BIOSCIENCES BIOTECHNOLOGY RESEARCH ASIA, September 2020. Vol. **17**(3), p. 507-515

Dengue Vector Control: A Review for *Wolbachia*-based Strategies

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http://dx.doi.org/10.13005/bbra/2854

(Received: 26 June 2020; accepted: 29 July 2020)

Mosquito-borne diseases continue to pose a major health problem globally and have had a significant impact on human life and economy. Consequently, many countries have implemented national vector control programs in an effort to suppress/eradicate mosquitoes contributing to spread of diseases including Malaria, Dengue, Yellow fever, Rift valley fever, West Nile fever, Zika, Chikungunya etc. Of these endemic diseases, Dengue fever is an arbovirus and transmitted primarily by *Aedes aegypti* mosquito that has become a rapidly emerging infection, especially in the tropical countries. Insecticides spraying remains the main method to control the transmition of dengue virus. However, the overuse and misuse of insecticides can result in negative consequences such as the development of insecticides resistance. This, in part, has led to the development of a more eco-friendly measures to suppress mosquitoes e.g. gene-drive based controls and *Wolbachia*-based approaches. The latter approach has the ability to block the dengue virus transmission by inhibiting virus intracellular replication in mosquito. In addition, *Wolbachia* decreases adult mosquito lifespan and can be naturally passed from one generation to the next. In recent years, *Aedes aegypti* mosquitos infected with *Wolbachia* released and tested in the field in several countries and have achieved very promising results. In this review, we focus and discuss the emerging *Wolbachia*-based biocontrol approaches that are already being deployed, evaluated and tested in the field.

Keywords: *Aedesagypti*, Dengue, *Wolbachia*, Cytoplasmic incompatibility (CI).

Global incidences of mosquito-borne diseases are growing up due to people travel, fast urbanization and ineffective of control programs measures[1]. Dengue fever (DENV) is the most serious arboviral epidemic threatening humanity and it is responsible of death cases in the tropical and subtropical regions. About 50 % of the inhabitants across the world are now at dengue risk. Official reports estimated around 390 million person are infected annually, half million of them are critical situations and require hospital treatment. About of 2.5 % of those infected cases die. Although several countries used vaccine against DENV in humans ranged between 9 and 45 years of age inhabiting in endemic areas, but the mosquito control is still the main approach to stop the dengue disease[2].*A. aegypti* mosquito is the main vector of Dengue, Zika,chikungunya

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and yellow fever diseases, also *A. albopictus* is a possible transmitter. A. aegypti mosquito is well adapted to mankind. The mosquito females obtain blood meals by biting and digestive it inside their bodies to produce their eggs. Unfortunately, the elimination of *A. aegypti* is not easy task due to their ability to lay the eggs in many sites included those of a little amount of water. Alsothe eggs able to stay alive months in the absence of water and hatch as soon as water is available. Moreover they have resistance to common insecticides[3,4]. All these conditions make the eradication of *A. aegypti* by traditional techniques useless[5]. The use of insecticides can be effective on mosquito control program, but it is often prohibitively, highly cost, harmful on non-target organisms, has negative environmentally effects.Furthermore, the long term use of insecticides led mosquitoes to develop resistance against insecticides [6,7]. Alternative methods were used to mosquitoes management such as the elimination of eggs laying sites, the using of animals that naturally preys on mosquitoes like copepods and fish[8] and avoid mosquito bites byprotection tools. These strategies are considered beneficial way in some cases but it can be difficult and high cost to apply in urban areas.Accordingly, Novel arbovirus vector control tools are needed. Currently, two novel techniques revealed promise in reducing the dengue transmission[9]. The first one depends on is a genetic management by spread mosquitoes that are treated with lethal or flightless trait[10] and the second technique is establishment of mosquitoes carrying *Wolbachia* bacterium. *Wolbachia* block and prevent the growth of the dengue virus inside *A. agypti* mosquitoes[11,12]. In this technique, the *Wolbachia*-infected mosquitoes are released into the wild. Because of cytoplasmic incompatibility (CI), the *wolbachia* are passed on through generations of mosquitoes and the ratio of *Wolbachia-infected mosquitoes*is growing upuntil it become high and predominance without any additional releases. This strategy is applied in several countries[13,14,15].

What is *Wolbachia*?

