Decimate Dengue : The Pre-Summit Webinars Series (7th Webinar)

DENGUE ANALYTICS AND CLINICAL DEVELOPMENT OF VACCINE, V181 UPDATE

MARCH 15, 2022

INTRODUCTION

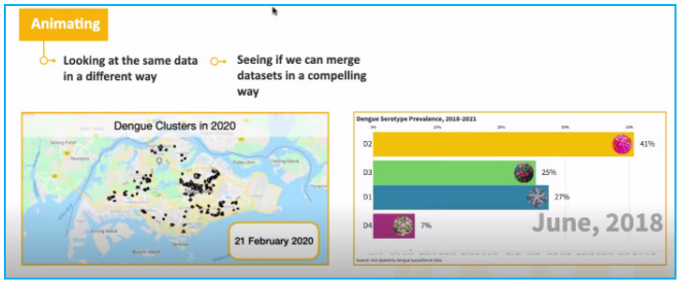
Due to the ongoing COVID-19 pandemic, 5th Asia Dengue Summit has been postponed to May 2022. In the meantime, the Asia Dengue Voice and Action (ADVA) Group, in collaboration with the Global Dengue and Aedes transmitted Diseases Consortium (GDAC), Fondation Merieux (FMx), International Society for Neglected Tropical Diseases (ISNTD) and Southeast Asian Ministers of Education Tropical Medicine and Public Health Network (SEAMEO) bring a series of online meetings titled "Decimate Dengue: The Pre-Summit Webinars. The 7th webinar of the series titled ***"Dengue Analytics and Clinical development of vaccine, V181 update"*** was held on January 20, 2022. **Prof. Zulkifli Ismail**, Consultant Pediatrician and Pediatric Cardiologist at KPJ Selangor Specialist Hospital, Malaysia, and **Prof. Emeritus Lulu Bravo**, Professor of Infectious and Tropical Diseases, College of Medicine, University of the Philippines chaired the webinar. The webinar featured talks by **Dr. Rosybel Drury**, Global Director of Medical Affairs for Vaccines at Merck Sharp & Dohme (MSD) Corp, France, and **Mr. Dafydd Green**, Business Development Director at Incuna (Digital healthcare), Singapore.

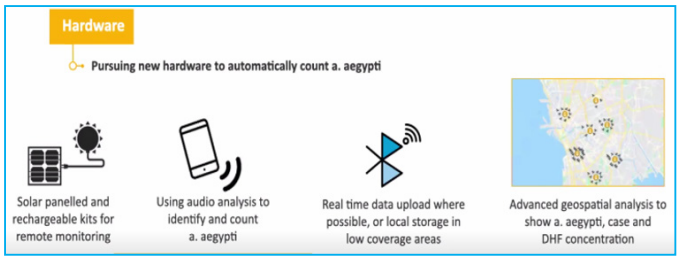
HACKING DATA TO EVOLVE HOW WE UNDERSTAND DENGUE

Mr Dafydd Green
Business Development Director
Incuna – Experts in digital healthcare
Singapore

- **Incuna's Dengue Data Hub**
  - Over the past few years, Incuna has worked to create and maintain a dengue database with the aim is to develop a Dengue Data Hub to exchange views, improve dengue awareness and support dengue control activities.
  - Incuna's approach to dengue data consists of working at three levels – publicly available data, data that can be shared and datasets under development. Incuna has broadened the scope to include additional relevant datasets from other disciplines such as etymology, environmental sciences, and genomics.
  - Incuna's dengue data set across Asia Pacific include epidemiological, clinical, meteorological, economic, entomological, and environmental data. The data is mixed and matched to generate more insight.

- **Data generation, maintenance, and representation**
  - Data is maintained in the database and automated analyses is performed using algorithms to detect changes and trends. (e.g., dengue virus serotypes prevalence, dengue clusters in communities)
  - Animated data offers visual representation of fluctuations over time and other variables.
  - Visualising data allows to find correlations that might be otherwise difficult to observe. Visual data allows to view impact of variables on outcomes. (E.g., impact of GDP on dengue over time, impact of urbanization on dengue prevalence over time)
  - Incuna aims to create more datasets through surveys. (e.g., A pilot project is planned to develop dataset on Dengue Cluster areas in Singapore). Other potential surveys to develop datasets include disease awareness, health economics behaviours and disease/vector attitudes and knowledge.





- **Using hardware to obtain data**
  - Another potential method of data collection is pursuing mobile phone hardware to automatically count Aedes aegypti population to allow continuous surveillance and geospatial mapping of Aedes aegypti and dengue cases.
  - Sonic technology and audio analysis can be used to identify specific sub-species of mosquitoes.
  - Solar panelled and rechargeable kits could be used for remote monitoring enabling real time data upload where possible or local storage in low coverage areas.
  - The new hardware technological approach will be able to support precision vector control, health resource optimization and vaccine strategy.
  - With effective device monitoring, sensible activity staggering, citizen science training and robust guidelines, it might be possible to conduct dengue surveillance in the field.

