Malaria vector control and insecticide resistance management through universal coverage with next-generation insecticide-treated nets: The case for prioritizing quality over quantity and timeliness over certainty

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The biological rationale for universal coverage with insecticide treated nets (ITNs)

Thirteen years ago my colleagues and I outlined a biological rationale for *universal coverage* with insecticide treated nets (ITNs)[1] that was rapidly adopted as global policy.[2] We developed behaviourally-explicit mathematical models of malaria transmission and control,[1] to illustrate why the personal protection ITNs provide is insufficient in itself, and challenged the global strategy of selectively targeting them to vulnerable young children and pregnant women.[3-6] Instead, we outlined why even imperfect coverage of all age groups, regardless of their vulnerability to malaria, is essential to achieve community-wide protection of users and non-users alike by killing off vector populations *en masse*.[1] Beyond explanatory models and a rich evidence base demonstrating benefits for non-users within communities with high usage,[7] the mass effect has even been visualized using data from a large-scale cluster-randomized control trial[8] in an area where the most important local vector subsequently disappeared[9]: Impacts extended hundreds of meters across landscapes, with entire communities lacking ITNs benefiting from nearby communities who received them.[8] Subseuqent scale up of ITNs towards these universal coverage targets has been spectacularly successful, accounting for most of the 1·3 billion fewer malaria cases and 6·8 million fewer malaria-related deaths that occurred globally in recent years.[10,11] In many cases, ITNs or indoor residual spraying (IRS) of insecticides have even eliminated populations of the most efficient, human-dependent vectors entirely.[12] These extreme examples illustrate the ultimate power of *mass effects* upon vector populations, creating scenarios in which personal protection plays no role in preventing malaria transmission by a vector species because it no longer exists locally.

While personal protection is far more obvious to funders, distributors and recipients of ITN, providing the primary motivation for uptake and use, it contributes only a minor fraction of the overall impact achieved (Figure 1).[13] The other component of reduced human-vector contact, specifically reduced exposure of vectors to infectious humans, is even smaller, especially for the most efficient and important vectors with strong preferences for human blood (Figure 1).[13]

