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Review Article

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Using Wolbachia to Combat Dengue in Indonesia: Weighing the Pros and Cons

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Abstract

Dengue fever is a major public health threat in Indonesia, resulting in millions of cases and tremendous health and economic costs annually. Traditional insecticide-based control methods have had limited effectiveness. The novel approach of using Wolbachia, a bacterium that inhibits dengue transmission when introduced into mosquito populations, shows promising potential but also involves key trade-offs. Based on the trial results, successful Wolbachia deployment could dramatically reduce the incidence of dengue, providing immense benefits. However, concerns exist around the unintended ecological impacts of releasing nonnative Wolbachia strains, challenges around public acceptance, and logistical/financial hurdles to scale-up and sustainability. While the public health imperative to combat dengue is clear, Indonesia must carefully evaluate the specific risks and ethical considerations involved with this approach through expanded field trials, rigorous environmental monitoring, and robust community engagement mechanisms. A balanced, stepwise strategy prioritizes responsible innovation and allows for the adjustment of policies as more evidence emerges on Wolbachia's safety and effectiveness within Indonesia's unique context. Dismissing Wolbachia outright could mean forgoing a groundbreaking opportunity, but unquestionably embracing it without adequate safeguards would be reckless. Thoroughly weighing the pros and cons will be vital for determining whether the promised benefits of Wolbachia outweigh the risks and ethical costs in the eyes of scientific experts and the Indonesian public.

Keywords: ***Wolbachia, dengue disease, mosquitoes, bacteria.***

Introduction

Dengue fever is a potentially life-threatening viral disease that is widespread globally across tropical and subtropical regions [1]. Dengue poses a major public health threat in Indonesia, with tens of thousands of cases reported annually (WHO South–East Asia, 2024; Zeng et al., 2021). Conventional methods of controlling dengue, such as insecticide spraying and eliminating mosquito breeding sites, have had limited effectiveness [4]. A novel approach being explored involves using Wolbachia, a bacterium that inhibits the ability of mosquitoes to transmit viruses such as dengue [5-7].

Wolbachia is naturally present in up to 50% of insect species, including butterflies and fruit flies, but it is not found in the main dengue vector mosquito, Aedes aegypti (World Mosquito Programme, 2022). When Wolbachia is introduced to Aedes mosquito populations, it can spread quickly because the two cytoplasm types are incompatible. This gives mosquitoes that carry Wolbachia an advantage in reproduction [9,10]. Once established, Wolbachia prevents the dengue virus from replicating inside the mosquito, preventing it from being transmitted to humans [10,11].

Field trials involving the release of Wolbachia-carrying Aedes mosquitoes have been conducted in various countries, including Indonesia, with promising results in reducing the incidence of dengue [12,13]. However, this technology raises ethical concerns about unintentionally releasing nonnative species and unknown long-term ecological impacts. There are also challenges related to public acceptance, ongoing monitoring requirements, and program sustainability. As Indonesia considers scaling up Wolbachia deployments, it must carefully weigh the potential benefits of suppressing dengue against the risks and obstacles involved.

Discussion

Dengue fever has been a persistent problem in Indonesia for decades, with tens of thousands of cases reported yearly. One innovative approach to controlling dengue is the use of Wolbachia, a bacterium that can be introduced into Aedes mosquito populations to suppress their ability to transmit viruses such as dengue.

The following are some key points about the global prevalence of dengue and its situation in Indonesia:

Global Dengue Prevalence [2,3]:

- Dengue is the fastest-growing mosquito-borne viral disease in the world. It is endemic to more than 100 countries in Asia, Africa, the Americas, the Caribbean, and the Pacific.

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- The World Health Organization (WHO) estimates that approximately 390 million dengue infections occur globally annually, of which 96 million results in illness.
- Approximately 70% of the actual burden is found in Asia, with the Asian region bearing approximately 67 million disability-adjusted life years (DALYs) from the disease.
- The highest risk areas are in the tropics and subtropics, as the Aedes mosquitoes that transmit dengue thrive in warm, humid environments.

