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Advances in the Study of Dengue Epidemic Spread: A Brief Overview

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Viral infectious diseases such as dengue, yellow fever, zika and chikungunya represent important public health problems around the world[1,2]. In particular, dengue is a systemic disease caused by arboviruses of the *Flaviviridade* family (*flavivirus* genus) from arthropods such as ticks, sand flies and mosquitoes[3]. Dengue's spreading is inexorably connected to the *Aedes* mosquitoes' behavior one of the most studied vectors due to their role in transmission. As a result of being pathogenic to humans and capable of being transmitted in densely populated areas, the hyperendemicity of multiple serotypes of the dengue virus DENV (1-4) causes an alarming impact on human health in national and global economies[4]. It is estimated that 390 million people are infected annually[5] and that 3.9 billion people occupy risk areas[6], and if it wasn't enough, the last decade has emerged a new type of DEV- 5 from macaques with a spillover into humans, resulting in the Sarawak outbreak. The exact reason for emergence of DENV-5 is not clear, but there are indications that the origin is ecological, as due to deforestation[7].

In a dengue epidemic, the abundance of mosquitoes and dynamic of infection plays a central role for the emergence and maintenance of this disease. The life cycle of mosquito present complete metamorphosis during egg, larvae, pupae, and adult stages. The male *Aedes* mosquitoes feed on flowers' nectar or plant juices, unlike the female ones that need a blood meal for reproduction[8]. Mosquitoes raised in the laboratory for research purposes use alternative diets instead of vertebrate blood[9]. The vector becomes infected when they feed on infected human blood, or vertically (transovarial), when an infected female transmits the virus to part of its progeny. Once it has acquired the virus, the mosquito remains infected throughout its life[10].

Taking into account the attribution of transovarial transmission, some results show that it can occur in some species of dengue mosquitoes[11–16], but the role of transovarial transmission in the spread of the dengue virus and the persistence of epidemics are not clearly understood[13,17]. Moreover, the transovarial transmission of the dengue virus in *Aedes aegypti* has been observed at a relatively low rate[15,18]. The role of the vertical transmission in vectors was studied from mathematical models[19–21]. In the study[19], Yang used a modeling based on differential equations to compare different effects of both horizontal and vertical ways of transmission on the spread of the dengue virus. His major conclusion is that there is a transovarial transmission threshold which plays an important role in the dengue spreading when the estimated reproduction number is one. In the study[20], the authors applied Ross and MacDonald's mathematical model to assess the dynamics of multi-strain competition taking into account molecular genotyping. The authors showed that even a low probability of vertical transmission can have a major impact on the long-term dynamics of dengue fever. Costa et. al[21] studied the transovarial transmission of DENV in *Aedes aegypti* in municipalities of the Amazonas state – Brazil – basin from a local model of xenomonitoring. Their results suggest that the transovarial transmission may be a key mechanism for the maintenance and the spread of the disease in Amazonas.

Climate and landscape factors are important determinants of mosquito abundance. Factors as temperature, rainfall, humidity, and seasonality, typical of tropical and subtropical regions, favor dengue epidemic spreading because these effects influence the offspring, life cycle, surviving of adult and larva mosquito and also the extrinsic incubation period. *Aedes aegypti* has a weak resistance at low or higher temperatures. Temperatures between 26 ˚C and 29 ˚C are ideal to its life cycle, and the extremes, below 18 ˚C and above 34 ˚C, have negative effects on its development[22]. The adult mosquito life span can range from two weeks to a month depending on environmental conditions. In the unfavorable temperatures, the life cycle of the mosquito is short; also, there is the production of small-sized mosquitoes, which may lead to the reduction of the extrinsic incubation period. The small-sized female mosquitoes may take more blood meals to produce eggs, which may lead to the increase in the number of infected mosquitoes and acceleration of the hyperendemic level in the favorable period[23,24].

