Modeling the potential of introducing different *Wolbachia*-infected mosquitoes to control *Aedes*-borne arboviral infections

Thesis submitted by

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To

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Declaration

I, the undersigned declare that the work presented in this thesis is my original work, carried out on my research during the academic program towards the degree of Doctor of Philosophy (Health) at James Cook University. The work has not been previously submitted anywhere for another degree or diploma at any university of the institution of tertiary education in or out of Australia. Information derived from the published or unpublished works of others has been acknowledged and referenced accordingly in the text.

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Samson Tosin Ogunlade	January 17, 2023
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Abstract

Arboviral diseases continue to spread and pose significant health challenges globally, infecting over 400 million of the world's population and causing at least 40 thousand deaths per year. The *Wolbachia*-based intervention strategy – which involves the release of mosquitoes infected with the naturally occurring *Wolbachia* bacterium – can disrupt vector reproduction and transmission and thus provides a promising route to disease control. However, several challenges, including potency in the face of unfavourable weather conditions, incomplete maternal transmission and lack of cytoplasmic incompatibility (CI) (i.e., unviable offspring of cross-infected adults) threaten the utility of *Wolbachia*-based strategies. To circumvent these challenges, the *Wolbachia* strains with more favourable properties have been proposed.

In this thesis, I develop single and multi-*Wolbachia* invasive models and investigate the ecological and transmission dynamics of vector populations. These models incorporate *Wolbachia* features in mosquitoes such as deleterous fitness effect, imperfect maternal transmission, induction of CI and *Wolbachia* infection loss due to high temperature. I modify these models to investigate several *Wolbachia* strains in mosquitoes and evaluate the optimal *Wolbachia* establishment approach in the wild-type mosquito population.

On investigating the paradigm where a single *Wolbachia* strain is introduced into the mosquito population, I take into account the unique *w*Au strain, which has a number of advantageous characteristics like improved viral blocking and maintenance at higher temperatures but not CI. Additionally, I examine the competitive behaviour between *w*Au-*Wolbachia*-infected and uninfected mosquito populations as well as the impact of imcomplete maternal

transmissions and investigate the trade-offs between CI and *Wolbachia* infection loss. I find that improved *Wolbachia* infection maintenance at high temperatures can compensate for the lack of CI induction to enable the invasion of *w*Au-*Wolbachia* infected mosquitoes.

For the multi-strain *Wolbachia* model, I consider supplemental *Wolbachia* strains that are more tolerant of higher temperatures and may work in concert with existing strains. In view of this, I model the ecological interactions between three different mosquito subpopulations: a wild-type population devoid of any *Wolbachia* infections; an invading population carrying a specific strain of the bacterium; and a second invading population carrying a different strain of the bacterium from the first invader. I investigate how variations in the features of each *Wolbachia* strain affect the prevalence of mosquitoes and analyse the differential system describing the *Wolbachia* infection dynamics. Further, I explore the impact of introducing two *Wolbachia* strains simultaneously and investigate the strains' coexistence and synergistic effects. I find that, coexistence would always be transient since the fitter *Wolbachia*-infected mosquito strain would prevail and eradicate the inferior strain. Additionally, the prevalence of *Wolbachia* strains was not increased by the temporary coexistence, rather, it either has no effect or decreased.

In order to validate these models using experimental data, I develop a mathematical model that incorporates both human and mosquito populations in the presence of *Wolbachia* infection and investigate how *Wolbachia* introduction affects the transmission dynamics of dengue. I examine the data from Townsville, Queensland and estimate the impact of dengue transmission probabilities from *Wolbachia* release programs. The model's findings demonstrate that dengue cases decreased by 80–90% following the discharge of *Wolbachia* because these *Wolbachia*-infected mosquito vectors are only 25% as likely to transmit dengue as non-*Wolbachia* mosquitoes.

This thesis offers a deeper comprehension of the evolving epidemiology of the optimal *Wolbachia* strategies from single and multi-*Wolbachia* strain combinations. Furthermore, it addresses the trade-offs between CI, *Wolbachia* infection loss and other strain properties,

determining which combinations lead to the greatest reductions in arboviral transmission, and thereby, contributing to the mitigation or elimination of global arboviral infections.

Keywords

Mathematical modelling

Transmission dynamics

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• McBryde, E. S., Meehan, M. T., Caldwell, J. M., Adekunle, I. A., **Ogunlade, S. T.**, Kuddus, M. A., Ragonnet, R., Jayasundara, P., Trauer, J. M., (2021). Modelling direct and herd protection effects of vaccination against the SARS-CoV-2 Delta variant in Australia. *The Medical Journal of Australia* 10.5694.

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Presentations

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Short courses

- Programming for everybody (Getting started with Python) (University of Michigan, USA)
- R programming (Johns Hopkins University, USA)
- Getting started with R and RStudio (James Cook University, Australia)
- Skills for international postgraduates (SKIP) (James Cook University, Australia)
- An introduction to statistics using SPSS (James Cook University, Australia)
- Publication Based Theses (James Cook University, Australia)
- Planning a Career in Academia (James Cook University, Australia)
- The Thesis Examination Process (James Cook University, Australia)
- Advanced statistics (SPSS) (James Cook University, Australia)
- EndNote for Systematic Reviews (James Cook University, Australia)
- 3-Minute Thesis (3MT) coaching session (James Cook University, Australia)
- Job Application Workshop (James Cook University, Australia)
- Julia programming language (University of Cape Town)
- Time management for productivity (UCI Division of Continuing Education)
- Academic and thesis writing (James Cook University, Australia)
- All compulsory higher degree by research (HDR) JCU courses (James Cook University, Australia)
- HDR Resilience - Building Resilience to Stress (e-Grad School, Australia)

Abbreviations

DENV	: Dengue Virus
ZIKV	: Zika virus
CHIKV	: Chikungunya virus
YFV	: Yellow fever virus
RNA	: Ribonucleic acid
DNA	: Deoxyribonucleic acid
CI	: Cytoplasmic Incompatibility
ITN	: Insecticide-treated bed nets
IRS	: Indoor residual spraying
SIT	: Sterile insect technique
GMM	: Genetically modified mosquitoes
RIDL	: Release of insects with dominant lethality
MT	: Maternal Transmission
IMT	: Imperfect Maternal Transmission
LWI	: Loss of *Wolbachia* Infection
R_0	: Basic reproduction number
R_{0u}	: Basic reproduction number for uninfected mosquitoes
R_{0i}	: Basic reproduction number for i-strain *Wolbachia*-infected mosquitoes
$R_{0i\|u}$	: Basic reproduction of mosquitoes infected with *Wolbachia* strain i, when introduced into a population of uninfected mosquitoes
$R_{0u\|i}$	: Basic reproduction of uninfected mosquitoes, when introduced into a population of mosquitoes infected with *Wolbachia* strain i
PRISMA	: Preferred Reporting Items for Systematic reviews and Meta-Analyses

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Chapter 1

Introduction

1.1 Biological background of Arboviruses

Arboviruses (arthropod-borne viruses) are transmitted via blood feeding arthropods such as *Aedes* mosquitoes, flies, and ticks [1]. These viruses are characterised by either a double-stranded DNA or an RNA genome [2]. Arboviruses are almost exclusively RNA viruses with one exception being the African swine fever virus (ASFV), which is a double-stranded DNA virus (mainly transmitted by ticks) and belongs to the *Asfarviridae* family of viruses [3]. Arboviruses with RNA genomes are members of either of the *Flaviviridae*, *Togaviridae*, *Bunyaviridae*, *Rhabdoviridae*, and *Reoviridae* families [4]. Specifically, *Aedes*-borne viruses are a subset of arboviruses that are mostly transmitted by female *Aedes aegypti* mosquitoes and sometimes by female *Aedes albopictus* mosquitoes [5, 6]. Examples of *Aedes*-borne arboviruses having RNA genomes are dengue virus (DENV), Zika virus (ZIKV), chikungunya virus (CHIKV), yellow fever virus (YFV), and Ross River virus (RRV) [7] (Figure 1.1). Other RNA arboviruses which are not *Aedes*-borne include West Nile virus (WNV) and Sindbis virus (*Culex*-borne) [8, 9], Tick-borne encephalitis virus and Crimean-Congo haemorrhagic fever virus (tick-borne) [10, 11], and Toscana virus (fly-borne) [12].

Aedes-borne viruses are fast spreading diseases that pose significant health problems

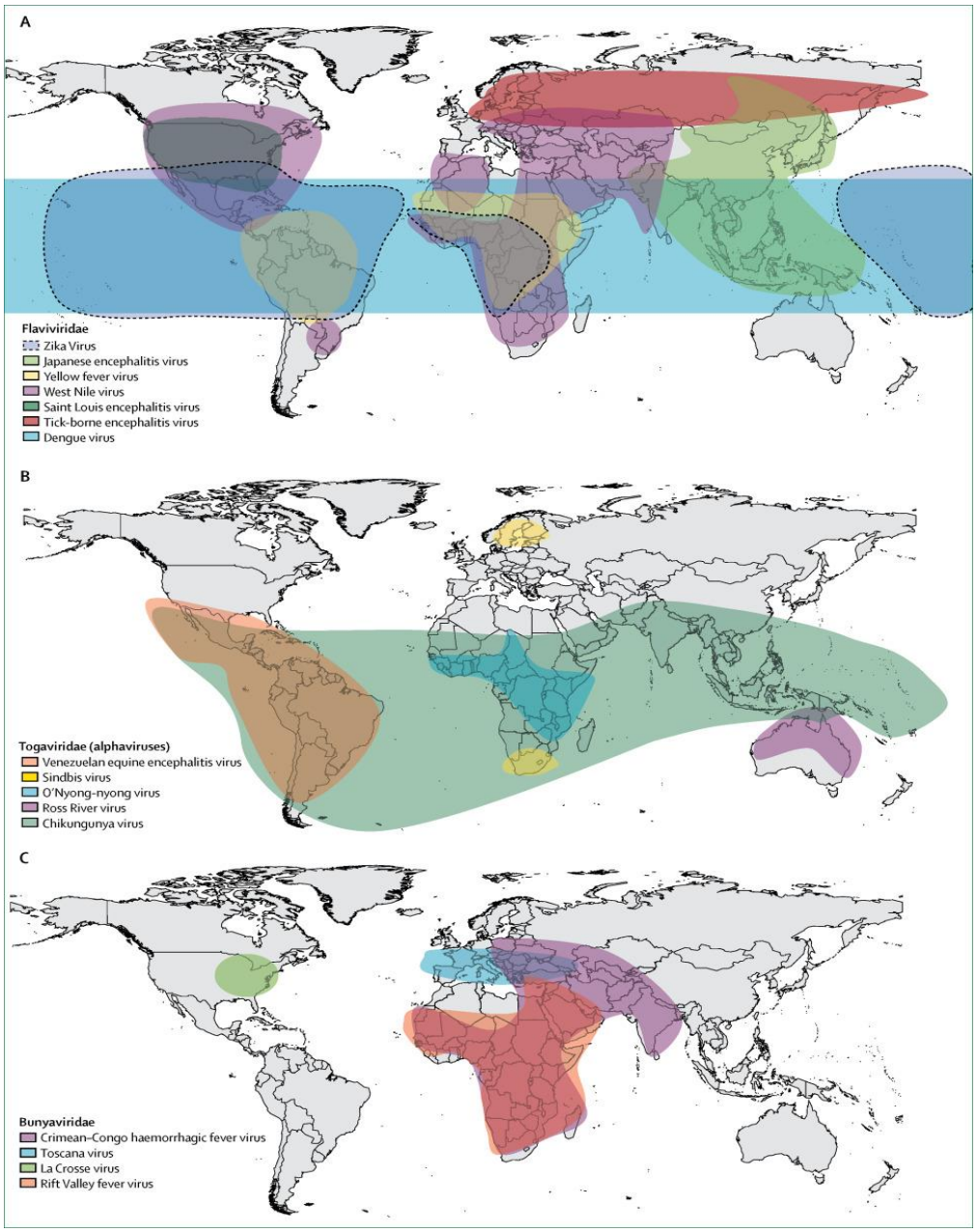

Figure 1.1: Global distribution of major arboviruses [7]. The *Aedes*-borne arboviruses described in this review belong to the *Flaviviridae* (ZIKV—light blue; YFV—yellow; DENV—blue) and *Togaviridiae* (CHIKV—green) families. [Reproduced with permission from Elsevier; License no. 4892881108152].

globally [13, 14, 15] (Figure 1.1). Of these viruses, the dengue virus alone currently infects approximately 390 million people annually with 96 million of these showing clinical symptoms [16, 17, 18, 19]. *Aedes*-borne viruses can be life-threatening, causing at least 40 thousand deaths per year [16, 20]. The global spread of these viruses is being fuelled by human

migration, urbanization, and animal transportation [14, 21, 22]. Presently, there are no specific treatments for *Aedes*-borne infections [4, 23]. However, supportive care for symptoms such as headache, seizure, and fever management and maintaining vital organs is available [2, 21]. Additionally, some vaccines with high efficacy have been developed to prevent arboviral infections. They include 17D YFV [24], Japanese encephalitis IXIARO [25] and tetravalent DENV vaccines [26]. However, research on the development of other arboviral infection vaccines such as ZIKV [27], WNV [28], RRV [29], and CHIKV [30] is still in progress but not yet approved. Full details of disease symptoms and available treatment alternatives are presented in Chapter 2.

To control the spread of *Aedes*-borne arboviral infections, several approaches such as those targeting human hosts, human-vector interactions and vectors specifically can be used [2]. Primarily, vector control strategies are used since they induce direct or biological reduction/elimination of the vectors without causing significant harm to human hosts [31]. The vector control strategies are classified into chemical, environmental, and biological control methods[1] [2, 31]. Presently, some of these methods are either widely practised or largely experimental (laboratory or field investigations).

Interestingly, one of the biological methods of vector control is the *Wolbachia*-based control method, which works by replacing existing wild-type mosquito vector populations with a *Wolbachia*-infected variant for which viral proliferation in its midgut is prohibited, rendering them less capable of transmitting the virus [36, 37, 38]. The *Wolbachia*-based control method, which is self-sustaining, is predominantly aimed at two mechanisms: distrupting arboviral transmission between vectors and hosts; and suppressing the mosquito vector population [39].

Several field studies have demonstrated the success and effectiveness of *Wolbachia* introduction into native mosquito populations [40, 41, 42, 43, 44]. The *Wolbachia* features that regulate the successful dominance of *Wolbachia* in the wild-type mosquito population include

[1]Although there is an emerging control method: mechanical control, which involves the mass trapping of mosquitoes using lethal traps and has been successful in controlling vectors transmitting dengue [32, 33, 34], mathematical models representing this approach are scarce [35].

immune system preactivation in the vectors, induction of cytoplasmic incompatibility (CI) rendering offspring unviable, imperfect maternal transmission of *Wolbachia*, loss of *Wolbachia* infection (LWI) due to high temperature, and superinfection of a second *Wolbachia* strain [45, 46, 47, 48]. Based on these features, there are some trade-offs exhibited by different *Wolbachia* strains, i.e., some strains induce CI (which is good) but also have LWI due to high temperature (which is bad) and vice versa [49, 50]. This provides the opportunity to develop mathematical models to account for the trade-offs between the effectiveness of CI and LWI in a single or multi-strain *Wolbachia* infection dynamics.

In recent years, the development of mathematical models to comprehend the dynamics of disease transmission has long been beneficial for disease control [51, 52, 53]. In the context of arboviral disease control, a number of mathematical models have been developed to examine the population dynamics of *Wolbachia*-infected mosquitoes invading wild-type mosquito populations [54, 55, 56, 57, 58]. These models are valuable as they confer precise and strategic solutions and provide comprehensive paradigms of the disease dynamics modelled. Additionally, mathematical models are able to maximize economic growth, help with policy and decision-making that could save lives [51, 59].

To the best of my knowledge, a systematic analysis of the importance of the trade-offs between the effectiveness of CI and LWI under complex and realistic environments has not been modelled. In addition, no study has explored these trade-offs in a single or multi-*Wolbachia* strain introduction into wild-type mosquito population, neither has any study investigated if multi (two) *Wolbachia* strain introduction is better than one. Therefore, in this thesis, I model and quantify the trade-offs in terms of the choice of *Wolbachia* with different features and release effectiveness on the reduction of arboviruses, in particular, DENV. Further, I want to know if two different *Wolbachia* strains rollout is better than one for sustainability of *Wolbachia* dominance, since it is important for vector control. I then examine the impact of a world-first *Wolbachia* mosquito release in Townsville, Australia on the transmission of DENV.

1.2 Research Aims

The first aim of this thesis is to investigate the impact of the trade-off between CI and LWI features when introducing a single *Wolbachia* strain to control arboviral infections in particular DENV via mathematical modelling. The second aim describes the extension of the single *Wolbachia* strain model to capture the introduction of two different *Wolbachia* strains with contrasting LWI and CI induction behaviours and investigate the ecological dynamics of the mosquito populations. The last aim of this thesis investigates the impact of the *Wolbachia* rollout in 2014 in Townsville on DENV.

1.3 Research Objectives

The main objective of this thesis is to develop useful general mathematical models that can account for any single or multi-strain *Wolbachia* introductions into the wild-type mosquito population. Furthermore, mathematical models involving the rate of importation of dengue will be used to fit the Townsville dengue dataset and estimate parameters driving infection. Prior to achieving these objectives, both narrative (biological) and systematic (mathematical) reviews of published studies on arboviral (dengue) infections and vector controls will be carried out to reveal the literature gaps motivating the objectives. The specific objectives of this thesis that I intend to achieve are as follows:

1. To critically appraise published literature on the available vector control methods and specifically highlight the use of the *Wolbachia*-based control method as a natural control measure for eradicating arboviral diseases.

2. To examine the role of mathematical models by systematically reviewing the present understanding of the effectiveness of vector control approaches via dengue transmission models.

3. To investigate the dynamics of the *Wolbachia*-features that may be of advantage in

fueling establishment.

4. To explore the dynamics of different *Wolbachia* strains and determine if a combined release of different strains could be better than releasing a single strain.

5. To study the role of *Wolbachia* intervention in Townsville and investigate its effects on the transmission of DENV via model validation using the Townsville dengue dataset.

The research objectives are elaborated below:

Objective 1

In this section, I narratively review published literature on the available vector control methods and specifically highlight the use of the *Wolbachia*-based control method as a natural control measure for eradicating arboviral diseases. This includes both theoretical investigations of the potential efficacy of *Wolbachia*-based strategies and field trials that provide concrete demonstration. Further, I provide important background information on the types, scale, severity, and treatment of *Aedes*-borne arboviral infections, focusing on vector control methods and specifically highlighting those amenable to *Wolbachia*-type control. The results, which reveal the literature gaps such as the challenge of degrading potency of the *Wolbachia*-based method due to unfavourable weather conditions and other limiting factors, will be instrumental in developing mathematical models to examine the impact of this strategy.

Objective 2

Here, I critically review the role several mathematical models played in vector control methods of the transmission of dengue (the most widespread arboviral disease) to identify literature modelling gaps in the last decade via the PRISMA guidelines. The review, based on the selected published articles provides detailed understanding of the three methods of vector controls and their effectiveness in averting dengue transmission. However, several factors may modify their impact as the magnitude of their effectiveness has some dependencies. Of these

controls, chemical methods in the long run may increase mosquitoes' resistance to chemicides thereby decreasing control efficacy. The biological methods, which may be self-sustaining and very effective, could be hampered by seasonality or heatwaves (resulting in, e.g., loss of *Wolbachia* infection). The environmental methods which could be more effective than the chemical methods are under-investigated.

Objective 3

In this study, I develop a one-strain *Wolbachia* transmission model to describe the competitive dynamics between *Wolbachia*-infected mosquitoes and wild-type mosquitoes. This model is capable of replicating all of the single *Wolbachia* strain features. To account for the *Wolbachia* features that may be responsible to fuel *Wolbachia* infection establishment in wild-type mosquitoes, I present the novel *w*Au-*Wolbachia* strain which possesses several favourable traits such as enhanced viral blockage and maintenance at higher temperature, but not cyctoplasmic incompatibility (CI) – when a *Wolbachia*-infected male mosquito mates with an uninfected female mosquito, producing no viable offspring. I incorporate these *w*Au-*Wolbachia* traits to determine if the *Wolbachia* retention advantages at high temperature outweigh the lack of CI. I also consider the imperfect maternal transmission (IMT) feature of the *Wolbachia* strain in the model.