Dengue in Indonesia [2]:

- Indonesia has one of the highest dengue burdens globally. It is a tropical nation with ideal conditions for mosquito breeding.
- Between 2015 and 2019, Indonesia reported an average of more than 200,000 dengue cases annually to the WHO.
- The disease is endemic in all 34 provinces, with cases occurring year-round and seasonal peaks during the rainy season.
- Major outbreaks occurred in 2016, with more than 200,000 cases and 1,598 deaths, and in 2019, with more than 130,000 cases.
- Java, Sumatra, and Bali are the most affected regions, with densely populated urban centers being high-risk areas.
- Demographic factors, such as urbanization, poor housing conditions, and a lack of reliable piped water, also contribute to the spread of dengue in Indonesia.

With increasing global travel, unplanned urbanization, and climate change impacts, the burden of dengue is expected to increase further, intensifying the need for effective prevention and control measures in endemic countries such as Indonesia [14].

Advantages of Wolbachia [15-17]

1. Effective dengue reduction: Field trials in countries such as Australia, Vietnam, and Indonesia have demonstrated that Wolbachia can significantly reduce dengue transmission rates in areas where it is deployed.
2. Self-sustaining and environmentally friendly: Once Wolbachia is established in a local mosquito population, it can persist and spread independently without requiring further release, providing long-term protection. It is also a natural and eco-friendly method with no toxic chemicals.
3. Cost-effectiveness in the long run: While the initial investment in a Wolbachia programme can be substantial, it is expected to be more cost-effective than ongoing insecticide campaigns or developing and distributing new vaccines over time.

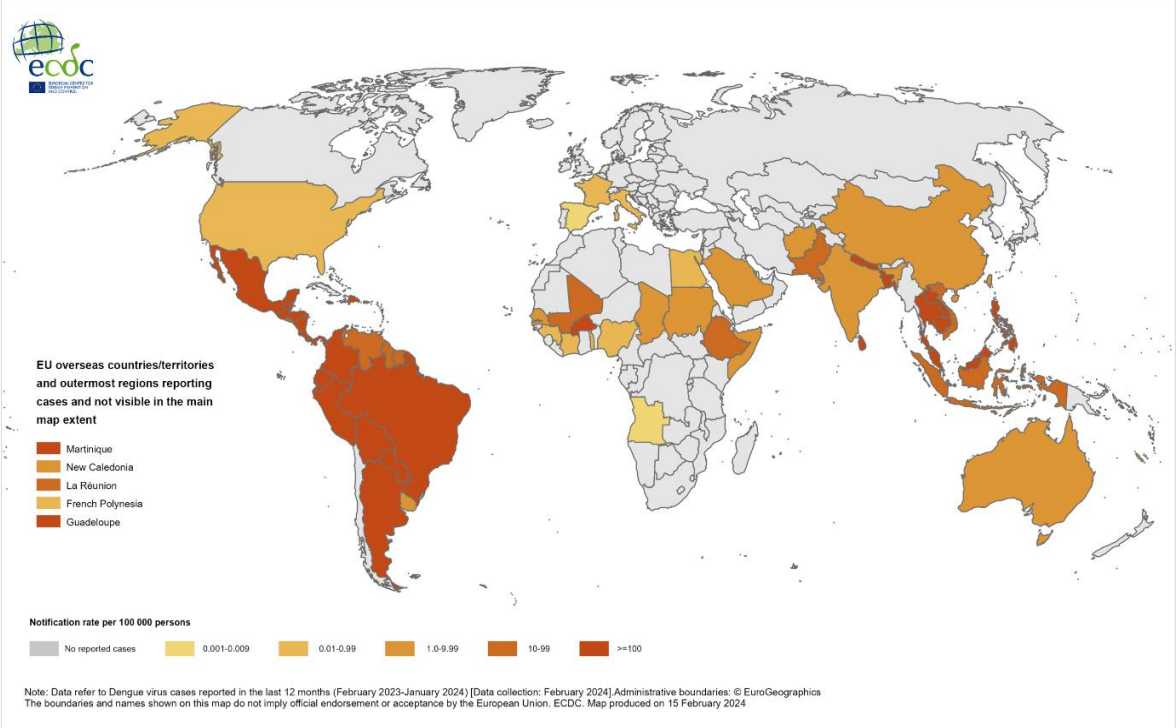

Figure 1. Prevalence Between 2015 and 2019 Indonesia reported an average of over 200.000 dengue cases annually to the WHO (Figure from ECDC, 2024).

