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12. Outbreaks of arboviruses, biotechnological innovations and vector control: facing the unexpected

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Abstract

Outbreaks of arboviruses have occurred in the last decades in many places around the world and a variety of responses have been taken in order to control them. Responses ranged from vaccination campaigns to the use of conventional vector control methods. Innovative approaches relying on biotechnological novelties, often still under development, have been considered despite the lack of solid evidence of their efficacy. While discussing these different aspects of the fight against vector-borne diseases with a focus on the context of outbreaks, this chapter considers the social and ethical aspects related to both the rhetoric and the discussion about the implementation of new and innovative approaches.

Keywords: *Aedes*, delay, emergence, hype, mosquito, risk, Zika

Introduction

A number of outbreaks of emerging or re-emerging arboviruses has been hitting populations worldwide in the last two decades in an unusual diversity and magnitude. They have been fought with a number of different tools, mainly in order to control the vectors. Even though some of these methods are well known for their efficiency when properly deployed, the difficulties experienced in the management of these epidemics have led, in some circumstances, to consider novel methods relying on biotechnological innovation. This occurs even while the measures are still under development and are lacking the required insight for their efficient use in public health. It appears then important to question the associated infatuation with a particular method and to look back at past achievements in the control of vector-borne diseases.

A bit of history

When considering innovations and the difficulties we are facing in the control of vector-borne diseases it seems indeed reasonable to look at what we can learn from history and especially from the success in the fight against vector-borne diseases obtained with proven, scalable and efficient vector control methods and tools. Not only the classical example of the eradication of the malaria mosquito *Anopheles gambiae* from the north-eastern part of Brazil quickly comes to mind (Killeen 2003, Killeen *et al.* 2002), there are also a number of other examples where populations of *Aedes* spp. have been drastically reduced, especially in Latin America and the Caribbean (Gorgas 1901, 1905). When looking at the map of Latin America (Figure 1) indicating the fluctuation of the presence of the yellow fever mosquito *Aedes aegypti* over 80 years (Gubler 2011), it appears clearly that while this vector was largely absent from a number of countries at the beginning in 1970, it has now reinfested a large part of the region, even being present in places where it was not detected in the nineteen thirties. This has obviously been associated with the presence and spread of dengue haemorrhagic fever in the sub-continent (Figure 2).

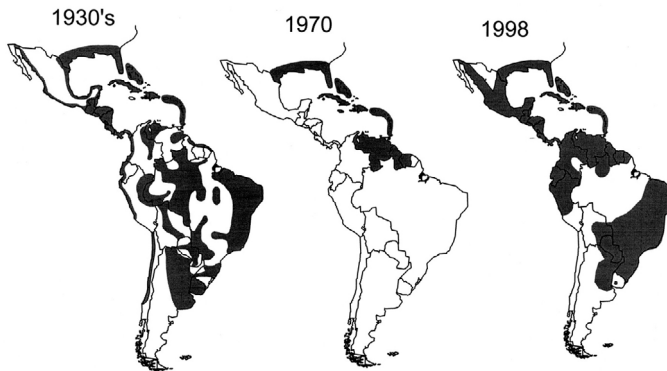


Figure 1. The distribution of *Aedes aegypti* in the Americas between the 1930's and 2015.

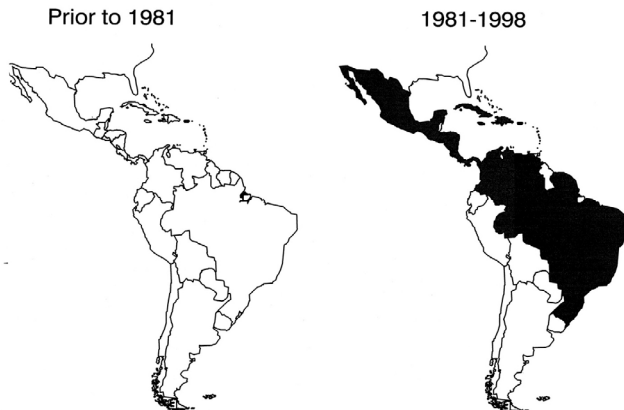


Figure 2. The spread of dengue haemorrhagic fever in the Americas.