Further, I analyse the system of ordinary differential equations (ODEs) to determine disease-free and endemic equilibria. I compute the basic and invasive reproductive numbers with respect to uninfected and *Wolbachia*-infected mosquitoes using the next-generation matrix method. Afterwards, I establish the local stabilities for the equilibrium points and performed a sensitivity analysis to investigate the model robustness due to uncertainties associated with the parameter value estimates. As a result, the potential of the *w*Au strain as a viable strategy to control arboviral infections is established. The results of this work show that enhanced maintenance of *Wolbachia* infection at higher temperatures can overcome the lack of CI induction to support *w*Au-*Wolbachia* infected mosquito invasion. This study will

support future arboviral control programs, that rely on the introduction of new *Wolbachia* variants.

Objective 4

In this section, I model general multi-strain *Wolbachia* dynamics by considering two *Wolbachia* strains: an invading population infected with a particular *Wolbachia* strain; and a second invading population infected with a distinct *Wolbachia* strain from that of the first invader. This model could be used to replicate any two *Wolbachia* strain characteristics. I explore how the range of possible characteristics of each *Wolbachia* strain impacts mosquito prevalence. Further, I analyse the differential system governing the mosquito populations and the *Wolbachia* infection dynamics by computing the full set of basic and invasive reproduction numbers using the next generation matrix method. Further, I use this set to establish stability of identified equilibria. The results show that releasing mosquitoes with two different strains of *Wolbachia* did not increase their prevalence, compared with a single-strain *Wolbachia*-infected mosquito introduction, provided that one of the strains had a higher invasive reproduction ratio.

Objective 5

In this component of the thesis, I describe the analysis of the pre and post-*Wolbachia* mosquito rollouts in Townsville and account for the impact on dengue transmission. In addition, I model dengue infection dynamics together with human and mosquito populations in the presence of *Wolbachia*, accounting for the seasonal fluctuation. Further I estimate the transmission rates to account for the reduction in dengue cases after *Wolbachia* introduction. The results show that transmission from *Wolbachia* mosquitoes to susceptible humans is a quarter of that from non-*Wolbachia* infected mosquitoes. With the projected transmission rates, *Wolbachia* was able to cut the burden of dengue by 80–90%.

1.4 Thesis structure

In this thesis, I address the research objectives through published articles included as thesis chapters. As at the time of submitting this thesis, three papers have been published, one has been accepted and one is under review. These published articles were prepared and written during my PhD candidature. A brief summary of each chapter is described below.

The first major part (Chapter 2) of this thesis comprises a narrative biological review of articles describing arboviral infections and controls, in particular, *Wolbachia*-based strategies. The next chapter (Chapter 3) describes the systematic reviews of literature examining the role of mathematical models in controlling the most wide-spread arbovirus, i.e. DENV. The subsequent three chapters (Chapter 4 to 6) discuss the original modelling contribution of this thesis. Finally, the last chapter (Chapter 7) describes the general discussion and inferred conclusions that is linked to future direction of research.

Chapter 2

Literature Review

Chapter publication:

Ogunlade, S. T.[1,2], Meehan, M. T.[1], Adekunle, A. I. [1], Rojas, D. P.[3], Adegboye, O. A., McBryde, E. S. [1] (2021). A review: *Aedes*-Borne Arboviral Infections, Controls and *Wolbachia*-Bssed Strategies. *Vaccines*, 9(1), 32.

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Summary

This chapter presents the critical appraisal of published literatures encompassing the description of arboviruses (e.g., dengue, Zika, chikungunya and yellow-fever viruses) and their methods of control. This review described a narrative review of articles by considering the biological perpective of *Aedes*-borne arboviruses and their controls, in particular, vector controls. The study discusses the *Aedes*-borne arboviruses and their control strategies in Section 2.1, and targetted the vector control methods, which is in fact, the primary method of arboviral control in Section 2.2. Further, one of the methods of vector control, in particular, *Wolbachia*-based control described in Section 2.3, shows a promising control strategy for eradicating *Aedes*-borne arboviruses. This can either be through the artificial introduction of *Wolbachia*, a naturally present bacterium that impedes viral growth in mosquitoes into heterologous *Aedes aegypti* mosquito vectors (vectors that are not natural hosts of *Wolbachia*) thereby limiting arboviral transmission or via *Aedes albopictus* mosquitoes, which naturally harbour *Wolbachia* infection. These strategies are potentially undermined by the tendency of mosquitoes to lose *Wolbachia* infection in unfavourable weather conditions (e.g., high temperature) and the inhibitory competitive dynamics among co-circulating *Wolbachia* strains (Section 2.4). Previous studies on mathematical models of *Wolbachia* were discussed in Section 2.5. Therefore, articles retrieved on the control strategies for arboviral transmissions via arthropod vectors were used to identify literature gaps that will be instrumental in developing models to estimate the impact of these control strategies and, in essence, the use of different *Wolbachia* strains and features (Section 2.6).

Keywords: Arboviruses, *Aedes* mosquitoes, vector control, *Wolbachia*, review.

2.1 Introduction

2.1.1 *Aedes*-Borne Arboviruses

Aedes-transmitted arboviruses can be life-threatening when contracted by human hosts depending on the infection severity [60, 61, 62, 63]. The primary vector responsible for the transmission of these arboviruses such as DENV, ZIKV, YFV, and CHIKV is the female *Aedes aegypti* (Yellowfever) mosquito, while female *Aedes albopictus* (Asian Tiger) mosquitoes also contribute to transmission [5, 6]. DENV, in particular, is the most widespread *Flavivirus*, and also the most recognisable and deadly among the known *Aedes*-borne viruses [14] (Figure 1.1). Dengue viral infection can lead to health complications such as dengue haemorrhagic fever with shock syndrome and even cause circulatory failure and death [64]. The mean estimated intrinsic incubation period of dengue virus in humans is 5.9 days, while the estimated extrinsic (temperature-dependent) incubation period of the virus in the mosquito vectors is 15 and 6.5 days at 25 °C and 30 °C, respectively [65] (Table 2.1). In recent decades, the incidence of dengue viral infection has continued to increase. Modelling studies recently estimated that approximately 390 million dengue infections occur per year, with 96 million of these exhibiting clinical symptoms [16, 17], and that the global population at risk of dengue is 3.9 billion [66].

Similar to DENV, ZIKV is transmitted through the infectious bite of *Aedes* mosquitoes. It was first isolated from a rhesus monkey in 1947 in an Ugandan forest: Zika [67]. Also, the vectors responsible for ZIKV transmission are *Ae. aegypti* and *Ae. albopictus* [68, 69]. Although Zika viral infection is mainly transmitted via mosquito bites, instances of human-to-human and perinatal transmission have been observed [70, 71, 72, 73]. There is evidence that ZIKV infection is associated with microcephaly, a congenital condition causing abnormal smallness of the head due to improper development of a baby's brain during pregnancy or after childbirth [74]. Other symptoms of ZIKV are shown in Table 2.1.

Unlike DENV, a *Flavivirus*, chikungunya (meaning "to become contorted" in the Ki-

makonde language) virus: CHIKV is an Alphavirus that causes incapacitating joint pain and is transmitted by *Aedes* mosquitoes [75]. CHIKV transmission has also been reported through blood exposure [76]; infection of the human cornea [77]; and maternal transmissions—the latter of which can lead to miscarriage [78].

Furthermore, YFV is a member of the *Flaviviridae* family and is usually transmitted by *Aedes* mosquitoes [79]. The YFV infection can be severe, causing a high proportion of deaths in endemic populations [79]. YFV is a single-stranded RNA virus with a single serotype whose antigens are conserved [80]. The single serotypic nature of YFV allows the developed vaccine to protect the infected host against all the virus strains [81]. Human hosts are highly susceptible to contracting yellow fever infections as well as some non-human primates and rodents [82, 83, 84]. Recently, some studies have suggested that coinfection of arboviruses (Table 2.1) can not only occur, but can also generate cross-protective immunity where initial exposure to the first viral infection activates the immune response and confers acquired immunity against the next viral infection, and can also reduce the risk of subsequent infections for some arboviruses, in particular, dengue [85]. However, not all arboviral antibody responses are cross-protective as the interaction between some arboviruses and antiviral antibodies may result in a phenomenon known as antibody-dependent enhancement (ADE) of infection, which allows viruses to enter into the host cell [86]. This effect modulates the immune response of the host, facilitates viral production and may increase the severity of the viral disease [87].

Table 2.1: *Aedes*-borne arboviral incubation periods and the asymptomatic fraction of infections

***Aedes*-borne Arboviruses**	**Virus Type**	**Transmitted By**	**Symptoms**	**Supportive Treatment**	**Coinfection with Other Arboviruses**	**Intrinsic Incubation Period (Days)**	**Extrinsic Incubation Period (Days)**	**Asymptomatic Proportion in Infected Humans (%)**
Dengue	*Flavivirus*[14]	*A. aegypti* *A. albopictus* [5, 6]	Sudden high grade fever, Headache, Nausea, Arthralgia, Eye and Muscle pain [88]	DENV vaccine and drug administration [89]	Yes (e.g. DENV and ZIKV) [90]	Median: 5.3 [91] Mean: 5.9 [65]	Mean: 15 (at 25^0C) 6.5 (at 30^0C) [65]	75 [92]
Zika	*Flavivirus*[93]	*A. aegypti* *A. albopictus* Human (via blood transfusion) [68, 69, 74]	Fever, Conjuctivitis, Muscle pain, Headache, Joint pain, Rash and Microcephaly [94, 95]	Fluid intake and drug administration (such as acetaminophen) [96]	Yes (e.g. ZIKV and CHIKV) [97]	Median: 6.8 [98] 6.2 [99]	Median: 5.1 (at 30^0C) 9.6 (at 26^0C) 24.2 (at 21^0C) [100]	80 [101]
Chikungunya	*Alphavirus*[102]	*A. aegypti* *A. albopictus* [103]	High fever, Joint pain, Myalgia, Arthritis, Conjuctivitis, and Dermatologic manifestations [104, 105]	Plenty of rest, Fluid intake and Acetaminophen) [75, 103]	Yes (e.g. CHIKV and DENV) [106]	Median: 3.0 [91]	Median: 2.0 [107]	Approx. 18 to 28 [108]
Yellow Fever	*Flavivirus*[79]	*A. aegypti* *A. albopictus* [109]	Headache, Nausea, Vomitting, Fever, Dizziness and Joint pain [110, 111]	YFV vaccine and Ribavirin [112, 113]	Yes (e.g. YFV and CHIKV) [114]	Median: 4.3 [115] 4.4 [91]	Median: 10 (at 25^0C) [115]	55 [116]

2.1.2 Control Strategies for *Aedes*-Borne Viral Infections

Aedes-borne viral infection control has proven effective in reducing disease burden [117]. These strategies include taking preventive measures such as ensuring environmental cleanliness and adequate drainage, avoiding contact with vectors, vaccinating susceptible individuals and using genetic control of mosquitoes and paratransgenesis [64, 118]. These measures can be grouped into three types of control measures depending on the stage of the transmission cycle that they target: (i) the human host; (ii) human-vector interactions; and (iii) vector control categories [2] (Figure 2.1).

Firstly, human host control strategies typically focus on reducing the susceptibility of humans to contracting *Aedes*-borne viral infections. This can be achieved through the use of vaccines and chemoprophylaxis (drug use) [24, 25, 26, 119]. These control measures are used to inhibit, suppress or clear the virus, preventing replication in the human host [120]. Some vaccines with high efficacy have been developed, including the 17D yellow fever vaccine [24] and the Japanese encephalitis vaccine [25]. Notably, the tetravalent dengue vaccine has high protective efficacy rates of 56.5% and 60.8% against virologically-confirmed dengue but lower for DENV-2 [26]. A modelling study explored the third-year results of phase III trials of Dengvaxia and suggested that the vaccine generated protection against dengue within partially-immune persons but also increased hospitalizations among vaccine-sensitized individuals infected with dengue [89]. However, this vaccine is still controversial as it has been linked to significant side effects in the Philippines for instance [121]. Research on the development of vaccines for other *Aedes*-borne viral infections such as ZIKV [27], Ross-River virus (RRV) [29] and CHIKV [30] is still in progress.

Secondly, human-vector preventive measures prevent contact between susceptible human hosts and infected mosquitoes (and vice-versa), particularly mosquito bites. Examples include insecticide-treated bed nets, repellents [122] and sensitization of people in areas with high transmission rates to take preventive measures such as ensuring a clean environment and a good drainage system to avoid water stagnancy during rainfall [123]. Other preventive

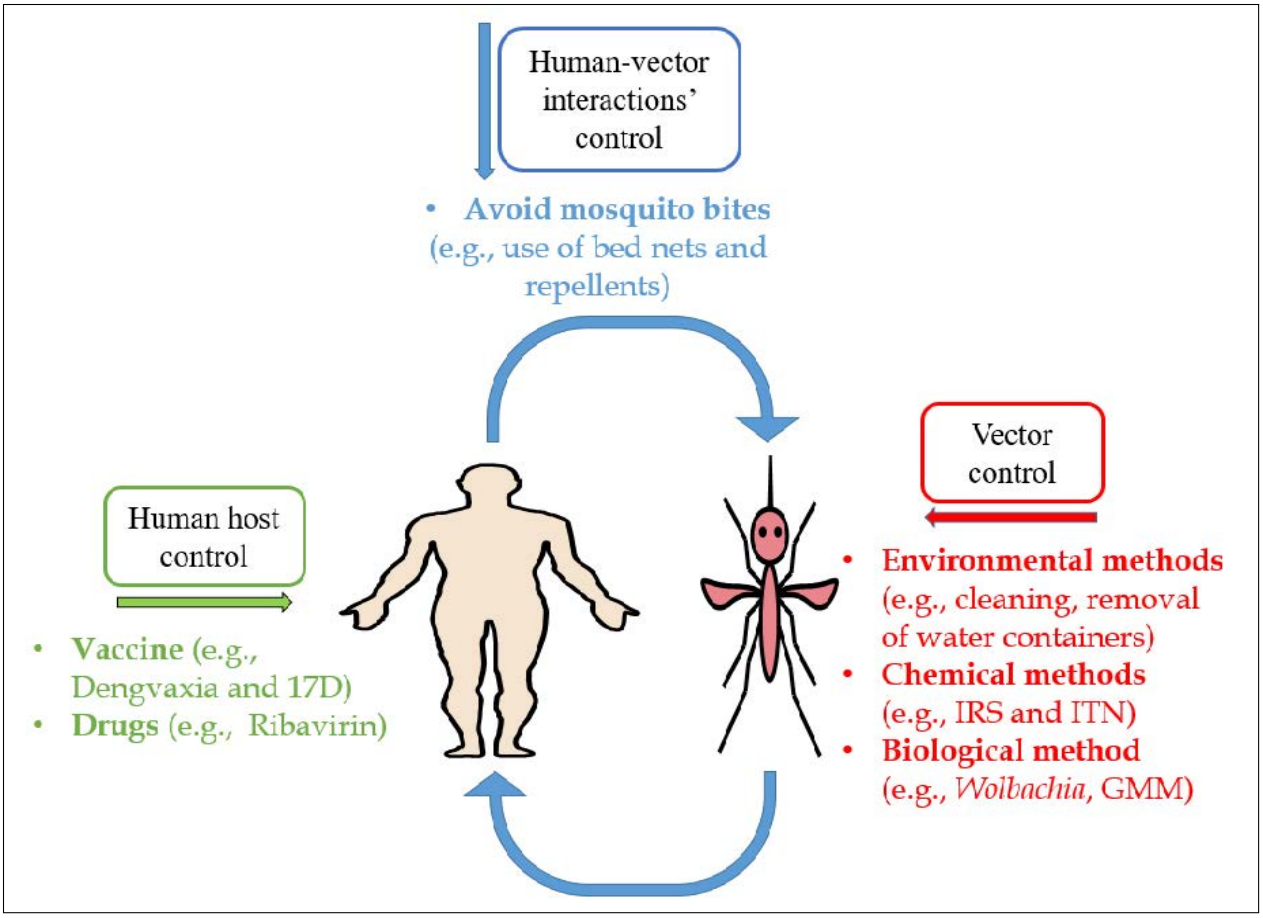

Figure 2.1: Diagram showing the summary of methods and examples (in brackets) that could be used to control *Aedes*-borne arboviral transmission: The green text refers to the human-host strategies, which could be used to prevent arboviral transmission via vaccines and drugs. The blue text refers to the human-vector interactions' strategies that could be used for arboviral transmission control via humans avoiding bites from infectious mosquitoes. The red text refers to the vector control strategies that include chemical, environmental or biological methods to control arboviral transmission (IRS—indoor residual spraying; ITN—insecticide-treated bed nets; GMM—genetically modified mosquitoes).

measures include the use of metofluthrin in the home as this has been shown to produce a rapid decrease in the observed biting frequency and increased kills among mosquitoes trapped inside the house [124]. Some studies in Australia and Vietnam have shown a significant reduction in mosquito population densities in homes treated with metofluthrin compared with those that were untreated [125].

Lastly, the vector control approach focuses on reducing the abundance, and inhibiting the transmission capacities, of virus-carrying mosquitoes [2]. Vector control can be challenging

in endemic areas due to inadequate and haphazard implementation. Nevertheless, vector control techniques remain the main control strategies for suppressing dengue transmission, but often require a great deal of both financial and labour investment to achieve sustainability and sometimes do pose an environmental contamination risk, such as the use of chemical larvicides [31, 126].

2.2 Vector Control Methods for *Aedes*-Borne Viral Infections

Vector control approaches are classified into three categories: environmental, chemical, and biological control methods [2]. Environmental methods include: cleaning of the environment, particularly, the mosquito vector breeding sites; covering or emptying water containers; and implementing strategic waste management schemes [31]. Chemical and biological control methods involve the use of insecticides such as Temephos and pyrethroids or orga nophosphates used in outdoor fogging [127]. Biological methods include the use of biological agents such as copepods, larvivorous fish, genetically modified mosquitoes and intracellular endosymbionts, e.g., *Wolbachia*, for control purposes [127, 128, 129]. Some of the environmental and chemical methods of vector control are widely practised while some biological methods are presently largely experimental.

2.2.1 Established Vector Control Methods

Environmental control methods for host vectors include common practices such as emptying, covering, or destroying water-filled containers, providing piped water, clearing and cleaning of the vectors' breeding sites, and setting up strategies to ensure waste management implementation [31].

The chemical method generally involves use of a chemical mixture, solution or material to directly expel or, in most cases, kill arthropods such as mosquito vectors [130]. This

method may be grouped into the use of: (a) durable treated materials such as door curtains and insecticide-treated bed nets (ITN); (b) insecticides for residual spraying, which include peri-domestic space treatments and indoor residual spraying (IRS) [131, 132]; and (c) larval breeding control that includes the application of chemical larvicides such as Temephos to destroy breeding habitats [118, 127]. Insecticides such as organophosphates and pyrethroids are most commonly used for the chemical control of *Aedes* mosqutoes [127]. However, there are limitations to chemical control methods. These limitations include environmental pollution, contamination, and toxicity [127], which may cause irritation to humans and endanger aquatic animal species.

Presently, chemical control methods are the most widely practised form of vector control, in particular the use of pyrethroids for outdoor fogging [133]. The direct killing of vectors using insecticides has been used for a long time and some studies have reported increased resistance to insecticides in mosquitoes, especially *Aedes aegypti* [131, 132]. One of these studies investigated the insecticide resistance in *Aedes aegypti* mosquitoes in Ceara, Brazil and reported that these mosquitoes are subjected to selective pressure by the larvicide used, Temephos, as they reduce its effectiveness in the field. This resistance may be difficult to reverse as it may take more than seven years [131].

2.2.2 Experimental Vector Control Methods

Experimental vector control methods include the introduction of biological agents such as larvivorous fish [134], copepods (a group of small crustaceans) [135] or Bacillus thuringiensis [136], typically for larvae control. A study investigating the community effectiveness and efficacy of the use of larvivorous fish for dengue vector control reported that although the use of larvivorous fish could be effective in reducing the immature vector stages in small settings such as containers, these results could be minimal as it would require large coverage of multiple production of larvivorous fish containers to achieve any impact in an area of dengue endemicity [134]. Another similar study systematically reviewed the community

effectiveness of copepods for dengue vector control in Vietnam [137]. The authors concluded that although there was an effective control of dengue transmission, the impact is difficult to determine as other control measures such as increased educational campaigns were combined with copepods [137]. A controlled study investigated the effectiveness of using *Bacillus thuringiensis israelensis* (BTI) spray to control the population of *Aedes* mosquitoes [136]. They showed that, although BTI treatment kills larvae, and thus suppresses adult mosquitoes indirectly, this effect is not sustainable over time [136]. Therefore, it can only be used together with other control measures as a supplement.