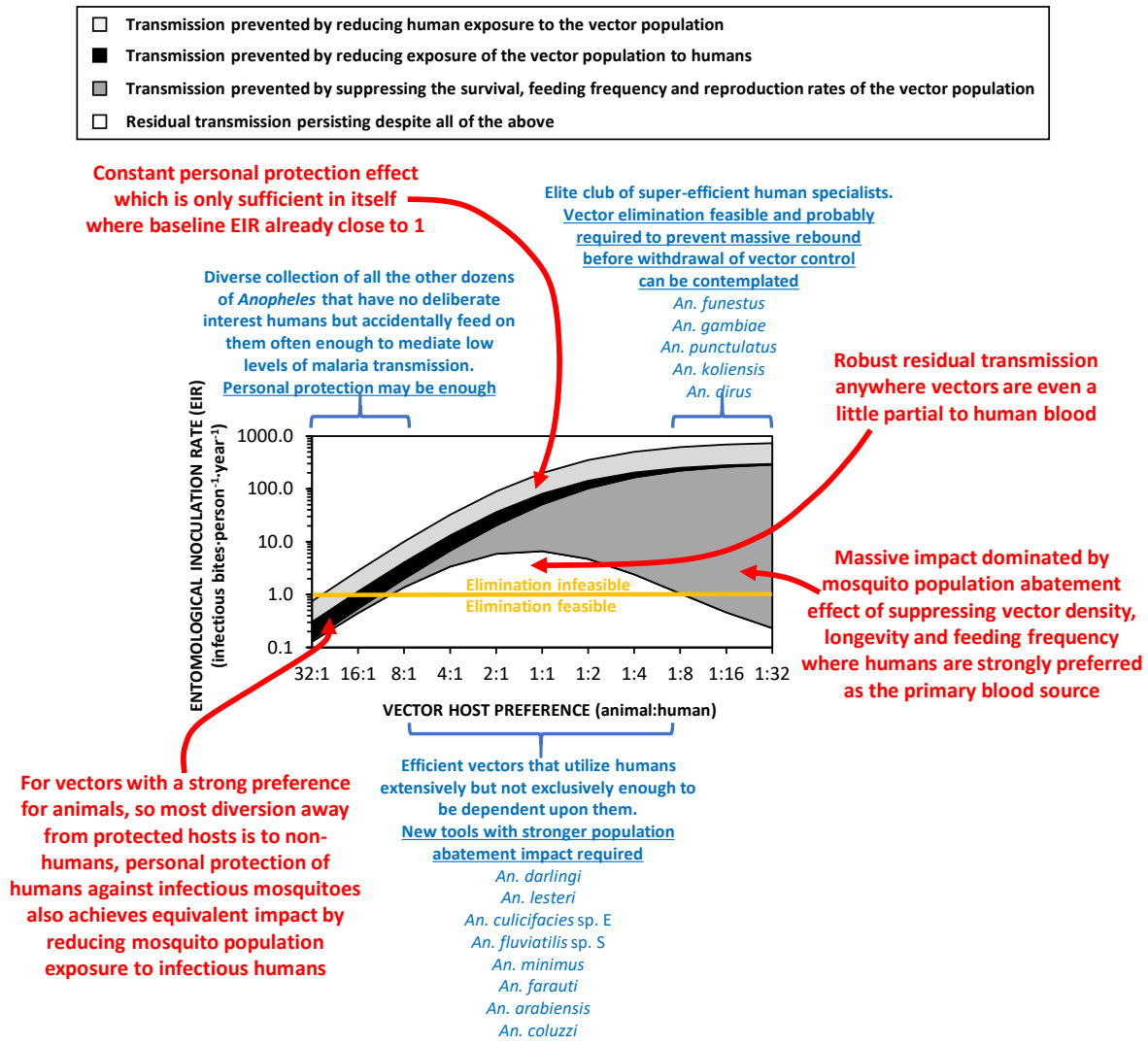

Figure 1. A simulation analysis of how the overall impacts of insecticide-treated nets (ITNs) are broken down by contributing underlying mechanism.[13]

As originally envisaged, adoption of the universal coverage targets was motivated by the need to suppress vector populations by maximizing their exposure to lethal insecticides while attacking humans.[1,13] This inevitably necessitates reaching all age groups rather than just the young children and pregnant women most physiologically vulnerable to malaria.[1] The term *universal* coverage was therefore coined to communicate the goal of maximizing coverage across all sections of the human population, rather than any necessity to protect every single person with their own net of:

> "Most commonly, the insecticide kills malaria vectors when they come into contact with the ITN. Therefore, by reducing the vector population, ITNs, when used by a majority of the target population, provide protection for all people in the community, including those who do not sleep under one themselves."[2]

In fact, one way we communicated the importance of mass effects was using modelling simulations to illustrate how as little as 35% use by the general population could provide community-wide protection of non-users equivalent to the levels of personal protection experienced by individual users.[1] Of course models are merely mathematically-explicit educated guesses, but again empirically-observed examples of local vector elimination with ITNs or IRS[12] provide a singular touchstone for testing the rigour of our thinking: while all

were associated with programmes that achieved high coverage, and actually exceed expectations based on standard models[12], none could claim to have reached every last person at all times and places.

Insecticide resistance management through universal coverage with next generation ITNs

Unfortunately, the original rationale for universal coverage with ITNs is now commonly misunderstood. More worryingly, such misconceptions underpin flawed global policies that may have irreversible consequences for future generations. I specifically worry about the future of new "next generation" ITNs (NG-ITNs)[14] which are now under evaluation[15] with encouraging early results.[16] NG-ITNs are treated with two or more complementary insecticides from different chemical classes, to prevent propagation of individuals carrying resistance traits against either insecticides by killing them with the other. NG-ITNs have unprecedented potential for not only delivering immediately improved impact against pyrethroid-resistant vectors[16] but also circumventing, or at least slowing, emergence of new resistance traits in the future. Evolution of physiological resistance against pyrethroids, until recently considered the only insecticide class safe enough for ITNs, has already eroded their public health value,[14,16,17] threatening a "looming public health catastrophe".[18] Heavily-subsidized ongoing investments will yield no more than three new insecticide classes for public health in the foreseeable future.[18-20] As explained herein, urgent corrective action is required to reform global policy regarding where, when and how new insecticides are used.[14] Specifically, policy needs to be fully realigned with the known biological basis of how ITNs work and the immediate need to deploy them for long term, pre-emptive insecticide resistance management (IRM) before it is too late.