Disadvantages of Wolbachia [10,18,19]

1. Limited protection: Wolbachia only targets the Aedes aegypti and Aedes albopictus mosquitoes that transmit dengue, chikungunya, Zika, and yellow fever. It does not impact other disease vectors, such as Anopheles mosquitoes, that transmit malaria.
2. Establishment challenges: High levels of Wolbachia in local mosquito populations can be difficult due to factors such as pesticide resistance, climate conditions, and competition from uninfected mosquitoes migrating into the area.
3. Public acceptance: Some community members may be sceptical or resistant to releasing Wolbachia-infected mosquitoes, even though the method has been proven safe. Educational campaigns are crucial to garner public trust and support.

As Indonesia continues to battle the economic and public health burdens of dengue, Wolbachia could be a powerful complementary tool alongside existing prevention strategies such as vector control and vaccine development [15]. However, careful consideration of local conditions, long-term monitoring, and public engagement will be key to maximizing its potential benefits while mitigating any

drawbacks. When Wolbachia bacteria are introduced into Aedes mosquitoes through special rearing and injection techniques, they establish themselves and are passed on from one mosquito generation to the next.

There are two key ways in which Wolbachia interferes with mosquitoes [20,21]:

1. Blocking Virus Replication

Wolbachia can directly inhibit the replication and dissemination of viruses such as dengue, chikungunya, Zika, and yellow fever inside mosquito bodies. The exact underlying mechanisms are still being researched, but Wolbachia may compete for resources, induce host immune responses, or cause physiological changes that create an antiviral environment.

2. Cytoplasmic Incompatibility

Wolbachia can cause a form of reproductive interference called cytoplasmic incompatibility. When an infected male mates with an uninfected female, their offspring do not survive. This allows the Wolbachia bacteria to spread through the mosquito population over successive generations.

