

Health Affairs

At the Intersection of Health, Health Care and Policy

Cite this article as:

David B. Ridley, Jeffrey L. Moe and Nick Hamon
A Voucher System To Speed Review Could Promote A New Generation Of
Insecticides To Fight Vector-Borne Diseases
Health Affairs 36, no.8 (2017):1461-1468
doi: 10.1377/hlthaff.2016.1640

The online version of this article, along with updated information and services, is
available at:

<http://content.healthaffairs.org/content/36/8/1461>

**For Reprints, Links &
Permissions :**

http://content.healthaffairs.org/1340_reprints.php

Email Alertings : <http://content.healthaffairs.org/subscriptions/etoc.dtl>

To Subscribe : <https://fulfillment.healthaffairs.org>

Health Affairs is published monthly by Project HOPE at 7500 Old Georgetown Road, Suite 600, Bethesda, MD 20814-6133. Copyright © by Project HOPE - The People-to-People Health Foundation. As provided by United States copyright law (Title 17, U.S. Code), no part of may be reproduced, displayed, or transmitted in any form or by any means, electronic or mechanical, including photocopying or by information storage or retrieval systems, without prior written permission from the Publisher. All rights reserved.

Not for commercial use or unauthorized distribution

By David B. Ridley, Jeffrey L. Moe, and Nick Hamon

ANALYSIS & COMMENTARY

A Voucher System To Speed Review Could Promote A New Generation Of Insecticides To Fight Vector-Borne Diseases

DOI: 10.1377/hlthaff.2016.1640
HEALTH AFFAIRS 36,
NO. 8 (2017): 1461-1468
©2017 Project HOPE—
The People-to-People Health
Foundation, Inc.

ABSTRACT Many in the scientific community are concerned about the potential increase in prevalence of insect-borne diseases such as Chagas disease, Chikungunya, dengue fever, malaria, and Zika in the United States and around the world. Beyond vaccines and drugs to prevent and treat these diseases, a comprehensive approach to fighting these diseases should include control of disease-carrying vectors, such as mosquitoes. Vector-control methods, such as using insecticides to treat bed nets and spray the walls of homes, have prevented millions of deaths from malaria. However, mosquitoes are becoming resistant to insecticides, and no new class of insecticides for vector control has been introduced in decades. We recommend the creation of a new type of incentive for the development and commercialization of safe new insecticides: a Vector Expedited Review Voucher, to be awarded to a sponsor that introduces a novel insecticide for public health use. The voucher could be redeemed to expedite registration of a second, more profitable, product by the US Environmental Protection Agency.

David B. Ridley (david.ridley@duke.edu) is faculty director of health sector management at the Fuqua School of Business, Duke University, in Durham, North Carolina.

Jeffrey L. Moe is a professor of the practice of global health at the Duke Global Health Institute, in Durham.

Nick Hamon is CEO of the Innovative Vector Control Consortium, in Liverpool, United Kingdom.

Vector-borne illnesses such as Chagas disease, Chikungunya, dengue fever, malaria, schistosomiasis, yellow fever, West Nile virus, and Zika could become more prevalent in the United States and around the world due to globalization and global climate change.¹ These diseases are already widespread in many countries. For example, malaria is estimated to have killed 429,000 people in 2015.²

Vaccines and drugs are important tools for preventing and treating infectious diseases, but they are insufficient.³ A comprehensive approach to fighting infectious diseases would include training for community health workers; education for communities; and control of disease-carrying vectors, including mosquitoes, fleas, ticks, sandflies, and freshwater snails. Vec-

tor-control methods, such as insecticides to treat bed nets and to spray the walls of homes, have reduced malaria transmission and prevented millions of deaths.^{4,5} However, greater insecticide use reduces the effectiveness of vector-control methods because insecticide-resistant mosquitoes survive, reproduce, and multiply, passing on resistant genes to their offspring.⁶ Furthermore, no new class of insecticide active ingredients has been developed for long-lasting insecticide bed net treatment in more than forty years. The limited commercial potential of novel insecticides provides insufficient financial incentive for commercial research and development.