Wolbachia is considered type of Gram-negative bacterium fall under the order *Rickettsiales* and the family *Anaplasmataceaet* (Table 1). This type of bacterium are naturally availablein invertebrates and infect about60% of insect community[11]. However, *Wolbachia* is naturally absent from *A.aegypti* mosquito,the main transmitter responsible for the spread of human diseases including dengue and other diseases of RNA-virus.*Wolbachia* has the ability to prevent the growth of several of RNA-viruses in mosquitoes and *Drosophila*. If infected or uninfected males fertilize *wolbachia*-possitive females, the resulting generations will be healthy and carrying *Wolbachia* and are expanded in the wild population. *Otherwise if infected males fertilize uninfected females, the resulting offspring could not developed. This event is named by the term of* cytoplasmic incompatibility (CI). Meanwhile, *Wolbachia*-positive mosquitoes produce less eggs and reduce mosquito lifespan.

In general, the *Wolbachia* species are named based on the source where they first discovered. For example, *Wolbachia pipientis* (wPip) strain was isolated for the first time from *Culex pipiens* mosquito. Also, wMel speciesfrom the fruit fly *Drosophila melanogaster*, while wAlb species isolated fromthe mosquito *Aedes albopictus*. Scientists have revealed that *Wolbachia* stimulate the resistance of arthropods against viruses and inhibit their reproductive ability inside the host. Recently, Australian researchers of the control program showed of dengue have showed that the expand of *wolbachia* into wild mosquitoes *A. aegypti* populations is considered promising technique to overcome the dengue virus transmission. This led WHO and health authoritiesto encourageuse *Wolbachia* approachas a way to overcome the transmission of dengue and arboviral diseases[12].

Wolbachia strategy provides eco-friendly and a safe alternative to insecticide use. Although *Wolbachia*-infected *A. aegypti* were originally developed for biocontrol of dengue, it may able toreduce the transmission of other mosquito-borne diseases including chikungunya and yellow fever[16], potentially malaria[17,18] and Zika[19].

Potential risk of *Wolbachia*-infected mosquitoes on human

There is no evidence indicate that wolbachia transfer to human or to the mosquito predators such as geckos and spiders. No antigenic or immune response developed by mosquitoes bites[20]. The Australian Commonwealth Scientific Organization produced a risk assessment of

releasing *Wolbachia* in the wild[21] before the official authorities granted the acceptance[13].

It is worth noting that the *Wolbachia* does not horizontally transfer to other organisms. Potentially, there is horizontally transfer of *Wolbachia* DNA into mosquito genomes, but this situation of transferhappen rarely[22,23,24,25].Such lateral transfer are unlikely to raise the risk related with the *Wolbachia*-positive mosquitoes release. *Wolbachia*-based biocontrol holds the promise of an environmentally and safe alternative that is not expensive to implement and has the chance to be effective on a global scale.

Biocontrol of Dengue Virus Using *Wolbachia* Strategy

Recently, the *wolbachia* has been studied by several researchers for its potential to useas a biocontrol strategy of *Aedes* mosquito[26]. Laven (1967) was the first researcher started the use of *Wolbachia*-infected *Cx. pipiens* mosquitoes to eliminate the the population of mosquito *Culex pipiens* through cytoplasmic incompatability (CI)[27]. CI is a phenomenon occurs when *wolbachia*-infected males are mating with uninfected females and the resulting offspring can not develop. In contrast,whenboth *Wolbachia*-positive male and femaleare mating, the offspring will hatch and develop normally[28].

Wolachia release was done in Yorkeys Knob and Gordonvale, Australia, in early January 2011,asfirst trial sites, both wMel-positive females and males of *A.aegypti* were weekly released for a totally of ten weeks.

After five weeks-post finishing release, *A. aegypti* mosquitoes were *Wolbachia* positive with the percentage of 100 % and 90 % in Yorkeys Knob and Gordonvale, respectively.

Second release was in January 2012 by wMelPop-infected *A.aegypti* in both Machans Beach and Babinda areas. A promising proportion of wMel Pop-positive *A.aegypti* was reported (with 49% and 75%, respectively) in the wild population during 2–3 weeks after the release start.However, one month post-finishing release, the proportions of wMelPop-infected *A.aegypti* decreased to less than 50 and 71 % in both Machans Beach and Babinda, respectively.This is may be attributed to inability of that *Wolbachia* strain to keep themselves for a long time in the field[29].