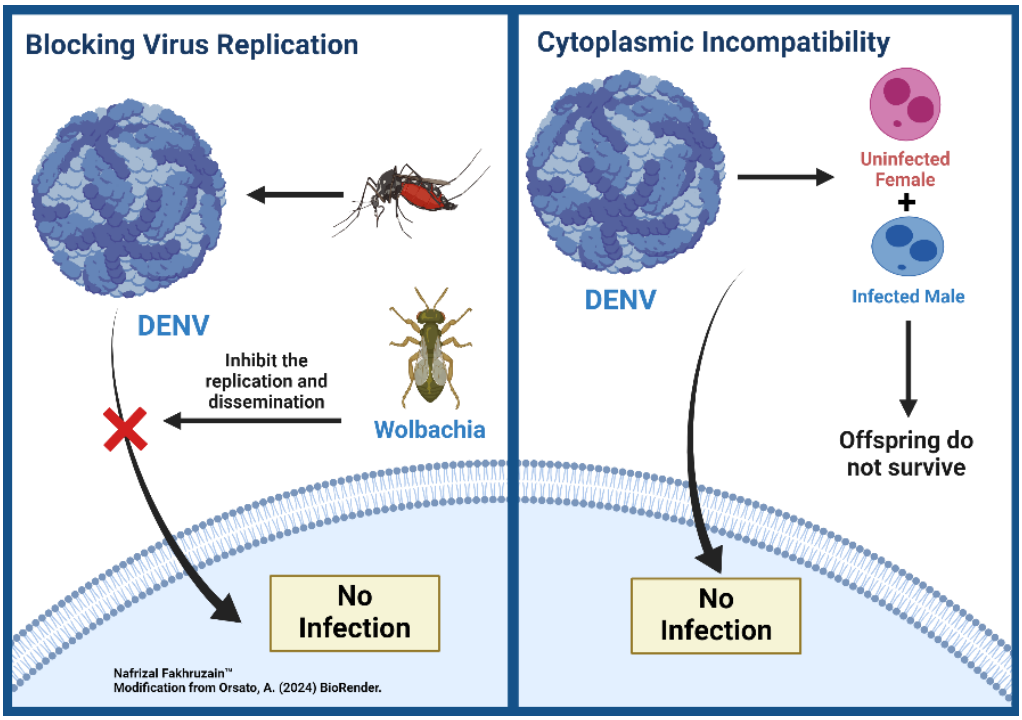

Figure 2. Dengue Virus (DENV) Inhibition by Wolbachia (created by Nafrizal used BioRender)

Combining these two effects means introducing Wolbachia, which reduces the number of mosquitoes capable of transmitting viruses. Field trials have shown that Wolbachia can suppress dengue transmission by more than 90% in some areas [20]. The advantages of Wolbachia include self-sustaining, eco-friendly, and relatively low maintenance abilities once established. However, care must be taken during implementation to achieve high population coverage and public acceptance [22].

The potential of using Wolbachia to reduce dengue transmission in Indonesia is promising but involves important trade-offs to consider [23]. On the one hand, successful Wolbachia deployment could significantly alleviate the substantial health and economic burdens of dengue in Indonesia [23]. Dengue affects approximately 7 million people across Indonesia annually, with more than 600,000 hospitalizations and hundreds of deaths. Beyond the human toll, treatment costs, productivity, and disease prevention efforts run into the billions of rupiah each year. If Wolbachia interventions can replicate the 77% reduction in dengue cases at trial sites, it could provide enormous public health value [23,24]. Moreover, the Wolbachia method is an attractive alternative to traditional insecticide control methods that are costly, have limited effectiveness due to increasing resistance, and carry environmental risks. As a biological control system that can continue to work independently, Wolbachia can provide long-lasting protection that does not require repeated applications or damaging ecosystems with chemicals once set up [25].

However, there are also significant disadvantages to weighing. Principally, there are uncertainties about the unintended effects of releasing Wolbachia-carrying mosquitoes into the environment. While Wolbachia strains are naturally occurring, they can spread into other insect populations in unforeseen ways, unbalancing ecosystems that humans depend upon, such as pollination or biological pest control by species such as dragonflies. More research is needed on downstream ecological impacts.

There are also ethical issues around the public's perceptions and consent regarding this biological approach. Previous attempts at controlling disease vectors such as mosquitoes have faced community resistance due to a lack of outreach [26]. Careful engagement and education may be required to overcome potential public distrust or concerns over "enhanced" mosquitoes.

Financially, the upfront costs of producing sufficient mosquitoes, mapping release sites, monitoring effectiveness, and managing the inevitable "urban leakage" of Wolbachia strains will be substantial for Indonesia. Ongoing funding sources and public–private partnerships would likely be required to scale and sustain this approach nationwide [23].

Ultimately, the use of Wolbachia based on early tests is a good idea. However, Indonesia needs to carefully look at the costs, risks, and social issues involved to see if this is the right and moral way to fight dengue in their situation [23]. With active public discussion and monitoring mechanisms, a measured, step-by-step approach might be prudent. Decisively combating dengue is a public health imperative but must be balanced against protecting vulnerable

ecosystems and communities [27]. As Indonesia evaluates this approach, a balanced, stepwise strategy is advisable. Investing in expanded controlled trial sites with robust monitoring systems could help quantify environmental impacts while paving the way for community outreach. A demonstrated ability to sustain releases, evaluate effectiveness, and respond to challenges at a local level could build confidence for wider deployments over time [28].

