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Long term prevention and vector control of arboviral diseases: What does the future hold?

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ABSTRACT

Background: Arboviral diseases are a global growing problem due to climate change, urbanization, population density, and global transportation. However, new technologies currently being developed in research labs are expected to play a relevant role in combatting arboviral diseases in the future, reducing the health and economic burden imposed by these diseases.
Objectives: This paper aims to anticipate the technologies that might be relevant for prevention and vector control of arboviral diseases in the future.
Methods: A web-based survey was conducted of over 2,000 experts from all over the world. Both the technologies and the respondents were identified from recent scientific publications on arboviral diseases indexed in the Web of Science Core Collection.
Results: Our results show that within 20 years the enveloped virus-like particles-based vaccine and the gene-edited mosquitoes through CRISPR/Cas9 will likely be the most promising technologies for, respectively, prevention and vector control of arboviral diseases.
Conclusions: If these expectations are confirmed, these new technologies, when fully developed, may support global public health efforts aimed at reducing transmission, mortality and morbidity of arboviral diseases.

Introduction

Arboviral diseases together account for around 17% of the estimated global burden of communicable diseases, and kill more than 700,000 people every year. More than 80% of the global population live in risk areas from at least one major vector-borne disease, and morbidity and mortality rates are higher in poorer populations (World Health Organization, 2017). These diseases restrict economic and social development and have a major toll on economies, including lost productivity and reduced working time.

Interventions designed to control arboviral diseases rely almost exclusively on insecticide-based approaches (Thomas, 2018), but widespread insecticide resistance in the vectors is now a challenge for public health authorities around the world (Weetman et al., 2018). Outbreak prevention and response remains reliant on vector control (Weetman et al., 2018). However, new technologies currently being developed in research labs are expected, in the future, to be more successful than traditional ones in dealing with arboviral diseases, reducing the health and economic burden imposed by these diseases (Achee et al., 2015). These include new diagnostic tools and serological tests (Nicolini et al., 2017), antiviral treatments (Parashar and Cherian, 2014), vaccines (Robinson and Durbin, 2017), and social interventions (Fritzell et al., 2016).

Therefore, the aim of this paper is to anticipate the emerging technologies that may play an important role in combatting arboviral diseases in the future. The focus of the research is mainly on vector control and vaccines, since combining these two interventions is seen as the best way of tackling these diseases (Achee et al., 2015). As such, a web-based survey of researchers with expertise in arboviral diseases was conducted. These experts were identified from scientific publications related to these diseases indexed in the Clarivate Analytics Web of Science Core Collection (WoS).

Few studies have attempted to foresee the emerging technologies most likely to be employed in the fight against arboviral diseases in

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the future. Most of them are based on literature reviews or address some specific arbovirus or technology (Achee et al., 2015; Messina et al., 2015; Reegan et al., 2016; Robinson and Durbin, 2017; Schaffner and Mathis, 2014). This study goes beyond the existing research by presenting a more comprehensive landscape on the future of arboviral diseases prevention and control based on the views of 2,155 experts from all over the world. In healthcare and public health fields, expert opinion future-oriented studies are becoming increasingly used to support decision making and long-term planning (Masum et al., 2010; National Institute for Public Health and the Environment, 2018; Schoemaker et al., 2019).

Materials and methods

In order to identify technologies that might be relevant for the prevention of arboviral diseases or the control of their vectors in the future, a literature review was conducted, based on recent scientific publications indexed in the WoS. The publications were identified according to the following search strategy:

(ts = ((dengue* or zika* or Chikungunya* or “Aedes aegypti*” or “yellow fever*” or arbovirus*) and (future* or foresight* or forthcoming* or prospective* or imminent*))) AND DOCUMENT TYPES: (News Item OR Review OR Editorial Material)

Indexes = SCI-EXPANDED Timespan = 2013–2018

The search strategy combined thesaurus terms from the Medical Subject Headings (ncbi.nlm.nih.gov/mesh) for arboviruses and free text words for terms related to the future. It was applied to the WoS advanced search mode using the tag Topic (ts), which covers the fields’ title, abstract, and keywords. The Science Citation Index Expanded (SCI-EXPANDED) was used to retrieve the natural science publications. The timespan was set to the last five years to collect recent information on emerging technologies.

