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Wolbachia-based control of mosquito-borne diseases: Evolutionary potential and limitations slightly engaging

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Abstract

Wolbachia is a maternally inherited, intracellular bacterium that infects a wide range of insects, with particularly high prevalence among dipteran species. In recent years, it has gained significant attention due to its potential use in reducing mosquito populations and limiting disease transmission. Mosquitoes act as vectors for several serious and often fatal illnesses, including dengue, malaria, chikungunya, Zika, yellow fever, West Nile fever, and Japanese encephalitis, placing a substantial strain on global public health systems. *Wolbachia* has been shown to interfere with the replication of multiple arboviruses within mosquito hosts, although the precise biological mechanisms behind this interference are still being investigated. The bacterium is vertically transmitted and can modify host reproductive biology in various ways, most notably through cytoplasmic incompatibility. This phenomenon has been exploited as a biological control strategy by deliberately introducing *Wolbachia*-infected mosquitoes into natural populations to suppress disease transmission. This review aims to explore the role of *Wolbachia* in modulating the mosquito immune system, its emergence as a promising tool for controlling mosquito-borne diseases, and the challenges associated with the practical application of this approach.

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

Introduction

Mosquitoes have survived for millions of years largely because of their remarkable ability to adapt to a wide range of environmental conditions (Couper *et al.*, 2021) [9]. Throughout their evolution, they have become hosts to diverse pathogenic, symbiotic, and endosymbiotic microorganisms. Several mosquito species belonging to the genera *Aedes*, *Anopheles*, and *Culex* serve as primary vectors for human pathogens. These mosquitoes are responsible for transmitting both emerging and re-emerging infectious diseases caused by a variety of organisms, including protozoa, viruses, and parasitic nematodes (Iturbe-Ormaetxe *et al.*, 2011) [14]. Illness and death resulting from mosquito-borne diseases are widespread and well recognized worldwide. Malaria, a parasitic disease transmitted by *Anopheles* mosquitoes, remains one of the most serious global health concerns. It is responsible for approximately 219 million infections each year and leads to over 400,000 deaths globally. A significant proportion of these fatalities occur among children younger than five years of age (WHO).

More than 3.9 billion individuals living across over 129 countries are currently exposed to the risk of dengue infection. Each year, the disease accounts for an estimated 96 million clinically apparent cases and approximately 40,000 deaths (Bhatt S *et al.*, 2013) [2]. In addition to dengue, mosquitoes of this genus are responsible for transmitting several other viral infections, including chikungunya, Zika, yellow fever, West Nile fever, and Japanese encephalitis (WHO 2012) [25]. These mosquitoes are not limited to viral transmission alone; they also spread parasitic diseases such as lymphatic filariasis. For instance, *Aedes polynesiensis* plays a major role in the transmission of lymphatic filariasis in parts of the South Pacific. Unique biological and ecological characteristics of the pathogen and its vector are believed to have contributed to the limited success of drug-based disease control programs in this region (Chambers EW, *et al.*, 2011 and O'Connor L *et al* 2012) [7]

Among mosquito-borne nematode diseases, lymphatic filariasis is primarily associated with infection by the filarial parasite *Wuchereria bancrofti*, while *Brugia malayi* and *Brugia timori* are less frequently involved. The dominant mosquito vectors responsible for transmission vary by region: *Anopheles* species play a major role in Africa, whereas *Culex* mosquitoes are the principal vectors in the Americas. Transmission can also occur through the bites of infected *Aedes* and *Mansonia* mosquitoes. Although lymphatic filariasis is classified as a neglected tropical disease, it represents the second most common cause of long-term physical deformity and disability worldwide, surpassed only by leprosy (Bizhani *et al.*, 2021; WHO, 2021) [5].

In contrast, mutualistic interactions can enhance host resistance to viral infections or supply essential metabolites when the host experiences nutritional stress ((Allman *et al.*, 2020; Kaur *et al.*, 2021) [1, 16].

