LETTERS

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Malaria in Venezuela requires response

The Americas have witnessed a substantial decline in malaria-related morbidity (62%) and mortality (61%) during the past 15 years as part of the implementation of the Global Malaria Action Plan (*1*). Venezuela, the first World Health Organization (WHO)–certified country to eradicate malaria in 1961 (*2*), has been the alarming exception in the region, displaying an unprecedented 365% increase in malaria cases between 2000 and 2015 (*1*). In 2016 alone, 240,613 malaria cases were officially reported (*3*). Worryingly, 2017 witnessed an increase of 68% in the cumulative number of cases compared to the previous year, totaling 319,765 malaria cases by 21 October (*4*). The disease has spread to areas where malaria was eradicated previously (such as near the capital, Caracas), prompting alarm in the health sector. Moreover, malaria cases have overloaded frontier health care infrastructure in Brazil and Colombia, where 78 and 81%, respectively, of imported malaria cases in 2016 originated in Venezuela (*5*).

Economic and political mismanagement have precipitated a general collapse of Venezuela's health system, creating an ongoing humanitarian crisis with severe social consequences (*6*, *7*). The malaria epidemic has been fueled by financial constraints for procurement of malaria commodities (such as insecticides, drugs, diagnostic supplies, and mosquito nets) and surveillance activities, internal human migration associated with illegal gold mining, and lack of provision and implementation of services (*2, 3*). The continued upsurge of malaria in Venezuela threatens to become uncontrollable, and it is jeopardizing the hard-won gains in the Americas' elimination agenda and global malaria targets. There is an urgent need for support and action from WHO, United Nations agencies, the U.S. Agency for International Development, the Global Fund, and other international organizations to control this epidemic. Failure to address this dangerous situation may result in one of the worst malaria epidemics in the history of the Americas.

Maria Eugenia Grillet,[1]* Leopoldo Villegas,[2] José Felix Oletta,[3] Adriana Tami,[4,5] Jan E. Conn[6]

[1]Laboratorio de Biología de Vectores y Parásitos, Instituto de Zoología y Ecología Tropical, Facultad de Ciencias, Universidad Central de Venezuela, Caracas, Venezuela. [2]Asociación Civil Impacto Social, Tumeremo, Venezuela. [3]Sociedad Venezolana de Salud Pública, Caracas, Venezuela. [4]University of Groningen, University Medical Center Groningen, Department of Medical Microbiology, Groningen, Netherlands. [5]Departamento de Parasitología, Facultad de Ciencias de la Salud, Universidad de Carabobo, Valencia, Venezuela. [6]Griffin Laboratory, Wadsworth Center, New York State Department of Health, Slingerlands, NY 12159, USA.
*Corresponding author.
Email: mariaeugenia.grillet@gmail.com

Venezuelans wait outside a health center for malaria treatment in November, 2017.

PHOTO: STRINGER/REUTERS/NEWSCOM

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Integrated approach to malaria control

To sustain reductions in child mortality due to malaria, J. Hemingway argues that new public health insecticides are required ("The way forward for vector control," Perspectives, 24 November 2017, p. 998). However, because of the heavy selection pressure placed on mosquito populations, the use of new compounds will likely lead to the development of new mechanisms to resist them. Integrated vector management programs should therefore devote equal attention to noninsecticide methods.

Numerous biological control agents, from viruses to predatory fish, have been evaluated for effectiveness in controlling malaria mosquitoes. Foremost, the use of the bacterium *Bacillus thuringiensis* var. *israelensis* has substantially diminished malaria when applied to aquatic habitats, such as in urban areas of Tanzania (*1*) and highland villages in Kenya (*2*). Adult mosquitoes can also be controlled with entomopathogenic fungi (*3*). Research has focused on the development of innovative delivery platforms of fungal spores (*4*) as well as genetic modification of the fungus to increase effectiveness (*5*).

