DECIMATE DENGUE: THE PRE-SUMMIT WEBINARS

WEBINAR 1: RANDOMIZED TRIALS OF WOLBACHIA FOR DENGUE CONTROL – A STEP TOWARDS ELIMINATION

INTRODUCTION

Due to the ongoing COVID-19 pandemic, 5th Asia Dengue Summit has been postponed to January 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 first webinar in this series titled, "Randomized trials of Wolbachia for dengue control – a step towards elimination" was held on October 28, 2020 and was presented by Prof. Cameron Simmons, Professor (Research) & Director, Institute of Vector Borne Disease (IVbD), World Mosquito Program. Prof. Ooi Eng Eong, Professor at Duke-National University of Singapore Medical School, chaired the webinar. The panelists included Prof. Sri Rezeki Hadinegoro - Professor in Department of Child Health at the University of Indonesia, Prof. Adi Utarini - Professor in the Department of Heath and Policy Management, Faculty of Medicine at Universitas Gadjah Mada, Indonesia and Prof. Ng Lee Ching - Director of National Environment Agency's Environmental Health Institute, Singapore

DENGUE BURDEN

Over the last 40 years dengue has dramatically spread all over the world with approximately half of the world's population living in areas of risk. The main drivers for spread of dengue include changing life styles, unplanned urbanization and overcrowding, globalization and lack of effective vector control.[1] Globally there are over 60 million symptomatic dengue infections per year resulting in about 10,000 deaths. Dengue burden is the highest in South East Asia with highest age-standardised incidence rates and highest dengue mortality rates.[2] Dengue prevention and control is a shared responsibility and multi-sectorial partnership between communities, healthcare professionals, policy makers and private sector and government agencies is essential.

THE WOLBACHIA INNOVATION

The Wolbachia innovation appears to be a potentially promising method for control of dengue transmission in endemic settings.[3] The Wolbachia are naturally occurring bacteria present in 60% of insect species, including mosquitoes. When Wolbachia infection is deliberately introduced in Aedes aegypti male mosquitoes, it causes cytoplasmic incompatibility resulting in suppression of viral replication and development of unviable eggs. Wolbachia infection in Aedes aegypti mosquitoes interrupts dengue transmission by reducing the mosquito competence to transmit dengue.[3] The World Mosquito Program (WMP) uses introduction of Wolbachia infection in Aedes aegypti mosquitoes to reduce their ability to transmit dengue, Zika, chikungunya and yellow fever viruses to humans. The WMP is currently operating in 12 countries across Asia, the Americas, the Pacific Islands and Australia.[4]

The WMP Wolbachia method is unique and self-sustaining

World Mosquito Program	Suppression methods
Wolbachia	Irradiation, Wolbachia, Genetically modified
Release male and female mosquitoes	Release males only
Aims to reduce pathogen transmission	Aims to reduce mosquito population
Release rate approximately 2-5 mosquitoes per person per week	Release rate approximately 10-350x higher
Scale demonstrated around 100 km2	Scale demonstrated up to 5 km2
Reapplication not required	Reapplication required

APPLYING WOLBACHIA TO ELIMINATE DENGUE (AWED) TRIAL

Study Objective

The AWED trial (Applying Wolbachia to Eliminate Dengue), a cluster randomized controlled trial to assess the efficacy of Wolbachia-infected mosquito deployments to reduce dengue incidence was conducted in Yogyakarta, Indonesia.[5] The primary endpoint of this trial was symptomatic, virologically confirmed dengue (VCD) infection of any severity.[5] Secondary endpoints included the impact of Wolbachia deployment on Zika and chikungunya, impact on routine dengue case notification, role of human mobility on measuring efficacy of Wolbachia deployment and prevalence of arbovirus-infected Ae. aegypti mosquitoes.[5]

Study Design

AWED trial was a parallel, two-arm, non-blinded cluster randomized controlled trial in 24 contiguous clusters of roughly equal area and population size. The study was conducted in Yogyakarta, Indonesia, in a population of approximately 350,000 people in an urban area of 26 km2. The study population was randomly allocated to either receive Wolbachia deployments or no intervention. Constrained randomization was used to allow spatial distribution of treated and untreated clusters.[5]

Study timeline

The World Mosquito Program (WMP)-Indonesia contributed to the planning and implementation of the AWED trial. Community outreach began in 2016 and randomization was performed in 2017. Following an extensive community engagement, written agreement was obtained from community leaders confirming the willingness of the community to participate in the trial. The first release of Wolbachia infected mosquitoes was conducted in November 2017 and last release was done

in January 2018. The clinical enrollment of the trial began in January 2018 and the trial was stopped in March 2020 due to the ongoing COVID-19 pandemic. An analysis of the data was conducted in June 2020.

