# 8

# THE MOSQUITO AND MALARIA

## Would mosquito control alone eliminate the disease?

*Willem Takken*

In the third decade of the twenty-first century, malaria continues to be one of the world's most devastating infectious diseases, mostly in low-income countries. The disease is caused by *Plasmodium* parasites, which are transmitted between humans by mosquitoes of the genus *Anopheles*. The World Health Organization reported 228 million cases in 2018, with around 405,000 deaths. The majority of these cases occurred in tropical Africa, and most deaths were children below age five (WHO 2019). With so many new annual infections and deaths, the disease levies enormous burdens, particularly in malaria-endemic countries. It is estimated that an African household spends on average 10% of its annual income on malaria prevention and control, and that the combined economies of Africa lose US$4 billion per year due to the disease (Sachs and Malaney 2002, Shretta et al. 2016, Sarma et al. 2019). For example, the average annual cost of malaria to society was recently estimated at US$7.80 per uncomplicated case and US$107.64 per severe case in an endemic area of Mozambique (Alonso et al. 2019). Using these figures and considering all cases to be uncomplicated, malaria prevention and treatment currently cost the world some US$1.7 billion per year.

Human malaria is caused by five species of the genus *Plasmodium*, of which *Plasmodium falciparum* and *Plasmodium vivax* are most prevalent, and most responsible for the disease. *P. falciparum* is the main malaria killer, being especially virulent in non-immune people, particularly young children (White et al. 2014). The parasite has a complex life cycle, starting when infectious sporozoites are injected into the human bloodstream by the bite of an anopheline mosquito. The parasite then undergoes a series of developments in the human host to eventually develop male and female gametes, which can be found in the peripheral blood (Figure 8.1). This development process can vary from 10 to 20 days, depending on the *Plasmodium* species and condition of the human host. After male and female gametes are ingested by an anopheline mosquito, the gametes fuse into a

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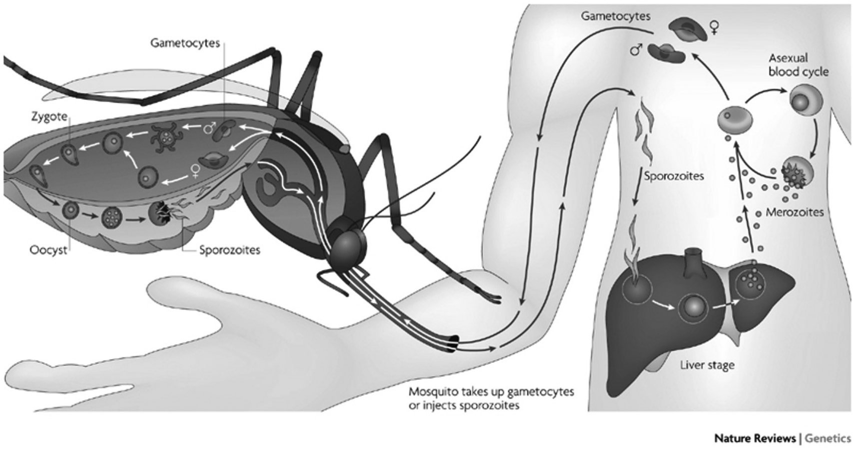


**FIGURE 8.1** *Plasmodium* life cycle (Source: Su et al., *Nature Reviews Genetics* 8: 497–506, 2007).

zygote, which subsequently develops into an oocyte. Next, oocytes migrate to the interior wall of the mosquito's midgut where they grow out into oocysts in which the sporozoites develop. After 7 to 10 days, mature oocytes burst, with the sporozoites migrating to the salivary gland, from where another mosquito bite can start the transmission cycle again (Warrell and Gilles 2002).

It was the discovery of Sir Ronald Ross in 1897 that malaria parasites developed in the mosquito which led to the realization of the importance of this creature to malaria transmission: without anopheline mosquitoes, human malaria could not exist (Ross 1900). Before Ross's discovery, malaria was generally treated by administering quinine and prevented, if possible, by temporarily vacating residences during the "fever season" for healthier areas or else draining nearby pestilential swamps thought to carry the "bad air" of malaria (Webb 2009).

## Malaria epidemiology and R0

Following his discovery of the life cycle of *Plasmodium*, and the role of mosquitoes in this process, Ross developed one of the earliest epidemiological models for the prediction of a vector-borne disease (Ross 1910). The model was based on the basic reproductive number, R0, and gave a central role to the mosquito vector. The model was further developed by McDonald (MacDonald 1957), and rapidly became a standard for the design of malaria control and prevention programmes (Figure 8.2).

