

Asian Tiger Mosquito: a RIDL breakthrough



Asian Tiger Mosquito: a serious health threat

The Asian Tiger Mosquito (*Aedes albopictus*), named due to its stripes, is a carrier of a host of diseases including chikungunya, dengue and West Nile virus. Originating in Southeast Asia, it has travelled further afield in the last 30 years due to increased human travel and is now

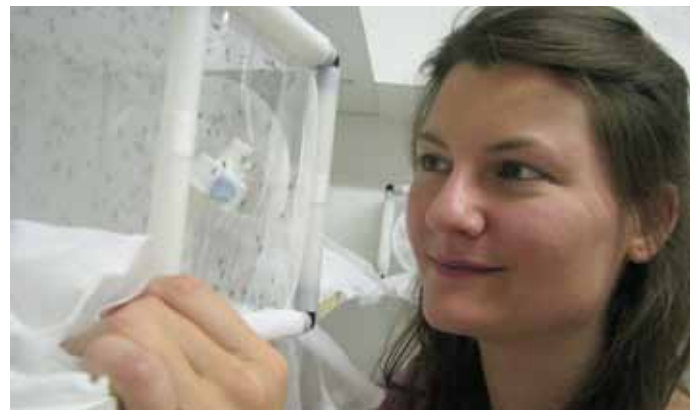
causing concern globally as a serious public health threat in many countries including the USA and China. It has even been detected in Northern Europe as demonstrated in an outbreak of chikungunya, a viral disease, in Italy in 2006. Once established, the virus can spread rapidly. In the same year an outbreak on the island of La Réunion in the Indian Ocean affected a third of the population - approximately 260,000 cases.

Diseases are spreading further afield due to increased human travel.

Conventional mosquito control strategies have so far failed to suppress the Asian Tiger Mosquito adequately and in the absence of either vaccine or antiviral drugs to combat the virus, new vector control options are urgently required.

The RIDL technology developed at Oxitec offers one such hope by providing an environmentally sustainable way to suppress target insect populations. However, the Asian Tiger Mosquito presented particular challenges in

adapting to laboratory rearing. In particular, the mosquito is rather selective about where it gets a blood meal. Oxitec do not use live animals to feed the female mosquitoes, so artificial blood feeding systems needed to be developed.



Geneviève Labbé

The Oxitec team, led by Geneviève Labbé, achieved the first germline transformation of this species and have now developed a RIDL strain of the Asian Tiger Mosquito. This strain shares the central common feature of RIDL strains: that female offspring resulting from a RIDL male mating with a wild female cannot survive. Hence releases of RIDL males in an area could significantly reduce local Asian Tiger Mosquito population.

The Oxitec team, working with collaborators, is now carrying out studies to demonstrate the potential for this new method of protecting people against diseases spread by the Asian Tiger Mosquito.



Healthy people, healthy environment

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Focus on South America: dengue fever

In recent years, dengue fever in South America has reflected the global trend: increasing incidence and severity in dengue cases. Whilst dengue is both seasonal and cyclical, the upward trend throughout the continent is alarming.

However in contrast to the rest of the world, South America has one unique element in its history – namely that through a systematic and highly organised campaign in the 1950s and 1960s, *Aedes aegypti* was almost eliminated from the continent. In 1947, Dr Fred Soper was appointed Director of the Pan American Health Organization (PAHO). He put in place elimination campaigns involving widespread use of DDT throughout the continent such that by 1960 *Ae. aegypti* were certified as eradicated from all but four American countries.

