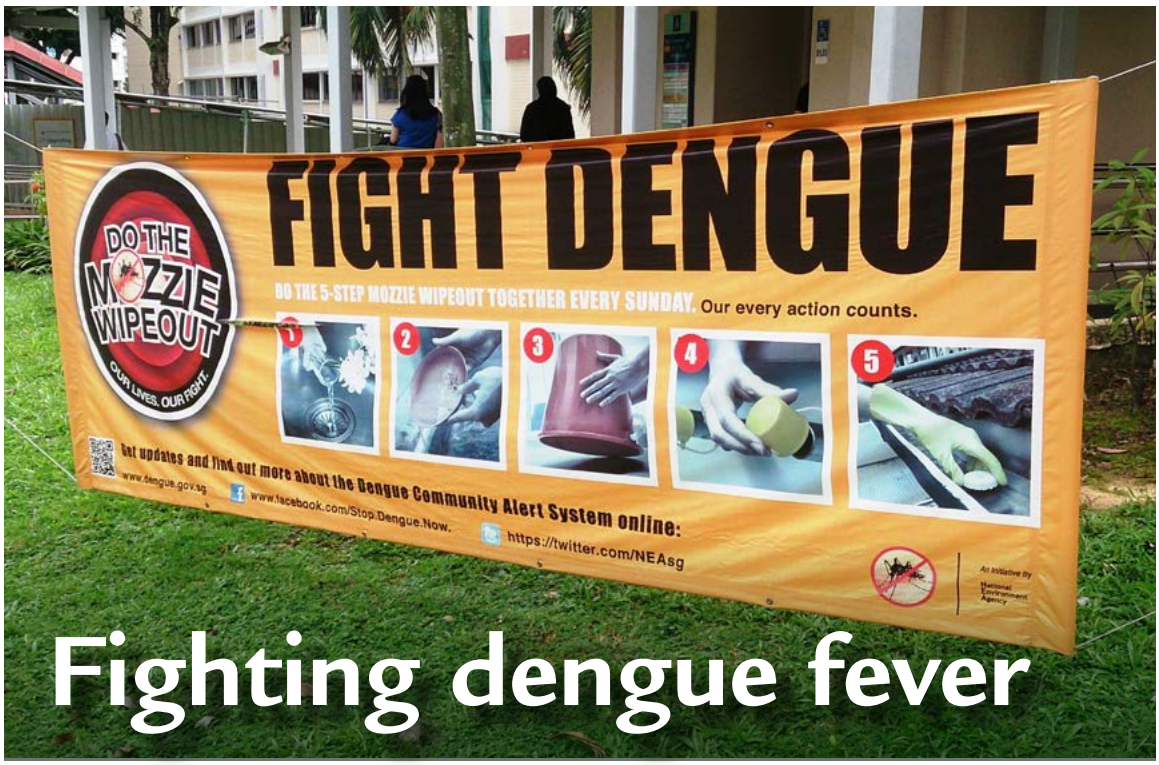
Stefania Hartley



Fighting dengue fever

Key words
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dengue fever
mosquito
bacteria

Stefania Hartley is a science teacher who grew up in Sicily. She now lives in Singapore where she recently contracted dengue fever. She decided to take a closer look at this disease which, according to the World Health Organisation, is the fastest-growing mosquito-borne disease in the world.