To encourage the development and commercialization of safe new insecticides, which are under the purview of the US Environmental

Protection Agency (EPA), we recommend that a proposed Vector Expedited Review Voucher (VERV, or vector voucher) be awarded to any sponsor that develops and commercializes a novel insecticide for public health use. The voucher could be redeemed to expedite the registration with the EPA of a more profitable product intended to protect crops, as a way to encourage large agrochemical companies to invest in the development of less profitable insecticides. The VERV program would be based on the Priority Review Voucher Program of the US Food and Drug Administration (FDA) that was created by the US Congress in 2007.⁷

Background On Insecticides

Long-lasting insecticide-treated bed nets create a protective barrier for people sleeping under them, preventing the people from being bitten by mosquitos that carry malaria. The nets not only protect the sleepers under them, but they also benefit the community by killing mosquitos that carry diseases.

The only insecticides currently recommended by the World Health Organization (WHO) for use in long-lasting insecticide-treated bed nets are synthetic pyrethroids.² Developed in the 1970s for use against agricultural pests, pyrethroids act on the sodium ion channel of the insect nervous system, causing overexcitation and death due to loss of coordination and paralysis.⁸ Pyrethroid insecticides are the sole chemical class and only mechanism of action used in long-lasting insecticide-treated bed nets. In addition, pyrethroids are one of only four chemical classes of insecticides used in residual spraying inside homes to eliminate mosquitos from dwellings. Because of favorable toxicity profiles and excellent residual contact activity on insects at very low doses,⁹ pyrethroid-treated bed nets and indoor residual spraying are the two insecticide-based interventions most commonly recommended by the WHO.²

Resistance to insecticides is emerging across much of the regions of Africa, India, and Southeast Asia where malaria is endemic.² Expanded use of insecticides naturally causes increased insecticide resistance. Mosquitoes develop enzyme-response mutations, target-site mutations, and other mechanisms to detoxify insecticides for themselves. Mosquitoes that survive exposure to vector-control insecticide pass on resistant genes to future generations, thereby creating new pyrethroid-resistant mosquito populations. Although resistance can be slowed using product combinations or rotations of different chemical classes (when available), insecticide resistance will continue to evolve,¹⁰ creat-

ing a need for novel insecticide tools.¹¹

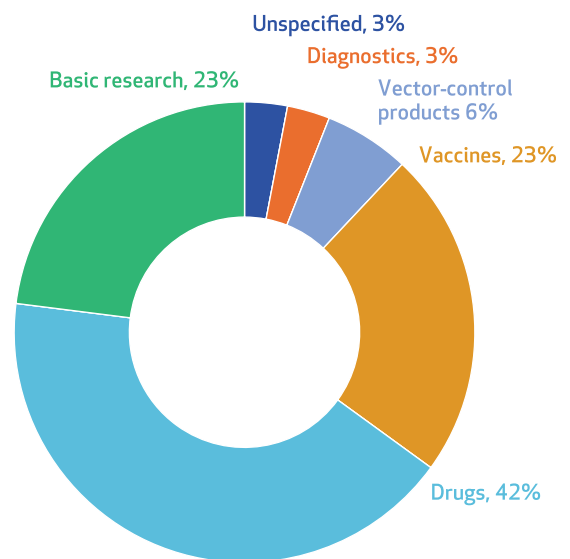
Governments, foundations, and companies invest little in vector-control research and development. For example, in 2015 only 6 percent of research and development funding for malaria was for vector-control products, whereas 65 percent was for drugs and vaccines (Exhibit 1).

According to UNITAID, “Vector control is not seen as an attractive target for investment in R&D by private industry—the sector is regarded as relatively small, high risk and price driven with low barriers to entry leading to returns on investment that are insignificant or non-existent.”¹² The vector-control market, with significantly less than \$1 billion in annual sales, is small compared to the market for agricultural chemicals, which exceeds \$47 billion in annual sales.¹³ The small size of the vector-control market limits incentives for agrochemical manufacturers to invest in the development of novel insecticide active ingredients dedicated to public health.

Additionally, the development of highly innovative products (including products that are not insecticides) is hampered by a lack of clear and efficient pathways to market, coupled with unclear utilization guidance for procurers and users about appropriate tools. Today, the development of a new crop-protection product takes more than eleven years from discovery to launch and costs an estimated \$286 million.¹⁴ Finally, governments or other large procurers typically

EXHIBIT 1

Global research and development funding for malaria, by research and product type, 2015



SOURCE Authors' analysis of data from Policy Cures. G-FINDER: neglected diseases. Sydney: Policy Cures; 2016 [cited 2017 Jun 22]. Available from: <http://policycures.org/gfinder.html>.

