The potential role of *Wolbachia* in controlling the transmission of emerging human arboviral infections

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**Purpose of review**

*Wolbachia* is a genus of Gram-negative intracellular bacteria that is naturally found in more than half of all arthropod species. These bacteria cannot only reduce the fitness and the reproductive capacities of arthropod vectors, but also increase their resistance to arthropod-borne viruses (arboviruses). This article reviews the evidence supporting a *Wolbachia*-based strategy for controlling the transmission of dengue and other arboviral infections.

**Recent findings**

Studies conducted 1 year after the field release of *Wolbachia*-infected mosquitoes in Australia have demonstrated the suppression of dengue virus (DENV) replication in and dissemination by mosquitoes. Recent mathematical models show that this strategy could reduce the transmission of DENV by 70%. Consequently, the WHO is encouraging countries to boost the development and implementation of *Wolbachia*-based prevention strategies against other arboviral infections. However, the evidence regarding the efficacy of *Wolbachia* to prevent the transmission of other arboviral infections is still limited to an experimental framework with conflicting results in some cases. There is a need to demonstrate the efficacy of such strategies in the field under various climatic conditions, to select the *Wolbachia* strain that has the best pathogen interference/spread trade-off, and to continue to build community acceptance.

**Summary**

*Wolbachia* represents a promising tool for controlling the transmission of arboviral infections that needs to be developed further. Long-term environmental monitoring will be necessary for timely detection of potential changes in *Wolbachia/vector/virus* interactions.

**Keywords**

arboviruses, chikungunya virus, dengue virus, Japanese encephalitis virus, prevention, transinfection, transmission, West Nile virus, *Wolbachia*, yellow fever virus, Zika virus

**INTRODUCTION**

Arthropod-borne viruses (arboviruses) are transmitted between vertebrate hosts and blood-feeding arthropod vectors including mosquitoes, sand flies, biting midges, mites, lice and ticks [1,2,3]. With the exception of African swine fever virus, which is a double-stranded DNA virus belonging to the *Asfarviridae* family [4], all other arboviruses have an RNA genome and belong to one of the following five families of viruses: *Flaviviridae*, *Togaviridae*, *Bunyaviridae*, *Rhabdoviridae* and *Reoviridae* [3]. The distribution of arboviruses across the globe is largely dependent on the distribution of susceptible vector species, which varies in response to climatic changes. Their spread is favoured by urbanization, human travel and livestock movements [1,5,6]. Arboviral infections cause a wide range of life-threatening manifestations, notably nervous system disease...
KEY POINTS

- *Wolbachia* is a Gram-negative intracellular bacteria that is naturally found in more than 50% of all arthropod species, but is absent in the major arbovirus vector *A. aegypti*.

- *Wolbachia* alters the reproductive fitness of arthropod vectors through selective male killing, parthenogenesis, feminization of male embryos and cytoplasmic incompatibility. It also alters the competence of transinfected arthropod vectors for the transmission of arboviruses through competition for resources, immune-priming, induction of the phenoloxidase cascade and induction of microRNA-dependent immune pathways.

- Field releases of *Wolbachia*-transinfected *A. aegypti* mosquitoes have been successfully used in the Eliminate Dengue Programme to suppress the dissemination of DENV in Australia, but the true epidemiological impact on dengue-related morbidity and mortality is yet to be assessed. The evidence regarding the efficacy of *Wolbachia* to prevent the transmission of other arboviruses including chikungunya, JEV, WNV and Zika is still limited to the experimental framework.

- It is possible that the *Wolbachia* strains that confer the strongest interference with pathogen transmission do not spread easily into local vector populations because of deleterious fitness effects. Adequate selection of the *Wolbachia* strain is therefore crucial in the implementation of *Wolbachia*-based biocontrol strategies.

- There has been some concern about potential exposure of humans to *Wolbachia* via mosquito bites. However, there is currently no evidence that such exposure occurs (or at least, is medically relevant). In addition, there is no evidence that the field release of *Wolbachia*-infected mosquitoes has any adverse effects on the environment.