Mechanisms Underlying *Wolbachia*-Mediated Pathogen Suppression

Wolbachia pipientis is an intracellular bacterial endosymbiont commonly known as *Wolbachia*. Initial studies demonstrated its ability to reduce virus-induced mortality in insect hosts such as fruit flies (Hedges LM *et* *al*., 2008) [12]. Subsequent independent investigations expanded this understanding by showing that *Wolbachia* can limit the development and transmission of a wide range of pathogens in *Aedes aegypti*, (Bian G *et al.*, 2010) [4] including *Plasmodium*, dengue virus, chikungunya virus, and filarial nematodes. Later research further confirmed its inhibitory effects on additional viruses, such as Zika virus, West Nile virus, bluetongue virus, and yellow fever virus (Kambris Z, et la., 2009 and Moreira LA, I 2009) [15, 18].

Materials and Methods

The ability of *Wolbachia* to interfere with pathogen transmission can be broadly grouped into three distinct categories, as summarized in Table 1. These include pathogen suppression in mosquitoes artificially infected with *Wolbachia* strains, interference observed in insects carrying naturally occurring *Wolbachia* infections, and the use of temporary somatic *Wolbachia* infections to reduce pathogen replication.

Table 1: Categories of *Wolbachia*-mediated pathogen interference

Pathogen interference mechanism		
In the trans infected Vectors	In Vector (Mosquitoes or flies) with native *Wolbachia* infection	Use of transient somatic *Wolbachia* to inhibit pathogen

Wolbachia infection in *Culex* species

Of the articles included in this review, eleven focus specifically on the epidemiology and infection patterns of *Culex* mosquitoes (Supplementary data). Although the genus *Culex* comprises numerous species, the studies analyzed primarily examined *Culex pipiens* and *Culex quinquefasciatus*. These species are well recognized as vectors of several human diseases, including arboviral infections such as West Nile virus and Japanese encephalitis, as well as lymphatic filariasis (Harbach, *et al.*, 1985; Omar, 1996; Paramasivan *et al*., 2003) [11, 21, 22].

The earliest evidence of *Wolbachia* infection in mosquitoes was documented by Hertig and Wolbach in 1924, who identified the bacterium in the reproductive tissues of *Culex pipiens*. Subsequent investigations have since reported varying levels of *Wolbachia* prevalence within this mosquito genus. Among them, *Ae. aegypti* and *Ae. albopictus* are the most known biological vectors of vector-borne diseases.

Result and Discussion

Wolbachia Strains and Mosquito Infection

A total of 56 primary research articles were included in this review. Among these, 32 studies reported the presence of *Wolbachia* in *Aedes* species, while 13 focused on infections in *Anopheles* mosquitoes. An additional 11 studies documented *Wolbachia* infections in members of the genus *Culex*.

Effects of *Wolbachia* Infection in Aedes Species

The use of *Wolbachia*-infected *Aedes* mosquitoes has emerged as a promising biological approach for reducing the transmission of vector-borne diseases (Brelsfoard and Dobson, 2011) [6]. Experimental evidence indicates that *Wolbachia*-infected females are capable of mating with both infected and uninfected males and subsequently producing viable offspring that carry the bacterium (Sinkins, 2004; O'Neill, 2018). In contrast, crosses between uninfected females and infected males result in cytoplasmic incompatibility, leading to the production of non-viable eggs (Charlat *et al.*, 2001; Poinsot *et al*., 2003 and Werren *et al*., 2008) [8, 23, 24].

This reproductive failure occurs because *Wolbachia*-associated modifications in the sperm prevent proper fusion with eggs lacking the bacterium, ultimately disrupting embryonic development or causing early embryonic mortality (Caragata *et al*., 2021). Additional studies have suggested that *Wolbachia* infection in males may influence nutritional allocation, which can reduce fertility and reproductive output in their mating partners (Islam and Dobson, 2006; Beebe *et al*., 2021). Overall, these effects interfere with normal zygote formation when infected males mate with uninfected females, thereby limiting successful reproduction (Serbus *et al*., 2008).

Population Suppression: Introducing male mosquitoes infected with *Wolbachia* into the environment can lead to sterile matings. These incompatible crosses reduce reproductive success, ultimately causing a decline in the mosquito population (Laven H. 2012 and O'Connor L, *et al*., 2012).