Other biological vector controls that are largely experimental at present may include both laboratory and field investigations. These investigations include the introduction of sterile insect techniques (SITs), genetically modified mosquitoes (GMM) and control agents that are incapable of transmitting viral pathogens [138], such as the *Wolbachia*-based strategy for disease control [36, 139].

SITs are a method of insect control involving the rearing of large numbers of sterilized male mosquitoes that are released to mate with wild-type female mosquitoes resulting in the reduction of the reproductive advantage of the females [140]. This may lead to vector population suppression if sufficient releases of sterile male mosquitoes are rolled out. Sterilization can be achieved using radiation in dedicated facilities [141]. There are some drawbacks to SITs, which include difficulties in isolating male mosquitoes for sterilization and transportation problems, and overdose of radiation as this may also affect the physical strength of the sterilized mosquitoes [142, 143]. The release of insects with dominant lethality (RIDL) which involves introducing a lethal trait into the female mosquitoes has emerged as a technique to overcome SITs difficulties [142, 144]. A resulting example of the RIDL technique is the production of female flightless *Aedes* mosquitoes [145]. These flightless mosquitoes are created via RIDL using an indirect flight muscle gene Act4 of the *Aedes aegypti* mosquito [145]. When this gene is switched on in developing female mosquitoes, it incapacitates the flight muscles leading to the death of the muscle cells and rendering the mosquitoes flightless [146].

This physical disability makes it difficult to fly, to find blood from human host, find a mate, and the mosquito easily becomes a prey for insectivores [146].

Studies have shown that genetic engineering can be used to modify the genetic features of mosquitoes to: resist viral infection; vaccinate humans against infection; and produce infertility in males [147]. However, studies describing ethical issues surrounding field trials of viral-resistant GMM deduced that for this technique to be rolled out, the disease of interest must pose a significant threat to public health in an area of isolation, as the greatest concern was for the protection of other community members who may be impacted but not enrolled in the study [148]. Additionally, the use of drives has interestingly increased the zeal for genetic control of mosquito vectors [149, 150]. A study tested the first gene drives developed in *Aedes aegypti* mosquitoes. The authors confirmed that these drives, which are split so as to allow for drive safety performed excellently at very high frequency and also predicts that the split drives can be suitable for field trials to control local disease spread once the effectors are linked [149].

Another vector control technique that requires the introduction of a biological agent such as bacteria to control arthropod vectors is *Wolbachia*-based control [41, 151]. Realistically, *Wolbachia*-based control is self-sustaining and the bacterium *Wolbachia* can be transmitted via transinfection to other insect species and is endosymbiotic in nature [152]. Although this strategy may require transinfection to successfully infect host vectors such as *Aedes* mosquitoes, it is not considered to be genetically modified because the *Wolbachia* bacterium is a natural endosymbiont that exists in most insect species [2].

2.3 *Wolbachia* Control Strategy

Wolbachia is an intracellular bacterium belonging to the *Anaplasmataceae* family [2]. This endosymbiotic bacterium naturally infects a wide range of invertebrate organisms such as arthropods and nematodes [152]. *Wolbachia* bacteria are found within the cytoplasm

of the cells of their hosts, and they naturally exist in more than 50% of all insect species [153, 154]. The *Wolbachia* endosymbiont is maternally (vertically) transmitted — the female *Wolbachia*-carrying arthropod passes the bacteria through the eggs to their offspring [40]. However, paternal (horizontal) transmission, which is very rare, has been observed in *Drosophila simulans* [155]. Paternal transmission can also occur under rare ecological circumstances such as the transmission of *Wolbachia* from infected to uninfected larvae of wasps sharing the same source of food [156]. While *Wolbachia* infection is not naturally present in all arbovirus-transmitting vectors such as *Aedes aegypti*, it can be introduced through stable transinfections of *Wolbachia* strains via microinjection [157]. The *Wolbachia* bacteria can be extracted from native hosts such as *Aedes albopictus* [158] and *Drosophila melanogaster* [40, 159] and then injected into heterologous arthropods as with *Aedes aegypti*.

Most *Wolbachia* strains have derived their names from the host in which they were first discovered (Table 2). The first *Wolbachia* strain to be discovered was *w*Pip (*Wolbachia* pipientis) found in *Culex pipiens* mosquitoes [160]. Other strains include: *w*Mel found in *Drosophila melanogaster* (Fruit fly), *w*AlbA and *w*AlbB found in *Aedes albopictus* (Asian Tiger mosquito), and *w*Au found in *Drosophila simulans* [161]. The features of these *Wolbachia* strains may vary in their mosquito hosts due to high fitness cost and environmental factors such as high temperature (Table 2.2) [162, 163, 164].

Table 2.2: Description of different *Wolbachia* strains, the arthropod (origin) in which they were found and the presence of the means of control of arboviral transmissions. CI – cytoplasmic incompatibility (Yes or No); MT – maternal transmission (Yes or No); WIR – *Wolbachia* infection retention (None, Low, Partial, High); VB – viral blockage (None, Low, Partial, High); and F – Fitness (None, Low, Partial, High). None – 0, Low – $< 20\%$, medium – 20% - 90%, high – $> 90\%$.

***Wolbachia* strain**	**Origin**	**Means of Control of Arboviral Transmission (CI, MT, WIR, VB, F)**	**References**
*w*Au	*Drosophila simulans / Fruit fly*	(No, Yes, High, High, Partial)	[162, 46]
*w*Mel	*Drosophila melanogaster / Fruit fly*	(Yes, Yes, Low, Partial, Partial)	[36, 40, 165]
*w*AlbA	*Aedes albopictus / Asian Tiger mosquito*	(Yes, Yes, Medium, Partial, High)	[161, 162]
*w*AlbB	*Aedes albopictus / Asian Tiger mosquito*	(Yes, Yes, Medium, High, Partial)	[151, 162]
*w*MelPop	*Drosophila melanogaster / Fruit fly*	(Yes, Yes, Low, High, High)	[162, 166, 167]
*w*Ri	*Culex pipiens / Mosquito*	(Yes, Yes, –, Low, Low)	[151, 168, 169]
*w*Pip	*Drosophila simulans (Riverside) / Fly*	(Yes, Yes, –, Partial, Low)	[151, 161]
*w*Inn	*Drosophila innubila / Vinegar fly*	(Yes [Only males], Yes, –, Partial, Low)	[151, 170]

The potential benefits of *Wolbachia*-based control techniques may be twofold: *Wolbachia* infection can disrupt arboviral replication and transmission; and the bacteria can also suppress vector populations [2, 41, 171].

2.3.1 *Wolbachia*-Based Disruption of Arboviral Transmission

The transinfection of *Aedes aegypti* with the endosymbiotic bacterium, *Wolbachia* could disrupt or inhibit arboviral transmission through four mechanisms [2]. The first is the competition for intracellular resource. Once present, *Wolbachia* bacteria can induce autophagy (cleaning or eating up damaged cells) in the arthropod's cells [172]. To be able to survive, *Wolbachia* typically hijacks and regulates the autophagy system both within and outside the cell [173]. Similarly, arboviruses such as DENV and CHIKV rely on the autophagy system to replicate [174]. However, *Wolbachia* has the ability to manipulate the autophagy system set-up and interfere with some arboviral replications. This in turn, reduces the nutritional

resources, such as cholesterol and iron, essential for viral growth [175]. Like *Wolbachia*, which is dependent on the arthropod cell cholesterol to multiply, *Aedes*-borne viruses such as DENV and CHIKV have been observed to manipulate the arthropod vector's cell iron reserves [175]. In each event, both *Wolbachia* bacteria and arboviruses continually compete for limited host intracellular nutrients, resources, and space [176].

The second arboviral inhibitory mechanism is immune-priming. Immune-priming—also known as immune system preactivation—occurs when *Wolbachia* infection is transmitted into heterologous arthropods (i.e., non-native hosts of *Wolbachia* such as *Aedes aegypti*) via transinfection [45]. This mechanism preactivates the arthropod host immune system, which allows it to defend itself against arboviral pathogens [45]. According to a recent study, immune-priming can be induced by signalling pathways such as Immune deficiency (IMD), Toll and Janus kinase-signal transducer and activator of transcription (JAK-STAT) [2]. One study investigated the response of innate immune-priming in *Aedes aegypti* mosquitoes in the presence of *Wolbachia*-dengue interference [177]. It was shown that *Wolbachia* induced some immune genes involved in melanisation, Toll pathways genes and antimicrobial proteins such as peptides. The JAK-STAT pathway, which regulates the antiviral immunity and growth processes in arthropods has been shown to prevent DENV infection in *Aedes aegypti* mosquitoes [178]. An experimental study recently showed that immune-priming during the aquatic (larval) stage of *Aedes aegypti* mosquitoes with dormant DENV induced protection against the virus in the adult *Aedes* mosquitoes [179].

The third disruptive mechanism induces phenoloxidase (PO – an enzyme that increases the rate of phenol oxidation) cascade [180, 181]. The importance of the PO cascade is that it produces melanin that accumulates around invading pathogens and at wound sites as this is known to have antipathogenic characteristics [181]. This cascade plays a critical role in the mosquito's innate immune response to arboviruses. Studies have shown that *Wolbachia* bacteria increase melanization via the phenoloxidase activities in both homologous and heterologous arthropod vectors [180, 181]. Therefore, a *Wolbachia*-induced phenoloxidase

cascade may likely serve as protection against several arboviral infections [154].

The fourth mechanism is the miRNA-dependent immune pathway [182]. This pathway is an important component that modulates the arthropod hosts' genes to control arboviral infection in many mosquito vectors [183]. Several miRNA-dependent immune responses and various metabolic processes needed for arboviral growth and replication are regulated in the presence of arboviral infections [184, 185].

2.3.2 *Wolbachia*-Based Vector Population Suppression

The transinfection of *Wolbachia* into arthropod vectors such as *Aedes* mosquitoes may decrease their fitness, which in turn, leads to a reduction in the mosquito population [171]. One study previously reported that the introduction of a particular *Wolbachia* strain (*w*MelPop) into a mosquito could halve its life-span [186]. Another study conducted a survival experiment for three different *Wolbachia*-infected mosquito populations (*w*Mel, *w*AlbB, *w*MelPop) and wild-type mosquitoes stratified by sex (male and female). They showed that for the females, all *Wolbachia*-infected mosquitoes had significantly higher mortality rates compared with their wild-type counterparts. Similar results were observed for males, except for *w*Mel-infected mosquitoes whose lifespans did not differ significantly from the wild-type [171].

In practice, infecting *Aedes* mosquitoes with *Wolbachia* may also alter their reproductive lifecycle — potentially conferring *Wolbachia*-infected variants a competitive advantage over wild-type populations. One such mechanism is cytoplasmic incompatibility (CI) [151, 187, 188]. CI is a mechanism that induces incompatibility between the eggs and sperm of arthropods, in particular mosquitoes, enabling them to produce unviable offspring (no offspring) [189, 190]. There are two types of CI: unidirectional and bidirectional CI. The former occurs when a *Wolbachia* infected male is crossed (mates) with an uninfected female mosquito (usually *Wolbachia* uninfected) and the resulting embryos are unable to mature into viable offspring [191, 192]. However, the latter (bi-directional CI) describes the above inhibition mechanism but happening between crosses with infected mosquitoes with differ-

ent strains of *Wolbachia* [193, 194, 195]. For example, the mating combination of a male and female mosquitoes infected with different *Wolbachia* strains are incompatible, thereby producing no viable offspring.

In general, the CI effect is not always dominant in all *Wolbachia*-infected arthropods as some *Wolbachia* strains do not exhibit this effect in some insect vectors. The CI effect may be fully present or absent depending on the *Wolbachia* strain and the arthropod host. For instance, in *Aedes* mosquitoes, studies have shown that the *Wolbachia* strains (*w*AlbA, *w*AlbB, *w*Mel) exhibit complete CI while *w*Au does not [46, 162]. Several studies, in the case of mosquitoes, have shown that CI fuels the persistence of *Wolbachia*-infected mosquito populations and also confers a reproductive advantage on *Wolbachia*-infected female mosquitoes over the uninfected ones [41, 47, 49, 151, 196]. This persistence phenomenon in the presence of CI occurs because all mating patterns except crosses between uninfected male and female mosquito lines, produce *Wolbachia*-infected offspring [151, 162].

Other features of *Wolbachia* infection that may suppress the vector population, include imperfect maternal transmission (IMT) [40, 188, 197], loss of *Wolbachia* infection (LWI) due to unbearable conditions (such as high temperature) [196], and superinfection of two strains of *Wolbachia* (which can occur in *Aedes albopictus* hosts) [198]. IMT rates may vary for different *Wolbachia* strains depending on some abiotic conditions such as altitude (higher IMT at high altitude compared to lower altitude) [199] and environmental factors (very low IMT under laboratory conditions but high IMT in the field) [200]. However, a particularly novel strain of *Wolbachia*: *w*Au, does not possess the CI feature [162]. Despite the non-induction of CI, *w*Au has been shown to produce high viral blockage and maintain *Wolbachia* infection at higher temperatures while other strains do not [162].

The effects created by the transinfection of *Wolbachia* in arthropods, which, in particular, resulted in viral blockage [46, 162] and population reduction in arthropod vectors [36], make it a promising control strategy for the reduction and elimination of *Aedes*-borne infections [2].

2.4 *Wolbachia*-Based Field and Experimental Studies

Recent field studies have reported that *Wolbachia* can be used to suppress vector-borne disease transmission [44, 151, 154, 40, 159, 162, 201, 202, 203]. These studies showed that suppression can be achieved by introducing a *Wolbachia* strain into wild mosquito populations in the hopes of replacing the vector transmitting agent *Aedes aegypti* with one that is incapable of transmission [44, 40, 159, 204]. The use of *Wolbachia* strains to control *Aedes*-borne viral infections such as dengue is categorized into three strategies: (a) introduction of *Wolbachia*-infected male mosquitos together with uninfected female mosquitoes causing CI [205]; (b) invasion of a strain of *Wolbachia* generating fitness reduction in an area of varying seasonality [186, 206], e.g., by halving the life-span of mosquitoes after the introduction of a *Wolbachia* strain; and (c) invasion of a strain of *Wolbachia* that inhibits transmission by reducing the ability of the virus-carrying vectors to transmit infections [40, 159, 203, 204]. These control strategies, which are not mutually exclusive, have reportedly been effective in Australia, Indonesia, Brazil, and Vietnam, leading policy makers, including The WHO, to encourage the use of these strategies in controlling the spread of *Aedes*-borne viral infections [151, 207, 208].

Previously, a study investigated the introduction of *w*AlbB *Wolbachia* strain into transgenic *Aedes aegypti* mosquitoes [209]. The study showed that the *w*AlbB infection in mosquitoes activates both IMD and Toll pathways and infection is maintained through maternal transmission (MT) [209]. Another study also showed that *Wolbachia* boosts immune responses and increase mosquitoes' resistance to viruses, which allows the immune system to actively fight against the viruses in the arthropod host [210]. In a study series of blood-feeding mosquito trials in response to the human host, it was shown that as mosquitoes infected with *w*MelPop-*Wolbachia* strain age, they feed less compared to their uninfected counterparts as a result of the observed bent proboscis. This defect may cause tissue damage in mosquitoes as they age leading to a decreased bite rate [211]. One study [40] described the successful transinfection of *Aedes aegypti* mosquitoes with a *w*Mel-*Wolbachia* strain. It

showed that this strain induces CI and high MT and also provides viral blockage of dengue serotype 2 infection transmission in *Aedes aegypti* mosquitoes.

Unlike other *Wolbachia* strains, the novel *w*Au strain displays some different characteristics in *Aedes* mosquitoes [162, 46]. Some of the features include high retainment of *w*Au-*Wolbachia* infection at high temperatures and IMT [162]. In particular, this *Wolbachia* strain has been shown to be highly efficient in blocking arboviral transmission in *Aedes aegypti* [162] and *Aedes albopictus* [46] mosquitoes. However, the *w*Au strain does not induce CI [162, 212] but may allow superinfection as bidirectional CI is ineffective in the presence of paternal transmission which itself is rare [155, 162, 46].

A study compared different *Wolbachia* strain features, such as high viral blockage and infection retention under high temperature, in transinfected *Aedes aegypti* mosquitoes [162]. The authors concluded that the *w*Au-*Wolbachia* strain was highly efficient in blocking DENV and ZIKV transmission and also provided more resilience to varying high temperature than the *w*Mel strain [162]. A similar study conducted in *Aedes albopictus* also showed that the special triple strain line (the generation of wAlbA-*w*AlbB-*w*Au line) created via *w*Au transinfection was completely resistant to arboviral infections like dengue and ZIKV [46]. Therefore, the *w*Au strain is a potentially promising control candidate as it maintains high frequency at high temperature and allows *Wolbachia* co-infection [162, 46]. To support this reasoning, modelling the transmission dynamics between different *Wolbachia* strains possessing different features could contribute to the global reduction and elimination of *Aedes*-borne arboviral diseases.

2.5 Previous Studies on Mathematical Models of *Wolbachia*

In recent years, human and animal invasions of new ecosystems, environmental degradation, global warming, and downward economic trends such as financial recession have given

rise to various types of arboviral diseases. These trends not only exacerbate infectious disease transmission, but also reduce access to efficient therapy due to poorer treatment retention or poorer living circumstances during recession periods [59]. In response to disease emergence, many researchers, epidemiologists in particular, have formulated and analysed mathematical models to understand the dynamics of disease transmission and to identify useful solutions [213, 214, 52, 53].

In general, the introduction of mathematical models to understand the infection dynamics of diseases has long been helpful in the area of disease control [51]. One of the applicable concepts of mathematical models is computing the basic reproduction number (R_0). R_0 is the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual throughout his/her entire infectious lifetime. R_0 can be used as a threshold to determine disease persistence ($R_0 > 1$) or extinction ($R_0 < 1$) [215].

In the context of arboviral control, mathematical models have been formulated to study the population dynamics of *Wolbachia*-infected mosquitoes invading naïve mosquito populations [197, 55, 54, 56, 58, 216, 217, 57, 218]. Some of these models introduced Wolbacbia strain(s) into a mosquito population and classified them into age-structured *Wolbachia*-infected and uninfected mosquito compartments [197, 56, 58, 57]. These models were constructed to accommodate the population progression from offspring maturing to adult mosquitoes and reproducing; and examine the effects of IMT and CI which may determine the status and production of offspring respectively following the adult mosquitoes' mating. A study by Ndii et al. [56] formulated a mathematical model for the *Wolbachia* interaction between the immature stages (aquatic stage), and the adult male and female mosquito populations to determine the persistence of mosquitoes infected with *Wolbachia* when competing with the uninfected ones. To do this, the authors derived the steady state solutions of the model and showed that maternal transmission, death, maturation, and reproductive rates determine the dominance of *Wolbachia*-infected mosquitoes. In a similar study, Xue et al. [57] considered the *Wolbachia*-induced fitness change and the CI effect. They showed that

if the basic reproduction number is less than one, at which the disease typically dies out, an endemic *Wolbachia* infection can still occur if a sufficient number of the mosquitoes are introduced into the population. This is caused by backward bifurcation, where stable disease free and endemic equilibria co-exist [219].

Modelling investigations that estimate the impact of *Wolbachia* introductions in arboviral-endemic countries are surging by the day, as these studies tend to give insights into the appropriate time-dependent strategy in deploying *Wolbachia* as a means of controlling *Aedes*-borne infections [42, 43, 44]. In their study, O'Relly et al. [44] combined multiple modelling methods to first estimate the burden of dengue disease across separate jurisdictions in Indonesia, and then forecast the change in dengue prevalence following a wide-scale *Wolbachia* release program. They predicted a dramatic reduction in dengue transmission after a nationwide release of the *w*Mel *Wolbachia* strain. In particular, they estimated that there were approximately 7.8 million cases of symptomatic dengue in Indonesia in 2015 and attributed most of the gap in previous estimates of disease burden to underreporting (that is, asymptomatic and non-severe clinical cases that were challenging to diagnose in walk-in patients in hospitals or instances where patients did not go for treatment). The nationwide rollout of *Wolbachia* over the long term was estimated to avert 86.2% of these dengue cases [44].