This search yielded 92 records of publications. These were then downloaded (in PDF format) and imported into the reference management software Citavi 6.1., where, after reading the full documents, 54 were selected, from which six groups of technologies were identified to form the basis of the questionnaire. Next, a web-based survey was carried out to identify researchers working in arboviral diseases. These were found from the email addresses on recent scientific publications indexed in WoS, according to the following query:

(ts=((dengue* or zika* or Chikungunya* or “Aedes aegypti*” or “yellow fever*” or arbovirus*))

Indexes = SCI-EXPANDED Timespan = 2013–2018

The search took place in October 2018 and yielded 19,659 records of scientific publications (all document types). The tag “topic” (ts) searched for variants of arboviral diseases and vectors in the publications’ titles, abstracts, and keywords. Only documents indexed in SCI-EXPANDED were retrieved because the aim was to find out about the expectations of natural scientists. The timespan was again set for the last five years (2013–2018) to identify authors who had published research findings recently.

All 19,659 records were imported into the data/text mining software VantagePoint 10.0, yielding 19,824 different authors’ email addresses, using the Super Profile script. About 79% of the emails were subsequently linked to their account owners using an in-house Python script. The list of respondents was then uploaded to the online survey platform SurveyMonkey (surveymonkey.com/), where the survey was managed. The number of emails was reduced to 15,417 after uploading due to opted out and bounced contacts.

The questionnaire covered a time horizon of 20 years (2018–2038) and was structured in three parts. The first part was designed to ascertain the respondents’ level of knowledge on arboviral diseases. Those who reported having no knowledge did not answer the rest of the questionnaire and were disqualified from the survey. The second part asked the respondents to indicate their expectation on whether arboviral diseases would still be a public health emergency of international concern in the next two decades. The final part was designed to gather the respondents’ expectations on six groups of emerging technologies: five in vector control (repellents, insecticides, mosquito traps, gene-edited

