Enhancing dengue prevention

Disease prevention strategies require consideration of the key factors affecting pathogen spread. Professor Thomas W Scott talks candidly about his study of the epidemiological and ecological factors affecting dengue fever transmission.

Can you introduce your research activities?

My research focuses on the epidemiology, ecology and prevention of mosquito-borne disease. I aim to generate the detailed, difficult-to-obtain data that are necessary for assessing current recommendations for disease prevention, rigorously testing fundamental assumptions in public health policy and developing innovative, cost and operationally effective strategic concepts for prevention of mosquito-borne disease. My focus is on applying innovative science to enhanced disease prevention and constructive contributions to the debate over improved public health policy.

Why are epidemiological heterogeneities proving important in your research?

Heterogeneity is the variability of properties of a system across space, time and/or the system’s individual constituents. It can have profound impacts on pathogen transmission and, consequently, efforts to prevent disease. My colleagues and I are particularly interested in how this variation leads to certain individuals, locations, age or social groups, host species and pathogen strains being disproportionately responsible for a high proportion of transmission events. For example, ‘super spreadering’ is when a few individuals drive a large amount of the pathogen transmission events.

What are the most important discoveries you have made about dengue transmission in recent years?

The most important discoveries are the global estimate of disease, the role of fine scale human movement in the dynamics and distribution of dengue virus transmission, and that people across the entire spectrum of disease are infectious to mosquitoes that bite them, including people who do not get sick and have no symptoms.

In 2014, you received a five-year, US $7.3 million grant from the National Institutes of Health (NIH) for a project entitled ‘Quantifying Heterogeneities in Dengue Virus Transmission Dynamics’ – a project whose impact the NIH review panel predicts to be ‘exceptional’ and ‘highly likely to achieve even its most ambitious aims’. What is the purpose of this project and what goals does it have?

Our project has three aims: to characterise the relationship between magnitude of human dengue viremia and infectiousness to the mosquito Aedes aegypti; to describe the temporal dynamics of human dengue infectiousness to Aedes aegypti; and to determine the relative capacity of people with unapparent or mild dengue infections to transmit viruses to Aedes aegypti.

Our long-term goal is to apply the information obtained from detailed field studies to the development of enhanced surveillance and intervention methods that will prevent human infection and disease.

What progress have you made on this project to date?

We have shown that – despite their lower average level of viremia – people with natural dengue infections and no clinical symptoms can contribute to virus transmission dynamics by efficiently infecting mosquito vectors. Moreover, at a given level of viremia, dengue-infected people with no detectable symptoms (or before the onset of symptoms) are significantly more infectious to mosquitoes than people with symptomatic infections. Because dengue viremic people without clinical symptoms may be exposed to more mosquitoes through their undisrupted daily routines than sick people – and represent the bulk of dengue infections – our data indicate that they have the potential to contribute significantly more to virus transmission than previously recognised.

Our coupled heterogeneities paper is the foundation for answering a number of key questions. To what extent is transmission heterogeneity a function of individual level characteristics, coupled heterogeneities or stochastic variation? If significant couplings are identified and predicted to have a disproportionate role in the emergence of transmission heterogeneity, how will that be used to develop disease mitigation strategies? Can disease mitigation strategies that target heterogeneities be more efficacious than those focused on individual traits?

Can you introduce your role within the Partnership for Dengue Control (PDC)?

I am currently on the Steering Committee in charge of vector control activities. My emphasis is on assessing vector control strategies for Aedes aegypti and designing randomised control trials for evaluating vector control to prevent dengue. Because the same mosquito transmits dengue, Chikungunya, Zika, and yellow fever viruses in the same settings, our proposal for trial design is directly relevant to several virus infections with growing public health importance.

What are PDC’s highest priorities at the moment?

The top priority for the PDC is to promote development and implementation of innovative, synergistic approaches for dengue prevention. For vector control, we aim to obtain funding to carry out a randomised control trial – informed from our NIH study in Peru – of Aedes aegypti control and dengue prevention. Results of that trial would be applicable to Chikungunya and Zika prevention.
Determined to improve upon current disease prevention strategies, researchers at the University of California, Davis, USA, are looking at the transmission of vector-borne disease with an entirely new perspective.

**Dengue Fever** is a severe public health problem in developing countries. Noted as a public health concern since World War II, recent population growth and increasing urbanisation in tropical and sub-tropical regions has rendered dengue an even more severe problem today; reported cases quadrupled between 1990 and 2013 and nearly 4 million people are infected annually. The dengue virus is the fastest spreading vector-borne disease in the world, and the prospects of those infected vary.

While typical symptoms include fever, headache and a characteristic rash, some victims may progress into dengue haemorrhagic fever, which can lead to blood plasma leaking out of capillaries and sometimes death. Approximately 20,000 people die every year from complications relating to the disease.