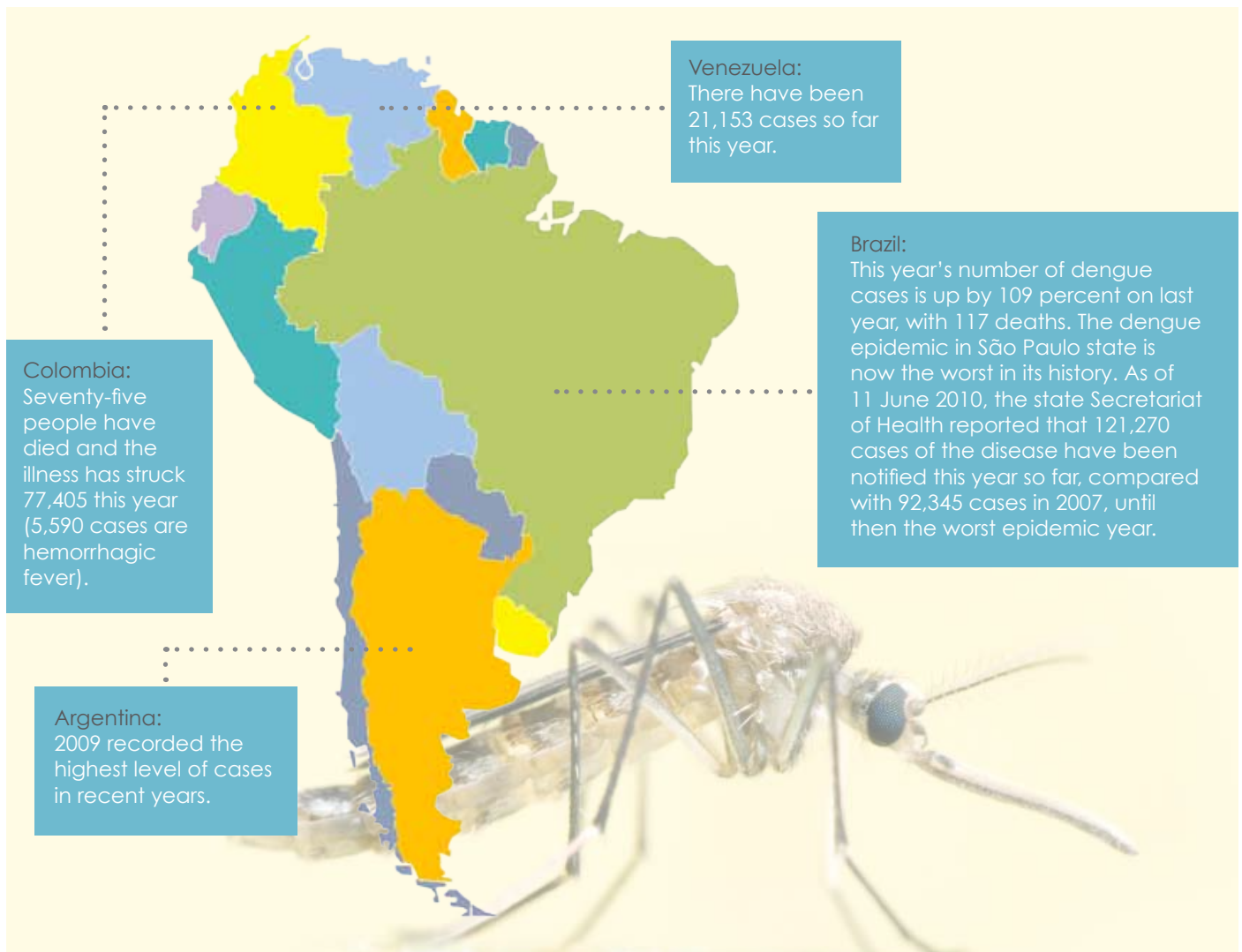
The remarkable resilience of *Ae. aegypti* was then demonstrated. As DDT was progressively withdrawn

and the resources reduced, so *Ae. aegypti* reinvaded the continent. Today the distribution of the species in South America exceeds the maximum range recorded earlier in the 20th century prior to the Soper campaigns.

In 2010, according to PAHO, the countries likely to be hardest hit by this year's outbreak are Brazil, Colombia and Venezuela.

The geographical spread of dengue is also in evidence. Until recently Argentina was free from the disease, but in 2009 the country showed the epidemic at its highest level (25,989 cases reported) since the virus reappeared there in the late 1990s. In El Salvador, Central America, the government declared a national state of emergency for dengue in February 2010.

Oxitec is currently establishing plans to carry out field trials in Brazil in 2011 to demonstrate the potential of the RIDL approach to combat dengue in South America.



The food chain

One of the questions often asked about the use of Sterile Insect Technique (SIT)-RIDL strategies for vector control is how it may affect the food chain. What could be the impact of the loss of the *Aedes aegypti* mosquito from the diet of predators, if Oxitec succeed in locally eliminating the mosquito?