What are outbreaks?

Outbreak or epidemic

Disease outbreaks or epidemics are localised increases in the numbers of cases of illness that are clearly in excess of normal expectancy. While an outbreak is usually limited to a small focal area, an epidemic covers larger geographical areas and may have more than one focal point. The number of cases that defines an outbreak depends on past patterns of the disease, the mode of transmission, contact and case fatality rates and potential spread to other areas (WHO 2012).

Worldwide alerts

Even when confined in space and time, outbreaks and epidemics tend to be of global concern. An overview of the online platform Health map (<http://www.healthmap.org/en/>) and a search on the number of alerts on a group of arboviruses (dengue, chikungunya, Zika, yellow fever, Rift Valley Fever, West Nile Virus) generate more than one hundred hits. It reveals the presence of information being reported in the media about these viruses during about four weeks in May/June 2019 (Figure 3). Note that the presence of a dot in Siberia does not indicate the emergence of any of those viruses in this part of the world but the fact that the newspaper 'Siberian Times' published an article warning Russian travellers about the risk of dengue infection in Thailand (Skarbo 2019). While this map aggregates information, this does not reflect the location of an epidemic or an outbreak but the importance with which a given outbreak is reported in online sources. Clearly, concerns about the emergence or re-emergence of vector-borne diseases are global.

Arboviral outbreaks

As mentioned earlier, over the last decades numerous outbreaks of arboviral disease have been hitting human populations worldwide. Dengue outbreaks have occurred in Latin America, in South-East Asia and in the Indian Ocean. More recently the chikungunya virus has emerged in the early 2000s with several epidemics in Reunion Island in 2005-2006 (Josseran *et al.* 2006, Weaver and Lecuit 2015) and again in 2009-2010 before reaching the West Indies in 2014 and the Americas (Chen *et al.* 2016). Despite the existence of an efficient vaccine for many years, yellow fever outbreaks continue to occur as in the Omo Valley in Ethiopia in 2012-2014 (Mulchandani *et al.* 2019) and more recently in Angola in 2016 (Woodall 2016).

Among the recent arboviral emergences, the Zika epidemic is, with little doubt, the one that has been the most reported, the most discussed and probably the most frightening. While first detected on the island of Yap in 2007 (Duffy *et al.* 2009), and next in French Polynesia (Cao-Lormeau *et al.* 2014), it has been of major concern when it was associated with neurodevelopmental abnormalities in

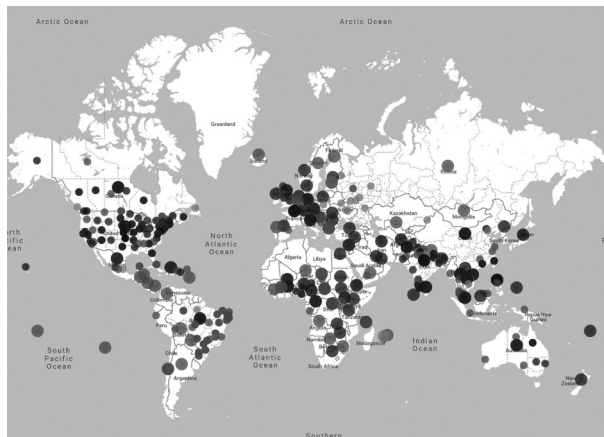


Figure 3. Representation of the global alerts on the presence of several arboviruses (dengue, chikungunya, Zika, yellow fever, Rift Valley Fever, West Nile Virus) in any online sources. The map represents a study done for a period of one month during May and June 2019.

new-borns in the northern part of Brazil in 2015 (Rasmussen *et al.* 2016, Rodrigues 2016). This has even led, in February 2016, to a declaration of Public Health Emergency of International Concern by the World Health Organization (WHO 2016).

