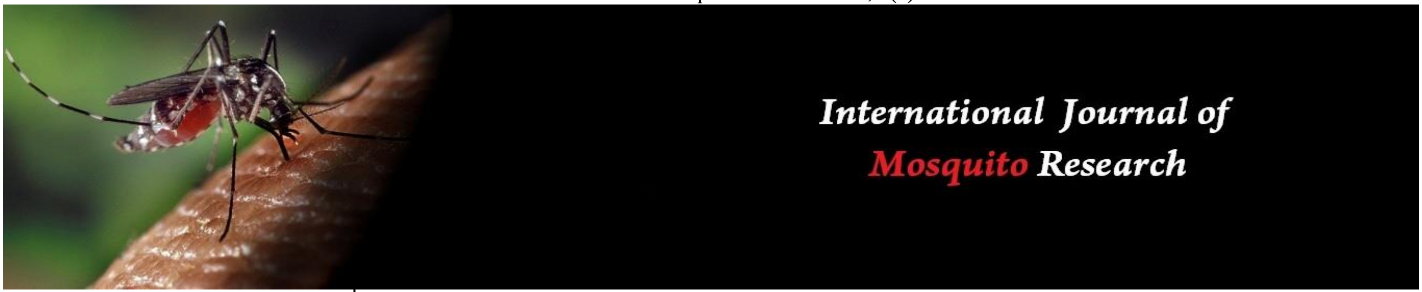

ISSN: **2348-5906**
CODEN: **IJMRK2**
IJMR 2022; 9(2): 65-68

www.dipterajournal.com
Received: 20-01-2022
Accepted: 22-02-2022

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Wolbachia: An evolutionary way to combat mosquito borne disease and the challenges in success of the strategy

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DOI: https://doi.org/10.22271/23487941.2022.v9.i2a.603

Abstract
Wolbachia is an intracellular bacterium that is found in many insects and very commonly in Dipterans. It is now being extensively studied as it aids in suppression of mosquito populations. Mosquitoes are causative agents of many life-threatening diseases (dengue, malaria, chikungunya fever, Zika virus fever, yellow fever, West Nile fever, Japanese encephalitis and put immense burden on health systems of many countries. *Wolbachia* is known to block replication of several arboviruses. However, the exact mechanism how it does so is still under progress. It is transmitted vertically & alters host biology in several ways, one of the keys is cytoplasmic incompatibility, a trait which is used to suppress mosquito population by artificially introducing them into host. Here, in this review we will try to unravel the story of *Wolbachia* by looking into its role in manipulating host immune system and also how it became a miraculous weapon for controlling mosquito borne diseases, and also the challenges related to implication of this system.

Keywords: *Wolbachia*, *Aedes*, cytoplasmic incompatibility, dengue, chikungunya, malaria, vector

Introduction

Suffering and mortality caused by mosquitoes is quite a common thing which in itself doesn't need much introduction. Malaria is a parasitic infection transmitted by Anopheline mosquitoes. It causes an estimated 219 million cases globally, and results in more than 400,000 deaths every year. Most of the deaths found in children were under the age of 5 years [1]. Dengue is the most prevalent and deadliest viral infection transmitted by *Aedes* mosquitoes [2]. More than 3.9 billion people in over 129 countries are at risk of contracting dengue, with an estimated 96 million symptomatic cases and an estimated 40,000 deaths every year [2]. Other viral diseases transmitted by these vectors include chikungunya fever, Zika virus fever, yellow fever, West Nile fever, Japanese encephalitis [1-3]. Virus is not the only pathogen transmitted by this genus of mosquito lymphatic filariasis is the other example of disease spread by *Ae. polynesiensis* in South Pacific specific features of this virus may have been the failure of drug-based control programme in that region [4, 5].

Although a vaccine has been developed for yellow fever but Dengue lacks an effective vaccine. Dengue control largely focuses on control of vector spreading this disease as there are no therapeutic or prophylactic drug against and effective vaccine. Current mosquito control programmes are struggling to address elimination of complete breeding sites of container breeder *Aedes*. There are comprehensive vector management is still long way to go in achieving the targets [6-9]. Although mass awareness could help in such issues but even if one household forgets to follow the measures breeding of mosquito continues hence, failing the purpose. Adulticides have also very limited effectiveness, which increases the risk of resistance development and also bed nets do not provide a solution to day-biting mosquitoes. In the changed urban settings to cope up vector control in high population density areas with environmental safety the present system of vector control may not be adequate there is a need to revise and incorporate new tools that are also suitable for environment. High population density, uncontrolled travels, inadequate manpower for surveillance, lack of integrated approach etc.

These seeks a new approach to combat the disease spread by mosquitoes and were the main reason for development of new genetic based approaches. Genetic based approaches solve many problems like they are extremely species – specific i.e., other populations of insects or mosquitoes will not be affected hence environmentally safe. However, drawback of genetic based approach is that it is not helpful for the diseases in which pathogen is spread by multiple species. One such genetic approaches uses *Wolbachia* an intracellular bacterium which once infect mosquito has property of causing cytoplasmic incompatibility and hence helping in the population control of that particular species of mosquito [4, 10, 11].