The basic reproductive number, R0, represents the rate with which malaria spreads through a human community and is defined as the expected number of cases directly generated by one case in a population where all individuals

$$R = \frac{ma^2 bp^n}{-r(\ln p)}$$

Legend:

| | |
|---|---|
| ma | = human biting rate |
| b | = proportion of mosquitoes developing parasites following infective blood meal |
| n | = extrinsic incubation rate |
| p | = daily survival rate of mosquito |
| 1/r | = days of infectivity per case |

**FIGURE 8.2** Basic reproductive number of malaria (adapted from Smith et al., *PLOS Biology* 5: 531–542, 2007).

are susceptible to infection (Anderson and May 1992, Wilson et al. 2020). It is assumed in this equation that no other individuals are infected by the pathogen or immunized to the disease. When R0 is greater than 1, the number of infected individuals will increase, whereas when R0 is less than 1, the disease will die out. The mosquito is represented in the model by its human biting rate *ma* and its daily survival rate *p*. Indirectly, the *Plasmodium* infections in the mosquito, represented by factor *b* (viz. the proportion of mosquitoes developing parasites), also relate to the role of the mosquitoes in the model.[1] Given the central role of mosquitoes in the basic reproductive number, it follows that effective vector control can lead to a rapid decline of new infections, meaning that vector control is one of the pillars of combatting malaria. In the history of malaria control, many efforts have been directed at eliminating the mosquito vectors to halt the spread of the disease.

## Short history of malaria control

Until the development of affordable (synthetic) malaria drugs, the disease was treated primarily with quinine, a drug originating from the Peruvian cinchona tree that acted on the parasite itself (Rocco 2003). Following the discovery of the role of the mosquito in malaria's transmission cycle, control strategies were reoriented towards reducing human–mosquito contact. At first this was done with environmental management through the removal or modification of breeding sites. Famous examples of these were the anti-malaria works at the Panama Canal (Dehne 1955) and the environmental management methods in Malaysia and Indonesia (Watson 1921, Takken et al. 1990) where the breeding sites of malaria mosquitoes (swamps) were drained and predatory mosquito-eating fish were released in rice fields. These methods were quite effective and led to strong reductions or even local elimination of malaria.

In the 1920s, Paris Green, an inorganic insecticide containing copper acetoarsenite, was developed for mosquito control. The compound was successfully used to eradicate the invasive African malaria mosquito *Anopheles arabiensis* (*Anopheles gambiae sensu lato*) from Brazil (Killeen et al. 2002) and in 1944 it was used on a widescale for malaria control in Italy (de Zulueta 1998).

During the Second World War, the synthetic insecticide dichlorodiphenyl-trichloroethane (DDT) was introduced as a novel, effective, mosquito control tool as it could be used to kill adult mosquitoes by treating the resting sites of the mosquitoes, especially walls and ceilings in houses and stables. At the same time, the synthetic malaria drug chloroquine was developed, and both tools were used in tandem for the dramatic control of malaria in many parts of the world. Initial results were so successful that the World Health Assembly launched a global malaria eradication campaign in 1955. The campaign was highly successful in eradicating malaria from temperate climate zones, but its application in tropical climate zones proved more complicated: the enormous scale of the malaria endemic combined with a rapid development of insecticide resistance and a growing scarcity of financial resources drew the global campaign to a halt. In 1969 the campaign was officially ended, with malaria persisting in large parts of the world, many considered as low-income countries, where malaria continued to cause heavy burdens. In many countries, malaria mosquitoes had become resistant to DDT, rendering this compound and its derivatives obsolete.

The discovery in the 1970s of a new class of insecticides, the synthetic pyrethroids, led to a renewed interest in malaria vector control. It was found that bed nets treated with these new synthetics, or Insecticide-Treated Nets (ITNs), gave far better protection against malaria than untreated nets. The insecticide on the nets killed mosquitoes landing on the net, as well as deterring them (Alonso et al. 1991, Lindsay et al. 1993). Large-scale trials with ITNs in several African countries proved so successful that the World Health Organization included them in its Roll Back Malaria programme (WHO 2005).

The new global malaria eradication campaign launched in 2007 appeared hopeful, and led to a 50% reduction of global malaria, of which at least 78% was due to vector control with ITNs and indoor residual spraying (IRS) (Bhatt et al. 2015). This rapid decline of malaria since the launch of the Roll Back Malaria programme in 2000 was, however, put to a halt after 2015, with little further progress reported since then (WHO 2019). One of the reasons for this halt in progress is the rapid and widespread development of insecticide resistance, a repeat of what happened in the DDT era (Hemingway et al. 2016, Ranson and Lissenden 2016). Should the high degree of insecticide resistance in many anopheline populations be a reason to abandon vector control, even with methods that go beyond insecticides? After all, it was through vector control that the earliest successes of malaria control were achieved, with only limited successes derived from anti-malarial drugs (Bhatt et al. 2015).

## The Global Vector Control Response

Despite significant reductions in malaria achieved under the Roll Back Malaria programme, an increase in programme costs and the rapid rise in insecticide resistance, a new approach to disease vector control was required. The WHO's Global Vector Control Response (GVCR) was launched in 2017 aiming for Integrated Vector Management (IVM), which is a toolbox of mosquito control methods designed to suppress or eliminate malaria vectors (WHO 2017). The toolbox includes environmental management, house improvement, biological and rationale methods as well as insecticides. With this greater emphasis on non-chemical methods, while strategically employing novel insecticides, it is expected that resistance can be delayed and insecticides can be utilized over a longer period. The GVCR encourages intersectoral collaboration and social aspects of vector control through community engagement.