While pyrethroid-based ITNs co-treated with the synergist piperonyl butoxide (PBO) have been available for many years (so I will not refer to them here as NG-ITNs), they have been grossly underutilized because WHO has been too slow and indecisive in recommending them for programmatic use.[14] While they have proven capable of restoring ITN impact over the short term,[17] they are no longer considered a robust tool for pre-emptively slowing emergence of pyrethroid resistance,[21] presumably because these traits are already widespread. However, much can be learned from the failure to adopt these not-so-new technologies decisively enough to exploit their full potential.[14,15] We cannot afford to repeat the same mistakes with NG-ITNs, and it is worrying that some current policies regarding PBO-ITNs[21,22] appear based on misconceptions about how ITNs actually work.

Prioritizing ITN lethality over coverage

The most recent position of WHO on adoption of pyrethroid-based ITNs co-treated with PBO is not only more than a decade overdue, it is also too indecisive[14] and misses the most important corollary of the rationale underpinning universal coverage targets: The immediate epidemiological benefits of reactive deployment against vector populations that are already resistant to pyrethoids depends far more upon maximizing vector mortality than upon maximizing human population coverage (Figure 2). In fact, mortality-induced vector population suppression is so important that overall impact may be undermined by excito-repellent insecticide formulations that enhance personal protection but deter mosquitoes from exposing themselves to lethal doses.[23-25] It may therefore be more important to emphasize the quality of ITNs in terms of their ability to kill mosquitoes, than to maximize coverage with personal protection by minimizing cost per unit. On that basis, I challenge the following statement regarding PBO-ITNs, which deviates from the original purpose of universal coverage:

"Deployment of pyrethroid-PBO nets must only be considered in situations where coverage with effective vector control (primarily LLINs or indoor residual spraying [IRS]) will not be reduced; the primary goal must remain the achievement and maintenance of universal coverage for all people at risk of malaria."[21]

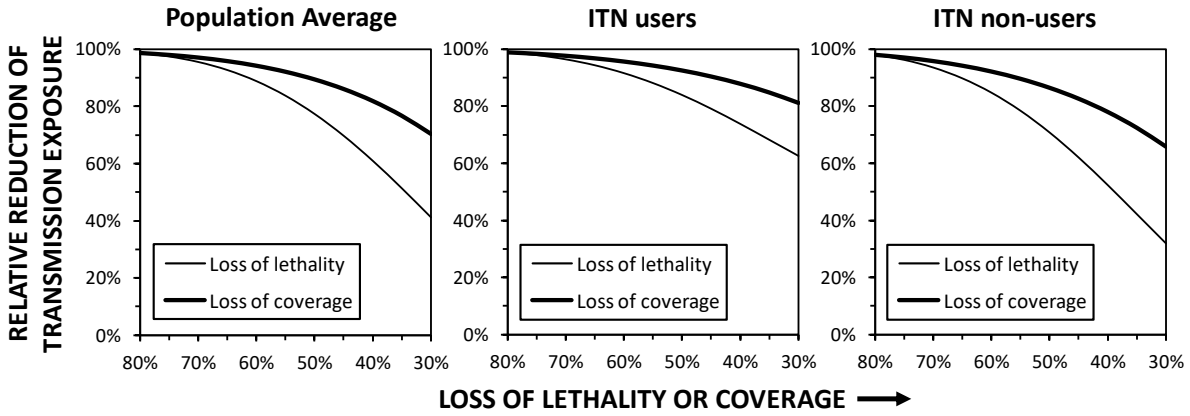

Figure 2. Process-explicit model simulations illustrating how the benefits of ITNs are attenuated far more by suboptimal lethality to mosquitoes than by poor usage rates. Simulations were carried out as previously described,[25] parameterized based on field estimates of host preference traits of *Anopheles gambiae*, the most important malaria vector in Africa, and one head of cattle for every five human residents. Note, however, that essentially identical results were obtained with parameter values consistent with the far more zoophagic African vector from the same species complex, *An. arabiensis*.

Furthermore, the second half of this quote, seems motivated by the perceived need to maximize equity through universal coverage with personal protection, and ignores the fact that communal mass effects are completely equitable[1,2]. Vector population suppression of benefits users and non-users equally,[1,2] and the latter exist in every malarious setting, regardless of how effectively ITNs are delivered and promoted. Even if universal coverage targets were achieved all across Africa, >200 million people would still lack a net and depend entirely upon communal vector population suppression.