A combined modelling-field study investigating the release of mosquitoes infected with the *w*AlbB strain was carried out in six different areas in Kuala Lumpur, the capital city of Malaysia [43]. The study showed that *w*AlbB-*Wolbachia* establishment was a success, maintained at high frequency in some sites and dominating at other sites following subsequent releases to overcome initial fluctuations.

Recently, one study modelled how the insecticide resistance of mosquitoes infected with *Wolbachia* could contribute to the local establishment of *Wolbachia* in a secluded area of Rio de Janeiro, Brazil, and validated the model results with experimental data [42]. After the release of two *Aedes aegypti* mosquito cohorts with different *Wolbachia* strains, *w*MelRio and *w*MelBr, the model clearly showed that *w*MelRio, which is resistant to pyrethroid pesticides,

was able to establish while *w*MelBr, which is pyrethroid-susceptible, did not [42]. This implies that *Wolbachia*-infected mosquitoes resistant to pesticides may drive and establish *Wolbachia* infections in wild-type mosquito populations more readily than their pesticide-susceptible counterparts.

Another *Wolbachia* invasion model incorporated IMT and the loss of *Wolbachia* infection and showed that CI alone does not guarantee the establishment of *Wolbachia*-infected mosquitoes as IMT and *Wolbachia* loss could be more deleterious than CI is advantageous [197]. In effect, CI is not enough for *Wolbachia*-infected mosquitoes to dominate as both their intrinsic fitness and the possibility of mixed offspring play a critical role. Hence, we are interested in understanding how different features of *Wolbachia* infection, such as non-induction of CI, the high maintenance of the *Wolbachia* infection at high temperature, and the superinfection with different *Wolbachia* strains (*w*Au and *w*Mel) in mosquitoes could drive a reduction in arboviral transmission.

2.6 Discussion

Aedes-borne arboviral infections continue to be a public health problem globally [2, 7, 220, 221, 222, 223]. Various control mechanisms for these viral infections are targeted at either suppressing the population of the virus-carrying vectors or inhibiting the viral replication in the vector hosts thereby hampering transmission [2]. Herein, we have typically described these control methods as: human host; human-vector interactions; and vector-focused (Figure 2.1). Of these control measures, the vector control methods, including environmental; chemical; and biological approaches, are the most widely used. Furthermore, this review highlights the importance of biological methods, specifically *Wolbachia*-based methods, in controlling *Aedes*-borne viral transmission.

The intracellular bacterium *Wolbachia* has been shown to reduce *Aedes*-borne viral infections such as DENV, ZIKV, CHIKV, and YFV in their endemic regions [151, 40, 159,

162, 203, 211, 165]. Although promising, the *Wolbachia* control strategy is not guaranteed to succeed as it faces the challenge of degrading potency at unfavourable weather conditions, among other limiting factors [196, 224]. However, a novel *Wolbachia* strain, *w*Au, does not induce CI [162] yet is maintained even at high temperatures. This strain has been shown to produce high viral blockage, and induces stable superinfection when combined with other *Wolbachia* strains such as *w*AlbB in the vector host [162].

To better understand the dynamics of *Aedes*-borne viral infection both in human and vector hosts, there is a need to investigate the strategies of introducing *Wolbachia*-infected mosquitoes to control arboviral infection transmission. This can be done by formulating and analyzing mathematical models of different *Wolbachia* strains to capture the various important infection-driven features and validate these models using experimental data.

The research gaps identified in this review are: no modelling work on the combined three-vector control methods and no introduction of two *Wolbachia* strains with different characteristics such as the novel strain *w*Au-*Wolbachia* infected mosquitoes and its combination with other *Wolbachia* strains to quantify arboviral infection burden and control, have yet been performed. Therefore, in this review, we focus on the vector control methods together with different strains of *Wolbachia*-based control. Apart from greatly controlling virus proliferation in the midgut of *Wolbachia*-infected mosquitoes, the CI-absent *Wolbachia* strain, when subjected to high temperature is being retained in mosquitoes. This could be a successful strategy towards eliminating *Aedes*-borne infections. Hence, the need for in-depth insight and understanding of the different *Wolbachia* mosquito infection and superinfection dynamics and its impact when introduced into a mixed mosquito and human populations in arboviral endemic regions is sought in this regard.

Therefore, future work will include developing and comparing models for vector control methods incorporating the chemical, biological, and environmental control methods and comparing interventions. This would give great insights as it may require combining strategies such as outdoor fogging or use of chemical larvicides, educational campaigns to ensure

clean drainages and covering of waterlogged containers, and sterile insect release or *Wolbachia*-infected mosquito rollout. In addition, the development of *Wolbachia* transmission models that describe the competitive dynamics between *Wolbachia*-infected and uninfected mosquitoes with different characteristics. It will also investigate the impact of releasing CI-absent *Wolbachia*-infected mosquitoes and its combination with other CI-present *Wolbachia*-infected mosquitoes in a human population infected with dengue and explore how single or combined strategies will impact on disease dynamics, in particular, the effectiveness of *Wolbachia* introduction in dengue endemic areas. These investigations will reveal the interactions between the different characteristics of *Wolbachia*-infected mosquitoes and dengue virus serotypes in the human host. These revelations will further contribute to the global effort to reduce or eliminate arboviral transmission.

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Chapter 3

Systematic Literature Review

Chapter publication:

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Contrbutions:

Ogunlade, S. T. wrote the manuscript presented in this chapter. Ogunlade, S. T. also performed the extensive search of literatures and analysed the final selected articles with the required quality assessment tool. Ogunlade, S. T. and McBryde, E. S., conceived the project work described in this chapter. Adekunle, A. I. and Meehan, M. T. assisted with the analysis of the selected articles and results. McBryde, E. S., Adekunle, A. I. and Meehan, M. T.

contributed to proof-reading and meticulously reviewing the manuscript.

Summary

In this chapter, I present a systematic review of studies investigating the role of mathematical models of the most wide-spread *Aedes*-borne arbovirus i.e., dengue virus (DENV) in vector control methods. The review describes the infection, transmission dynamics and vector controls of DENV in Section 3.1. In the next Section (Section 3.2), I describe the methods and the selection criteria for the extensive articles search using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Further, data extraction which includes the aims and objectives, year of publication, modelling methods, study location, type of vector control and key findings together with the assessment of study quality are presented. The results of the search strategies and general study characteristics which include the distribution of the vector control modelling articles were presented in Section 3.3. The selected modelling studies are categorised into the vector control types and discussed in details based on their effectiveness with respect to the R_0, cost-effectiveness analysis, sensitivity and optimal control strategies to gain clarity in Section 3.4. The final section (Section 3.5) discusses the study assessment of the selected articles, provides detailed understanding of the vector controls and their effectiveness and highlights the study strengths and limitations.

Keywords: Dengue, *Aedes* mosquitoes, vector control, review, transmission.

3.1 Introduction

Dengue is one of the world's most threatening and wide-spread mosquito-borne disease [5, 14]. In recent decades, dengue has accounted for approximately 390 million new infections each year, with 96 million of these being symptomatic [16, 31]. Most of the new annual infected cases (approximately 70% of 390 million) are distributed across Asia while Africa, The Americas and Oceania shared infection distribution of approximately 16.4%, 13.8%, 0.2% respectively [16]. The main vectors responsible for dengue transmission are *Aedes aegypti* and *Aedes albopictus* [6]. Dengue virus (DENV) has four distinct, but closely related serotypes of the genus *Flavivirus*, namely: DENV-1; DENV-2; DENV-3; and DENV-4. When one recovers from one of these serotypes, it may provide lifelong immunity against that serotype. However, the cross-reactive immunity of the other types of serotype is only temporary and partial [225]. Therefore, the subsequent infection of different serotypes of dengue virus poses an increase in the risk of severe dengue viral infection [225]. The clinical manifestation includes headache, arthralgia, sudden high-grade fever, eye pain, nausea and muscle ache [88]. Currently, there is no specific treatment for dengue. The efficacy of the vaccine that targets young patients depends on prior immunity to dengue, and it provides heterogeneous protection against the different serotypes [226, 227]. The extent and severity of the burden imposed by dengue infection and disease has renewed calls for immediate intervention and control [228, 229, 230, 231].

Vector control remains the most widely adopted technique to suppress the transmission of dengue [31, 232]. This is because reducing the prevalence of dengue-carrying mosquitoes or inhibiting their transmission capacities typically poses negligible risk of environmental contamination and demands little provision to sustain control [31, 2].

There are three main approaches to vector control, namely, the chemical, environmental and biological approaches [31, 127]. Chemical methods involve the direct killing of mosquito vectors either by insecticide via indoor-residual spraying (IRS) or by limiting the reproduction of the vector population through chemically destroying mosquito breeding sites [31, 132, 233].

Environmental methods include emptying or covering water-filled containers, installing adequate water supply pipes, implementing efficient waste management strategies and ensuring a clean environment [31]. Biological methods rely on the introduction of biological control agents such as lavivorous fish, copepods, genetically modified mosquitoes and *Wolbachia*-infected mosquitoes which are incapable of transmitting arboviral pathogens [234, 235, 236]. Of these biological control methods, the *Wolbachia*-based strategy is becoming increasingly popular for controlling viral diseases (such as dengue) because it is potentially self-sustaining [2, 162, 237, 41].

In practice, vector control – which addresses the suppression of the vector population and disruption of the viral transmission capabilities of mosquitoes – is the primary method for reducing dengue viral transmission. Unfortunately, these methods typically require heaps of labour and monetary investments to achieve successful and sustained control, and may also pose environmental risks (e.g. through the use of chemicides) [31, 127]. The authors in [39] reviewed published articles on arboviral infections (such as dengue, Zika and chikungunya) and their vector (*Aedes* mosquitoes) controls in general. They further assessed *Wolbachia*-based control studies for mitigating or eliminating arboviral infections and discussed gaps such as the combination of the three (Biological, Chemical and Environmental) vector control methods and the use of two different *Wolbachia* strains that could be instrumental in developing models to estimate the impact of the controls. In this study, we examine the role of mathematical models to control the transmission of dengue and explore the present understanding of the effectiveness of vector controls in the last decade. This requires an extensive systematic search of literatures using the field-related search terms in three different databases.

The introduction of mathematical models to understand viral infection dynamics has long been helpful in the area of disease control [197, 238, 239, 240, 241, 242, 243]. Several models involving vector control of the transmission of different dengue serotypes have been formulated and analysed [197, 239, 240, 241, 242, 243, 244, 245, 246, 247, 55, 248, 44, 58, 49, 249,

250, 251, 252, 253, 254, 54, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267]. Some of the studies [242, 243, 245, 55, 268, 58, 54], reviewed dengue transmission models capturing the different dengue serotypes together with their vectors. Further, they described the dengue models by either host-vector transmission dynamics or purely by interactions between vectors. Here we review mathematical models of dengue vector control and identify literature modelling gaps in the last decade (from 2010 to 2020). We limited the time range to the last decade because some vector control techniques such as *Wolbachia*-based techniques were only recently successfully introduced [41, 40] and a systematic review of dengue transmission models which accounts for vector control has been described up to early 2012 [243]. Another similar study by Perkins et al. [269], reviewed the dengue transmission models that covered a 40-year period (i.e. from 1970-2010). They used standardized questionnaire to describe the various biological assumptions (corresponding to the Ross-Macdonald model assumptions) guiding each model and then gave both qualitative and quantitative findings. We carefully appraise published research articles describing the dengue transmission models and specifically classify these models according to the vector control method studied within a decade (i.e. from 2010-2020). This, in turn, will help reveal the literature gaps that will inform the development and modification of dengue models to account for effective vector control techniques.

3.2 Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [270] were used to conduct a systematic literature search. This search was performed using the MEDLINE, Web of Science (WOS) and SCOPUS databases from March to December, 2020. We systematically used various keywords and/or synonyms such as "dengue" OR "arbovirus" together with "model" AND "control" OR "strategy" OR "technique" (see Supplementary material S1). Other keywords such as "flavivirus", "dengue

virus", "insect control" and "communicable disease control" were used to expand the search terms as some of the terms have been used interchangeably in the pool of literature. This review is aimed at mathematical modelling of vector control methods in dengue transmission models. For each vector control method, we identify the underlying structure of the mathematical model, parameter assumptions, and thresholds of implementations and limitations.

3.2.1 Selection criteria

At the initial stage of the search process, there were no restrictions for the time frame of the selected articles from each databases used. However it was later limited to the yearly range of 2010-2020. This is because, (i) biological vector control techniques, in particular, *Wolbachia*-based control were not significantly discussed until the last decade where the successful establishment of *Wolbachia* infections and its ability to block viral transmission in *Aedes* mosquitoes were reported [41, 40], and (ii) another systematic review of the structure of dengue epidemiological transmission models which includes vector control strategies has been carried out up to March 2012 [243].

The titles and abstracts of the articles irrelevant to the scope of study were excluded from the articles of discussion (See details in the Results section). Study articles published in non-English languages were removed from the considered pool of articles. Other referencing types such as conference proceedings, serial, books and book sections were also removed. The inclusion criteria for these articles include the following:

- A representation of vectors or vector-host dynamics to control dengue transmission.
- A deterministic (DM), stochastic (SM) or network (NM) modelling approach using systems of ODEs
- A vector control strategy leading to dengue viral reduction or elimination.

3.2.2 Data extraction

The selected articles for this study were evaluated according to the modelling characteristics in terms of contributions made. These study features include the aim and objectives, modelling methods, study location, vector control types and key findings. It is important to mention that the vector control effectiveness of these studies was extracted from the findings and conclusions (Table 3.1). This is because the conclusive findings described in the studies provides a means for comparison and inferences based on study effectiveness. Models were also categorised based on the year, vector control types, methods and location of study to capture the general trend and geographical clusters of these models (Table1). Figure 1 showed the distribution of the selected articles, stratified using the vector control types and location in which the controls were carried out. In other words, this showed the geographic clustering for where the vector control modelling studies were taking place (Figure 3.1).

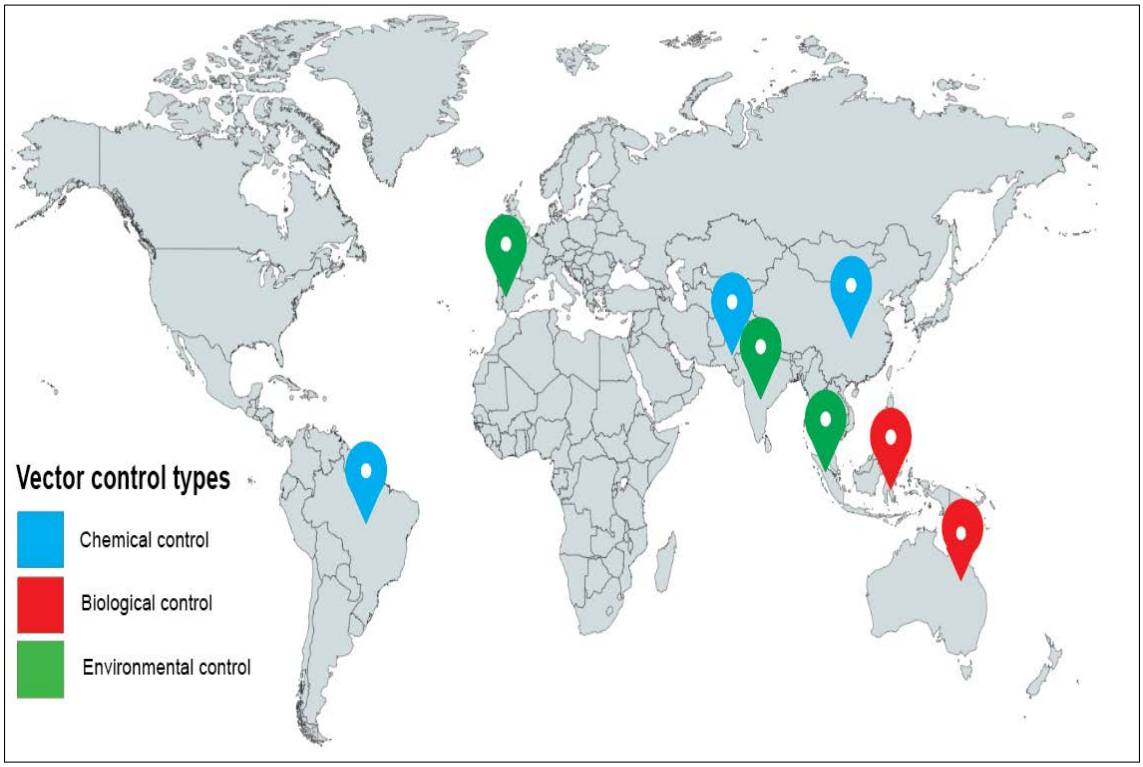

Figure 3.1: The global distribution of the location of the selected modelling studies describing the vector control types.

3.2.3 Assessment of Study Quality

We adapted and built upon the tool for Assessment of Modelling Studies (AMS) [271] which is used for assessing modelling work in health and economics. In particular, we built upon the AMS by adding two more criteria (modelling methods and reporting conflicts of interest) to the ten existing criteria in AMS (Table 3.2). The newly modified ASM tool used the quality assessment value formats in [272]. The tool comprises 12 criteria and these criteria described the characteristics of each of the articles selected for this review. Each criterion in the adapted tool used was assigned the rating of 0 to 2, where 0, 1 and 2 represent the criteria being absent, partially present or present respectively. Herein, the highest score for the modelling studies is 24 points. To compute the score y (in percentage) for an article, we have: $y = \left(\frac{x}{24} \times 100\right)\%$, where x is the number of points estimated for an article. Below, the quality of the articles are stratified into four categories: low ($y \leq 50\%$); medium ($50\% < y \leq 65\%$); high ($65\% < y \leq 80\%$); and very high ($y > 80\%$) (Table 3.2).

3.3 Results

3.3.1 Search strategies and general study characteristics

A total of 2158 articles were identified from the standard databases: MEDLINE – 1069, WOS – 643 and SCOPUS – 446. Of these, 336 duplicated studies were found and subsequently removed. Of the remaining 1822 studies screened, 644 records were excluded. This exclusion includes 8 books, 27 book sections, 19 conference proceedings, 4 serials, 134 non-English articles and 452 articles whose years were less than 2010. The 1178 remaining articles were screened via reading the titles and abstracts. 1106 studies were excluded because they were deemed irrelevant; not containing information governing the inclusion criteria and the scope of the review. In total, 72 full-text study assessments were performed. Of these, we excluded 40 articles which either did not describe deterministic/stochastic/network models or the vector control methods as a technique for dengue control, and whose aim is closely related

to one of the selected articles. Finally, 32 articles were selected and considered in this review (Figure 3.2). The distribution of these review articles by calendar year is shown in Figure 3.3. In Figure 3.3, more than half of the 32 selected modelling articles were published from 2017, i.e. over the past four years.

