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REVIEW

Declining malaria, rising of dengue and Zika virus: insights for mosquito vector control

Giovanni Benelli[1] · Heinz Mehlhorn[2]

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Abstract The fight against mosquito-borne diseases is a challenge of huge public health importance. To our mind, 2015 was an extraordinary year for malaria control, due to three hot news: the Nobel Prize to Youyou Tu for the discovery of artemisinin, the development of the first vaccine against *Plasmodium falciparum* malaria [i.e. RTS,S/AS01 (RTS,S)], and the fall of malaria infection rates worldwide, with special reference to sub-Saharan Africa. However, there are major challenges that still deserve attention, in order to boost malaria prevention and control. Indeed, parasite strains resistant to artemisinin have been detected, and RTS,S vaccine does not offer protection against *Plasmodium vivax* malaria, which predominates in many countries outside of Africa. Furthermore, the recent outbreaks of Zika virus infections, occurring in South America, Central America and the Caribbean, represent the most recent of four arrivals of important arboviruses in the Western Hemisphere, over the last 20 years. Zika virus follows dengue (which slyly arrived in the hemisphere over decades and became more aggressive in the 1990s), West Nile virus (emerged in 1999) and chikungunya (emerged in 2013). Notably, there are no specific treatments for these arboviruses. The emerging scenario highlights that the effective and eco-friendly control of mosquito vectors, with special reference to highly invasive species such as *Aedes aegypti* and *Aedes albopictus*, is crucial. The concrete potential of screening plant species as sources of metabolites for parasitological purposes is worthy of attention, as elucidated by the Y. Tu's example. Notably, plant-borne molecules are often effective at few parts per million against *Aedes, Ochlerotatus, Anopheles* and *Culex* young instars, can be used for the rapid synthesis of mosquitocidal nanoformulations and even employed to prepare cheap repellents with low human toxicity. In addition, behaviour-based control tools relying to the employ of sound traps and the manipulation of swarming behaviour (i.e. "lure and kill" approach) are discussed. The importance of further research on the chemical cues routing mosquito swarming and mating dynamics is highlighted. Besides radiation, transgenic and symbiont-based mosquito control approaches, an effective option may be the employ of biological control agents of mosquito young instars, in the presence of ultra-low quantities of nanoformulated botanicals, which boost their predation rates.

Keywords Arbovirus · Artemisinin · Biological control · Boosted SIT · Nanosynthesis · Sex pheromones · Sterile insect technique · Sound traps · Swarming behaviour · Vaccine

Towards the decline of malaria burden?

The fight against mosquito-borne diseases is a challenge of huge public health importance (Jensen and Mehlhorn 2009; Mehlhorn et al. 2012). To our mind, 2015 was an extraordinary year for malaria control, due to three major issues. First, Youyou Tu had won the 2015 Nobel Prize in physiology or medicine, due to the development of the antimalarial drug artemisinin (Fig. 1) (Callaway and Cyranoski 2015). This highlights the key importance of natural product research in the fight against parasites. In the 1960s, within a Chinese national project aimed to discover new tools against malaria,

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✉ Giovanni Benelli
g.benelli@sssup.it; benelli.giovanni@gmail.com

[1] Insect Behaviour Group, Department of Agriculture, Food and Environment, University of Pisa, via del Borghetto 80, 56124 Pisa, Italy

[2] Department of Parasitology, Heinrich Heine University, Düsseldorf, Germany

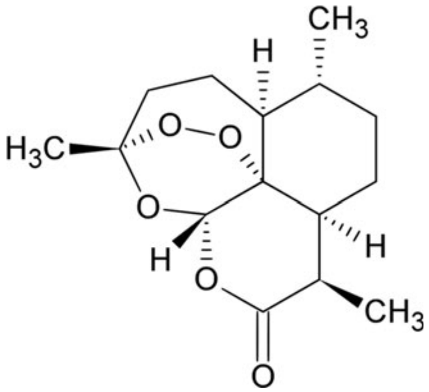

Fig. 1 Artemisinin, discovered by the Nobel Laureate Youyou Tu, and its semi-synthetic derivatives are the drugs showing the most rapid action against *P. falciparum* malaria

Y. Tu and her team screened more than 2000 Chinese herbal remedies to search for drugs with antimalarial activity. The extracts of *Artemisia annua* were especially effective against *Plasmodium* parasites, and by 1972, Y. Tu and colleagues had isolated the artemisinin (Tu 2011).