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**Table 1.** Summary of strategies that could be used to prevent the transmission of arboviruses to humans

| Level of action          | Ultimate goal                                                                 | Strategies that could be used                                                                                     |
|--------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| Vector                   | Reduce the prevalence of vectors and their capacity to transmit viruses       | Direct killing of vectors by spreading of insecticides [12]                                                     |
|                          |                                                                               | Limitation of vectors’ reproduction by [13–16]:                                                              |
|                          |                                                                               | - Destroying breeding sites and promoting good sanitary conditions                                            |
|                          |                                                                               | - Releasing sterile or genetically modified vectors                                                           |
|                          |                                                                               | - Introducing biological control agents                                                                     |
|                          |                                                                               | *Wolbachia*-based methods: population replacement with transinfected vectors displaying reduced vector competence [17,18**], or population suppression (Incompatible Insect Technique) [19] |
| Host-vector interface    | Avoid bites [6]                                                               | Use of bed nets                                                                                               |
|                          |                                                                               | Use of repellents                                                                                             |
|                          |                                                                               | Sensitization of travellers and communities at risk                                                           |
| Human host               | Reduce host susceptibility to arboviruses                                    | Vaccine [20–23]                                                                                                |
|                          |                                                                               | Chemoprophylaxis [24]                                                                                         |
sufficient and/or always affordable, there is an urgent need for the development of novel strategies for vector control, prompting a high level of interest in using the bacterium Wolbachia to control the transmission of arboviruses.

Wolbachia is a genus of Gram-negative intracellular bacteria belonging to the order Rickettsiales and the family Anaplasmataceae. These bacteria only infect invertebrate organisms and are naturally found in more than 50% of all arthropod species and in several nematodes [1,30,31]. However, Wolbachia is naturally absent from Aedes aegypti (also called Stegomyia aegypti), but can be introduced [1,32]. A. aegypti is a widespread human blood-feeding mosquito responsible for the transmission of several arboviruses including dengue, yellow fever, Zika, Murray valley, chikungunya and Rift valley fever viruses. Generally, the different strains of Wolbachia are named according to the host in which they were first discovered. For instance, Wolbachia pipiensis (wPip) was the first strain discovered in the mosquito Culex pipiens [33]. Similarly, wMel was first isolated from the common fruit fly Drosophila melanogaster, whereas wAlb was first isolated from Aedes albopictus [34]. Several studies have demonstrated that Wolbachia increases arthropods’ resistance to viruses [35–37] and/or alters their reproductive capacities [17,38]. More recently, researchers of the Eliminate Dengue Programme in Australia have demonstrated that the transfer of this bacterium into wild populations of the mosquito A. aegypti represents an effective measure to control the transmission of dengue [18**].

Here, we review the scientific evidence supporting the use of Wolbachia-based strategies to control the transmission of these arboviral infections and discuss the related risks, challenges and limitations.

**INDUCTION OF VIRAL RESISTANCE IN ARTHROPOD VECTORS**

Wolbachia is thought to induce resistance to arboviruses through four complementary mechanisms (Fig. 1): competition for resources, preactivation of the immune system (also referred to as immune-priming), induction of the phenoloxidase cascade and induction of microRNA-dependent immune pathways that are essential for host defence against viruses [46,47**].

**Competition for resources**

Autophagy is a cellular degradation and recycling process by which unnecessary or dysfunctional cellular components are incorporated in lysosomes for digestion. The resulting nutrients are made available for further metabolic processes [48]. Wolbachia is not only able to induce autophagy in arthropod vector’s cells but also to hijack the autophagy system in order to ensure its own survival both in vitro and in vivo [49]. As both flaviviruses and alphaviruses are dependent on the autophagy pathway to replicate [50,51], it has been hypothesized that Wolbachia interferes with the replication of some arboviruses.
through its ability to manipulate the autophagy system, thus reducing the amount of nutrients available for viruses.

Wolbachia-mediated antiviral resistance might also be favoured by competition with viruses for iron and cholesterol. The bacterium is known to manipulate host cell iron reserves, as does the dengue virus (DENV) and the chikungunya virus (CHIKV) [52,53]. Like other members of the order Rickettsiales, Wolbachia is unable to synthesize cholesterol de novo and therefore relies on host cell cholesterol reserves for its replication and growth [54]. Similarly, mosquito-borne flaviviruses and alphaviruses have been shown to rely on host cell cholesterol for cell invasion, replication, virion assembly, infectivity and release from the infected cells [55–62].

