EPA incentive promotes novel public health use insecticides

A Two-Part Series examines the need for the incentive and explains EPA's Vector Expedited Review Voucher Guidance to Industry

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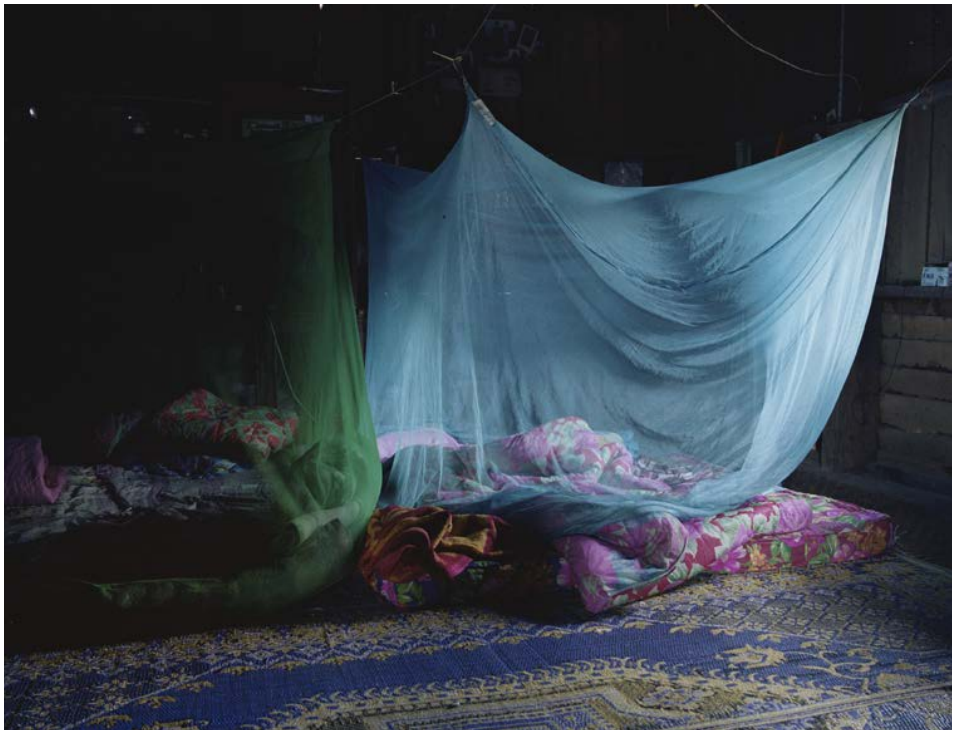

Insecticide treated bed-net. Photo: Nok Kunst https://www.flickr.com/photos/nokkunst/4519661641/

Late last year, US President Biden signed the Pesticides Registration Improvement Act of 2022. The act includes the Environmental Protection Agency's (EPA) new Vector Expedited Review Voucher (VERV) programme. VERV rewards the registrant of a new insecticide, effective against insecticide-resistant mosquitoes, with a voucher for faster review of a second, unrelated product. Faster market entry of the second product has monetary value which mitigates the typical investment costs to discover and develop a novel insecticide. VERV can also be sold. EPA must launch the new programme no later than December 29, 2023 and is currently developing guidance to industry. (Moe J, et al, 2023)

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In this two-part series, we first review the public health insecticide market and vector-borne disease conditions that inspired the US Congress to legislate the VERV programme (Part 1). Part 2 will explain EPA's industry guidance for the new VERV programme, focusing on how insecticide registrants can participate and the areas of policy clarity and uncertainty as the agency launches the new programme.

Part 1 - Underinvestment in public-health insecticides; increasing mosquito resistance

VERV was modelled after the US Food and Drug Administration's (FDA) 15-year experience with the priority review voucher (PRV) programme. A sponsor receiving FDA approval of a new treatment for selected tropical neglected diseases, rare paediatric disorders or medical countermeasures receives a voucher. The voucher can be exercised to receive priority review of a second treatment. Priority review is faster than standard review which then has value due to faster market entry.

When PRVs were sold, they fetched as much as $350 million. As the supply of vouchers has increased (due to expanded eligibility), the market value has declined to about $100 million for recent sales. FDA has awarded over 60 vouchers since PRV was launched in 2008. (www.priorityreviewvoucher.org)

PRV was an innovative policy response to the under-investment in "neglected" global diseases. Diseases like Chagas, leishmaniasis, dengue and African sleeping sickness are dubbed "neglected" (neglected tropical diseases, NTDs) because they don't attract adequate investment to discover and develop new treatments or diagnostics. Malaria is included in FDA's "neglected tropical disease" eligibility although malaria is not typically included in contemporary lists of NTDs.

Compared to the typical costs of many $100 millions for research and development, PRV value is a small, but a meaningful off-set or mitigation. Since its inception in 2008, PRV has attracted enough interest, so NTD drug sponsors maintained their product development investments with the promise of winning vouchers, often in product development partnerships (PDP).

