Commentary

Combining malaria vector control interventions: some trial design issues

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Invited Commentary on 'Combination of malaria vector control interventions…' by Corbel et al.

Long-lasting insecticidal nets (LLIN) and indoor residual spraying (IRS) are the two most powerful and broadly reliable weapons in the anti-malaria arsenal, but until recently, little attention was paid to the value of deploying them in combination. There was a good reason for this: most of the population at risk in Africa had little hope of benefiting from either of these technologies. Therefore, in most settings, the priority objective was to cover the majority of the target population with one method or the other, not to cover a smaller population with both. At that stage, therefore, scientific debate was mostly about the choice between LLINs and IRS, asking about cost-effectiveness and the prospects of high and sustained coverage in different settings.[1]

Since then, there has been a substantial increase in funding available for malaria control, with the creation of the Global Fund in 2002 and the President's Malaria Initiative in 2005. Then, in 2007, WHO started to recommend full coverage with LLINs as a basic policy for all malarious areas of Africa.[2] This led to greater interest in the question of whether IRS has additional value when deployed in combination with LLINs. More recently, the rapid spread of insecticide resistance through malaria vector populations in many African countries[3] has raised further questions about the possible positive and negative effects of the IRS + LLIN combination on resistance evolution. In particular, the WHO's new Global Plan for Insecticide Resistance Management in malaria vectors (GPIRM) recommends *against* the use of pyrethroid IRS in combination with LLINs (on the grounds that this is likely to strengthen selection for resistance), and recommends *for* the use of non-pyrethroid IRS with LLINs (as a means of reducing the selective advantage of pyrethroid-resistance genes).

These policy developments have been welcomed by experts and control programme managers, but so far they are supported only by observational studies and small-scale trials; evidence from village-scale field trials has been lacking. Hence, the recent multi-intervention trial by Corbel *et al.*[4] is important and challenging. It was carefully executed in 28 villages in Southern Benin, where there are high levels of pyrethroid resistance in the local populations of *Anopheles gambiae*. It compared four interventions: (1) LLINs alone with targeted coverage of pregnant women and children; (2) LLINs alone with universal coverage; (3) LLINs targeted coverage + IRS with the carbamate insecticide bendiocarb; and (4) LLINs universal coverage + wall-lining made of bendiocarb-treated plastic-sheeting. The design was, therefore, somewhat complex, and included several comparisons of direct relevance to the WHO policies mentioned above. The results, by contrast, were very simple: there were no significant differences between any of the intervention arms, in any of the most important outcomes: malaria incidence, geometric mean parasite density, mosquito abundance (man-biting rate), or the change in frequency of *kdr* pyrethroid-resistance genes in village mosquito populations.

This outcome is somewhat surprising. From our knowledge of how these interventions work, and from previous trials in experimental huts, we would expect the combination to be more effective than each of the components alone. IRS and LLINs both kill some but not all of the mosquitoes that enter a treated room (containing either a treated net or sprayed walls). In the presence of both treatments, we would expect the mosquitoes that survive one to have a good chance of being killed by the other, and if so, then the combination should be more effective than either of the single interventions alone. Exactly this result has been observed in experimental huts, by the same research team in southern Benin: the combination of a non-pyrethroid on the wall plus LLINs did indeed cause significantly greater vector mortality and improved feeding inhibition, compared to LLINs alone.[5] Moreover, in an analysis of survey data from several settings, Kleinschmidt *et al.*[6] found that in five out of eight studies, people covered by both interventions had less risk of malaria than those covered by just one or the other. More recent analysis of malaria indicator survey data from Equatorial Guinea show that people sleeping in IRS treated houses under bednets continue to benefit from additional personal protection against malarial infection compared to

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those who are protected by IRS alone, possibly because the duration of residual activity of the insecticide (Bendiocarb) does not last throughout the year-long transmission season.[7,8] Overall, the data were consistent with the basic hypothesis that the two interventions gave protection independently of each other, i.e. they each reduced the risk of malaria by a constant proportion. However, the use of IRS + LLIN combinations is already so widely practised and recommended that a solid body of evidence from community-randomized field-trials is really required.

A major shortcoming of all previously published work on this question is that it derives from observational studies from which the effects of important confounders cannot be ruled out. The Benin study has to be welcomed therefore as the first published trial on this issue that used a cluster randomised trial (CRT) design. It is appropriate to examine with some care the methodology used in this pioneering trial in Benin. Is there is any possible methodological explanation for the lack of observed contrasts between the interventions? How much better would the combination have to be, in order for the difference to be detected in a trial with this design in this setting?

