Perspective Piece

Modeling Key Malaria Drugs' Impact on Global Health: A Reason to Invest in the Global Health Impact Index

Nicole Hassoun*

Department of Philosophy, Binghamton University, Binghamton, New York

Abstract. Millions of people cannot access good quality essential medicines they need for some of the world's worst diseases like malaria. The World Health Organization estimates that, in 2013, 198 million people became sick with malaria and 584,000 people died of the disease, while the Institute for Health Metrics Evaluation estimates that there were 164,929,872 cases of malaria in 2013 and 854,568 deaths in 2013. There are many attempts to model different aspects of the global burden of tropical diseases like malaria, but it is also important to measure success in averting malaria-related death and disability. This perspective proposes investing in a systematic effort to measure the benefits of health interventions for malaria along the lines of a model embodied in the Global Health Impact Index (global-health-impact.org).

A BRIEF FOR THE GLOBAL HEALTH IMPACT INDEX: MODELING MALARIA DRUGS' CONSEQUENCES AND INVESTING MORE IN MEASURING IMPACT

Millions of people suffer and die every year from diseases like malaria, but what is the impact we are having in combating this scourge?^{1–5} There are many attempts to model different aspects of the global burden of tropical diseases like malaria, but, until now, there is no measure of success in averting malaria-related death and disability due to this disease.^{6,7} To address this problem, we propose investing in a systematic effort to measure the benefits of health interventions. One such effort is embodied in the Global Health Impact Index. It evaluates key artemisinin-based combination therapies (ACTs) effects on death and disability in each country. It also aggregates the impacts of medicines in many ways—e.g., across countries and by the originator company (global-health-impact.org). It, thus, provides a picture of key global effects of pharmaceutical companies' innovations on malaria. In subsequent iterations, it can be extended over time and expanded to include the impacts of newer therapies including artesunate injections and it may also be possible to estimate effects relative to the baseline of chloroquine that is still used even in some parts of Africa where resistance is high.⁸

Understanding where we are having an impact, and where we are not, may help us better address the burden of malaria in different countries. Many countries simply lack the resources necessary to provide medicines to their population.⁹ In other cases, we may need to improve country procurement procedures and logistic distribution systems.^{10–12} There are also significant problems with drug quality in many contexts.¹³ The drugs' efficacy declines as resistance rates rise.^{14,15} To achieve full coverage, we must extend access to antimalarials. However, we also require quick and accurate diagnosis, good patient management and education, improvements in infrastructure, and control programs. There are also many things beyond existing drugs that are necessary for adequately addressing the burden of malaria—including insecticide-treated bed nets, vector control, and new means of preventing and treating the

disease. The Roll Back Malaria Partnership has set targets for reducing the burden of malaria and The Global Fund provides the resources and leadership to help people secure ACTs.^{9,14} Many other organizations, agencies, and coalitions also help combat malaria through their training, research, funding, control, and advocacy efforts. However, many challenges remain. If we know where drugs are having an impact, and where they are not, we can both extract lessons regarding best practices and see where we need to address problems that are preventing progress in fighting the disease.¹⁶

Researchers, companies, and regulators can use the index to evaluate performance, set targets, and guide the distribution of resources. They can mine the data to figure out what causes and consequences of global health innovations will have the most impact and to answer many other important questions.

THE GLOBAL HEALTH IMPACT INDEX

The Global Health Impact malaria model estimates the five most-widely recommended first-line ACTs for *Plasmodium falciparum* malaria's impact on death and disability, in 2010, using publicly available data on need, access to treatment, and efficacy. The need for different essential medicines is calculated in disability-adjusted life years (DALYs) lost to the diseases they treat. Access is an estimate of the number of people with access to treatment divided by the number of people who need treatment with each drug in each country.^{17–20} Efficacy data are estimated from a systematic review of clinical trial data provided by the World Health Organization (WHO).^{15,19} Very roughly, the impact I of drug i for disease state j in the base year (2010) in each country c , was calculated as

$$I_{icj} = d_{icj} t_{icj} e_{icj}$$

where d_{icj} represents the DALYs lost to disease state j in country c that we estimate can be averted with i ; t_{icj} the proportion of people who need treatment of j who we estimate are receiving i in c ; and e_{icj} estimated treatment effectiveness of i in c for j .^{20–22} Each drug's score is the sum of its scores in each country. To improve the index in future iterations, we will extend it over time and better estimate how many DALYs would be lost in the absence of treatment. This will require gathering data on all variables for all years from updated World Malaria Reports, Demographic and Health