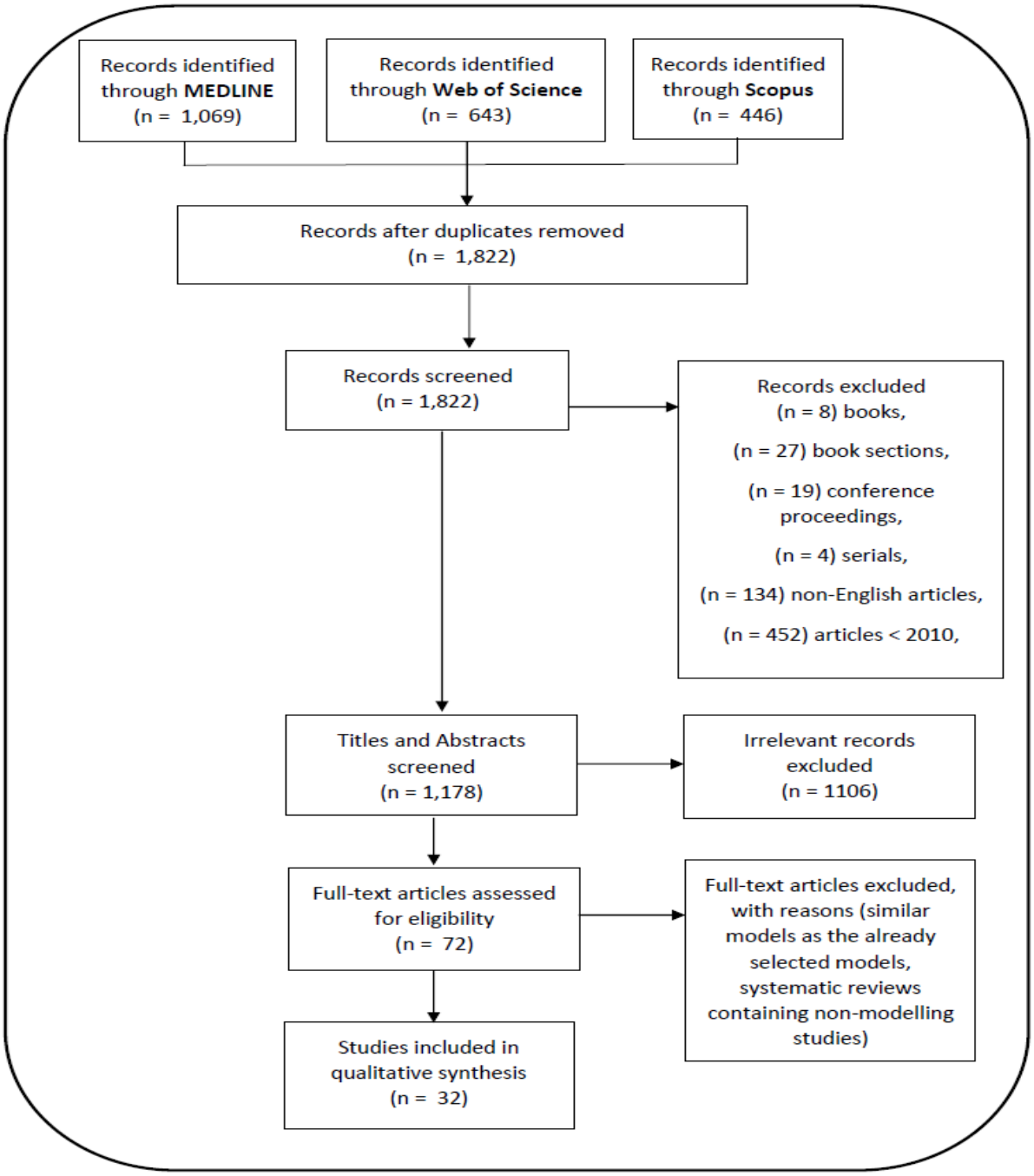

Figure 3.2: PRISMA Flow chart for articles' selection process.

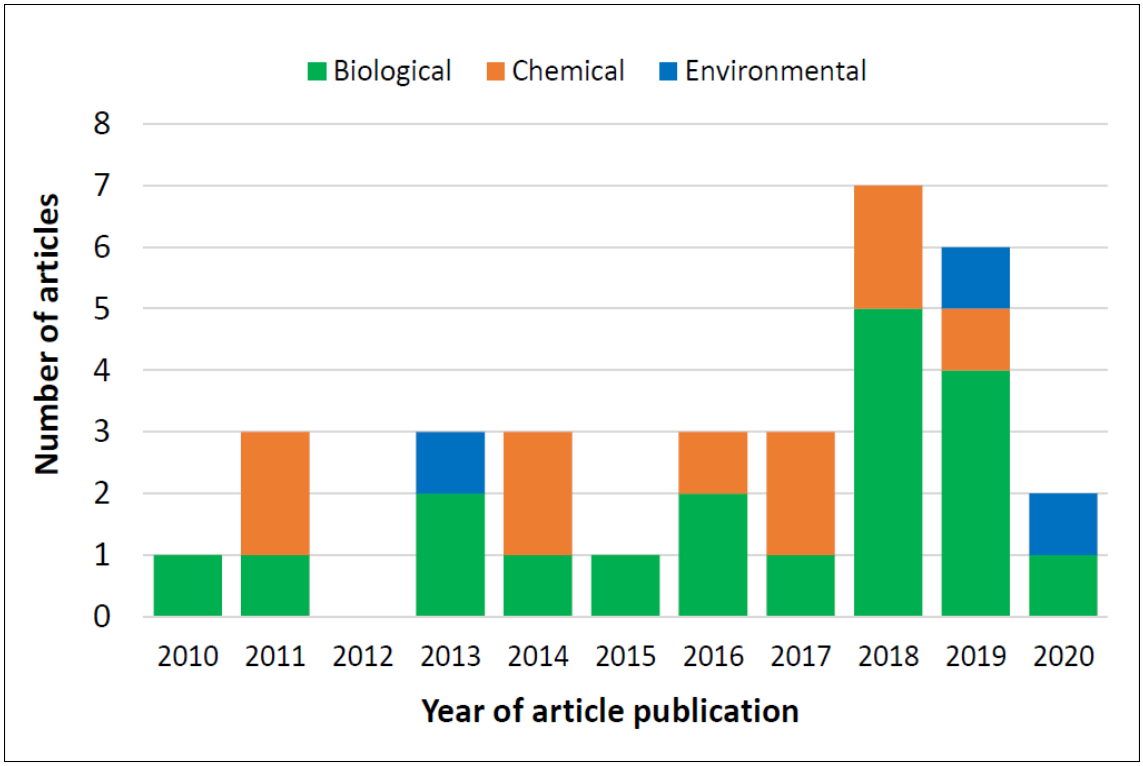

Figure 3.3: The yearly distribution of the number of selected published modelling articles with respect to the vector control types.

3.3.2 Distribution of vector control modelling articles

In this review, 32 modelling articles were considered and included in the study. These articles were published between 2010 and 2020 (Figure 3.3). The stacked bar chart in Figure 3 showed the distribution of the three different vector control strategies through the years. Beginning with the biological vector control, there is an increasing trend in the number of published articles and this is mostly seen in the last two years. This increase may have been fuelled by the largest dengue viral outbreak in the Americas, South East Asia, Europe, sub-Saharan Africa and the Oceanian regions and by greater recognition of this novel strategy [273]. The number of publications addressing Chemical methods of vector control remains approximately constant over the years, reflecting its ongoing dominant role in contemporary vector control [274]. Only three papers address Environmental controls (Figure 3), two of the

three in the last two years of publications in this study, suggesting this may have a growing area of interest [31]. Of the overall articles selected, three are stochastic modelling studies [240, 250, 262], one is a network modelling study [257], and others are deterministic modelling studies of dengue transmission dynamics (Figure 3.4).

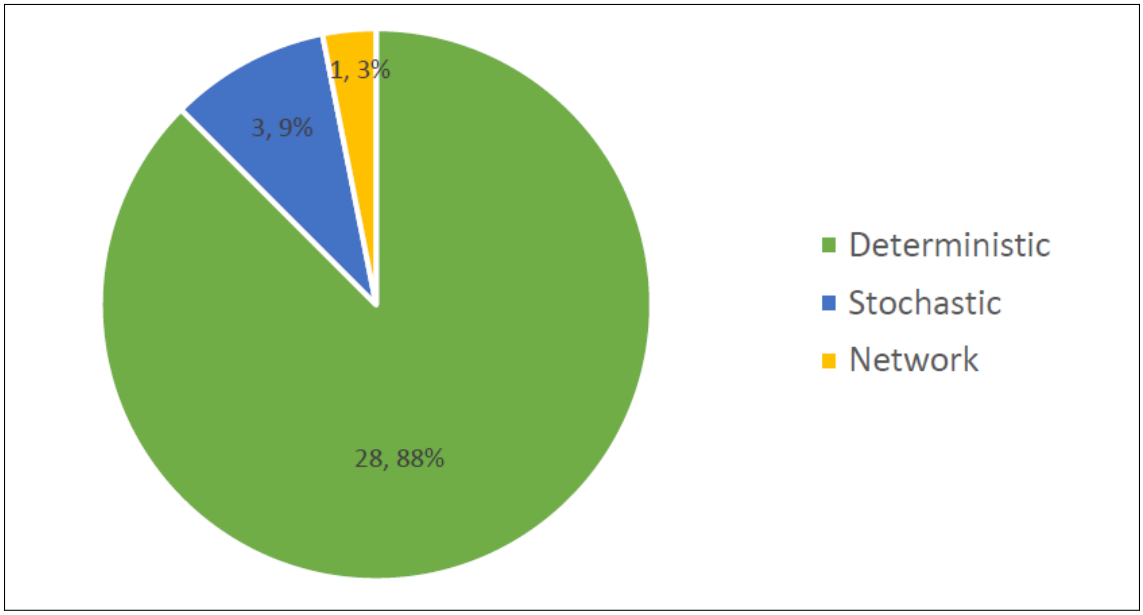

Figure 3.4: Distribution of modelling types (number, percentage) for the total selected articles.

Ten (10) of these studies investigated the Chemical method for vector control [240, 244, 249, 250, 251, 252, 256, 258, 263, 265]; nineteen (19) articles described the Biological method of control [239, 241, 242, 245, 247, 55, 268, 44, 58, 253, 254, 54, 255, 257, 259, 260, 264, 266, 267]; while only three of the articles partially discussed the Environmental methods for the vector control [246, 261, 262]. The pie chart distribution showcasing the vector control technique types are revealed in Figure 3.5. This chart showed that 60% (more than half) of the selected modelling studies were categorised under the biological control methods. The chemical methods of control articles were 31% while the least i.e., 9% was that of the environmental methods (Figure 3.5). We now discuss the vector control methods elaborately below.

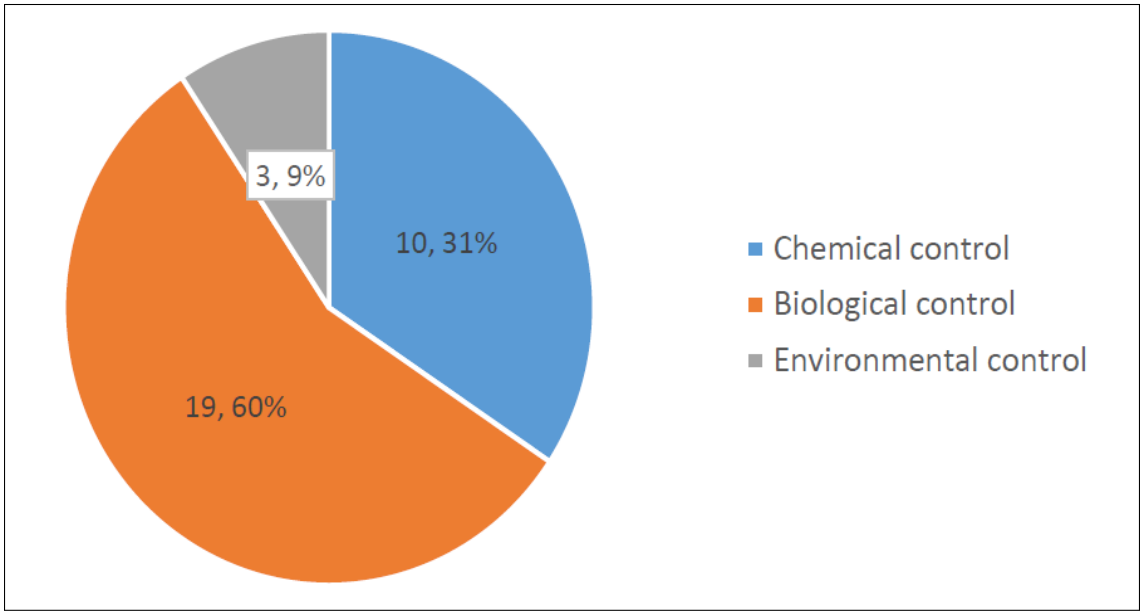

Figure 3.5: Distribution of types of vector control methods for dengue control modelling for the selected studies.

3.4 Vector control methods

The selected dengue modelling have been characterised into the aims and objectives, year of publication, modelling methods, study location, vector control types and summary of the articles to gain clarity (Table 3.1).

3.4.1 Chemical control methods

This method describes the use of chemical solution, mixture, aerosol or material to directly repel, expel or in some cases kill arthropod vectors such as mosquitoes [275, 276, 277]. Chemical control includes the use of: pyrethroids for outdoor fogging [278, 279], insecticides for indoor and outdoor residual spraying [132, 280], insecticide-treated bed nets (ITN) [281, 282], insecticide-treated house screens (ITHS) [283] and insecticide-treated door curtains (ITC) [284], and chemical larvicides such as Temophos to directly kill or destroy mosquito vectors and their breeding sites [285, 286].

Ten dengue transmission modelling studies in the selected articles incorporate chemical control methods [240, 244, 249, 250, 251, 252, 256, 258, 263, 265]. Of these, eight are based on deterministic models (DM) [244, 249, 251, 252, 256, 258, 263, 265], while the other two used stochastic modelling (SM) [240, 250]. Some studies based on the DM featured vector populations only [265] or both human and vector populations [244, 249, 251, 252, 256, 258, 263] while SM studies considered coevolution dynamics of both humans and mosquitoes. For some of the DMs modelling both human and vector populations, the basic reproductive number (R_0) with respect to dengue was computed and further illustrated that the disease-free equilibrium (DFE) is stable if it is less than unity (i.e. $R_0 < 1$) [249, 252, 256, 263] or in the presence of backward bifurcation where DFE may coexist with an endemic equilibrium [244]. A study estimated the value of R_0 during the 2014 Guangdong Province dengue outbreak in China to be around 1.74 and after implementing impulsive vector control strategies, reduced to 0.17 [263], while the R_0 for the 2017 dengue outbreak in Pakistan was estimated to be approximately 2.65 [244] and another study estimated R_0 to be 8.16 [252]. One study predicted that the dissemination of pyriproxyfen would, under some optimistic, realistic and worse-case epidemiological scenarios (based on parameter modification such as daily vector death rate, vector-to-human ratio, among others), reduce the values of R_0 with respect to *Aedes*-borne viruses such as dengue, Zika, and chikungunya, (which was estimated to be between 3-45, i.e. range of optimistic to worse-case scenarios) by 100-1000 fold [249].

Almost half (13 out of 32) of the selected studies performed sensitivity analysis [240, 242, 244, 245, 268, 44, 58, 255, 256, 259, 261, 263, 267]. Four of the studies [242, 244, 261, 263] used the Latin Hypercube Sampling (LHS) and partial rank correlation coefficients (PRCC) and provided evidence that the most effective parameters in curtailing dengue viral spread include reducing: the transmission probability per contact of either infectious mosquitoes with susceptible humans or susceptible mosquitoes with infectious humans; mosquito recruitment and death rates; and human recovery rates [244, 263]. Other highly sensitive parameters include the epidemic size, date of arrival of the infectious human and mean annual temper-

ature [261]. One study used a probabilistic sensitivity and threshold analyses and showed that if the cost of adult mosquito control was greater than 16 times that of larval control, all the adult vector control strategies are dominated [256]. Another study investigated the sensitivity of the vector model with respect to the parameter values used for SIT method for dengue vector control and showed that shorter mosquito lifespan significantly prevent the disease from occurring, however, disease could possibly persist (few cases) if the mosquito lifespan is less than its extrinsic incubation period [245]. To account for the robustness of the transmission models with respect to the corresponding biological implications, two studies [58, 267], performed sensitivity analyses on a large range of parameter values and found that the fitness cost and maternal transmission parameters are the main factors that determines the establishment of *Wolbachia*-infected mosquitoes in a wild-type population [58, 267]. The effect of these factors could induce a backward bifurcation when the fitness cost is large [267]. A study by Li et al, investigated the robustness of the release strategy of the model for different values of CI. The authors showed that there is no significant difference between the different values of CI chosen and as such, suggested excellent robustness [255]. Similarly, some researchers explored the uncertainty in asymptomatic cases for dengue viral transmission. They simulated two scenarios: with 50% and 100% transmission rates for asymptomatic individuals and found that there is a similar reduction in dengue cases for both rates [240]. A study that described the dengue transmission dynamics using boosted SIT approaches performed a sensitivity analysis on the model parameters and showed that for low release rate boosting the SIT methods reduced the elimination threshold the most [259]. Some of the modelling studies [249, 250, 251, 263, 265] revealed that the use of insecticides or fumigation significantly reduces the emergence and production of vectors (in particular, *Aedes* aegypti mosquitoes) and, in turn, reduces the burden of dengue [240, 249, 252, 258]. However, continual long-term mosquito larvae control may prove ineffective due to the evolution of mosquito resistance [256].

Further, some studies considered cost-effectiveness and benefits as part of their analy-

sis [244, 245, 55, 44, 251, 256, 264, 265]. Cost-effectiveness analysis – which includes the calculation of the infection averted ratio (IAR), average cost-effectiveness ratio (ACER) and incremental cost-effectiveness ratio (ICER) – describes the advantages and the costs with respect to the control strategies, allowing one to identify the most effective strategy [244, 245, 251, 256]. The authors in [251] investigated the cost benefits of dengue control strategies via insecticide-treated bed-nets (ITN) and spraying interventions. They found that the combination of both strategies with low cost weight is most effective in reducing dengue infections (IAR = 0.76, ACER = 5.65), however, insecticide spraying strategy only is the most cost-effective (IAR = 0.71, ACER = 4.35) [251]. Another study investigated the potential costs per dengue case averted by SIT control strategy based on the average cost estimates derived from an SIT data. They showed that the yearly mean per capita cost of the vector control measures is \$0.765. That is, the yearly control cost of the simulated two million people would be \$1.53 million and for about 5,000 people, that would be \$3,825. This would save a large percentage of infection [245]. A study described 43 insecticide-based interventions together with the cost-effectiveness of different (larval and adult mosquito) control strategies and stratified the control efficacy into high (90% mosquito mortality [MM]), intermediate (60% MM) and low (30% MM) with annual application frequencies [256]. They showed that the high-efficacy adult vector control strategies dominated the larval control strategies because of increasing resistance of larvae within the 5 year time horizon. Of the frequencies examined, twice annual control was the most efficient (ICER = \$615), whereas six times annual control was the most effective (ICER = \$1267), with the increased cost per disability-adjusted life years (DALY) saved meeting the willingness to pay threshold. This suggests that of all the vector controls, the one that most significantly reduced the DALYs lost was the high efficacy adult mosquito control with six application frequencies [256]. Authors in study [44] investigated the impact of *Wolbachia*-based strategy in reducing dengue burden and estimated over 330 thousand DALYs lost and are attributed to dengue in Indonesia. Of the DALYs lost, approximately a quarter is caused by fatality while the rest is

due to disability [44].

A number of studies explored optimal control strategies associated with cost benefits of dengue control strategies [244, 55, 264, 265]. A study of dengue in Pakistan introduced two time-dependent control variables: use of insecticide and vaccination [244]. They investigated the effect of costs on the cost weights of insecticide and vaccination use and found out that as the cost of insecticides increases, the use of vaccination also increases. However, when vaccination decreased as a result of increase in cost, an exiguous increase in the use of insecticide is observed. Although the two control strategies avert almost equal number of infections in the Pakistani region, this occurred as a result of the existence of a reciprocal relationship between insecticide cost and vaccination use [244]. Another similar study which also described the minimum effort in mitigating dengue via suppressing the vector (female mosquito) population considered the production cost of SIT, insecticide application cost and social (dengue disease-related) cost. They showed that, social cost is very important in reducing the female mosquito population and should be considered in controlling vectors responsible for transmitting dengue [264]. Further, researchers in [55] considered optimal control approach for establishing *Wolbachia*-infected mosquitoes and compared two options: (a) Importance of both time and production cost of *Wolbachia*-infected mosquitoes; and (b) Time is more important than cost of production. The option (b) results in overpopulation of *Wolbachia*-infected mosquitoes as this is a negative side effect while the option (a) can annul the overpopulation effect as releases are suspended for about 5.5 weeks earlier [55]. One study investigated mosquito reduction management and cost using Temephos and fumigation. They showed that the most effective strategies in mitigating dengue burden with the cheapest cost is initiated when control is initiated with a small number of vectors together with a simultaneous combination of both Temephos and fumigation control measures [265].