Releases of wAlbB-infected *Ae. Aegypti* mosquitoes were done in greater Kuala Lumpur, Malaysia, including 6 diverse sites with high dengue cases. The *wolbachia* strain was established successfully with very high population frequency at some sites and fluctuations at other sites which were supported by additional releases. Based on the monitoring of the situation and compared to control sites, decrease in human dengue cases was observed in the release sites. The wAlbB strain of *Wolbachia* offers a promising strategy as a tool for dengue control, especially in very hot weather[30].

Durovni*et al*., 2019 described study for evaluatingthe impact of wide-scale *Wolbachia* releases on the control of dengue, chikungunya and Zika in Brazil. The study is in progress and the monitoringand data analysis will continue until 2023. In case of success, the experiment will be expanded nationally and regionally. Releases programs of mosquito carrying *Wolbachia* are implemented or still in progress in 8 countries, fortunately no record of dengue, chikungunya and zika cases in areas where wide spread of *Wolbachia*-infected mosquitoes are established[31].

Table 1. Taxonomy of *Wolbachia* and *AedesAegypti*

Taxon	Name Wolbachia	Taxon	Name AedesAegypti
Domain	*Bacteria*	kingdom	*Animalia*
Phylum	*Proteobacteria*	phylum	*Arthropoda*
Class	*Alphaproteobacteria*	Class	*Insecta*
Subclass	*Rickettsidae*	Order	*Diptera*
Order	*Rickettsiales*	Superfamily	*Culicoidae*
Family	*Rickettsiaceae*	Family	*Culicidae*Meigen, 1818
Genus	*Wolbachia*	Genus (112)	*Culex, Aedes, Anopheles, etc*
Species	*Wolbachiapipientis,* Hertig 1936	Species	*Aedesaegypti* Linnaeus, 1762

Adekunle *et al*., 2019 described a dynamic model adjusting for deficient vertically transmission and decline of *Wolbachia* infection. This model shows clearly that the disadvantages of CI could outweigh the advantages and the *Wolbachia* may be lost. They set the optimal release strategy that determines the ability of *Wolbachia* for invasion and also, they deduced locally and globally stability of the equilibrium points[32].

Mathematical modelling represents a significant tool to understand the effect of factors in infectious diseases dynamics and help in making decisions regarding the implementation of control programs[33]. These models simulate the invasion of *Wolbachia*-infected*A. aegypti* into wild mosquito populations[34,35,36]. CI represents important factor on the replacement between *Wolbachia*-uninfected and *Wolbachia*-infected mosquitoes populations[37]. Ndii *et al*. described a model for the competition between both infected and infected mosquitoe populations and demonstrated the main factors that control on this competition[38]. Xue *et al*. developed the same model as Ndii *et al* and sex type is incorporated into the model and demonstrated that successful establishment of infected populations need releasing high amount of mosquitoes carrying *Wolbachia*[39]. Mathematical equations were used to develop model for the mosquito contests between *wolbachia*-positive and *wolbachia*-negative ones, Zheng *et al*. demonstrated that the succeeded alteration of *wolbachia*-negative mosquitoes by positive ones need a careful release strategy and *Wolbachia* strain play rolein this task[36]. Qu *et al*. developed a model of designed release methods and extend the model to include the idea that mosquito female mate once[40]. The model by Li and Liu was designed and took in consideration the combined variables of birth-rate, mortality rate, *wolbachia* type and the amount of *wolbachia*-infected mosquitoes released[41].

OReilly *et al*. used different models to evaluate the negative consequences of dengue in Indonesia. They expect that *Wolbachia* technique can avoidup to75 % of disease consequences in the country.Area-wide interventions such as *wolbachia* can display an effective way to protect humans more than individually measures, such as vaccinations, in such huge population density[42]. Finally, all above mentioned models support the approach of ability of *Wolbachia*-infected mosquitos to replace the uninfected ones in wild populations

Novel *Wolbachia* strains in *Anopheles* malaria vectors from Sub-Saharan Africa

Malaria is mosquito-borne disease and transmit to human by some *Anopheles* mosquito species. Historically, *anopheles genus has been considered Wolbachia-free* but has recently discovered in 5 *Anopheles* species in west Africa, *Anopheles coluzzii, Anopheles gambiae, Anopheles*

