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Wolbachia, Is It Dangerous or Useful? A Literature Review

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ABSTRACT

Over the past few decades, mosquito-borne arboviral infections, including chikungunya, dengue, yellow fever, and Zika, have become a serious public health concern. This infection covers more than 50% of people worldwide. According to the WHO Global Vector Control Response 2017–2030, dengue fever causes an annual total of 96 million illnesses, 1.9 million DALYs, and 9,110 fatalities. The number of cases has been increasing. Vaccinations against dengue and yellow fever are only currently available for people 9 to 45 years old who are seropositive for the disease in dengue endemic countries. The findings suggest that two general categories for mosquito population management measures exist: population replacement and population reduction. Population replacement involves adding an anti-pathogenic phenotype or decreasing the target population to reduce the number of contacts between arbovirus- delivering both human hosts and mosquitoes. The aim for effective control of arboviral illnesses is thought to be the mosquito vector, which serves as the pivot for the transmission of arboviruses. The findings allow for a general classification of mosquito population control measures into two groups: both population decrease and replacement. Biological control, of which Wolbachia is one of the programs, is one way to stop the spread of dengue. Wolbachia can be used for biological control of mosquito-borne diseases, a public health problem in the tropical and sub-tropical world and some developed countries. Dengue "elimination" is the most ambitious use of Wolbachia for disease control that has yet been suggested. But there are also reports that say that wolbachia can cause Japanese encephalitis. This article will try to determine whether Wolbachia has more benefits than dangers

Keyword: *Wolbachia, population reduction, Japanese encephalitis*

1. INTRODUCTION

The author of The Mosquito: A Human History of Our Deadliest Predator, Timothy C. Winegard, states, there may be as many as 110 trillion mosquitoes in the globe. Estimates of the number of mosquitoes worldwide range into the quadrillions. Since they are impossible to count and have a limited lifespan, no one can say for sure.1

The lifespan of a male mosquito can reach ten days. The lifespan of a female mosquito is up to nine weeks. latent eggs have a maximum of eight months to lie latent. The eggs hatch when they have enough moisture from rain, flooding, and humidity. Worldwide, there are about 3,500 distinct species of mosquitoes. Although not fatal, most mosquito bites are uncomfortable. Very few organisms may spread disease to people; the majority of human deaths are caused by about 12 species. Mosquitoes are the world's deadliest insects, killing millions of people each year from diseases including dengue, malaria, and yellow fever. All countries on Earth have mosquitoes, with the exception of Antarctica and Iceland. Researchers must determine the precise cause of Iceland's mosquito-free status. It can be the chemical makeup of the Icelandic soil or the freezing and thawing temps. Mosquitoes cannot survive in Antarctica due to its extreme temperature and lack of food supply.2

The countries with the highest concentration of mosquito species include Malaysia, Thailand, Indonesia, Brazil, and Malaysia. The deadliest menace to humanity is the mosquito. An estimated 2.7 million people die each year from illnesses spread by mosquitoes. Sadly, children account for the majority of fatalities. There have been billions of human deaths due to mosquitoes. It has been noted that Brazil, Indonesia, Malaysia, and Thailand are the nations with the greatest diversity of mosquito species. The most endemic regions are found in Brazil, Indonesia, the Philippines, Australia, and Indonesia. 2

Over the past few decades, mosquito-borne arboviral infections, including Zika, dengue, yellow fever, and chikungunya have all become a serious public health concern, posing a hazard to over half of the global population. These arboviruses have removed the need for amplification in wild animals to start human outbreaks. The primary disease vectors are Aedes aegypti and Aedes albopictus mosquitoes, and people simultaneously serve as reservoirs, multipliers, and disseminators. Because arboviral illnesses are spread through complex mechanisms involving interactions between viruses, mosquito vectors, and vertebrate hosts—all of which are continually evolving in constantly changing environments—treating arboviral illnesses remains extremely difficult. The need for developing novel treatments for the management of arboviral infections has been underscored by the disheartening lack of progress in the development of broad-spectrum vaccines against arboviruses.3

One way to control the number of mosquitoes that cause dengue fever is to reduce the population. Biological control, of which Wolbachia is one of the programs, is one way to stop the spread of dengue. Numerous methods have been investigated regarding Wolbachia's ability to regulate dengue spread, but there are also reports that say that wolbachia can cause Japanese encephalitis. This article will conduct a review to see whether the use of wolbachia to reduce the population of mosquitoes that cause dengue fever has more benefits or harm