One key issue is the question of statistical power, and the law of diminishing returns. In general, demonstrating effectiveness is much harder when an intervention is deployed as a supplement to another very effective intervention than when it is used on its own. In this case, the sample size for the trial was intended to give 80% power to detect a 50% lower risk of malaria with the supplementary wall-treatments than with LLINs alone. However, it does seem possible that the assumptions underlying this calculation may have been rather optimistic. For example, it appears that the malaria incidence assumed in the sample size calculation (1.5 episodes per child per year) was substantially higher than that subsequently observed during the trial (approximately 0.6 episodes per child per year in the baseline group, table 3). More important, it was assumed that there would be a high degree of homogeneity between villages (coefficient of variation [In the paper this was called the design effect] =0.25), despite previous local studies showing heterogeneity.[9] It is not clear whether this optimistic assumption was confirmed by the actual coefficient of variation observed in the trial data, but according to Hayes *et al.*,[10] observed design effects in four previous African vector control trials were all between 1.0 and 1.5. As a result of these non-conservative assumptions in the power calculation, the chances of a type 2 error may have been increased considerably beyond the intended 20% (80% power).

The other key issue is contamination. Conventional designs for field trials of vector control interventions are based on the concept of the 'transmission unit'. The idea is that the vectors, hosts, and parasites all circulate freely within but not between units, and movement of infected hosts and/or vectors between transmission units is small enough or slow enough to be negligible within the timescale of the trial. Of course this is a convenient fiction — the real biological world is not normally so clear-cut. Nevertheless, this approach can be effective and valid in practice. In several of the large African-treated net trials of the 1990s, village-scale intervention caused a substantial reduction in the prevalence of malaria infection, not only in users of treated nets but also in non-net-users in intervention villages,[11,12] the later being due to reduced longevity in the local vector mosquitoes.[13]

However, there are cases where this did *not* happen. In the Gambian trials of treated nets, there was no observable mass effect. There was clear evidence for strong personal protection of individual users of treated nets,[14] but there was no difference between treated and non-treated villages either in the risk of malaria for people not using a net,[15] or in the density and infection-rate of human-biting mosquitoes.[16] Contamination between experimental units is one likely explanation for this. Mosquito dispersal is highly variable between settings, and is largely driven by the female mosquito's repeated alternation between searching for a bloodmeal and then searching for an oviposition site.[17] In the dry flat landscape of The Gambia, major breeding sites (e.g. irrigated ricefields) are often located in the gaps between villages, and this may mediate the movement of mosquitoes between villages.[16] Such movement is expected to dilute the contrasts between the mosquito populations of neighbouring villages, and thus between intervention arms in a community-randomized trial.

Of course, some outcome measures are more vulnerable than others to this kind of inter-village dispersal. According to the science of population genetics, gene frequencies are especially susceptible to this kind of dilution process: it takes very little movement between neighbouring populations to homogenize the genetic make-up of two partially-separated populations.[18,19] Thus, the observed rate of gene frequency change by village is unlikely to be very useful as an indicator of the relative strength of selection for resistance exerted by alternative interventions in a village-scale trial. It seems that we need to develop proxy village-level indicators that can be used instead for this purpose.

We must also bear in mind that many other vector control methods, including IRS and larviciding, confer little or no individual-level protection, and rely entirely on large-scale effects on local mosquito populations.[20] Thus, the fact that village-scale designs have done well in epidemiological trials with

LLINs does not mean that contamination is never an issue, or that village-scale designs are equally suitable for all forms of vector control.[20,21]

In conclusion, it is certainly disappointing that no significant differences were detected between the key outcomes in any of the intervention arms in this trial. However, it does seem possible that the trial had considerably less power than intended, and that for some outcomes, contrasts between intervention arms were diluted by contamination due to mosquito movement between villages. Since the combination interventions evaluated in this trial are recommended by WHO and already in use, further evidence from well designed trials is obviously needed.

Three CRTs with sample sizes far larger (in some cases an order of magnitude larger) than the Benin trial are currently underway or have recently been completed and some early results have been reported, albeit not yet in peer reviewed publications. These trials all have similar two arm study designs comparing IRS plus universal coverage of LLINs with universal coverage of LLINs alone as the reference. Despite these similarities, initial reports do not represent a clear picture of whether the combination of LLINs with IRS provides additional protection compared to LLINs alone. In a trial in the Gambia the combination of IRS using DDT with universal coverage of LLINs provided no added protection against incidence of clinical malaria compared to universal coverage of LLINs alone.[22] In contrast to this, early results reported from a trial in western Tanzania showed that there was some evidence of added protection against malarial infection in the study arm in which IRS with Bendiocarb was combined with universal coverage of LLINs, again relative to LLINs alone, at universal coverage.[23] In a very large CRT in Sudan, early indications are that there is no added protection against plasmodial infection or clinical malaria resulting from combining IRS and high coverage LLIN use compared to the reference of LLIN alone (unpublished data).

When the details of these trials have been published it will be important to analyse carefully what could explain the contrasting conclusions they appear to point to and why they differ in some cases from some of the earlier observational studies. Differences in LLIN usage rates and factors such as inadequate insecticide residual or insecticide resistance would be high on the list of possible explanations that will have to be investigated. It is particularly important, and particularly difficult, to develop methods to measure selection for resistance by alternative strategies and products in village-scale trials. We are only just starting to build a body of field-trial evidence on combination interventions for malaria vector control, and methods for evaluating resistance management strategies are even less well developed. The village-scale trial approaches that we used so successfully in the early days with LLINs will no doubt be useful, but we need to gain more experience, and in some cases to go back to methodological first principles, in order to modify these established methods to our new purposes.

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