SINGAPORE — With dengue cases reaching a record high in Singapore during the last two weeks, the National Environment Agency (NEA) and hospitals island-wide have their work cut out for them in the perpetual fight against the spread of the mosquito-spread virus, also referred to as ‘breakbone fever’. While numerous efforts are being made to increase the number of mosquito habitat site visits by the NEA — with Singapore setting a high standard for vector control — “one cannot rely exclusively on vector control strategies to solve the problem,” says Dr Paul MacAry from NUS’s Department of Microbiology and Life Sciences Institute’s Immunology Programme.
By Alexandra Dawn Westcott -

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“Our colleagues in the NEA are doing a great job in mosquito surveillance and control, but it is virtually impossible to eradicate dengue in endemic countries,” adds Dr Indumathi Venkatachalam from the Division of Infectious Diseases at National University Hospital. “From time to time the virus escapes the usual control measures, and it is not surprising that every five to seven years numbers escalate. Renewed vigilance is important as control measures do not change.”

“There is certainly a stark increase in the number of dengue cases reported this year compared to previous years,” continues Dr Venkatachalam. “In keeping with that we are seeing a surge of cases at our dengue outpatient management (DOM) service at NUH. Fortunately we are better equipped to manage this outbreak with our enhanced outpatient service which provides all dengue patients with appropriate dengue care without their having to be admitted into the wards. As care is provided in the outpatient setting, it is cheaper.”

However, exciting developments in dengue antibody research continue to unfold in the pursuit of a vaccine as case numbers continue to rise. Dr MacAry and his team of research scientists made news last year after they uncovered a human antibody that can neutralise and kill the dengue virus within two hours. The team was a collaboration between the NUS Yong Loo Lin School of Medicine, Duke-NUS Graduate Medical School and the Defence Medical & Environmental Research Institute at DSO National Laboratories with funding from the Singapore National Research Foundation under its Singapore NRF Fellowship, National Medical Research Council and DR Tech. At that juncture, only the antibody for one type of dengue serotype, dengue-1, had been identified.

Since then, an antibody for a second type, dengue-2, has been developed, and preparation for work on the remaining two has already begun.

“There are four different dengue serotypes: dengue-1, 2, 3 and 4,” says Dr Venkatachalam. “When a person is infected with one particular serotype, he (or) she develops lasting immunity to that particular serotype and is protected from infections from the other serotypes for a period of two to three months. Secondary dengue infection, which refers to a second episode of dengue infection with another serotype, is associated with a higher risk of severe infection. Typically one particular serotype dominates in an epidemic and this is probably reflective of the immunity in the population rather than serotype specific transmission factors,” she says.
In 2005, Singapore experienced a massive outbreak of dengue-1; in 2007, 70 to 80 per cent of the cases were infected with serotype 2. The outbreak this year is seeing a high prevalence of serotype 1.

“What isn’t appreciated about the dengue virus is that all four serotypes are endemic in the tropical belt, including Singapore,” says Dr MacAry. “If you look at the relative frequencies of the serotype infections here they are predominantly serotypes 1 and 2. What we’re seeing are periodic shifts between serotype 1 and 2 in terms of dominance; 3 and 4 are less frequent; in fact, cases are rare in Singapore and the region. Of course it was obvious that we would focus on dengue-1 first, being the most prevalent serotype, but we are casting a wider net as we have achieved concrete results,” says Dr MacAry.

Dr MacAry’s lab is also currently negotiating with pharmaceutical entities, and they hope to have clinical trials begin within the next 18 months. There are extensive clinical criteria that a drug needs to go through before it can become available and it can take seven to eight years for a treatment to become available given the phases involved in the three-phase testing process — examining toxicity and efficacy, first locally, and then internationally.

“Antibodies are a subset of molecules used very broadly in diagnostics and therapy,” says Dr MacAry. “About one third of drugs produced worldwide are antibodies. This represents a new and upcoming subset of emerging biological therapeutics. However, up until recently, antibodies have not been used to treat infectious diseases. My lab is keen to explore pushing antibody technology into infection. We have numerous different methodologies for making antibodies and have employed these methodologies to target dengue.”

Dr MacAry’s team were already focused on and experienced in antibody studies prior to embarking on dengue research. They have collaborated extensively with Professor Dale Fisher, Head of Infectious Diseases at NUH and Professor Leo Yee Sin, the Director of the Communicable Disease Centre at Tan Tock Seng Hospital.

The proposed treatment exploits the natural immune response that patients generate to recover from dengue, which according to data from the World Health Organization puts dengue infections at about 50–100 million worldwide every year, killing between 20,000 and 50,000. Statistically, most people affected with this disease recover, attributed to the fact that the human body produces an immune response that targets and kills the virus. This immune response is based on antibodies that bind to the virus and fight for its clearance from the blood. Dr MacAry set out to isolate the components of a natural immune response against dengue — components that resolve dengue fever — and then produce these proteins in larger quantities with a view to giving these to infected patients. Essentially, one could administer the components for an immune response to shut the infection down almost immediately.

The international medical community’s response to Dr MacAry’s research has been positive.
“I think perhaps the inherent novelty hasn’t been fully conveyed” he says. “There were a few firsts with this study: This is the first human antibody that’s been thoroughly characterised for dengue; we produced the first high resolution image of a human antibody of a virus; we were the first to show virus neutralisation with a human antibody,” he says.

Research involving antibodies is still largely experimental, and Dr MacAry’s lab has not used mouse proteins that is typical of research of this nature.

“We went straight to human blood samples, and that is extremely challenging,” says Dr MacAry. “In your blood you have all the antibodies that you’ve ever been vaccinated against or infected with, so identifying the tiny amount of components that target dengue specifically as opposed to all the flu types you’ve had and so on, is fantastically challenging. To give you a rough idea — we have gone through over 200,000 antibody templates to find a dengue antibody.”

The greatest challenge that the team has faced is persistence: The research involves repeating the same process over and over again over the course of two to three years, and this requires extreme mental fortitude.

Dr MacAry is now looking to recruit patients from outside of Singapore to develop antibodies for dengue 3 and 4; they are primarily looking at recruiting from Sri Lanka and Puerto Rico where instances of serotypes 3 and 4 are high, and recruiting patients who have been affected by these rare serotypes locally.

“What is most exciting about the research results from dengue is that, in theory, the same process can be applied to any infectious disease where the human body has a natural immune response. There is, for example, a small subset of HIV-positive individuals who display natural immune responses to the virus, so the treatment possibilities are extensive with this type of research and the possibilities are tremendously exciting.”