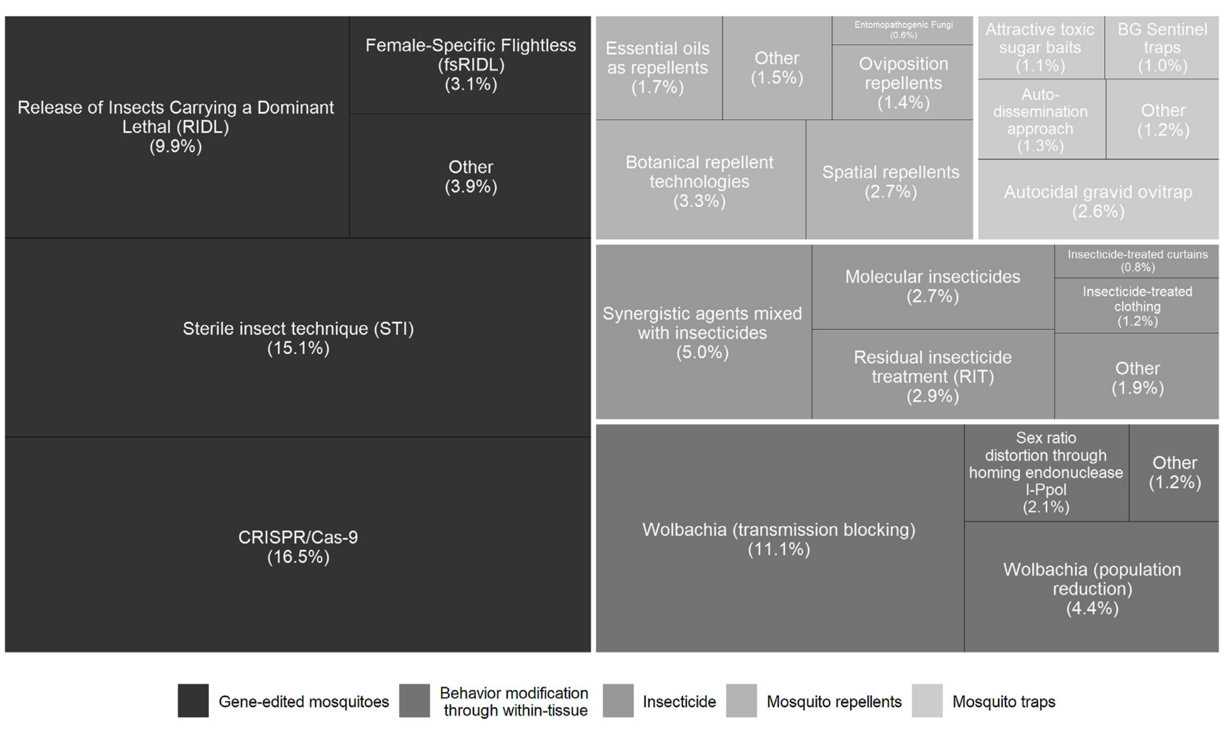

Figure 1. Ranking of vector control technologies most likely to succeed in undermining arboviral diseases in the next twenty years.

mosquitoes, and behaviour modification through within-tissue technologies) and one in prevention (vaccines). First, they were asked which of the five groups of vector control was the most likely to succeed in undermining arboviral diseases (e.g., repellents) and then, within the selected group, which specific technology was the most promising (e.g., botanical, spatial, essential oils, oviposition or entomopathogenic fungi repellent). For vaccines, the respondents were asked to rank four different technologies from the most likely to the least likely to succeed.

Prior to the formal study, a pilot survey was run with a random sample of roughly 5% of the list of emails (717) to test the questionnaire, get the respondents' feedback, and assess the study protocol. The 35 respondents who answered the pilot did not give any suggestions, so neither the questionnaire nor the study protocol was modified. The data collected at this stage was therefore included in the statistical analysis of the survey.

The web-based survey was conducted in November 2018 during a two-week period. All the respondents were informed about the purpose of the study before data collection in the invitation email and subsequently in the reminder emails. They were also notified that all the data collected would be anonymous and individuals would not be identified. Those who agreed to participate voluntarily answered the questionnaire, which was available for completion for eight consecutive days after the invitation email was sent. Suggestions from the relevant literature on web surveys were considered to get optimal results. The emails included the author's name, the title of the author's publication, the purpose of the study, a link to the questionnaire, and the period of time in which it would be available. Three reminder emails were set up to be sent to non-responders (Sauermann and Roach, 2013).

Results

The response rate to the survey was 14.3% (2,204 responses). The 15,417 invitations sent out yielded 2,155 valid responses (already excluding 49 from the 'no knowledge' category), 1,863 (86.45%) of which consisted of fully completed questionnaires. This result is statistically significant based on a representative sample with a confidence level of 99% and a margin of error of 3%. Sixty percent of the valid responses were from respondents with a good knowledge of arboviral diseases, while 38% were from researchers who reported having some knowledge of the subject. The results reported in this paper are from these two knowledge groups combined, since there was no statistically significant difference between them.

First, respondents were asked to share their opinion on whether arboviral diseases will still be a public health emergency of international concern in the next two decades. Of all respondents, 95,7% believe this hypothesis to be likely, compared to 2,22% that think this is unlikely and 2,08% that considered it to be unknown.

Next, in the section containing technology-specific questions, the experts were initially asked which of the five groups of vector control technologies would be the most likely to succeed in undermining arboviral diseases in the future. Then, they were asked to pick the most promising technology from the selected group. Figure 1 presents the results. The most promising group of technologies was believed to be gene-edited mosquitoes (49.25%), followed by behaviour modification through within-tissue technologies (19.23%). The former includes altering mosquito genes and the latter involves the introduction of new agents to mosquito tissue. The other three groups of technologies – insecticides (14.54%), repellents (9.39%), and traps (7.59%) – were not expected to have much of an impact in the next two decades.