The World Health Assembly adopted the GVCR unanimously in May 2017, with member states subsequently playing an active role in adapting this latest push for improving health through their national malaria control programmes.

## Current tools for malaria vector control

- Environmental management: mosquitoes depend on aquatic sites for egg-laying and larval development. Drainage of such sites can be highly effective, but often requires engineering works which can be costly. Irrigated rice fields offer special potential as breeding sites for anopheline mosquitoes. Intermittent irrigation is another effective method for periodic killing of immature mosquitoes (Liu et al. 2004) and can be conducted at small and large scales. At the community level, removal of small puddles and water bodies in the peridomestic area has been practised as a method for malaria vector control (van den Berg et al. 2018).
- Housing improvements: many *Anopheles* species, in particular those that feed readily on humans, have developed the habit of using houses as feeding and resting sites. The most important African malaria vectors, *Anopheles gambiae sensu stricto*, *An. coluzzii* and *An. funestus,* are highly anthropophilic and take nearly all blood meals indoors during nocturnal hours. This is the reason why bed nets are such effective tools for malaria prevention (see below). Screening of doors and windows, and screening or closure of eaves, has been shown to prevent mosquito entry, and even to reduce malaria risk (Kirby et al. 2009). Housing improvement is considered an important component of malaria control and currently several studies are under way to develop this into a practical tool (Lindsay et al. 2002, Tusting et al. 2017, Mburu et al. 2018).

- Biological control: natural products or organisms that kill mosquitoes are used for biological control. These include predatory fish, pathogenic fungi and bacteria. Of the last organisms, *Bacillus thuringiensis israelensis* (*Bti*) and *Bacillus sphaericus* have been particularly popular for malaria vector control (Fillinger et al. 2009, Tusting et al. 2013, Afrane et al. 2016, Dambach et al. 2019). Such bacteria can be described as biological insecticides.
- Bio-rationale methods: these approaches for control are based on disrupting the growth and development of mosquitoes as well as their communication systems. The most widely used bio-rationale (or "biorational") tools are insect growth regulators (IGRs). These are products that mimic juvenile hormones and interfere with the growth and development of an insect. In mosquito control, common products are methoprene (Altosid®), pyriproxyfen and diflubenzuron (Dimilin®), and they are mostly used as larvicides. IGRs have been widely used for the control of nuisance mosquitoes as well as for the control of mosquitoes transmitting viruses like dengue, chikungunya and Zika. By contrast, insect growth regulators are rarely used for malaria control.
- Chemical control: despite the widespread presence of insecticide resistance in many species of malaria mosquitoes, insecticide-impregnated bed nets continue to provide good protection, albeit to a lesser degree than in the period before insecticide resistance (Yang et al. 2018). It is less clear if there will still be a role for indoor residual spraying (IRS) in future malaria programmes, as this method does not provide protection against mosquito bites, unlike bed nets, once the mosquitoes have become resistant. The Innovative Vector Control Consortium (IVCC), which consists of a network of private and public organizations, is working on the development of novel classes of insecticides and novel strategies for application of insecticides, as by combining several different classes of insecticides or combining an insecticide with a synergist (Hemingway 2017, Gleave et al. 2018). It is expected that within a few years, new chemical products will be available to replace current insecticides (Knapp et al. 2015, Killeen 2020).
- Behavioural control: mosquitoes respond to visual, acoustic and chemical cues for intra- and interspecific interactions. Knowledge of these cues can be used to manipulate the behaviour of the mosquitoes, leading to reduced vector densities and possibly vector eradication. Some behavioural control depends on mosquito gender, as outlined below.

  Male mosquitoes: males form swarms when searching for a mate using aggregation cues. These swarms can be manipulated by acoustic and chemical cues aimed at mating disruption (Cator et al. 2011, Wooding et al. 2020). Male mosquitoes feed on nectar, and toxic sugar baits have been developed to alter the mosquitoes' nectar-feeding behaviour, leading to significant reductions in mosquito populations (Traore et al. 2020).

  Female mosquitoes: female anophelines feed primarily on vertebrate blood. Vertebrate hosts are located with odorous cues emitted by the host

(Takken and Knols 1999), and synthetic odour cues that mimic a human have been employed to mass trap host-seeking mosquitoes with the aim for reducing their biting intensity and, subsequently, *Plasmodium* transmission rate. In a recent study in Kenya it was shown that mass trapping with odour-baited traps led to a 30% reduction in malaria prevalence (Homan et al. 2016). Female mosquitoes can also be manipulated to lay their eggs in selected sites, using odorant cues that attract gravid females (Lindh et al. 2015, Eneh et al. 2016, Schoelitsz et al. 2020). Such sites can be laced with a biological larvicide (*Bti*), as an alternative and efficient way of larval control.

