Acta Tropica 174 (2017) 91–96

Contents lists available at ScienceDirect

Acta Tropica

journal homepage: www.elsevier.com/locate/actatropica

Invited Review

Current vector control challenges in the fight against malaria

Giovanni Benelli[a,*], John C. Beier[b,*]

[a] Department of Agriculture, Food and Environment, University of Pisa, via del Borghetto 80, 56124 Pisa, Italy
[b] Department of Public Health Sciences, University of Miami Miller School of Medicine, Miami, FL, United States

ARTICLE INFO

Keywords:
Anopheles
Malaria
Epidemiological impact
Insecticide treated bed nets
Pesticide resistance
Plasmodium parasites

ABSTRACT

The effective and eco-friendly control of *Anopheles* vectors plays a key role in any malaria management program. Integrated Vector Management (IVM) suggests making use of the full range of vector control tools available. The strategies for IVM require novel technologies to control outdoor transmission of malaria. Despite the wide number of promising control tools tested against mosquitoes, current strategies for malaria vector control used in most African countries are not sufficient to achieve successful malaria control. The majority of National Malaria Control Programs in Africa still rely on indoor residual spraying (IRS) and long-lasting insecticidal nets (LLINs). These methods reduce malaria incidence but generally have little impact on malaria prevalence. In addition to outdoor transmission, growing levels of insecticide resistance in targeted vectors threaten the efficacy of LLINs and IRS. Larvicidal treatments can be useful, but are not recommended for rural areas. The research needed to improve the quality and delivery of mosquito vector control should focus on (*i*) optimization of processes and methods for vector control delivery; (*ii*) monitoring of vector populations and biting activity with reliable techniques; (*iii*) the development of effective and eco-friendly tools to reduce the burden or locally eliminate malaria and other mosquito-borne diseases; (*iv*) the careful evaluation of field suitability and efficacy of new mosquito control tools to prove their epidemiological impact; (*v*) the continuous monitoring of environmental changes which potentially affect malaria vector populations; (*vi*) the cooperation among different disciplines, with main emphasis on parasitology, tropical medicine, ecology, entomology, and ecotoxicology. A better understanding of behavioral ecology of malaria vectors is required. Key ecological obstacles that limit the effectiveness of vector control include the variation in mosquito behavior, development of insecticide resistance, presence of behavioral avoidance, high vector biodiversity, competitive and food web interactions, lack of insights on mosquito dispersal and mating behavior, and the impact of environmental changes on mosquito ecological traits. Overall, the trans-disciplinary cooperation among parasitologists and entomologists is crucial to ensure proper evaluation of the epidemiological impact triggered by novel mosquito vector control strategies.

1. What's new in malaria management?

Malaria (from Middle Age Italian, "*mala aria*" which literally translates to "bad air", since ancient populations believed that the disease was associated with swampy, marshy areas where the air smelled bad) is a disease of huge public health importance caused by *Plasmodium* parasites that are transmitted to humans through the bites of infected females belonging to the mosquito genus *Anopheles* (Diptera: Culicidae) (Capanna, 2006; Hempelmann and Krafts, 2013). The last two years registered hot news in the field of malarial prevention and treatment. Hot news included the Nobel Prize to the Chinese scientist Y. Tu for the discovery of artemisinin (Callaway and Cyranoski, 2015). This molecule and its semi-synthetic derivatives are the drugs showing highly rapid action against *Plasmodium falciparum* malaria (Tu, 2011; Su and Miller, 2015). Furthermore, the first vaccine against *P. falciparum* malaria, RTS,S/AS01 (also known as Mosquirix), has been developed as a result of a partnership between GlaxoSmithKline Biologicals (GSK), the PATH Malaria Vaccine Initiative (MVI), with support from the Bill & Melinda Gates Foundation, and from a network of African research centers that performed the studies (RTS,S Clinical Trials Partnership, 2015; WHO, 2015; Benelli and Mehlhorn, 2016). However, in a large clinical trial in sub-Saharan African children, only transient protection by RTS,S/AS01 against malaria was found, with special reference to infants (Gosling and von Seidlein, 2016).