The EPA should require the sponsor of a new vector-control product to include in its application a plan for providing global access.

purchase insecticides through a public tender process, with sales frequently going to the lowest bidder rather than the product with the most public health impact. Such downward price pressure limits the commercial potential of novel insecticides.

Research and development strategies for novel insecticides vary according to the size of the firm. Small chemical manufacturers tend to repurpose existing products for new uses. They will participate in the development of vector-control products if the costs are sufficiently low to extract additional value from existing chemical agents with minimal additional investment. Conversely, large Fortune 500 crop-protection companies invest heavily in the discovery of novel agents. Vector-control products account for a small fraction of overall income and have low margins, thus diluting earnings (before interest and taxes) and making it harder to meet profit targets. Agrochemical manufacturers recognize the importance of their contribution to reaching public health goals but tend to regard the development of vector-control products as a corporate social responsibility rather than a significant source of profit or growth. A new type of market incentive could help corporate leaders justify and accelerate the development of new vector-control tools.

Vector Expedited Review Voucher Proposal

We propose a new incentive—based on the FDA's Priority Review Voucher Program for drugs intended to treat neglected diseases—to encourage the development of insecticides that reduce the spread of vector-borne diseases such as malaria, dengue fever, and Zika. Under the FDA's program, a drug sponsor receiving approval for a novel medicine to treat an eligible disease is

granted a voucher for priority review to be used for a second drug of the manufacturer's choosing. The voucher may be sold to another company, which can increase the voucher's value.¹⁵ The value of priority review for a potential blockbuster drug may be hundreds of millions of dollars because of the time value of money, the competitive effects of launching earlier relative to the competition, and a potentially longer period on the market under patent.¹⁶ Priority review is one of four types of expedited review offered by the FDA (the other three are accelerated approval, fast track, and breakthrough therapy). Priority review does not reduce requirements for safety and efficacy studies. As of the end of 2016, the FDA had awarded twelve priority review vouchers, which have been sold for as much as \$350 million.

We propose the creation of a Vector Expedited Review Voucher program. Under the program, the developer of a new insecticide active ingredient registered successfully with the EPA to control an insect vector for a targeted disease would receive a voucher for the EPA's expedited regulatory review of a second product (for example, for a plant-protection product targeted at a major crop).

The VERV would be transferable, so the company granted the voucher could sell it to another company. However, we anticipate that typically the voucher would be applied to another product in the same company's research and development pipeline, for reasons explained below.

Each VERV would involve two products. The first is the vector product (for example, a novel mosquito-control agent), and the second is the voucher product (for example, a plant-protection chemical for growing corn, to whose review the voucher is applied).

The program's proposed expedited review schedule is based on the Pesticide Registration Improvement Act (PRIA) passed by the US Congress in 2003 and most recently renewed in 2017. PRIA provides a schedule of pesticide types or uses, review times, and fees for reviews. The VERV program would reduce the review time without sacrificing scientific rigor or safety.

To be eligible for a vector voucher, a new vector-control product would have to meet three criteria. First, the product would have to contain a novel insecticide active ingredient not previously registered by the EPA or another stringent regulatory authority. An ester or salt of a previously approved active ingredient would not be eligible. Second, the product would have to meet all EPA data requirements. Third, the product would have to control a specific neglected public health vector. The EPA and the Centers for Disease Control and Prevention would collaborate

with the WHO to create and maintain a list of global public health pests that would be used to determine a product's eligibility for a VERV.

The VERV program could place increased demands on the EPA and thus could delay the review of other applications. Therefore, we propose that a sponsor seeking a VERV pay up to double the existing PRIA-established fee for reviewing the new vector product. Increasing the fee would provide the EPA with the resources to review more vector products following adoption of the VERV program, while maintaining rigor and safety. The review fee amount for the voucher product would be set according to the PRIA schedule when a VERV is redeemed.

The EPA should require the sponsor of a new vector-control product to include in its application a plan for providing global access to the product, distributing windfall profits, and ensuring that appropriate measures be taken to avoid the development of resistance by insects to the new product. The access plan would be publicly disclosed when a vector-control product was approved and updated after three years. The plan would identify the product's manufacturing location or locations (including those of any licensed third-party manufacturers), distribution and procurement processes for selected countries where the relevant disease is endemic, and the manufacturer's price for common quantities of the product.