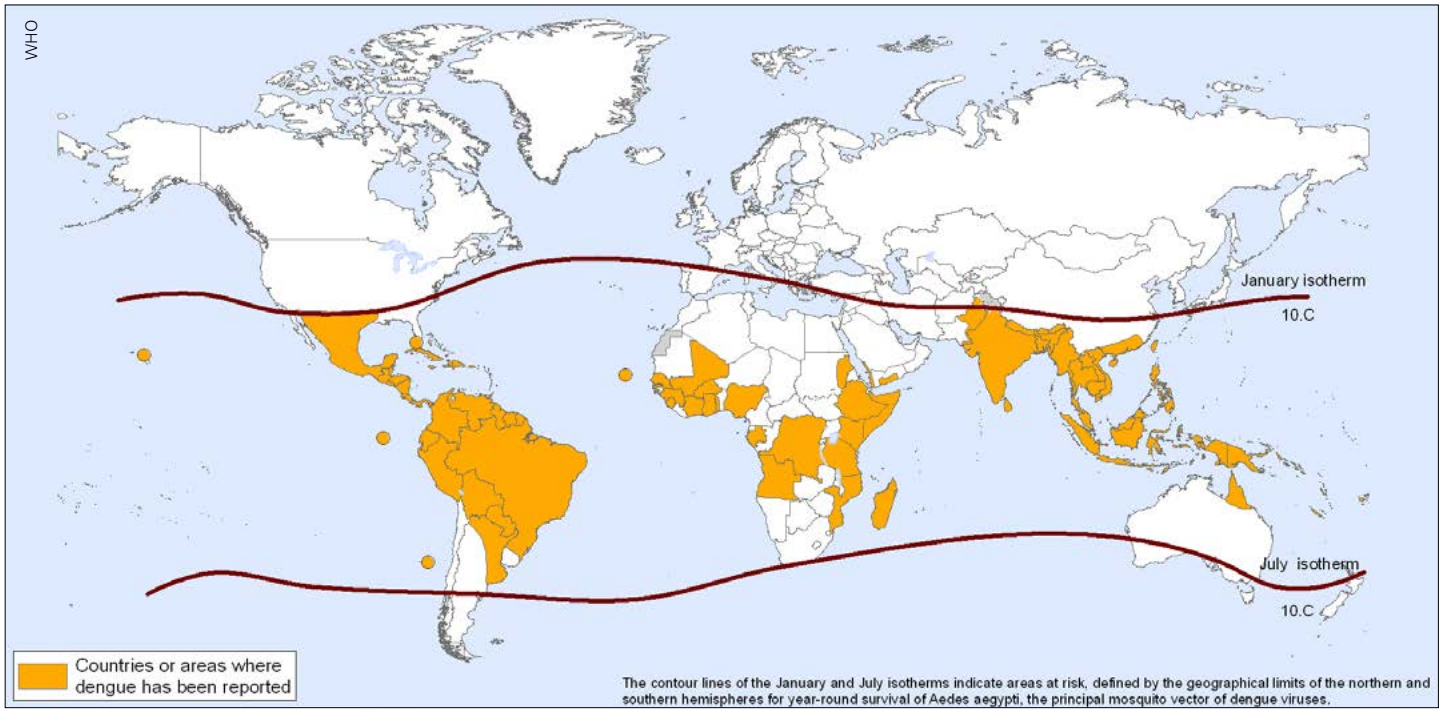
A growing concern

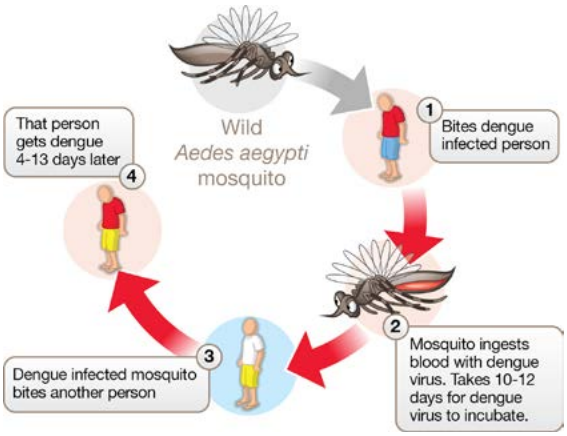
Rates of dengue infection increased thirty-fold between 1960 and 2010, with the disease spreading to countries that had never seen it before (from 9 countries in 1970s to over 100 now). More than 2.5 billion people – about 40% of the world's population – are currently at risk and more than 50 million people contract the disease every year – I was part of the 2014 batch!

Historically affecting only tropical climates, the adaptation of the vector (all the technical terms are explained in the glossary) mosquito to cooler climates is causing the disease to spread to new areas outside tropical regions. In 2010 some local cases of dengue were reported in France and Croatia and in 2012 an outbreak of dengue in the Portuguese island of Madeira caused 2000 infections.

Dengue virus

The dengue virus belongs to the family *Flaviviridae* and is passed from one human host to another through the bite of the mosquito *Aedes aegypti*, the main vector.