Clinical enrollment

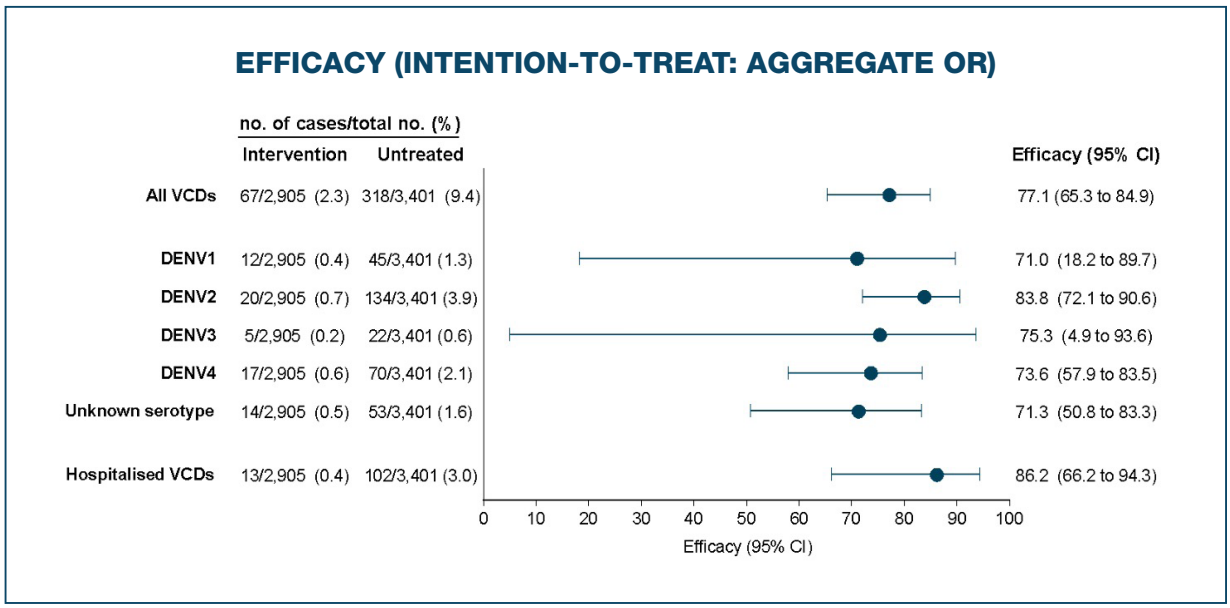
Febrile patients were enrolled from 18 primary care clinics from January 2018 to March 2020. Exposure status (intent-to-treat, ITT) was determined by residence in Wolbachia treated or untreated cluster. Intent to treat analysis of primary outcome was calculated by comparing odds of residence in Wolbachia treated cluster between virologically confirmed dengue cases and test negative controls.[5] Clinical enrollment was based on presence of undifferentiated fever cases in individuals 3-45 years of age who lived in the study area. The diagnostic criteria for VCD included PCR, ELISA and IgG/IgM.[5]

Study Power

The study was powered to detect 50% reduction in VCD. The sample size of 1000 cases and 4 times as many controls was determined to be sufficient to detect a 50% reduction in VCD case incidence with 80% power.[5]

Results of AWED trial

1. The efficacy analysis in ITT population showed a 77% reduction (98% CI: 65% to 85%) in incidence of dengue in areas treated with Wolbachia. VCD was confirmed in 2.3% cases in the Wolbachia intervention arm compared to 9.4% cases in untreated arm
2. Most prevalent serotypes in the trial cohort were DENV2 and DENV4. Point estimate of efficacy for DENV2 and DENV4 was 84% and 74% respectively. There was no evidence of difference in efficacy across different DENV serotypes. (permutation test of chi-squared statistic. p=0.586)
3. There was a robust efficacy outcome [efficacy (98% CI): 86.2% (66.2 to 94.3)] for preventing hospitalization in VCD cases. The incidence of hospitalized VCD in Wolbachia intervention arm was 0.4% compared to 3% in untreated arm.
4. High and stable Wolbachia frequencies (average 93%) were seen in intervention clusters throughout the 27 months in the trial. As expected, some contamination of untreated clusters was seen by 1 year in to clinical enrollment.
5. Despite the discontinuation of the trial in March 2020, Wolbachia continues to stay on in the mosquito population without the need for reapplication.



TAKE HOME MESSAGES

- The AWED trial is the only trial of an intervention targeted to A. aegypti that has demonstrated a reduction against VCD case incidence
- Wolbachia intervention has demonstrated a significant public health benefit with 77% reduction (98% CI: 65% to 85%) in incidence of dengue in areas treated with Wolbachia
- Wolbachia intervention is self-sustaining (no need to reapply), resilient (to disruptions of COVID-19, financial crises or change in government/personnel where traditional public health measures do not work) and equitable (intervention continues to offer benefit irrespective of socio-economic circumstances)
- Results of AWED trial are likely an underestimate of true effect size because of “exposure contamination” due to human mobility and Wolbachia spread
- Wolbachia has the potential to be a cost-effective and cost-saving intervention
- Wolbachia is now being deployed across Yogyakarta city, first city in Asia to have citywide deployment
- People in the Yogyakarta are very excited as Wolbachia intervention will allow them to live without the constant fear of being infected with dengue
- World Mosquito Program (WMP) plans to implement Wolbachia program all over the world. The success in Yogyakarta, Jakarta is just the beginning.

