Researchers trace the Asian origins of Zika's global spread

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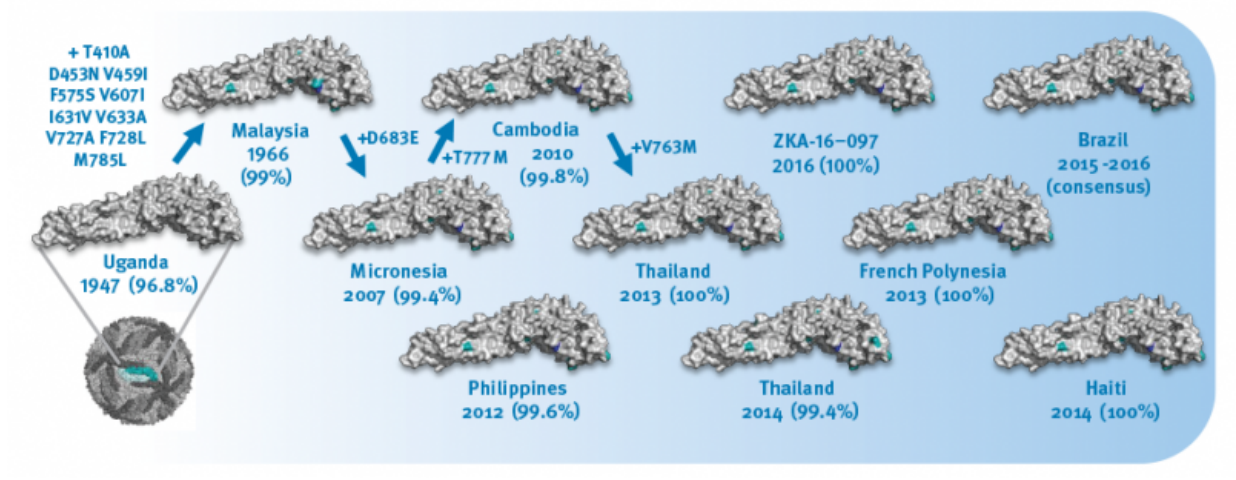

Mutations on the envelope protein surface of different Zika virus strains. Credit: Reproduced from Ref. 1 and under CC BY 4.0 © 2017 Sebastian Maurer-Stroh et al.

Genomic detectives have traced the most recent outbreak of Zika—a mosquito-borne virus that became a pandemic linked to neurological defects—back to a strain in South-east Asia.

A Zika strain was first identified in South-east Asia in the 1960s, and it is thought to have maintained a low-key presence across the region since. Two mosquito species, Aedes aegypti and Aedes albopictus, are the virus' principal carriers and can be found across a wide band straddling

the equator, extending patchily beyond the subtropics. A member of the Flavivirus genus, which also contains the dengue and West Nile viruses, Zika usually causes no or mild symptoms—a fever, rash, and aching joints.

Given its localized history, scientists are still baffled as to why a Zika strain suddenly headed east to French Polynesia in 2013, causing a suspected 32,000 cases within a year. From there, it moved on to the Caribbean and Brazil, where it exploded. Most worryingly, between late 2015 and early 2016, more than 4,000 Brazilian infants were born with abnormally small heads; a result of microcephaly, stunted growth of sections of the fetal brain. Brazil is previously thought to have had roughly 1,000 cases annually. In February 2016, the World Health Organization (WHO) declared neurological complications linked to Zika a public health emergency. To date there are thought to have been between three and four million cases of Zika across 84 countries.

Part of the global scientific response was the consolidation of a cross-disciplinary group of A*STAR researchers, already connected after working together on SARS and later swine flu. They were uniquely positioned to study the first known Zika outbreak in Singapore in August 2016, identifying it as separate from the strain that had reached South America—which some consider an important clue about the evolution of the virus in Asia1. Some of these insights might help explain why the pandemic suddenly spread east from Asia.