It is crucial to note that public health officials or scientists cannot make decisions alone. The affected communities must have a voice and stake in weighing the pros and cons. Ethical deliberations and mechanisms for public feedback will be vital for assessing whether the promised benefits of Wolbachia outweigh the potential risks in the public's eyes [29].

Dengue has tormented Indonesia for too long. Wolbachia provides a novel, though imperfect, opportunity to combat this scourge. With thoughtful planning, open dialog, and a stepwise approach, Indonesia could lead the way in realizing this technology's public health promise responsibly and sustainably [30]. The path forward requires carefully weighing the trade-offs but represents a chance to turn the tide against this deadly virus.

The use of Wolbachia-infected mosquitoes as a biological control strategy for dengue fever has garnered significant attention in recent years. Several studies highlight the potential benefits of this approach, particularly in reducing dengue transmission. For instance, [31] demonstrated that releasing Wolbachia-infected Aedes aegypti mosquitoes significantly reduced dengue incidence in field trials in Australia, suggesting that Wolbachia can effectively interfere with the virus's ability to replicate within the mosquito host.

Conversely, concerns regarding the ecological impact of introducing Wolbachia-infected mosquitoes have been raised. A study by [22] emphasized the need for careful ecological assessments, as the long-term effects of releasing genetically modified organisms into the wild remain uncertain. The potential for Wolbachia to alter mosquito behavior or interactions with other species could have unforeseen consequences on local ecosystems.

Another critical factor is the cost-effectiveness of Wolbachia-based interventions. A cost analysis by [32] indicated that while initial release programs may be expensive, the long-term savings in healthcare costs due to reduced dengue cases could justify the investment. However, the economic feasibility may vary significantly across different regions, necessitating localized assessments.

Public acceptance of Wolbachia-infected mosquitoes is essential for the success of such programs. A survey conducted by [33] found that community awareness and understanding of the benefits of Wolbachia were crucial in gaining public support. Misconceptions about genetically modified organisms could hinder acceptance, highlighting the importance of effective communication strategies.

Moreover, the sustainability of Wolbachia as a control method is a topic of ongoing research. A study by [34] indicated that the stability of Wolbachia in mosquito populations over time is critical for maintaining its effectiveness. If the infection rate declines, the potential for dengue resurgence could pose a significant risk.

The role of Wolbachia in enhancing the resilience of mosquito populations against other pathogens has also been explored [35] found that Wolbachia-infected Aedes aegypti showed reduced susceptibility to other viruses, suggesting a potential dual benefit of controlling dengue while simultaneously limiting other mosquito-borne diseases. Ethical considerations surrounding the release of genetically modified organisms into the environment are paramount.

Finally, the integration of Wolbachia-based strategies with existing vector control measures could enhance overall effectiveness. A study by [36] proposed a multi-faceted approach that combines Wolbachia releases with traditional insecticide use, potentially leading to synergistic effects in reducing dengue transmission.

Conclusion

Dengue represents a major public health crisis in Indonesia that demands innovative solutions. The Wolbachia method of suppressing dengue transmission shows promising potential but also carries important trade-offs to carefully consider. On the pro side, successful deployments could dramatically reduce dengue cases, save lives, and provide enormous economic benefits by alleviating the costs of this widespread disease. Wolbachia is also an environmentally friendly and self-sustaining alternative to insecticides.

However, the risks cannot be ignored. The unintended ecological consequences of releasing Wolbachia-infected mosquitoes require further study. Public acceptance issues and logistical challenges around production, monitoring, and funding streams must also be addressed. There are no easy answers, but dismissing Wolbachia outright could mean passing up a transformative opportunity in dengue control.

Declarations

Ethical Approval

Not Applicable

Data Availability

Available on corresponding author upon reasonable request.

Author Contributions

Syahrul Tuba: Writing - Review & Editing, Project Administration, Validation, Investigation,

Widyati, Nur Abdul Goni, Apip Hadi, Budi Sumaryono, Adi Priyono: Validation, Investigation, Writing - Review & Editing.

Conflict of Interest

The authors declare that there are no competing interests related to this study.

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