Notably, and perhaps most importantly, in the last 5 years, malaria incidence among populations at risk fell by 21% globally; during the same period, malaria mortality rates among populations at risk decreased by 29%; an estimated 6.8 million malaria deaths have been averted globally since 2001. However, in 2015, 91 countries and areas had ongoing malaria transmission. Among them, the African Region

* Corresponding authors.
E-mail addresses: benelli.giovanni@gmail.com (G. Benelli), JBeier@med.miami.edu (J.C. Beier).

http://dx.doi.org/10.1016/j.actatropica.2017.06.028
Received 12 June 2017; Accepted 30 June 2017
Available online 03 July 2017

continues to carry a really high share of the global malaria burden. In 2015, the region was afflicted by 90% of malaria cases and 92% of malaria deaths. Thirteen countries − mainly in sub-Saharan Africa − account for 76% of malaria cases and 75% deaths globally (White et al., 2011; Bhatt et al., 2015; White, 2015; WHO, 2017a). Malaria, as well other mosquito-borne diseases, has a major impact on the economic development of developing countries, through direct medical costs and indirect costs such as loss of productivity and tourism (Gallup and Sachs 2001; Sachs and Malaney 2002; Malaney et al., 2004; WHO 2016a).

In this framework, the research on novel antiplasmodial drugs is crucial to face the growing problem of *Plasmodium* resistance to currently employed compounds, including chloroquine and artemisinin (Jensen and Mehlhorn 2009; WHO 2016b; Benelli et al., 2017; Burrows et al., 2017). Two further key challenges are the reduction of the transient effect to of RTS,S/AS01, and the development of malaria vaccines against *Plasmodium* species not covered by Mosquirix (e.g. *Plasmodium vivax*, which is dominant in Asian countries and the Americas). In addition, besides these tools, the effective and environmentally sustainable control of *Anopheles* vectors still plays the most important role in any malaria management program (Benelli 2015a,b; Hemingway et al., 2016; Chanda et al., 2017).

2. The importance of Integrated Vector Management

Following the concept of Integrated Vector Management (IVM), it is strongly suggested to avoid "vertical" management structures relying only on one form of mosquito vector control (e.g. indoor spraying), as it was common in the malaria eradication era (Nájera et al., 2011; WHO 2017b). To reduce the burden and threat of mosquito-borne diseases that affect humans, with special reference to malaria and dengue fever, WHO (2016a) supports the development of effective, locally adapted sustainable vector control. To do this, the Global Vector Control Response (GVCR) key pillars of action include (*i*) strengthen inter- and intra-sectoral action and collaboration, (*ii*) enhance vector control surveillance and evaluation of interventions, (*iii*) scale up and integrate tools and approaches, (*iv*) engage and mobilize communities. The foundation at the basis of the above-mentioned pillars of action includes enhancing vector control capacity and capability, as well as increasing basic and applied research and innovation (WHO, 2016a).

At variance with earlier malaria vector control attempts, current IVM strongly suggest making use of the full range of vector control tools available. This should be flanked by regular assessments of local disease transmission dynamics, as well as agreeing on decision-making criteria and on procedures to meet targets and thresholds for transmission reduction (WHO, 2017b). Currently, a number of tools have been proposed to control malaria mosquito vectors (Benelli, 2015a; Bourtzis et al., 2016). However, indoor residual spraying (IRS) and long-lasting insecticidal nets (LLINs) still represent the two most widely adopted control tools in malaria management programs (WHO 2017a). Furthermore, in agreement with the IVM criteria, LLINs and IRS can be effectively employed in synergy with new paradigms in mosquito control recommended by the Vector Control Advisory Group (VCAG), including larval source management with larvicides (e.g., *Bacillus thuringiensis* serovariety *israelensis* and *Bacillus sphaericus*, Bravo et al., 2007; Lacey, 2007; Boyce et al., 2013; botanical larvicides, Pavela, 2015; WHO, 2017c).

