

Review

Wolbachia Pipientis as a Natural Biocontrol Agent to Inhibit Dengue Virus Replication in *Aedes Aegypti* Mosquitoes

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Abstract. *Wolbachia pipientis* is an endosymbiotic bacterium commonly found in insects, arthropods, and certain nematodes, playing a pivotal role in host reproductive manipulation and pathogen resistance enhancement. This review aims to provide a comprehensive understanding of the characteristics, physiology, and ecological roles of *Wolbachia pipientis*, as well as its potential in vector control strategies to combat insect-borne diseases. A literature-based approach was employed, utilizing peer-reviewed scientific journals from reputable sources such as Scopus and Web of Science. The analysis revealed that *Wolbachia pipientis* is a Gram-negative bacterium with a small size (0.2 to 0.5 μm) that reproduces through binary fission within host cells and relies on the host for essential nutrients. It modulates host gene expression and enhances host immunity, thereby reducing the transmission of pathogens like dengue, Zika, and chikungunya through cytoplasmic incompatibility. Furthermore, *Wolbachia pipientis* has shown potential in managing filariasis by inhibiting nematode reproduction. The bacterium's ability to alter host reproductive dynamics through mechanisms like feminization and parthenogenesis makes it an effective tool in biocontrol programs. The findings underscore the importance of *Wolbachia pipientis* in improving public health and environmental sustainability by controlling disease vectors and supporting ecological balance. This review highlights the need for further research to explore genetic engineering approaches to enhance the effectiveness of *Wolbachia pipientis* in global health management.

Keywords: Biocontrol; Endosymbiont; Vector Control; *Wolbachia pipientis*

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INTRODUCTION

Wolbachia pipientis is an endosymbiotic bacterium commonly found in the bodies of insects, arthropods, and some types of nematodes. This bacterium plays a crucial role in the life of its host, particularly in reproductive manipulation, enhancing resistance to pathogens, and its potential as a vector control agent. In the field of biocontrol, the use of microorganisms like *Wolbachia pipientis* is a strategy that continues to be developed to reduce the spread of insect-borne diseases. *Wolbachia pipientis* bacteria have been applied in various biocontrol programs in different countries to reduce the population of disease-carrying insects, such as *Aedes aegypti* mosquitoes that transmit dengue, chikungunya, and Zika. The presence of *Wolbachia pipientis* in the host not only affects ecological dynamics but also contributes to efforts in improving public health and environmental sustainability.

Wolbachia pipientis is a Gram-negative bacterium that lives within its host cells and is vertically transmitted through the maternal lineage. According to (Werren et al., 2008) this bacterium can influence host reproduction through several mechanisms, including cytoplasmic incompatibility (CI), parthenogenesis induction (PI), feminization, and male killing. The most common mechanism is cytoplasmic incompatibility, where eggs that

are not infected with *Wolbachia pipientis* fail to develop when fertilized by sperm from an infected male. Consequently, the proportion of individuals carrying *Wolbachia pipientis* within a population increases.

Wolbachia pipientis has been utilized as a biocontrol strategy for vector-borne diseases, such as dengue fever caused by the dengue virus (Hoffmann et al., 2011). The bacterium is known to inhibit dengue virus replication within *Aedes aegypti* mosquitoes, thereby reducing the likelihood of disease transmission to humans. And mosquitoes infected with *Wolbachia pipientis* exhibited lower virus replication rates compared to uninfected mosquitoes (Dutra et al., 2016). Further added that *Wolbachia pipientis* not only impacts human disease vectors but also affects agricultural insects. This bacterium has the potential to reduce pest populations by modifying the reproduction of its insect host, making it a promising strategy for biological control (Zhang et al., 2015).

Moreover, (Bian et al., 2010) revealed that *Wolbachia pipientis* can enhance host resistance to certain pathogen infections by stimulating a more active immune response. Their research demonstrated that mosquitoes infected with *Wolbachia pipientis* had a higher resistance to *Plasmodium*, the parasite responsible for malaria. Despite its numerous benefits, the application of *Wolbachia pipientis* in vector control programs still faces various challenges. Environmental factors, such as temperature, host availability, and the stability of infection within insect populations, can affect the effectiveness of *Wolbachia pipientis* spread. Therefore, further research is needed to understand the interaction between *Wolbachia pipientis* and its host and to optimize its utilization in the fields of environment and public health.

