Dengue vaccines

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Dengue is globally the most important arboviral infection of humans with an estimated 100 million infections per annum and 2.5 billion people at risk in >100 countries[1,2]. The burden of dengue is substantial in economic terms and in the strain it places on already fragile health systems[3]. There are currently no licensed vaccines or therapeutics and disease control relies, mostly unsuccessfully, on suppressing the mosquito vector[4].

The development of a dengue vaccine poses several challenges[5]. Firstly, there are four antigenically distinct serotypes, each capable of causing disease, and hence a vaccine will need to elicit multi-serotype immunity. Secondly, there are no validated correlates of dengue immunity. Thirdly, there are no animal models of disease to enable rational preclinical development. Finally, the immune response to infection plays a key role in pathogenesis with secondary heterotypic infections associated with more severe disease[5]. This observation is, in part, explained through the concept of antibody-dependent enhancement (ADE) of virus infection in Fc-receptor bearing cells during secondary heterotypic infections[6]. ADE is postulated to increase the number of virus-infected cells *in vivo* and elevate the risk of disease complications. The role of the immune system in disease pathogenesis has led to concerns that a vaccine may actually enhance disease risk if vaccine-elicited antibody responses wane over time. A disease-enhancing vaccine is not without precedent; for example, an early respiratory syncytial virus (RSV) vaccine candidate[7].

Against this backdrop, the commencement in Australia in October 2010 of the first phase III clinical trial of a dengue vaccine represents a major milestone[8]. The vaccine candidate being tested, called ChimeriVax-Dengue, has been developed by Sanofi-Aventis over the last decade. This live vaccine is a tetravalent formulation of recombinant Yellow Fever 17D vaccine strains expressing the prM and E genes from each dengue virus serotype[9]. ChimeriVax-Dengue has been given safely to over 5,000 adults and children and induces seroconversion after two or three doses to all four serotypes in Flavivirus-naïve and immune individuals[10]. The commencement of the phase III trial overlaps with an ongoing phase II trial under way in Thailand and involving 4,000 four- to 11-year-old children. Thus, there is the possibility that efficacy data against at least one dengue virus serotype could be available even before the conclusion of the multicounty phase III trial. For reference, other dengue vaccine candidates are at significantly earlier preclinical or phase I stages of development.

As the field-testing of ChimeriVax-Dengue enters its final stages, there will be heightened efforts in developing the economic arguments for its cost-effectiveness. This is of some importance as dengue is a disease of predominantly middle-income countries where donor-support for vaccine implementation may not be forthcoming. A second challenge is to identify where this vaccine could best fit into existing paediatric vaccination programs; this is pertinent because ChimeriVax-Dengue currently has a three-dose schedule spaced six months apart. Despite these challenges, the prospect of a licensed dengue vaccine in the next five years represents a major advance towards reducing the substantial global burden of dengue.

References

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Biography

Jamie Whitehorn is an infectious diseases physician and holder of a Wellcome Trust training fellowship in tropical medicine and international health through the London School of Hygiene and Tropical Medicine. He is based at the Oxford University/Wellcome Trust Clinical Research Unit in Ho Chi Minh City, Vietnam and his research interests are in clinical research and dengue.

Cameron Simmons is a Wellcome Trust Senior Research Fellow and has recently returned to the University of Melbourne after 10 years at the Oxford University Clinical Research Unit, Vietnam. Cameron's background is in microbiology and immunology and his main research interest is dengue. Cameron's group are interested in improving the understanding of dengue pathogenesis and conducting randomised controlled trials designed to improve patient outcomes or stop disease transmission in the community.