Population Replacement: When both male and female mosquitoes carrying *Wolbachia* are released, successful reproduction occurs primarily between infected individuals. Over successive generations, the proportion of *Wolbachia*-infected mosquitoes increases, gradually spreading the bacterium throughout the population Bian G, *et al*., 2013 and Curtis CF *et al.*, 1998 [3, 10]

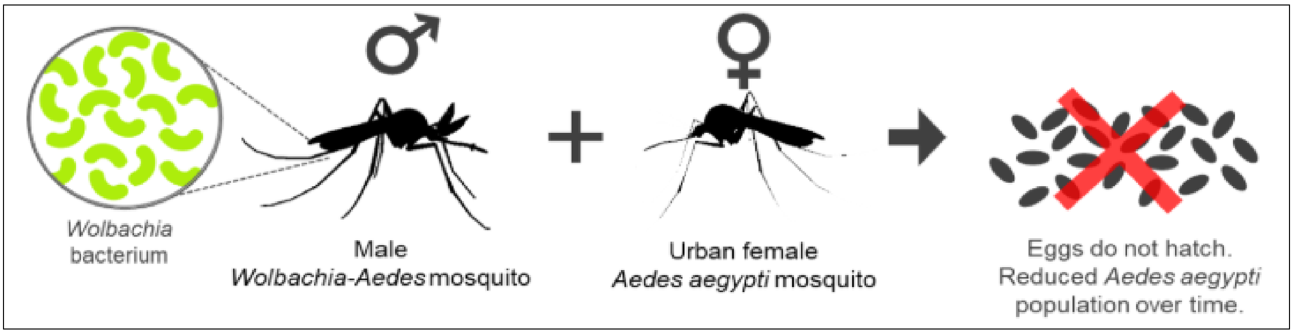

Fig 1: *Wolbachia* is used in biological control strategies

To reduce *Aedes albopictus* populations in the field, (Zheng *et al*. 2019) [26] applied Incompatible Insect Technology (IIT), which relies on *Wolbachia*-induced sterilization through a maternally inherited endosymbiont. However, the accidental release of females carrying the same *Wolbachia* strain as the released males can compromise the effectiveness of this approach (Zheng *et al*., 2019) [26]. Addressing this challenge, a study in Nanyan, Singapore, conducted by (Ong *et al*. 2022) implemented a combined IIT and Sterile Insect Technique (IIT-SIT), in which *Wolbachia*-infected male mosquitoes were irradiated with X-rays before release. This strategy achieved a 98% reduction in *Aedes aegypti* populations and corresponded with an 88% decrease in dengue incidence.

Conclusion

Different *Wolbachia* species and strains have been identified over time, each showing varying effects on mosquito hosts. When *Wolbachia*-infected mosquitoes are released into the environment, they can reduce disease transmission through two main mechanisms: (1) decreasing mosquito population density or survival, and (2) limiting the ability of mosquitoes to transmit pathogens by inhibiting pathogen replication or development. *Wolbachia* induces cytoplasmic incompatibility, alters host phenotypes, and competes with other pathogens for nutrients. These effects collectively reduce adult mosquito survival, interfere with reproduction, and prevent pathogen propagation. Additionally, *Wolbachia* infection can increase mosquito susceptibility to insecticides. Due to these characteristics, *Wolbachia* represents a promising tool for the biological control of mosquito-borne diseases, which remain a major public health concern in tropical, subtropical, and some developed regions. It has been shown to reduce transmission of diseases such as malaria, lymphatic filariasis, dengue, chikungunya, yellow fever, Zika, and West Nile fever.

Although the potential of *Wolbachia* is significant, further research is necessary before large-scale field applications. A deeper understanding of the mechanisms behind *Wolbachia*-mediated pathogen blocking is essential to ensure safety and maximize effectiveness. Despite some gaps in knowledge, current studies provide encouraging evidence that *Wolbachia* can play a key role in controlling mosquito-borne diseases.

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