Currently, there is no commercially available vaccine to protect against dengue infection. At present, the primary approach is to control the primary vector: the yellow fever mosquito, *Aedes aegypti*. Despite initial successes in mosquito population control, mosquito control for dengue has proven difficult to do and hard to sustain. There is growing interest in enhancing control impacts by combining vector control with a vaccine when one becomes broadly available.

To facilitate development of a more potent strategy, it is vital to improve understanding of where transmission is most vulnerable to interruption. That requires greater knowledge of dengue transmission dynamics because it is within the context of the details of transmission that crucial public health questions must be answered.

**Investigating Heterogeneities**

Based at the University of California, Davis, Professor Thomas W Scott saw numerous knowledge gaps in the field of dengue transmission dynamics. Not only was there a lack of rigorous trials to evaluate the efficacy of current prevention methods, but at a fundamental level, patterns of dengue transmission had not been characterised and were not well understood. Scott noticed there were heterogeneities in the contribution of certain individuals and places to dengue transmission. He also noticed that a simple reduction in the *Ae. aegypti* population would not miraculously cause human exposure to dengue virus to plummet, and there were intersecting, complicating factors that had not been accounted for.

With colleagues, Scott began studies looking into heterogeneities that drive the introduction, spread and persistence of dengue. “We saw a critical gap in understanding of the potential for people across the entire continuum of dengue disease to influence virus transmission,” he explains. Insights into the factors driving the expansion of dengue would improve understanding of transmission dynamics and could inform new disease prevention strategies.

Motivated by a desire to reverse the expansion of the disease in developing countries, Scott and his colleagues began to study the biting behaviour of *Ae. aegypti*. *Ae. aegypti* do not fly far, and they bite people during the day when humans are engaged in their daily routines. Scott’s team chose to investigate local human movements as a primary mechanism for the virus to spread within communities. Could human movements among buildings in urban areas drive underlying patterns in dengue fever transmission? The researchers collected freshly engorged *Ae. aegypti* and human DNA from cheek swabs of people living in Iquitos, Peru. Despite dengue often being considered a paediatric disease, they discovered that *Ae. aegypti* was more likely to bite those who remained at home and people with larger body surface area (adults). Further research demonstrated that infection risk could be...
increased by visits to places where contact with infected mosquitoes was likely, and in spite of a lack of significant climatic variation, incidence of dengue cases peaked at certain times each year.

Results from this research provide a different way of thinking about dengue. They show that virus transmission is affected by social routines and relationships – even local visits to friends’ houses could cause local spikes in transmission rates. For individual people, infection risk is defined by contact with the virus across the places a person recently visited and was bitten by mosquitoes. They saw that variation in people’s movement patterns underlies the highly variable spatial patterns of infection that are characteristic of dengue. At a population level, dengue transmission is shaped by overlapping movements of people who visit the same places, like the homes of their family and friends. “Disease prevention strategies need to consider the people and places contributing to spikes in the incidence and spread of the virus and make sure those sites are not missed,” Scott notes.

HIDDEN DANGERS

While dengue fever affects many people, only a fraction become sick enough to seek health care. Because there was evidence that severely sick people might be more infectious to mosquitoes, people without symptoms or mild disease were considered a ‘dead end’ for transmission. Scott, however, was intrigued by the unknown contribution of asymptomatic people in dengue transmission dynamics. “Clarifying the enigma surrounding unapparent dengue infections is fundamental to enhancing surveillance and evaluation and application of vector control and vaccines,” Scott says.

With his colleagues, Scott investigated how dengue virus is transmitted from human to mosquito. Previous studies suggested that infected humans could infect mosquitoes several days before and after the onset of fever, and that these mosquitoes were then able to transfer the virus to another person after two weeks of incubation. These studies, however, only included people with symptomatic dengue infections because they were easy to identify, and it was assumed that people without overt symptoms would not have high enough virus in their bloodstream (viremia) to infect mosquitoes. “We were testing the prediction that though severity of disease may last longer than either method by itself.

Although dengue has been the focus of Scott and his colleagues’ work, the influence of their studies of heterogeneities in dengue virus transmission could be applied to Chikungunya, Zika and yellow fever viruses, which are transmitted by the same mosquito species in the same environment. The concepts of movement and integrated intervention could similarly be explored for malaria and lymphatic filariasis, diseases that disproportionately affect the most disadvantaged people in the world. “What drives me is the opportunity to improve public health for populations that need the most help. Our next steps need to be the application of insights gained from research in lquito to carefully designed clinical trials of tools and strategies. That will provide a solid, empirical basis for recommendations to enhance public health policy and its implementation,” Scott concludes.