

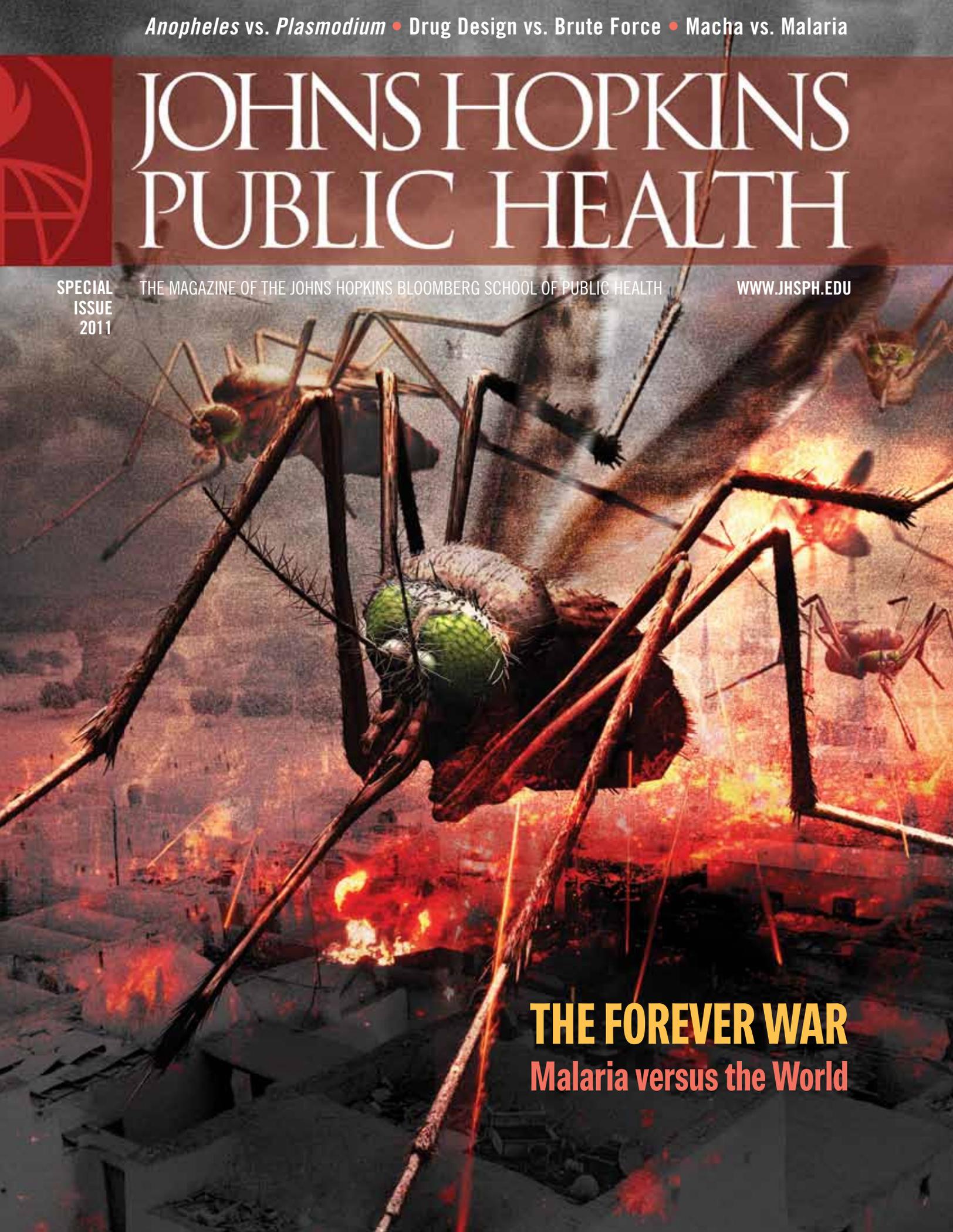
*Anopheles vs. Plasmodium • Drug Design vs. Brute Force • Macha vs. Malaria*

# JOHNS HOPKINS PUBLIC HEALTH

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**THE FOREVER WAR**  
Malaria versus the World



MICHAEL J. KLAG, MD, MPH

# Getting to Know Malaria

In medical school, I hated malaria—for all the wrong reasons.

The parasite's life cycle was complex, and I had to memorize it every time I took a standardized test. Once I took the exam, I promptly forgot all about gametocytes, sporozoites, trophozoites and other details of the *Plasmodium* parasite. After all, there were no patients with malaria in Philadelphia in the 1970s.

Then, soon after I became dean, I went to Zambia.