The dengue epidemic presents a typical seasonality corresponding to biotic and abiotic factors and, is associated to several parameters such as transition and mortality rates in the aquatic phase, mortality rate of adult mosquitoes, oviposition rate, virus incubation rate in humans and mosquitoes, behavior, density, vectorial capacity of mosquito population, and human infectious rate have been associated with the initiation and maintenance of the epidemic after the introduction of the virus into a community[25–27]. Moreover, these parameters vary with temperature and precipitation[28–30]. Taking into account entomological and epidemiological factors of dengue epidemics, Yang et al[31] evaluated through a mathematical model entomological parameters of dengue mosquito are affected by climatic factors such as temperature and precipitation. The database used was collected from the city of Campinas, São Paulo, Brazil and only one serotype of dengue were considered. The goal was to estimate the maximum and minimum temperatures and precipitations in the City of Campinas to fit dengue transmission parameters from humans to mosquitoes and vice-versa. The entomological and epidemiological parameters presented there, as function of the temperature, make it possible to extrapolate them to regions with different climatic conditions and to build mathematical models.

Since there are no specific medicines licensed for the treatment of this potentially fatal disease, currently, public health programs have focused attention on the reduction of mosquito' populations and larvae with the use of chemical substances such as insecticide and larvicide[27], respectively. Different chemical components have been employed to control them[32–34]. However, these chemicals exhibit toxicity that causes ecological damage to the environment as they can be accumulated in food, water and in bodies of vertebrates. There are studies that show that insecticides and larvicides used in mosquito control are harmful to humans as they can be cancerous[35,36]. Mosquitoes, on the other hand, present resistance to different chemical substances that survive the application of insecticides and therefore increasing doses are necessary to control the vectors[37]. The increase of insecticide resistance in vector populations has seriously decreased the efficacy of this approach.

In parallel, educational campaigns for population awareness have been employed in an attempt to eliminate the main breeding of mosquitoes, such as man-made containers with standing water that are conducive to vector proliferation[10]. This procedure is encouraged by professionals, leading to public awareness, which can help empower people to take control of mosquito breeding in their surrounding areas. However, this method cannot be applied in certain areas, because of the limitation of social culture or context[38]. The mechanical trap is another alternative of control which imprisons the insects, the eggs, and the larvae. Likewise, the use of fish[39], bromeliads[40] and other predators as ecological alternatives to prey on mosquitoes at their distinct stages of development are encouraged. These measures, however, do not yield meaningful results to reduce epidemic outbreaks[27].

Besides these traditional control strategies, modern mosquito control strategies such as sterile insect by radiation technique (SIRT), incompatible insect technique (IIT), multi-locus assortment (MLA), release of insects carrying a dominant lethal genetic system (RIDL), population replacement strategies (PR), and Wolbachia related technique have been used, but these methods demand the creation of large numbers of mosquitoes in laboratory for continuous release in the environment over an extended period of time[41,42]. For instance, the control strategy based on Wolbachia has been highlighted with potential usefulness to protect the human population from dengue spreading[43]. The endosymbiotic Wolbachia inhibits the viral replication and it is commonly transmitted vertically from the mother to its offspring. Indeed, studies showed that after the 14th day of infection, the Wolbachia completely blocks the dengue transmission in at least

37.5%. In another strategy, the male mosquitoes reared in the laboratory is exposed to low radiation and sterilized, while keeping the copulation capacity. The insects produced with impaired fertility are released into the environment to mate with wild insects and to produce sterile eggs, thereby reducing the next generation of mosquitoes.

Currently, the genetic engineering has been applied in the study of dengue mosquitoes to produce transgenic insects, which carry a dominant lethal allele capable of killing mosquito generations[44]. The genetic modification is inherited by the offspring of these transgenic insects. The transgenic male mosquitoes are released into the environment, where they mate with the wild females in the mosquito population. While male offspring, which carries the gene, survives and continues to pass the genetic trait to further generations, the female offspring dies. With fewer females, the mosquito population is drastically suppressed[45,46]. Oxitec[1] has conducted releases of transgenic mosquitoes in the Grand Caymans, Malaysia, Brazil, and Florida.

Due to the failure of traditional vector control strategies based on chemical, mechanical, and biological methods, as well as the lack of efficient antiviral treatment, a dengue vaccine has long been sought to reduce both dengue transmission and the increasing disease burden in the world[27]. Interestingly, Dengvaxia® was a vaccine developed by Sanofi Pasteur, the only registered and licensed dengue vaccine available so far. Until now, the dengue vaccine has been approved in more than 18 countries and the first mass immunization campaigns occurred in the Philippines and Brazil between 2015 and 2018.