Second, a vaccine that confers partial protection against *Plasmodium falciparum* in young children has been recently developed (Cohen et al. 2011; WHO 2015a). RTS,S/AS01 (RTS,S) (Mosquirix™) is the result of a partnership between GlaxoSmithKline Biologicals (GSK) and the PATH Malaria Vaccine Initiative (MVI), with support from the Bill & Melinda Gates Foundation, and from a network of African research centres that performed the studies. Notably, WHO reports that the clinical testing of RTS,S is at least 5–10 years ahead of other candidate malaria vaccines (WHO 2015a).

Third, according to the latest estimates from WHO, between 2000 and 2015, malaria incidence rates (new malaria cases) fell by 37 % globally, and by 42 % in Africa (WHO 2015b). During this same period, malaria mortality rates fell by 60 % globally and by 66 % in the African Region. Since 2000, the malaria mortality rate declined by 85 % in the Southeast Asia Region, by 72 % in the region of the Americas, by 65 % in the Western Pacific Region, and by 64 % in the Eastern Mediterranean Region. For the first time, the European Region reported zero indigenous cases of malaria in 2015. In 2015, malaria killed an estimated 306, 000 under-fives globally, including 292, 000 children in the African region. Between 2000 and 2015, the mortality rate among children under five fell by 65 % worldwide and by 71 % in Africa (White 2015; WHO 2015b).

The rise of dengue, Zika virus and other arboviruses

Dengue, a viral infection mainly vectored by *Aedes* mosquitoes, slyly arrived in the Western Hemisphere over decades, then its incidence has grown dramatically from the 1990s. The actual numbers of dengue cases are underreported and many cases are misclassified (WHO 2015c). A recent estimate indicates 390 million dengue infections per year (95 % credible interval 284–528 million), of which 96 million (67–136 million) manifest clinically (with any severity of disease) (Bhatt et al. 2013). Another study, of the prevalence of dengue, estimates that 3900 million people, in 128 countries, are at risk of infection with dengue viruses (Becker et al. 2012; Brady et al. 2012; Mehlhorn 2012, 2016).

There is no specific treatment for dengue. However, the development of three tetravalent live-attenuated vaccines is in progress (phase II and phase III clinical trials) (WHO 2015c). In addition, recent research highlighted the potential of plant-synthesized nanoparticles as inhibitors of dengue growth (Sujitha et al. 2015; Benelli 2016a). From a mechanistic point of view, green-synthesized silver nanoparticles act as inhibitors of the production of dengue DEN-2 viral envelope (E) protein in Vero cells, and downregulate the expression of dengue viral E gene (Murugan et al. 2015a). However, a certain level of cytotoxicity of the tested nanoparticles has been reported (e.g. about 30 % in cell viability reduction when tested at 50 μg/ml. Later on, it has been elucidated that *Centroceras clavulatum*-synthesized silver nanoparticles tested at 50 μg/ml did not show relevant toxicity against Vero cells, but inhibit DEN-2 viral growth of more than 80 % (Murugan et al. 2016). Once again, this highlights the concrete potential of screening an extensive number of plant species as sources of metabolites for parasitological purposes, with special reference to the potential treatment of arboviral diseases.