Quickly, I learned malaria was not merely a frustrating challenge to my memorization skills. Malaria is a killer that claims the lives of young children and pregnant women and threatens the well-being of millions. In February 2006—during the rainy season—I stood in a rural hospital in a part of southwestern Zambia called Macha. A father sat on a chair cradling his son who had just emerged from a coma caused by cerebral malaria. The little boy was blind and deaf. Despite his son's afflictions, the father was so happy to see him alive. He smiled as he fed the child spoonfuls of porridge.

I knew how lucky that boy was to have survived.

Nearly 800,000 people die from malaria every year. Despite humanity's efforts, the disease still afflicts a significant percentage of the global population in a wide belt around the equator. It is an ancient disease that's long been with us, and it is not going away anytime soon.

Malaria mostly kills children, who should have their entire lives ahead of them. They lose their lives; we lose their contributions to our world. Even those who survive malaria lose much to its repeated infections—national economies are drained of productivity and resources that could be applied to other needs.

Fortunately, in recent years, malaria has attracted unparalleled attention. The UN

Secretary-General's commitment to universal bed net coverage in sub-Saharan Africa, Bill & Melinda Gates Foundation's support for malaria research and control, the President's Malaria Initiative and the NBA's Nothing but Nets Campaign are just several diverse examples.

Closer to home, the Johns Hopkins Malaria Research Institute (JHMRI) was founded 10 years ago with a gift from Michael R. Bloomberg. That remarkable gift allowed the School to hire more faculty, build new laboratory space and establish a malaria research site in Macha, Zambia.

JHMRI founding director Diane Griffin displayed particular genius by using the complex life cycle that I had hated to memorize as a weapon against the parasite. She used it as a strategic plan for recruiting world-class researchers, each of whom would target a specific phase in the parasite's life cycle—seeking an Achilles' heel. With Diane's initial vision and Nobel laureate Peter Agre's current leadership, JHMRI's faculty are now delivering fundamental insights about the parasite and the *Anopheles* mosquito that are advancing global efforts to treat and control the disease.

As you read this issue, you will learn about their recent discoveries and promising research pathways for the future, as well as about malaria's global impact, its personal toll and its astonishing complexity.

What we do best at the School is educate bright minds, create knowledge and develop the evidence that translates into lifesaving interventions and rational policy.

JHMRI is an exemplary model of this process.

As I often tell friends and students of the Bloomberg School, we like tackling big problems that affect the health of populations. Malaria certainly fits that bill. Our goal is clear: Create the scientific basis for the eradication of malaria. ♦



MICHAEL J. KLAG

*In February 2006, I stood in a rural hospital in southwestern Zambia. A father sat on a chair cradling his son who had just emerged from a coma caused by cerebral malaria. The little boy was blind and deaf.*

## Will it be possible to eliminate or eradicate malaria?

For 30 years, the malaria “E” words were not discussed in polite company. (Elimination is the interruption of local mosquito-borne malaria transmission; eradication is the permanent reduction to zero of worldwide incidence of malaria infection.) Those who raised the possibility of country-by-country elimination, let alone global eradication, would quickly be branded as naïve dreamers and insufficiently knowledgeable about the complexities of malaria.

All that changed dramatically on October 17, 2007, when Bill and Melinda Gates called for nothing less than global malaria eradication.

However, this renewed attention does not mean that elimination in the short-to-medium term is an advisable goal for every country battling the disease. It is a worthwhile goal for countries located on the endemic margins, which have already greatly reduced malaria within their borders. We identified 32 of these countries in the recent series of papers on malaria elimination in *The Lancet*, published on November 6, 2010.

Achievement and maintenance of controlled, low-endemic malaria is the natural goal for the remaining 67 malarious countries in the malaria heartland. The task for them is to massively scale up the effective interventions and thereby reduce transmission to low levels, bring malaria mortality close to zero and greatly reduce malaria morbidity rates. When this is achieved, a discussion about elimination can begin.

We expect to see a gradual shrinkage of the malarious zone to a final battleground in the lowland, humid and tropical parts of Africa. The speed of progress will depend on the development and deployment of better drugs, better diagnostics and a series of increasingly effective vaccines. These new tools, combined with continued international support and effective program management, will propel us towards global eradication, which I believe will be achieved by roughly 2060.

*Sir Richard Feachem, DSc(Med), PhD, is the director of the Global Health Group at the University of California, San Francisco, and professor of Global Health at UCSF and UC Berkeley.*

## What is the most promising near-term approach for malaria control?

What is beginning to develop in several countries is that the use of bed nets, when applied by really good programs with coverage rates in the 70 percent range, is driving down transmission rates, as reflected by parasitemia prevalence, to levels we had not anticipated, and it potentially has the ability to change the mindset on how we approach malaria. It's not some theory; I've seen the data—it's not published yet—and it's encouraging.

