for, and corresponding operational issues with, each of the three distribution policies. Randomly distributing both ITNs and IRS presumes that all households within a community are equally accessible for distribution, and that all community members are equally inclined to seek out and/or receive control tools. This is a hypothetical situation indeed. The second distribution policy, simulating preferential use of both tools together, might be deemed more realistic concerning domicile accessibility and control-seeking behaviour (those who use bed nets are more likely to seek out and accept the use of IRS within their homes). However, assigning low IRS priority to non-ITN houses, thereby leaving some community members completely unprotected, seems unacceptable. It might be argued that community-wide benefits are experienced even by individuals who are not personally protected by ITNs [28] or IRS [29]. Our model formulation allows for this population-level reduction in transmission efficacy via enhanced mosquito mortality and extended host-searching duration (equations (2.1), (2.2) and (2.5)). Nevertheless, the trade-off between these factors and enhanced transmission through heterogeneities in bite rates that also result from control implementation is a complex matter [3]. Thus, for the time being, leaving individuals unprotected with the expectation that community-wide benefits will be experienced cannot be recommended.

The third scenario whereby IRS is distributed to households that do not already have ITNs might be considered more ethical, but less practical for the accessibility and human proclivity reasons mentioned. Our analysis suggests that in order to optimize the combination strategy 3 with DDT, even where additional spray is available to provide for all households without ITNs and to some households with ITNs, DDT should be withheld from households that use ITNs. Although unexpected, this result is logical. It has long been known that a key function of ITNs is imposing vector mortality [30]. The negative effect of reducing rates of vector encounters with ITNs through repellent IRS, therefore, is not a counterintuitive result. Nevertheless, extensive field testing would be necessary to substantiate such a potentially controversial strategy.

Despite a growing body of evidence showing that ITNs and IRS are highly cost-effective malaria-control interventions [31,32], the sufficiency of combining these tools for malaria elimination is a matter of some debate [33,34]. There is serious paucity of empirical data on the combined efficacies, and cost-efficacies, of ITNs with IRS which desperately needs addressing [4]. Through mathematical modelling, we have demonstrated potential for strong synergy between IRS and ITNs, when combined appropriately, and begun to lay down the groundwork for designing field studies to analyse the efficacy of this integrated approach to controlling malaria.

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