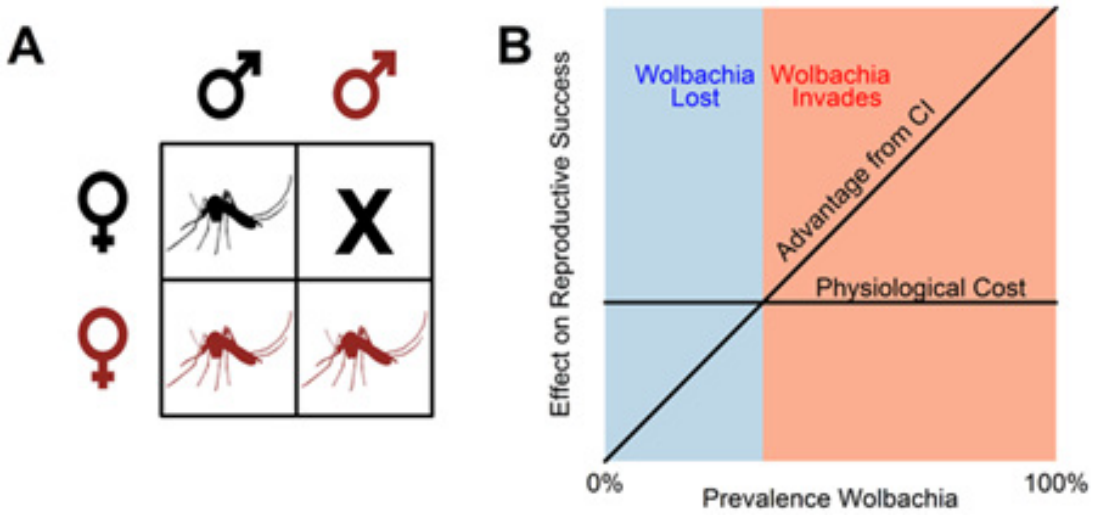

Fig. 1. (A) Mosquito mating between female and male and effect of Cytoplasmic incompatibility (CI) on resulting offspring (B)Role of release density in the invasion of *Wolbachia* in the population (https://doi.org/10.1371/journal.pbio.2002780.g001)

arabiensis, Anopheles moucheti and *Anopheles species A*.These novel strains of *Wolbachia* have possibility to establish *Wolbachia*-infected anopheles mosquitoes, which could be used for control strategies to overcome the *plasmodium* parasite responsible for malaria incidence[43].

Prevalence dynamic of *Wolbachia* and Cytoplasmic incompatibility (CI)

It is known that *Wolbachia* passed on from generation to the next generation by vertical transmission. Infected-males cause excitation of cytoplasmic incompatibility (CI) and modification of their sperm and lead to offspring death in early development stages (Figure 1A). However, in females case, *Wolbachia* make encoding that keep the offspring to stay alive and successful development allowing the bacterium to dominate over the populations (Figure A1)[44]. When *Wolbachia* spread with high rate then the reproductive advantage of infected females will be greatest. Otherwise, If *Wolbachia* is low, females rarely mate with *Wolbachia*-infected males, then low chance of compatibility with these males and *Wolbachia* could be lost from the population (Figure 1B). Similar case happens when infected females don't carry *Wolbachia* to the whole offspring. *Wolbachia* release should be with high amount to avoid losing the infection after release stop[45,46,47]. Releasing of *Wolbachia*-positive*A. aegypti* was implemented in 2011 in both isolated Yorkeys Knob and Gordonvale areas and the infection kept spread for 2 year-post release stop[46]. Recently release was applied in Cairns area where the mosquitos' migration may occur from the release areasto surrounding areas and vice-versa, this may lead to decrease of *Wolbachia* infection level and ultimately the loss of *Wolbachia*. However, the infection was developed well showing that *Wolbachia* approach can be implemented in a wide-scale[48].

Wolbachia* and pathogen interference in *Aedes aegypti

Creative strategy to control mosquito-born diseases started by using artificially *Wolbachia*-infected mosquitoes. Data from the field work has proved that *Wolbachia* represents promising technique to reduce natural populations of *Aedes aegypti* and control the diseases they transmit.