The delay

One of the major issues with any outbreak is that it calls for a collective action in the timeliest manner as possible in order to reduce both the spatial and the temporal extension of the disease. This corresponds then to reducing the delay before a collective action is undertaken. As already mentioned in the case of responses to global disease outbreaks (Hoffman and Silverberg 2018), the nature of the delay can be of two types: (1) a delay between the emergence of an outbreak' index case and the detection of the outbreak by health care providers or public health authorities or (2) a delay between the outbreak' detection and the widespread recognition of it as an international concern.

In order to minimise this delay, there is a need for a rapid response as stated in the COMBI document (Communication for behavioural impact – A toolkit for behavioural and social communication in outbreak response) (WHO 2012) and this largely relies on social mobilisation. This is defined by the WHO as 'the process of mobilising all societal and personal influences with the aim of prompting individual and family action'. It is also based on the promotion of the outbreak control with the idea of mitigating the social disruption by communicating with the public in ways that build, maintain and restore trust. Overall, speed of reaction to an outbreak is critical but this should be done in a manner that does not erode the trust of the public nor the expected social mobilisation.

Responses to the outbreak(s)

When considering the responses to several recent arboviral outbreaks it is interesting to look at the differences of the discussion and rhetoric about outbreak management and vector control (Figure 4).



Figure 4. Responses to different outbreaks of arboviral diseases that have occurred in the last 20 years.

Yellow fever in Angola

When the yellow fever outbreak hit Angola in 2015, the major strategy against it was centred on vaccination. Indeed, the disease started to spread in the capital city, Luanda, at the end of 2015 and then to five provinces of the country as well as to several other African countries (Democratic Republic of Congo, Kenya and Morocco) as well as to China because of returning unvaccinated Chinese workers (Boëte 2016). Given the vaccine shortage leaving a high risk of expansion of the disease, an interim solution was suggested with the use of a one-tenth-dose vaccination (Monath *et al.* 2016). Not only was this evidence of a lack of adequate means in front of an epidemic with a pathogenic agent known since decades, but also the lack of an efficient regional coordinated plan to ensure a quick reaction toward an epidemic.

Chikungunya in Reunion Island

Chikungunya emerged in Reunion Island in 2005 (Josseran *et al.* 2006) and, in the absence of a vaccine, the response has been on vector control with a variety of tools and methods: the removal of breeding sites, the use of larviciding as well as the killing of adult mosquitoes with fumigation.

Dengue in Reunion Island

When dengue fever started affecting Reunion Island in 2018, the answer was very similar to the one against the earlier 2005 chikungunya outbreak and focused again on vector control.

Zika in Brazil

Similarly to other outbreaks, a variety of tools aiming at reducing both the larvae and the adult populations of mosquitoes has been used in the context of the Zika outbreak in Brazil. However, contrary to other recent outbreaks, there also has been a strong interest for novel and innovative approaches and two of them received particular attention: the use of 'release of insects carrying a dominant lethal' (RIDL) (partially-sterile) mosquitoes developed by the British company Oxitec, and the use of *Wolbachia*-infected mosquitoes (Yakob and Walker 2016). In the first case, the idea behind this approach is the theoretical reduction in density of the *Ae. aegypti* population (Atkinson *et al.* 2007) while in the second situation the idea is to replace the local species of mosquitoes by *Wolbachia*-infected mosquitoes purportedly unsuitable for Zika replication (Caragata *et al.* 2016).

As the global concern around Zika arose in 2016, it was important to measure how much evidence was available about the potential efficiency and deployment of such technologies at that particular time.

Innovations: do we have (enough) solid evidence?