The Regulatory Process

The EPA evaluates a product based on what it contains; where it will be used; and how it will be used, stored, and eliminated. It considers products' effects on human health, including short-term toxicity and long-term effects such as cancer and reproductive system disorders.¹⁷ Like the FDA, the EPA evaluates and approves the wording on a product's label to ensure clarity and safety. But unlike the FDA, the EPA focuses heavily on environmental effects of products—in the case of insecticides, including contamination of surface and groundwater and harm to wildlife and plants. Also, whereas the FDA awards orphan drugs seven years of market exclusivity, the EPA does not block competition in this way for the products it regulates.

Registration fees accompany the submission of products for EPA registration. The fee system, created by Congress in PRIA and reauthorized twice, is intended to offer shorter review periods for higher fees and to make the timing of the evaluation process more predictable.

The VERV program could benefit people at risk for vector-borne diseases and a wide variety of other stakeholders.

Estimating The Value Of The New Voucher

The VERV program could benefit people at risk for vector-borne diseases and a wide variety of other stakeholders. The public would benefit from lower risk for the diseases. International public health organizations would benefit from the availability of more effective products for use in developing countries. Developers of voucher products would benefit from faster EPA review. Farmers would benefit from faster access to crop-protection products using vouchers.

To determine whether the VERV program would encourage the development of new insecticides, we analyzed the potential costs and benefits of the program to a product developer. We estimated the commercial value of expedited review of the voucher product through VERV based on three effects, which we describe next.

The first effect is the direct effect of additional months of sales for the voucher (non-vector control) product. This is the expected net present value of sales for the additional months on the market. We assumed that a given voucher product would have 90 percent probability of approval (Exhibit 2), because company executives tend not to submit products for regulatory review without being confident about their approval, especially if they are using a voucher. In determining net present value, we adjusted for the opportunity cost of capital and wait time. We assumed a wait time of two years between receiving a voucher and applying for approval of the voucher product, and another year and a half for expedited review of that product (Exhibit 2), for a total of three and a half years. We assumed a discount rate of 7 percent,¹⁸ a tax rate of 28 percent, and marginal cost of 20 percent.

The second effect of additional months of sales for the product is the growth effect from moving the beginning of the sales curve earlier. Product sales gradually grow over time, so the earlier a

EXHIBIT 2**Assumptions used to estimate the value of a vector voucher for a second product**

Item	Quantity	Source
Annual sales at launch	\$200 million	Authors' analysis of Phillips McDougall (see Note 20 in text)
Annual sales growth	5%	Phillips McDougall (see Note 13 in text)
Discount rate	7%	KPMG (see Note 18 in text)
Market-share increase from 6 months faster to market	2%	Régnier and Ridley (see Note 19 in text)
Tax rate	28%	Mintz and Chen ^a
Standard regulatory review	24 months	Environmental Protection Agency website ^b and Pesticide Registration Improvement Act (PRIA) of 1993
Expedited regulatory review	18 months	Authors' assumptions
Product life	14 years	Authors' assumptions
Probability of EPA approval of the voucher (second) product	90%	Authors' assumptions
Marginal cost	20%	Authors' assumptions
Time between receiving the voucher and applying for approval of the second product	24 months	Authors' assumptions
Market share without voucher	25%	Authors' assumptions

SOURCE Authors' analysis of data from the sources listed. **NOTES** The voucher awarded for a vector product is used for a second, or voucher, product (for details, see the text). ^aMintz J, Chen D. The U.S. corporate effective tax rate: myth and the fact [Internet]. Washington (DC): Tax Foundation; 2014 Feb [cited 2017 Jun 22]. (Special Report No. 214). Available from: <https://files.taxfoundation.org/legacy/docs/SR214.pdf>. ^bEnvironmental Protection Agency [home page on the Internet]. Washington (DC): EPA; [last updated 2017 Jun 20; cited 2017 Jun 22]. Available from: <https://www.epa.gov/>.

product launches, the more its sales can grow. We assumed annual sales growth of 5 percent based on industry reports (Exhibit 2).¹³

The third effect is the competitive effect on the market from the accelerated introduction of a product. Early entrants can reduce later competitors' market share, because products reaching the market sooner than their competitors tend to lock in consumers and have a sustained greater market share.¹⁹ We assumed that under expedited review rather than standard review, a product would be approved six months earlier and gain 2 percentage points of market share, based on results from Stéphane Régnier and David Ridley.¹⁹ For example, the product sales would increase from 25 percent to 27 percent—an absolute increase of 2 percent and a relative increase of 8 percent. We assumed that the voucher product would take 8 percent of the market share from its competitor, so we increased both of the first two effects by that amount.