Machine Learning approach was applied to dengue vaccine in a recently published paper[47]. In this study, the authors found that the vaccine is protective against three types of dengue (serotypes 1, 3 and 4) if applied in the ages between 2 and 16 years old, regardless of previous exposure, with significantly better results than those vaccinated in the ages of 9-16. The study also showed that the efficacy against the remaining type of dengue (serotype 2) is significant only in pre-exposed subjects. However, a recent work published according to the data provided by the Vaccine Confidence Project[TM,48] measured the impact of the falling efficiency of the vaccine in the Philippines by comparing confidence levels between 2015 and 2018. According to these results, there was a decline in confidence among those who agreed that the vaccines are safe, from 82% in 2015 to only 21% in 2018. Likewise, confidence in the vaccine efficacy fell from 82% in 2015 to only 22% in 2018. Regarding the importance of the vaccines, the numbers also show a decrease, from 93% in 2015 to 32% in 2018.

Created to prevent first and recurrence of infections, there are evidence[49] which show patients developed dengue fever, and others types like dengue hemorrhagic fever or dengue shock syndrome after being immunized by vaccine. Moreover, secondary heterotypic infection or waning immunity of infants born to mothers infected by DENV has been observed to significantly increase the likelihood of acquiring severe disease. The authors verify antibody (Ab)-dependent enhancement (ADE) of dengue viruses' has been thought to be involved in the immunopathogenesis of severe dengue forms and in recurrence disease in humans. The antibody against DENVs are responsible for both protection as well as pathogenesis. It found also that immune correlate for enhanced severe dengue disease is distinct from that for protection[49].

However, the recent document presented by the European Medicines Agency[50] through the Committee for Medicinal Products for Human Use (CHMP) addressed the benefit-risk balance of Dengvaxia®. By majority decision, the committee is indicated this vaccine for the prevention of the dengue disease caused by all dengue virus serotypes in individuals from 9 to 45 years old with prior dengue virus infection and living in endemic areas.

In this mini review article, we gave a brief overview of the important topics in the field "spread of dengue epidemics" which include key themes such as the relevance of dynamics of epidemics, controls and treatments through vaccine. We hope that this theme will encourage further studies in the various fields of dengue epidemics.

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Competing Interests

The authors declare no competing interests.

References

1. Goncalves A, Peeling RW1, Chu MC, et al. Innovative and New Approaches to Laboratory Diagnosis of Zika and Dengue: A Meeting Report. J Infect Dis. 2017; 217: 1060–1068.
2. Staples JE, Fischer M. Chikungunya virus in the Americas--what a vectorborne pathogen can do. N Engl J Med. 2014; 371(10): 887-9.
3. Baylis M. Potential impact of climate change on emerging vector-borne and other infections in the UK. Environ Health. 2017 5;16(Suppl 1):112.
4. WHO. Treatment, prevention and control global strategy for dengue prevention and control 2. World Health Organization 2012.
5. Bhatt S. The global distribution and burden of dengue. Nature. 2013; 496: 504–507.

[1]https://www.oxitec.com/

6. Brady OJ, Gething PW, Bhatt S, et al. Refining the Global Spatial Limits of Dengue Virus Transmission by Evidence-Based Consensus. PLoS Neglected Trop Dis. 2012; 6: e1760.

7. Col L. ScienceDirect Discovery of fifth serotype of dengue virus (DENV-5): A new public health dilemma in dengue control. 2014; 1: 5–8.

8. Whitehead SS, Blaney JE, Durbin AP, et al. Prospects for a dengue virus vaccine. Nat Rev Microbiol. 2007; 5: 518–528.

9. Gonzales KK, Rodriguez SD, Chung HN, et al. The Effect of Skito Snack, an Artificial Blood Meal Replacement, on Aedes aegypti Life History Traits and Gut Microbiota. Sci Rep. 2018; 8.

10. Kweka EJ. Ecology of Aedes Mosquitoes, the Major Vectors of Arboviruses in Human Population. in Dengue Fever - a Resilient Threat in the Face of Innovation IntechOpen, 2019. doi:10.5772/intechopen.81439

11. Ferreira-de-Lima VH, Lima-Camara TN. Natural vertical transmission of dengue virus in Aedes aegypti and Aedes albopictus: A systematic review. Parasites and Vectors. 2018; 11: 1–8.