***Wolbachia* infection in mosquitoes**

There is much hope for the potential use of *Wolbachia* in the fight against dengue with the approach limiting (or partially blocking) the replication of the virus (Moreira *et al.* 2009). Since several years, there is indeed evidence of the negative impact of the infection of mosquitoes that carry the *Wolbachia* strain *wMel* on dengue replication in both *Ae. aegypti* (Walker *et al.* 2011) and *Aedes albopictus* (Blagrove *et al.* 2012). Some of this information was already available and peer-reviewed at the time of the Zika epidemic in Brazil. At the same time, there was also contrary

evidence published on the impact of the *Wolbachia* strain wAlbB on the replication of the West Nile virus in *Culex tarsalis* (Dodson *et al.* 2014).

Disturbingly, however, there was no evidence of a positive or negative impact of *Wolbachia*-infected *Ae. aegypti* on the replication of the Zika virus at the time of the epidemic. That information became available only later in the year (Aliota *et al.* 2016, Carneiro Dutra *et al.* 2016).

Release of genetically modified partially-sterile mosquitoes

Regarding the other approach considered by Yakob and Walker (2016), the efficacy of genetically modified (GM) partially-sterile mosquitoes OX513A developed by Oxitec to control the Zika epidemic, was also not backed up by solid data. There was no evidence at that time of any positive impact of their use at curbing the number of cases of infected persons in any arboviral epidemic. Note that these genetically-modified mosquitoes are often presented as a sterile insect technique, including by its promoters (Lacroix *et al.* 2012), while in fact, they are able to produce viable offspring. Most of the progeny of an OX513A male does indeed not reach adulthood because late stage larvae or early stage pupae are designed not to survive in the absence of tetracyclin (an antibiotic). However, studies have shown that about 3 to 5% of the progeny of females that have mated with GM OX513A males survive in laboratory experiments (Phuc *et al.* 2007). To make matters worse, a recent study has even shown the introgression of the transgenic population of OX513A males into the wild population in Brazil (Evans *et al.* 2019) increasing the genetic variability of the target population. The only study conducted in Brazil at the time of the Zika epidemics was one whose results were reported by Carvalho *et al.* (2015). While the study was presented as the suppression of a field population of *Ae. aegypti* in the suburb of Juazeiro, Bahia, Brazil, a detailed analysis of the data and especially the ones presented in the supplementary section reveals a different and less satisfying situation for a number of reasons (Boëte and Reeves 2016) (Figure 5). In fact, Carvalho *et al.* (2015) do not compare the adult density in the treated area with the untreated one. There is no direct information about the adult density in the control area. Another disturbing point about the methodology is a change in the methods for the monitoring of the adult mosquito populations during the experiments with aspiration being used in the beginning and mosquito traps later. In their re-analysis of the data, Boëte and Reeves (2016) have presented the estimates of the adult population size for males and females (Figure 5A) as well as comparing the frequency of egg positive traps (ovi-index) in the two release areas as well as in the no-release area (control) (Figure 5B) (Boëte and Reeves 2016). This latter graph clearly shows that the *Ae. aegypti* population not only decreased in the two release areas but also in the control one. This highlights the fact that the release of the OX513A partly sterile mosquitoes did not solely lead to a major decrease in mosquito density, making it less efficient than it seemed.

Another important comment regarding the RIDL¹ approach is the statement by the WHO's Vector Control Advisory Group (VCAG) claiming that 'Results from epidemiological trials remain the primary missing information for assessment of the public health value of this product. Epidemiological studies must be carried out to assess the public health value of reducing vector populations through the application of OX513A' (WHO 2017a).

Clearly, recommending the use of these two innovative and under development approaches against Zika appeared as rushing towards methods that at the time had been imperfectly tested.

¹ Recently Oxitec has withdrawn the RIDL technology for further use (source: WHO-VCAG) while currently developing a daughter-killing approach against mosquitoes.

