Subject strapline: Public Health

Malaria nets shape up for resistance

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Standfirst

Adding a flap on the top of an insecticide-treated bednet helps to intercept blood-seeking mosquitoes, and allows a wider range of insecticides to be used together. Net-buyers must now make a challenging decision for each target area: which net-product will be most cost-effective, given the resistance in the local vectors?

(274 words)

Main text

The technology of LLINs – long-lasting insecticidal nets - has been remarkably successful, however you measure success. A series of field-trials in the 1990s demonstrated that insecticide-treated nets were remarkably effective at preventing all-cause mortality in under-five children, and a subsequent economic analysis showed that they were as cost-effective as measles vaccine, as a child-survival intervention[1]. This was remarkable, because at the time, measles vaccine was regarded as a gold standard of cost-effectiveness. It led to massive investment in increasing coverage, through the Global Fund, the President's Malaria Initiative, and UNICEF[2]. In Africa, coverage has increased from less than 2% in the year 2000 to more than 50% by 2017[3], and a project tracking LLIN supplies to malaria control programmes recently announced the delivery of the two-billionth LLIN[4]. This scaling-up, together with standardisation of designs and sizes, has contributed to a reduction in the mean unit price of a conventional pyrethroid-treated LLIN, which has come down from about USD$4.50 in 2006-9 to about $2.50 per LLIN in 2013-6[5]. Nevertheless, LLINs remain the largest single item in most malaria budgets: for example, the commodity costs of LLINs represented more than 42% of the total expenditure on malaria by the Global Fund in 2010[2].

The resulting public health impact has been equally impressive. According to WHO, the scaling up of coverage of modern malaria interventions from 2000 to 2015 prevented approximately six million deaths due to malaria, mostly among young children in tropical Africa[6]. A separate analysis found that LLINs were responsible for the bulk of the decline in malaria burden during the same period: 68% was due to LLINs, the remainder to other forms of vector control, improved drugs and case management, etc.[7].

However, increased coverage also had another effect: it accelerated the evolution of insecticide resistance in the African vectors. Resistance is present widespread, and in some places, the dose needed to kill the local mosquitoes is now several hundred-fold higher than it would be in the absence of resistance[8]. In the African region, insecticide resistance is by far the most dangerous threat facing malaria control: the achievements described above are at risk and could be lost.

In response to this threat, the WHO developed the ‘GPIRM’, the Global Plan for Insecticide Resistance Management in malaria vectors. The GPIRM offers strategic recommendations about how to deploy products containing new non-pyrethroid insecticides, alone or in combination with conventional pyrethroids, in order to preserve susceptibility and slow down the evolution of resistance. The first problem is finding non-pyrethroid insecticides that are both safe and effective as a net-treatment. Some well-known insecticides, developed originally for agriculture, are effective enough against the mosquitoes, but too toxic to be used in fabric that will surround sleeping children, and lie in close contact with their faces[9]. A clever idea to address this problem has been investigated by Murray et al, and their findings are reported in this issue of Nature Microbiology[10].

This idea arises from previous studies, carried out by Phillip McCall’s team in the Liverpool School of Tropical Medicine. They used video to describe how female mosquitoes approach a mosquito-net with a person inside. These studies suggested that the approach route is typically downward from above: the mosquito makes initial contact with the roof, and then tracks sideways across the roof. Their simple innovation was to attach a vertical flap or baffle of netting to the roof of the net, which acts as a barrier to, and therefore tends to be contacted by, insects tracking sideways across the top of the net (Figure 1). McCall and colleagues painstakingly identified the most cost-effective size, shape and orientation, and then compared the performance of the modified nets to that of ordinary nets in experimental huts. It was observed that the addition of a barrier treated with fenitrothion (an organophosphate) to an ordinary pyrethroid-treated LLIN produces a substantial increase in the proportion of female mosquitoes that are killed as they seek a meal inside the experimental hut. The researchers then used this data to predict that if the new design nets were deployed, and if the performance-improvements in ordinary houses were as good as those seen in experimental huts, then substantial epidemiological benefits would be expected.

Some caveats must be mentioned. Experimental huts try to replicate the conditions in ordinary houses, but they do so imperfectly. In particular, it seems possible that horizontal air movement in ordinary houses may be both larger and more variable than in experimental huts. Also, it would probably be preferable to use a different insecticide: there are other organophosphates that are less malodorous and have a better reputation for safety in practical spraying programmes. Moreover, nets are often taken down for washing, and may be used as a sheet for sleeping on or under, leading to at least some direct contact with the insecticide on the barrier. There would have to be a formal risk assessment, using WHO-recommended methods, to take such additional exposures into account.

The evolution of LLINs, as a technology, has so far been relatively simple. Stage 1 was the ITN, the insecticide-treated net, which was treated in the field by dipping in an emulsion of insecticide. Unfortunately, ITNs need to be re-dipped annually, and in practice, this rarely happened. The first LLINs, which were designed to last 3 years without the need for re-treatment, appeared in the early 2000s. WHO soon developed standards and specification to define what an LLIN is, and it then suggested that public health agencies should give up ITNs and buy only WHO-recommended LLINs. Since these standards were fixed, there has been conspicuously little further technological evolution in LLIN design. With most paradigm-changing technologies, the process of becoming widely adopted is accompanied by rapid and substantial technical evolution, through incremental improvement and adaptation. In the case of LLINs, this process seems to have been constrained.

The Global Fund is the most important buyer of LLINs[2]. It relies on WHO for all technical matters, and its procurement process has no technical content. It therefore treats all WHO-recommended nets as identical, although some nets perform better than others. Durability is a conspicuous example: it is a key determinant of cost-effectiveness, and more cost-effective LLINs, that are slightly more expensive per unit but much more long-lasting, could certainly be developed. Yet manufacturers who tried to introduce such products (e.g. Bayer's Lifenet[7]) found no interest among institutional buyers. Thus, any new technical advance in net design must consider the way in which it can win market-share. The WHO does test new LLINs, comparing each new product with a set of minimum standards. However, these methods do not take any account of insecticide resistance, and there is no system to compare products with other.

A range of LLIN products, with new active ingredients, are now arriving on the scene. Most come with a higher price but also impressive claims of improved performance. The arrival of nets with roof-barriers, containing yet more insecticides, could make this range considerably wider. This is of course a very good thing from the point of view of resistance management, but it means that buyers will now face a new and bewilderingly complex choice: which product to buy for given target area? A further dimension of complexity comes from fact that the relative cost-effectiveness of alternative products depends on the resistance in the local vectors, and this also varies, both geographically and between species. Therefore, procurement decisions will need to be tailored to the local situation, and informed not only by evidence on the characteristics of alternative products, but also by data on local resistance. The system used to make such decisions will determine the future technological evolution of

LLINs. However, decisions of this kind are currently not within the mandates of either the WHO or the Global Fund.

The roof barriers on nets studied by Murray et al are clearly a good idea, but before they can become widely used, we will have to see some shift in the structures and processes by which donor-funded agencies choose which net to buy for a given target area.

Competing Interests

Jo Lines was Coordinator of the Vector Control Unit of the Global Malaria Programme, WHO Geneva, from 2009 to 2011, and during this period he led the development of the WHO's *Global Plan for Insecticide Resistance Management in malaria vectors*.

Figure legend

Figure 1. This new bednet design improves the performance of long-lasting insecticidal nets, and enables the use of new combinations of insecticides. A vertical flap containing insecticide is attached to the roof of standard nets, to intercept blood-seeking female mosquitoes attracted by the odour of, and searching for access to, the person sleeping inside the net.

(54 words, 362 characters).

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