An Entomology Agenda to Improve the Human Condition

Briefing Paper

Summit on the Aedes aegypti Crisis in the Americas

Joining Together to Address a Grand Challenge

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Executive Summary

The Entomological Society of America (ESA) and Sociedade Entomológica do Brasil (SEB) are hosting a critically new entomological summit with participation from leaders throughout the Americas. The purpose of this summit will be to explore how, as societies, we can marshal our collective entomological expertise to address mosquito-borne disease in the Americas. The concept is that, if we band together, we will form a novel coalition that can enhance existing efforts as well as develop new initiatives that may significantly contribute to reducing the public health crisis caused by this insect. This Grand Challenge undertaking, while daunting, is practical and will have significant benefits to the constituent societies and our members.

This one-day summit will be held in conjunction with the joint Brazilian and Latin American Congresses of Entomology in the city of Maceió in Brazil in March of 2016. All national societies of entomology are invited to send a representative to attend this important meeting. Additional attendees include important government agencies, industry representatives and interested/potential funding partners.

The work and outcomes of the Summit will identify the key challenges and opportunities that must be addressed to resolve the crisis, ideas for how entomological societies can rally those resources, and an initial action plan to be carried forward in a sustainable manner to ensure success. This effort will be highlighted in a global summit planned for the International Congress of Entomology meeting in Orlando in September 2016.

The Problem

Mosquito-borne diseases, particularly dengue fever and chikungunya, have taken a heavy human toll in South and Central America over the last 10 years. Prior to 1970, only nine countries had ever experienced epidemic dengue. Now the disease is endemic in more than 100 countries and, in the Americas alone, 2.35 million human cases were reported in 2013, and 2.5% of those cases were fatal (1).

Chikungunya invaded the Americas rapidly. The first evidence of a local chikungunya case in the Americas was in December 2013. Since then local transmission has been confirmed in 33 countries and territories of the Americas. By the middle of 2014, a total of 659,367 cases, including 37 deaths, had been reported in the Americas (2). A year later, by mid October 2015, nearly a million new cases had been reported (3).

Most recently, the Zika virus appeared in the Americas. This virus from Africa first appeared on Chile's Easter Island in 2014 and was first found on the mainland in Brazil in April 2015. Since then, it has spread very rapidly throughout Latin America and is now found as far north as northeastern Mexico. Though infection of healthy adults does not produce symptoms as severe as dengue or chikungunya, it appears to be linked to microcephaly in babies born to mothers infected in the first trimester of pregnancy. To date, the incidence of microcephaly in Brazil has increased 20-fold nationally since the Zika virus began to circulate there. It is currently considered the most important public health threat in Brazil.

Prior to these outbreaks, the continent was rocked with epidemic yellow fever in Bolivia, Paraguay, and Brazil in 2007-2008. The WHO fought that outbreak using vaccines, consuming the entire global supply of yellow fever vaccine (4), and just barely avoided catastrophic epidemics in the large coastal cities such as Lima, Caracas, Rio de Janeiro, Buenos Aires, etc (5). Still, with a case fatality rate exceeding 60%, many thousands died and panic ensued (5).

Why did these large-scale outbreaks of different diseases, not seen in decades if ever, all occur in the five years between 2007 and 2013? They are all primarily vectored by the same mosquito, the yellow fever mosquito, *Aedes aegypti*. This mosquito had been the target of an international eradication effort in the Americas that had largely been successful (6). However, as the mosquito population declined to very low levels, eradication efforts were abandoned and the mosquito resurged. As it did, human disease reappeared and the pathogens vectored by this mosquito exploded soon thereafter.

These viruses are not the only ones transmitted by this mosquito and, unless this mosquito can be better controlled, other viruses will cause future outbreaks. We know how to control the mosquito, but we rely on funding sources to support our work. Inevitably, a funding source dries up and our management efforts suffer. The real need here is for a sustainable program that will upgrade existing mosquito management programs, maintain those programs, and allow for incorporation of new research on novel approaches to mosquito management. Such a program must address critical issues in research as well as those in implementation of integrated vector management programs.

Critical Issues

RESEARCH NEEDS

Two mosquito species, *Aedes aegypti* and *Ae. albopictus*, are the principal vectors that must be targeted. Both species breed in human-made containers, are highly anthropophagic but differ in terms of behavior and biology. Both are widely distributed in the Americas, from the United States to Argentina (7) and the critical research needs are similar for both as well. There are many needs, but examples of critical areas of research include insecticide resistance, *Wolbachia*, and transgenic mosquitoes (8).

Chemical Control and Insecticide resistance

Insecticides have been central to vector management for decades, but it is still an active area of product development either for new modes of action or new formulations. One of the most promising new modes of action includes the dopamine receptor antagonists (DRA) that have proven effective in *Aedes* and *Culex* mosquitoes (9). These insecticides can be used as both adulticides and larvicides, have no known environmental impact, are selective to just mosquitoes, and should be cost-competitive with other insecticides. Research leading to development/deployment of these new insecticides should clearly be a top priority.

