Dengue fever remains a challenge for public health – will biological control be of help in the future?

A bacterium found in the microbiome inhibits the transmission of dengue and Zika viruses.

It's probably too far-fetched to draw a line between the sudden drop of about 60 meters of the Singapore flight SQ 321, which was fatal for two passengers on the 21st of May this year, and the dengue fever. The tropical Indian Ocean was recently identified as a weather hot spot responsible for causing dengue epidemic trends (1). Anyway, the airliner accident happened as it passed through a part of the tropical Indian Ocean. 'Temperature anomalies' out of the blue are dangerous for aircraft, and Myanmar is one of the endemic areas for dengue in Southeast Asia bordering the Indian Ocean. Asia alone accounts for about 70% of the cases, with the year 2023 witnessing a significant surge (2).

Dengue fever in 2023

Countries like Vietnam, Bangladesh, Thailand, and Malaysia reported high numbers. The Americas recorded 4.5 million cases with 2300 deaths (2). Dengue fever is prevalent in over 100 countries in the world's tropic- and subtropic regions and is transmitted by Aedes mosquitos (3).

Clinical features

For most people getting the infection, the symptoms of dengue fever are mild and gone after one to two weeks. For the unlucky patients, a flagrant symptom correctly proves the name of the disease as 'break-bone fever.' The high fever triggers severe headaches and muscle and joint pains. Vomiting, swollen glands, and a rush are not uncommon. The dengue virus belongs to the flavivirus. The group of single-strand RNA viruses causes hemorrhagic fevers, and the dengue virus, in severe cases, causes bleeding gums or noses. The patient might vomit blood and have a dark stool, the symptom of blood seeping into the intestine. The severe symptoms could be observed after the fever and need immediate care, best in an experienced hospital for tropical diseases. In former times, children were affected. However, this changed, and also adults will suffer from the disease (2).

Therapy could only be directed toward the symptoms occurring. For pain, Acetaminophen (paracetamol) should be used, and non-steroidal anti-inflammatory drugs (ibuprofen) and Acetylsalicylic acid (aspirin) should be avoided because of the danger of hemorrhagic events (2). A causative therapy against the virus is missing.

Immunology and vaccination

Vaccination against dengue fever is somewhat tricky. This is because of a dangerous immunological phenomenon called 'antibody-dependent enhancement' (ADE). Being infected with one serotype will cause immunity against this type, but being infected with another serotype out of the four serotypes is causing ADE and might result in hemorrhagic dengue shock syndrome (3, 4). The newest attempts in Brazil developing a two-dose vaccine

against all four serotypes based on one attenuated, weakened strain of one serotype and genetically hooking the other tree serotypes on this 'backbone,' so far protected 64% of people with dengue before and 53% of those not exposed to the virus before (5). The first approved vaccine by Sanofi caused ADE in children who did not have dengue before, and it was banned from the Philippines.

Epidemiology

The spread of dengue fever is favored by the larval breading habits of its vectors, liking to do so in water-filled flower pots, buckets, or waste such as tires that are no longer used and filled with stagnant water. Urbanization helps vectors migrate to countries with suitable temperature conditions, such as Thailand. The principal vector in urban areas is Aedes aegypti. For breeding, clean water is preferred in domestic containers near human lodgings. The water can contain organic material for the other vector, Aedes albopictus. Natural containers outside human homes in rural and remote areas are convenient breeding places for this vector, but overlapping both vectors is possible (6).

Unlike the vectors for malaria, Aedes vectors prefer to bite during the daytime. To suggest using repellents for the general Thai population is not feasible. Sleeping under mosquito nets during nighttime will not prevent mosquito biting during the daytime. What remains is the spreading of insecticides in breeding places when the vector is endemic. Besides environmental control measures, additional advanced approaches and biological control attempts in entomology have been discussed in a former entry of this blog (7). Roughly it is explained how the virus passes, together with the blood sucked by the female mosquito through the mosquito gut and finally being injected into the next host. On its way through the gut, the mosquito has a wide facet to adapt to the virus ingested by the blood meal (8).