Furthermore, the recent outbreaks of Zika virus infection occurring in South America, Central America and the Caribbean, represents the most recent of the four key arrivals of arboviruses in the Western Hemisphere over the last 20 years (Attar 2016; Fauci and Morens 2016). Indeed, Zika virus follows dengue, West Nile virus, which emerged in 1999, and chikungunya, which emerged in 2013 (Morens and Fauci 2014). The Zika virus belongs to the genus *Flavivirus*. It is mainly vectored by *Aedes* mosquitoes (Marcondes and Ximenes 2015). These mosquitoes (e.g. *Aedes aegypti*, *Aedes albopictus*, *Ochlerotatus japonicus*, Fig. 2) are constantly spreading over the continents (Becker et al. 2012; Melaun et al. 2015, Figs. 3 and 4). Zika virus was first identified in Uganda in 1947 in *Rhesus* monkeys, within a monitoring network of sylvatic yellow fever. Later on, it has been identified in humans in 1952, in Uganda and the United Republic of Tanzania (Dick et al. 1952). In latest years, several important outbreaks of Zika virus have been reported from the Pacific (i.e. Yap, 2007; French Polynesia, 2013), as well as from the Americas (Brazil and Colombia, 2015) and Africa (Cape Verde, 2015). Moreover, 13 countries more in the Americas have registered sporadic Zika virus infections, highlighting the rapid geographic expansion of this arbovirus (WHO 2016; Petersen et al. 2015).

Zika symptoms last 2–7 days and are comparable to those characterizing other arbovirus infections, with special reference

Fig. 2 Macrophoto of an *Aedes* female

to dengue; symptoms include fever, skin rashes, conjunctivitis, muscle and joint pain, malaise and headache. However, the surveys conducted on the high numbers of cases of Zika virus infections in French Polynesia (2013) and Brazil (2015) highlighted potential neurological and autoimmune complications. During the Zika virus outbreaks in French Polynesia, a concomitant epidemic of 73 cases of Guillain–Barré syndrome and other neurologic conditions was observed in a population of about 270,000 people (Oehler et al. 2014). In Northeast Brazil, during 2015, the increase in Zika virus infections has been reported in close concurrence of an increase in babies born with microcephaly (European Centre for Disease Prevention and Control 2015). WHO (2016) pointed out that further research is urgently needed to shed light on the relationship between these potential complications and Zika virus infections.

Unfortunately, as already known for other arboviruses such as dengue, West Nile and chikungunya, no vaccines or other specific treatments are available, and avoidance of mosquito bites remains the best strategy (WHO 2016). Current prevention tools are represented by the employ of mosquito repellents (Amer and Mehlhorn 2006a, b; Mehlhorn et al. 2005), light-coloured clothes covering as such of the body as possible, and sleeping under mosquito nets (Benelli 2015a). Concerning chemically derived repellents, the number of these products has been considerably reduced by the European Community. Therefore, there are rather few compounds left, including DEET (N,N-diethyl-mtoluamide), IR3535 (3-N-acetyl-N-butylamino-proprionic ethyl ester), icaridin (i.e. Saltidin®, 1-piperidine-carboxylic acid 2–2 hydroxyethyl-1-methylester), and also an *Eucalyptus citriodora* derivative (para-menthane-3,8-diol) (Abdel-Ghaffar et al. 2015; Mehlhorn 2016). People living in regions with endemic mosquito borne diseases should synergize these strategies with the reduction or removal of Culicidae breeding sites, as well as with mosquitocidal treatments using chemical or microbiological ovicides, larvicides and pupicides (Amer and Mehlhorn 2006c, d; Semmler et al. 2009; Benelli 2015b). Concerning the employ of synthetic pesticides, particular attention should be given to the development of mosquito-resistant strains, as well as to concerns for human health and the environment (Hemingway and Ranson 2000; Naqqash et al. 2016).

Furthermore, biological control programmes based on the release of larvivorous organisms are frequently not suitable in the majority of urban environments exploited by larvae of some *Aedes* species, and require further research (Bowatte et al. 2013). Renewed interest has been recently devoted to the potential of sterile insect technique (SIT) for suppression of mosquito vectors, with special reference to the genus *Anopheles* (Lees et al. 2014; Bourtzis et al. 2016). Interestingly, SIT has been recently combined with auto-dissemination (i.e. adult females contaminated with dissemination stations of juvenile hormone to treat breeding habitats), a technique recently proved very efficient to control *Aedes* species but that cannot be used at large scales.