The perception is, in the minds of some policy-makers and funders, that bed nets—even if used perfectly by the whole population and combined with effective drugs—do not have the intervention power to actually intervene on malaria transmission at a community-wide level. The sense is that these interventions can't get you to a place where malaria becomes so low that a program could be oriented to addressing transmission in a focal way, finding parasitemic people and treating them. And that view has been taken to the extreme of saying we need to be careful of how much money we invest in programs based on currently available interventions like bed nets. We need continued investment in both vaccine research and intervention programs.

The real challenge now is selling transmission control as a compelling near-term strategy, but it's not sexy. And the evolving evidence that current interventions have greater power to control transmission than we previously understood will help to focus research on malaria vaccines that actually block transmission.

*Carlos C. “Kent” Campbell, MD, MPH, is director of the Malaria Control Program at Program for Appropriate Technology in Health (PATH).*

## Why don't we have a malaria vaccine?

The evidence overwhelmingly supports the idea that a malaria vaccine is possible, but the advances are slow and are frequently prohibitively expensive to reproduce on a mass scale.

For example, people have been vaccinated against malaria experimentally by using attenuated forms of the parasite, but to induce an immune response, you need to use the sporozoite form of the parasite, which is derived from the salivary gland of the mosquito. So you must get the salivary gland, dissect it, take out the sporozoites, irradiate the parasites and use these forms to vaccinate. It is impractical and extremely expensive. For countries with endemic malaria, there is no way they can afford a vaccine that is made under such expensive conditions.

There has never been a successful, mass-produced vaccine against a parasite before. The challenge is to identify a way of producing and preserving billions of parasites on an industrial scale so they can be used to immunize people in endemic areas.

The alternative—and this malaria vaccine research has been going on for a couple of decades—is to identify the molecules of the parasite that the immune system can react against and try to make a synthetic vaccine that can be produced on a large scale and can be kept under relatively easy conditions without refrigeration so it can be administered in endemic areas. But there have been no successful vaccines so far that are based on the use of an isolated protein.

But I'm convinced that it [a malaria vaccine] will happen, and it should happen. The scientific basis for a malaria vaccine is stronger than for some forms of hepatitis C or HIV. I'm extremely optimistic for the long term.

*Fidel Zavala, MD, is a professor in the Bloomberg School's W. Harry Feinstone Department of Molecular Microbiology and Immunology and a faculty member of the Johns Hopkins Malaria Research Institute.*

# six experts six answers

*Interviews by Jackie Powder*



## What are history's lessons for malaria eradication?

There are a lot of lessons from the effort to eradicate malaria in the 1950s and '60s that have not been learned:

A number of pilot projects in Africa were highly successful, but in every case malaria came back in epidemic form. You can't turn your back on that reality. Once you go down that road [of eradication], you'd better sustain it. And it is extraordinarily difficult to sustain in areas where you do not have broad-based socioeconomic development.

Another lesson is: Everything takes longer than you think it's going to take. Everything costs more than you think it's going to cost. In general, in the places where they did eradicate malaria, they thought it was going to cost 50 cents per person but it turned out to be \$2 per person. When Taiwan began its eradication campaign in the early '50s, they went from 889,000 cases to 600 in 4 to 5 years, but it took another 5 or 6 years to go from 600 cases to zero—and Taiwan's an island. That sort of endgame is costly from a per-case perspective. It's much more extensive than we tend to think about.

One of the other lessons is there is never enough attention paid to the challenge of getting people to use the technology in an appropriate manner. The need to achieve buy-in in the population is a really important issue. All these social science efforts have been severely underfunded. The notion that you get 80 percent coverage with bed nets doesn't mean people are using the nets and using them properly.

The absence of adequate health services was one of the major obstacles to success of eradication in many places. Without health services, it is impossible to identify new cases and prevent the renewal of transmission. Getting people treated efficiently and effectively in a timely manner is difficult in many places in sub-Saharan Africa. We're putting a lot of energy into drugs or nets, but we're putting little into basic health services.