HALF OF PEOPLE ON EARTH ARE AT RISK FOR ARBOVIRAL DISEASES

According to the WHO Global Vector Control Response 2017–2030, dengue fever causes an annual total of 96 million illnesses, 1.9 million DALYs, and 9,110 fatalities. The number of cases has been rising. Even Nevertheless, more dengue vaccine candidates are being studied in clinical trials, vaccinations against dengue and yellow fever are only currently available for people 9 to 45 years old who are seropositive for the disease in dengue endemic countries. Since there are no medications to treat these infections, vector control is the main method of prevention. Given that mosquitoes reproduce quickly and are adapted to live in urban areas (they may develop in small, ephemeral water volumes, including roof gutters and water containers, and their egg stage can tolerate desiccation),—effective control of this vector is challenging to attain and maintain. This mosquito has also benefited from the fast urbanization of society. Because of this, a number of cutting-edge technologies are being developed because current vector management methods by itself have typically not been able to permanently control it or the diseases it spreads. These include mosquitoes released with a dominant fatal gene ("RIDL"), various sterile insect techniques ("SIT"), regarding the application of Wolbachia species for suppression, population replacement, or decrease.[4]

BIOLOGY OF WOLBACHIA

The endosymbiotic microbe Wolbachia, an initially undetectable α-proteobacterium found in Culex mosquito ovaries in 1924, is likely the most well-known in the biosphere. It is predicted to infect up to 76% of the estimated 2-4 million insect species on Earth. It has been suggested that the ability of these minuscule (0.5–1µm), intracellular bacteria to induce a range of reproductive disorders in their hosts is related to their ability to enhance the reproductive success of infected females, hence amplifying the transfer of Wolbachia from mothers to their offspring. These include the transformation of genotypic men into phenotypic females, the modification of male sperm to prohibit females from procreating unless they mate with males infected with the same strain of Wolbachia, and the induction of parthenogenetically reproducing females. Wolbachia can also enhance host fitness directly through effects on illness resistance, oogenesis or fertility, and nutrition and development. It's interesting to note that some strains of Wolbachia have the capacity to drastically reduce the lifespan of their hosts and don't seem to be able to coordinate their reproduction with the host cell. A Wolbachia strain (wMelpop) that can reduce an adult Drosophila's lifetime by up to 50% was found through research on fruit fly lifespan mutants. This strain, often called "popcorn" due to its tendency to overreplicate and fill the brain tissues of infected flies, has been proposed as a potential weapon for the control of mosquito-borne diseases since it shortens the lifetime of adult female mosquitoes.[5]

DENGUE FEVER

The Aedes aegypti mosquito is the primary urban vector of dengue, yellow fever, chikungunya, and zika viruses. As its main source of blood meals, humans and Aedes aegypti have a strong relationship. It also prefers to feed on blood, sleeps indoors, and uses water-filled containers close to populated areas as a larval habitat. Because of these behaviors, Ae. aegypti is infamously hard to manage, especially in densely populated metropolitan settings. Receptacle habitat reduction, eradication, insecticide treatment, and/or adulticide application—as space sprays or targeted indoor residual applications—have been the mainstays of Ae. aegypti control. The efficacy of these control methods is jeopardized by insecticide resistance and the unsustainable nature of the government's current control initiatives. More long-term strategies are needed to manage Ae. aegypti and the arboviruses that are linked to it. This is especially important because there are currently no effective vaccinations (except from yellow fever) or antiviral treatments to control the disease.[6]

Dengue fever, which is primarily carried by mosquitoes in urban areas, is the most prevalent infectious disease in tropical and subtropical regions. Dengue disease is caused by four distinct serotypes of the flaviviridae virus, which are known as dengue virus (DENV)-1, DENV-2, DENV-3, and DENV-4. A lifelong protective immunity to the targeted serotype results from infection recovery, but only temporary and incomplete protection against other serotypes. As a result, having several dengue fever infections is feasible.[7-9]