CLINICAL DEVELOPMENT OVERVIEW OF AN ATTENUATED QUADRIVALENT DENGUE VACCINE, V181

Dr. Rosybel Drury
Global Director of Medical Affairs (GDMA) for Vaccines
Merck Sharp & Dohme (MSD) Corp, France

MSD Dengue Vaccine V181 - Live, attenuated, quadrivalent dengue vaccine in development

- Vaccine licenced by National Institutes of Health (NIH).
- NIH has been conducting Phase 1 and 2 clinical trials for the past 20 years.[1-5]
  - Safety – generally well-tolerated in data from >1000 subjects
  - Immunogenicity – 90% trivalent or tetravalent seroconversion post dose[1]
  - Efficacy – 100% efficacy in human challenge studies for DENV2[6] and DENV3 (results not yet published).
- NIH Phase 2 studies conducted in Thailand and Bangladesh
- Phase 2 and Phase 3 trials will be conducted in Brazil by Instituto Butantan.[7] MSD and Instituto Butantan are collaborating on the development of the V181 dengue vaccine originally developed by the NIH.
- Two vaccine formulations are used. TV003 formulation uses 10^3 pfu for each dengue serotype. TV005 formulation uses 10^3 pfu of DENV1, DENV3 and DENV4 components and 10^4 pfu of DENV2

  * pfu – plaque forming unit (number of virus particles capable of forming plaques/unit volume)

MSD V181 Phase 1 Study

- **Study design[8]**
  - Multicentre, 3-arm, randomized, double-blind placebo-controlled trial to evaluate the safety, tolerability, and immunogenicity of V181 across 3 sites in USA and 2 sites in Puerto Rico
  - 50% participants were baseline flavivirus-experienced (BFE) and 50% baseline flavivirus-naive (BFN)
  - 200 healthy adults aged 18-50 years were randomized 2:2:1 to receive 0.5 mL subcutaneous dose of vaccine TV003 (n=80), TV005 (n=80), or placebo (n=40) on Days 1 and 180
  - Immunogenicity was measured with Neutralization Test with 60% cut-off ($VRNT_{60}$)

- **Viraemia and immunogenicity[8]**
  - Vaccine viraemia (measure of vaccine infectivity) was detected in all 4 DENV serotypes after first dose of TV003 and TV005
  - $VRNT_{60}$ Geometric Mean Titres (GMTs) measured by $VRNT_{60}$ increased significantly after the first dose of TV003 and TV005 in both subgroups for all DENV serotypes. Minimal increase was observed after second dose.
  - GMTs in the TV003 and TV005 BFE and BFN subgroups stayed above the baseline 1 year after dose 2
  - TV003 and TV005 increased DENV $VRNT_{60}$ seropositivity to all 4 dengue serotypes in both baseline flavivirus-experienced (BFE) and baseline flavivirus-naive (BFN) groups
  - Overall viremia and immunogenicity with TV003 was higher than that of TV005.
  - This data supports the continued development of the V181 TV003 formulations as a single-dose vaccine for the prevention of DENV disease

- **Adverse effects**
  - No subject discontinued the study due to adverse experiences in any vaccination group
  - Rash, headache, fatigue, and myalgia were most common adverse events.[8]
  - Post vaccination rash was not seen after the 2nd dose. Similarly, no viremia was detected post 2nd dose for any dengue serotypes. There seems to be a link between viraemia and appearance of rash.

REFERENCES: 1. Durbin et al. The American Journal Of Tropical Medicine and Hygiene. 2001; 65(5), 405-413. **2.** Durbin et al. The Journal of Infectious Diseases. 2013; 207(6), 957-965. **3.** Kirkpatrick et al. The Journal of Infectious Diseases. 2015; 212(5), 702-710. **4.** Durbin et al. The Journal of Infectious Diseases. 2016; 214(6), 832-835. **5.** Whitehead et al. PLOS Neglected Tropical Diseases. 2017;11(5):e0005584. **6.** Kirkpatrick et al. Science and Translational Medicine 2016. 8(330),330ra336. **7.** Kallas et al. The Lancet Infectious Diseases. 2020; 20(7), 839-850. **8.** Russel et al. Hum Vaccin Immunother. 2022 Mar 15;1-12. doi: 10.1080/21645515.2022.2046960. Online ahead of print.

Co-convenors: ADVA Asia Dengue Voice & Action Group · Fondation Mérieux · gdac Global Dengue+Aedes-Transmitted Diseases Consortium · SEAMEO TROPMED · The International Society for Neglected Tropical Diseases