We expect that vouchers would be used to expedite approval of products with high potential commercial value. Hence, our assumptions were based on sales of top-selling products. We assumed annual sales at launch of \$200 million (Exhibit 2) and, as noted, annual sales growth of 5 percent, so annual sales would reach \$400 million after thirteen years. In 2010, six-

teen crop-protection products (six fungicides, six herbicides, and four insecticides) had sales above \$400 million, while four products (one fungicide, one herbicide, and two insecticides) had sales greater than \$800 million.²⁰

Possible Limitations Of A Vector Voucher Program

There are several possible concerns about the creation of a vector expedited review program. First, the program could create “windfall profits,” wherein developers receive (and profit from) vouchers for products that would have been developed anyway, as has been observed in the Priority Review Voucher Program.^{21,22} While windfalls are possible with any sort of competitive prize, they are unlikely in the vector-control market, because the public health market overall is relatively unprofitable. Recall that the vector-control market is small, with less than \$1 billion in annual sales.¹³ Furthermore, products for public health use rarely have a parallel agricultural market. This is because the ideal chemical product for agriculture lasts for only a short time and is water soluble, while the ideal chemical product for public health is long lasting and water resistant (so as to remain on a bed net for three years and stay effective for twenty

washes). Nonetheless, manufacturers should be required to submit a plan for the use of any windfall profits to the EPA.

Second, while the VERV program would reward innovation, it would not guarantee access to a new product. As described above, we recommend requiring that the developer submit a global access plan to the EPA before approval and to update the plan after three years. To avoid putting a large monitoring burden on the EPA, the agency could require that the access plan be submitted but then rely on global public health advocates to pressure the developer to implement the plan.

Third, the VERV program could impose a burden on EPA staff members, who would be expected to work faster to review a product using a VERV. However, the increased fee for reviewing a new voucher product (described above) is intended to provide the EPA with more resources, as the fee for a priority review voucher does for the FDA.

Fourth, the value of the vector program would depend on whether the EPA fairly and reliably administered the VERV program—in particular, whether the agency met expedited review time frames.

Fifth, requiring registration at the EPA might be excessively onerous if a product is not intended for use in the United States. Instead of requiring EPA registration in such cases, VERV eligibility could be contingent upon registration or listing by the vector-control group of the World Health Organization Prequalification Team or another recognized, stringent regulatory authority.

Commercial Value Of A Vector Voucher

The value of a vector voucher would depend on the speed of regulatory review and the commercial sales potential of the voucher product. For example, we estimated that the value of a vector voucher that reduced review time from 24 to 18 months would be \$77 million for a conventional pesticide with initial annual sales of \$200 million (Exhibit 3). The value of the voucher is proportional to sales, so cutting sales in half reduces the voucher value by half (though values in Exhibit 3 are not exactly double due to rounding).

If the review time were decreased not from twenty-four months to eighteen months but from eighteen months to twelve months—as would be the case for new active ingredients for food use with reduced risk (Exhibit 3)—then the value of the voucher would be somewhat greater (\$78 million), because increased sales are more valuable when they are received earlier.

We estimated that about half of the voucher value would come from the direct effect (additional months of sales). About 40 percent of the value would come from the growth effect (moving the beginning of the sales curve earlier), and less than 10 percent of the value would come from the competitive effect (accelerated introduction of a product, which takes market share away from competitors).

The value of the voucher would depend on the discount rate. At a discount rate of 10 percent,²³ the value of the voucher for a conventional pesticide with initial annual sales at launch of \$200 million would decrease from \$77 million to \$67 million, while at a discount rate of 3 percent, the value would increase to \$94 million.

EXHIBIT 3

Estimated voucher value based on varied initial annual sales, by PRIA dossier review category and timeline for conventional pesticides

PRIA dossier review category	Change in review time		Estimated voucher value (\$ millions) based on initial annual sales (\$ millions) of:		
	Current PRIA time (months)	Proposed voucher time (months)	\$100	\$200	\$400
	New active ingredient, food use	24	18	\$38	\$77
New active ingredient, food use, reduced risk	18	12	39	78	156
New active ingredient, non-food use; outdoor	21	15	39	77	155
New active ingredient, non-food use; outdoor, reduced risk	16	12	25	51	102
New active ingredient, non-food use; indoor	20	14	39	78	155
New active ingredient, non-food use; indoor; reduced risk	14	12	12	25	50

SOURCE Authors' analysis based on Pesticide Registration Improvement Act (PRIA) dossier review categories and timelines from the Environmental Protection Agency; estimated voucher values are from the authors.