Push-pull: repellents are compounds that deter mosquitoes so that they move away from feeding and resting zones. Currently, there is much interest in the pyrethroid compound transfluthrin, as this acts not only as an insecticide, but also as a strong repellent, disrupting the mosquito's ability to land and/or bite. Transfluthrin can be impregnated into fabrics and nettings, producing mosquito-free zones (Syafruddin et al. 2020). When repellents are combined with an attractant, a push–pull system can be created that is under investigation as a novel tool for malaria control (Menger et al. 2015, Hiscox et al. 2019, Mmbando et al. 2019).

- Genetic control: advanced technologies in molecular and cellular biology have made it possible to identify and manipulate mosquito genes that regulate specific traits of their biology (Adolfi and Lycett 2018). For example, genes that regulate reproduction can be knocked out leading to sterilization of mosquito populations. It is also possible to modify genes that increase susceptibility of *Plasmodium* infections, thus rendering mosquito populations vulnerable and unable to transmit the malaria parasite. A third genetic method relies on introducing a gene that regulates host-seeking behaviour, so that mosquitoes no longer recognize their preferred blood host. Some of these technologies are in advanced stages of development, but some are also under strong ethical scrutiny, meaning that these technologies should not be applied in the field until proven safe and acceptable to society (James et al. 2018).
- Community engagement: for decades, malaria control was undertaken as a vertically led programme, often run by national or regional public health offices. Communities were generally ill-informed as it was thought that any form of effective malaria control, conducted by the health office, was acceptable because it would lead to less morbidity and fewer deaths, and therefore was of unquestionable benefit to those communities. Public health officials were often poorly trained in public information technologies, and the community typically learned very little through their health centres about how they could obtain malaria treatment and which vector control tools would be applied. Communities were often not consulted beforehand about their own wishes or needs.

Much has changed since insecticide-treated bed nets were introduced globally (Nabarro 1999). Bed-net users needed to be instructed how to use the nets, and also how to care for their nets, with nets being especially needed for children under five years old. Public information campaigns were organized, which led to the awareness that involving the community in malaria control could be hugely beneficial. Also, the advent of the internet, mobile phones and other tools of communication have led to radical changes in the exchange of public health information. Indeed, community engagement has become one of the four pillars of the GVCR and no malaria intervention programme today can do without it (Mutero et al. 2015, Oria et al. 2015, Gowelo et al. 2020).

## Future trends and prospects

Malaria is a pernicious disease that can only be managed by integrating several tools designed to kill the parasite in malaria patients, and by preventing new infections by interrupting the transmission of *Plasmodium* parasites. As the mosquito is responsible for malaria transmission (by biting twice!), mosquito control or elimination remains central to any programme of malaria prevention until a vaccine becomes available. As discussed, insecticide-impregnated bed nets and indoor residual spraying combined with good disease diagnostics and treatment are currently the best options for malaria control (WHO 2019). Great efforts are being made to develop malaria vaccines (Wilson et al. 2019), but until effective vaccines are widely available, our best options are to continue with efforts of mosquito control combined with proper disease management (Ashley et al. 2018). Rapidly advancing resistance against common malaria drugs is a serious cause for concern (Menard and Dondorp 2017, Uwimana et al. 2020), and illustrates the urgency of developing an effective vaccine.

The control of mosquito vectors remains a solid strategy for preventing malaria. The insecticide-based methods are considered a temporary solution, as the selective pressures caused by these insecticides on the target mosquito population will inevitably result in new forms of genetic or behavioural resistance (Hemingway 2018). It is now well accepted that Integrated Vector Management should be the leading strategy for controlling malaria vectors, and this strategy is emphasized in the Global Vector Control Response (WHO 2017). New in this programme is the emphasis on, firstly, community engagement, to obtain better support from the target communities and, secondly, monitoring and surveillance, to better understand the dynamics and extent of malaria disease and its mosquito vectors.

This chapter focuses on the mosquito vector, because of its central role in the transmission of malaria parasites. In the opinion of the author, it is unlikely that malaria vectors can be eliminated completely from a region or continent because of their high resilience against interventions. It should be realized that in all places where malaria has been successfully eliminated (Europe, North America), the mosquito vectors are still around. Malaria vectors were combatted to reach temporary low levels of population density so that the parasite reservoir could be more easily cleared with case management. Similarly, in many cases today, it is feasible to reduce mosquito populations to such low densities that the *Plasmodium* reservoir drops below a threshold and can be cleared from the human population. In such areas, "anophelism without malaria" (Aitken et al. 1954), can be the mainstay for many years, with active surveillance detecting the occasional and accidental malaria reintroduction. In most malaria-endemic areas, however, this total clearance of disease appears difficult, and the malaria control strategy should be aiming for low levels of transmission, possibly with known hotspots for targeted clearance, and adequate and effective public health teams for case management and health information.