**Immune-priming**

Transinfection of Wolbachia into heterologous arthropod vectors (i.e. vectors that are not naturally infected by any, or that specific Wolbachia strain; such as the mosquito A. aegypti) preactivates their immune system, enabling it to combat microbes (including viruses) more effectively. This is done by inducing three major signalling pathways of the innate immune system: Toll, Imd (immune deficiency) and Janus kinase-signal transducer and activator of transcription (JAK-STAT) [1,46]. Toll (from the German adjective ‘toll’ meaning ‘wonderful’) are transmembrane proteins encoded by the eponymous gene in Drosophila [63]. The JAK-STAT pathway is made up of one cell surface receptor called JAK and two proteins acting as STAT [64]. Activation of these signalling pathways leads to the transcriptional upregulation of antimicrobial peptide genes – such as those that encode drosomycin, cecropin and defensin – and several other immune genes [65–68], resulting in increased resistance of arthropod vectors to various arboviruses [1,69–75].

**Induction of the phenoloxidase cascade**

The phenoloxidase cascade is important in mosquitoes’ immune response to viruses [76], and Wolbachia has been recently shown to trigger this pathway both in homologous and heterologous host vectors [77].

**Induction of miRNA-dependent immune pathways**

Wolbachia upregulates the microRNA aae-miR-2940 in mosquitoes [78] and this has two consequences: the upregulation of the metalloprotease m41fsh and the downregulation of the DNA cytosine-5-methyltransferase gene, AaDnmt2, thus favouring DNA
cytosine methylation. The latter is indispensable for host immune defence, gene regulation, genome stability, organ differentiation and ageing [79].

It is also noteworthy that both the metalloprotease m41fish and DNA cytosine methylation are essential for maintaining a high density of Wolbachia infection in host cells [78]. Therefore, the upregulation of microRNAs could potentiate the competition for resources (Fig. 1), as a high density of Wolbachia creates unfavourable conditions for viruses by decreasing the amount of available resources (iron, cholesterol and other lipids) [35,80].

APPLICATION OF THE WOLBACHIA-BASED STRATEGY FOR CONTROLLING THE TRANSMISSION OF ARBOVIRAL INFECTIONS: CURRENT RESULTS, POTENTIAL RISKS AND FUTURE CHALLENGES

The phenotypic effects of Wolbachia on arthropod vectors’ reproduction and resistance to viruses make it a promising tool for controlling the transmission of arboviral infections. Indeed, Wolbachia has already been successfully used to control the transmission of dengue, whereas its role in combating other infections is still being assessed.

Initial successes in the Eliminate Dengue Programme

Dengue is the most important mosquito-borne viral disease of humans with an estimated 2.5 billion people at risk in more than 100 countries worldwide, and 50–100 million infections acquired each year [81]. It is transmitted principally by the mosquito A. aegypti, which is present in more than 150 countries and is not naturally infected by Wolbachia [82**]. The Eliminate Dengue Programme emerged in 2008 from the work of Professor Scott O’Neill and colleagues [83] (www.eliminatedengue.com). Early efforts focused on using the life-shortening wMelPop strain to reduce the number of dengue vectors reaching maturity. This approach took account of the fact that mature mosquitoes are more likely to transmit dengue, as the DENV must incubate in the mosquito for several days before becoming infectious [83]. However, as transfection of A. aegypti with the wMelPop strain induced significant fitness costs (reduction of the longevity of infected adult females and reduction in the viability of eggs, whether or not they were in diapause (i.e. physiological state of dormancy induced by unfavourable environmental conditions)) [45], there were some concerns about its ability to rapidly invade wild mosquito populations following test releases of Wolbachia-infected mosquitoes. Indeed, the greater the fitness costs, the higher the initial Wolbachia frequencies required for invasion. According to mathematical predictions, as the fitness cost of infection approaches 0.5, spatial spreading of Wolbachia slows to zero [84]. For this reason, researchers of the Eliminate Dengue Programme turned to the wMel strain that has a lower fitness cost but still confers sufficient resistance to DENV [35,37]. In 2011, they reported stable transinfection of A. aegypti with wMel [83,85]. They subsequently demonstrated that this strain reduced the capacity of A. aegypti to transmit dengue and successfully invaded wild mosquito populations [86,87]. This laid the foundations for the large-scale release of Wolbachia-infected mosquitoes in dengue-endemic areas in Australia, resulting in successful suppression of DENV replication in and dissemination by mosquitoes as confirmed by vector competence experiments carried out 1 year following field release [18**]. The success of the Eliminate Dengue Programme in Australia has led to further trial releases of Wolbachia-carrying A. aegypti in other dengue-endemic countries throughout the world, notably Colombia, Indonesia, Vietnam and Brazil [82**]. Recent mathematical models have demonstrated that this strategy could reduce the transmission of DENV by 70% [82**,88**]. However, the true epidemiological impact (reduction of the incidence of dengue and the relative risk of infection between Wolbachia-treated and untreated areas) of Wolbachia-based biocontrol strategies for dengue is yet to be properly assessed through prospective cohort studies and cluster randomized trials [89**].