*Randall M. Packard, PhD, is director of the Institute of the History of Medicine at Johns Hopkins University and the author of The Making of a Tropical Disease: A Short History of Malaria.*

## How do we maintain the recent momentum in the fight against malaria?

We must treat goals, such as the UN Millennium Development Goals, as deadlines, not as so many UN targets that come and go. We're on track to meet our December 31, 2010, goal of universal bed net coverage—that's 350 million nets—in sub-Saharan Africa, thanks in part to the clear business plans and roadmaps that malaria-endemic countries developed. We're talking about countries like Nigeria, which had around 2 percent bed net coverage just a few years back, and now has 65 million nets to cover 130 million people. To get there, almost \$3 billion was raised in less than a year. Three years ago, before the Secretary-General set a 2010 deadline, none of that money existed.

We've worked with heads of state and heads of international organizations, along with leaders in the private sector, and we have also used branding, marketing and innovative use of social media to keep malaria on the public's radar screen. For instance, there was a special episode of *American Idol* last year, "Idol Gives Back," that raised over \$30 million in an hour. It shows great buy-in and awareness in the U.S. of a disease that doesn't affect anyone in this country. Our 50 "social media envoys" are exciting "opinion leaders," with at least a million followers each on Twitter.

But sprints are one thing, and marathons are another. Bed nets become ineffective and have to be replaced every three years; that's how fragile the success is. We're already seeing malaria rebound in a few countries where we had scored successes against the disease. Not one of these gains can be sustained unless African leaders take ownership of and responsibility for this effort, which is increasingly happening. I'm confident we'll win the marathon. Many people didn't think we'd get this far—we can't let these gains go to waste, not again.

*Suprotik Basu, MHS '02, is managing director of the Office of the UN Secretary-General's Special Envoy for Malaria.*

## How likely is it that the *Plasmodium* parasite will acquire resistance to artemisinin on a global scale, as it has with chloroquine?

If we control malaria, it won't. But if we don't control malaria, global resistance is inevitable, and whether that's in 1, 10 or 1,000 years we can't be sure. There is clearly evidence of resistance to artemisinin in western Cambodia, and there's a lot of talk about it having spread, but none of that is strongly evidence-based.

All the treatments for *falciparum* malaria are based on artemisinin combination therapy. The worst-case scenario is that artemisinin resistance will do what chloroquine did before it, and that would be to [lead to the deaths of] between 1 and 10 million African children. The possibility is so horrendous and awful that we should take some radical action.

One form that might take is to treat everybody in western Cambodia with antimalarial drugs to eliminate all malaria from the region. That means treating a lot of people who aren't sick and exposing a lot of people to toxicity. I'm not saying that is the right course of action or that I have all the answers by any means, but we need to get the best scientific opinions, and try and reach a consensus, and we haven't done that yet. We've basically asked people on the operational side, "What do you want to do?" And, as they are all generally doing a good job already, why would they want to take a more radical and uncomfortable course of action?

International health is very politically based. It's difficult to take executive action and move quickly, the various donors all pull strings in different directions, it's not clear who's in charge, and we just don't have the appetite for making difficult decisions. But this is a really serious problem with the potential to derail current malaria control and elimination efforts, and it may be preventable—so to do that will need a truly high-level, coherent international effort.

*Nicholas White, FRS, is chairman of the Wellcome Trust South-East Asian Tropical Medicine Research Programmes.*



# A Special Issue



The Bloomberg School has a habit of leading.

Groundbreaking discoveries and innovative solutions to public health challenges are routine for our faculty. And in the Office of External Affairs, we work hard to lead in our own way as well.

This issue of *Johns Hopkins Public Health* represents the latest example. While a single issue focused on a single disease separates this effort from previous ones, that's not the only reason this issue is special. It is also the first in our new publication schedule. We will now publish *Johns Hopkins Public Health* three times per year.

Few publications are expanding these days, and fewer still have the luxury to focus on a single topic. Our culture of mass distraction seems to demand constantly changing info bites with little context. If there is any topic that requires our long-term attention and our commitment, it is malaria. As you have read already, malaria is an ancient human enemy that still exacts a global toll of nearly 800,000 deaths every year. There are plenty of grim reminders of malaria's costs in human lives and health, and this issue does not shrink from them. (See Myaing Nyunt's personal story on the facing page.) But we also present a candid, open view of the current state of malaria research and its future promise and obstacles. With support from government as well as generous individuals and foundations, we will continue to make inroads against malaria and ultimately vanquish the disease.

At a time when publishing companies and other schools' publications are shrinking, we are ramping up. Why? Because we think it's important to share more of the remarkable public health stories that originate with our researchers and their partners here in Baltimore and around the world. I have the good fortune to meet

regularly with faculty here at the Bloomberg School and am constantly amazed by their creativity, their intellects and their world-changing research. Each of our more than 500 full-time faculty have a story to tell, an insight to share and a fresh perspective on an important public health issue.

