Malaria innovations: pursuing value in an evolving market

Vector control has been a key factor in the progress towards malaria elimination.[1] From 2001 to 2015, of the 663 million cases of malaria prevented, 68% were estimated to have been due to vector control products such as long-lasting insecticide nets (LLINs).[2] This progress might be threatened, however, by insecticide resistance to pyrethroids, which are currently the main WHO-recommended chemical component of LLINs.[3] Since pyrethroid resistance was confirmed (in 60 countries in 2015),[3] the vector control market has seen unprecedented innovation, including next-generation LLINs treated with synergist components and other classes of insecticides.[4] On Oct 27, 2017, Unitaid released a call for investment proposals that aim to speed up market entry of next-generation LLINs.[5] Despite being well intentioned, this initiative does not resolve another substantial challenge that the current vector control market presents for the malaria community—namely how to establish the comparative effectiveness of next-generation vector control products.

An example of the need for this process is the case of a combination net, a pyrethroid and piperonyl butoxide (PBO) treated net. These nets target metabolic pyrethroid resistance in vectors by inhibiting the mixed function oxidases that are responsible for metabolising the insecticide.[6] Data to identify the incremental public health importance of pyrethroid-PBO nets compared with pyrethroid-only LLINs was deficient, as were funds to generate these data. An impasse in the market ensued, without clear guidance on the necessary next steps. Although a 2017 review of trial designs has now specified which outcomes are needed to identify the importance of next-generation vector methods to public health;[6] which criteria are to be met to identify incremental effectiveness against resistant vectors, and at what level the corresponding incremental cost is acceptable for the given product have not been clarified. For example, the next-generation LLINs can be deemed cost-effective for the purpose of antagonising resistance in areas of high resistance, but might not be so for universal coverage purposes.

With the arrival of other next-generation vector control products, the establishment of comparative effectiveness is becoming increasingly complex. Early on in the assessment process, the focus might have been on meeting global standards of quality, safety, and efficacy for interventions.[7] There was no impending need in the market to select one potent intervention over another on the basis of their incremental superiority per unit cost, especially when the resistance issue might have not have been as substantial. Currently, there is no established process for vector methods that incorporates the trade-offs that must be made if a next-generation method is chosen over another for a given product. In mature markets, data on cost effectiveness is essential in the appraisal of a next-generation health technology.[8] Since 2017, cost and cost-effectiveness data collection is now encouraged as part of the phase 4 process by WHO's Vector Control Advisory Group (VCAG), although according to the latest available guidance, VCAG will not draw on cost data to assess the importance of a product to public health.[9] Instead, there is a reliance on economies of scale when large volumes of product are sold. A priori collection of economic data in pragmatic randomised trials could inform price negotiations of next-generation LLINs before economies of scale are achieved. The International Decision Support Initiative (iDSI) created a guide for economic assessments as a reference for others to plan, complete, and report findings from economic evaluations so that both the approach to the analysis and the presentation of the results are coherent, transparent, and respond to the relevant decision problem.[10]

The catalytic funding initiative plans on a time-limited co-payment of the price difference between pyrethroid-only LLINs and next-generation net products while evidence on both effectiveness and cost-effectiveness is generated. We do not know when this limited time period will end, or how the evidence generation conditionality will be enforced. Similarly, it is unclear how disinvestment might take place if the promise of superior results is not fulfilled. Without decisive conditionality and boundaries, top-up funding like the catalytic investment is an impromptu added force that could skew the risk-bearing balance within the malaria vector control market. It might signal to manufacturers that there are enough funds in the LLIN market, irrespective of evidence on incremental effectiveness, to justify higher product costs. In turn, this knowledge could disincentivise price negotiations,

