Developing antivirals against Zika and dengue viruses

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Dengue (DENV) and Zika (ZIKV) viruses are spread by the female mosquitoes of the *Aedes* family, particularly *Aedes aegypti*. These mosquitoes cause large scale outbreaks throughout the tropical and subtropical regions, making DENV and ZIKV significant health threats.

DENV cases have been increasing rapidly over the last three decades from 26 million to 58 million. Last year, over 14 million dengue cases were recorded globally, surpassing the recorded cases from previous years. Unfortunately, these cases are vastly underestimated, as numerous countries lack surveillance resources to record cases. While most individuals with DENV infection present no symptoms, there can be complications like dengue haemorrhagic fever and dengue shock syndrome that can be life-threatening. As a result, DENV infections can cause direct and indirect cost like hospitalisations, long term disabilities, and productivity losses, showcasing the broader implications beyond health impacts.

Similar to DENV, ZIKV is another global threat. The last ZIKV epidemic occurred in Latin America during 2015. This epidemic resulted in at least 1.5 million cases and a rise in complications in pregnant women. One of these complications is called microcephaly, which causes the head size of the foetus to reduce. This complication causes developmental delays and affects the child's quality of life. More recently in 2024, over 44,000 Zika cases were recorded globally. While these cases are relatively lower compared to the last Zika epidemic, majority of the globe is at risk for ZIKV transmission which is why we need to be prepared.

ZIKV and DENV cases are expected to rise worldwide, including Aotearoa, due to factors like global warming. Currently, Aotearoa has imported cases of ZIKV and DENV because we do not have *Aedes aegypti* mosquitoes to spread both viruses. However, the climate of Te Ika a Maui (North Island) is warm enough for these mosquitoes to survive. Hence, we are likely to see local transmission of ZIKV and DENV cases here soon, so we must be ready with safe and effective treatments.

Unfortunately, we have no clinically approved antivirals against either virus at this time. While there are vaccines against DENV, they are not available for everyone and can cause severe side effects. Since there is an urgent need for treatments, this research project aims to develop antivirals against ZIKV and DENV.

This research project has tested a small panel of drugs from the Auckland Cancer Research Society that target signalling pathways in the body, including one called PI3K. While this pathway is essential for humans, it is also fundamental for both viruses to reproduce and spread. We are in the process of examining a range of drugs that target these essential pathways in the body to see if they can stop dengue and Zika viruses from

reproducing without toxic effects on the cells. We are aiming to identify a drug that can switch off the pathway just long enough to allow our immune system to shut down the viral infection.

This research aligns with Te Niwha's mission to improve pandemic preparedness. Significant evidence from previous viral epidemics and pandemics highlight that Māori and Pacific communities experience elevated risks of severe outcomes for viral infection. For example, Māori and Pacific communities had 5.2 times higher influenza-associated hospitalisations recorded than non-Māori between 2014 and 2016. In the more recent COVID-19 pandemic, Māori and Pacific peoples were 1.9 and 2.1 times more likely to be hospitalised (respectively) than other ethnicities in Aotearoa due to COVID-19 Omicron cases in 2022. These disproportionate impacts faced by our Māori and Pacific peoples connotes the need to protect our communities from DENV and ZIKV in the future.

This research project addresses this need by developing antivirals to proactively prepare for future outbreaks caused by ZIKV and DENV. Antiviral development will not only keep our unique communities in Aotearoa safe but also support other countries currently battling the health burden created by DENV and ZIKV.