Based on the explanation above, the study of *Wolbachia pipientis* plays a crucial role in understanding its function as an endosymbiont that contributes to ecosystem balance and its potential in vector control. Therefore, this article will review the characteristics, habitat, physiology, and morphology of *Wolbachia pipientis pipientis*, as well as its ecological role in host population dynamics and its application in the fields of health and environment.

MATERIALS AND METHODS

The method used in this review article is a literature study with a research approach based on scientific journal publications from reputable sources, such as journals indexed in Scopus, Web of Science, and related reference books. This research process was conducted systematically through several key stages. The first stage is data collection, which was obtained from the latest scientific journals discussing various aspects of *Wolbachia pipientis*, including its characteristics, habitat, ecological role, and applications. The selected journals are peer-reviewed scientific publications to ensure the validity of the data used.

After the data is collected, the next stage is the analysis and synthesis of information aimed at identifying patterns and relationships between various factors that influence the life and function of *Wolbachia pipientis pipientis*. This analysis includes the bacterium's physiological and morphological characteristics, its distribution in different ecosystems, as well as its interactions with hosts and its impact on population dynamics. Furthermore, this review article also examines various applications of *Wolbachia pipientis* in the fields of health and environment based on relevant case studies. These case studies cover the role of *Wolbachia pipientis* in vector control, its utilization in insect pest biocontrol, and its potential to enhance host resistance to certain pathogens. Through this literature-based approach, this review article aims to provide a comprehensive understanding of *Wolbachia pipientis* and its potential in various environmental and health-related fields.

RESULTS AND DISCUSSION

Wolbachia pipientis

Since its discovery, research on *Wolbachia pipientis* has advanced rapidly due to its ability to adapt to its host and its impact on insect populations (Werren et al., 2008). The development of *Wolbachia pipientis* research gained momentum between the 1970s and 1990s when scientists discovered the bacterium's complex symbiotic relationship with its host. Early research by Yen & Barr *Wolbachia pipientis* could cause cytoplasmic incompatibility in certain insect species, leading to further investigation into its effects on host ecology and evolution.

Over time, molecular and genomic research on *Wolbachia pipientis* has expanded, particularly with the rapid advancement of DNA sequencing technology. In 2004, the first *Wolbachia pipientis* genome was successfully sequenced by Foster, providing deeper insights into the bacterium's genetic mechanisms and adaptation to its host (Foster et al., 2005). This breakthrough paved the way for further research on *Wolbachia pipientis*'s role in manipulating insect reproductive systems and its potential applications in biotechnology (Bourtzis et al., 2014). To date, research on *Wolbachia pipientis* continues to evolve, focusing on its interaction with hosts and its potential in biotechnology and biological control. Recent studies have shown that this bacterium is not only

widely distributed across various insect species but also exhibits a complex and dynamic symbiotic relationship with its host (Kaur et al., 2021).

Characteristics and Traits of *Wolbachia pipientis*

Table 1. Scientific Classification of *Wolbachia pipientis*

Taxonomy	Name
Kingdom	: <i>Bacteria</i>
Phylum	: <i>Proteobacteria</i>
Class	: <i>Alphaproteobacteria</i>
Ordo	: <i>Rickettsiales</i>
Family	: <i>Anaplasmataceae</i>
Genus	: <i>Wolbachia</i>
Species	: <i>Wolbachia pipientis</i>

Wolbachia pipientis possesses several unique characteristics that distinguish it from other endosymbiotic bacteria. It belongs to the *Alphaproteobacteria* group and is a Gram-negative bacterium with a small rod-shaped structure, measuring approximately 0.2–0.5 μm . Its membrane structure contains lipopolysaccharides, which function to protect the bacterium from the host's intracellular environment (Baldo et al., 2006). As an obligate intracellular bacterium, *Wolbachia pipientis* is found in various host tissues, particularly in reproductive organs, somatic tissues, and insect hemolymph (Serbus et al., 2008). Its presence in reproductive tissues allows the bacterium to be vertically transmitted through the egg cells, while in somatic tissues, *Wolbachia pipientis* can influence the host's metabolism and immune system (Taylor et al., 2005).