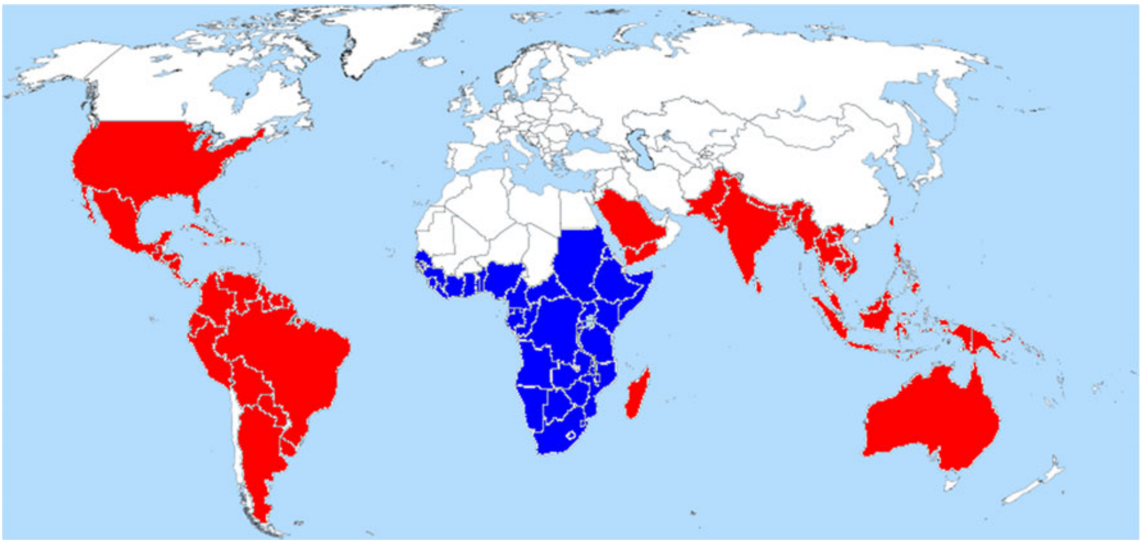

Fig. 3 Worldwide distribution of *A. aegypti* [*blue* = countries with native populations; *red* = countries with non-native (established) populations (from Becker et al. 2012)]