*Address correspondence to Nicole Hassoun, Department of Philosophy, Binghamton University, 4400 Vestal Parkway East, Box 6000, Binghamton, NY 13902-6000. E-mail: nhassoun@binghamton.edu

FIGURE 1 Countries where drugs for malaria are averting the loss of the greatest number of malaria disability-adjusted life years (DALYs).

Survey/Multiple Indicator Cluster Survey, and the Global Burden of Disease 2013 study.^{21–23} Changing treatment guidelines will also have to be taken into account, and sensitivity analyses should be updated. More information about the current data sources along with details of the methodology/spreadsheet and sensitivity analysis results is available on the website global-health-impact.org.

It is clear from Figure 1 that the impact is highest in Nigeria, followed by the Democratic Republic of Congo and Tanzania.

The kind of information the index provides illustrates its value. First, the model suggests that key malaria drugs are, together, ameliorating about 33% of the global burden of malaria, while 67% of the burden remains unaddressed by these medicines. If these results are confirmed, there is great opportunity for policy makers, pharmaceutical companies, countries, and other stake-holders, which can help increase access to essential medicines to have a larger impact.

Second, the most impactful drugs for malaria in the current model are the ACTs artemether–lumefantrine (AL), artesunate + amodiaquine, and artesunate + sulfadoxine–pyrimethamine, as they are some of the most widely recommended drugs for uncomplicated *P. falciparum* malaria.²⁴ Even though this is so, artesunate–mefloquine, for instance, appears to have higher efficacy in the model. Policy makers should consider why the most effective drugs are not the most impactful—there are many possible explanations including price differentials, resistance patterns, and so forth.

Third, the model estimates the widely varying impact drugs are having on malaria across countries. The Global Health Index suggests that key drugs are having the largest impact on the burden of malaria in Nigeria.²⁵ Even though a small percentage of people who need the drugs are accessing them (approximately 30%), there is great need for the medicines so that they avert a lot of death and disability there. The model suggests that drugs are also having a significant impact in several other places including parts of sub-Saharan Africa, but not in other parts of the subcontinent.

Finally, according to the Global Health Index, Sanofi and Novartis hold the patent on some of the drugs that have the largest impact on the global burden of malaria.^{26–33} It is important to note, however, that companies are not the only

ones responsible for the drugs' impacts. Country-level health systems and international organizations distributing drugs have a large impact as well. The Drugs for Neglected Disease initiative played a key role, for instance, in the development of artesunate + sulfadoxine–pyrimethamine. Still, as the next section explains, aggregating drug scores by the companies holding the patents/licenses provides a mechanism for incentivizing new innovation.

MECHANISMS FOR PROMOTING POSITIVE CHANGE

If the Global Health Impact Index is expanded to many other drugs and diseases, it will provide an alternative to, but have some advantages over, the Access to Medicines Index (there are preliminary models for the other big global health scourges—tuberculosis and human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) as well as some neglected tropical diseases.^{12,33} Unlike the Access to Medicines Index, the Global Health Impact Index is focused on evaluating companies' global health impacts in a rigorous way, and not on companies' efforts or policies.³⁴

An expanded version of the Global Health Impact Index will provide a mechanism for incentivizing greater access to a wide range of essential medicines. Elsewhere, I have argued for leveraging this kind of index to give the best companies, in a given year, a Global Health Impact label to use on their products.^{35,36} There is some preliminary empirical research supporting the idea that a Global Health Impact label influences consumers' willingness to pay for products as diverse as sunscreen and pain medication (S. Chatterjee, Y. Zheng, unpublished data).³⁷ If the Global Health Impact label captures 1% of the market in generic and over-the-counter medications, it may yield more than 2 billion dollars' worth of incentive for pharmaceutical companies to increase their Global Health Impact and secure the label.³⁸ Interviews with key decision makers in pharmaceutical companies suggest that they will seriously consider this proposal, and companies with large consumer portfolios may gain a lot from using the label (N. Hassoun, J. Spinnato, C. Hough, B. Morrison, personal communication). The proposal is significantly different from

the Affordable Medicines Facility for malaria “green logo” for precertified products—which is used to control drug quality.^{39–41}