Figure 2 illustrates how maximizing lethality to mosquitoes is more important than maximizing coverage for ITN users and non-users alike. Indeed, non-users are particularly vulnerable to loss of lethality because they depend entirely upon area-wide vector population suppression for protection against malaria. Such equity considerations were central to the original rationale for universal coverage, intended to maximize communal rather than personal protection.[1,2] Of course, equitable access to ITNs is an important goal, and coverage is an important driver of their completely equitable mass effects. However, current policy[21,22] seems based on a one-sided view of this issue, so a more balanced, nuanced and accurately-weighted view of how ITNs really work is needed. Specifically, recommendations should place greater emphasis on the more equitable mass effects of ITNs upon vector populations. Policy should therefore prioritize distribution of the most efficacious nets that kill mosquitoes most effectively, rather than maximizing the absolute number of nets made available at the lowest price.

These arguments are not intended to undermine the goal of universal coverage in any way, but rather to re-emphasize its intended purpose. Nor am I advocating for lowering of universal coverage targets, because higher coverage with a given product will always deliver greater benefits than low coverage. However, maximizing coverage is just one of several competing priorities that need to be traded off against each other. ITN lethality may be prioritized above coverage, requiring quantity to be compromised in favour of quality. However, as explained below, smaller quantities of higher quality nets need not necessarily compromise coverage if

they last longer. Most important of all, deploying diversified product suites for pre-emptive IRM over the long-term may be more important than maximizing the coverage or impact immediately achievable with any single product.

Prioritizing ITN durability over affordability

Another key aspect of quality is durability, which may contribute more to high coverage than net distribution rates. Figure 3 illustrates a scenario in which coverage is boosted to the current WHO universal coverage target of 80%, by switching to an ITN product that is 50% more expensive to procure but lasts two years rather than one. While supply rates for this more expensive hypothetical product were obviously lower within the constraints of a fixed budget, the resulting drop in procurement rate was not as dramatic as the increase in procurement price (25% versus 50%, respectively). This is because a large fraction of the overall cost of supplying to the end user is associated with in-country delivery rather than procurement per se[26]: [26]: Assuming delivery costs per net are approximately constant, regardless of how long they last, more durable nets will offset some of the incremental costs of procuring them by reducing total delivery costs per year for a given number of nets. Investing in more expensive, higher quality nets that last longer may increase coverage (Figure 3) and improve equity of ITN benefits[26] through both personal and communal protection mechanisms.

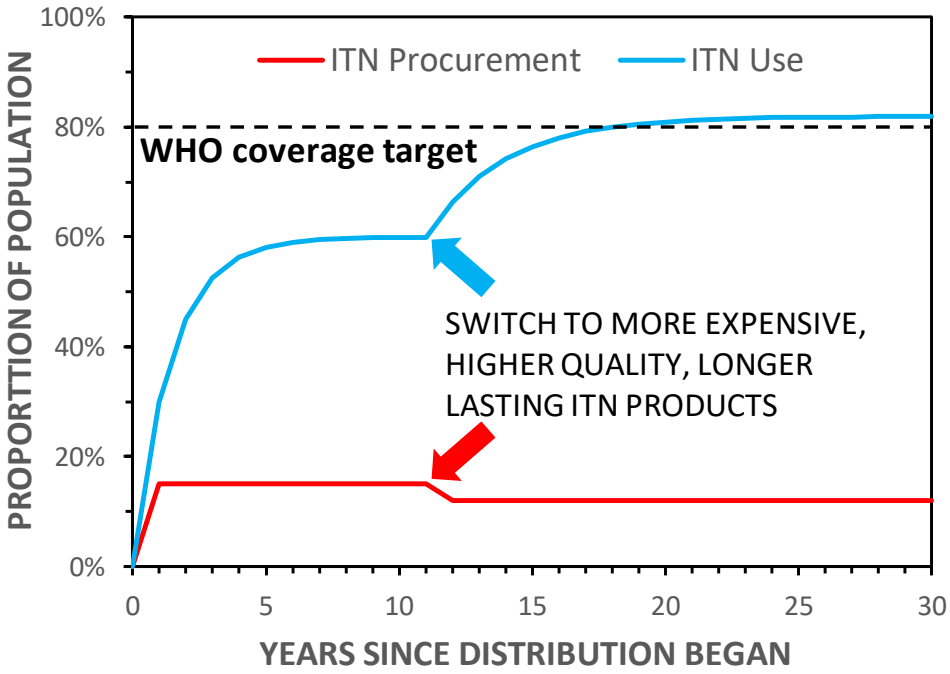

Figure 3. Simulation of a scenario in which a national malaria control programme began distributing ITNs costing $2 per unit[27] with an in-use half-life of 1 year[28], but then switched to a higher quality product costing $3 with a 2 year half-life, resulting in boosting of coverage to surpass the WHO universal coverage targets. Assumptions: A hypothetical national malaria control programme serving 50 million people has a fixed annual budget of $30 million for insecticide treated nets, for which the delivery cost per net are $2 each.[26]