We expect that vouchers would be used to expedite approval of products with high potential commercial value.

Discussion

The Priority Review Voucher Program of the FDA created incentives for the development of drugs to treat vector-borne diseases. However, drugs are not the only tools for fighting these diseases; vector control is also needed.³ Hence, we propose a Vector Expedited Review Voucher program to encourage the development of new insecticides for use in public health vector-control efforts.

We propose that the developer of a novel vector-control product be rewarded with a voucher for faster review of a second product, such as a crop-protection product. For a crop-protection product with annual sales at launch of \$200 million, launching six months earlier would be worth about \$77 million to the manufacturer. This estimate is based on an additional half-year of sales (\$100 million), reduced to account for marginal costs, taxes, the uncertainty of EPA approval, and the wait time between receiving the voucher for the vector product and using the voucher for the second product. It also accounts for moving the beginning of the sales curve earlier and taking market share from a competitor.

The voucher value for the second product could be greater than we estimated if faster review allowed that product to be launched just in time for the next growing season. Conversely, the value would be lower if the product were approved just after the window of opportunity for the current growing season.

Whereas most companies that received a priority review voucher from the FDA sold it to another company, we expect most companies that receive a VERV to retain it. In the pharmaceutical industry, a company that receives a voucher for a drug for a rare pediatric disease might sell the voucher to a company with a cho-

lesterol drug. In other words, the company that receives the voucher competes in a different space than the company that uses the voucher.¹⁵ Because in the agrochemical industry competitors are likely to be operating in the same space, an innovative company granted a vector voucher would probably use it on another product in its own pipeline. Hence, while there is a risk that the pharmaceutical market could become flooded with vouchers, thus driving their value down,¹⁶ this is less likely in the agrochemical market.

Of course, other options can address the failed market for vector-control insecticides. Programs could spur innovation by reducing development costs (“push mechanisms”) or increasing revenue (“pull mechanisms”). One example of a push mechanism would be a tax credit for research and development of new products. In the Orphan Drug Act of 1983, Congress introduced such a credit to cover half of a drug developer’s clinical trial costs.

Another push mechanism would be direct funding of research and development by nongovernmental organizations (NGOs), such as the Innovative Vector Control Consortium, with which one of the study authors is affiliated. While we expect most VERV winners to be large companies, a small company might pursue a VERV with funding support from an NGO. If the VERV were awarded to a small company, then the NGO could share in the returns from the sale of a VERV. Hence, for NGOs, the VERV program could create a virtuous cycle in which the NGO provides push-funding and then shares in some of the returns from the sale of a VERV with the funds reinvested in the development of other products.

One possible pull mechanism is an advance market commitment in which governments or private-sector donors commit to subsidizing part of the cost of a product—which would increase the manufacturer’s revenues and thus its incentive to launch the product.²⁴

The aforementioned push and pull mechanisms would be useful tools, but they would have to be funded from government or donor budgets. In contrast, the VERV program would be inexpensive because the value of a VERV would come from the difference between the costs and benefits of faster review for a product. Furthermore, the fee paid by the manufacturer is intended to reduce the burden of the expedited review on the regulator. Hence, the VERV is a low-cost tool that could complement other tools for encouraging the development of new products to fight infectious diseases on a global scale. ■

David Ridley and Jeffrey Moe received funding from the Innovative Vector Control Consortium (IVCC), in Liverpool, United Kingdom, which is funded by

foundations including the Bill and Melinda Gates Foundation. Nick Hamon is CEO of IVCC. The authors are grateful for helpful insights and edits from Greg

Ciccarelli, Mathias Mondy, and Dana Randall.