12. Martins VE, Alencar CH, Kamimura MT, et al. Occurrence of Natural Vertical Transmission of Dengue-2 and Dengue-3 Viruses in Aedes aegypti and Aedes albopictus in Fortaleza, Ceará, Brazil. PLoS ONE. 2012; 7: e41386.

13. Joshi V, Mourya DT, Sharma RC. Persistence of dengue-3 virus through transovarial transmission passage in successive generations of Aedes aegypti mosquitoes. Am J Trop Med Hyg. 2002; 67: 158–161.

14. Cruz LC, Serra OP, Leal-Santos FA, et al. Natural transovarial transmission of dengue virus 4 in Aedes aegypti from Cuiabá, State of Mato Grosso, Brazil. Rev Soc Bras Med Trop. 2015; 48: 18–25.

15. Günther J, Martínez-Muñoz JP, Pérez-Ishiwara DG, et al. Evidence of Vertical Transmission of Dengue Virus in Two Endemic Localities in the State of Oaxaca, Mexico. Intervirology. 2007; 50: 347–352.

16. Joshi V, Singhi M, Chaudhary RC. Transovarial transmission of dengue 3 virus by Aedes aegypti. Trans R Soc Trop Med Hyg. 1996; 90: 643–644.

17. Shroyer DA. Vertical maintenance of dengue-1 virus in sequential generation of Aedes albopictus. Jounal Am Mosq Control Assoc. 1990; 6: 312–314.

18. Rosen L, Shroyer DA, Tesh RB, et al. Transovarial transmission of dengue viruses by mosquitoes: Aedes albopictus and Aedes aegypti. Am J Trop Med Hyg. 1983; 32: 1108–1119.

19. Yang HM. The transovarial transmission in the dynamics of dengue infection: Epidemiological implications and thresholds. Math Biosci. 2017; 286: 1–15.

20. Murillo D, Murillo A, Lee S. Vertical Transmission in a Two-Strain Model of Dengue Fever. Lett Biomath. 2014; 1: 249–271.

21. da Costa CF, Dos Passos RA, Lima JBP. et al. Transovarial transmission of DENV in Aedes aegypti in the Amazon basin: a local model of xenomonitoring. Parasit Vectors. 2017; 10.

22. Mordecai EA, Cohen JM, Evans MV, et al. Detecting the impact of temperature on transmission of Zika, dengue, and chikungunya using mechanistic models. PLOS Neglected Trop Dis. 2017; 11: e0005568.

23. Gubler DJ. Dengue and dengue hemorrhagic fever, 1996. Epidemiol Bull. 1996; 17: 12–4.

24. The control of neglected tropical diseases, W. The control of neglected zoonotic diseases: from advocacy to action report of the fourth international meeting held at WHO Headquarters. in From advocacy to action (Geneva-Switzerland, 2015). doi:https://www.who.int/neglected_diseases/zoonoses/9789241508568/en/

25. Kamal S, Jain SK, Patnaik SK, et al. Epidemiological and entomological investigation of dengue fever in Sulurpet, Andhra Pradesh, India. Dengue Bull. 2006; 30: 93–98.

26. Cromwell EA, Stoddard ST, Barker CM, et al. The relationship between entomological indicators of Aedes aegypti abundance and dengue virus infection. PLoS Negl Trop Dis. 2017; 11: 1–22.

27. Carvalho SA, da Silva SO, Charret IDC. Mathematical modeling of dengue epidemic: control methods and vaccination strategies. Theory Biosci. 2019. doi:10.1007/s12064-019-00273-7

28. Yang HM, Macoris Mde L, Galvani KC, et al. Follow up estimation of Aedes aegypti entomological parameters and mathematical modellings. Biosystems. 2011; 103: 360–371.

29. SB, PD. Seasonal pattern of abundance of Aedes albopictus in urban and industrial areas of Dibrugarh district. Asian J Exp Biol Sci. 2012; 3: 559–564.

30. Lai YH. The climatic factors affecting dengue fever outbreaks in southern Taiwan: an application of symbolic data analysis. BioMedical Eng OnLine. 2018; 17.