Of all the vector control technologies, CRISPR/Cas-9 (16.5%) was considered the most likely to succeed in undermining arboviral diseases within 20 years. Next, sterile insect technique (STI) (15,1%) and release of insects carrying a dominant lethal (RIDL) (9,9%) were other technologies highlighted by the experts in the gene-edited mosquitoes group. *Wolbachia* (virus transmission blocking) ranked third, with 11.1% amongst all types of technologies and first within the behavior modification through within-tissue group.

Next, the respondents were asked to rank four vaccine technologies from most likely to least likely to succeed in preventing arboviral diseases. The technologies in question were virus-like particles (eVLPs), DNA-based methods, baculovirus-insect cell expression systems, and mosquito saliva-based immunization strategies. Traditional approaches such as inactivated or attenuated vaccines were not included because the latest literature indicates that these more novel methods are the most promising

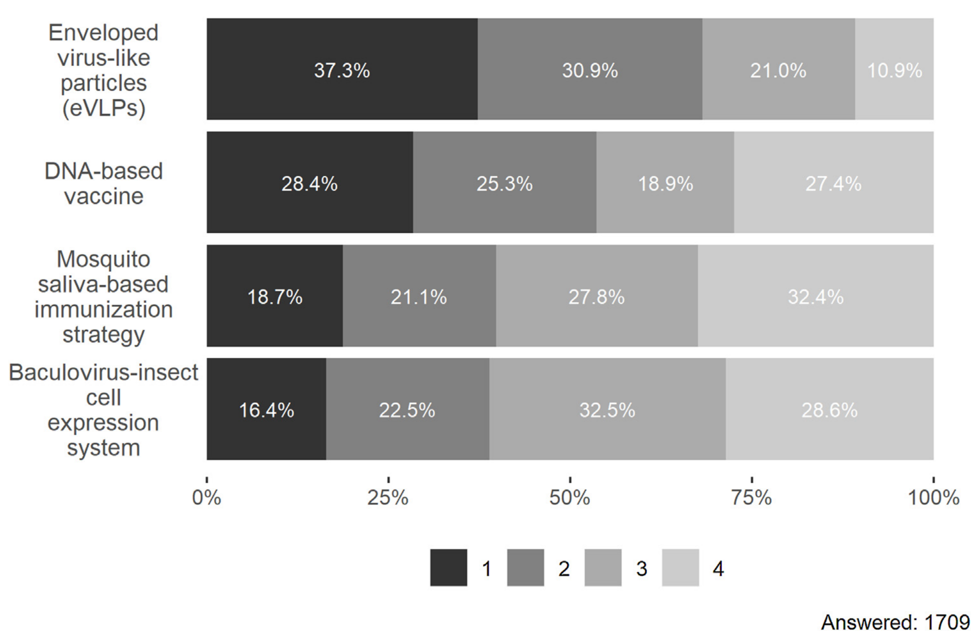

Figure 2. Ranking of vaccine technologies most likely to succeed in undermining arboviral diseases in the next twenty years.

techniques for the coming two decades (Graham et al., 2018). Figure 2 shows the results.

The first choice for 37.3% of the respondents and the second choice for 30.9%, eVLPs were considered the most promising vaccine technology. The DNA-based vaccine ranked second, being the first choice for 28.4% of the respondents and the second for 25.3%. The baculovirus-insect cell expression system (also known as baculovirus expression vector system, or BEVS) was the first choice for only 16.4% of the respondents, while the mosquito saliva-based immunization strategy had the highest percentage of last choices (32.4%). These technologies ranked third and fourth, respectively.

Discussion

Arboviruses are a group of viruses that infect vertebrate hosts through insect vectors, such as mosquitos or ticks. They include members of the *Togaviridae, Flaviviridae, Bunyaviridae, Rhabdoviridae, Reoviridae*, and *Orthomyxoviridae* family of viruses (Hernandez et al., 2014). In recent decades, some flaviviruses have emerged around the world and are now considered a major 21st century global public health challenge, including yellow fever, dengue, chikungunya, and Zika (Weetman et al., 2018).

