Introduction

Mosquito-borne diseases are an increasing global health challenge, threatening over 40% of the world’s population. Despite major advances in malaria control since 2000, recent progress has stalled. Additionally, the risk of *Aedes*-borne arboviruses is rapidly growing, with the unprecedented spread of dengue and chikungunya viruses, outbreaks of yellow fever and the 2015 epidemic of Zika virus in Latin America. To counteract this growing problem, diverse and innovative mosquito control technologies are currently under development. Conceptually, these span an impressive spectrum of approaches, from invasive transgene cassettes with the potential to crash mosquito populations or reduce the vectorial capacity of a population, to low-cost alterations in housing design that restrict mosquito entry. This themed issue will present articles providing insight into the breadth of mosquito control research, while demonstrating the requirement for an interdisciplinary approach. The issue will highlight mosquito control technologies at varying stages of development and includes both opinion pieces and research articles with laboratory and field-based data on control strategy development.

This article is part of the theme issue ‘Novel control strategies for mosquito-borne diseases’.

1. Introduction

Diseases transmitted by mosquitoes are of global importance. Malaria is responsible for more than 400,000 deaths each year, and dengue, yellow fever, chikungunya and Zika have caused severe disease outbreaks in many urban areas [1–3]. Approximately half of the world’s population is expected to be at risk of arbovirus transmission by 2050 [4]. The principal methods available for reducing the public health burden of most mosquito-borne diseases are vector-based interventions. Prior to the development of insecticides, these interventions relied on environmental management and focused on the removal of mosquito breeding sites and the improvement of housing with screens to prevent access of mosquitoes through doors and windows. Following World War II, DDT, dieldrin and other compounds were produced for indoor and outdoor use, and insecticides were eventually incorporated into bed nets [5].

The use of long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) accounted for most of the unprecedented reductions in malaria burden achieved in the twenty-first century [6]. However, LLINs and IRS are not sufficient to eliminate malaria transmission in many settings because of operational constraints or because the mosquito vectors are not susceptible to the insecticides used [7]. Some species naturally avoid contact with insecticides, but there is also evidence for the emergence and spread of resistance through metabolic detoxification, and this has driven the need to develop LLINs with synergists and additional compounds for use in IRS [8]. Despite these developments and the sustained efforts to control mosquitoes, epidemics and the spread of mosquito-borne diseases continue to threaten the health of billions of people worldwide and hamper economic development [9]. As with
malaria, vector control products have been used to limit the transmission of the disease agents transmitted by *Aedes* mosquitoes, and again there is concern about the continued use of existing tools against these mosquitoes. Larviciding or space spraying of pyrethroids and organophosphates is challenged by high costs, low community adoption and slow operational implementation, and insecticide resistance in *Aedes* is now widespread [10, 11].

The recent coronavirus outbreak has further highlighted the need for new tools, particularly those that are less labour intensive to implement. Mitigation strategies to curtail the transmission of SARS-CoV-2 have been introduced in many countries around the world and are expected to have averted millions of SARS-CoV-2 infections [12, 13], but are disruptive to vector-borne disease prevention activities. While the World Health Organization (WHO) has urged countries not to scale back their planned malaria prevention, diagnostic and treatment activities [14], bed net distribution programmes and IRS could be reduced or cancelled in some areas: bed nets are typically distributed centrally from distribution points, which may be cancelled or poorly attended because of societal measures against COVID-19, and for IRS to continue, spray operators need additional personal protective equipment and training. Modelling studies suggest that, in sub-Saharan Africa, a halt to such activities could lead to the malaria burden in 2020 ultimately being double that of 2019 [15]. Mass drug administration of malaria chemoprevention could mitigate excess malaria deaths during the COVID-19 epidemic, but other tools covered in this theme issue may also find particular value in the current climate.

The process for developing novel interventions is multi-staged. It begins with defining the target product profile, which outlines the features and performance targets of the intended vector control tool, and the mode of action [16]. Proof of concept is demonstrated by conducting phase I studies in the laboratory, to explore the effect of the tool and duration of efficacy, and phase II studies in small-scale field or semi-field conditions. These confirm product performance and user acceptability in specific settings and typically only have entomological outcomes, such as human vector contact, without determining any direct impacts on disease transmission.