Some studies investigated optimal control strategies to avert disease burden [244, 251, 252, 258, 265] and the effect of seasonality [251, 252, 258]. A study investigated the optimal control strategies for insecticide spraying and use of insecticide-treated bed nets (ITN) to

mitigate human infections and intervention cost [251]. They showed that the most effective strategy in averting dengue infections is the combination of ITN and insecticide spraying. However, insecticide spraying alone (without additional ITN) should be implemented in areas of at least low seasonality, being both effective and the most cost-beneficial. In the absence of seasonality (amplitude of seasonal force) for mild climate scenarios, ITN could not eliminate disease (within a year time-frame). However, combining ITN with insecticide spraying reduced the infection prevalence and led to no infection within five months. Wijaya and Gotz also investigated the application of optimal control models via two categories: chemical dissemination of aquatic mosquitoes (eggs and larvae), and fumigation of adult mosquitoes [265]. Results from numerical simulations suggest that, although maintaining fumigation instead of the use of chemicals such as Temephos may be beneficial, combining the two control strategies mostly significantly reduced the vector (mosquito) population [265].

Another study, which sought to reveal two optimal timings at which pesticide is sprayed within the seasonal period in a year, investigated two optimization scenarios of pesticide spraying [252]. The first scenario described fixing the peak number of dengue-infected hosts at specific intervals and afterwards, detect the optimal timing through repetition of pesticide application timings that generates the minimum amounts of pesticide per application required. The second scenario inversely considered fixing the amount of pesticides and minimising the dengue infection peak. It was shown via the first scenario that the optimal timing of the first pesticide application varies between 33-43 days while the second remains approximately constant at 220 days before the peak of infection. However, the second scenario revealed that the optimal timing for the first pesticide application remains constant (around 28 days) while the second takes values between 232-281 days [252]. Two similar studies also investigated the optimal timing of insecticide fogging together with seasonality (where both wet and dry seasons were considered) [258, 287]. The authors in [258] simulated four scenarios of the model which include adding seasonality, endemic state and different transmission intensities by systematically increasing the number of mosquitoes per person (that is, from

low (2) to very high endemicity (15)). They concluded that the optimal timing of application wobbled between the beginning of the wet season (dengue season) and the prevalence peak [258]. This occurred because the timing could interfere with the exponentially growing epidemic. Further, researchers in [287] investigated the optimal timing of fogging which includes the deployment of ultra-low volume (ULV) and targeted indoor residual spraying (TIRS) using different spraying strategies such as yearly, biannually or when the number of dengue cases exceeds the adaptive threshold of the average incidence. They used a simulation-based model to parameterize data from 2000 to 2010 in Iquitos, Peru. They showed in general, TIRS has higher efficacy and averted more dengue infections than ULV. Of the different spraying strategies applied to both ULV and TIRS, the adaptive threshold strategy for TIRS is the most effective, with a 97% reduction in the number of infections from baseline and requiring fewer days of spraying (three quarters of a year) [287]. Sensitivity analysis was performed to explore how the adaptive threshold spraying strategies could be affected by the delays in reporting or underreporting. They found that these delays do not affect the serotype-specific calibration of the model [287].

3.4.2 Biological control methods

Biological methods for vector control of dengue encompass the introduction of biological agents such as small fishes, crustaceans and bacteria [127, 277, 288]. These agents typically include larvivorous fishes [134, 289], cyclopoid copepods [137, 135] and Bacillus thuringiensis israelensis (BTI) [290, 291, 292]. Additionally, biological control methods may also include the alteration of the genetic materials of vectors, thereby inhibiting them from transmitting dengue virus [127]. This subclass includes sterile insect techniques (SIT) [141, 293], genetically modified mosquito (GMM) methods [294, 295] such as release of insect carrying a dominant lethal (RIDL) gene [294, 296], and *Wolbachia* bacterium introduction (WI) [2, 162, 237, 39, 38].

Prior to formulating models to biologically control vectors fuelling the transmission of

dengue, it is worth mentioning in general, some factors to be considered in governing model interests and initiation. These factors include: describing the biological agents (vectors) to be used [127, 243, **?**, 255, 288, 289]; understanding ecological patterns between the vector and dengue virus [2, 285, 297]; and identifying the methods of control [2, 39, 269, 293, 294]. Different model structures account for the biological vectors used by modelling vector–only transmission dynamics involving dengue virus [39, 247, 266]. These models account for the competitive interaction between wild-type and biologically-infected vectors in particular, mosquitoes [245, 268]. Of the three factors, the ecological patterns between the vector and the virus can be modelled using a human-vector transmission models [54, 259, 298], which capture the interaction between the viral-infected mosquitoes and uninfected humans and vice versa. The control method are being considered by incorporating a control type such as *Wolbachia*-based control that may consider complex features like CI and IMT effects in vectors [242, 293, 296, 38]. These are some of the complexities in model structures used for different forms of biological controls.

Dengue models formulated by investigating the effects of the biological methods of vector control are described in these 19 studies [239, 241, 242, 245, 247, 55, 268, 44, 58, 253, 254, 54, 255, 257, 259, 260, 264, 266, 267]. Except one [257], which is a network model (NM), all of the other 18 studies use deterministic models (DM). Of all the 19 modelling studies, seven articles [242, 245, 268, 44, 54, 257, 259] model the interaction between human and vector populations while 12 studies [239, 241, 247, 55, 58, 253, 254, 255, 260, 264, 266, 267] model the vector population dynamics, where the vector population in all cases is considered in the presence of a biological control mechanism such as SIT, GMM or *Wolbachia* introductions. Presently, the biological method of dengue vector control is the most commonly modelled and analysed (Figure 3.5) as compared to about a decade ago (prior to the successful introduction of some biological techniques such as WI) when mostly chemical control methods were considered [40].

Different studies have recognised key determinants of success-mating competitiveness of

SIT versus wild-type mosquitoes in combination with other control methods, and recruitment and release rates to control dengue viral infection [239, 241, 247, 257, 259, 264]. These DM of SIT studies [239, 241, 247, 264] model the vector population dynamics and investigated the release rates and sizes. Another DM study [259] considered both vector and vector-human population dynamics and one NM study [257] only described human-vector population dynamics. These models involved state variables which may include young and adult sex-structured vector populations. One similar study assumed that the male mortality rate is higher than that of the female [239]. These studies considered constant [239, 241, 247] and periodic [239, 241, 264] releases of sterile insects to achieve elimination. For the constant releases (usually sterile males), the number of sterile mosquitoes released at the initial stage of the release timeframe is constant. This demonstrates that every solution of the system tends to an equilibrium point (especially disease-free equilibrium) for constant release of sterile mosquitoes even in the presence of a time delay in the developmental stage of the uninfected mosquitoes [241, 247]. For periodic releases, control is achieved at a lesser cost compared to constant release control [241].

A study [247], which modelled the interactive competitiveness between wild-type and sterile mosquitoes, considered and analysed the delay in time to releasing sterile mosquitoes. They showed that the delay imposed while releasing the sterile mosquitoes at a constant rate does not significantly affect the system dynamics. However, if both wild-type and sterile mosquitoes are released at the same rate, there is a profound effect on the system dynamics especially as the delay in release time increases as a result of Hopf Bifurcations [247]. In contrast to constant release, delay in periodic releases of sterile males (i.e. release rate proportional to the wild mosquito population) may greatly affect the system dynamics. As the time delay increases, the system's solution may show an oscillatory behaviour through Hopf bifurcations. At this point, both the sterile and wild mosquito populations can coexist [247].

Several SIT control approaches require the sterile mosquitoes to compete almost equally

with the wild counterparts to be effective as its effectiveness may depend on the size of the wild populations [241]. The study [241] further suggested that the mating competitiveness of SIT control method should tend to one (as good as the wild-type) to boost effectiveness. Otherwise, the SIT efficacy may diminish provided there are existing wild-type mosquitoes. Another study [259] showed that when the SIT is supplemented with pupicide pyriproxifen (PP), it could increase the effectiveness of the intervention by averting over 95% of the total rollout and in turn decrease dengue burden. Additionally, a network model [257] revealed that SIT application can be successful depending on the rate of recruitment and coupling strength of the migration parameter.

The modelling of genetically-modified mosquitoes (GMM) such as release of insect carrying a dominant lethal (RIDL) methods are analysed in three studies [245, 260, 266][34, 54, 60]. A dynamical model that accounts for the RIDL release of pupal and adult mosquitoes unveiled via simulations that for regular recurring releases, the most effective RIDL approach is evident when only adult-carrying RIDL mosquitoes are released every day [266]. The adult-only RIDL mosquito approach outperforms both pupal and combined mosquitoes' releases because, the adult male RIDL mosquitoes are already sexually matured and as such would perform well in increasingly maintaining the RIDL mosquitoes after release until the next day's release. Unlike adult RIDL releases, the pupal-only RIDL releases would require that the pupa gradually develop into adults males and therefore are affected by high mortality between the pupal to sexually active adult time, causing a disadvantage. Whereas, for long-term suppression of wild population scenarios with infrequent RIDL releases, the combination of pupae and adult mosquitoes' release could maintain and sustain suppression every week when compared with pupal or adult only releases. Similarly, about 1.9 million combined mosquitoes' release (73% pupae and 27% adults) was able to maintain suppression while pupal or adult only mosquitoes' release could maintain suppression if the population sizes were increased to 2.7 and 2.8 million respectively [266]. Further, another model considered a GMM "reduce and replace" (RR) technique which introduced insects possessing

genetic features which include female-killing and antipathogenic attributes [260]. The authors showed that continuous release of RR mosquitoes, resulted in a long-term decrease in the overall density of the vectors (mosquitoes) [260]. When a proportion of RR male-only mosquitoes were released for a year, the population density of the adult female mosquitoes decreased with a rapid reduction in the density of the competent vectors than the population density of the total female mosquitoes. The competent vector density decreased rapidly due to increase in the frequency of the antipathogenic allele. However, when the release ceased, the female population recovered to its initial size but the competent vector remained at an insignificantly low density [260]. Considering the release of RR female mosquitoes, and comparing with male-only and both-sex mosquito releases for 100 days with release ratio of one, the female-only releases mostly reduced the total adult female wild population. Although the total female population surged initially as a result of releasing more RR females, the total density of the adult female was effectively reduced for longer periods of time. Concisely, it was shown that suppressing the vector population density would be dependent on release proportion and duration, and adult female mosquitoes' inclusion in the GMM releases [260]. Increasing the fitness cost associated with antipathogenic gene for a year simulation of male-only RR rollout at release ratio of two led to a reduction in the competing vector density [260]. Modelling the effect of releasing RIDL from the cost-effectiveness perspective, [245] showed that the RIDL control technique could quickly eradicate dengue at low cost, and was therefore highly cost-effective.

From the study articles selected for this review and then stratified into biological vector control so far, *Wolbachia* control strategies are the most modelled, and have been analysed to inform the effective control of *Aedes* mosquito vectors to mitigate dengue burden [242, 55, 268, 44, 58, 253, 254, 54, 255, 267]. *Wolbachia*-based control is the introduction of intracellular bacterium, *Wolbachia* into arthropods to suppress vector populations, disrupt arboviral transmission or both [39]. *Wolbachia* infection is transmitted maternally (that is, from the adult female arthropod to the offspring). There are various strains of *Wolbachia* such

as *w*Au, *w*Mel, *w*Pip, amongst others. *Wolbachia* possess some features which may depend on the strains such as: uni- or bidirectional cytoplasmic incompatibility (CI): the phenomenon that causes incompatibility between the sperms and eggs of arthropods (mosquitoes) resulting in unviable offspring; imperfect maternal transmission (IMT); viral blockage; *Wolbachia* infection loss; and mosquito fitness cost [39]. Sex-structured models accounting for the interactive competitiveness of wild-type and *Wolbachia*-infected mosquitoes were described in [55, 58, 255, 267]. Some models have investigated *Wolbachia*-carrying mosquito features such as fitness effects, IMT, viral blockage, CI and *Wolbachia* loss [197, 55, 268, 49, 254, 267]. These features have been suggested to affect the spread, establishment and dominance of *Wolbachia* infections in mosquitoes [197, 49, 298]. One study showed that the evolution of complete CI could drive the successful invasion of *Wolbachia* in a wild-type mosquito population; however, incomplete CI by genetic evolution may compromise successful invasion [254]. In other words, the authors revealed that the successful establishment or failure of *Wolbachia*-infected mosquitoes may rely on the selected *Wolbachia* strain [254].

Other human-vector dynamical models in the presence of *Wolbachia* have been analysed as these models, together with experimental data, have provided insights on how the presence of *Wolbachia*-infected mosquitoes rollouts have significantly reduced dengue disease [242, 268, 44, 253, 54]. One of these studies [44] focusing on dengue infection and *Wolbachia*-infected mosquito rollout dynamics in Indonesia, used the combination of multiple modelling methods together with available data to show that approximately 7.8 million dengue cases were estimated to be symptomatic in 2015. However, this analysis may be an over-estimation as it is highly sensitive to the assumed under-reporting rate where about five million cases were estimated to have individually managed the symptoms via informal healthcare services. Additionally, of the total estimated symptomatic cases, only 14.1% were estimated to have been hospitalized resulting in over three thousand deaths [44]. The researchers in [44] also estimated that the *Wolbachia* rollout program conducted in Indonesia averted 86.2% of dengue cases over a year. Similarly, another modelling article used an estimated transmission rate of

0.1648 new human transmissions per dengue-infected mosquito per day by fitting a deterministic model to experimental data from a northern Queensland city: Cairns, in Australia. The authors estimated an 80% decrease in overall dengue cases after a *Wolbachia* rollout [268]. Further, they showed that for weekly introduction of *Wolbachia* in Cairns, half of the dengue cases were reduced for a year while about 60% were reduced for quarterly time periods. The researchers in [268] further showed that the duration of dengue outbreaks could be decreased by between 2 and 6 weeks yearly in the presence of *Wolbachia*-infected mosquito rollouts based on the seasonality strength. This decrease may have been caused by a reduction in the mosquito's lifespan [268]. The study [54] also described modelling the use of *Wolbachia* for dengue control. They showed that, infecting *Aedes* mosquitoes with *Wolbachia* bacteria decreases the basic reproductive number for Dengue virus and in particular, for wAlbB *Wolbachia* strain, the reproductive number is reduced by around two thirds, which would be sufficient to prevent epidemic outbreaks [54].

3.4.3 Environmental control methods

Environmental control programs focus on the reduction of mosquito breeding and reproduction via mediums of modifications to the surrounding environment. These mediums include: installing efficient piped water supplies and good drainage systems; emptying, covering or destroying stagnant waterlogged cans and containers; practising proper environmental hygiene (cleaning of the environment such as mosquito breeding sites); and implementing waste management schemes. Additionally, environmental factors such as seasonal variation and changes in temperature may also serve as environmental modification of vectors to mitigate their abundance. Of all the vector control methods, environmental control does not pose environmental contamination risks as it predominantly entails common hygienic practices and maintenance, addressing seasonal fluctuations in cases. Its impact can be lifelong and does not require further investments for sustainability.

Mathematical models of environmental control studies have sparsely been formulated as

these models are not often described (in just three of the selected articles) [246, 261, 262]. The deterministic models in [246, 261] showed that seasonal variations could affect the dengue epidemic dynamics, that is, autumn and summer seasons could greatly increase dengue transmission in the presence of an infectious individual within a short time period [261]. This suggests that large outbreaks of dengue could have been fuelled by warm temperatures [261]. A model [246] which considered seasonal variations via periodic forcing in the vector density and the impact of vector control methods in the 2005 Singapore dengue outbreak estimated the basic reproductive number to be 1.363 [246]. The authors showed that dengue infection will not persist except if the recruitment rate is more than the ratio of the periodic vector recruitment rate with a yearly period to the square of the basic reproductive number [246]. This showed that the basic reproduction number, under periodic environment (or asymptotic behaviour of the system - bifurcation) described the threshold for disease persistence. They also revealed that the dengue incidence which occurred in the 10th month of each year (2003-2005) was described by a lag of 4.2 months with the highest mosquito density [246]. Similarly, another model accounts for seasonality via varying temperature over time by periodic forcing in the dengue transmission in Madeira Island, Portugal [261]. Considering the different simulated arrival dates of an infectious individual into the population of uninfected/susceptible, it was revealed that an epidemic outbreak is expected to occur between July and November each year [261]. Therefore, with an infected individual arrival time in August and October, the shortest and longest epidemic time simulated was 93 days and 411 days respectively. For the shortest epidemic time, approximately one tenth of the susceptible population was infected while 3.4% of susceptibles were infected in the longest epidemic time [261]. A general multi-patch model of dengue dynamics in Kolkata, India revealed that control methods with higher environmental persistence such as treatment of surface and materials (TSM) mostly decreased dengue cases as compared to the use of ultra-low volume (ULV) spray of insecticides and lethal ovitraps (LO) [262]. Specifically, the comparison between the single applications of the three strategies: use of ULV, LO and TSM showed reductions of 2.9%,

48% and 49.1% respectively with TSM ranking highest. Considering pairwise and three-way comparisons of the control methods, any combination with TSM ranked highest as the three-way combination reduced 72.7% of the total cumulative cases [262]. In all, the above review suggests that environmental vector control modelling studies have lots of potential but is currently under-investigated and therefore more modelling studies need to be conducted accounting for the environmental vector control impacts towards the eradication of dengue.

Table 3.1: Characteristics of selected articles describing the year, aims and objectives, modelling methods, settings location, main vector control method and summary of studies. DM $\longrightarrow$ deterministic model, SM $\longrightarrow$ stochastic model, and NM $\longrightarrow$ network model. C $\longrightarrow$ Chemical control, B $\longrightarrow$ Biological control, and E $\longrightarrow$ Environmental control.

S/No.	Reference	Year	Aims and Objectives of study	Modelling methods	Settings	Vector control technique	Summary of findings/Conclusion
1.	Abad-Franch et al., [249]	2017	Explored the mosquito-disseminated larvicide pyriproxyfen for vector control via arboviral blockage	DM	Brazil: Manacapuru	C	Following the mosquito disseminated insecticides (pyriproxyfen), there were drastic decrease in the emergence and catch of both adult and young *Aedes* mosquitoes respectively. This reduction inhibits the transmission of *Aedes*-borne viruses such as dengue, chikungunya and Zika.
2.	Agusto and Khan, [244]	2018	Developed a deterministic dengue virus transmission model and parameterized it using 2017 dengue outbreak data in Pakistan. Sensitivity analysis was conducted and optimal control theory was applied.	DM	Pakistan	C	There is a strong reciprocal relationship between vaccination and the use of insecticides. Nonetheless, the use of insecticides slightly increases when there is a decrease in vaccination level as a result of increase in cost. Application of the two time-dependent controls derived from the sensitivity analysis could decrease the total number of infected mosquitoes and humans.
3.	Alphey et al.,, [245]	2011	Combined epidemiological models and mosquito population dynamics to investigate the effect of releasing RIDL (Release of insects carrying a Dominant Lethal) on dengue virus transmission.	DM	n/a	B	Having derived a preliminary estimate of the potential cost-effectiveness of vector control, it was predicted that the genetic control technique could swiftly eliminate dengue disease from a human community at very low expense.
4.	Andraud et al., [246]	2013	Developed a simple periodic-forced vector-host model. This model was based on a previous formulated model which investigated the impact of vector control techniques during a dengue outbreak in Singapore in 2005. The model in this work considers the seasonal variations in vector density and estimated the parameters using dengue fever incidence data from August 2003 to the end of 2007.	DM	Singapore	E	After fitting the model outputs with the dengue incidence data, there was a good fit which suggests that the impact of seasonality on dengue transmission dynamics is highly essential, even though the model does not consider the complex life cycle of the vector. Additionally, the seasonal fluctuations of the mosquito vector population occurred in phase with the variations in temperature. This signifies a strong climatic effect on the vector abundance thereby affecting the dengue virus transmission dynamics.
5.	Barmak et al., [250]	2014	Presented a stochastic dynamical model for the transmission dynamics of dengue. This model accounts for the co-evolution of the human hosts and the spatial Aedes aegypti dynamics.	SM	n/a	C	For insecticide spraying techniques with different efficiencies, it was observed that the most efficient fumigation strategies could be effective during a dengue virus outbreak. Also, isolating infected humans with high compliance level is an effective strategy, however, imposing restrictions on their movement is not likely to be effective. Therefore combining fumigation and infected human isolation during a dengue outbreak would be suitable strategies in mitigating the outbreaks.
6.	Bliman et al., [239]	2019	Proposed a sex-structured model that captured the constant and periodic impulsive releases of sterile male *Aedes* mosquitoes in the hopes of eliminating the wild-type mosquitos. This model serves as a foundation for vector control strategies.	DM	n/a	B	A mixed control strategy that requires the combination of open-loop and close-loop outputs produces the best results regarding the total number of releases of sterile male mosquitoes to be effectively rolled out during the rollout program and the time required to achieve elimination.