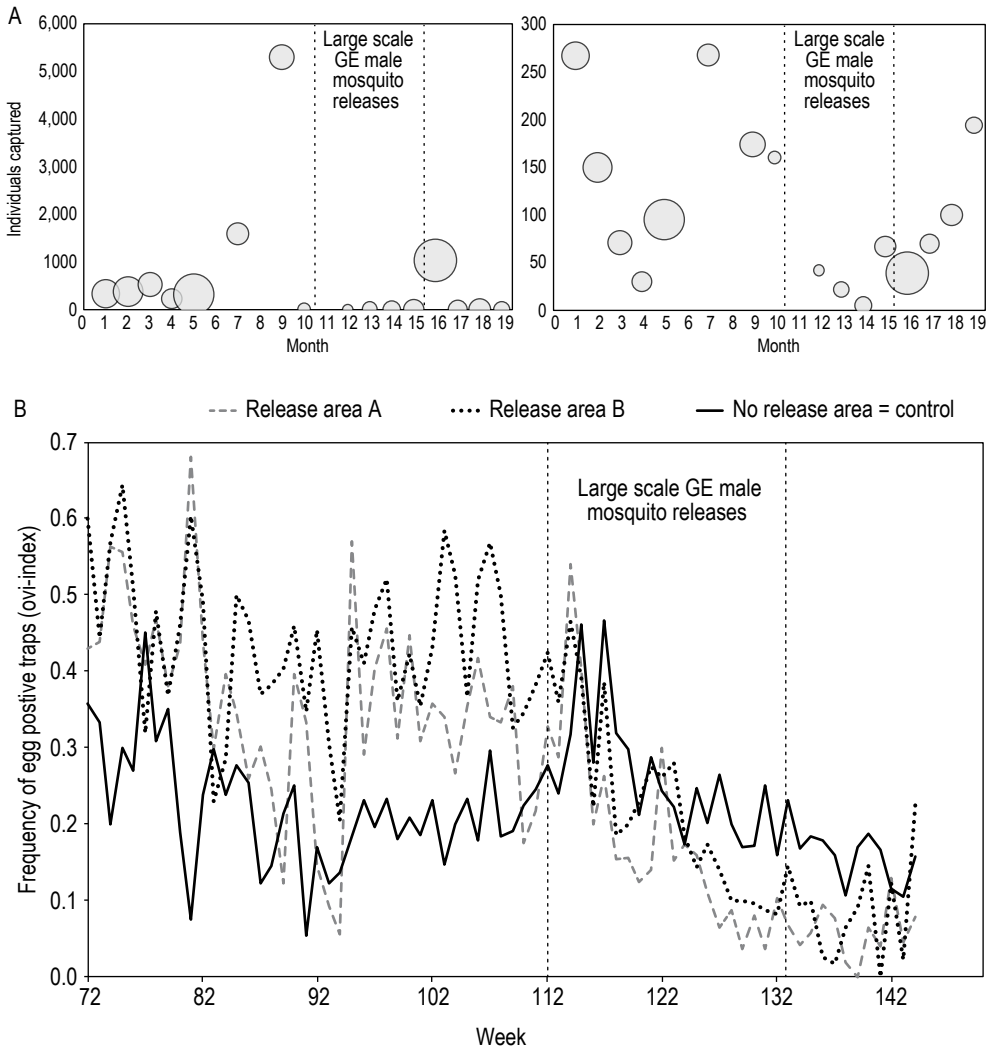


Figure 5. Re-presented data from the largest trial of 'release of insects carrying a dominant lethal' (RIDL) mosquito population suppression in N.E. Brazil. (A) Data from the only RIDL trial to make direct estimates of adult population size. Datapoint size is scaled by monthly collecting effort. The reported value of 95% adult suppression was calculated using only the wild male data (and the frequency of genetically modified males, not shown). (B) Egg trap data providing the basis for the reported 81% population suppression. Note that while the estimates of population size based on egg traps have equivalent control data, the estimate of adults does not. This figure is based on an illustration from Boète and Reeves (2016).