The Aedes aegypti*-dengue lifecycle*

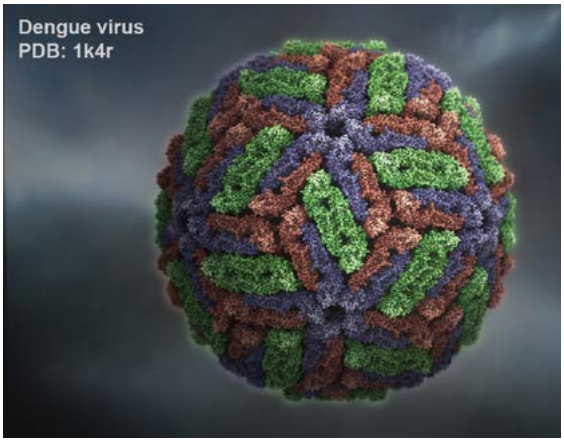
Unlike other mosquitoes, *Aedes aegypti* bites during the day. It thrives in urban habitats, where it breeds in stagnant water found in man-made containers. *Aedes albopictus*, a less common dengue vector, is further cause for concern because, being able to tolerate cooler temperatures, it is spreading to North America and Europe, mostly through the import of goods like used tyres and lucky bamboos (which are mosquito breeding habitats).

'Lucky bamboo' (actually not bamboo but Dracaena braunii*) is often imported in water to keep the plants green. The water can harbour* Aedes albopictus*, a vector of the dengue fever virus.*

Pathogenesis

After a female *Aedes* mosquito takes a blood meal from an infected person, the virus gradually spreads through the body of the mosquito until it reaches the salivary glands. It takes 8-10 days for this to happen (extrinsic incubation) and, from then on, the mosquito will transmit the virus through its saliva at every bite, for the remaining 2-4 weeks of its life.

The dengue virus (a lipid-enveloped positive-strand RNA virus) binds to and enters white blood cells, causing symptoms ranging from mild to severe (in 6% of cases), resulting in death in about 2.5 % of cases.



A model of the dengue virus – the different colours represent different regions of its surface; image from PDB 1k4r by J.Y.Sgro, UW Madison

Initial symptoms are non-specific: fever, severe headache, pain behind the eyes, muscle and joint pain, nausea, vomiting, swollen glands, gum bleeding and rash. If the disease progresses into severe dengue, the liver and the bone marrow can also be affected, causing a drop in blood pressure, platelet and white blood cell counts. Liver enlargement, respiratory distress and damage to various organs with spontaneous internal haemorrhages can also occur. There is no cure for dengue fever so patients are given palliative care and hydration to counteract the leakage of plasma out of the blood vessels. In some cases, blood transfusions are necessary.

How the viruses cause all of this (the pathogenesis) is not entirely known. The intriguing fact is that the highest risk of developing severe dengue doesn't occur during the peak of fever and virus count, but only afterwards, when the patient seems to be recovering. This suggests that the body's immune response might be the cause for the increased severity of the symptoms. The discovery of antibodies against the patients' own platelets, endothelial cells and coagulatory molecules in the blood of patients with severe dengue, support this hypothesis.

Vaccine development

There isn't yet an effective and safe vaccine against the dengue virus, although there are a few at various stages of trial. Developing a vaccine is proving difficult for several reasons:

Our knowledge of the pathogenesis of the disease is incomplete.

There are five types (serotypes) of the virus (the fifth one only discovered in 2013).

There is a danger of Antibody-Dependent Enhancement (ADE), which make it paramount that the vaccine should be equally effective against all serotypes (see Box).

There are no suitable animal models for trials: the dengue virus replicates poorly in mice.

There is a need to keep the cost of the vaccine affordable to those who most need it.