Prioritizing ITN product diversity over efficacy

While it is obviously important that ITNs kill mosquitoes today, it is even more important that they continue to do so in the future, especially bearing in mind how long it takes to develop these products and bring them to market. The term *quality* must also embrace strategic long-

term functionality, in terms of enabling proactive, pre-emptive IRM. While individual NG-ITN products with two or more active ingredients diversify the insecticidal modes of action mosquitoes must simultaneously evolve resistance mechanisms against, the possibility of using different products with different insecticide combinations in rotations or mosaics[29] has even greater potential. If one accepts that diversification of NG-ITN products to enhance pro-active IRM is a good idea, it follows that no single product should be prioritized above all others. Even if one product performs better than others in a given time and setting (eg references 16 and 17), relying too exclusively upon it over the short term will inevitably undermine the potentially greater long terms benefits of pre-emptive IRM with a diversified suite of complementary products. It is unlikely that any two NG-LLINs with different active ingredients would have identical effects on malaria transmission but it would still be preferable to use both for pre-emptive IRM, rather than rely solely on the product with the highest efficacy. I therefore challenge the latest policy proposal that new NG-ITN products need to be evaluated in a fragmented set of largely unproven new classes, for which epidemiological superiority to pyrethroid-only nets needs to be conclusively demonstrated:

> "ITNs would be categorized into [five] classes. For each class, a 'first-in-class' product will have to demonstrate epidemiological impact against malaria in at least two trials conducted in geographically separate settings for WHO to issue a policy recommendation." [30]

Instead, I applaud the bolder approach of the new WHO pre-qualification system, which has already taken some NG-ITNs products closer to a defragmented market by listing them alongside pyrethroid-only ITNs on the basis that they are "…assumed to provide an epidemiological impact that is at least as good as that of a pyrethroid-only net".[30] I also appeal for accelerated product diversification, ideally within a single, integrated NG-ITNs product class. Ultimately they are all NG-ITNs, so while proof of equivalence for products with a given combination of active ingredients is essential to prevent inferior products entering the market, insisting on equivalence between the proposed numerous different classes may be counterproductive: Even products with active ingredients and modes of action that prove less efficacious than others may be useful for pre-emptive IRM schemes, in which they are deployed alongside others with different insecticides, as rotations, mosaics or micro-mosaics. Perhaps the most difficult challenge facing programmes undertaking pre-emptive IRM is accepting and justifying somewhat lower impact than would be possible with a single optimal product over the short term, so that the impact can be sustained over the long term. The proposed new policy fragments ITNs into so many classes that the most novel, and therefore useful, of these will become available too late for pre-emptive IRM alongside those already closer to market.

Another drawback of current policy is the disincentive it creates for manufacturers to develop new insecticides and ITN products. Why would any manufacturer invest in a new high quality ITN product with IRM functionality when they see others gathering dust on the shelves for over a decade?[14,21,22] Similarly, innovation is heavily disincentivized when new NG-ITNs are separated into several new intervention classes, each requiring supporting epidemiological evidence bases in their own right.[30,31] Recent progress[15] is encouraging, as is the most recent stance of the prequalification system to market defragmentation[30] but far more is needed to accelerate acceptance of NG-ITN as merely a variant of the ITN product class, thus mitigating prohibitive investment risks that stifle innovation in this "high risk and low reward" market.[32]

Prioritizing timely recommendations for new products over evidence-based certainty

In any case, the long-term benefits of such proactive, pre-emptive interventions with multiple active ingredients, to retard emergence of new resistance traits, are impossible to rigorously

demonstrate in epidemiological terms until it's too late to use them for this purpose (Figure 4). NG-ITNs which can pre-emptively slow emergence of resistance need not confer any measurable epidemiological advantage when used early enough to do so: The resistance traits they are intended to prevent emergence of should still be so rare that the combination of insecticides may have no measurable advantage in terms of improved mosquito mortality or epidemiological impact (Figure 4). I therefore challenge current recommendations for PBO-ITNs on the basis that they are illogical in principle:

> "Pyrethroid-PBO nets are not expected to have any added benefit in areas where the main malaria vectors are susceptible to pyrethroids and/or do not harbor resistance mechanism(s) that are affected by PBO, i.e., monooxygenase-based resistance mechanism."[21]

If PBO-ITNs or NG-ITNs appear to have no noticeable advantage in terms of killing mosquitoes or reducing malaria transmission, because no resistance mechanism yet exists that attenuates their efficacy, this actually represents an opportunity to deploy them before their full potential for long term, pre-emptive IRM is lost.

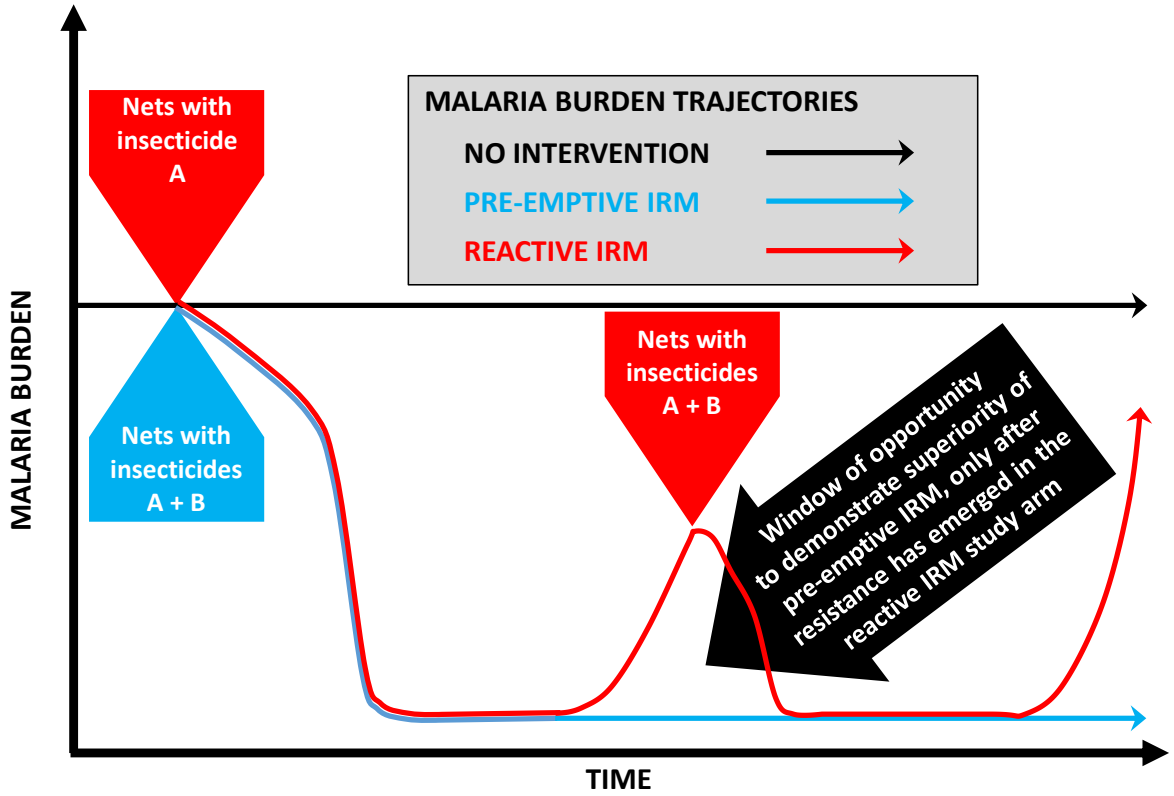

Figure 4. A hypothetical illustration of the epidemiological trajectories expected in an experimentally controlled study to demonstrate the incremental long-term benefits of deploying NG-ITNs for pre-emptive insecticide resistance management, to prevent resistance traits from emerging in the first place.

I therefore challenge the logic of awaiting clear evidence for epidemiological superiority of any new tool with potential for use in pre-emptive IRM schemes intended to tackle new resistance traits before they become common enough to cause resurgence of malaria:

> "VCAG will review further epidemiological trial data as soon as they become available… [to] … allow the conditional endorsement of pyrethroid-PBO nets to be converted into the full establishment of the class."