PANEL DISCUSSION

The panel members included **Prof. Sri Rezeki Hadinegoro** - Professor in Department of Child Health at the University of Indonesia, **Prof. Adi Utarini** - Professor in the Department of Heath and Policy Management, Faculty of Medicine at Universitas Gadjah Mada, Indonesia and **Prof. Ng Lee Ching** - Director of National Environment Agency's Environmental Health Institute, Singapore.

Prof. Sri Rezeki Hadinegoro highlighted that control of breeding places and community behavior are main problems in dengue prevention. This year we face 2 burdens due to dengue and ongoing COVID-19 pandemic. The AWED study by the World Mosquito Program has demonstrated significant Impact of Wolbachia intervention on dengue control with 77% reduction in incidence of VCD in Yogyakarta, Jakarta. Wolbachia implementation throughout Indonesia will require further effort and support from all stakeholders especially communities and policy makers. Wolbachia has the potential to complement and strengthen dengue prevention strategies.

Prof. Adi Utarini indicated that the local community in Yogyakarta is extremely excited and happy with the results of the trial and impact of Wolbachia intervention on their community. There is ongoing collaboration between communities, WMP and government to scale ahead with national Wolbachia implementation.

Prof. Ng Lee Ching said that the AWED trial results in Yogyakarta have been ground breaking. The community engagement is this program is impressive. Prof. Ng Lee Ching also shared the Wolbachia experience in Singapore.

Q/A SESSION:

1. **How did you convince the community for AWED trial?**
   Prof Adi Utarini: Community engagement was the most crucial part in this trial. The community was educated and informed about the trial as early as in the year 2014. Mass media approach (TV, social media) was used to educate community members. Community consent was necessary and was obtained at the district level. Representatives of community were present during the process.

2. **Did you face any challenges during community participation?**
   Prof. Adi Utarini: Community acceptance was very high. The challenges were more practical, e.g. Families with elderly parents or young babies were not ready to take care of the small buckets of eggs.

3. **What is the future of arbovirus control? Should public health programs focus on one method or a set of them? Which are the most promising?**
   Prof. Sri: Rezeki Hadenegoro : Elimination of dengue is very difficult. Geographical variation, environmental conditions, vector control, community participation and vaccine coverage play an important role in dengue control.

   Prof. Ng Lee Ching: We cannot eliminate dengue by just dealing with Aedes Aegypti, as Aedes albopictus is also responsible for low lying numbers of dengue. Aedes albopictus needs to be controlled as well. Zika can be blocked with the Wolbachia intervention but we still have Chikungunya, Japanese enchephalitus and West Nile viruses to control.

4. **Are there going to be any bridging studies after AWED trial?**
   Prof. Cameron Simmons: Our strategy is to do demonstration studies in major endemic countries to show that biology of Wolbachia is unchanged with geography. We cannot conduct a RCT in every country due to funding constraints. We need a pragmatic approach that builds on gold standard evidence from RCTs and demonstration studies to replicate public health outcome.

5. **Mosquito population index has one peak /year in Indonesia while there are 2 peaks/year in Singapore. Why?**
   Prof. Adi Utarini: This depends on the rainy season and people behavior.

6. **While raising Wolbachia infected mosquito stocks, is there an alternative to human blood source?**
   Prof. Ng Lee Ching: Different laboratories use different blood sources. Cow, sheep or pig blood is used as an alternative to human blood.

References: 1. Gubler D. Dengue, Urbanization and Globalization: The Unholy Trinity of the 21st Century. Trop Med Health. 2011 Dec; 39(4 Suppl): 3–11. **2.** Stanaway J et al. The Global Burden of Dengue: an analysis from the Global Burden of Disease Study 2013. Lancet Infect Dis. 2016 Jun; 16(6): 712–723. **3.** Dorigatti I et al. Using Wolbachia for dengue control: insights from modeling. Trends Parasitol. 2018 Feb; 34(2): 102–113. **4.** World Mosquito Program. **5.** Anders KL et al. The AWED trial (Applying Wolbachia to Eliminate Dengue) to assess the efficacy of Wolbachia-infected mosquito deployments to reduce dengue incidence in Yogyakarta, Indonesia: study protocol for a cluster randomised controlled trial. Trials 2018; 19:302.

Co-convenors: ADVA Asia Dengue Voice & Action Group; Fondation Merieux; gdac Global Dengue + Aedes-Transmitted Diseases Consortium; SEAMEO TROPMED; World Mosquito Program; The International Society for Neglected Tropical Diseases

Supported by: Takeda

Supported with unrestricted educational grants from Takeda Pharmaceutical Co Ltd. and Fondation Merieux.

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