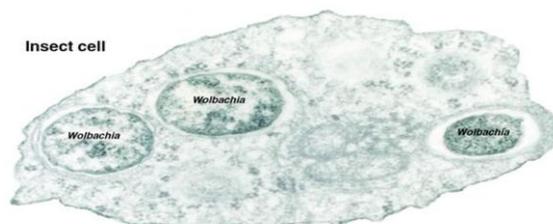


Figure 1. *Wolbachia pipientis*

Another unique characteristic of *Wolbachia pipientis* is its ability to manipulate the reproductive system of its host. Various mechanisms, such as cytoplasmic incompatibility, parthenogenesis, and feminization, have been observed in different insect species (Werren et al., 2008). Cytoplasmic incompatibility occurs when sperm from *Wolbachia pipientis*-infected males cannot fertilize eggs from uninfected females, leading to embryonic developmental failure (Russell & Stouthamer, 2011). In addition, genomic research has revealed that *Wolbachia pipientis* possesses a highly dynamic genome with a tendency for horizontal gene transfer to the host genome. A study by LePage & Bordenstein found that certain portions of the *Wolbachia pipientis* genome can integrate into the host genome, influencing host gene expression and strengthening the symbiotic relationship between the two (LePage & Bordenstein, 2008).

Several strains of *Wolbachia pipientis* exhibit distinct characteristics in their interactions with hosts. For instance, some strains provide benefits to their hosts, such as enhancing resistance to certain viruses or improving host fertility (Teixeira et al., 2008). On the other hand, certain strains can be pathogenic and cause negative effects on hosts, such as sterility or developmental deformities (Hedges et al., 2020). With its unique characteristics, including intracellular lifestyle, host reproductive manipulation, and dynamic genome, *Wolbachia pipientis* has become one of the most intriguing bacteria in microbiology and biotechnology research today. Ongoing studies aim to further understand the complex interactions between *Wolbachia pipientis* and its host, which can be harnessed for various biological applications.

Habitat and Distribution of *Wolbachia pipientis*

Wolbachia pipientis is found in various ecosystems and has a wide distribution, primarily due to its ability to infect a diverse range of host species. According to research (Zug & Hammerstein, 2012), more than 60% of insect species worldwide are infected with *Wolbachia pipientis*, demonstrating the extensive spread of this bacterium in natural ecosystems. One of the primary habitats of *Wolbachia pipientis* is within the bodies of vector insects. This bacterium is commonly found in mosquito species such as *Aedes aegypti*, *Culex pipiens*, and *Anopheles gambiae*, which serve as vectors for human diseases (Werren et al., 2008). Moreover, *Wolbachia*

pipientis has also been identified in various other insects, such as fruit flies (*Drosophila* spp.) and beetles, highlighting the ecological flexibility of this bacterium (Baldo et al., 2006).

In addition to insects, *Wolbachia pipientis* is also found in filarial nematodes that cause diseases such as filariasis in humans. Several nematode species, such as *Brugia malayi* and *Wuchereria bancrofti*, have a symbiotic relationship with *Wolbachia pipientis*, which contributes to the pathogenesis of diseases transmitted by these worms (Taylor et al., 2005). The infection of *Wolbachia pipientis* in these nematodes has become a research target in developing antibiotic therapies to treat filariasis (Ioannidis et al., 2013). The presence of *Wolbachia pipientis* in natural ecosystems heavily depends on the presence of its host. This bacterium is found in various habitats, such as tropical forests, urban areas, and agricultural lands, following the distribution of the host species they infect (Serbus et al., 2008). The adaptation of *Wolbachia pipientis* to its host demonstrates its high evolutionary capability to survive in diverse environments.

