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Spread of Zika virus: The key role of mosquito vector control

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ABSTRACT

Mosquitoes (Diptera: Culicidae) represent a key threat for millions of humans and animals worldwide, since they act as vectors for important parasites and pathogens, including malaria, filariasis and a wide number of arboviruses. The recent outbreaks of Zika virus infections occurring in South America, Central America, and the Caribbean, represent the most recent four arrivals of important arboviruses in the western hemisphere, over the last 20 years, namely dengue, West Nile virus, and chikungunya. Since there are no specific treatments for Zika virus and the other arboviruses mentioned above, it should be highlighted that the eco-friendly and effective control of mosquito vectors is of pivotal importance. 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 presence of ultra-low quantities of green-synthesized nanoparticles, which magnify their predation efficiency. Furthermore, behaviour-based control tools relying on the employ of swarming behaviour manipulation (*i.e.* the "lure and kill" approach), pheromone traps, sound traps need further research attention. In particular, detailed basic information on the physical and chemical cues routing mosquito swarming and mating dynamics is urgently required.

1. Introduction

Arthropods are dangerous vectors of important pathogens and parasites, which may hit as epidemics or pandemics in the increasing world population of humans and animals [1]. In particular, mosquitoes (Diptera: Culicidae) represent a key threat for millions of humans and animals worldwide, since they act as vectors for important parasites and pathogens, including malaria, filariasis and important arboviruses such as dengue, yellow fever, West Nile, Japanese encephalitis, St. Louis encephalitis viruses (Flaviridae, genus *Flavivirus*); chikungunya, Eastern equine encephalitis, Venezuelan equine encephalitis, Western equine encephalitis, Ross River, Sindbis, Mayaro, and Getah viruses (Togaviridae, genus *Alphavirus*); Potosi, San Angelo, La Crosse, and Jamestown Canyon viruses (Bunyaviridae, genus *Bunyavirus*); Rift Valley fever (Bunyaviridae, genus *Phlebovirus*) and Orungo viruses (Reoviridae, genus *Orbivirus*) [2,3].

Malaria is caused by *Plasmodium* parasites, mainly *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*. Notably, periodic reports highlighted the presence of simian malaria parasites found in humans, most of them implicating *Plasmodium knowlesi*. *Plasmodium* parasites are vectored to people through the bites of infected *Anopheles* mosquitoes, which bite mainly between dusk and dawn. There were about 198 million cases of malaria in 2013 and an estimated 584 000 deaths. However, malaria mortality rates have fallen by 47% globally since 2000 and by 54% in the African region. Most deaths occur among children living in Africa, where a child dies every minute from malaria. Malaria mortality rates among children in Africa have been reduced by an estimated 58% since 2000 [4]. Besides the fall of malaria infection

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rates worldwide, with special reference to sub-Saharan Africa, 2015 was an *annus mirabilis* for malaria control, due to the Nobel Prize to the Chinese scientist Youyou Tu for the discovery of artemisinin and the development of the first vaccine against *Plasmodium falciparum* malaria [*i.e.* RTS,S/AS01 (RTS,S)] [5].

2. Zika virus outbreaks

Concerning arboviruses of public health relevance, the occurrence of Zika virus outbreaks have been recently highlighted [5]. Zika virus was first identified in Uganda in 1947 in Rhesus monkeys, within a monitoring network of sylvatic yellow fever. Then, Zika virus has been identified in humans in 1952, in Uganda and the United Republic of Tanzania [6]. In latest years, several important outbreaks of Zika virus have been reported from the Pacific (*i.e.* Yap Islands, 2007; French Polynesia, 2013), as well as from the Americas (Brazil and Colombia, 2015) and Africa (Cape Verde, 2015). Moreover, thirteen countries more in the Americas have registered sporadic Zika virus infections, highlighting the rapid geographic expansion of this arbovirus [7,8].

Notably, 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 [9,10]. Indeed, Zika virus follows dengue, West Nile virus, which emerged in 1999, and chikungunya, which emerged in 2013 [10,11]. The Zika virus belongs to the genus *Flavivirus*, and is mainly vectored by *Aedes* mosquitoes [12], which are constantly spreading over the continents [5,13,14].

3. Zika virus symptoms and potential complications

Zika symptoms last from two to seven days, and are comparable to those characterizing other arbovirus infections, with special reference to dengue. Zika virus symptoms include fever, skin rashes, conjunctivitis, muscle and joint pain, malaise, and headache [8]. 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 [15]. 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 [16]. World Health Organization [8] pointed out that further research is urgently needed to shed light on the relationship between these potential complications and Zika virus infections [5].

4. Zika virus treatment and prevention

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 [2,8]. Current prevention tools are mainly represented by the employ of mosquito repellents [17,18], light-coloured clothes covering as much of the body as possible, and sleeping under mosquito nets [2]. 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-m-toluamide), 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) [19].

However, 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 [20–26]. 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 [27,28].

5. Eco-friendly control of mosquito vectors

Mosquito population control is a crucial tool in the fight against Zika virus infections. Recently, renewed interest has been devoted to the potential of sterile insect technique (SIT) for suppression of mosquito vectors, even if with special reference to the genus *Anopheles* [29,30]. Notably, 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 efficient to control *Aedes* species but that cannot be used at large scales. 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 [31]. Lees *et al.* [32] also pointed out that, until perfect sexing mechanisms exist, combination of *Wolbachia*-induced phenotypes, such as cytoplasmic incompatibility and pathogen interference, and irradiation may prove to be the safest solution for population suppression. To enhance the success of these control approaches, detailed basic knowledge about Culicidae mating ecology, with special references of exact behavioural quantification of the events leading to mating success, is urgently needed.

Biological control programs against mosquito young instars are based on the release of predatory aquatic organisms, and this strategy is frequently not suitable in the majority of urban environments exploited by larvae of some *Aedes* species, therefore further research is required [33]. However, the employ of biological control agents of mosquito young instars in presence of ultra-low quantities of plant-synthesized metal and carbon nanoparticles, may lead to the successful reduction of vector populations, since the sub-lethal doses of these nanoformulations are toxic towards the Culicidae, but not to their natural enemies. Notably, they are also able to boost the biocontrol agent predation rates [34–39].

6. Conclusions and future challenges

Overall, since there are no specific treatments for Zika virus infection, as well as for other emerging arboviruses of public health relevance, the effective control of mosquito vectors with eco-friendly tools is of crucial importance. Besides the use of synthetic and plant-borne repellents to avoid Culicidae bites, as well as the classic pesticide-based control programs targeting mosquito young instars, further effective options will include radiation, transgenic and symbiont-based control approaches. In

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