Flaviviruses emerged about a thousand years ago, and evidence suggests some of them were originally monkey viruses (Holmes and Twiddy, 2003). Their recent resurgence is down to a number of factors, including urbanization, increased population density, and a large and growing web of international transportation systems (Gould et al., 2017). Climate change is also having an effect on vector-borne diseases, since mosquitoes can only multiply in specific climate and ecological conditions (Lillepold et al., 2019). The crisis following the Zika epidemic across South America in 2015–2016 and its association with microcephaly in newborns has also raised global awareness of arboviral diseases (Weetman et al., 2018). There are currently many public health strategies in the prevention and control of arboviruses and maintenance of those strategies combined with new technology developments are key to long term prevention and vector control of arboviral diseases.

Regarding the survey results, considering the threat that these diseases pose almost all of our respondents expect arboviral diseases to be a public health emergency of international concern (PHEIC) in the next twenty years. A PHEIC is a formal declaration by the World Health Organization (WHO) and, to be considered a PHEIC, a disease has to meet two criteria: constitute a high risk to other countries through its international spread, and potentially require an immediate, coordinated international response (World Health Organization, 2005). To this date, only four diseases have been put on this list: H1N1, in 2009; polio and Ebola, in 2014; and Zika, in 2016.

For technology alternatives more likely to be relevant in the future, despite being cheaper and having a track record over many years in the fight against arboviral diseases, traditional approaches such as the use insecticides, repellents and traps were not pointed out as relevant by many of our respondents. On the other hand, gene-edited mosquitoes using CRISPR/Cas9 (clustered, regularly interspaced, short palindromic repeat/CRISPR associated) techniques were highlighted by most of our respondents.

CRISPR/Cas9 is a bacterial adaptive immune system that is being used as a tool in genome editing in various fields (Taning et al., 2017). Alterations in *Aedes* mosquito genes have been made with other tools such as TAL-effector nucleases (TALENs) and zinc-finger nucleases (ZFNs), which work differently than CRISPR/Cas9. The latter is able to generate site-specific mutations rather than engineering a DNA-binding protein, as is the case of the other two (Kistler et al., 2015). Recent work has shown that the CRISPR-Cas9 system is an effective tool for genome editing in *Aedes* mosquitoes (Kistler et al., 2015). However, there are still concerns over the biosafety of this approach, due to its potential to alter entire populations and ecosystems (Taning et al., 2017). Compared with the second most selected technology, the sterile insect technique (SIT), CRISPR/Cas9 provides both a lower release scale and lower duration and resistance to immigration pressure, reducing intervention time and costs (Adelman and Tu, 2016).

Another possibly promising technology was SIT, which consists of releasing male insects that are sterilized using ionizing radiation (Hendrichs and Robinson, 2009). This technique has been used for some time and has proved effective for controlling insect populations. However, it still faces several challenges, including sex separation methods, marking systems, and the mass production of sterile males (Kalajdzic and Schetelig, 2017). This type of genetic strategy provides effective mosquito control only as long as sterilized male mosquitoes continue to be released, which calls for a long term commitment (Adelman and Tu, 2016).

In the next technology group, behavior modification through within-tissue, the most relevant was transmission blocking using *Wolbachia*. *Wolbachia* are natural bacteria present in nearly 60% of insect species, but are not found in *Aedes* mosquitoes. By introducing them to these mosquitoes, their reproductive capacity could be reduced or resistance to RNA viruses could be induced (Kamtchum-Tatuene et al., 2017). The transmission blocking strategy involves reducing infection rates, virus loads, transmission, and dissemination (Johnson, 2015). There are different strains of naturally occurring *Wolbachia* available, and so far only a few of them have been tested on *Aedes* mosquitoes. These different strains of *Wolbachia* have different intracellular characteristics and present different tropisms within hosts (Ant et al., 2018).

The release of insects carrying a dominant lethal (RIDL) was also well evaluated, being selected by 9.9% of the respondents. RIDL is a form of SIT, where a transgene system is used to induce repressible female-specific lethality. Despite ranking fourth in our survey, this technology is considered to be an evolution from SIT because it does not require sterilization by radiation. In this case, a dominant lethal transgene is inserted and its expression is artificially repressed to allow the insects to be reared (Alphey et al., 2013).

