Transformative Tools for Malaria Elimination

Author
PATH Malaria Center of Excellence

A Report of the CSIS Global Health Policy Center

December 2014
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Transformative Tools for Malaria Elimination

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Over the past 15 years, malaria has gained increased attention and action from the public health community, with researchers, global and national funders, and, most importantly, national governments and communities in endemic areas. Renewed efforts to fight the disease have resulted in an unprecedented 50 percent reduction in malaria deaths in African children since 2000. This progress has been achieved in large part because effective, efficient, and affordable tools emerged as a result of earlier investments in research and development.

To build on momentum and stay ahead of malaria parasite and mosquito vector resistance and prevent resurgence, many endemic countries and global financing organizations are now championing the development of comprehensive country programs that expand their focus to include both reduction of malaria deaths and illnesses and elimination of malaria parasite transmission.

Advancing from malaria control (reducing malaria burden to a level where it is no longer a public health problem) to malaria elimination (reducing the incidence of malaria parasite infection to zero local transmission through targeted efforts within a defined geographical area) will require a sustained, long-term, well-planned effort to increase coverage of existing interventions. However, even optimal application of currently available tools may not be adequate to achieve elimination goals in some endemic areas. Resistance (both the

A Tale of Two Species
Although global emphasis to date has been on Plasmodium falciparum, the most lethal parasite, tools to efficiently detect and treat Plasmodium vivax, another malaria-causing species, are also critical for elimination. Although P. vivax typically leads to nonlethal infections, these parasites remain dormant in a human’s liver and can reactivate after weeks or months to cause renewed blood infections and malaria. Malaria caused by P. falciparum occurs primarily in sub-Saharan Africa, whereas malaria caused by P. vivax occurs primarily in South America, Southeast Asia, Latin America, and the Horn of Africa.

1 PATH is an international nonprofit organization that transforms global health through innovation. We take an entrepreneurial approach to developing and delivering high-impact, low-cost solutions, from lifesaving vaccines and devices to collaborative programs with communities. Through our work in more than 70 countries, PATH and our partners empower people to achieve their full potential. In 2014, the PATH Malaria Center of Excellence was launched as a mechanism to elevate PATH’s collective impact toward malaria elimination by aligning our malaria work across platforms—from diagnostics to system and service innovations to vaccines. PATH is committed to working with partners to create a malaria-free future.
parasite to drugs and the mosquitoes to insecticides), residual transmission, and the difficulty of reaching hard-to-reach populations such as those in conflict settings pose challenges to our existing arsenal of tools. Continued investments in a next generation of tools will save time and money in the long run by accelerating progress toward elimination and bringing an end to recurring costs associated with ongoing treatment and prevention of malaria.

Fortunately, exciting innovations aimed at malaria elimination needs are expected to emerge within the next 10 to 15 years. These transformative tools, combined with new approaches and strategies for their delivery, will have a dramatic impact in accelerating national and regional malaria elimination efforts. Sustained funding for development and introduction of these tools will be required, however, to ensure continuing success in the efforts to eliminate malaria.

This paper provides an overview of the next generation of transformative tools currently being developed that hold the potential to accelerate efforts toward the elimination, and eventual global eradication, of malaria.

Malaria 101

The lifecycle of a malaria parasite (Figure 1) begins when a female Anopheles mosquito takes blood from an infected person, ingesting blood containing the Plasmodium parasite sexual stages. The parasite fertilizes and matures in the mosquito’s midgut, then migrates into the salivary glands, and is injected into the skin when the mosquito bites another person. Following the mosquito’s bite, the parasite travels quickly to the liver, where it resides and multiplies for seven to ten days—without causing symptoms. Parasites then burst into the bloodstream from the liver cells, and invade red blood cells, releasing toxins that can
cause headaches, fever, joint pain, diarrhea, vomiting, exhaustion, coma, and death.

From Malaria Control to Elimination: The Iceberg

Imagine malaria burden as an iceberg. To date, efforts to prevent and control malaria have focused on the tip of the iceberg. This involves:

1. Using interventions that kill mosquitoes before they can infect humans, such as:
   - Indoor residual spraying (IRS): spraying the surface area of households with insecticides to kill mosquitoes when they land after taking blood from a human.
   - The use of long-lasting insecticide-treated bed nets (LLINs): bed nets that create a protective barrier for sleeping humans and kill mosquitoes when they are in the vicinity of the vapor created by the insecticide coming off the net.