The absence of solid evidence is not only obvious for their entomological and epidemiological efficacy but also for the associated unevaluated consequences at the population level.

Why the obsession?

If the fight against Zika in Brazil was associated with some interest for tools whose evidence about their efficacy was not clear at that time, one might wonder if this is related to the limitation of our ability to deploy efficient tools for *Aedes* management. It may also well be associated with the lure of the novelty and its associated hype. Clearly, this infatuation for recent and 'modern' unproven approaches is not innocuous and the lack of evidence around them goes along with several risks.

Which risks?

Besides the most obvious risk associated with the use of an inefficient tool with which the problem cannot be fixed while it is expected to do so, there are also a number of other major flaws. An incomplete assessment of the tool considered can indeed lead to a premature implementation of the technology and the deployment of interventions that can be, at minimum, ineffective or, at worse, be the source of other problems that need to be solved because the associated risks have not been accurately evaluated. Speed towards the implementation of mis-evaluated approaches could also be easily associated with misinformed policy debates about the real and objective benefits and risks. Of course the risks associated with innovation is clearly not a novel topic in the area of vector control as it has already been the subject of numerous reports and publications dedicated to GM mosquitoes (Lavery *et al.* 2008; WHO/TDR & FNIH 2014). However, some reports were published after the release of such mosquitoes by Oxitec in the Cayman Islands in the fall of 2009.

As this release took many scientists and the public health world by surprise, since then a number of reports about the ethics of GM mosquitoes as well as guidelines for their safe and responsible use have appeared, demonstrating that the scientific world and international organisations consider the potential risk associated with the introduction of new technologies (WHO/TDR & FNIH 2014, James *et al.* 2018); this has led to a different approach to the technology with no release yet until a range of criteria have been met (NASEM 2016; Johns Hopkins Center for Health Security 2020).

However, and apart from the technical aspects of deploying a tool despite lack of evidence, there is also a risk of creating a gap between the promises and the deliveries by not fulfilling the expectations. There is also a real danger to favour or increase the loss in public trust. This clearly does not get along with the recommendations by the WHO where trust is considered paramount in the response to an outbreak (WHO 2012).

Finally, another important risk, which may be overlooked by innovators, is the harmful diversion of research resources as discussed many years ago with the question of the value of investment in genomics in the fight against malaria (Curtis 2000).

Novel tools: which requirements before application?

In the case of an outbreak it has been seen earlier that minimising the delay between the emergence or the detection and the collective action is essential. This can then easily lead to haste in favour of novel and so-called promising tools. There are however a couple of requirements that should not be overlooked even in such pressing conditions. Among the most obvious ones, the efficacy is key and it should not only be at the entomological level but also at the epidemiological one. One should keep in mind that the VCAG recently requested two trials with entomological and epidemiological endpoints in contrasted epidemiological settings when evaluations of novel

tools for vector control are conducted. As a corollary, the effectiveness of proposed tools should enter the equation because cost is often an issue for countries affected by vector-borne diseases. Considering again the case of the patented GM OX513A mosquito by Oxitec, the question of cost remains quite vague with important variations in the estimation of the cost per person per year ranging for a 2-year programme from 10 USD/person/year to more than 40 USD/person/year (Alfaro-Murillo *et al.* 2016, Meghani and Boëte 2018, Notimérica 2015). While this may be related to different contexts, situations or economy of scale, such discrepancy remains troubling and does not help concerned communities and public health authorities to take informed and accurate decisions.

As seen earlier as a major point according to the COMBI document dedicated to the fight against outbreaks (WHO 2012), trust is crucial when a novel tool is considered for implementation; its corollary being the acceptability by the population.

Obviously the question of trust and acceptability leads to several other points: the way risk assessments are performed but also how the deliberations and decision-making process are conducted at the community level (Meghani and Boëte 2018).