Given the rise in dengue fever cases worldwide, there is reason for alarm. Dengue incidences have multiplied every ten years, from 8.3 million in 1990 to 58.4 million in 2013. According to a different survey, there were around 105 million cases of dengue reported in 2017. Dengue also caused a rise in deaths; from 16,957 in 1990 to 40,467 in 2017.[9-10] Outbreaks of dengue fever have already grown into epidemics, primarily in South and Southeast Asia, with high rates of illness and mortality as well as detrimental consequences on the region's economy. The World Health Organization (WHO) reports 390 million instances a year, of which only 25% are symptomatic. However, a recent study found that many people living in dengue hotspots have been exposed to the disease without actually contracting it. This suggests that the population may be infected with dengue unknowingly, necessitating the implementation of extensive public health measures to combat the outbreak.[8,9,12,13,14,15]

A PLAN FOR MANAGING MOSQUITO-BORNE ILLNESES

The mosquito vector, which acts as the hub for arbovirus transmission, is considered the goal for efficient control of arboviral infections. The findings suggest that two general categories for mosquito population management measures exist: population replacement and population reduction. To lessen the amount of contact between arbovirus-carrying mosquitoes and human hosts, population replacement entails either shrinking the target population or introducing an anti-pathogen phenotype into it. The current strategy involves using insecticides to lower the number of mosquito vectors; however, because there is no program in place to monitor vector populations, it is uncertain how these pesticides may affect the region's biodiversity. Additionally, there is a chance of creating mosquitoes that are resistant to insecticides, which reduces the effectiveness of the control and calls for the application of more species-specific alternative techniques. As an alternative to removing the target population from the field, which would disturb the ecology and raise the possibility of secondary pest development, replacement of the target population has been proposed. By substituting a pathogen-refractory strain for the target population, which would maintain the population in its natural biological niche and specifically inhibit the spread of the pathogens, the risk of secondary pest emergence may be reduced.[3,16,17]

The only proven way to stop the spread of disease at the moment is to remove the mosquito vectors, as there is currently no viable vaccination. Aedes aegypti is limited to built-up regions, but Aedes albopictus is widely distributed in Singapore. The main dengue vector in the world, Aedes aegypti, is linked to localized dengue transmission, which is defined as two or more cases occurring within 150 meters of one another and with onset dates occurring no more than two weeks apart. Unpublished research indicates that the risk of dengue transmission is increased when the ratio of Aedes aegypti:Aedes albopictus breeding is seen during normal and epidemic inspections. Furthermore, sentinel gravitrap surveillance indicates that a high population of Aedes aegypti (>6% positive traps per week) increases the likelihood of transmission by adult Aedes mosquitoes. Taking everything into account, our results indicate that Aedes aegypti is the main vector causing dengue in Singapore, with Aedes albopictus most likely playing a supporting role. The spread of dengue in Singapore is probably going to be significantly reduced by a strategy that specifically targets Aedes aegypti.[18]

In order to minimize mosquito breeding sites throughout the larval, pupal, and adult phases, chemical pesticides and community mobilization are the main methods of controlling dengue disease. Many unfavorable outcomes, such as chemical resistance, harmful effects on nontarget organisms, and hazards to human and environmental health, have been linked to the use of these chemical insecticides.[19]

WOLBACHIA'S EFFICACY AS A RELIABLE BIOLOGICAL CONTROL

Biological control, of which Wolbachia is one of the programs, is one way to stop the spread of dengue. Numerous methods have been investigated regarding Wolbachia's ability to regulate dengue spread. The three major ways that Wolbachia prevents dengue are by directly lowering the virus or limiting the mosquito's ability to spread it, lowering the vector density by suppressing the population, and shortening the mosquito's life span. Nevertheless, the wMel and wAlb strains of Wolbachia, two distinct strains, served as the foundation for all of these findings. Not every strain of Wolbachia was able to stop the spread of DENV. According to research, the wMel and wAlb strains are the only ones that can effectively stop the spread of dengue.[17,20.21]

Dengue "elimination" is the most ambitious use of Wolbachia for disease control that has yet been suggested. Currently endemic on three continents, dengue is a viral disease that affects around one-third of all people on Earth. The main vector of dengue virus (DENV) is the mosquito Aedes aegypti, which lacks a natural Wolbachia infection. Wolbachia were introduced into Ae. aegypti in an effort to shorten the duration that female mosquitoes transmit DENV. It was anticipated that life-shortening would have minimal impact on the demography of the mosquito population, but that it might have a major impact on disease transmission by drastically reducing the percentage of females old enough to transmit the virus.[22]