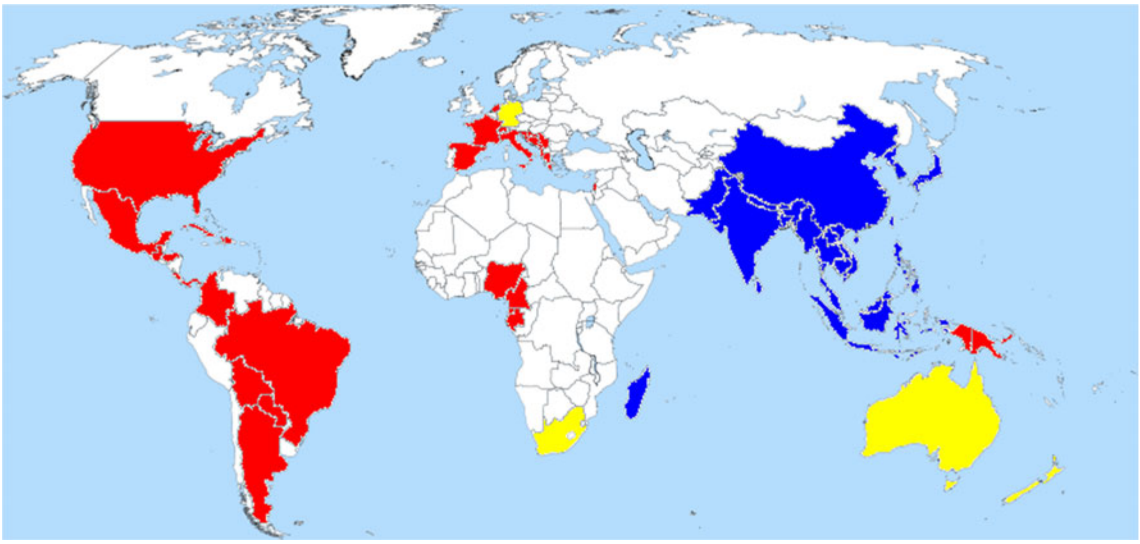

Fig. 4 Worldwide distribution of *A. (Stegomyia) albopictus* [*blue* = countries with native populations; *red* = countries with non-native (established) populations; *yellow* = countries with sporadic occurrence—not established populations (from Becker et al. 2012)]

This has led to formulate a new control concept, named "boosted SIT" that might enable the area-wide eradication of mosquitoes and other vectors of medical and veterinary importance (Bouyer and Lefrançois 2014). Lees et al. (2015) also highlighted that, until perfect sexing mechanisms exist, a combination of *Wolbachia*-induced phenotypes, such as cytoplasmic incompatibility and pathogen interference, and irradiation may prove to be the safest solution for population suppression.

Eco-friendly control of malaria and arbovirus vectors: a crucial issue

Despite the exciting research news mentioned above, both the malaria and arbovirus control will be difficult in the future. Here, we focus on at least three main limitations that will maintain the management of mosquito-borne diseases challenging in the future. First, it should be pointed out that the RTS,S/AS01 (RTS,S) vaccine does not offer protection against *Plasmodium vivax* malaria, which predominates in many countries outside of Africa (Figs. 5 and 6) (WHO 2015a; Carlton et al. 2008a, b). This vaccine is being assessed as a complementary malaria control tool that could potentially be added to, and not replace, the core package of proven malaria preventive, diagnostic and treatment measures (see WHO 2015a). Second, artemisinin-resistant *Plasmodium* has been detected, and the WHO Global Malaria Programme issues regular updates about the status of artemisinin resistance in affected countries (WHO 2015d). Third, a number of malaria prevention and control tools currently available are quite expensive, thus not readily available for poor and marginalized populations in tropical and subtropical areas worldwide (Benelli 2015a).

Arbovirus vector management also has to face significant challenges, due to the peculiar traits of *Aedes* vectors, which have huge physiological and ecological plasticity, including the ability to exploit small water reservoirs as breeding habitats (Benelli 2015a). Among them, the Asian tiger mosquito, *A. albopictus* (Skuse), deserves a standing-alone focus. Indeed, this is currently the most invasive mosquito worldwide (Benedict et al. 2007), and its medical and veterinary importance is magnified by its daytime human-biting behaviour and the ability to vector, besides dengue, a wide number of other viruses, including La Crosse encephalitis, West Nile and chikungunya (Bonizzoni et al. 2013). In addition, the possibility that the Zika virus may adapt to exploit *A. albopictus* as a vector is a noteworthy concern, since it has been previously highlighted that other arboviruses transmitted by Culicidae have adapted to domestic animals, including

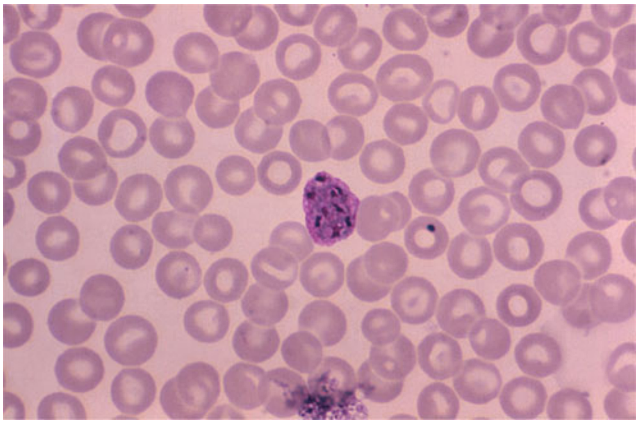

Fig. 5 The malaria vaccine RTS,S/AS01 (RTS,S)] has been developed to fight *P. falciparum*, while it does not offer protection against *P. vivax*, which predominates in many countries outside of Africa. Here, magnified ×1000, a Giemsa-stained photomicrograph revealing ultrastructural morphology exhibited by an immature *P. vivax* schizont (courtesy of Public Health Image Library, Centers for Disease Control and Prevention, Dr. Mae Melvin)