Wolbachia pipientis

The microbiota of the mosquito gut, harboring multitudes of different microorganisms, emerged as a promising aspect for biological control trials. The Wolbachia approach is well-known among entomology experts. Wolbachia pipientis is a bacteria living as an endosymbiotic microorganism in half of all arthropod species. Male mosquitos and uninfected females don't produce viable embryos, and the males become sterile. Crossing between infected male and female mosquitos results in viable larvae so that, theoretically, the prevalence of infection will reach a hundred percent within a population. The process is called 'cytoplasmic incompatibility,' and how this process is working is still under investigation (9, 10). Trials used Wolbach-infected males released in an area with not-infected females called the 'Incompatible Insect Technique' (ITT). Another approach intends to increase the Wolbachia to replace its uninfected mosquitos. Wolbachia restricts the transmission of the virus, which has been shown for Dengue virus, Zika, and similar disease pathogens (10).

Innovative biological weapon investigated in the Yunnan Province, China

Another innovative biological way to fight dengue fever was recently published from the neighborhood of Thailand investigated in the Yunan province of China. An introductory note

in Science included a picture showing 'Tiger' Mosquitoes feat nectar from floral plants (11). (The name of the mosquito originated from the white stripes across the center and head of the Aedes insect, and the white rings around the legs are recognized easily by the naked eye. It is simple to realize that an Aedes species has bitten you in case you observe the attack.) What the mosquitos are supposed to collect commonly is called 'nectar.' Plant science, however, distinguishes between different kinds of fluids called 'sap.' Of interest are the two main types, i.e., Phloem sap and Xylem sap.

Phloem- and Xylem sap

The xylem transports water, minerals, and nutrients from the soil through the roots to the upper parts of the plant. The phloem is a living tissue that is metabolically active. It has a very high sugar content and non-essential amino acids, ribosomes, mitochondria, and microbes. For insects, such as mosquitos, it is a source of nutrients (11, 12).

Dengue fever in the Yunnan province

The Yunnan province was of particular interest in this investigation. The province is generally considered to be an endemic area for dengue fever. However, the incidence of the disease between areas differed considerably. In two administrative units, Lincang and Xishuangbanna, from almost non-existent to very low, increased to about 50 to 90% for the Puer and Wensham areas. All four regions resemble the terrain, environment, and density of the mosquito mosquito vectors (13). A former investigation into the 'heterogeneous distribution of dengue incidence' in the border area of Yunenan to Myanmar somehow remained inconclusive but hinted towards environmental factors. It was concluded that more in-depth investigations are needed to identify the factors causing the apparent differences in the incidence of dengue fever (14).

Rosenbergiella YN46

Recent advances in entomology hinted towards the midgut of the Aedes vectors and here to explore the gut microbiome (8). In catching female A. albopictus mosquitos in the field, using sophisticated proteomics technology, a bacterial 'isolate, out of fifty-five bacterial species, was identified to largely suppress the virus DENV2 (13). The symbiotic bacteria isolated belonged to the genus Rosenberggiella (15). Rosenbergiella are known to be contained in the microbiol of mosquitos feeding from the plant Phloem sap. The bacterium isolated from Yunnan subsequently was named Rosenbergiella sp. YN46. 'The bacterium was found 'highly prevalent in the gut of mosquito caught in the low dengue-incidence sites' (13).

The mechanism to inactivate the virus was found to be a protein called Rosenbergiella_YN46 glucose dehydrogenase (RYGDH). Glucose dehydrogenase makes gluconic acid out of glucose so that the bacterium reduces the pH of the gut lumen, inactivating flavivirus virions, which cannot enter the mosquito gut epithelial cells, inhibiting the transmission to the next host.

A. albobictus mosquitos caught in the field were released in outdoor tents, where the eggs were laid in water containing Rosenbergiella_YN46. Larva and adult mosquitos got the

bacterium in their guts. Finally, it could be proved that Rosenberggiella_YN46 lowered flavivirus infection, meaning that dengue fever and Zika infection could be affected (13).

Conclusion

In Asia, including Thailand, Dengue fever confronts public health authorities to fight against the vector. The biting and breeding habits of the vector make it challenging to control the endemic. Although the fatality rate is low, the infection itself is painful and immobilizes the victims for quite some time. Additionally, the fatal outcome is high enough not to be acceptable. Besides intervention with the Wolbachia bacterium, another naturally occurring Rosenbergiella_YN46 bacterium taken up by the vector could be an additional suitable biocontrol means. The situation found in Yunnan might not be very different from that in the endemic areas of Thailand. Similar investigations here result in reducing transmission in A. Agypti and A. albopictus will be worthwhile.

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