The WHO requires novel vector control products falling outside an established intervention class to provide epidemiological evidence of public health impact [17]. The efficacy of a vector control tool implemented under optimal conditions can be assessed through a phase III field study that includes epidemiological outcomes. Based on the results of phase III trials, WHO will make recommendations for pilot implementation to assess the effectiveness of the vector control tool when it is delivered and used under ‘real-world’ conditions. Once the public health value has been confirmed, and policy recommendations have been established, a product can be given a WHO product listing provided that efficacy, safety and quality standards are met [18].

If control and elimination targets for malaria and other mosquito-borne neglected tropical diseases are to be met over the next decade, vector control interventions need to play an increasingly prominent role. In this theme issue, we present current studies and opinions on novel control strategies for mosquito-borne diseases.

2. Use of randomized controlled trials and mathematical modelling

Rigorous field trials are required to evaluate novel vector control tools, but financial, temporal and other resource restrictions may prevent such studies being conducted and stop valuable vector control tools from being rolled out. Where there are established links between entomological and epidemiological indicators, it has been argued that new products within the same product category may be rapidly evaluated through smaller scale experiments without the need to repeat lengthy and expensive randomized controlled trials (RCTs) [16]. Further, mathematical modelling that can translate experimental hut data to product efficacies, or relate entomological outcomes to epidemiological outcomes, may reduce the need for phase III studies in some instances. In this theme issue, Hellywell et al. [19] discuss the role of modelling in predicting the impact of using the mass deployment of spatial repellent emanators, containing transfluthrin, together with LLINs to target outdoor as well as indoor transmission of malaria. Using entomological field data to parameterize the models, the resulting simulations for all of the different scenarios tested indicated that emanators provided an additional benefit over LLINs alone. Although the modelling results are encouraging, the authors conclude that a better understanding of aspects of emanators and human behaviour is required to further inform predications of impact.

Mathematical approaches can also be used to help decide which tools to use where. For example, there is a marked difference in IRS product efficacy in settings with different mosquito populations. By analysing mosquito mortality, blood-feeding and deterrence data, transmission dynamics mathematical modelling can be employed to predict the public health impact of different IRS insecticides in areas with different levels of LLIN coverage and pyrethroid resistance [20]. Such approaches may bypass the need for multiple RCTs with new IRS products and provide a framework to allow decision makers to evaluate IRS cost-effectiveness based on local entomology, local epidemiology, product price and budget.

However, when possible, RCTs offer the most robust, and least biased, method to estimate whether an intervention will be effective, as discussed by Jones et al. [21]. Their paper focuses on the benefits and challenges of using island settings to conduct cluster-randomized trials, in order to evaluate interventions for the control of vector-borne diseases, and the Bijagós archipelago of Guinea-Bissau is used as a case study. The islands are co-endemic for malaria and neglected tropical diseases, such as lymphatic filariasis, scabies and soil-transmitted helminths, and have been targeted for a mass drug administration programme using ivermectin.

Ivermectin operates as a systemic insecticide, or endectocide, that can reduce the survivability of *Anopheles gambiae* mosquitoes and impair the development of *Plasmodium falciparum* [22–24]. It could be administered to eligible members of an at-risk community as a complementary tool for vector control, but there is also the possibility of controlling human vector-borne diseases through the treatment of livestock, as explored by Chaccour [25]. This approach would be most impactful against residual malaria in areas where malaria transmission is driven by zooplastic vectors. It is supported by modelling and semi-field data on the transmission of malaria in some settings, as well as Chagas and human African trypanosomiasis [26, 27].
3. Household-level vector control tools

Residual transmission of malaria is defined as the persistence of transmission following the implementation in time and space of a widely effective malaria programme. While insecticide-treated bed nets, IRS and prompt treatment of clinical malaria cases with artemisinin-based combination therapy are estimated to have been the main contributors to the reduction in infection prevalence in endemic Africa [6], socioeconomic development and improvements to housing are also expected to have promoted reductions in transmission in some settings [28,29]. Indeed, improved housing should be considered a promising intervention for malaria control, and there are opportunities to modify house designs to prevent mosquito house entry and reduce mosquito production around the home.