The Singapore outbreak

The city-state's researchers, agencies and clinicians were already well-prepared when the Singaporean outbreak started in August 2016. Identified first in the Kallang-Aljunied neighbourhood, a total of 455 cases were reported across three months and were centered around 15 major clusters. Through enhanced surveillance coupled with intensive

vector control, Singapore's Ministry of Health (MOH) and National Environment Agency (NEA) quickly identified and managed infected people, and eradicated mosquitoes and removed breeding sites. New cases were reduced by 48 per cent within a month.

Zika patients were initially isolated in the Communicable Disease Centre at the multidisciplinary Tan Tock Seng Hospital, one of the city's largest. Staff there had a chance to trial a new diagnostic test it had been developing with Masafumi Inoue, a molecular pathologist at the A*STAR Experimental Therapeutics Centre (ETC), along with colleagues at the Environmental Health Institute (EHI) and the Bioinformatics Institute (BII) also at A*STAR. Inoue reports that it worked exceedingly well on real Zika infections. "Clinical results showed the test is between six and 32 times more sensitive to Zika and dengue than the hospital's old dengue antibody assay test," he says.

The test itself uses a blood sample, from which ribonucleic acid (RNA) is extracted and copied through a technique called polymerase chain reaction (PCR), improving analysis. It harnesses simple hospital machinery, yielding results in three to four hours, and tests for all four key strains of dengue and all lineages of Zika—important, as approximately 12,000 cases of dengue were also reported to have been circulating for the first nine months of 2016. Inoue now hopes to submit the test for use internationally.

Crucially, within a week of Singapore's first localized case of Zika, the National Public Health Laboratory (NPHL) and A*STAR's Bioinformatics Institute (BII) had looked at the whole genome of the virus and confirmed that this wasn't the Brazilian Zika doubling back to Asia via international travel. "To our surprise, the Zika strain causing the local outbreak was derived from a local version that has been circulating in South-east Asia since the 1960s," says BII virus bioinformatician, Sebastian Maurer-Stroh.

Zika strains identified prior to 2013 have not been linked to severe neurological complications.

Which strain of Asian Zika caused the Zika outbreak?

There have only been a few confirmed cases of microcephaly in Asia—in Thailand and Vietnam. The initial BII analysis suggested that Singapore's new Zika strain diverged in early 2010 from the strain that spread to Brazil. Comparing emergent South-east Asian or Pacific strains like this one, says Maurer-Stroh, could be key to understanding why the microcephaly pathology was a huge problem in Brazil and not in Asia.

Researchers from A*STAR's Singapore Immunology Network (SIgN), Lisa F.P. Ng and Florent Ginhoux, have recently helped link the Polynesian strain, which sits between the Asian and the Brazilian in strain lineage, to brain inflammation in fetal brain cells. But, they question why microcephaly hasn't been observed in other parts of Asia. "We don't know why there's microcephaly in Brazil and not in other places in the world where the virus is still circulating like parts of the Pacific or even Singapore," Ng says. The link between Zika and microcephaly is still unclear, she adds, but studies at SIgN have observed a link to immunodeficiency in mice. One theory is that parts of the Americas population could have been immunodeficient or genetically predisposed to microcephaly. To Ng, two of the key questions that researchers should be asking are whether host genetics are at play, and whether the population in Brazil might have been pre-exposed to other risk factors.

Maurer-Stroh has another hypothesis. Microcephaly, he says, could be the result of an unidentified genetic mutation in the virus that developed

somewhere between South-East Asia and Brazil. "That it's been under the radar in Asia for so long would indicate that the change happened after the first big outbreak," says Maurer-Stroh.

He's working with Bruno Reversade, a molecular biologist at the A*STAR Institute of Medical Biology and the NEA, comparing Asian strains and the Brazilian strain in search of important changes in toxicity and pathogenicity. Maurer-Stroh says it's a work in progress, but they are starting to see differences.