Endosymbiotic bacteria called Wolbachia reside in the cells of a wide variety of arthropods, including insects like mosquitos. These bacteria provide a number of benefits to their insect hosts, such as defense against parasitoids and immunity to viruses. These microorganisms are especially numerous in insects and are thought to be the most frequent endosymbiont found in arthropods. There are several strains of Wolbachia, and each is specific to a particular host species. Up to 75% of Aedes aegypti wild populations are thought to have Wolbachia-caused wounds.[20]

In 1991, studies on human filarial worms showed that some people had abnormally high quantities of Wolbachia in their blood cells, which was the first evidence of Wolbachia infection in mosquito species. They believed the bacterium to be the cause of cytoplasmic incompatibility, a condition in which females harboring the bacterium produce eggs lacking sperm, hence impeding the development of the eggs into viable offspring. Researchers studying the yellow fever virus found in 1999 that Wolbachia might potentially make mosquitoes develop cytoplasmic male sterility (CMS). This meant that because they lacked sperm, males with Wolbachia would be unable to procreate. Furthermore, the mosquito Culex pipiens was the source of the initial discovery of the Wolbachia pipientis (wPip) strain. It's also been demonstrated that Aedes albopictus carries wAlb. The Australian government's Eliminate Dengue Programme approved the introduction of Wolbachia into mosquitoes in order to halt the dengue virus's spread. Several public health organizations employ Wolbachia to fight the dengue virus and other viruses transmitted by arthropods. Pesticide resistance is rising in several towns and cities, including Jeddah, Makkah, Jizan, and Al-Madinah. Therefore, a lot of work is going into developing eco-friendly strategies to reduce mosquito populations or limit their capacity to transmit disease.[23]

It is mainly transmitted vertically, interfering with host reproduction in order to enhance transmission from mother to child through the eggs. In addition to other sex ratio distortion features that favor females, Wolbachia can promote parthenogenesis, feminization, male-killing, and cytoplasmic incompatibility (CI) in the progeny. In the CI phenotype, wolbachia-infected females are preferred over non-infected females and males. With time, our comprehension of the molecular mechanisms controlling the CI has grown. The mechanism behind CI and its rescue is toxin-antidote interactions, whose affinity between partners dictates the fate of the rescue. For example, wPip's cidA and cidB are crucial for the development of CI characteristics in Cx. pipiens during the first embryonic mitosis, when the B factor demonstrates its poisonous activity and the A factor acts as a rescue antidote to produce the CI effect. Wolbachia bacteria can travel from cell to cell or be inherited from contaminated embryonic lineages; they are present in both somatic tissues and reproductive organs.[24-26]

Numerous processes, including the formation of reactive oxygen species, competition for limited resources like cholesterol, and host gene control through indirect mechanisms (RNAi, sfRNA), have been proposed as the molecular underpinnings of the pathogen-blocking phenotype. There is increasing evidence that following a Wolbachia infection, the transcriptome profiles of mosquitoes were changed. Insect immune pathways such Toll, IMD, and JAK/STAT pathways were activated in Wolbachia-infected Ae. aegypti, which significantly inhibited the growth of CHIKV, DENV, and Plasmodium. A number of genes have been demonstrated to be elevated in addition to immunological factors, indicating that they might be able to prevent viral replication. It has also been demonstrated that the genes that regulate the production of reactive oxygen species and the overexpression of Wolbachia-mediated methyltransferase prevent DENV replication in Ae. aegypti. Because Wolbachia can prevent viruses from growing in mosquitoes, mosquitoes with Wolbachia are less likely to transmit illnesses like chikungunya, dengue hemorrhagic fever, and Zika.[27-28]

The ability of mosquitoes infected with Wolbachia to inhibit viruses may be lost due to changes in their gene expression patterns. The two main categories of viral blocking mechanism hypotheses are competition for host cell resources and/or mosquito immune gene activation. Immunological genes, on the other hand, are activated by transinfected Wolbachia but may not be necessary for blocking in hosts that are already infected. Important examples of antiviral mechanisms in insect cells include the activation of signaling pathways such as reactive oxygen species (ROS), Toll signalling, and Janus kinase-signal transducer and activator of transcription (JAK-STAT). Many anti-microbial proteins and compounds, including the interferon-like Vago and Dnmt2, can be induced. These molecules can modify viral RNA and make it more susceptible to methylation-mediated destruction. Nevertheless, there is currently no direct connection between the inhibiting effect and any of these mechanisms. In Wolbachia-infected cells, the exonuclease XRN1 is activated and has been linked to the breakdown of viral RNA. In Wolbachia-infected cells, RNA interference is also triggered, however it might not be a significant viral blocking mechanism.[6]

IS WOLBACHIA DANGEROUS?