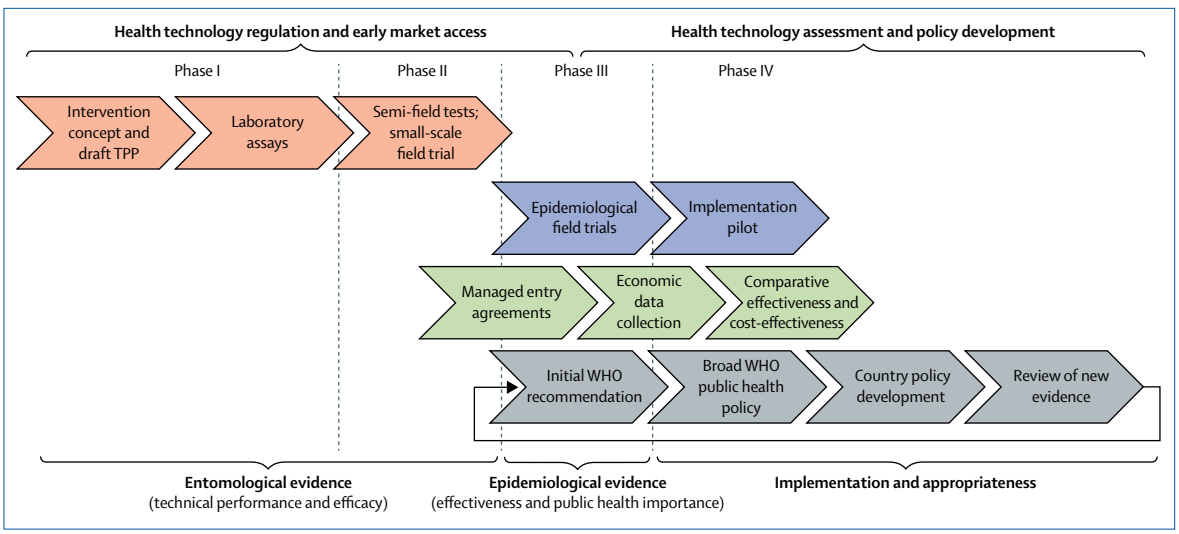

Figure: **Considerations for the prequalification pathway**
Constructed from domains of health technology regulation, assessment, and management. Adapted with permission from WHO pathway.[11] TPP=target product profile.

making it a difficult market to function in for countries graduating from donor funding. Conversely, it could also signal uncertainty as to what evidence is needed to inform purchasing decisions or who is accountable for gathering such evidence, making further investments in research and development less likely.

Until now, there has been little need for guidelines on similar epidemiological approaches and cost effectiveness of vector control products, as pyrethroid-only LLINs were the sole option. Unitaid's funding offers a unique opportunity for much needed evidence generation on next-generation LLINs. However, it does not substitute the need for standardised, deliberative, and prescriptive processes for synthesis, appraisal, and policy translation of generated evidence to inform investment options in next-generation methods and allow a rationale for policy to be revisited and reviewed in light of new evidence. Manufacturers need to take a more proactive role to prove the added value of their next-generation vector control product. To establish the importance of incremental public health and comparative effectiveness of next-generation methods, VCAG should expand its mandate to include cost-effectiveness data in their review and expand its guidance and expertise accordingly. We have listed the potential areas of improvement according to the corresponding phases of vector control method assessment and offer a potential way forward (figure).[11]

*Debra ten Brink, Mohamed Gad, Francis Ruiz
Zoutkeetlaan 3, 2343BD Oegstgeest, Netherlands (DtB); and International Decision Support Initiative, Imperial College, St Mary's Hospital, London W2 1NY, UK (MG, FR)
debra.tenbrink@gmail.com

DtB reports personal fees from WHO, outside the submitted work. Both other authors declare no competing interests. We thank Kalipso Chalkidou for her diligent reviews and comments on this document.

1 WHO. Global technical strategy for malaria 2016–2030. Geneva: World Health Organization, 2015.
2 Bhatt S, Weiss DJ, Cameron E, et al. The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015. *Nature* 2015; **526:** 207–11.
3 WHO. World malaria report 2016. Geneva: World Health Organization, 2016.
4 WHO. Pesticide products under WHOPES laboratory and/or field testing and evaluation. 2016. http://www.who.int/whopes/Products_Under_WHOPES_Evaluation_Nov_2016.pdf?ua=1 (accessed Oct 23, 2017).
5 UNITAID. Call for proposals: catalyzing the market introduction of next-generation, long-lasting insecticidal nets (LLINs). https://unitaid.eu/call-for-proposal/catalyzing-market-introduction-next-generation-long-lasting-insecticidal-nets-llins/#en (accessed Oct 30, 2017).
6 WHO Expert Advisory Group. Design of epidemiological trials for vector control products. Geneva: World Health Organization, 2017.
7 WHO. Overview of the WHO prequalification of vector control product assessment. Geneva: World Health Organization, 2016.
8 Clement FM, Harris A, Li JJ, Yong K, Lee KM, Manns BJ. Using effectiveness and cost-effectiveness to make drug coverage decisions: a comparison of Britain, Australia, and Canada. *JAMA* 2009; **302:** 1437–43.
9 WHO. Sixth meeting of the vector control advisory group. Geneva; World Health Organization, 2017.
10 International Decision Support Initiative (iDSI). iDSI reference case for economic evaluation. 2017. http://www.idsihealth.org/resource-items/idsi-reference-case-for-economic-evaluation/ (accessed Oct 26, 2017).
11 Wilson A, Boelaert M, Kleinschmidt I, et al. Evidence-based vector control? Improving the quality of vector control trials. *Trends Parasitol* 2015; **31:** 380–90.