2. Testing and treating people exhibiting symptoms of malaria with drugs.

Elimination will require new tools and strategies to address the large, asymptomatic human reservoir that currently transmits parasites to mosquitoes but goes undetected. Clearing infections from this asymptomatic population and clearing all parasites from a community ensures that mosquitoes do not become infected and that the cycle of transmission does not continue from one person to another.

The Approach to Eliminating Malaria Is Simple...yet Challenging

The basic approach to eliminating malaria is to shorten the lifespan of the mosquito and to quickly clear malaria parasites from infected people. When well-coordinated elimination interventions are implemented with high coverage, infected mosquitoes will be killed before they can transmit parasites to people, and there will be no infectious human reservoir to infect mosquitoes. Although this two-pronged approach seems fairly straightforward, developing and deploying tools that can efficiently
accomplish this in resource-constrained settings has been, and continues to be, the paramount challenge for malaria researchers and program implementers.

Game-changers

The types of innovations outlined below are being developed to shorten the mosquito lifecycle and clear malaria parasites from people. They hold the potential to dramatically accelerate efforts toward elimination.

Vector Control

Multiple new, safe, and effective insecticides are needed to replace currently used pyrethroids in order to halt the advance of insecticide resistance.

How would this transform progress toward elimination?

The use of LLINs and IRS for vector control will continue to be integral components of malaria elimination programs. New insecticides must be developed to maintain their efficacy, as increased resistance to pyrethroids has been detected in two-thirds of malaria endemic countries.

Promising leads that could be the platform for categorically more effective and durable tools:

- **New insecticide ingredients:** Nine classes of new active ingredients have been discovered that may form the basis of new insecticides. Once these are developed, vector surveillance to monitor the emergence of resistance will be critical to ensure sustained efficacy of new insecticides and inform decisions to rotate use.

- **Ivermectin:** Ivermectin, a drug used extensively in mass campaigns for elimination of lymphatic filariasis and onchocerciasis (river blindness), and used to treat a certain type of diarrhea (strongyloidiasis), is a rapidly evolving and innovative tool in malaria control. It has been shown to be a “mosquito-cide” because it kills mosquitoes that ingest human blood containing ivermectin.

Who are the key actors/developers?

Researchers at the Innovative Vector Control Consortium (IVCC) are working to select three newly identified active ingredients for insecticides for further development. Having at least three insecticides will allow for their use in rotation, so that the mosquito population does not become insecticide resistant. Research has shown that resistance emerges much more quickly when only one insecticide is used.

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6 Ibid.
million mosquitoes is naturally resistant to one insecticide, one in 100 trillion is resistant to two forms of insecticide, and only one in $10^{28}$ is resistant to three.\textsuperscript{7}

**Drugs**

There is a need for single-exposure radical cure and prophylaxis (SERCaP), a combination therapy that can radically cure all malaria lifecycle stages and species while providing post-treatment prophylaxis in a single dose.\textsuperscript{8}

*How would this transform progress toward elimination?*

To clear all parasites from the body, a process known as “radical cure,” artemisinin-based combination therapies (ACTs)—currently the fastest-working and most effective drugs to treat *P. falciparum* malaria—must be taken twice a day for three days. This difficult regimen leads to poor adherence, especially when people can feel better after taking just one day’s worth of pills. Adherence to current treatment to clear *P. vivax* malaria is also challenging because primaquine, the currently used drug, requires patients to take a 14-day course.

A new drug that requires only one dose will increase impact by eliminating the possibility that doses will be missed. A single dose also allows for directly observed treatment by a health care worker, eliminating the resource-intensive task of case follow-up.

Promising leads that could be the platform for categorically more effective and durable tools:

- **OZ439/PQP:** A drug known as OZ439/PQP is a potential next-generation combination therapy to cure uncomplicated malaria in a single dose. It could provide an alternative to artemisinin derivatives. A phase 2a trial to evaluate the efficacy and stability of OZ439 in malaria patients has defined the dose to take forward into combination studies. The new drug is expected to be effective against emerging artemisinin-resistant strains of malaria.\textsuperscript{9}

- **Low-dose gametocytocidal drugs:** Current drugs used for *P. falciparum* case management are not effective in killing gametocytes that lead to continued transmission. Low doses of primaquine kill this form of the parasite, thus potentially reducing transmission and accelerating elimination. Safety and efficacy studies are currently being conducted to assess efficacy on a programmatic level and to address concerns about adverse reactions after taking primaquine for patients with glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency.\textsuperscript{10}

\textsuperscript{7} Ibid.