The potential use of Wolbachia to control other arboviral infections

Although Wolbachia-infected mosquitoes were initially generated for the biocontrol of dengue, there is increasing evidence from experimental studies that they could also be used to control the transmission of other arboviruses, notably CHIKV [90], JEV [91*] and YFV [92]. Concerning WNV, results are more controversial. In 2009, it was reported for the first time that Wolbachia could increase resistance to WNV in Culex quinquefasciatus [80]. However, subsequent reports highlighted the fact that most C. quinquefasciatus populations are naturally infected with Wolbachia but are still capable of transmitting WNV. Moreover, it appears that transinfection with the wAlbB strain from A. albopictus enhances WNV infection in Culex tarsalis, a naturally uninfected mosquito which is an important vector of WNV in North America [93*]. Finally, it has been demonstrated recently that Wolbachia-infected mosquitoes are highly resistant to infection with two currently circulating Zika virus isolates.
Monitoring evolutionary changes
Evolutionary changes occurring in Wolbachia, the arboviruses or the arthropod hosts should be monitored over time as they could modulate the efficacy of the Wolbachia-based prevention strategy. Furthermore, it is still too early to say to what extent the Wolbachia-mediated viral resistance in vectors could trigger the emergence of potentially more virulent strains of arboviruses.

Obtaining community acceptance
Adequate public engagement is indispensable for the success of Wolbachia-based mosquito control strategies. Indeed, all public health interventions need to be well explained in order to be approved by local regulatory authorities and to ensure the support of the vast majority of people within the target communities. The lessons learned from the Eliminate Dengue Programme should be applied, and adapted to local conditions, for other arboviral diseases and the respective communities affected.

Accounting for geographical specificities
Wolbachia-based biocontrol strategies might not be equally efficient or applicable in all geographical areas. Indeed, in regions endemic for two or more arboviral diseases with different vectors, the need to allow spread of a newly released Wolbachia-infected vector could require that the application of insecticides be halted (at least temporarily), thus allowing other vectors to thrive, and potentially leading to increased risks of a disease outbreak. The same concern could arise in areas where a disease is transmitted by two or more vector species. For instance, dengue and Zika viruses are transmitted by A. aegypti and A. albopictus, and both species have increased viral resistance after transinfection with wMel [17,86]. However, large-scale field releases are currently restricted to Wolbachia-transinfected A. aegypti. Moreover, in areas where rare vector species are more important for disease transmission than the most widespread ones, Wolbachia-based vector control strategies might be less cost-effective than insecticides that target all potential vectors at the same time. Finally, it is still unclear whether the results obtained with the Eliminate Dengue Programme can be replicated for dengue or other arboviral infections in the tropics, where arthropod vectors’ density and efficiency are expected to be higher because of higher temperatures [101].

CONCLUSION
The naturally occurring endosymbiont Wolbachia has several effects on reproduction and vector
competence in arthropod vectors and therefore represents a promising tool for controlling the transmission of arboviral infections with apparently almost no health or environmental risk. Indeed, mass releases of Wolbachia-transinfected A. aegypti have already been used successfully in Australia to block the transmission of DENV with no known adverse effects. However, more research is required before the same strategy could be used for other infections. Indeed, it needs to be confirmed if the wMel strain is the optimum one, in terms of both pathogen interference and rate of spread, for other vectors of arboviruses. Furthermore, implementation of Wolbachia-based prevention strategies should account for geographical specificities and be accompanied by adequate public engagement programmes to ensure community acceptance. These strategies should also be adequately monitored over a long period for timely detection of potential adverse effects or changes in Wolbachia/vector/virus interactions.

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- of special interest
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