Frequent treatment of mosquitoes make them a poor food source for predators.

Aedes aegypti is an African species of mosquito that has become much more widespread in recent history, with the advent of significant international travel and trade. It has been studied extensively due to its impact on human health. Regarded as an invasive species in most of the world, it achieved Pan-Tropical distribution in the 1930s. *Aedes aegypti* is highly anthropophilic, living exclusively within and around human habitations and relying on any water-containing vessel such as flower pots, buckets and tree-holes as breeding sites. It is sufficiently tied to the environment that accompanies human habitation, that the removal of such breeding sites is a primary means of controlling the *Aedes aegypti* population.

As it is a recent invasive species that has not co-evolved with the native ecosystem (except in parts of Africa), it is highly unlikely that native predators will be



Aedes aegypti larvae breeding in rain water in a shallow container

dependent on this species. Additionally, as it is a disease vector, treatment of *Aedes aegypti* populations by health authorities is often mandatory and so control programmes are frequent, making the mosquito an inconsistent and poor food source for predators. This is corroborated by research conducted in Germany in 1997, which showed that consumption of all mosquitoes represented only a small proportion (0.16%) of an amphibian diet.

Additionally, existing control methods such as insecticides in the form of larvicides, which are added to water, and chemical sprays or fogs, impact many organisms and hence many food chains. By contrast, the suppression of *Aedes aegypti* mosquitoes by RIDL targets this species alone, minimising the environmental impact of treatment.

360 develops new diagnostic kit



360 Genomics, Oxitec's spin out created to capitalise on Oxitec innovations in molecular biology, will begin the manufacture and supply of two kits aimed at detection of BRAF V600E. This is a key mutation responsible for a number of cancers including malignant melanoma, ovarian, colorectal and thyroid cancer. The company's first kits will be supplied both as a stand-alone enrichment process, and as a combined enrichment and detection kit based on

pyrosequencing, which is used routinely worldwide in diagnostics laboratories as a standard method for mutation screening.

Initial trials have proven PointMan's™ enhanced sensitivity and specificity.

The company has also begun trials with a leading UK hospital in Oxford to evaluate its BRAF V600E kit as part of a large clinical trial. Initial data has proven the sensitivity and specificity of BRAF V600E PointMan™ Pyrosequencing kit down to 1:100,000 compared to the leading commercial competitor, which detects down to 1:100. This trial has been designed to establish the clinical relevance of ultra-sensitive detection of BRAF V600E and the potential for early detection, and hence potential treatment, using 360's PointMan™ technology. 360 expect data from this trial to be available later in 2010.

Planning for field trials

An island paradise or an inland town – what makes a good site for a field trial of our RIDL mosquitoes?

As we begin to take our RIDL strains out to the field, we need to select suitable sites for these first trials. But what makes a site 'suitable' is not entirely obvious. There are many factors to consider, from the nature of the target pest insect population at the site to the structures and timescales of the regulatory system of the host country.

In selecting a trial site we consider many factors: from pest population to community engagement to geography and weather.

Some are straightforward issues: for example there must be a pre-existing population of the pest if we are going to demonstrate the population-suppressing power of our RIDL approach. Also, community engagement is an integral part of all trials. Other issues are more nuanced – how large should the site be, how far is it from the operational base, what skills and resources does the customer or in-country partner already have? Are there seasonal fluctuations in the pest population or are natural hazards like floods or hurricanes a concern?

We are developing a comprehensive checklist for systematic comparison of these issues. One factor in particular that affects the choice of site for early-stage trials is the degree of isolation of the site. We want to demonstrate the ability of RIDL to suppress or eliminate a target pest population in a defined area. Therefore an isolated site is important otherwise immigration of the same species moving into the trial area from surrounding untreated areas may distort the result. The border area



Hypothetical field site: a small town surrounded by ocean and uninhabited land

affected by such immigration will vary depending on the pest. For *Aedes aegypti* this might only be a few hundred metres as they do not fly very far. Water, hills and vegetation can all form natural barriers for the insect and can be used to isolate the trial site.

Taking these considerations into account, the Oxitec field team, together with our in-country partners, has identified promising sites for mosquito trials in several countries and discussions are underway with the relevant regulatory agencies.



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