Lindsay et al. [30] explore relatively simple changes to the built environment, including the installation of tight-fitting screened doors, the closing or screening of eaves and replacement of thatched roofs with roofs made from solid materials, such as metal or tile. An important message is to combine a package of interventions for maximum impact. An example of the impact of such an approach comes from a study in Burkina Faso, which indicated that children living in houses with mud roofs had a significantly higher risk of getting *P. falciparum* infection compared to those living in iron-sheet rooted houses [31]. This suggests that modifications to roof construction may help to reduce the burden of malaria through reducing exposure to mosquitoes. However, the increased indoor temperatures associated with metal roofs may encourage some people to sleep outside during hot nights [32]. Changes in roof materials should, therefore, be coupled with other features to increase ventilation, which will not only bring down internal temperatures but also prevent the concentration of carbon dioxide that acts as an attractant to mosquitoes [33].

Further research is needed in this emerging field, and many knowledge gaps remain to be filled. Among these is a better understanding of how mosquitoes enter buildings. In this issue, Barreaux et al. [34] consider the role of both human and mosquito behaviour on the efficacy of a house-based intervention designed to reduce malaria transmission by preventing mosquito access through windows and eaves. PVC eave tubes fitted with electrostatic netting containing an insecticide-treated screen were inserted into the closed eaves of houses in a study village in Côte d’Ivoire. The houses were also fitted with window screens. Monitoring of the treated houses in the study villages revealed that doors and windows were both left open for large parts of the evening and morning by the household residents, despite the modifications made to make them more mosquito proof. However, studies with experimental houses showed that, even when doors and windows were open in line with normal householder behaviour, the screening and eave tube treatment still led to significant reductions in mosquitoes indoors relative to standard control houses. The results of a large scale cluster-randomized trial investigating the epidemiological impact of the window screens and eave tubes [35] are keenly awaited.

4. Biotechnological control of mosquitoes

Further to these relatively simple mosquito control strategies, new biotechnologically advanced methods that build upon their successful use against agricultural pests are being developed for use against vectors that transmit human diseases. These technologies, including the use of genetic modification and *Wolbachia* endosymbionts, have been worked on for the last 20 years or so, and show great promise. Despite the exciting possibilities, there remain some important challenges to their widespread introduction, such as regulatory considerations, logistical difficulties and technical issues, as well as social and cultural issues, which can influence acceptance of these methods.

One technical challenge, in particular, is introduced by Leftwich et al. [36]. Releasing modified versions of an insect species is likely to result in mating occurring with wild species within the target area. This could lead to DNA from modified insects entering into the wild population if mating is successful between modified and unmodified insects. The authors discuss how background genetics may affect genetic pest management and the importance of strain selection. They conclude that introgression is likely to be harmless and could even provide additional benefits to a release programme.

Gene drive, whereby a genetic modification is intended to spread through a population at higher rates of inheritance than normal, is another promising new technology for the control of mosquito-borne diseases. Recent years have seen the development of gene-drive technologies in the primary sub-Saharan malaria vector, *An. gambiae*. Depending on design, the gene-drive system could have the capacity to either suppress a wild mosquito population or reduce its transmission competency by spreading genes that interfere with parasite development. In this issue, Dr Tony Nolan provides an overview of recent progress in the development of gene-drive systems in *Anopheles* mosquitoes and discusses the major limitations and challenges facing their deployment in the field [37]. Adelman et al. [38] highlight a particular issue with translating gene-drive technologies developed in the laboratory into practice in the field, caused by difficulties in removing gene-drive transgenes from nature. The authors present the possibility of including self-elimination mechanisms into homing-based gene-drive transgenes and suggest that this system, even if acting at a rate of just 10%, would be enough to overcome the problem, tolerating substantial rates of failure. This self-elimination technology may also facilitate field-based testing of gene drives by establishing strict time limits on the existence of gene-drive transgenes in nature.