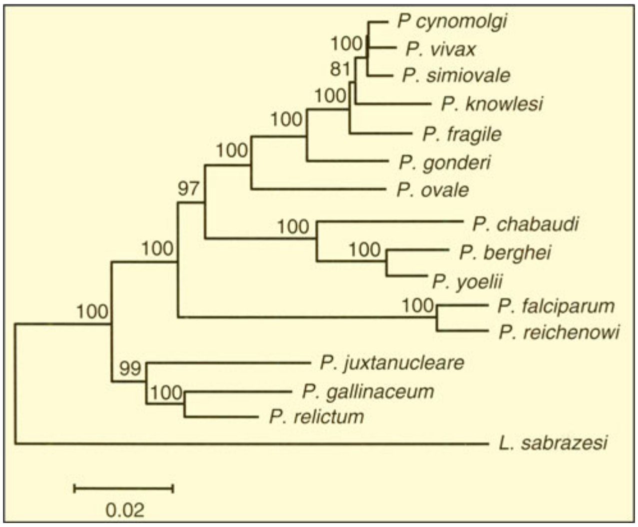

Fig. 6 Dendrogram of the relationship of *Plasmodium* species based on the mitochondrial genome. The limiting line below shows the number of nucleotid substitutions. The bird parasite *Leucocytozoon sabrazesi* was selected as an "outgroup" (from Carlton et al. 2008a, b)

horses (e.g. Venezuelan equine encephalitis) and pigs (e.g. Japanese encephalitis), to other vertebrate hosts, as well as to non-*Aedes* mosquitoes found in different areas of human habitation, as occurred for West Nile virus (Fauci and Morens 2016).

Plants and fungi as a reservoir of mosquitocidal products?

The emerging scenario highlights that the eco-friendly control of mosquito vectors, with special reference to highly invasive species, is crucial (Benelli 2015a). In particular, the concrete potential of screening plants and fungi as sources of metabolites for parasitological purposes, is worthy of attention, as elucidated by the Y. Tu's example. Notably, plant-borne molecules are often effective at few parts per million against *Aedes, Anopheles* and *Culex* young instars (see Benelli 2015b and Pavela 2015 for recent reviews) can be used for the rapid synthesis of mosquitocidal nanoformulations (Benelli 2016b) and even employed to prepare cheap repellents with low human toxicity (Semmler et al. 2009). Besides radiation, transgenic and symbiont-based control approaches (e.g. Wiwatanaratanabutr et al. 2010; Oliva et al. 2012; Moretti and Calvitti 2013; see Bourtzis et al. 2016 for a dedicated review), an effective option readily available in tropical and subtropical areas worldwide may be the employ of biological control agents of Culicidae young instars, in the presence of ultra-low quantities of nanoformulated botanicals, which boost their predation rates (e.g. Murugan et al. 2015b, c; Subramaniam et al. 2016).

Behaviour-based control tools

As regards behaviour-based control tools, the importance of basic knowledge concerning the Culicidae mating ecology, with special reference to their sexual chemical ecology, has been widely underestimated in the past (Benelli 2015a). Indeed, detailed information on the mating ecology of mosquito vectors is of interest to improve the success of mosquito control programmes in a number of different scenarios. First, this information is crucial for any control programme against mosquito vectors of medical and veterinary importance, since it is widely known that the success of SIT is largely dependent to the ability of sterile males to compete for mates with wild ones in the field (Lees et al. 2014, 2015; Oliva et al. 2013, 2014).