There is a growing consensus among specialists that no single intervention will be sufficient to control arboviral diseases and that public health policies will likely rely on a combination of vector control approaches and vaccination (Achee et al., 2015). There are currently many challenges regarding vaccination for arboviral diseases, including difficulties to reach a high coverage for arboviral vaccines and higher prices.

Experts expect eVLP vaccines as the most likely to be relevant in the near future. This technology involves supra-molecular assemblages that have key immunologic features of viruses but lack the viral genome. Its flexible structure allows it to accommodate multiple copies of antigens and to create more potent immune responses (Mohsen et al., 2017). The eVLP technology is regarded as a promising candidate for future vaccination for different diseases because of its safeness and effectiveness in inducing potent immunogenicity (Pitoiset et al., 2015). In fact, recent vaccines are already using this technology, such as GlaxoSmithKline's Engerix® (HBV) and Cervarix® (HPV), and Merck and Co., Inc.'s Recombivax HB® (HBV) and Gardasil® (HPV) (Mohsen et al., 2017; Pitoiset et al., 2015).

The DNA-based vaccine ranked second. This technology is also an evolution from previously inactivated or attenuated vaccines, but unlike VPL-based vaccines, it involves introducing plasmid containing the DNA of the antigen delivered into the skin or muscle (Ferraro et al., 2011). This type of vaccine can yield a strong and lasting immune response because the plasmid containing the antigen's gene is expressed by the cellular machinery of the person receiving the vaccine (Josefsberg and Buckland, 2012).

Next, BEVS ranked third. BEVS is a technology that enables the production of recombinant proteins and is well known for its applications in protein production for basic research and vaccines. There is even some discussion as to whether BEVS could be combined with VLP for increased production of antigens and cost reductions (López-Vidal et al., 2015). As for the saliva-based immunization strategy, despite receiving less attention in the literature, it is considered a creative solution for immunization because immune factors present in the mosquitoes' saliva are what account for the disease's establishment[8]. A subunit vaccine using mosquitoes' salivary proteins could potentially undermine features responsible for disease transmission. However, given the relatively less attention received by this strategy, the results in our survey were not unexpected.

The research method could have certain limitations. There could be a response bias, meaning that the respondents could overestimate the success of the technologies they were most familiar with because they were invested in them. Over-optimism in predictions for the future is nothing new and is well documented in the literature (Brandes, 2009). However, the possibility of over-optimism in future studies does not preclude the use of expert opinion-based methods (Cuhls, 2001; Grupp and Linstone, 1999). Another limitation is uncertainty when dealing with large time-spans. However, the literature shows that expectations about the long-range outcomes of a certain technology are usually more pessimistic than they are for short-range predictions (Linstone and Turoff, 2002). The twenty-year timespan adopted here should help overcome the problem of over-optimism.

Finally, it was decided not to include demographic questions in the questionnaire because age, gender, ethnicity, education, employment, location, etc. were not expected to interfere with our results. Specific populations are less likely to have a selection bias (Schonlau et al., 2009), thus we did not include demographic data as a means of measuring selection bias in participants through sample weighting (Armstrong and Overton, 1977; Bethlehem, 2010).

Conclusion

This paper presented the results of a web-based survey on the future prevention of arboviral diseases and control of their vectors. The results indicate that arboviral diseases will still be a major global public health problem in the next twenty years. Traditional vector control strategies such as repellents, insecticides, and traps were considered less likely to have a positive impact in the future – perhaps because they are susceptible to resistance by mosquitoes after being used for some time (Norris and Coats, 2017). To fight these diseases, gene-edited mosquitoes were reported as the most promising vector control approach, especially through CRISPR/Cas-9. For their turn, eVLP-based vaccines were considered the most likely to succeed in preventing arboviral diseases. It is hoped that the findings will help governments and science and health organizations to plan and allocate their budgets to address this major public health issue.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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