\textsuperscript{10} Ibid.
• **A radical cure: tafenoquine:** Tafenoquine is a single-dose treatment for radical cure of relapsing *P. vivax* malaria. It will enable effective treatment for patients with *P. vivax* malaria, reduce the *P. vivax* reservoir, and move toward elimination of *P. vivax*. A phase 2b study conducted at seven trial sites demonstrated superiority of single-dose tafenoquine plus chloroquine compared with chloroquine alone to cure relapsing malaria. On this basis, tafenoquine entered phase 3 trials in April 2014.11

*Who are the key actors/developers?*

GlaxoSmithKline and Medicines for Malaria Venture (MMV) are collaborating in the development of tafenoquine (see website for complete list of the current pipeline).

*Diagnostics*

A highly sensitive field test is needed to rapidly detect low-density parasitemia and identify all infected individuals.

*How would this transform progress toward elimination?*

Progress toward elimination requires improving access to currently available tests and developing new, more sensitive tests that will detect asymptomatic, low-density infections. Missed infections can result in suboptimal treatment coverage and inefficient use of resources, thereby contributing to persistent regional transmission. Effective diagnostic and surveillance systems can enable tracking recurrent problem areas and the impact of interventions deployed there to ensure resources are allocated effectively.

In addition, although *P. vivax* is less likely than *P. falciparum* to lead to severe malaria and death, it is more difficult to control and eliminate since current diagnostics cannot detect the dormant liver-stage or low-level blood-stage infections. This is because *P. vivax* is more difficult to treat than *P. falciparum*. The only drugs that totally cure patients with *P. vivax* are 8-aminoquinoline drugs for which G6PD deficiency is a risk factor for drug-induced hemolysis. Consequently, safe, widespread access to these drugs requires point-of-care tests for G6PD deficiency. Separately, current tests for *P. vivax* are not very sensitive and miss a large proportion of cases. Thus, improved *P. vivax* tests are also a high priority.

Promising leads that could be the platform for categorically more effective and durable tools:

• **Isothermal nucleic acid amplification:** Recent developments in isothermal molecular diagnostics have enabled the use of traditionally laboratory-based nucleic acid detection tests in lower resource areas without sophisticated equipment and infrastructure. Loop-mediated isothermal amplification (LAMP) is one promising isothermal method that has been evaluated for sensitive detection of malaria parasite DNA.

11 Ibid.
• **Next generation rapid diagnostic tests (RDTs):** Leveraging the success of RDTs as effective control-stage diagnostics, next-generation RDTs with five to 50 times improved sensitivity are currently under development to support elimination activities. To enable identification of asymptomatic populations comprising the transmission reservoir, the Infection Detection Test (IDT) is aimed at a sensitivity ten times improved over current RDTs while maintaining a high level of ease of use and affordability.

• **Reference methods:** The proportion of low-density infections increases as regions approach elimination thus, in regions where elimination strategies call for detection and treatment of all infections, many infections will fall below the limit of detection of the current gold standard, microscopy. New reference standards that leverage the detectability of antigens, nucleic acids, and possibly other biomarkers in infections well below the detection limit of microscopy are needed to standardize the metrics of detecting low-density infections.

• **Point-of-care test for G6PD deficiency:** This test is intended to support scaling up of treatment of *P. vivax*. It may also be required for safe use of low-dose primaquine as a gametocytocidal drug. PATH and GSK are collaborating with diagnostic partners to develop point-of-care tests that meet the specifications that would support *P. vivax* case management.

**Who are the key actors/developers?**

FIND and partners are continuing to improve the utility of LAMP by improving sample preparation methods and increasing throughput. The Bill & Melinda Gates Foundation and PATH have developed partnerships to advance a portfolio of next-generation RDTs and reference methods to enable consistent standardized detection and measurement of low-density infections. PATH and partners are pioneering new methods of nucleic acid detection without electricity.

**Vaccines**

The Malaria Vaccine Technology Roadmap, updated in 2013, restates the interim goal (set in 2006) for a first-generation malaria vaccine of at least 50 percent efficacy by 2015, and targets 2030 as the date to have licensed vaccines against *P. falciparum* and *P. vivax* with at least 75 percent protective efficacy against clinical malaria and/or that reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria parasite infection.

While there is no approved malaria vaccine today, there are roughly three dozen vaccine candidates in clinical development worldwide, of which the RTS,S candidate is the most advanced in development having recently completed a large-scale, phase 3 efficacy and safety trial. Efforts to develop vaccines to interrupt malaria parasite transmission are already underway, as are efforts to develop a more highly efficacious vaccine against disease.
How would this transform progress toward elimination?