Second, behavioural knowledge about mosquito swarming and mating behaviour may be used to perform comparisons of courtship and mating ethograms among different vector species and strains, allowing monitoring and optimisation of quality of mass-reared males (i.e. sexual competitiveness and mating success) over time in SIT programmes and "boosted SIT" programmes, as well as to monitor the mating performances in mass-reared *Wolbachia*-induced phenotypes (Benelli 2015a, c). As a general trend, quantitative analyses of mating ethograms in Culicidae are rare, and mainly focuses on the elaborate courtships found in the genus *Sabethes* (Zsemlye et al. 2005; South and Arnqvist 2008, 2009, 2011) and *Wyeomyia* (Philips et al. 1996). In particular, the majority of the studies focused on the sexual behaviour of medically important *Aedes* species focused on comparisons of insemination ability in sterilized and wild males (e.g. Balestrino et al. 2010; Wiwatanaratanabutr et al. 2010; Boyer et al. 2011; Oliva et al. 2012; Bellini et al. 2013; Hamady et al. 2013; Moretti and Calvitti 2013; Madakacherry et al. 2014), without behavioural quantification of courtship and mating events (but see Oliva et al. 2013; Benelli 2015c; Benelli et al. 2015). Notably, limited information is also available on the potential molecules mediating aggregation and mating dynamics in mosquitoes (Cabrera and Jaffe 2007; Fawaz et al. 2014; Pitts et al. 2014).

Third, the possibilities to control mosquito populations by using sound traps deserve further attention (Diabate and Tripet 2015). This fascinating and eco-friendly control method was firstly experimented in Cuba in 1949 against *Anopheles albimanus*, where the use of a sound trap allowed the collection of an elevate number of males (Kahn and Offenhauser 1949). Later on, similar approaches led to successful removal of *Culex tarsalis* males, reducing female insemination (Kanda et al. 1988), and diminished the quote of *Culex tritaeniorhynchus* paorus females (Ikeshoji 1981). However, even if it has been claimed that the partial overlapping of wing-beat frequencies may potentially be advantageous, attracting more than a single mosquito species, it should be pointed out that there are at least two major shortcomings that reduce the field success of sound traps against mosquitoes (Diabate and Tripet 2015, see also Cator and Harrington 2010). Indeed, the design and production of sound traps able to attract mosquitoes from long distances, with proper amplification features, is quite difficult. Furthermore, to achieve effective results, the traps should be placed in sites, which are close to the best one selected by mosquito vectors for swarming. To allow this, novel and efficacious methods of identification of swarming sites, in particularly for anophelines, are urgently required (Diabate and Tripet 2015).

Fourth, the "lure and kill" approach, already used with success against a number of arthropod pests (Benelli et al. 2014), has been recently revisited to apply also in the fight against mosquito vectors (Diabate and Tripet 2015), with special reference to the genus *Anopheles*. Indeed, for anophelines, visual stimuli are probably the most important used to converge in a swarming site (Charlwood et al. 2002; Diabate et al. 2011; see also Dabiré et al. 2014). Consequently, recent research has highlighted the possibility to disrupt or enhance swarms, manipulating artificial markers. These efforts may lead to create "kill zones" (e.g. within or in close proximity of villages) where high numbers of mosquitoes can be attracted and killed. To gain further applied interest, this novel tool requires the development of rapid and cheap methods of identification of swarming sites, which are currently ongoing (see Diabate and Tripet 2015 for a dedicated review).

As a final remark, further research on the exact nature of chemical cues routing mate searching and choice dynamics in mosquito vectors is required, as well as behavioural studies dissecting the relative importance of visual (with special reference to swarming landmarks), vibrational, olfactory and tactile cues perceived during swarming and mate recognition (Benelli 2015a).

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Compliance with ethical standards

Conflict of interests The authors declare that they have no conflict of interest. Heinz Mehlhorn and Giovanni Benelli are Editor in Chief and Editorial Board Member of *Parasitology Research*, respectively. This does not alter the authors' adherence to all the *Parasitology Research* policies on sharing data and materials.

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