By selecting the correct tools from the available toolbox, malaria can be controlled effectively. It is expected that further development of new tools may lead to more effective management and control of malaria, possibly leading to local elimination of the disease.

As this volume goes to press, the world has been deeply affected by the emergence and impact of COVID-19. The resources for dealing with this pandemic have had serious consequences for the control programmes of other infectious diseases, in particular the neglected tropical diseases such as malaria. Indeed, it was recently predicted that if malaria activities such as case management and distribution of Long-Lasting Insecticide Nets (LLINs) is halted, the malaria burden could more than double within one year (Sherrard-Smith et al. 2020). As these malaria prevention activities are highly dependent on the availability of scarce resources, this is one more reason to switch to a control programme that is based on the IVM principle, which is more sustainable and makes malaria-endemic countries less dependent on external resources.

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## Note

1 Many readers will recognize the R0 from news about the COVID-19 pandemic; however, it is important to realize that in many malaria endemic areas, R0 is frequently greater than 5, which allows for a very rapid spread of the disease, and is proof of the difficulty faced by malaria control programmes, where R0 must be reduced to less than 1.

## Bibliography

Adolfi, A., and G.J. Lycett. 2018. Opening the toolkit for genetic analysis and control of *Anopheles* mosquito vectors. *Current Opinion in Insect Science* 30: 8–18.

Afrane, Y.A., N.G. Mweresa, C.L. Wanjala, T.M. Gilbreath, G.F. Zhou, M.C. Lee, A.K. Githeko, and G.Y. Yan. 2016. Evaluation of long-lasting microbial larvicide for malaria vector control in Kenya. *Malaria Journal* 15: 577–577.

Aitken, T.H.G., J. Maier, and H. Trapido. 1954. The status of anophelism and Malaria in Sardinia during 1951 and 1952. *American Journal of Epidemiology* 60: 37–51.

Alonso, P.L., S.W. Lindsay, J.R. Armstrong, M. Conteh, A.G. Hill, P.H. David, G. Fegan, A. de Francisco, A.J. Hall, F.C. Shenton, et al. 1991. The effect of insecticide-treated bed nets on mortality of Gambian children. *Lancet* 337: 1499–1502.

Alonso, S., C.J. Chaccour, E. Elobolobo, A. Nacima, B. Candrinho, A. Saifodine, F. Saute, M. Robertson, and R. Zulliger. 2019. The economic burden of malaria on households and the health system in a high transmission district of Mozambique. *Malaria Journal* 18: 360. https://doi.org/10.1186/s12936-019-2995-4

Anderson, R.M., and R.M. May. 1992. *Infectious Diseases of Humans: Dynamics and Control*. Oxford: Oxford University Press.

Ashley, E.A., A. Pyae Phyo, and C.J. Woodrow. 2018. Malaria. *The Lancet* 391: 1608–1621.

Bhatt, S., D.J. Weiss, E. Cameron, D. Bisanzio, B. Mappin, U. Dalrymple, K.E. Battle, C.L. Moyes, A. Henry, P.A. Eckhoff, E.A. Wenger, O. Briet, M.A. Penny, T.A. Smith, A. Bennett, J. Yukich, T.P. Eisele, J.T. Griffin, C.A. Fergus, M. Lynch, F. Lindgren, J.M. Cohen, C.L.J. Murray, D.L. Smith, S.I. Hay, R.E. Cibulskis, and P.W. Gething. 2015. The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015. *Nature* 526: 207–211.

Cator, L.J., B.J. Arthur, A. Ponlawat, and L.C. Harrington. 2011. Behavioral observations and sound recordings of free-flight mating swarms of *Ae. aegypti* (Diptera: Culicidae) in Thailand. *Journal of Medical Entomology* 48: 941–946.

Dambach, P., T. Baernighausen, I. Traore, S. Ouedraogo, A. Sie, R. Sauerborn, N. Becker, and V.R. Louis. 2019. Reduction of malaria vector mosquitoes in a large-scale intervention trial in rural Burkina Faso using *Bti* based larval source management. *Malaria Journal* 18: 311.

de Zulueta, J. 1998. The end of malaria in Europe: An eradication of the disease by control measures. *Parassitologia* 40: 245–246.

Dehne, E.J. 1955. Fifty years of malaria control in the panama area. *The American Journal of Tropical Medicine and Hygiene* 4: 800–811.

Eneh, L.K., H. Saijo, A.K. Borg-Karlson, J.M. Lindh, and G.K. Rajarao. 2016. Cedrol, a malaria mosquito oviposition attractant is produced by fungi isolated from rhizomes of the grass cyperus rotundus. *Malaria Journal* 15: 478. https://doi.org/10.1186/s12936-016-1536-7

Fillinger, U., B. Ndenga, A. Githeko, and S.W. Lindsay. 2009. Integrated malaria vector control with microbial larvicides and insecticide-treated nets in western Kenya: A controlled trial. *Bull World Health Organization* 87(9): 655–665.