Genetically modified control approaches share commonalities with *Wolbachia*-based population replacement strategies [39]. Various strains of the bacterial endosymbiont *Wolbachia* have now been transferred from their native host species into *Aedes aegypti*, where they have the capacity to block the transmission of dengue and Zika viruses. Several field studies have documented the release of *Wolbachia*-infected *Ae. aegypti*, which are expected to spread from release sites and become fixed in the target population, providing a viable strategy for arbovirus control through the modification of wild mosquito populations [40,41]. The long-term success of this approach depends on the capacity for the *Wolbachia* strain to maintain virus transmission blocking over time frames of many years. Here, Ahmed et al. [42] test the capacity of a field-adapted *w*AlbB-carrying *Ae. aegypti* strain collected from release sites in Kuala Lumpur, Malaysia, to block dengue virus transmission. The authors report that virus blocking by *w*AlbB was not compromised by 18 months of *Wolbachia*-host coevolution in the field. The *w*AlbB strain also retained the ability to induce complete unidirectional cytoplasmic incompatibility, which is vital for maintenance at a high population infection frequency. The results provide additional support for the continued scale-up of *w*AlbB-infected *Aedes* releases for dengue control.
As with genetic modification, population replacement approaches with *Wolbachia* are dependent on field releases of mosquitoes. Indeed, release programmes must be sufficiently large to ensure that a threshold prevalence is exceeded, otherwise the *Wolbachia* infection will probably be lost once releases stop [43]. It has, therefore, been necessary to develop suitable rear and release protocols for these mosquitoes. Similarly, although typically on a much larger scale, the sterile insect technique (SIT) involves the mass-rearing of a target species, their sterilization (usually by exposure to radiation or chemosterilants) and their release into a wild population. The subsequent induction of infertility in the wild population reduces its reproductive potential, and if releases are maintained over sufficient generations, a target population may be suppressed or even eliminated [44]. SIT is most effective and economical when the sterile release populations consist solely of males. Mechanisms for sexing mosquitoes have traditionally relied on mechanical sorting that exploits natural size dimorphisms between male and female pupae. However, novel genetic methods that use sex-linked markers may be able to increase the accuracy and efficiency of high throughput sex-sorting. In this issue, Augustinos et al. [45] report the generation of *Ae. aegypti* strains carrying chromosomal translocations that link eye pigmentation markers with the *Ae. aegypti* male sex-determining locus. In combination with classical rearing methods that help maintain the integrity of the sexing strains, the authors present a proof-of-principle camera-based mass-rearing system that detects eye colour differences in pupae and sorts males from females, providing foundational steps towards a possible high accuracy and high throughput mass-rearing system.

5. The future of vector control

Further active and exciting areas of research on potential new tools for vector control include the development of targeted sugar baits, which kill mosquitoes that are attracted to and feed on toxic sugar meals sprayed on plants or used in bait stations [46]. Transgenic fungi can also be disseminated from bait stations and have shown very promising results in semi-field trials [47].

Mosquito traps have been used for decades for purposes of surveillance, but are also considered as tools for mosquito control provided that they are sufficiently specific in attracting target species. This can be achieved through a combination of attractant cues, and relies on our understanding of mosquito behaviour. Host-seeking behaviour is activated by the synergistic effect of carbon dioxide and the volatile odour compounds produced by the host’s body and microbiota. Because body odour is affected by host genetics, there is a high degree of heterogeneity in mosquito attractiveness towards different people. Martinez et al. [48] provide an in-depth review of the biological factors that influence a person’s attractiveness to mosquitoes and discuss the potential role that volatile odour compounds could have in future vector control efforts.

Finally, there are tools that are in earlier stages of development, including acoustic larvicides [49], RNAi-based bioinsecticides [50] and technologies for improving the incorporation of insecticides and repellents into clothing and other materials [51]. We eagerly anticipate results from studies with these and other approaches.

Once any new technology is implemented, monitoring of its success in reducing the disease prevalence is a logistical challenge. An alternative method to screening human populations is xenomonitoring, wherein mosquito surveillance is used as a proxy for human infection. Cameron & Ramesh [52] discuss how this approach offers logistical benefits for predicting disease transmission in humans and the difficulties that remain in achieving standardization across different diseases and countries.

Most vector-borne diseases can be prevented by vector control, if it is implemented well [53]. The alternative strategies that are becoming available, and which are covered in this theme issue, will provide additional options for the control of mosquito-borne diseases and may add value to existing strategies.

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References


32. Lindsay SW et al. 2019 Reduced mosquito survival in metal-roof houses may contribute to a decline in malaria transmission in sub-Saharan Africa. Sci. Rep. 9, 1. (doi:10.1038/s41598-019-43816-0)


41. Ryan PA et al. 2020 Establishment of wMel Wolbachia in Aedes aegypti mosquitoes and reduction of local dengue transmission in Cairns and surrounding locations in northern Queensland, Australia. Gates Open Res. 3, 1547. (doi:10.12688/ gatesopenres.13061.2)