The major challenge with chemical control is that insecticide resistance is increasingly widespread (10). Several countries have reported resistance of *Ae. aegypti* to organophosphate and pyrethroid adulticides. Both metabolic and target site resistance can be found in field populations. Resistance to the most common larvicides is also growing. Other than rotating insecticides with different modes of action, we have few methods to manage developing resistance. Even in cases where good options are available, they are often poorly utilized. There is a need for better resistance management strategies for mosquito management programs.

Wolbachia

Wolbachia is a genus of naturally occurring bacteria that manipulate the reproduction of their host so as to be vertically transmitted from the mother to offspring. This bacterium is believed to be present in at least 40% of all insect species worldwide but it has not been found in *Ae. aegypti*. When experimentally introduced into *Ae. aegypti*, *Wolbachia* can block dengue virus transmission and significantly reduce Chikungunya virus titer in these mosquitoes. Currently, an international program (in Australia, Indonesia, Vietnam, Colombia and Brazil) is conducting field tests with a *Wolbachia* strain in an attempt to reduce vector competence (11).

Another approach using *Wolbachia* relies on "cytoplasmic incompatibility." When *Wolbachia*-infected males mate with uninfected females the eggs do not hatch, but infected females produce viable eggs whether crossing with infected or uninfected males. Thus releasing *Wolbachia*-positive males only (whereas on the pathogen interference strategy both genders are released) will sterilize wild females and reduce the population. This strategy is similar to the sterile insect technique (SIT) applied to many insects worldwide.

Transgenic mosquitoes

Transgenic approaches for generating sterile males have also been tested in a few countries. In *Ae. aegypti*, a lethal feedback loop was inserted into its genome, producing high levels of a toxic and lethal protein to the mosquito if an antidote (the antibiotic tetracycline) is not present during larval development. Homozygous males that have been raised in the presence of tetracycline mate with wild females and their (heterozygous) progeny die. Field tests in Bahia, Brazil showed that this technique can reduce *Ae. aegypti* populations up to 95% (12).

Newer methods of genetically modifying mosquitoes involve "gene drive" techniques. The idea is to use a gene editing system, such as CRISPR-cas9, to replicate desired (modified) genes from one chromosome to another, thereby causing the modified gene to spread throughout a wild population. Examples of current mosquito research projects using this approach include making *Anopheles* mosquitoes resistant to malaria (13) and disrupting reproduction (14). These techniques are still controversial, but their potential for rapid and widespread reduction in mosquito-borne disease is so great that research in this area should be a priority.

IMPLEMENTATION NEEDS

As noted above, the target species here are peridomestic container-breeding mosquitoes. They are thus mostly problematic in municipalities, often in urban centers with established mosquito management programs. Yet they still continue to transmit disease. The problem is that few cities support best practices in mosquito management, and often haphazardly and/or incompletely control mosquitoes (15). The protocol and best practices of mosquito control are well known (16) – they're just not being utilized. Areas of municipal mosquito control that need improvement include mosquito sampling/mapping for decision making, improved decision tools (e.g. models and thresholds), better execution of control efforts, and improved community involvement programs (17, 18, 19).

The real problem with previous implementation efforts is that they have not been sustainable (15). We know how to control mosquitoes and how to organize our efforts for efficient control, but we have so far not been able to structure programs that persist for decades over wide areas. Traditional approaches to mosquito management programs have not worked for different reasons: single/few investigator programs have been too limited in scope; government programs are eventually discontinued and, in any case, are limited to the jurisdiction of the government; and multi-institution programs are limited to the duration of the funding. Regardless of the reasons, it is clear that a new approach is needed.

Why This Effort is Different

This initiative is different from other efforts in that it will enable national entomological societies in the region to join forces and develop a collective approach for the specific purpose of supporting existing vector management efforts. Each society would recruit members to work on this effort within its own country and focus on creating or contributing to effective, sustainable programs that can be maintained within that country while contributing to a hemisphere-wide effort.

This represents a very different approach to applied vector management programs. This program will increase each individual society's influence within its own country and increase its international visibility. It will encourage new memberships and support, especially from the public health sector. Members who participate in this effort will have funding opportunities to support other work. Finally, and most importantly, each society will be providing a service to fellow countrymen—a service that is sorely needed.

The Summit

There are many questions to answer before starting such an undertaking. What activities, exactly, will be done in this project? Where will money come from and how will it be distributed? What are the specific commitments that are being asked from each society?

To answer these questions (and many more), we call for a summit of presidents of national entomological societies of the Americas. The summit will be held March 13, 2016, in conjunction with the Annual Meeting of the Sociedade Entomológica do Brasil in Maceió, Brazil. At this summit we will discuss how other societies have addressed grand challenges successfully, explore key aspects of the *Aedes aegypti* crisis in the Americas, learn what existing initiatives and funding organizations are doing in this area, and collectively identify the best opportunities for entomological societies to make a contribution.

We ask that each society have a leadership person, preferably a presidential officer, attend this summit, along with a medical entomologist from your country. We would encourage participation by a public health official from your country as well. In addition to society leaders, we will also have representatives from the Pan American Health Organization, funding agencies, industry, and key figures from governmental organizations such as the USA's Centers for Disease Control and Prevention.

This will be a critically important meeting and all national entomological societies, including those that do not have a strong medical entomology component, should be represented at this summit. A more specific agenda will follow this briefing paper in early 2016.

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