Moreover, the Global Health Impact Index can support a wide range of other initiatives—from socially responsible investment funds to fair licensing policies—where highly rated companies receive preferential access to licenses for technology from universities. Alternately, good company performance on the index might be made a condition for receiving priority review vouchers for the development of new essential medicines. If any of these initiatives are successful, the index will give companies a reason to produce new medicines and extend access on existing medicines that will save millions of lives.²⁶

If the index is expanded over time and across interventions, it is not at risk of rubber-stamping a few antimalarial medicines. Given the WHO’s T3 initiative to test, track, and treat malaria and their guidelines for antimalarial treatment, it is not surprising that a few ACTs have a large impact in the index.⁴² Perhaps it is not even surprising that AL is the most impactful drug. More than 80 countries recommend ACTs as the first-line therapy for *P. falciparum* malaria, and AL is widely used in Africa (where burden is highest).⁴³ National-level malaria control programs monitor drug efficacy, and AL is very effective.⁴⁴ However, as new drugs are developed and used (and as guidelines change), they will be incorporated into the index. Moreover, as the index develops, it can highlight the importance of new malaria medicines in light of their potential impact. Drug development takes time, and there is already evidence of resistance to ACTs developing in some places.¹⁵ As resistance rises, impact scores in the model will fall and this may help make an argument for further investment.

On the other hand, how companies will respond to differential performance across diseases is an open question. If a company performs well on the malaria index but very poorly on the HIV/AIDS index, they might abandon their HIV/AIDS program (though they will receive credit for both their malaria and HIV/AIDS drugs in proportion to their impacts). On the other hand, the company may decide to invest more in programs with more room for improvement. An expanded model that gives each disease due weight (providing something akin to the Institute for Health Metrics’ evaluation of the global disease burden) will provide an incentive for companies to have the greatest global health impact possible. Greater specialization within companies may improve global health but, if it does not, the index will not incentivize such specialization.

Even in the absence of sufficient investment to expand the model broadly, there may be nothing wrong with evaluating drugs’ performance only in addressing the burden of malaria. I believe it would be a great thing if we can reduce costs, address stockouts and logistics problems, increase funding, and improve access to ACTs around the world. Again this will require addressing different issues in different countries, but the index helps us see where we are succeeding in addressing the global burden of malaria, and where we are not, and creates an incentive to address relevant issues wherever they occur.^{10–12,17–19,38,43,45–47}

CLOSING THE KNOWLEDGE GAP

There are several ways the Global Health Impact malaria model might be refined, especially as better data become available, but one of the benefits of the model is to make

clear the gaps in global malaria surveillance efforts.^{48–50} It is important to move from data on efficacy from clinical trials to actual estimates of global effectiveness.⁴⁶ Moreover, there is reason to move beyond a model that only credits originator companies who hold, or have acquired, the patent for these drugs. There are inevitably partner firms and others that deserve credit for the drugs’ impact. By using the WHO’s global price reporting mechanism data on drug disbursement, researchers may come up with a fuller picture of where credit can be given. Having the drug scores, opens the door to other possible ways of attributing credit as well. Researchers might consider the impact of those developing different drug formulations and the impact of other organizations besides companies.

Although there are many ways of improving the Global Health Impact malaria model, it is noteworthy for providing the first global estimate of success in averting malaria deaths and disability. The model should be of interest to policy makers, researchers, companies, investors, and consumers. It will, for instance, open the door to many new ways of incentivizing companies to have a greater impact on global health. Although this will not solve all of the health problems people face, it may help many people secure essential medicines—like a new malaria vaccine—that can save millions of lives every year.

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Author’s address: Nicole Hassoun, Department of Philosophy, Binghamton University, Binghamton, NY, E-mail: nhassoun@binghamton.edu.

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