31. Yang HM, Boldrini JL, Fassoni AC, et al. Fitting the Incidence Data from the City of Campinas, Brazil, Based on Dengue Transmission Modellings Considering Time-Dependent Entomological Parameters. PLOS ONE. 2016; 11: e0152186.

32. Rueda AG, Otero ALC, Duque JE, et al. Synthesis of new α- amino nitriles with insecticidal action on Aedes aegypti (Diptera: Culicidae). Rev Bras Entomol. 2018; 62: 112–118.

33. Marcombe S, Chonephetsarath S, Thammavong P, et al. Alternative insecticides for larval control of the dengue vector Aedes aegypti in Lao PDR: insecticide resistance and semi-field trial study. Parasit Vectors. 2018; 11.

34. Monnerat R. Evaluation of Different Larvicides for the Control of Aedes aegypti (Linnaeus) (Diptera: Culicidae) under Simulated Field Conditions. BioAssay. 2012; 7.

35. Dhouib I, Jallouli M, Annabi A, et al. Carbamates pesticides induced immunotoxicity and carcinogenicity in human: A review. J Appl Biomed. 2016; 14: 85–90.

36. Rivero J, Henríquez-Hernández LA, Luzardo OP, et al. Differential gene expression pattern in human mammary epithelial cells induced by realistic organochlorine mixtures described in healthy women and in women diagnosed with breast cancer. Toxicol Lett. 2016; 246: 42–48.

37. Hemingway J, Ranson H. Insecticide Resistance in Insect Vectors of Human Disease. Annu Rev Entomol. 2000; 45: 371–391.

38. Matysiak A, Roess A. Interrelationship between Climatic , Ecologic , Social , and Cultural Determinants Affecting Dengue Emergence and Transmission in Puerto Rico and Their Implications for Zika Response. 2017; 2017.

39. Han WW, Lazaro A, McCall PJ, et al. Efficacy and community effectiveness of larvivorous fish for dengue vector control. Trop Med Int Heal. 2015; 20: 1239–1256.

40. Santos CB, Leite GR, Falqueto A. Does native bromeliads represent important breeding sites for Aedes aegypti (L.) (Diptera: Culicidae) in urbanized areas? Neotrop. Entomol. 2011; 40: 278–281.

41. King JG, Souto-Maior C, Sartori LM, et al. Variation in Wolbachia effects on Aedes mosquitoes as a determinant of invasiveness and vectorial capacity. Nat Commun. 2018; 9.

42. Pereira TN, Rocha MN, Sucupira PHF, et al. Wolbachia significantly impacts the vector competence of Aedes aegypti for Mayaro virus. Sci Rep. 2018; 8.

43. Bian G, Xu Y, Lu P, Xie Y, et al. The Endosymbiotic Bacterium Wolbachia Induces Resistance to Dengue Virus in Aedes aegypti. PLoS Pathog. 2010; 6: e1000833.

44. Carvalho DO, McKemey AR, Garziera L, et al. Suppression of a Field Population of Aedes aegypti in Brazil by Sustained Release of Transgenic Male Mosquitoes. PLOS Neglected Trop Dis. 2015; 9: e0003864.

45. Hoang KP, Teo TM, Ho TX, et al. Mechanisms of sex determination and transmission ratio distortion in Aedes aegypti. Parasit Vectors. 2016; 9.

46. Reis NN, Silva ALD, Reis EPG, et al. Viruses vector control proposal: genus Aedes emphasis. Brazilian J Infect Dis. 2017; 21: 457–463.

47. Dorigatti I, Donnelly CA, Laydon DJ, et al. Refined efficacy estimates of the Sanofi Pasteur dengue vaccine CYD-TDV using machine learning. Nat Commun. 2018; 9.

48. Larson HJ, Hartigan-Go K, de Figueiredo A. Vaccine confidence plummets in the Philippines following dengue vaccine scare: why it matters to pandemic preparedness. Hum Vaccin Immunother. 2018; 15: 625–627.

49. Katzelnick LC, Gresh L, Halloran ME, et al. Antibody-dependent enhancement of severe dengue disease in humans. 2017; 932: 929–932.

50. CHMP C for MP for HU. European Medicines Agency. 2018; 44. https://www.ema.europa.eu/en/documents/assessment-report/dengvaxia-epar-public-assessment-report_en.pdf