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

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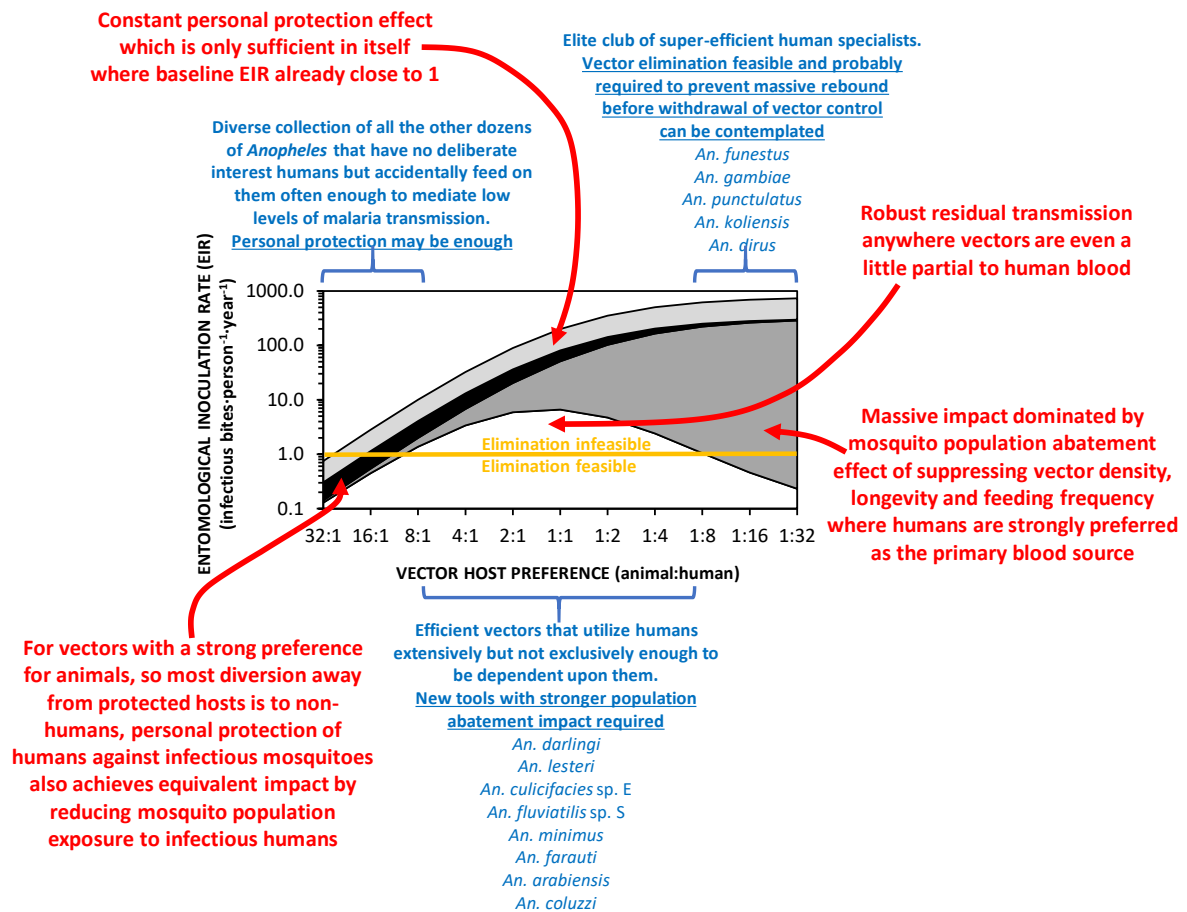
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13 **The biological rationale for universal coverage with insecticide treated nets (ITNs)**

14 Thirteen years ago my colleagues and I outlined a biological rationale for *universal coverage*  
15 with insecticide treated nets (ITNs)<sup>1</sup> that was rapidly adopted as global policy.<sup>2</sup> We developed  
16 behaviourally-explicit mathematical models of malaria transmission and control,<sup>1</sup> to illustrate  
17 why the personal protection ITNs provide is insufficient in itself, and challenged the global  
18 strategy of selectively targeting them to vulnerable young children and pregnant women.<sup>3-6</sup>  
19 Instead, we outlined why even imperfect coverage of all age groups, regardless of their  
20 vulnerability to malaria, is essential to achieve community-wide protection of users and non-  
21 users alike by killing off vector populations *en masse*.<sup>1</sup> Beyond explanatory models and a rich  
22 evidence base demonstrating benefits for non-users within communities with high usage,<sup>7</sup> the  
23 mass effect has even been visualized using data from a large-scale cluster-randomized control  
24 trial<sup>8</sup> in an area where the most important local vector subsequently disappeared<sup>9</sup>: Impacts  
25 extended hundreds of meters across landscapes, with entire communities lacking ITNs  
26 benefiting from nearby communities who received them.<sup>8</sup> Subsequent scale up of ITNs towards  
27 these universal coverage targets has been spectacularly successful, accounting for most of the  
28 1.3 billion fewer malaria cases and 6.8 million fewer malaria-related deaths that occurred  
29 globally in recent years.<sup>10,11</sup> In many cases, ITNs or indoor residual spraying (IRS) of  
30 insecticides have even eliminated populations of the most efficient, human-dependent vectors  
31 entirely.<sup>12</sup> These extreme examples illustrate the ultimate power of *mass effects* upon vector  
32 populations, creating scenarios in which personal protection plays no role in preventing malaria  
33 transmission by a vector species because it no longer exists locally.