Vaccines are a highly effective public health tool. Researchers and product developers are pursuing a variety of vaccine approaches taking aim at every stage of the parasite’s lifecycle. A vaccine targeting disease and death, used alongside current prevention methods, could have a significant public health impact. The goal of elimination is prompting the development of other vaccine approaches that attempt to interrupt transmission of the parasite between humans and mosquitoes, whether by preventing infection or by stopping the parasite before it enters the human body.

What leads currently exist that could be developed?

- **RTS,S**: RTS,S, is a pre-erythrocytic vaccine candidate for prevention of clinical *P. falciparum* disease in young African children. It has completed a large-scale phase 3 efficacy and safety trial among 15,459 infants and young children. RTS,S is currently under regulatory review and subject to World Health Organization recommendation, which is expected to occur no sooner than late 2015.

- Malaria vaccines will continue to be a research priority. Development of vaccines that reduce parasite transmission and thereby substantially reduce the incidence of human malaria infection are a top research priority to accelerate elimination in multiple settings. As noted above, there are a number of vaccine candidates in clinical development, with additional earlier-stage projects moving through the pipeline. These include vaccines against *P. falciparum* and *P. vivax* malaria, with the bulk of funding going to support the former.

Who are the key actors/developers?

The PATH Malaria Vaccine Initiative (MVI) and European Vaccine Initiative (EVI) are key actors in the product development arena. Both employ a portfolio-based (rather than project-based) approach to their work, with MVI focused exclusively on malaria vaccines and EVI targeting other poverty-related or neglected diseases in addition to malaria. Among product developers, GSK is the largest corporation involved, followed by a number of other for-profit, governmental, and nonprofit organizations.

Conclusion and Recommendations for Accelerating Malaria R&D

The forthcoming World Health Organization Global Malaria Technical Strategy and Roll Back Malaria Global Malaria Action Plan II have put forth bold elimination goals to end the recurring costs associated with ongoing treatment and prevention of malaria in a number of endemic countries. A solid pipeline of innovations to accelerate progress toward malaria elimination is required to ensure that these goals are attained.
The past decade provides solid evidence of the substantial benefits of investment in malaria R&D, with investments from funders having contributed to the development of new product candidates as well as a range of products with a demonstrable health impact. Increased, sustained funding will allow for the development and introduction of more efficacious and efficient interventions that will enable elimination in endemic regions. The following recommendations can help ensure that there is a stable stream of innovations to accelerate progress toward malaria elimination:

- **Maximize investments by ensuring that U.S. agencies supporting malaria research and development (R&D) identify and fill gaps, ensuring that resources are targeted at products with the greatest potential for public health impact in low-resource settings.** Given the limited resources available, the U.S. government should focus on developing tools that meet the needs of malaria-endemic countries and that are able to meet the requirements of international normative bodies, such as the World Health Organization.

  Additionally, funding commitments should consider the timelines of product development, and products should be supported throughout the entire development lifecycle—from preclinical research through product introduction and wide-scale adoption. Commitments should also focus on coordination between scientists conducting basic research and those involved in product development to enable the translation of discoveries into products for public health impact.

  Lastly, funding for product developers employing a portfolio-based approach ensures that risks are spread across a large number of projects and that only the most promising projects advance through the pipeline. This also ensures that funding can be shifted among projects at various stages of development, as well as from a failing project to a more promising one.

- **Support mechanisms to encourage private-sector engagement in the development of new malaria innovations.** Private-sector companies have expertise and resources to contribute to malaria product development, yet a lack of commercial incentives may inhibit their involvement. Mechanisms such as product development partnerships, which are supported by several U.S. agencies, allow the expertise of the private sector and other key partners to be tapped.

  In addition to financial support for R&D, U.S. agencies can play a role in building capacity to develop, register, and scale up new malaria technologies.

- **Strengthen regulatory pathways and capacities to facilitate registration of new malaria products.** In countries most affected by malaria, weak regulatory systems can prevent products from being registered and rapidly used. Technical assistance from the U.S. Food and Drug Administration to national regulatory authorities to ensure a minimum capacity and enforceable standard of oversight could ensure quality and promote access to new malaria products. Furthermore, harmonization and capacity strengthening should encourage collaboration of poorly resourced bodies with better-resourced and more experienced regulatory authorities.

- **Strengthen endemic country health systems to enable rapid scale-up of new products.** The U.S. Agency for International Development is well-placed to support national
decisionmaking regarding the use of new malaria tools. Such efforts could help ensure timely and informed decisionmaking on adoption of lifesaving technologies as they become available.