S/No.	Reference	Year	Aims and Objectives of study	Modelling methods	Settings	Vector control technique	Summary of findings/Conclusion
7.	Buonomo and Della Marca, [251]	2018	Considered a mathematical model accounting for the use of insecticide-treated bed nets (ITN) by humans. The effect of seasonality together with some varied rainfall and mean temperature scenarios were investigated. Optimal control problem was used to mitigate the number of infected individuals and cost effectiveness analysis was carried out to assess the most appropriate strategy in the elimination of dengue infection.	DM	n/a	C	The cost-effectiveness analysis showed that benefits of the cost of intervention efforts is influenced by the shift in periodic amplitude of the seasonal fluctuation. In general, of all the combination strategies for dengue disease control via its vectors considered, the most effective, averting the highest proportion of infections, is the use of ITN and insecticide spraying techniques. However, for areas with low seasonality effect, only insecticide spraying campaigns should be carried out in dengue control program as this is beneficial in terms of cost.
8.	Cai et al., [247]	2018	Considered an interactive dynamical model of wild-type and sterile mosquitoes and accounted for delay of the growth stage of the wild-type mosquito population. Analysis of the effect of the time delay of releasing sterile mosquitoes in two different rollout was performed.	DM	n/a	B	At a constant release rate of sterile mosquitoes, the delay pose an insignificant effect on the system dynamics and all the solution of the system tend to an equilibrium point. But at a release rate of sterile mosquitoes proportional to that of the wild-type mosquitoes, the delay exhibit a significant effect on the system dynamics via some parameter ranges. For a small delay, the solutions tends to an equilibrium point. However, as delay increases, the solutions of the system possess oscillatory behaviour by the way of Hopf bifurcations.
9.	Campo-Duarte et el., [55]	2018	A sex structured population model was proposed describing the interaction between uninfected (male and female) and mosquitoes infected (via deliberate transinfection) with *w*MelPop-*Wolbachia* strain in the same region. This model incorporates the natural introduction of the control or decision variable and introduces optimal control approach to capture the dynamics of *w*MelPop *Wolbachia* infection of the uninfected *Aedes aegypti* mosquito population. This is a targeted quest at estimating the number of *Wolbachia*-infected mosquitoes to be released in daily control action.	DM	n/a	B	The release policies derived from the model results, which is also consistent with Yeap et al. (2014) recommendations: (a) The release of *Wolbachia*-infected mosquitoes should be of considerable quantities. (b) Releases of *Wolbachia*-infected mosquitoes should occur for a long time period. (c) The *w*MelPop *Wolbachia* strain invasion is only likely feasible in relatively isolated mosquito populations. Additionally, the method derived in this study can advantageous to vector control interventions such that if the population density of wild-type mosquitoes is minimized at the earlier stages by other control measures such as SIT and insecticide spraying, the invasion of *w*MelPop *Wolbachia* strain and replacement of wild mosquitoes can be swiftly attained with low cost.
10.	Chavez et al., [252]	2017	Presents an SIR model accounting for vector-host transmission dynamics and vice versa. The model incorporates pesticide control and seasonal variations of vector resurgence and disease transmission rates. Also, the effectiveness of the control strategy is investigated.	DM	n/a	C	On investigating the seasonal fluctuations, it was revealed that the timing of the applications of pesticide is highly influential in controlling dengue viral infection, i.e. in the required amount of pesticide to achieve tolerably moderate levels of infection. Also, time variations in the second pesticide application showed induced destabilization caused by a periodic-doubling bifurcation. Therefore, the solution with a year period loses stability and a class of stable solutions with two-year period occurs. Hence the numerical investigations showed that avoiding the two-year periodic solution is best due to drastic increase of dengue viral infections under the period.
11.	Hancock et al., [253]	2016	Proposed a mathematical model to explain the transmission dynamics between *Aedes aegypti* mosquitoes and intracellular bacterium, *Wolbachia* which accounts for larval density dependent fluctuation in fitness components of *Wolbachia*-infected and wild mosquitoes. This model is applied to study *Wolbachia* field releases	DM	n/a	B	The investigated models incorporating larval density-dependent demographical variation in mosquito traits are effective in elaborating *Aedes aegypti* mosquitos and *Wolbachia* dynamics in experimental mosquito populations. These models highlight strong effects of mosquito density-dependence on *Wolbachia* dynamics in the field as well as can help in controling arboviral transmission such as Zika, dengue and chikungunya via the effective use of *Wolbachia*.

S/No.	Reference	Year	Aims and Objectives of study	Modelling methods	Settings	Vector control technique	Summary of findings/Conclusion
			and reveal how *Wolbachia* invasion end results can be highly dependent on the severity of the population density-dependent competition at the rollout locality. Following *Wolbachia* rollout programs, the period for establishing *Wolbachia* in the wild mosquito population can differ by over 2 years as this depends on the relative mosquito fitness of field and laboratory conditions.				
12.	He et al., [254]	2017	Proposed a multi-scale modelling incorporating the combination of a birth-pulse model with a genetically induced discrete model for the allelic frequencies. This model described the invasive spread of *Wolbachia* infection in mosquitoes resistant to CI.	DM	n/a	B	The results showed that the strategy for population eradication may not be actualised. However, population replacement strategy may be feasibly realized with success to sensitive or resistant allele. The failure or success of population replacement by Wolbachia may be dependent on the appropriate *Wolbachia* strain selected. Also, *Wolbachia*-induced parameters may cause catastrophic shifts in the stable states of the model system and may affect the rate of population replacement and density of wild mosquitoes.
13.	Hughes and Britton, [54]	2013	Developed a mathematical model used to describe the Human-mosquito dynamics in the presence of *Wolbachia* infection. The model further accounts for introduction of *Wolbachia*-infected mosquitoes which serves as a potential control measure for dengue transmission.	DM	n/a	B	The model results showed that *Wolbachia* bacterium has potential in controlling dengue transmissions in regions of moderate endemicity (that is, when the reproductive number, R_0, is not too large). But if R_0 is very high, *Wolbachia* can only have slight effect on the population as it can only reduce but not eradicate the transmission of dengue. Moreover, if control strategies such as mosquito population reduction are adapted, combining the introduction of various strains of *Wolbachia* that completely inhibit dengue transmission may be worthwhile.
14.	Li and Lui, [255]	2018	Established a sex-structured model with birth pulse and investigated *Wolbachia* invasion dynamics and spread into *Aedes* mosquito population. Additionally, it also studies the release strategies of *Wolbachia*-infected mosquitoes into the wild mosquito populations.	DM	n/a	B	The modelling results showed that perfect maternal transmission drives a successful invasion of *Wolbachia* infection in mosquitoes. However, in the case of imperfect maternal transmission, either partial replacement of *Wolbachia* infection or *Wolbachia* extinction may occur. Further simulations revealed that the partial success of *Wolbachia* replacement strategy is dependent on the number of initial *Wolbachia*-infected mosquitoes present.
15.	Luz et al., [256]	2011	Developed a model describing the transmission dynamics of dengue that accounts for the evolution of insecticide resistance and immune responses in humans. In line with this, the dengue health burden of disability-adjusted life years was measured and a cost-effectiveness analysis of insecticide control use was performed. Also, sensitivity and threshold analyses were done to investigate the uncertainties of the parameters used on the results.	DM	n/a	C	Continual yearlong larval control can be ineffective fuelling an increase in the burden of dengue epidemics as a result of evolution of insecticide resistance and herd immunity loss. Additionally, annual six high-efficacy adult vector control applications has cost-effectiveness ratio that may align with that of WHO's laydown standard.

S/No.	Reference	Year	Aims and Objectives of study	Modelling methods	Settings	Vector control technique	Summary of findings/Conclusion
16.	Marini et al., [240]	2019	Developed a stochastic transmission model which accounts for geographical distribution of *Aedes* mosquitoes and human population and spatial transmission dynamics of dengue in a Porto Alegre, Brazil. This model described the estimation of dengue cases that were avoided by ultra-low volume (ULV) insecticide spraying in the study region.	SM	Brazil:Porto Alegre	C	It was shown that a quarter of all the symptomatic cases were averted by insecticide spraying and low-income induced *Aedes aegypti* mosquito death decreased intervention performance as almost half of the mosquito population are killed by insecticide spraying.
17.	Mishra et al., [257]	2018	Proposed a network model that described the host-vector dynamics in n patches to control dengue transmission. In this case, the control is based on the Sterile Insect Techniques (SIT). The required R_0's were computed and existence and stability criteria for the steady states were analysed. Bifurcation effects were also investigated in relation to the disease-free and endemic equilibrium for isolated patch.	NM	n/a	B	Following the analytical and numerical solutions, it was shown that dengue can be controlled in a network by adopting SIT in only one patch as it is less required to apply SIT in all the network. This could be done by patches' coupling. The applicable success of SIT relies on the coupling strength of the migration parameter and the recruitment rate of the sterile mosquito population.
18.	Ndii et al., [268]	2016	Developed a mathematical model to investigate the effect of an endosymbiotic intracellular bacteria, *Wolbachia*, on the transmission dynamics and seasonality of dengue disease. The study focused on areas where dengue is not endemic but can spread as a result of human movement especially with dengue imported cases.	DM	Australia: Cairns	B	The results of the study showed that *Wolbachia* decreased the total dengue case number by about 80%. Also, dengue outbreaks time could be reduced by approximately 1.5 months annually in the presence of *Wolbachia*. The most significant effect is obtained when the seasonal force amplitude is low. Furthermore, the benefits of *Wolbachia* is dependent on the transmission rate.
19.	Oki et al., [258]	2011	Formulated an SEIR model for dengue transmission capturing seasonal change in mosquito lifespan and optimal timing of insecticide fogging to mitigate dengue disease burden in several wet season scenarios. Also, assessment of insecticide fogging was simulated and studied at low and high levels of dengue endemicity over a 500-year time period producing an endemic state.	DM	n/a	C	The results showed that seasonal variation and the level of transmission intensity largely influenced the optimal timing of insecticide fogging and its impact. Insecticide fogging application at optimal timing can control a substantial number of dengue virus cases.
20.	O'Reilly et al., [44]	2019	Used the combination of multiple modelling methods for estimating the dengue disease burden to predict dengue national case burden stratified by disease severity. Three different sources of data were used to map the spatial distribution of disease burden. Following a national release program of *Wolbachia*, the estimation of decreased dengue case was performed using a collection of transmission models.	DM	Indonesia: Yogyakarta city	B	The results showed that about 7.8 million was estimated to have symptomatic cases of dengue in Indonesia in 2015. This estimated number of cases was related to about 3.23 thousand DALYs. Majority of the this burden was due to underreporting as some asymptomatic or less severe dengue patients sought medical attention or had difficulty with disease diagnosis respectively. The implementation of the national *Wolbachia* rollout program was estimated to significantly decrease dengue cases by 86.2% over a long term.
21.	Pleydell and Bouyer, [259]	2019	Modelled the dynamics of *Aedes* mosquito populations incorporating the SIT, boosted SIT with pupicide pyriproxifen (BSIT), and/or auto dessemination technique (ADT). Additionally, the rate at rolling out sterile male mosquito and competitiveness threshold were identified.	DM	n/a	B	Boosting decreased the thresholds in sterile male release rate and fuels the mosquito's destabilisation. There is no bifurcation in the ADT submodel. Also, BSIT can avert by over 95% of the overall rollout to mitigate dengue burden than SIT suggesting that BSIT is effective in the control management of Aedes mosquitoes.

S/No.	Reference	Year	Aims and Objectives of study	Modelling methods	Settings	Vector control technique	Summary of findings/Conclusion
22.	Qu et al., [58]	2018	Developed a two-sex mosquito model to describe the potential effectiveness of *Wolbachia* transmission for controlling the mosquito-borne diseases. This model accounts for the *Wolbachia* transmission dynamics and incorporates aquatic stage and various pregnant stages of adult female mosquitoes, and heterosexual transmission. The R_0 was computed. A threshold effect which is driven by a backward bifurcation with three coexisting equilibria is identified. The sensitivity analysis of the model parameters and effectiveness of different migration strategies were investigated.	DM	n/a	B	It was shown that if R_0 is less than one, the endemic equilibrium can still be stable via backward bifurcation effect. Furthermore, there is a threshold condition for which a proportion of mosquito must exceed for *Wolbachia* establishment to occur in the wild-type mosquitoes. In addition, the best way to establish *Wolbachia* infection in mosquitoes is to decrease the wild-type mosquito population either by insecticide spraying or mosquito traps and then introduce male and pregnant female mosquitoes infected with *Wolbachia* infections.
23.	Robert et al., [260]	2013	A reduce and replace (RandR) strategic model, which numerically accounts for release of insects (dengue vector *Aedes aegypti* mosquitoes), possessing the anti-pathogenic and female-killing trait, was proposed. In other words, this model described the strategic release of *Aedes aegypti* mosquito carrying RandR strain to suppress mosquito-borne diseases such as dengue.	DM	n/a	B	Following the modelling results, it was shown that continuous release of RandR, may temporarily reduce the density of the *Aedes* mosquito population and this reduction may be long-lasting in the absence of fitness cost being related with the anti-pathogenic gene. Also, the swift RandR strain releases have a long-term reduction of vector densities compared to only female-killing rollout. Furthermore, the degree of reduction in overall mosquito densities depends on female inclusion in the rollout strategy, the release duration and release proportion.
24.	Salami et al., [261]	2020	A deterministic model was adopted to portray the transmission dynamics of dengue in *Aedes aegypti* mosquito population. This model accounts for the influence of seasonal fluctuating temperatures by integrating empirical and idealistic parameter tools. The epidemic dynamics of the seasonality influence were investigated following an imported case via the arrival of an infectious person. A sensitivity analysis was also performed on the interested quantities: peak time, epidemic peak size, and final epidemic size.	DM	Funchal, Madeira Island	E	The model results showed that the autumn and summer seasons could fuel dengue transmission with the arrival date of an infectious person greatly affecting the time and peak size distribution of the dengue epidemic. Interestingly, late-summer infectious individual arrivals could generate large epidemics within a short time amplitude. It was also revealed that seasonality affects the epidemic dynamics. This suggests that large epidemics with short time amplitude could be produced with starting warm temperatures and vice versa. The sensitivity analysis showed that the interested quantities were most sensitive to changes in arrival date, seasonal temperature, mortality and transmission rates and mosquito population.
25.	Senapati et al., [262]	2019	A general multi-patch dengue model was formulated to describe the spatio-temporal transmission dynamics of dengue disease and effectiveness of various adult mosquito controls (i.e. efficacy and environmental persistence) to reduce dengue burden. This model is fitted to monthly data of dengue cases in five regions of Kolkata, India for the period of two years (from 2014 to 2015).	SM	India: Kolkata	E	The results showed that control strategies with higher environmental persistence is more effective compared to the strategies with low environmental persistence. Also, the effectiveness of the adult control strategies is greatly influenced by the spatial coupling (connectedness) between the regions. Amongst the three control strategies considered: Ultra-low-volume (ULV) spray of insecticides; Insecticide treatment of surfaces and materials; and use of lethal ovitraps, the most effective in reducing dengue cases is treatment of surfaces and materials while the least effective is ULV.
26.	Strugarek et al., [241]	2019	Derived a minimalistic mathematical model incorporating the sterile insect technique (SIT) and incompatible insect technique (IIT) to eliminate *Aedes* mosquito population. Unlike other previous models, the model considered in this study is bistable as it accommodates mosquito population elimination and its survival. Different types of releases, which are constant, periodic or impulsive releases were considered as the necessary conditions for elimination were shown. Estimation of parameters using an *Aedes* polynesiensis population study, and both sufficient and minimal treatment times were performed. And both analytical and numerical results were analysed.	DM	n/a	B	The results showed that the mating competitiveness of SIT control strategy needs to be close to one for effectiveness. If not the case, there may be limited efficacy if there is a few number of the wild-type mosquito population. Also, the mating parameter in the model is very important in duration of controlling vectors via SIT method and suggested that entomologists focus more on the probability of mating between a male and a female mosquito with respect to the size of their habitat in their prospective experiments.

S/No.	Reference	Year	Aims and Objectives of study	Modelling methods	Settings	Vector control technique	Summary of findings/Conclusion
27.	Tang et al., [263]	2016	Developed a mathematical model to imitate the impulsive vector control program and continuous treatment of patient and isolation in Guangdong Province of China in 2014 dengue outbreak. This vector program occur every week (specifically on Friday afternoon) since its inception. The dengue accumulated infection data was fitted using the parameterized model to perform a retrospective analysis. This analysis was used to estimate the basic and control R_0, and the mosquito killing ratios.	DM	China: Guangdong	C	The results showed the estimation of both basic and control R_0 to be 1.7425 and 0.1709 respectively, suggesting a highly effective control of dengue outbreak during the intervention program. It was also observed that when a Friday is skipped during the integrated program, this would not increase the control R_0 to one, rather, it would increase the number of accumulated infections at the end of the disease outbreak. In all, a rapid and regular impulsive vector control implementation leads to effective decrease in the control R_0 which in turn significantly reduce new infections.
28.	Thome et el., [264]	2010	Presented a mathematical model that captured the introduction of sterile male mosquitoes, besides the use of chemicals (insecticides), to biologically control mosquito population. Optimal control strategy was used to search for minimal effort required to decrease female mosquitoes that are productive by considering the cost of sterile male mosquito production, cost of delivery to experimental cites together with social cost and cost of chemical application such as insecticide.	DM	n/a	B	The model results showed that social cost should be considered in controlling mosquito vectors as its exception when reducing the cost of other control strategies could result in unsuitable strategies. Furthermore, at the initial stage of the control strategy, high chemical insecticide application is required and then gradually decrease with time. Unless the social cost is multiplied by hundred, the sterile male mosquito release should follow a bell-like curve with an increase and decrease at both ends together with a moderately flat middle.
29.	Wijaya et al., [265]	2014	Presented an optimal control model, which describes the dynamics of mosquito reduction management using chemical such as Temephos and carrying out fumigation in dengue endemic regions where mosquitoes are prevalent. The basic R_0 is computed and equilibrium stabilities were analysed.	DM	n/a	C	The results showed that if R_0 is less than 1, the disease free equilibrium (DFE) exists and is locally asymptotically stable, while the coexistence equilibrium (CE) does not exist. On the other hand, if R_0 is greater than 1, the DFE is unstable but the CE exists and is globally asymptotically stable in a positive region. Also, the best mosquito control strategies obtained from the optimal control analysis are obtained if the number of mosquitoes is small at the initial stages of control and additionally combine the use of Temephos and fumigating activities.
30.	Winskill et al., [266]	2014	Designed a compartmental model that accounts for the release dynamics of adult and pupal mosquito carrying RIDL. This model was used to fit a field experimental data, which described the large-scale pupal mark release recapture phenomena to determine the pupal release dynamics. Simulation of pulsed releases of adult, pupae or the combination of both were shown. And various release mechanisms of mosquito-carrying RIDL, to sustain a long-lasting decrease of the wild-type mosquito population are investigated.	DM	n/a	B	For regular recurring releases, model simulations showed that releasing only adult-carrying RIDL mosquitoes performs better compared to the other releases: pupae only and combined adult-pupae releases, and vice versa for a less recurring releases. Also the relative efficacy of releasing pupae is affected by the pupal emergence rate from release apparatus. For a sustained long-lasting reduction of wild-mosquitoes in the presence of low recurrence, the combined adult-pupae mosquito releases is most effective than the pupal-only or adult-only releases.
31.	Zhang and Lui, [242]	2020	Developed a mathematical model to investigate the *Wolbachia* transmission dynamics in *Aedes-aegypti* mosquitoes as a means to suppress the spread of dengue. This model considered only female mosquitoes as they give infectious bites or obtain protein via bites to maturate their eggs. Equal number of male and female mosquitoes are assumed. Sensitivity and optimal control analysis were performed on model parameters.		n/a	B	The model analysis revealed that without release, the model is bistable. This indicates that only one interior steady state is stable whenever it exists. Optimal control theory showed that halting a release after a continuous release for two years, would allow the *Wolbachia*-only equilibrium be locally asymptotically stable with time, suggesting the invasion of *Wolbachia* in all the mosquitoes and then resulting in the prevention of the spread of dengue viral infection.