Gleave, K., N. Lissenden, M. Richardson, L. Choi, and H. Ranson. 2018. Piperonyl butoxide (PBO) combined with pyrethroids in insecticide-treated nets to prevent malaria in Africa. *Cochrane Database of Systematic Reviews*, 11: CD012776.

Gowelo, S., R.S. McCann, C.J.M. Koenraadt, W. Takken, H. van den Berg, and L. Manda-Taylor. 2020. Community factors affecting participation in larval source management for malaria control in Chikwawa District, Southern Malawi. *Malaria Journal* 19: 195. https://doi.org/10.1186/s12936-020-03268-8

Hemingway, J. 2017. The way forward for vector control. *Science* 358: 998–999.

Hemingway, J. 2018. Resistance: A problem without an easy solution. *Pesticide Biochemistry and Physiology* 151: 73–75.

Hemingway, J., H. Ranson, A. Magill, J. Kolaczinski, C. Fornadel, J. Gimnig, M. Coetzee, F. Simard, D.K. Roch, C.K. Hinzoumbe, J. Pickett, D. Schellenberg, P. Gething, M. Hoppe, and N. Hamon. 2016. Averting a malaria disaster: Will insecticide resistance derail malaria control? *Lancet* 387: 1785–1788.

Hiscox, A., M.M. Njoroge, A.K. Mutai, B. Otieno, D. Masiga, J. van Loon, U. Fillinger, and W. Takken. 2019. Developing push-pull strategies for surveillance and control of malaria vectors. *Chemical Senses* 44: E23–E23.

Homan, T., A. Hiscox, C.K. Mweresa, D. Masiga, W.R. Mukabana, P. Oria, N. Maire, A.D. Pasquale, M. Silkey, J. Alaii, T. Bousema, C. Leeuwis, T.A. Smith, and W. Takken. 2016. The effect of mass mosquito trapping on malaria transmission and disease burden (SolarMal): A stepped-wedge cluster-randomised trial. *The Lancet*, 388 (10050): 1193–1201.

James, S., F.H. Collins, P.A. Welkhoff, C. Emerson, H.C.J. Godfray, M. Gottlieb, B. Greenwood, S.W. Lindsay, C.M. Mbogo, F.O. Okumu, H. Quemada, M. Savadogo, J.A. Singh, K.H. Tountas, and Y.T. Toure. 2018. Pathway to deployment of gene drive mosquitoes as a potential biocontrol tool for elimination of malaria in sub-saharan Africa: Recommendations of a scientific working group. *American Journal of Tropical Medicine and Hygiene* 98: 1–49.

Killeen, G.F. 2020. Control of malaria vectors and management of insecticide resistance through universal coverage with next-generation insecticide-treated nets. *The Lancet* 395: 1394–1400.

Killeen, G.F., U. Fillinger, I. Kiche, L.C. Gouagna, and B.G. Knols. 2002. Eradication of *Anopheles gambiae* from Brazil: Lessons for malaria control in Africa? *Lancet Infect Dis* 2: 618–627.

Kirby, M.J., D. Ameh, C. Bottomley, C. Green, M. Jawara, P.J. Milligan, P.C. Snell, D.J. Conway, and S.W. Lindsay. 2009. Effect of two different house screening interventions on exposure to malaria vectors and on anaemia in children in The Gambia: A randomised controlled trial. *Lancet* 374: 998–1009.

Knapp, J., M. Macdonald, D. Malone, N. Hamon, and J.H. Richardson. 2015. Disruptive technology for vector control: The innovative vector control consortium and the US military join forces to explore transformative insecticide application technology for mosquito control programmes. *Malaria Journal* 14: 371–371.

Lindh, J.M., M.N. Okal, M. Herrera-Varela, A.-K. Borg-Karlson, B. Torto, S.W. Lindsay, and U. Fillinger. 2015. Discovery of an oviposition attractant for gravid malaria vectors of the *Anopheles gambiae* species complex. *Malaria Journal* 14: 119.

Lindsay, S.W., P.L. Alonso, J.R. Armstrong Schellenberg, J. Hemingway, J.H. Adiamah, F.C. Shenton, M. Jawara, and B.M. Greenwood. 1993. A malaria control trial using insecticide-treated bed nets and targeted chemoprophylaxis in a rural area of the Gambia, west Africa. 7. Impact of permethrin-impregnated bed nets on malaria vectors. *Transactions of the Royal Society Tropical Medicine and Hygiene* 87 Suppl 2: 45–51.

Lindsay, S.W., P.M. Emerson, and J.D. Charlwood. 2002. Reducing malaria by mosquito-proofing houses. *TRENDS in Parasitology* 18: 510–514.

Liu, W.H., K. Xin, C.Z. Chao, S.Z. Feng, L. Yan, R.Z. He, Z.H. Zhang, G. Gibson, and W.M. Kang. 2004. New irrigation methods sustain malaria control in sichuan province, China. *Acta Tropica* 89: 241–247.

MacDonald, G. 1957. *The Epidemiology and Control of Malaria*. London: Oxford University Press,.