In surveys about the magazine and in conversations with alumni and friends of the School, we have heard loud and clear that readers want to hear from us more than twice a year. So, with Dean Michael J. Klag's support, we are answering that call. Our new schedule allows us to begin each calendar year with an in-depth special issue that will illuminate a topic of prime public health importance. In May, our spring issue will feature our traditional bold mix of compelling stories from the world of public health.

You should also know that our commitment to telling the stories of public health is not limited to print. We realize the world is changing. You already can enjoy video and audio interviews on the magazine's website ([magazine.jhsph.edu](http://magazine.jhsph.edu)). And one day, you will not be reading this magazine on paper or a website but as an e-publication on an iPad or some other device yet to be invented.

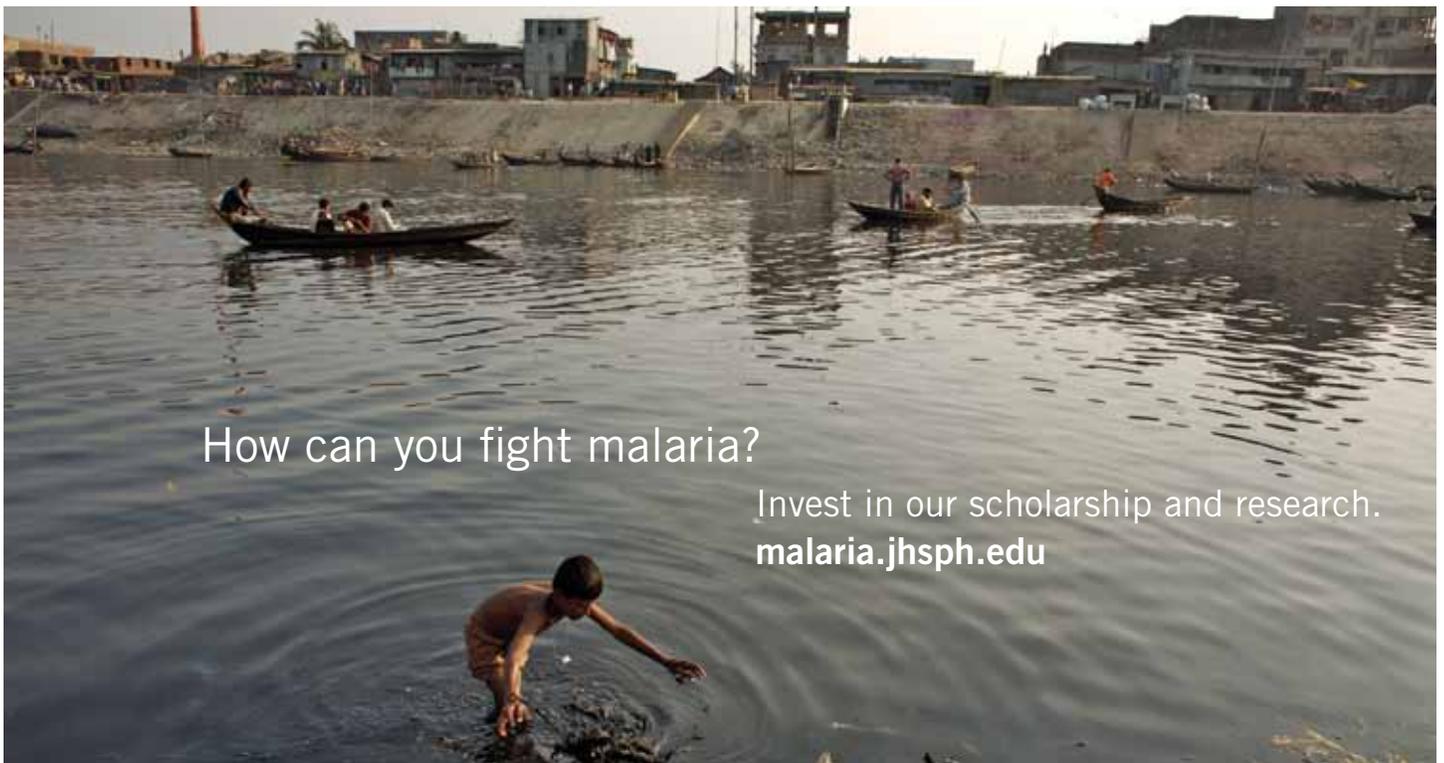
We intend to lead in that area as well.

**PAUL B. SEIFERT**

*Associate Dean, External Affairs*

*Johns Hopkins Bloomberg School of Public Health*

*[pseifert@jhsph.edu](mailto:pseifert@jhsph.edu)*



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