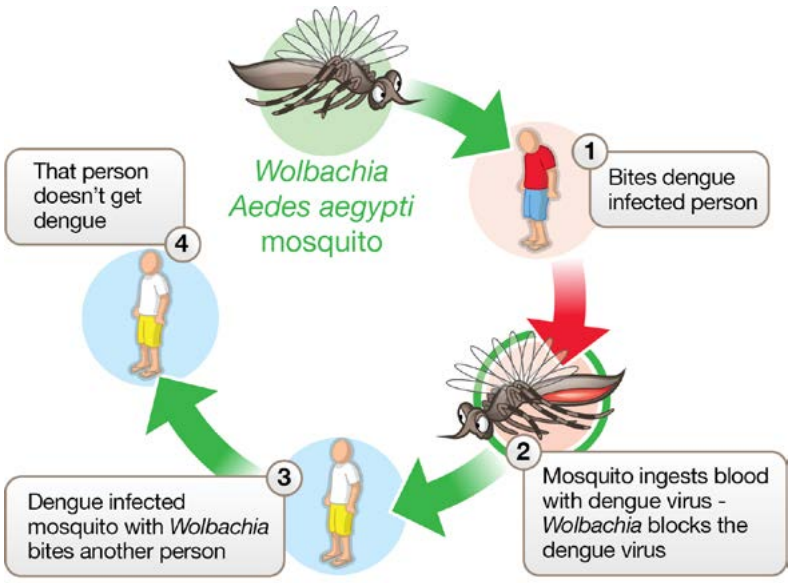
Immunity and reinfection

Once infected with one serotype, patients have lifelong immunity to that serotype but cross-immunity to the other serotypes is partial and short-lived. To make matters worse, patients are at increased risk of developing severe dengue if subsequently infected with one of the other serotypes. The explanation for this is a mechanism called Antibody-Dependent Enhancement (ADE). Some of the antibodies in an ex-dengue patient will partly recognise the new infecting serotype but will be unable to neutralise it. The virus-antibody complex will gain entry into the white blood cells (even those white cells which do not have the usual surface receptors to which the virus binds) through their Fc receptors – those which bind to the Fc region of the antibody.

Vector control

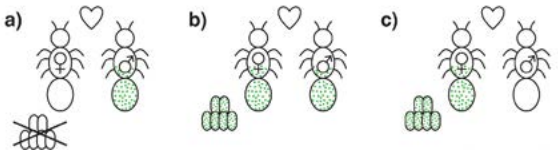
Without a vaccine and without a cure, it's not surprising that vector control is currently the method of choice in the fight against dengue. The firm Oxitec has produced genetically modified *Aedes* mosquitoes which, released into the wild, will mate with their wild counterparts and pass on their lethal traits (features) to their offspring. This method requires periodic releases of GM mosquitoes, as the lethal traits cannot perpetuate themselves.

Another approach, using the *Wolbachia* bacteria, has been developed and tested by a research group at Monash University, Melbourne, led by Prof Scott O'Neill. *Wolbachia* bacteria are naturally found in about 60% of all insect species – not including *Aedes aegypti*. The research group has infected *Aedes aegypti* mosquitoes with *Wolbachia* bacteria and discovered that the presence of *Wolbachia* reduces the mosquito's ability to transmit dengue viruses.



The Wolbachia*-mosquito lifecycle*

Furthermore, once *Wolbachia*-infected mosquitoes are released into the wild, the *Wolbachia* infection spreads through the wild population, so that after only about 17 weeks all the mosquitoes in area will carry *Wolbachia*. This method is thus low-cost and self-sustaining.



How Wolbachia *spreads:* **a** *When a non-*Wolbachia *female mates with a* Wolbachia*-infected male, the eggs do not hatch;* **b** *and* **c** *The eggs of a* Wolbachia *female are infected whether or not the male is also infected.*

Dengue is very common in Brazil. Here the first release of Wolbachia *mosquitos occurs in Tubiacanga near Rio De Janeiro.*

The *Wolbachia* method has also been proven to reduce the *Aedes* mosquito's ability to transmit other viruses for which it is a vector (Chikungunya and yellow fever) and there is hope that this approach will also work on the mosquitoes that transmit malaria and other diseases.

Stefania Hartley lives in Singapore.

Glossary

Extrinsic incubation: the period between when a vector acquires the infectious agent and when it starts being able to transmit the agent to the host.

Pathogenesis: the mechanism that causes the development of a disease, including cellular events and reactions.

Palliative care: care that relieves the symptoms rather than eliminating the causes.

Serotype: within a species, a group distinguished by different antigens.

Vector: an insect or animal that transmits a disease or parasite from one animal or plant to another.

Look here!

More about the fight to eliminate dengue fever: *www.eliminatedengue.com*

Make a model of the dengue virus: *http://bit.ly/1oQ2YXK*