Mechanism of *Wolbachia* action

The bacterial endosymbiont *Wolbachia pipientis* more commonly referred to as *Wolbachia* was previously used to protect flies from virus induced mortality [12]. Later three independent studies presented its scope to inhibit pathogens like, *Plasmodium*, Chikungunya, Dengue and filarial nematode in *Ae. aegypti* [13-15]. Further, it was shown to inhibit Zika, West Nile, bluetongue virus and yellow fever [16-17]. Pathogen interference by *Wolbachia* can be classified into three types as tabulated in table 1.

Table 1: Three types of pathogen interference mechanisms

Pathogen Interference		
In the trans infected mosquito [10, 18, 19]	In mosquito or flies with native *Wolbachia* infection [20-23]	Use of transient somatic *Wolbachia* to inhibit pathogen.[24-26]

But, the most intriguing phenotype that is induced by *Wolbachia* is cytoplasmic incompatibility which results when a *Wolbachia* infected male mates with female that either is uninfected or infected with some other strain of *Wolbachia* leads to sterile mating leading to embryonic death [27]. Although the mechanism behind cytoplasmic incompatibility is unknown one of the accepted hypotheses is that when male infected with *Wolbachia* mates with either uninfected female or female infected with some other strain, it leads to condensation of paternal chromosome, which is then lost in early embryonic development. However, when the mating takes place between partners infected with same *Wolbachia* strain the paternal material somehow restores functionality resulting in successful embryonic development [28]. When *Wolbachia* is infected in female mosquito it is vertically inherited i.e., will always be passed on from one generation to the next but if only males have *Wolbachia* then there is sterile mating with females i.e., no successful embryonic development

So, this mechanism in turn gives two strategies to use against mosquito borne disease

1. **Population suppression:** If we release males infected with *Wolbachia* in environment, sterile mating's will ultimately lead to suppression of mosquito population [29, 30].
2. **Population replacement:** Release of female mosquitoes infected with *Wolbachia* along with infected males, thus only chances of successful mating will be that between uninfected mosquitoes or between infected mosquitoes which over the period of generation will keep on increasing and thus resulting in invasion of *Wolbachia* into population [31-34-,10].

Challenges faced in this system

One of the challenges among other is that *Wolbachia* is naturally not present in mosquitoes hence mosquito needs to be transfected in lab only.

Does *Wolbachia* affect life history trait of mosquito?

When infecting mosquito or any other organism with organism that is not native to it the prime question is whether or not will this affect the life-history of organism concerned. Fortunately, in the case of infecting mosquito with *Wolbachia* there was no impact on inter and intra-specific competition. Studies on development time showed controversial result hence this aspect can be said to be dependent on mosquito species and *Wolbachia* strain being used [35]. However, presence of *Wolbachia* reduces the starvation tolerance in *Ae. aegypti* [36].

Can *Wolbachia* infected mosquito population successfully invade the wild population?

Population density of wild mosquitoes pose a threat to the invasion of *Wolbachia* infected mosquitoes [37, 38]. Not only the same species that pose threat to *Wolbachia* infected mosquito invasion but also other species of mosquitoes that share the breeding ground also forms an obstacle in invasion. So, before releasing the mosquitoes infected with *Wolbachia* in environment the estimation of population size of different mosquitoes that share the same breeding ground needs to be done. So, that the optimum size of population that needs to be released in that particular site can be ascertained [38-43]. Researchers have all but obliterated populations of the world's most invasive mosquito species - the Asian tiger mosquito (*Aedes albopictus*) - on two islands in the Chinese city of Guangzhou [44].

Is it good to release a self-sustaining genetic system into environment?

For any self-sustaining genetic system it is a must that evolutionary responses do not compromise its effectiveness i.e., an initial ability of system to curb the thing for which it is made in this case fertility of mosquito over generation then only it can be called as evolutionary successful genetic model [45] While the strategy of *Wolbachia* provides a promising result its long-term effects still need to be studied, like for how many generations it will affect or whether this approach can lead to development of resistant strains of virus [46-49]. According to a study, wMelPop infected.

Ae. aegypti require human blood to lay viable eggs in contrast to normal uninfected one. This study suggests that introducing *Wolbachia* might give selection to human biting preference in mosquito [50].

These issues are major concerns to look at before releasing this self- sustaining system in environment, as this decision can surely have repercussions. On the one hand *Wolbachia* vouch for being a natural remedy for this situation on the other hand it can also throwback surprises on evolutionary front.

Conclusion

Wolbachia has come up with having lots of potential to be an alternate approach in suppressing mosquito-borne diseases. Its virus blocking property has made people invest more in research relating to *Wolbachia.*

However, before applying this on field lot of research still needs to be done as no one would ever want a laboratory grown thing to backfire. Despite of the fact that we still don't have all the knowledge how *Wolbachia* works to block the transmission of virus it is giving us positive results. So, in order to utilize *Wolbachia* to its full potential mechanism behind it needs to be understood more clearly.

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