Similarly, VERV is an innovative policy response to under-investment in public health insecticides. Public-health insecticides can be considered "neglected" too, and also bear a biological inevitability: with limited options available and increasing resistance.

There are very few vaccines and drugs which are available to prevent and/or treat vector-borne diseases and prevention through mosquito control is often more efficient than treatment. One comprehensive analysis showed that malaria cases were reduced 78% (2000 – 2015) or 663 million cases averted, through the use of insecticide treated bed nets and indoor residual spraying. (Bhatt s, et al, 2015)

But as insecticide use increases, so does resistance selection. Even when new vector

control tools are designed to reduce resistance pressure and are rotated with other insecticides, resistance development is often inevitable and insecticide efficacy declines. Resistance is highest among the pyrethroid class of insecticides because they have been widely used for nearly 20 years on insecticide-treated bed nets (ITN). Newer ITNs combine pyrethroids with chlorfenapyr or pyriproxyfen to improve efficacy against pyrethroid-resistant mosquitoes and reduce the likelihood of resistance development. But unless new insecticides are developed to work in rotation with these, rapid resistance development is highly likely.

Countries that monitor resistance are showing that other classes of insecticides used for malaria vector control, eg organochlorines, carbamates and organophosphates, show resistance some years after they have been introduced. Dual-ingredient ITNs, coupled with resistance management rotation programmes, can slow resistance. But with limited tools available resistance is somewhat inevitable and innovative new active ingredients must be discovered, developed, and commercialized in order to maintain progress against diseases such as malaria.

Policy Cures analysis on investments in anti-malarial vector products found a total of $304 million in funding over an eleven-year period (2007 – 2018) with annual investments fluctuating between $10m - $40m. The sources of the funding were primarily The Bill & Melinda Gates Foundation, a few governments (eg the UK's Foreign, Commonwealth & Development Office, formerly DFID) and a small handful of private ag/chem companies (eg BASF, Bayer, Sumitomo). These investments resulted in the introduction of the first dual-ingredient ITN, the Interceptor® G2, developed by BASF in partnership with IVCC which is an improvement in ITN performance and slows resistance (G-Funder, 2020). But compared to investments in drug treatments or vaccines, $10s of millions for vector control products annually is very small.

The introduction of new vaccines like RTSS and R21, combined with drugs, increases our hope to prevent deaths that occur from malaria. Yet, treatment and vaccine efficacy assume a background of effective vector control to reduce overall transmission of the malaria parasite. We must have effective concurrent vector control for vaccine and drug programmes to be optimal.

For agrochemical companies, public health insecticides represent a very small market relative to crop protection. In addition, the procurement environment in malaria vector control is affected by uncertainty with mainly tender-based purchasing. New innovations with novel chemistry are likely to have a higher price point than older, off-patent products and thus it is a challenge for industry to generate a return on investment in this environment.

The instability of demand makes it difficult to secure R&D investments or sustain manufacturing of insecticide products intended for public health use. Malaria represents the largest market, but also the largest burden, for mosquito insecticides and products need to pass through the WHO Prequalification process in addition to country registrations. Other mosquito-borne diseases, eg dengue or West Nile virus, are even smaller, uncertain commercial markets.

An estimated 241 million people had malaria in 2020, 95 percent of them in Africa, with 627,000 deaths occurring mostly among children under age 5. The 2021 World Malaria Report notes, "nineteen countries (20%) had made progress in reducing malaria case incidence but by less than the expected target; twenty-seven countries (29%) had increased case incidence, and 14 countries (15%) had an increase of 40% or more in malaria case incidence in 2021 compared with 2015".

These recent results show the difficulty in meeting anti-malaria targets in spite of increases in the number of persons sleeping under ITNs, 100s of millions of rapid diagnostic tests in use, and increased availability of anti-malarial medicines. Since 2020, missed performance goals in malaria are largely due to resources being diverted to respond to the global COVID pandemic.

As the COVID pandemic attenuates, we must re-build commitments to malaria treatment and vector control. Those re-commitments must respond to other pending challenges such as the potential impact of climate change. As earth's average surface temperatures rise, weather patterns modify. Mosquitoes expand their ranges into warming locations, disease transmission seasons become potentially longer, and biting behaviour changes too. Countries like the US, Italy, and Greece, that had eradicated malaria for decades, are now reporting historical anomalies: locally acquired malaria cases. (Boccolini D, et al, 2017. Jordan R, 2019)

VERV legislation authorises EPA to award a voucher upon approval of a product which:

controls insecticide-resistant mosquitoes which are vectors of selected tropical diseases including malaria,

uses a mechanism or mode of action that is different from insecticides already registered with EPA, and

can be used in interventions such as (but not exclusively) Insecticide Treated Nets and Indoor Residual Spraying.

In Part 2 we will discuss EPA's guidance to industry with particular attention to the ways registrants can participate in the new program, the issues addressed by the guidance; and those left unanswered as the program launches. ■

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