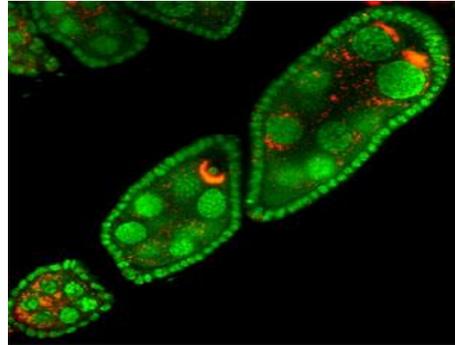


Figure 2. Adaptation of *Wolbachia pipientis*

(Sources: https://microbewiki.kenyon.edu/index.php/Wolbachia_pipientis_pipientis)

Several studies have also shown that *Wolbachia pipientis* can transfer between hosts through specific ecological interactions, such as predator-prey relationships or via other parasitic vectors (LePage & Bordenstein, 2008). This phenomenon further expands the distribution of *Wolbachia pipientis* within ecosystems and highlights the need for further research to understand the ecological role of this bacterium in the food chain and insect population dynamics. Additionally revealed that *Wolbachia pipientis* can undergo genetic variation, allowing better adaptation to different environmental conditions. Factors such as temperature, humidity, and host type can influence the infection rate and distribution of this bacterium in nature. With its widespread presence in various hosts and habitats, *Wolbachia pipientis* has become one of the most influential endosymbiotic bacteria in the global ecosystem. Further studies are continuously being conducted to understand its distribution patterns, impact on biodiversity, and potential applications in biological disease control.

Physiology and Morphology of *Wolbachia pipientis*.

The metabolism of *Wolbachia pipientis* heavily relies on its host due to its status as an obligate endosymbiont. According to research (Newton & Rice, 2020), *Wolbachia pipientis* cannot survive outside the host cell and depends on the host's metabolism to acquire essential nutrients. Its morphological structure includes a Gram-negative cell wall with an outer lipopolysaccharide membrane, which protects the bacterium from the host's immune response. The bacterium is relatively small, with a diameter ranging from 0.2 to 0.5 μm . It takes the form of a short rod or coccus, allowing *Wolbachia pipientis* to adapt to the intracellular environment of its host. Its genetic structure shows genome reduction due to evolution as an endosymbiont, resulting in the loss or mutation of many essential genes.

According to research by (Serbus et al., 2008), *Wolbachia pipientis* reproduces within vacuoles located in the host cell's cytoplasm. Its division occurs through binary fission, following the host's life cycle to ensure its transmission to the next generation. These vacuoles protect *Wolbachia pipientis* from degradation by the host's immune system. In terms of physiology, *Wolbachia pipientis* relies on the host for metabolic pathways, such as amino acid and essential cofactor biosynthesis. According (LePage & Bordenstein, 2008), the bacterium utilizes the host's metabolic resources, including ATP produced by the host's mitochondria. Some *Wolbachia pipientis* strains are also capable of synthesizing vitamins and bioactive molecules that play a role in host development. The interaction mechanism between *Wolbachia pipientis* and its host involves altering host gene expression, particularly those related to the immune system and reproduction. A study (Ioannidis et al et al., 2013) revealed that *Wolbachia pipientis* can modulate the expression of host immune genes to enhance its survival within the host body. These interactions can vary depending on the host species and the specific *Wolbachia pipientis* strain involved.

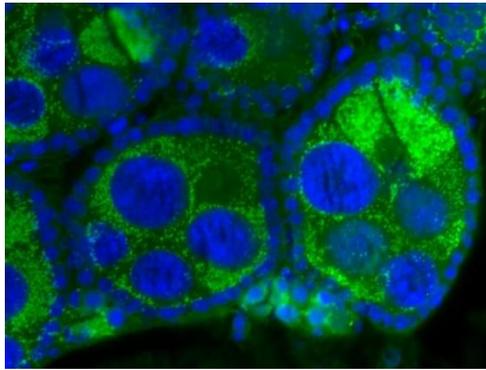


Figure 3. morphology of *Wolbachia pipientis*

(Sources: [https://nginx-oregon.labroots.com/trending/microbiology/5429/secrets-Wolbachia pipientis -revealed](https://nginx-oregon.labroots.com/trending/microbiology/5429/secrets-Wolbachia-pipientis-revealed))

In terms of morphology, *Wolbachia pipientis* possesses a thin cell wall characteristic of Gram-negative bacteria, consisting of a simpler peptidoglycan layer compared to Gram-positive bacteria. This feature allows *Wolbachia pipientis* to be more flexible in adapting to the intracellular environment. Electron microscopy analysis reveals that *Wolbachia pipientis* has a double membrane structure, which helps maintain stability in intracellular conditions. This bacterium is found in various host tissues, including the ovaries, testes, somatic tissues, and the nervous system. The distribution of *Wolbachia pipientis* within the host's body heavily depends on the infection pathway and the host species being colonized. Infection in the host's reproductive tissues ensures the vertical transmission of the bacterium from one generation to the next. Certain *Wolbachia pipientis* strains are also known to induce changes in the host's physiology (Baldo et al. (2006).