Mburu, M.M., M. Juurlink, J. Spitzen, P. Moraga, A. Hiscox, T. Mzilahowa, W. Takken, and R.S. McCann. 2018. Impact of partially and fully closed eaves on house entry rates by mosquitoes. *Parasites & Vectors* 11: 383. https://doi.org/10.1186/s13071-018-2977-3

Menard, D., and A. Dondorp. 2017. Antimalarial drug resistance: A threat to Malaria elimination. *Cold Spring Harbor Perspectives in Medicine* 7(7): a025619.

Menger, D.J., P. Omusula, M. Holdinga, T. Homan, A.S. Carreira, P. Vandendaele, J.L. Derycke, C.K. Mweresa, W.R. Mukabana, J.J.A. Van Loon, and W. Takken. 2015. Field evaluation of a push-pull system to reduce malaria transmission. *PLoS ONE* 10(4): e0123415. https://doi.org/10.1371/journal.pone.0123415

Mmbando, A.S., E.P.A. Batista, M. Kilalangongono, M.F. Finda, E.P. Mwanga, E.W. Kaindoa, K. Kifungo, R.M. Njalambaha, H.S. Ngowo, A.E. Eiras, and F.O. Okumu. 2019. Evaluation of a push-pull system consisting of transfluthrin-treated eave ribbons and odour-baited traps for control of indoor- and outdoor-biting malaria vectors. *Malaria Journal* 18: 87. https://doi.org/10.1186/s12936-019-2714-1

Mutero, C.M., C. Mbogo, J. Mwangangi, S. Imbahale, L. Kibe, B. Orindi, M. Girma, A. Njui, W. Lwande, H. Affognon, C. Gichuki, and W.R. Mukabana. 2015. An assessment of participatory integrated vector management for malaria control in Kenya. *Environmental Health Perspectives* 123: 1145–1151.

Nabarro, D. 1999. Roll back Malaria. *Parassitologia* 41: 501–504.

Oria, P.A., C. Leeuwis, A. Hiscox, D. Masiga, W. Takken, and J. Alaii. 2015. Malaria control with solar-powered mosquito trapping systems: Socio-economic and perceived health outcomes of house lighting in Rusinga Island, Western Kenya. *American Journal of Tropical Medicine and Hygiene* 93: 115–115.

Ranson, H., and N. Lissenden. 2016. Insecticide resistance in African *Anopheles* mosquitoes: A worsening situation that needs urgent action to maintain Malaria control. *Trends in Parasitology* 32: 187–196.

Rocco, F. 2003. *The Miraculous Fever-Tree: Malaria and the Quest for a Cure That Changed the World,* 1st ed. New York: Harper Collins.

Ross, R. 1900. The relationship of Malaria and the mosquito. *The Lancet* 156: 48–50.

Ross, R. 1910. *The Prevention of Malaria*. London: Murray.

Sachs, J., and P. Malaney. 2002. The economic and social burden of malaria. *Nature* 415: 680–685.

Sarma, N., E. Patouillard, R.E. Cibulskis, and J.L. Arcand. 2019. The economic burden of Malaria: Revisiting the evidence. *American Journal of Tropical Medicine and Hygiene* 101: 1405–1415.

Schoelitsz, B., V. Mwingira, L.E.G. Mboera, H. Beijleveld, C.J.M. Koenraadt, J. Spitzen, J.J.A. van Loon, and W. Takken. 2020. Chemical mediation of oviposition by *Anopheles* mosquitoes: A push-pull system driven by volatiles associated with larval stages. *Journal of Chemical Ecology* 46: 397–409.

Sherrard-Smith, E., A.B. Hogan, A. Hamlet, O.J. Watson, C. Whittaker, P. Winskill, F. Ali, A.B. Mohammad, P. Uhomoibhi, I. Maikore, N. Ogbulafor, J. Nikau, M.D. Kont, J.D. Challenger, R. Verity, B. Lambert, M. Cairns, B. Rao, M. Baguelin, L.K. Whittles, J.A. Lees, S. Bhatia, E.S. Knock, L. Okell, H.C. Slater, A.C. Ghani, P.G.T. Walker, O.O. Okoko, and T.S. Churcher. 2020. The potential public health consequences of COVID-19 on malaria in Africa. *Nature Medicine* 26: 1411–1416.

Shretta, R., A.L.V. Avancena, and A. Hatefi. 2016. The economics of malaria control and elimination: A systematic review. *Malaria Journal* 15: 593. https://doi.org/10.1186/s12936-016-1635-5

Syafruddin, D., P.B.S. Asih, I.E. Rozi, D.H. Permana, A.P. Nur Hidayati, L. Syahrani, S. Zubaidah, D. Sidik, M.J. Bangs, C. Bøgh, F. Liu, E.C. Eugenio, J. Hendrickson, T. Burton, J.K. Baird, F. Collins, J.P. Grieco, N.F. Lobo, and N.L. Achee. 2020. Efficacy of a Spatial repellent for control of Malaria in Indonesia: A cluster-randomized controlled trial. *The American Journal of Tropical Medicine and Hygiene* 103: 344–358.