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

- Transmission prevented by reducing human exposure to the vector population
- Transmission prevented by reducing exposure of the vector population to humans
- Transmission prevented by suppressing the survival, feeding frequency and reproduction rates of the vector population
- Residual transmission persisting despite all of the above



39

40 **Figure 1. A simulation analysis of how the overall impacts of insecticide-treated nets (ITNs) are broken**  
 41 **down by contributing underlying mechanism.**<sup>13</sup>

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

49 “Most commonly, the insecticide kills malaria vectors when they come into contact with the  
 50 ITN. Therefore, by reducing the vector population, ITNs, when used by a majority of the  
 51 target population, provide protection for all people in the community, including those who do  
 52 not sleep under one themselves.”<sup>2</sup>

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

59 were associated with programmes that achieved high coverage, and actually exceed  
60 expectations based on standard models<sup>12</sup>, none could claim to have reached every last person  
61 at all times and places.

## 62 **Insecticide resistance management through universal coverage with next generation ITNs**

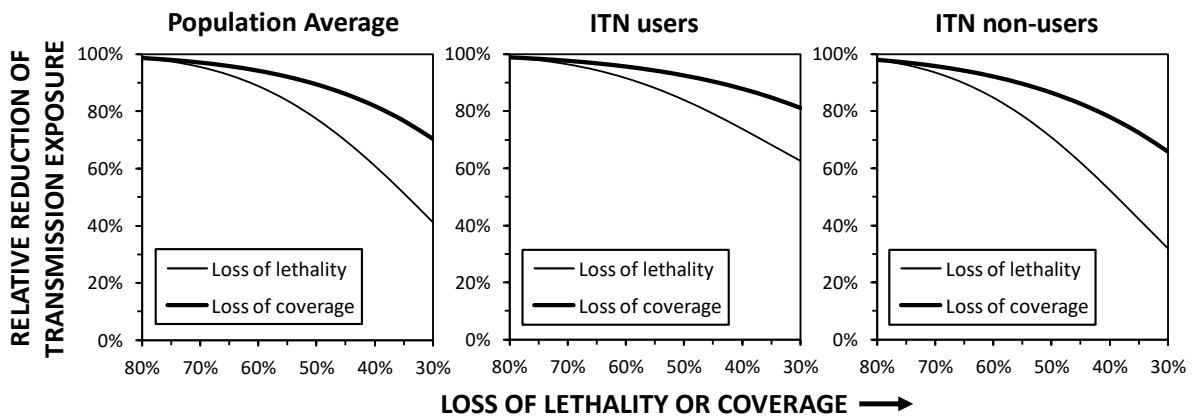
63 Unfortunately, the original rationale for universal coverage with ITNs is now commonly  
64 misunderstood. More worryingly, such misconceptions underpin flawed global policies that  
65 may have irreversible consequences for future generations. I specifically worry about the future  
66 of new “next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

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

## 91 **Prioritizing ITN lethality over coverage**

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

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



109  
 110 **Figure 2. Process-explicit model simulations illustrating how the benefits of ITNs are attenuated far more**  
 111 **by suboptimal lethality to mosquitoes than by poor usage rates.** Simulations were carried out as previously  
 112 described,<sup>25</sup> parameterized based on field estimates of host preference traits of *Anopheles gambiae*, the most  
 113 important malaria vector in Africa, and one head of cattle for every five human residents. Note, however, that  
 114 essentially identical results were obtained with parameter values consistent with the far more zoophagic African  
 115 vector from the same species complex, *An. arabiensis*.