Wolbachia pipientis infection can enhance the host's resistance to other pathogens by triggering an innate immune response (Kaur et al., 2021). Additionally, changes in lipid and carbohydrate metabolism in infected hosts have also been observed in various studies. The physiology of *Wolbachia pipientis* also includes its ability to synthesize certain proteins that play a role in host interaction. One key protein is the *Wolbachia pipientis* Surface Protein (WSP), which is believed to be involved in bacterial adhesion and interaction with host cells. WSP serves as a primary molecular marker in phylogenetic studies and strain identification of *Wolbachia pipientis*. Research on the metabolic system of *Wolbachia pipientis* continues to advance through omics-based approaches, such as genomics and proteomics. these approaches help uncover the primary metabolic pathways of *Wolbachia pipientis* and its role in symbiosis with the host. Identifying essential genes involved in *Wolbachia pipientis* metabolism is expected to provide further insights into the complex symbiotic relationship between this bacterium and its host (Taylor et al., 2005).

The Utilization of *Wolbachia pipientis* in Natural Biocontrol

Wolbachia pipientis has various applications in disease and environmental control. One of its key uses is in vector control. *Wolbachia pipientis* is employed in biocontrol strategies to reduce the spread of diseases such as dengue, Zika, and chikungunya through the release of *Wolbachia pipientis* -infected. Additionally, the release of *Wolbachia pipientis* -infected male mosquitoes can lead to cytoplasmic incompatibility, causing the eggs produced to fail to hatch. This method has been utilized as an insect population sterilization strategy to control the spread of mosquito-borne diseases. In controlling diseases caused by filarial nematodes, antibiotics targeting *Wolbachia pipientis* can be used to manage filariasis. By suppressing *Wolbachia pipientis* growth within parasitic nematodes, the pathogens lose their ability to reproduce and eventually die.

The uniqueness of *Wolbachia pipientis* also lies in its ability to suppress viral transmission through competition mechanisms within the host cell. the presence of *Wolbachia pipientis* in mosquito populations can inhibit viral replication, thereby reducing the risk of transmission to humans (Kaur et al., 2021). This bacterium exhibits high evolutionary flexibility as it can adapt to various hosts. This adaptability allows *Wolbachia pipientis* to spread widely in insect populations and provide significant ecological benefits. This adaptation also makes *Wolbachia pipientis* a promising candidate for pest control in agriculture. In ecosystems, *Wolbachia pipientis* plays a role in maintaining the balance of certain insect populations. By controlling the number of disease vector insects, the bacterium can aid in managing healthier ecosystems. This makes it a potential tool in environmentally friendly agricultural strategies.