NOTES

- 1 McMichael AJ. Globalization, climate change, and human health. *N Engl J Med*. 2013;368(14):1335–43.
- 2 World Health Organization. Malaria: fact sheet [Internet]. Geneva: WHO; [updated 2017 Apr; cited 2017 Jun 22]. Available from: <http://www.who.int/mediacentre/factsheets/fs094/en/>
- 3 Mahmoud A, Zerhouni E. Neglected tropical diseases: moving beyond mass drug treatment to understanding the science. *Health Aff (Millwood)*. 2009;28(6):1726–33.
- 4 Bhatt S, Weiss DJ, Cameron E, Bisanzio D, Mappin B, Dalrymple U, et al. The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015. *Nature*. 2015;526(7572):207–11.
- 5 Hemingway J. Malaria: fifteen years of interventions. *Nature*. 2015;526(7572):198–9.
- 6 Trape JF, Tall A, Diagne N, Ndiath O, Ly AB, Faye J, et al. Malaria morbidity and pyrethroid resistance after the introduction of insecticide-treated bednets and artemisinin-based combination therapies: a longitudinal study. *Lancet Infect Dis*. 2011;11(12):925–32.
- 7 Ridley DB, Grabowski HG, Moe JL. Developing drugs for developing countries. *Health Aff (Millwood)*. 2006;25(2):313–24.
- 8 National Pesticide Information Center. Pyrethrins: general fact sheet [Internet]. Corvallis (OR): NPIC; [cited 2017 Jun 22]. Available from: <http://npic.orst.edu/factsheets/pyrethrins.pdf>
- 9 Centers for Disease Control and Prevention. Insecticide-treated bed nets [Internet]. Atlanta (GA): CDC; [last updated 2015 Dec 28; cited 2017 Jun 22]. Available from: http://www.cdc.gov/malaria/malaria_worldwide/reduction/itn.html
- 10 Tabashnik BE. Managing resistance with multiple pesticide tactics: theory, evidence, and recommendations. *J Econ Entomol*. 1989;82(5):1263–9.
- 11 Ranson H, N'guessan R, Lines J, Moiroux N, Nkuni Z, Corbel V. Pyrethroid resistance in African anopheline mosquitoes: what are the implications for malaria control? *Trends Parasitol*. 2011;27(2):91–8.
- 12 World Health Organization, UNICTAID Secretariat. Malaria vector control commodities landscape. 2nd ed. [Internet]. Geneva: WHO; 2014 Dec [cited 2017 Jun 27]. p. 2. Available for download from: <http://www.malariaeradication.org/download/file/fid/717>
- 13 Phillips McDougall. AgriService: industry overview of the 2012 market. Pathhead (UK): Phillips McDougall; 2013.
- 14 Phillips McDougall. The cost of new agrochemical product discovery, development and registration [Internet]. Pathhead (UK): Phillips McDougall; 2016 Apr [cited 2017 Jun 22]. Available from: <http://191hmt1pr08amfq62276etw2.wpengine.netdna-cdn.com/wp-content/uploads/2015/09/Matthew-Phillips.pdf>
- 15 Gans JS, Ridley DB. Innovation incentives under transferable fast-track regulatory review. *J Ind Econ*. 2013;61(3):789–816.
- 16 Ridley DB, Régnier SA. The commercial market for priority review vouchers. *Health Aff (Millwood)*. 2016;35(5):776–83.
- 17 Environmental Protection Agency. About pesticide registration [Internet]. Washington (DC): EPA; [last updated 2017 May 4; cited 2017 Jun 23]. Available from: <https://www.epa.gov/pesticide-registration/about-pesticide-registration>
- 18 KPMG. Cost of capital study 2015: value enhancement in the interplay of risks and returns [Internet]. Hamburg: KPMG AG; 2016 [cited 2017 Jun 22]. Available from: <https://assets.kpmg.com/content/dam/kpmg/pdf/2016/01/kpmg-cost-of-capital-study-2015.pdf>
- 19 Régnier SA, Ridley DB. Market watch: forecasting market share in the US pharmaceutical market. *Nat Rev Drug Discov*. 2015;14(9):594–5.
- 20 Phillips McDougall. AgriService: product analysis. Pathhead (UK): Phillips McDougall; 2011.
- 21 Kesselheim AS, Maggs LR, Sarpatwari A. Experience with the priority review voucher program for drug development. *JAMA*. 2015;314(16):1687–8.
- 22 Outtersson K, McDonnell A. Funding antibiotic innovation with vouchers: recommendations on how to strengthen a flawed incentive policy. *Health Aff (Millwood)*. 2016;35(5):784–90.
- 23 DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. *J Health Econ*. 2016;47:20–33.
- 24 Berndt ER, Glennerster R, Kremer MR, Lee J, Levine R, Weizsäcker G, et al. Advance market commitments for vaccines against neglected diseases: estimating costs and effectiveness. *Health Econ*. 2007;16(5):491–511.