The mechanism of *Wolbachia* interference with the pathogens is complicated issue and need to be understood. Several scientists have attempted to explain the pathogen blocking by *Wolbachia*. They have discussed the properties of mosquito's samples collected from the field and other related insects. They demonstrated the correlation between *Wolbachia* density and the ability to block pathogen by high load that destroy host tissue.Also the probability of induction the immune response system of the host which could resist the pathogens inside the insect. Furthermore, recent studies showed that *Wolbachia* play role in immune system modulation of the host and affecton the immunity system of *A. aegypti* and *Culex quinquefasciatus* to suppress Dengue andWest Nile virus replication[49]. Other mode of action suggests modification of the cell membrane of the host, lead to preventing the vector to transmit the pathogens. Other explanation suggests competition development between *Wolbachia* and pathogens inside the host[50].We mentioned above that wMelPop cause reducing in the lifespan of mosquito, this limits the pathogens spread because the lifespan of mosquito became shorter and not enough to complete the incubation interval for pathogens[51,52]. Moreira *et al*. (2009) have described unusual behavior regarding the blood-feeding in *wolbachia*-infected *A.aegypti*, where proboscis becomes more prominent in elder mosquitoes, this phenomenon led to reduce the biting activities which eventually decrease the reproductive capacity[53]. Additionally, *Wolachia* was found to enhance mosquito immune responses against pathogens. Bian *et al*. showed that the genes responsible for immune, Defensin, Cercropin, Diptericin, GNBPB1, SPZ1A, Cactus, Rel1 and Rel2 were adjusted in *wolbachia*-infected *A.Aegypti* mosquitoes, which could explain their ability to resist dengue virus[54].

***Wolbachia*-based strategy to control other arboviral infections**

The technique of *Wolbachia*-infected mosquitoes was fucused initially for dengue control, experimental studies proved that this approach can extend to control other mosquito-borne diseases, particularly Chikungunya, Japanese encephalitis and Yellow fever. Regarding West Nile virus, it was recorded in 2009 that *Wolbachia* approach working to increase host resistance to West Nile virus in *Culexquinque fasciatus*

mosquito[55]. Subsequently, reports described that majority of *Culexquinque fasciatus* mosquitoes are naturally *Wolbachia*-infected but are still able to cause infection with West Nile virus. Furthermore, the *Wolbachia* strain isolated from *Aedes albopictus* play role in the enhancement of West Nile virus infection in *Culex tarsalis*, which is an important transmitter of West Nile virus in North America and naturally does carry *Wolbachia*[56]. Finally, *Wolbachia*-infected mosquitoes showed high resistance to the transmission of two isolates of Brazilian Zika virus.Fortunately, no evidence that *Wolbachia*-infected *A.aegypti* is carrying Zika virus in the saliva, indicating that *Wolbachia*-based strategy can prevent the infection with of Zika virus[57].

***Wolbachia* strategy in Saudi Arabia**

In the Kingdom of Saudi Arabia (KSA) dengue disease was recorded for the first time in 1994[58] and the number of cases is growing up as reported by researchers, Malaria cases also represent issue especially in Jazan region. Although the control activities during the past period, but people remain at risk as the epidemics transmission does not stop. Thus, new control strategies are needed to overcome these health problems. Accordingly, the strategy of *Wolbachia*-based biocontrol of dengue is started and still in the initial stages. Outcomes will be subject to evaluation and reported after finishing releases. If the experiment achieved success, it could be implemented on a large-scale.

CONCLUSION

Mosquitoes transmit Dengue and several diseases.We discussed here the current available informations about the relation between *Wolbachia* and moaquitoes. Insecticide-based approaches are currently the key tools in combat of major mosquito-borne diseases.However, the ability of mosquitoes to develop resistance against insecticides in addition to its harmful effects to ecosystem push to thinking to find alternative strategies. *Wolbachia* is a promising as a bio-control technique in fighting mosquitoes-borne diseases. More research is urgently needed to find better understand about behavior of artificially *Wolbachia*-infected mosquitoes and the mechanisms of interference between *Wolbachia*, pathogens and hosts.

ACKNOWLEDGEMENTS

We would like to present gratitude to King Abdulaziz City for Science and Technology, Ryidh, Saudi Arabia for their technical support.

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