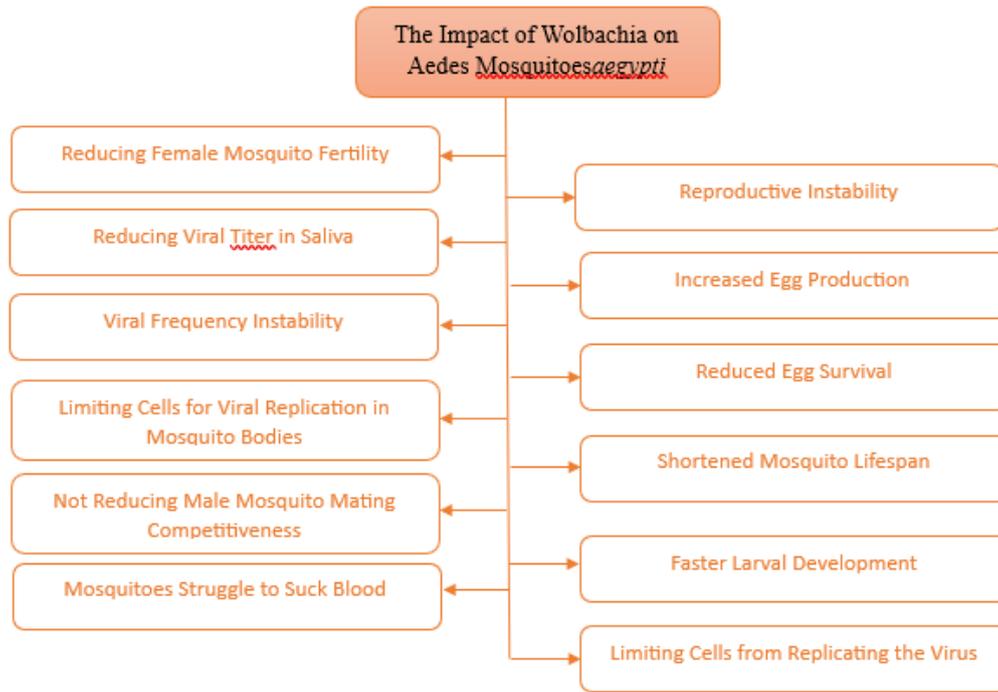


Figure 4. The Impact of Wolbachia on aedesaegepty mosquitoes

The effects of *Wolbachia pipientis* on *Aedes aegypti* mosquitoes include: reproductive abnormalities, increased egg production, reduced egg survival, extended mosquito lifespan, faster larval development, reduced body size, difficulty in blood-feeding, decreased female fertility, 15-25% reduction in total cholesterol, lower viral titers in mosquito saliva, reduced virus frequency in the mosquito body, and disruption of mosquito behavior. The effects of *Wolbachia pipientis* on the dengue virus include: *Wolbachia pipientis* uses host microRNAs to manipulate mosquito genes, a reduction of 10^4 virus and RNA copies, virus blocking that persists in *Wolbachia pipientis* -infected mosquitoes, prevention of virus infection in humans, mediation of antiviral protection against various RNA viruses, and blocking the transmission of dengue serotypes.

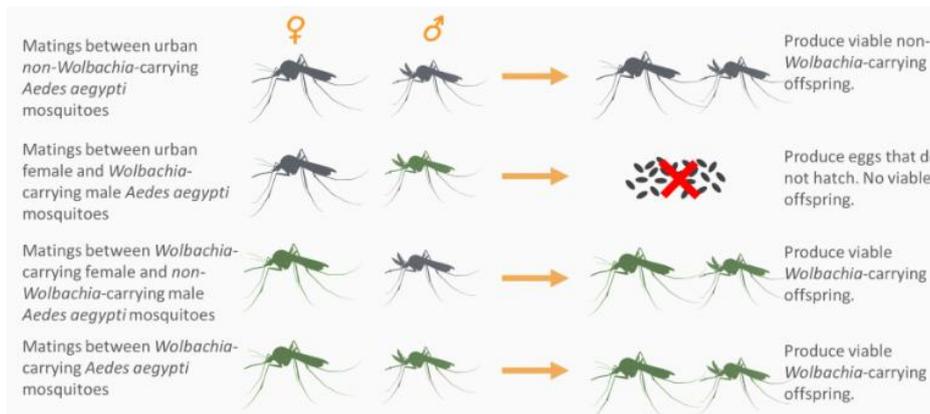


Figure 5. the concept of Cytoplasmic Incompatibility caused by *Wolbachia pipientis*

(Sources : [https://www.nea.gov.sg/corporate-functions/resources/research/environmental_health_institute/Wolbachia pipientis -aedes-mosquito-suppression-strategy/Wolbachia pipientis -aedes-mosquito-suppression-strategy-how-it-works/cytoplasmic-incompatibility](https://www.nea.gov.sg/corporate-functions/resources/research/environmental_health_institute/Wolbachia_pipientis_aedes-mosquito-suppression-strategy/Wolbachia_pipientis_aedes-mosquito-suppression-strategy-how-it-works/cytoplasmic-incompatibility))

It has been explained that the DNA and genome of *Wolbachia pipientis* contain genes capable of modifying the host's reproductive system, such as causing cytoplasmic incompatibility (CI). The image above illustrates the concept of Cytoplasmic Incompatibility caused by *Wolbachia pipientis* in *Aedes aegypti* mosquitoes. The explanation is as follows:

1. Mating between a female mosquito not infected with *Wolbachia pipientis* and a male mosquito also not infected with *Wolbachia pipientis*
 - In this condition, the reproductive process proceeds normally as there is no interference from *Wolbachia pipientis* .