People affected by malaria often reside in poorly constructed houses with opportunities for mosquito entry. Improved housing and living conditions protect against malaria (*6*), as well as providing other health benefits, such as reducing exposure to *Culex* mosquitoes, vectors of the parasitic disease filariasis (*7*).

Lastly, manipulating mosquito behavior through exploitation of volatile infochemicals presents opportunities for pesticide-free vector control. For example, a large intervention trial using odor-baited mosquito traps removed up to 70% of the *Anopheles funestus* population, resulting in a 30% decrease in malaria (*8*).

Integration of a variety of tools for malaria control is central to the Global Vector Control Response 2017–2030 (*9*). The plan emphasizes integrated vector management as a pillar of sustainable malaria control, in addition

to engagement of communities, investments in research, and capacity building. Pesticide resistance needs to be addressed in this context, not by a narrow focus on new pesticides alone. Only with an integrated approach can we make malaria elimination a realistic target.

Constantianus J. M. Koenraadt* and Willem Takken
Laboratory of Entomology, Wageningen University, 6700 AA, Netherlands.
*Corresponding author.
Email: sander.koenraadt@wur.nl

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Response

Koenraadt and Takken argue that, in addition to finding new mosquito vector control insecticides to replace those that are currently failing due to resistance, we devote equal attention to alternative methods. We agree with the principle of reducing selection pressure on new insecticides by combining them with other robust, cost-effective, operationally viable vector control activities. The challenge lies in finding properly evaluated interventions that can be recommended for use and deployed cost-effectively in a variety of transmission settings. The alternative interventions cited by Koenraadt and Takken have never been successfully used operationally on a large scale. Although some interventions have been shown to be effective in small-scale studies, the vector control literature is awash with poorly designed intervention "trials" that are riddled with bias, lack robust controls, and have insufficient statistical power (*1*–*3*). Financial support for malaria control is already well below the investment needed for interventions that work (*1*–*3*). Reducing coverage even further by diverting resources to unproven alternative interventions is ethically unacceptable.

In 2004, the Cochrane infectious disease group began commissioning a series of systematic reviews to assess the evidence for various interventions. One review concluded that electronic buzzer devices, sold directly to the public as mosquito repellents, do not work and should not be used to reduce mosquito bites or malaria infection rates (*1*). The 2013 review on larval source management, which assessed all published and unpublished data from 1900 to 2012, located only 13 studies of sufficient quality to include in the assessment. The authors concluded that larval source management is a valid policy option in limited situations where sufficient breeding sites can be targeted. However, they pointed out that further research is still needed to evaluate larval source management feasibility in rural Africa (*2*).

The review on larvivorous fish (2013) concluded that there were no reliable studies demonstrating an impact on malaria infection rates in nearby communities and that all the studies reporting reductions in mosquito numbers had a high risk of bias. The evidence for use of fish was insufficient to recommend their use (*3*). The review on larvicides, which will include *Bacillus thuringiensis* var. *israelensis*, was commissioned in 2017, and the protocol for the study search has been published (*4*). It remains to be seen how many of the publications on larval interventions are sufficiently robust and lacking in bias to warrant inclusion.

Other potential interventions, such as entomopathogenic fungi, are not yet at the point where the evidence can be sensibly evaluated. The fatal flaw in this intervention, which has yet to be overcome despite the efforts of several groups, is the inability of the spore formulation to survive for any significant periods of time at tropical storage temperatures, severely limiting its shelf life.

A few interventions, such as odor-baited traps and house eave tubes, are entering large-scale trials, most with substantial funding from the Bill and Melinda Gates Foundation (*5*). These trials take several years and will need to be completed before they generate the evidence that may allow them to be recommended for wide-scale operational use.

Reviews on long-lasting nets (2004) and indoor residual spraying (2010) supported the use of these interventions (*6*, *7*). Therefore, limited resources should be directed to these solutions.

Janet Hemingway
Liverpool School of Tropical Medicine, Liverpool L3 5QA, UK. Email: janet.hemingway@lstmed.ac.uk

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