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

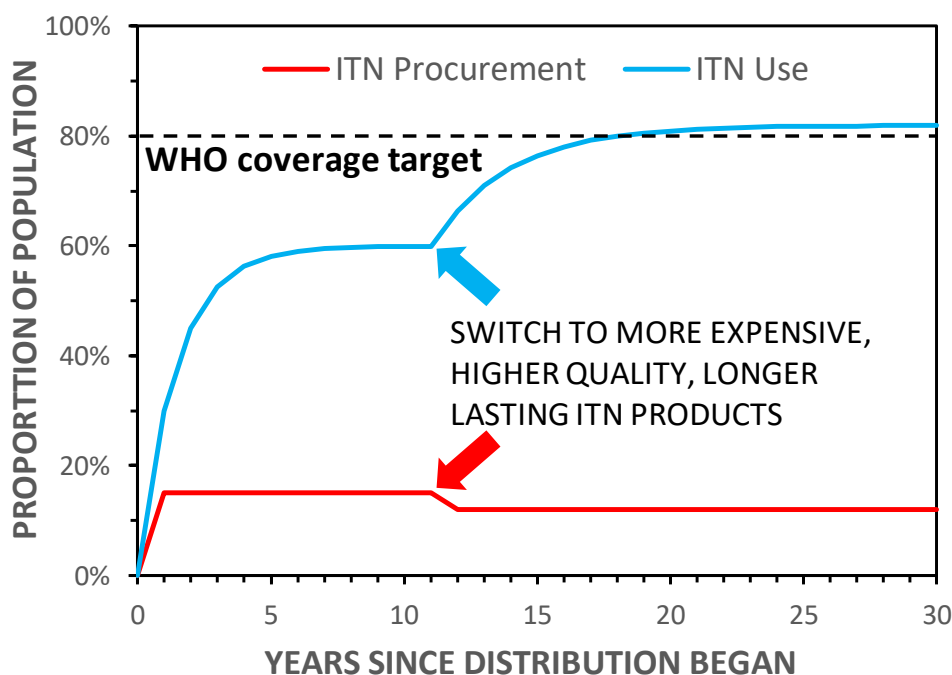
123 Figure 2 illustrates how maximizing lethality to mosquitoes is more important than maximizing  
 124 coverage for ITN users and non-users alike. Indeed, non-users are particularly vulnerable to  
 125 loss of lethality because they depend entirely upon area-wide vector population suppression for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

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

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

### 145 **Prioritizing ITN durability over affordability**

146 Another key aspect of quality is durability, which may contribute more to high coverage than  
147 net distribution rates. Figure 3 illustrates a scenario in which coverage is boosted to the current  
148 WHO universal coverage target of 80%, by switching to an ITN product that is 50% more  
149 expensive to procure but lasts two years rather than one. While supply rates for this more  
150 expensive hypothetical product were obviously lower within the constraints of a fixed budget,  
151 the resulting drop in procurement rate was not as dramatic as the increase in procurement price  
152 (25% versus 50%, respectively). This is because a large fraction of the overall cost of supplying  
153 to the end user is associated with in-country delivery rather than procurement per se<sup>26</sup>.  
154 Assuming delivery costs per net are approximately constant, regardless of how long they last,  
155 more durable nets will offset some of the incremental costs of procuring them by reducing total  
156 delivery costs per year for a given number of nets. Investing in more expensive, higher quality  
157 nets that last longer may increase coverage (Figure 3) and improve equity of ITN benefits<sup>26</sup>  
158 through both personal and communal protection mechanisms.



159  
160 **Figure 3. Simulation of a scenario in which a national malaria control programme began distributing**  
161 **ITNs costing \$2 per unit<sup>27</sup> with an in-use half-life of 1 year<sup>28</sup>, but then switched to a higher quality**  
162 **product costing \$3 with a 2 year half-life, resulting in boosting of coverage to surpass the WHO universal**  
163 **coverage targets.** Assumptions: A hypothetical national malaria control programme serving 50 million people  
164 has a fixed annual budget of \$30 million for insecticide treated nets, for which the delivery cost per net are \$2  
165 each.<sup>26</sup>

### 166 167 **Prioritizing ITN product diversity over efficacy**

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

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

186 “ITNs would be categorized into [five] classes. For each class, a ‘first-in-class’ product will  
187 have to demonstrate epidemiological impact against malaria in at least two trials conducted in  
188 geographically separate settings for WHO to issue a policy recommendation.”<sup>30</sup>