Many insects carry Wolbachia as a maternally transmitted bacterial symbiont. Wolbachia has a number of peculiar characteristics that make it a good candidate for cutting-edge biological control strategies for diseases carried by vectors. Dengue "elimination" is the most ambitious use of Wolbachia for disease control that has yet been suggested. Currently endemic on three continents, dengue is a viral illness that affects around one-third of all people on Earth.[22]

Local communities are impacted when mosquitoes are released into the environment—in this case, the area around human habitation. The community must be involved at every stage of the process, from offering literature and information sessions to being included in expert panels. Experts from the community were able to provide a significant contribution to the assessment of the likelihoods, explaining the economic implications and CMH avoidance strategies. Although they were invited to contribute to the other nodes' populating, community experts felt that the other nodes' technical underpinnings were either incomprehensible or unrelated to their own experiences.[29]

Given that Wolbachia-infected JEV vectors are unable to spread the virus, this biocontrol approach may be able to dramatically lower JE morbidity and mortality. Contrary to popular belief on social media, Wolbachia-carrying mosquitoes are not linked to Japanese encephalitis or brain inflammation. Mosquitoes are the vector of Japanese encephalitis.

Nonetheless, the Culex mosquito acts as the vector or spreader of the disease. In the meantime, the Aedes aegypti mosquito is the source of the Wolbachia bacterium infection in our nation.[30]

The discharge of male Aedes mosquitoes harboring Wolbachia into the environment carries little to no damage to the environment or public health. This is the rationale behind it: Wolbachia (wAlbB strain) is unlikely to proliferate in the environment (beyond its intended host). Wolbachia is an obligatory and fastidious endosymbiotic bacteria that can only survive inside its host's cells. In vitro studies indicates that Wolbachia can only survive outside of a host cell in a medium with a high concentration of amino acids. It is therefore not anticipated to survive in an environment other than that of the host that carries it. When the insect host dies, Wolbachia will also decompose along with it, leaving behind residue that is identical to the organic debris that naturally occurs in the environment; Wolbachia has been present in nature constantly for millions of years. There is currently no conclusive scientific evidence to support the theory that Wolbachia-carrying mosquitoes may transmit the bacteria to vertebrate hosts through blood feeding. A new Australian study claims that human volunteers bitten by Aedes aegypti mosquitoes did not develop an immunological reaction, indicating that Wolbachia or any of its components are not spread to people by mosquito bites; There have not yet been any instances of Wolbachia infections in mosquito predators, such as fish, lizards, frogs, and spiders, following ingestion of naturally Wolbachia-carrying insects. Despite being fed Aedes aegypti, which is known to carry Wolbachia, spiders are immune to the disease, according to a recent Australian study; Should a significant number of female Wolbachia Aedes be inadvertently and persistently discharged, the population of Aedes aegypti in metropolitan areas might potentially be supplanted by Wolbachia-Aedes aegypti. The female Wolbachia-Aedes mosquitoes will have no effect since, in accordance with our design, there would be a very small number of females that could be released alongside the males in comparison to the overall population in the environment. It would not be enough to allow the Wolbachia bacteria to proliferate in any way. There is very little chance that Wolbachia-Aedes aegypti will displace the WT Aedes aegypti population. Studies carried out in Australia, Vietnam, Indonesia, and other countries aiming at introducing Wolbachia-Aedes to replace the WT population have shown that regular large-scale releases of females are required to achieve replacement. Any potential harm to the ecology, should this occur, is thought to be minimal. Over 60% of insects natively carry the bacterium Wolbachia.[18]

2. CONCLUSION

It is anticipated that the effective establishment of Wolbachia strains will have a significant long-term impact on lowering disease transmission. These strains either shorten the lifespan of mosquitoes or disrupt the pathogen in their vector. Encouraging multidisciplinary participation and strong community engagement helps guarantee the program's success. Numerous vulnerability factors that could affect the efficacy require more extensive research. Lastly, the Wolbachia program's excellent practicability may eventually alter how dengue sickness is combated globally.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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