Takken, W., and B.G.J. Knols. 1999. Odor-mediated behavior of *Afrotropical* malaria mosquitoes. *Annual Review of Entomology* 44: 131–157.

Takken, W., W.B. Snellen, J.P. Verhave, B.G.J. Knols, and S. Atmosoedjono. 1990. *Environmental Measures for Malaria Control in Indonesia. A Historical Review on Species Sanitation*. Wageningen: Agricultural University.

Traore, M.M., A. Junnila, S.F. Traore, S. Doumbia, E.E. Revay, V.D. Kravchenko, Y. Schlein, K.L. Arheart, P. Gergely, R.D. Xue, A. Hausmann, R. Beck, A. Prozorov, R.A. Diarra, A.S. Kone, S. Majambere, J. Bradley, J. Vontas, J.C. Beier, and G.C. Muller. 2020. Large-scale field trial of attractive toxic sugar baits (ATSB) for the control of malaria vector mosquitoes in Mali, West Africa. *Malaria Journal* 19 (72): 2324. https://doi.org/10.1186/s12936-020-3132-0

Tusting, L.S., C. Bottomley, H. Gibson, I. Kleinschmidt, A.J. Tatem, S.W. Lindsay, and P.W. Gething. 2017. Housing improvements and Malaria risk in sub-saharan Africa: A multi-country analysis of survey data. *Plos Medicine* 14 (2): e1002234. https://doi.org/10.1371/journal.pmed.1002234

Tusting, L.S., J. Thwing, D. Sinclair, U. Fillinger, J. Gimnig, K.E. Bonner, C. Bottomley, and S.W. Lindsay. 2013. Mosquito larval source management for controlling malaria. *Cochrane Database System Review* 8: CD008923. doi: 10.1002/14651858.CD008923.pub2

Uwimana, A., E. Legrand, B.H. Stokes, J.-L.M. Ndikumana, M. Warsame, N. Umulisa, D. Ngamije, T. Munyaneza, J.-B. Mazarati, K. Munguti, P. Campagne, A. Criscuolo, F. Ariey, M. Murindahabi, P. Ringwald, D.A. Fidock, A. Mbituyumuremyi, and D. Menard. 2020. Emergence and clonal expansion of in vitro artemisinin-resistant plasmodium falciparum kelch13 R561H mutant parasites in Rwanda. *Nature Medicine,* 26: 1602–1608.

van den Berg, H., M. van Vugt, A.N. Kabaghe, M. Nkalapa, R. Kaotcha, Z. Truwah, T. Malenga, A. Kadama, S. Banda, T. Tizifa, S. Gowelo, M.M. Mburu, K.S. Phiri, W. Takken, and R.S. McCann. 2018. Community-based malaria control in southern Malawi: A description of experimental interventions of community workshops, house improvement and larval source management. *Malaria Journal* 17: 266. https://doi.org/10.1186/s12936-018-2415-1

Warrell, D.A., and H.M. Gilles. 2002. *Bruce-Chwatt's Essential Malariology*, 4th ed. Boca Raton, FL: CRC Press.

Watson, M. 1921. *The Prevention of Malaria in the Fedreated Malay States*, 2nd ed. London: John Murray.

Webb, James L.A., Jr. 2009. *Humanity's Burden: A Global History of Malaria*. New York: Cambridge University Press.

White, N.J., S. Pukrittayakamee, T.T. Hien, M.A. Faiz, O.A. Mokuolu, and A.M. Dondorp. 2014. Malaria. *Lancet* 383: 723–735.

Wilson, A.L., O. Courtenay, L.A. Kelly-Hope, T.W. Scott, W. Takken, S.J. Torr, and S.W. Lindsay. 2020. The importance of vector control for the control and elimination of vector-borne diseases. *PLoS Neglected Tropical Diseases* 14: e0007831.

Wilson, K.L., K.L. Flanagan, M.D. Prakash, and M. Plebanski. 2019. Malaria vaccines in the eradication era: Current status and future perspectives. *Expert Review of Vaccines* 18: 133–151.

Wooding, M., Y. Naude, E. Rohwer, and M. Bouwer. 2020. Controlling mosquitoes with semiochemicals: A review. *Parasites & Vectors* 13: 80. https://doi.org/10.1186/s13071-020-3960-3

Word Health Organization. 2005. *The Roll Back Malaria Programme*. Geneva, p. 52.

Word Health Organization. 2017. *Global Vector Control Response 2017–2030.* W. H. Organization [ed.]. Geneva, p. 53.

Word Health Organization. 2019. *World Malaria Report 2019.* Geneva, p. 232.

Yang, G.G., D. Kim, A. Pham, and C.J. Paul. 2018. A meta-regression analysis of the effectiveness of mosquito nets for Malaria control: The value of long-lasting insecticide nets. *International Journal of Environmental Research and Public Health* 15: 546–546.