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

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

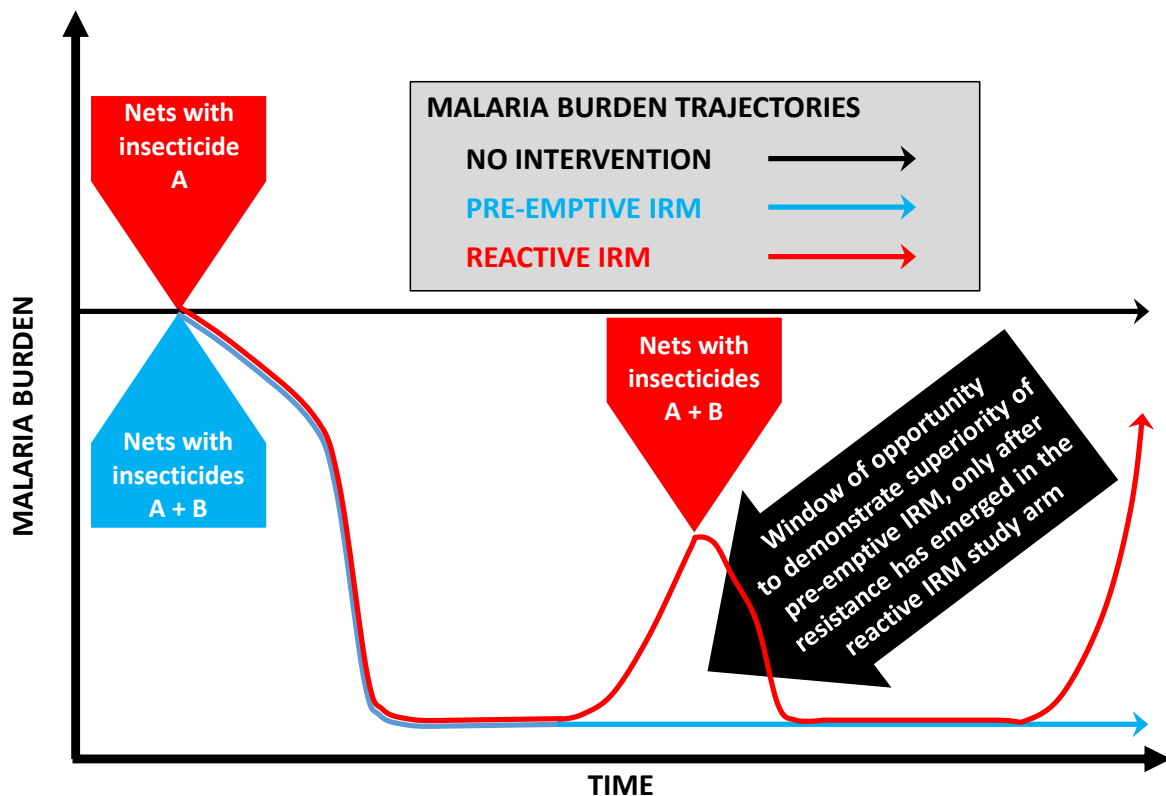
### 215 **Prioritizing timely recommendations for new products over evidence-based certainty**

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

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

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

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



232  
 233 **Figure 4. A hypothetical illustration of the epidemiological trajectories expected in an experimentally**  
 234 **controlled study to demonstrate the incremental long-term benefits of deploying NG-ITNs for pre-**  
 235 **emptive insecticide resistance management, to prevent resistance traits from emerging in the first place.**

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

239 “VCAG will review further epidemiological trial data as soon as they become available...  
 240 [to] ... allow the conditional endorsement of pyrethroid-PBO nets to be converted into the  
 241 full establishment of the class.”



242 “WHO will formulate specific policy recommendations for these ‘first-in-class’ products  
243 provided the data demonstrate that these products have public health value ... based on the  
244 demonstration of ... entomological and epidemiological efficacy against vectors and human  
245 infections and/or disease, respectively.”<sup>30</sup>

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

### 257 **Learning from decisive historical recommendations for antimalarial drug combination** 258 **therapies**

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

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

274 “the potential value of drug combinations...to improve efficacy, delay development and  
275 selection of drug-resistant parasites and thus prolong the therapeutic life of existing  
276 antimalarial drugs.”<sup>38</sup>

277 This landmark recommendation was made despite similar uncertainties <sup>41</sup> to those we face  
278 today regarding NG-ITNS, not least of which were:

279 “Lack of evidence of its effectiveness in delaying development of resistance in areas of high  
280 transmission”<sup>39</sup>

281 WHO not only recommended rapid adoption of artemisinin-based combination therapies, it  
282 simultaneously did so for five different combinations of active ingredients and also  
283 “established a system for pre-qualification of manufacturers”<sup>40</sup> like the one accelerating  
284 progress of some NG-ITN products to market.<sup>30</sup> Soon afterwards, WHO recommended both  
285 regulators and manufacturers immediately remove artemisinin monotherapies from the  
286 market.<sup>42</sup>

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

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

#### 308 **Contributors**

309 GFK is the sole contributor to this article.

#### 310 **Declaration of interests**

311 I declare no competing interests.

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