"WHO will formulate specific policy recommendations for these 'first-in-class' products provided the data demonstrate that these products have public health value … based on the demonstration of … entomological and epidemiological efficacy against vectors and human infections and/or disease, respectively."[30]

It may be possible to successfully conduct a rigorously-controlled, cluster-randomized phase III experimental study that conclusively demonstrates the long-term merits of pre-emptive versus reactive IRM strategies, in which complementary active ingredients were respectively introduced simultaneously in combinations rather than sequentially as stand-alone active ingredients (Figure 4) However, such studies would inevitably undermine the usefulness of the decisions they were meant to inform: No advantage of pre-emptive IRM would be obvious until resistance had emerged at high frequency in the clusters assigned to the reactive strategy (Figure 4), from where they would spread throughout the study area and beyond. Waiting on availability of unambiguous epidemiological evidence is therefore illogical unless one assumes new active ingredients can be developed as quickly as new resistance traits emerge and that a reactive, post-emergence resistance mitigation strategy is acceptable.

Learning from decisive historical recommendations for antimalarial drug combination therapies

While it is clearly preferable to make confident decisions based on a robust evidence base [33], sometimes that is not available and will not be available fast enough to intervene pre-emptively. Logical frameworks for making timely health policy decisions in the absence of unambiguous evidence, drawing as much on societal considerations and intuitive common sense, are well established but underutilized[34-36] and need greater emphasis for timely adoption of new vector control methods.[14,37] It is also worth remembering that almost all the most successful vector control programmes in history (ITNs are the only exception) were established before modern standards of rigorous evidence[37], yet none of us would question the validity of those decisions today.

Elsewhere in the malaria arena, the World Health Organization (WHO) has an impressive track record of making bold, timely recommendations in relation to pre-emptive resistance management. When malaria parasites developed resistance against commonly-used antimalarial drugs at the turn of the century, WHO was swift to act.[38-40] Prompt recommendations for multiple combination therapies,[40] the benefits of which we still enjoy today, were based on widely-accepted recognition of:

"the potential value of drug combinations…to improve efficacy, delay development and selection of drug-resistant parasites and thus prolong the therapeutic life of existing antimalarial drugs."[38]

This landmark recommendation was made despite similar uncertainties [41] to those we face today regarding NG-ITNS, not least of which were:

"Lack of evidence of its effectiveness in delaying development of resistance in areas of high transmission"[39]

WHO not only recommended rapid adoption of artemisinin-based combination therapies, it simultaneously did so for five different combinations of active ingredients and also "established a system for pre-qualification of manufacturers"[40] like the one accelerating progress of some NG-ITN products to market.[30] Soon afterwards, WHO recommended both regulators and manufacturers immediately remove artemisinin monotherapies from the market.[42]

Applying the same bold leadership philosophy to ITNs today would translate into immediate, unreserved and universal recommendations for all first-in-class PBO-ITN and NG-ITN products that have proven capable of killing resistant mosquitoes more effectively than pyrethroid-only ITNs. The proposal to enable rapid adoption of equivalent products based on laboratory and semi-field entomological evidence alone is welcome but should avoid fragmenting the regulatory framework into too many classes, each requiring its own supporting epidemiological evidence base. It should also place less emphasis on the need to achieve equivalent efficacy because: (1) As explained above, diversity of product active ingredients and modes of action may be more important for long term IRM than immediate efficacy, (2) While antimalarial drugs act over periods of days in the standardized environment of the human body, ITNs need to remain efficacious for years in diverse physical and social environments, so durability and performance of different products are best evaluated in the field[28,43,44] through routine programmatic monitoring.[45,46] Already, the first such programmatic evaluations reveal net lifetimes varying greatly between products and settings, ranging from approximately one to three years [28,43,44]. It is neither practical nor affordable to evaluate all products across all settings with rigorous large-scale trials, nor can programmes afford to wait on unambiguous evidence, so routine post-marketing assessments are the only realistic way forward[45,46].

WHO has historically provided the kind of decisive leadership needed to combat resistance against anti-malarial drugs, by rapidly recommending combination therapies. It is now time to extend these traditions to stewardship of NG-ITNs, to safeguard their future as tools for pre-emptive IRM with the same urgency.

Contributors

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Declaration of interests

I declare no competing interests.

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