One of the probable evolutions could have been in virus concentration levels. Indeed, in April, an international group of scientists including Singaporean researchers Julien Pompon, Menchie Manuel, Jun Hao Tan and October Sessions, at the Duke-NUS Signature Research Program noted a key difference between the South American and the Asian strains. By feeding mosquitoes Zika-infected blood, the consortium found that the Americas strain of Zika is more effectively transmitted than the Polynesian strain by Aedes aegypti— showing in the mosquitoes' saliva faster and at significantly higher concentrations.

Developing a searchable 'Zika Server'

As this strain information becomes clearer Maurer-Stroh hopes to amass it in a computer-based server through which users could search for different Zika strains—similar to the BII's FluSurver, which is a functioning part of WHO's virus surveillance network. The 'ZikaSurver' would help governments determine the risk associated with the strain, and perhaps eventually help inform individual prognoses and treatments.

Releasing genomic information particularly in Asia-Pacific will be the key, says Maurer-Stroh. "The fact that we found this intermediate strain in Singapore … fast filled a gap in what we know about the global spread and evolution of the virus. But, globally I haven't seen the same

release of information, especially in other south-east Asian countries that have the same virus," he says, and suggests that trepidation from tourism and business bodies might play a role.

A*STAR is trying to lead by example. BII released an early analysis of Zika genomes to WHO in March 2016, and after the recent outbreak, Singapore was again quick to share. "Because no genomes from this recent regional strain were known," says Maurer-Stroh, "NPHL immediately shared the genome sequence with WHO and published the initial results within three weeks of the first detected case while the outbreak was ongoing". A*STAR's Genome Institute of Singapore (GIS) also sequenced another 100 Zika genomes from the Singapore outbreak using a novel enrichment technology developed by Duke-NUS and GIS affiliate, October Sessions. Ng agrees that the limited sampling in Asia has hindered efforts to identify the source of the recent outbreak, but she's hopeful.

The big problem with flaviviruses

Another obstacle is that there is still no specific and licensed treatment for Zika. Ng's theory is that there are still multiple strains of Zika in circulation with "wide antigenic diversity and immunity". She says there is no generic therapy, so many approaches of "vaccines, antiviral medicines, antibody treatment" should be made available, but must be complementary.

Recently, a team led by Laurent Rénia, the executive director of SIgN, has been working on using the antibodies of fellow flavivirus dengue to treat Zika. Flaviviruses are all largely mosquito-borne—and include tropical diseases like Ross River Fever and Yellow Fever. Zika is so similar to dengue that this is yielding results says Rénia.

The team at SIgN has identified a particularly promising Zika-

neutralizing antibody and shown that it has an effect even on mice with immune deficiencies. This is especially significant in light of the link SIgN has observed between immune deficiency and microcephaly. Two mutations of this dengue antibody he notes also lowered Zika viral loads in fetal organs and placentas in pregnant mice, and were able to stop related fetal growth problems. "Of course, these findings provide the basis for any partner with pre-clinical vaccine candidates to screen for drugs," says Rénia. Once pre-clinical trials are done, these antibodies could be developed into treatments.

The similarity of Zika to dengue is also a concern. Dengue has been particularly resistant to vaccine development for many decades because of a unique phenomenon called 'antibody dependant enhancement' or ADE. Because dengue strains are similar but not identical, antibodies against one strain can bind to other strains, but imperfectly. As a result, when a person contracts two different strains of dengue over the years, the antibodies he has against first strain may enhance the new infection instead of fighting it, leading to more severe illness. The worry is that Zika will do the same. Ng says this underlines the need to develop a wide a range of treatment and prevention options.

For now, the global impact of Zika appears to be waning. Maurer-Stroh notes this is probably due in part to the protective effect of prior infections, but also because of the effectiveness of targeted responses such as that in Singapore. Nonetheless, Zika is still being found in countries with the vector mosquito species, and research on treatments, detection and genomic tracing will continue.

More information: Sebastian Maurer-Stroh et al. South-east Asian Zika virus strain linked to cluster of cases in Singapore, August 2016, *Eurosurveillance* (2016). DOI: 10.2807/1560-7917.ES.2016.21.38.30347

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