- Support initiatives that encourage research and development in countries most affected by malaria to help ensure solutions that respond to existing and emerging needs. U.S.-supported initiatives for scientific exchange and capacity building strengthen a budding scientific infrastructure in low- and middle-income countries that will ultimately allow innovators from endemic countries to drive the development of locally led solutions.

Elimination is a challenging yet worthy goal. The approach is clear. The required new tools and technologies are currently being developed by researchers, national governments, the private sector, foundations, nongovernmental organizations, and other stakeholders. What is needed is further investment to accelerate progress toward elimination. To win this evolving battle, we must be as adaptive as the malaria parasite itself to achieve the ultimate goal of defeating malaria once and for all.
## Summary of Existing and Emerging Technologies

<table>
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<th>Approach</th>
<th>Existing technologies, tools, and interventions</th>
<th>Limitations of current technologies</th>
<th>Emerging technologies</th>
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<tr>
<td><strong>Vector control</strong></td>
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<tr>
<td><strong>Shorten the lifespan of the mosquito</strong></td>
<td>Insecticide-treated bed nets: Working at the individual level (by protecting the person sleeping under the net) and at the community level (by killing infectious mosquitoes thereby stopping onward transmission to another) Indoor residual spraying: Spraying the inside of homes with an insecticide (pyrethroids) to kill mosquitoes to stop transmission</td>
<td>Growing resistance to existing class of pyrethroids. Behavior—getting people to sleep under bed nets. Mobile populations that don’t sleep under nets or don’t have permanent structures to spray with IRS.</td>
<td>Multiple new insecticides, which are safe and effective, to replace current use of pyrethroids to stop growing insecticide resistance and be used in rotation to ensure that the mosquito population has little chance of developing future resistance.</td>
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<tr>
<td><strong>Drugs</strong></td>
<td>Artemisinin-based combination therapies (ACTs): Recommended as the first-line treatment of P. falciparum malaria; a combination of fast-acting artemisinin-based compounds (kills the majority of parasites at the start of the treatment) and a more slowly acting companion drug (clears the remaining parasites). Chloroquine: The first-line treatment for P. vivax malaria. 8-aminoquinoline-based drugs (primaquine, tafenoquine): Clears the dormant liver forms of these parasites once the parasite has been eliminated from the bloodstream (radical cure). May cause acute hemolysis in patients with G6PD deficiency. Requires a 14-day course. Intermittent preventive treatment during pregnancy (IPTp): Administration of a curative dose of sulfadoxine-pyrimethamine (SP) to all pregnant women, whether or not they are infected with the malaria parasite.</td>
<td>Adherence to multiple day drug courses.</td>
<td>Single exposure radical cure and prophylaxis (SERCaP), a combination therapy able to radically cure all malaria parasite lifecycle stages and species, while providing post-treatment prophylaxis in a single dose.12 Single exposure chemoprevention (SEC), a compound ideal for prevention that provides month-long protection against all species of malaria with a single dose, suitable for mass administration, and has a different mechanism of action to medicines used for treatment.13</td>
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12 PATH, From Pipeline to Product.
13 Ibid.
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<td>Seasonal malaria chemoprevention (SMC): The intermittent administration of full treatment courses of an antimalarial medicine to children during the malaria season.</td>
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**Diagnostics**

- **Rapid diagnostic tests (RDTs):** detect malaria parasites in 20 minutes—allowing for inexpensive, accessible, and easy diagnosis of malaria cases. Microscopy is the long-standing incumbent standard for establishing the existence and extent of disease.
- **Improved specificity and sensitivity of point-of-care diagnostics needed—especially for elimination settings.**
- **New reference methods** that do not rely on the detectability of parasites in peripheral blood are needed to identify and quantify low levels of infection.
- **Improved RDTs, particularly for non-*falciparum* species.**
- **A highly sensitive field test** that can rapidly detect even low levels of infection in blood samples and can be used to help reach elimination by detecting asymptomatic infections.
- **New reference methods** that leverage the detectability of nucleic acids and antigens in low-level infections are under development.
- **A point-of-care rapid test** to identify patients with G6PD enzyme deficiency who may have severe side effects when treated with the frontline drug.14

**Vaccines**

- **There is currently no malaria vaccine.**
- **A first-generation malaria vaccine** that has a protective efficacy of more than 50 percent against severe disease and death and lasts longer than one year is targeted by 2015.15
- **Second-generation vaccines** targeting disease, infection, and/or parasite transmission are already under development, with a target date of 2030.16

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14 Ibid.
16 Ibid.