Current research is focused on the development of further tools for effective mosquito vector control. Among them, a noteworthy relevance has been achieved by "eave tubes" and attractive toxic sugar baits (ATSB). The first method consists in a cheap and easy-to-do modification of the ventilation gaps under house eaves. Malaria mosquito vectors usually prefer to enter in houses exploiting the gap between the walls and the roof, which is common in rural houses on African countries (Knols et al., 2016). The "eave tubes" technology rely to the insertion of plastic tubes under the roofline; the rest of the gap is then sealed. At the end of each eave tube, the mosquito will encounter a adulticide-coated mesh. This method can be viewed as an "attract and kill" strategy, where the human odor from each house lure mosquitoes, allowing their contact with a contact insecticide (Sternberg et al., 2016; Waite et al., 2016). Still in the framework of "lure and kill" control tools, the ATSB method relies on the use of sugar bait attracting sugar-feeding malaria mosquito vectors. The ATBS can be provided in bait stations or sprayed on plants; both male and female mosquitoes feed on them (Allan, 2011; Beier et al., 2012). The ATSB are co-formulated with low-risk toxic substances, with special reference to boric acid, which kill mosquitoes upon ingestion (Xue et al., 2006; Xue et al., 2008; Müller et al., 2008; Muller et al., 2010; Xue et al., 2011; Stewart et al., 2013; Naranjo et al., 2013). Overall, both "eaves tubes" and ATSB methods have been reported as highly effective, target-specific, and with minimal non-target effects and contamination of the environment.

Further control strategies being developed for malaria vector control can include *Wolbachia* endosymbiotic bacteria inducing cytoplasmic incompatibility in mosquitoes (Wiwatanaratanabutr et al., 2010), Sterile Insect Technique (SIT) and "boosted SIT" (Oliva et al., 2012, 2013; Bouyer and Lefrançois, 2014), the use of genetically modified mosquitoes (e.g. Release of Insects carrying a Dominant Lethal, RIDL) (Bourtzis et al., 2016), as well as more "classic" control tools, including selective microbial and plant-borne pesticides effective against mosquito young instars (Benelli 2015a; Pavela, 2016; Pavela and Benelli 2016a), oviposition deterrents (Xue et al., 2001), also in nano-formulations (Benelli 2016; Rajaganesh et al., 2016), insecticide-treated clothes and other materials for the personal protection of risk specific groups (Banks et al., 2014), spatial repellents reducing human-vector contact Achee et al. (2012), and synthetic and plant-borne compounds repelling adults from humans (see reviews by Lupi et al., 2013; Pavela and Benelli, 2016b).

In addition, aquatic predators (e.g. cyclopoid copepods, *Toxorhynchites* mosquitoes, waterbugs, backswimmers, odonate young instars, tadpoles, and fishes) have been used as biological control agents of mosquito young instars (Marten et al., 1994; Hwang and Strickler, 2001; Bowatte et al., 2013; Murugan et al., 2015). The efficacy of larvivorous fishes (e.g., the mosquitofish *Gambusia affinis* and the guppy, *Poecilia reticulata*) is widely acknowledged, despite their impact on non-target aquatic species (see Walshe et al., 2013 and Benelli et al., 2016 for recent reviews).

Lastly, another strategy showing a promising potential in malaria vector control is the employ of the endectocide ivermectin. This molecule has been employed extensively for more than thirty years in the framework of onchocerciasis and lymphatic filariasis control (Ōmura and Crump, 2005; Chaccour et al., 2017). Ivermectin acts as feed-through insecticide against malaria vectors. Indeed, it has been showed that ivermectin that remains in the human bloodstream following a standard oral dose can kill blood-feeding *Anopheles* mosquitoes (Omura and Crump, 2017; Chaccour and Rabinovich, 2017a,b).

3. A brief research agenda for malaria vector control

Overall, the strategies for Integrated Vector Management (IVM) (WHO, 2004, 2007, 2012; Beier et al., 2008) require novel technologies to effectively reduce outdoor transmission of malaria (The malERA Consultative Group on Vector Control, 2011). Despite the promising control tools recently tested against mosquitoes, current strategies for malaria vector control used in most African countries are not sufficient to achieve successful malaria control and local elimination (Hemingway et al., 2016; WHO, 2016a). As outlined in the paragraphs above, the majority of the National Malaria Control Programs in Africa rely on LLINs and IRS (WHO, 2006). Notably, both methods used exclusively inside houses reduce transmission by > 90%, thus the incidence of new infections and malaria-related morbidity and mortality (Lengeler, 2004; WHO, 2008; Pluess et al., 2010). However, beyond low transmission sites or on islands (WHO, 2008; Bhattarai et al., 2007; Kleinschmidt et al., 2007; Keating et al., 2011) these methods have a