Zika outbreak: what was the unexpected?

When considering the Zika epidemic of 2015-2016, the real unexpected aspect of it was the emergence of neurodevelopmental abnormalities with many microcephaly cases occurring in Brazil and the magnitude of their occurrence in the northern part of the country. Less surprising is the vector of Zika, the yellow fever mosquito *Ae. aegypti*. It is not an unknown vector of arboviral diseases and, even worse, it has been responsible for several outbreaks of dengue haemorrhagic fever as well as outbreaks of chikungunya in Brazil in recent years (Nunes *et al.* 2019).

What seems then essential here is to refrain from undermining the existing tools we have to conduct vector control actions even if they are imperfect or challenging to use. This is sadly an old tune we read too often in papers, especially when these latter ones present biotechnological development even without a potentially efficient use in vector control in the near future. Another major point is that vectors and vector-borne diseases management are not the only challenges populations often have to face. As shown for Zika as for many other vector-borne diseases, they tend to affect more often the poorest of the poor (Human Rights Watch 2017). When considering Brazil with about seven million houses with no access to rubbish- and waste collection and 10 million houses with no access to clean water (Henriques *et al.* 2016), there is some doubt that use of a repellent for personal protection twice a day can be a sustainable solution, as stated by Gómez *et al.* (2018).

This calls not only for a questioning the health policies but also for major socio-economic changes able to alleviate the burden of vector-borne diseases among other challenges human populations are faced with. Addressing them would permit to avoid the too often use or promises of a technological fix.

Novel tools: what do professionals expect?

When considering the use and implementation of novel tools in the particular context of an outbreak, it is interesting to notice that the incentive to use them usually arises from members of the academic world or from developers of such novelties. If referring to the recommendations

presented in the WHO report 'Global Vector Control Response 2017-2030' (which is not specifically dedicated to the context of outbreaks) it emphasises the success of the existing strategies of vector control in the global health agenda and the importance of building on broad experience in favour of existing tools in a process favouring the consultation with the affected communities (WHO 2017b). Regarding innovative tools, this report recognises their importance but also recommends that their development follows the recommendations of the VCAG and that the efficacy on vectors and on human infection should be strongly supported by evidence, which is too often not the case apart from long-lasting insecticide-treated mosquito nets (LLINs) and indoor residual spraying (IRS).

Drawing a parallel with a recent Delphi survey (unpublished data, C. Boëte) focusing on the perception of experts in the field of malaria control with a particular focus on emergency settings might be useful too. Even if outbreaks are not equivalent to emergency settings as defined by the WHO (Wisner *et al.* 2012) it is informative to notice that the favoured novel tools for the control of malaria both in emergency settings and in non-emergency settings are mostly next-generation LLINs and IRS whereas high-tech approaches (sterile insect technique via irradiation, genetic modification of insects for population replacement or suppression) receive a much weaker support. Clearly, this highlights the fact that the recommended approaches are the ones in the continuity of the existing tools and their amelioration over disruptive ones. While there is most likely a balance between on the one hand, the amelioration of available tools and the way we use them and, and on the other hand, the innovation of new tools, there is also a need for honesty and reservation when discussing promising results and their potential applications.

Conclusions: next emergence ... the unexpected

If vector control remains the first choice when fighting vector-borne diseases, we should keep in mind a very simple aspect of vector control: tackling a vector species can affect the transmission of more than one virus. As a serendipitous fact, keeping *Ae. aegypti* under control when trying to avoid dengue epidemics can well limit the occurrence and the spread of a Zika outbreak.

This is clearly valid for a number of known (or unknown) arboviruses and their vectors and especially for the future potentially emerging or re-emerging and invading ones that one can hardly and reasonably pick up from a list (Figure 6) of the (more or less known and characterised) usual suspects.



Figure 6. Representation of various arboviruses and their potential vectors that may be (or not) involved in the potential emergence of a vector-borne disease outbreak in the future.

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