- Both mosquitoes have cytoplasm that is "sterile" from *Wolbachia pipientis*, allowing cell division, fertilization, and embryo development to occur smoothly.
 - The final result is healthy offspring that are also not infected with *Wolbachia pipientis*.
2. Mating between a female mosquito not infected with *Wolbachia pipientis* and a male mosquito infected with *Wolbachia pipientis*
 - *Wolbachia pipientis* in the male mosquito modifies the sperm during the spermatogenesis process.
 - This modification causes the sperm DNA to undergo epigenetic changes that cannot be recognized by the cytoplasm of the female mosquito that is not infected with *Wolbachia pipientis*.
 - As a result, the embryo fails to develop, and the eggs do not hatch. This is known as Cytoplasmic Incompatibility.
 - The natural purpose of *Wolbachia pipientis* doing this is to ensure that only infected mosquitoes can reproduce, allowing *Wolbachia pipientis* to continue spreading within the host population.
 3. Mating between a female mosquito infected with *Wolbachia pipientis* and a male mosquito not infected with *Wolbachia pipientis*
 - The female mosquito infected with *Wolbachia pipientis* has cytoplasm that is already "programmed" by *Wolbachia pipientis* to recognize the modified sperm DNA, even if the sperm comes from an uninfected male mosquito.
 - Since the female can recognize these changes, the fertilization process and embryo development proceed normally.
 - The final result is offspring infected with *Wolbachia pipientis* because *Wolbachia pipientis* is maternally transmitted (from mother to offspring) through the cytoplasm of the egg cell.
 4. Mating between a female mosquito infected with *Wolbachia pipientis* and a male mosquito also infected with *Wolbachia pipientis*
 - Since both mosquitoes are already infected with *Wolbachia pipientis*, the modification in the male mosquito's sperm can be recognized by the female mosquito's cytoplasm, which is also influenced by *Wolbachia pipientis*.
 - The fertilization process proceeds normally, and all offspring produced are also infected with *Wolbachia pipientis*.
 - This strengthens the spread of *Wolbachia pipientis* throughout the mosquito population from generation to generation.

Apart from vector control, *Wolbachia pipientis* can also enhance the host's resistance to other pathogens by triggering an innate immune response. *Wolbachia pipientis* infection can strengthen the host's immune system, providing additional protection against secondary infections. *Wolbachia pipientis*'s ability to alter host reproduction has also attracted attention in biotechnology research. This bacterium can cause various phenomena such as feminization, parthenogenesis, and cytoplasmic incompatibility, which contribute to the dynamics of insect populations in nature. Several studies have also shown that *Wolbachia pipientis* can play a role in enhancing the fertility of its host.

Wolbachia pipientis strains have been linked to an increase in, the reproductive rate of insect hosts, thereby accelerating the spread of this bacterium within the population. From an ecological interaction perspective, *Wolbachia pipientis* affects the dynamics of insect communities by manipulating reproductive patterns and interspecies interactions. Consequently, this bacterium can establish complex relationships within the trophic network of ecosystems. The application of *Wolbachia pipientis* in biocontrol continues to evolve with genetics-based and modern technological approaches. genetic engineering of *Wolbachia pipientis* can enhance its effectiveness in vector disease control, opening new opportunities in global health management (Hoffmann et al., 2020).

CONCLUSION

Based on various studies, *Wolbachia pipientis* is an endosymbiotic bacterium with great potential in the biological control of disease vector insects and in maintaining ecosystem balance. Its role in suppressing virus transmission, altering host reproductive patterns, and enhancing resistance to pathogens makes it one of the most effective biocontrol agents. Additionally, its evolutionary flexibility in adapting to various hosts opens up broader opportunities for applications in multiple fields, including public health and sustainable agriculture.

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