S/No.	Reference	Year	Aims and Objectives of study	Modelling methods	Settings	Vector control technique	Summary of findings/Conclusion
32.	Zhang et al., [267]	2015	Proposed a model which described the spread and invasion of *Wolbachia* infections accounting for the effects of CI and fitness effects. This model explored whether augmentation can inhibit the transmission of dengue in the field and also considered the question of why some rollout strategies were unsuccessful and what caused this failure in establishing population replacement.	DM	n/a	B	The stability analysis showed that some phenomena may have contributed to the failure of the *Wolbachia* invasion in wild mosquitoes. Such attractors include backward bifurcation and augmentation mechanism like frequency, quantity and timing. In all, the modelling result revealed that successful establishment of *Wolbachia* infection via replacing the wild mosquitoes with *Wolbachia*-infected mosquitoes would depend on the type of *Wolbachia* strains selected for deployment and an appropriate augmentation techniques.

Table 3.2: Description of the quality assessment of included studies adopting the tool: Assessment for Modelling Studies (ASM)

S/No.	Author	Year	Aims and Objectives/ Abstract	Intervention comparators	Outcome measures defined	Model structure and flowchart	Modelling methods	Parameters specified	Assumptions explicit and justified	Quality of data and uncertainty and/or sensitivity analyses	Model validation	Presentation of results	Interpretation and discussion of results	Conflicts of or Competing interest declared	Final point	Final score (%)	Rating
1.	Abad-Franch et al., [249]	2017	2	2	2	1	2	2	2	0	2	2	2	2	21	87.50	Very High
2.	Agusto and Khan, [244]	2018	2	1	2	2	2	2	2	2	2	2	2	0	21	87.50	Very High
3.	Alphey et al.,, [245]	2011	2	1	2	2	2	2	2	2	1	2	2	2	22	91.67	Very High
4.	Andraud et al., [246]	2013	2	2	2	1	2	2	2	0	2	2	2	0	19	79.17	High
5.	Barmak et al., [250]	2014	2	2	1	1	2	2	1	1	2	2	2	2	20	83.33	Very High
6.	Bliman et al., [239]	2019	2	1	1	1	2	2	2	0	1	2	2	2	18	75.00	High
7.	Buonomo and Della Marca, [251]	2018	2	2	2	1	2	2	2	0	1	2	2	0	18	75.00	High
8.	Cai et al., [247]	2018	2	1	1	1	2	2	2	0	1	2	2	0	16	66.67	High
9.	Campo-Duarte et el., [55]	2018	2	2	2	1	2	2	2	2	1	2	2	0	20	83.33	Very High
10.	Chavez et al., [252]	2017	2	1	2	1	2	2	2	0	1	2	2	0	17	70.83	High
11.	Hancock et al., [253]	2016	2	1	2	1	2	2	2	1	2	2	2	2	21	87.50	Very High
12.	He et al., [254]	2017	2	1	1	1	2	2	2	0	1	2	2	2	18	75.00	High
13.	Hughes and Britton, [54]	2013	2	1	2	2	2	2	2	1	1	2	2	0	19	79.17	High
14.	Li and Lui, [255]	2018	2	2	1	1	2	2	2	1	1	2	2	0	18	75.00	High
15.	Luz et al., [256]	2011	2	2	2	2	2	2	1	2	1	2	2	2	22	91.67	Very High
16.	Marini et al., [240]	2019	2	1	1	2	2	2	2	2	2	2	2	2	22	91.67	Very High

S/No.	Author	Year	Aims and Objectives/ Abstract	Intervention comparators	Outcome measures defined	Model structure and flowchart	Modelling methods	Parameters specified	Assumptions explicit and justified	Quality of data and uncertainty and/or sensitivity analyses	Model validation	Presentation of results	Interpretation and discussion of results	Conflicts of or Competing interest declared	Final point	Final score (%)	Rating
17.	Mishra et al., [257]	2018	2	1	1	2	2	2	2	0	1	2	2	0	17	70.83	High
18.	Ndii et al., [268]	2016	2	2	1	2	2	2	2	2	1	2	2	0	20	83.33	Very High
19.	Oki et al., [258]	2011	2	2	1	1	2	2	2	0	1	2	2	2	19	79.17	High
20.	O'Reilly et al., [44]	2019	2	2	1	2	2	1	2	2	2	2	2	2	22	91.67	Very High
21.	Pleydell and Bouyer, [259]	2019	2	1	1	1	2	1	2	2	1	2	2	2	19	79.17	High
22.	Qu et al., [58]	2018	2	2	1	2	2	2	2	2	1	2	2	0	20	83.33	Very High
23.	Robert et al., [260]	2013	2	2	1	1	2	2	2	0	1	2	2	2	19	79.17	High
24.	Salami et al., [261]	2020	2	2	1	2	2	2	2	2	2	2	2	0	21	87.50	Very High
25.	Senapati et al., [262]	2019	2	2	1	1	2	2	2	0	2	2	2	0	18	75.00	High
26.	Strugarek et al., [241]	2019	2	1	1	1	2	2	2	0	1	2	2	0	16	66.67	High
27.	Tang et al., [263]	2016	2	1	1	1	2	2	2	2	1	2	2	0	18	75.00	High
28.	Thome et el., [264]	2010	2	2	1	1	2	2	2	0	1	2	2	0	17	70.83	Very High
29.	Wijaya et al., [265]	2014	2	2	1	1	2	2	2	1	1	2	2	0	18	75.00	High
30.	Winskill et al., [266]	2014	2	2	1	1	2	2	2	0	2	2	2	2	20	83.33	Very High
31.	Zhang and Lui, [242]	2020	2	1	1	2	2	2	2	2	1	2	2	2	21	87.50	Very High
32.	Zhang et al., [267]	2015	2	2	1	1	2	2	2	1	1	2	2	0	18	75.00	High

3.4.4 Quality assessment of study results

The selected studies possessed an Assessment of Modelling Studies (AMS) score range between 66.67 – 91.67% (Table 3.3). Thus all scored at least a 'High' methodological quality (cut-off for high is 65%). Additionally, of the 32 studies included, thirteen scored above 80% as these studies fell into the 'Very High' category of the Assessment of Study Quality (ASQ). In all, the selected studies provided in detail: the description of model structure, methods and validation, parameter specifications, assumptions made, intervention comparators and quality of data and uncertainty/sensitivity analysis.

Table 3.3: Table showing the distribution of study quality with respect to the vector control types. $n \longrightarrow$ number of studies.

Vector control types	**Study quality** n **(%)**				
	Very High	High	Medium	Low	Total
Chemical control	5 (50)	5 (50)	0	0	10
Biological control	8 (42)	11 (58)	0	0	19
Environmental control	0 (0)	3 (100)	0	0	3

To further investigate if there was there a difference in quality of studies (Very High and High) across the different vector control methods (Chemical, Biological and Environmental), a bivariate analysis was performed using the Fisher's exact test. Our analysis showed that there is no significant difference in the study quality (Very High and High) of the different vector control methods (p=0.4). In other words, there was no statistically significant difference in the proportion of "High" versus "Very High" quality studies across the vector controls (Figure 3.6).

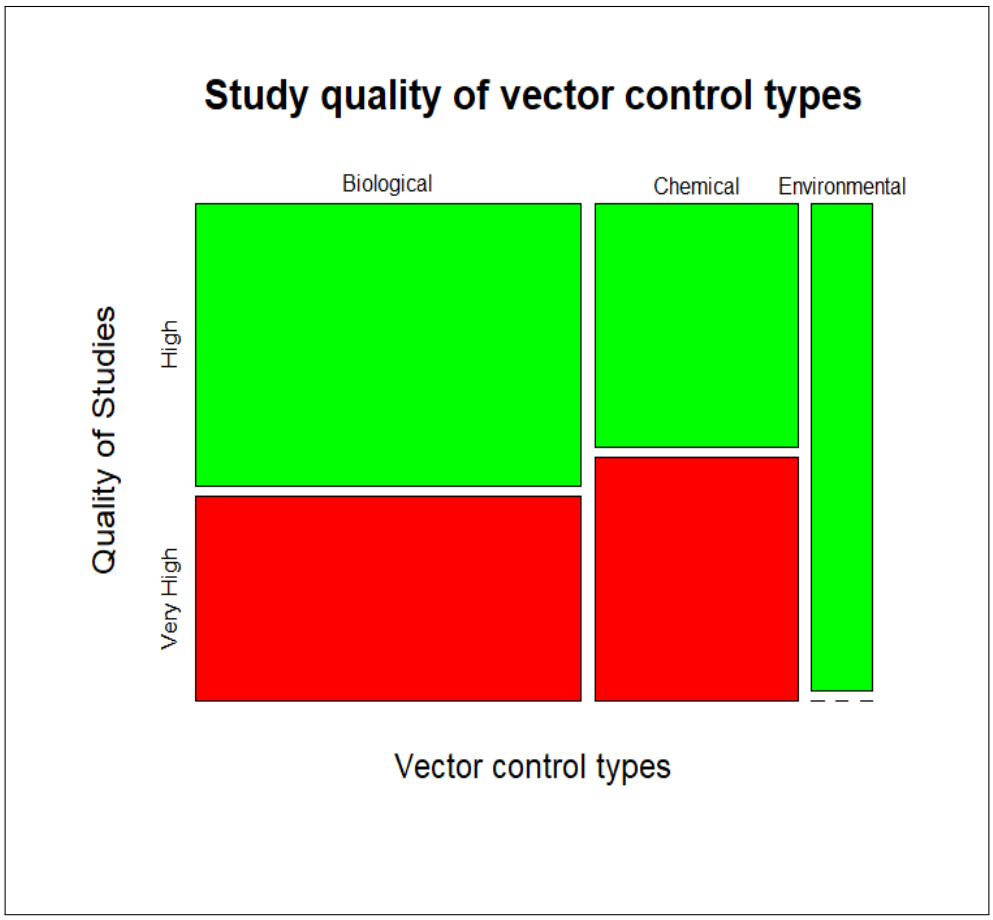

Figure 3.6: Mozaic plot showing the distribution of the bounded area of study qualities of the vector control types.

3.5 Discussion

The mathematical modelling of dengue transmission can be useful in understanding disease dynamics [299, 300, 301]. It is a significantly tool that can assist in predicting and curtailing outbreaks of dengue disease, and help in reducing transmission of infection and mitigate dengue burden [242, 268, 250, 256, 261, 262]. Overall, our study reviews the effectiveness of mathematical modelling of different vector control approaches to reduce the spread of dengue disease. In this review, we identified 32 articles that met our search criteria. We then stratified the selected articles into the modelling types: Deterministic, Stochastic

and Network modelling methods. The articles mainly consisted of deterministic modelling methods for dengue vector control (88% of the total selected studies). Other modelling approaches such as stochastic and network modelling shared 9% and 3% of the total selected studies respectively. Based on the vector control approaches, we grouped the selected articles into three vector control approaches: Chemical (11), Biological (18) and Environmental (3).

Modelling studies demonstrate that the chemical vector control methods such as the use of insecticides for outdoor fogging or indoor residual spraying, insecticide-treated bed nets (ITN), insecticide-treated house screens (ITHS) and insecticide-treated door curtains (ITC) for dengue transmission could be highly effective in reducing the burden of dengue when scaled up [240, 249, 252, 258]. They also showed that when dengue burden is high, chemical controls are best used in combination, while a single control technique such as insecticide spraying may be adequate for areas with low endemicity [251]. One important prediction from modelling is that long-time usage of this method could fuel mosquitoes' resistance to the chemicides and then result in a less effective and efficient control strategy [256]. These modelling results need to be considered in addition to the known threat to the environment via contaminating water bodies and air pollution [127].

On the other hand, the biological vector control methods are gaining global popularity and usage as some of these methods are self-sustaining [39, 197]. Accordingly, various mathematical models accounting for the biological control of vectors to mitigate dengue spread have been formulated in the last decades [239, 241, 247, 257, 259, 264]. These modelling studies consider the transmission dynamics of releasing sterile insect techniques (SIT), genetically-modified mosquitoes (GMM) and *Wolbachia*-infected mosquitoes (among other interventions) to curb the spread of dengue infection. Our review has presented understanding on SIT techniques and how it could be very effective in controlling dengue infection however, when boosted with pupicide pyriproxifen (PP) this could greatly reduce the number of sterile males required to eliminate the mosquito population [259]. This would only be established in areas with high but not low mosquito densities. According to a network model, SIT could be very

effective in reducing dengue viral infection as that would depend on the rate of recruiting sterile mosquitoes, migration parameters and coupling effect [257]. For GMM methods such as RIDL techniques, which could be less expensive to carry out [245], the effectiveness of these methods could depend on proportion of RIDL release, duration of release and most especially the inclusion of adult-RIDL female mosquitoes [260].

Wolbachia-infected mosquito rollouts have been very effective in averting dengue cases, with an estimated reduction of over 80% in countries like Indonesia and Australia [268, 44]. Since then, there has been increasing numbers of models addressing transmission dynamics and features that drive successful strategies, with ten of the 18 models on biological methods focused on *Wolbachia*-based mosquito control. The effectiveness of *Wolbachia*-carrying mosquitoes is dependent on reproductive advantage CI, fitness effect, maternal transmission and viral blocking strength [162]. Furthermore, *Wolbachia*-infected mosquito release programs could also decrease the duration of feasible outbreaks of dengue infection by a month and half [44].

Regarding the mathematical modelling of environmental control methods, there are few articles describing the modelling impact. Although some of these models are conjoined with other control methods such as chemical and biological methods, model outcomes suggest that environmental interventions - for instance treating surfaces and materials and seasonal variations could have greater impact in reducing dengue cases when compared to chemical methods such as insecticide spraying without the attendant environmental contamination [246, 261, 262]. This sparse modelling work is encouraging and future studies on environmental actions alone and in combination with other control measures are needed.

This review relied on the modelling results of articles taken from the extensive database search describing the vector controls of dengue transmission dynamics models. These models showcased the different control techniques in mitigating dengue viral transmission. As far as the authors are aware, this review is the first to explore the present understanding of vector control approaches and the effective role of mathematical models in mitigating or eliminating

dengue. However, the selected articles were not evenly distributed as more than half of the studies were from 2017 onwards. This may have been a consequence of the severe dengue outbreaks in the Americas, some parts of South East Asian region in 2018 to 2019, arousing the interest in vector control and modelling studies [273]. Further, only published English journal articles were considered as non-English studies were excluded to avoid oversight. Other referencing types such for, book sections, conference proceedings and serials were excluded as they do not contain sufficient detail to assess the studies. In addition, the other referencing types are approximately 3% of the searched articles after removing the duplicates and as such, their exclusion has an insignificant impact. Essentially, the AMS tool used in appraising the included articles relies in part on the authors' knowledge and as such could create grounds for possible bias [271]. Overall, there is a chance of information bias as some articles may not have been included in the databases used for this research study.

In conclusion, our study, based on the selected published articles provided detailed understanding of all three methods of vector controls and their effectiveness. However, the magnitude of their effectiveness has some dependencies. The chemical method has some drawbacks based on the evolution of vector resistance resulting in decreased efficacy of these methods. The biological method could be a self-sustaining form of control as trans-infected mosquitoes (with *Wolbachia*) could pass on the *Wolbachia* infections to the offspring thereby inhibiting the transmission of dengue. This has been shown to be very effective; however, factors such as seasonality and heatwaves could reduce effectiveness through loss of *Wolbachia* infection in mosquitoes. Environmental control methods have lots of potential but are currently under-investigated, therefore there is need to further model environmental parameters such as healthy drainage systems, covering of water containers and good hygiene, to inform the impact on dengue burden. In all, there is a strong need to consider the combination of the three methods of vector control via mathematical modelling studies to evaluate the impact on the eradication or elimination of dengue disease at large.

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Chapter 4

Modeling the potential of *wAu-Wolbachia* strain in mosquitoes to control *Aedes*-borne arboviral infections

Chapter publication:

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Contrbutions:

Ogunlade, S. T. wrote the manuscript presented in this chapter. Ogunlade, S. T. also developed the model, analysed the differential system governing the disease dynamics and the results and wrote the simulation codes for the disease model.

Ogunlade, S. T. and Adekunle, A. I. conceived the project work described in this chapter. Adekunle, A. I. assisted with the model formation and interpretation. Adekunle, A. I. and Meehan, M. T. assisted with the analysis of the results. McBryde, E. S., Rojas, D. P., Adekunle, A. I. and Meehan, M. T. contributed to proof-reading and meticulously reviewing the manuscript.

Summary

The first section (Section 4.1) of this chapter introduces arboviral infections such as dengue, Zika and chikungunya. These infections are fast spreading diseases that pose significant health problems globally. In order to control these infections, an intracellular bacterium called *Wolbachia* has been introduced into wild-type mosquito populations in the hopes of replacing the vector transmitting agent, *Aedes aegypti* with one that is incapable of transmission. In the next section (Section 4.2), I developed a *Wolbachia* transmission model for the novel *w*Au strain which possesses several favourable traits (e.g., enhanced viral blockage and maintenance at higher temperature) but not cyctoplasmic incompatibility (CI) – when a *Wolbachia*-infected male mosquito mates with an uninfected female mosquito, producing no viable offspring. In Section (4.3), the model describes the competitive dynamics between *w*Au-*Wolbachia*-infected and uninfected mosquitoes and the role of imperfect maternal transmission. By analysing the system via computing the basic reproduction number(s) and stability properties, the potential of the *w*Au strain as a viable strategy to control arboviral infections is established. The results of this work show that enhanced maintenance of *Wolbachia* infection at higher temperatures can overcome the lack of CI induction to support *w*Au-*Wolbachia* infected mosquito invasion (Section 4.4). This study will provide support for future arboviral control programs, that rely on the introduction of new *Wolbachia* variants.

Keywords: Arbovirus, *Aedes* mosquitoes, *Wolbachia*, Stability, Sensitivity, Control

4.1 Introduction

Arthropod-borne viruses, or arboviruses, are viruses that are transmitted via blood feeding arthropods [1]. Arboviral infections such as dengue, Zika and chikungunya are fast spreading diseases that pose significant health problems globally [13, 14, 15, 302]. These viral infections, in particular dengue, are transmitted mainly by *Aedes aegypti* and sometimes by *Aedes albopictus* (Asian Tiger) female mosquitoes when taking a blood meal from the host [5, 6]. Approximately 390 million dengue infections are estimated to occur worldwide annually, putting 40% of the total human population at risk [303]. Dengue infection is the most geographically wide-spread of the arboviral infections [14, 303]. It has different severity levels which are classified according to disease progression from dengue without warning signs to dengue with warning signs and then severe dengue [304]. Clinical manifestation includes sudden high-grade fever, headache, nausea, arthralgia, eye pain, muscle ache and rash in some cases [88]. Presently, there is no specific universal treatment for dengue infections: the vaccine envelopment targets young populations; the efficacy of the only vaccine licensed depends on prior immunity to at least one serotype of dengue; and it provides heterogeneous protection against the different serotypes [226, 227].

Other arboviral infections such as Zika, chikungunya and yellow fever are also of global health concern [305]. These arboviral infections have occurred simultaneously with dengue [305, 306]. Some of these infections share many similar clinical manifestations with dengue infection and also allow arboviral coinfection such as dengue and chikungunya [106], chikungunya and Zika [97] and yellow fever and chikungunya [114]. Although, there are no specific treatments for Zika and chikungunya viral infections, these infections can be managed by supportive treatment of symptomatic individuals and adequate rest. This treatment includes fluid intake and administering drugs such as acetaminophen to suppress pain and fever [96, 307]. However the prevention strategy for yellow fever infection is available i.e. vaccination [112, 111].

To control these infections, an intracellular bacterium called *Wolbachia* can be used to

suppress transmission in arthropods such as mosquitoes and flies [151, 162, 202, 154]. *Wolbachia* infection inhibits arboviral transmission in mosquitoes via four mechanisms: immune priming - preactivation of the mosquito immune system; induction of the phenoloxidase cascade - triggers immune response to viruses; competition of intracellular resources - inducing authophagy; and induction of microRNA-dependent immune pathways - essential for gene regulation and stability, immune defense, ageing and organ differentiation [2]. This endosymbiotic bacterium which exists naturally in more than 50% of all insect species can be found within the cytoplasm of the cells of their hosts [152, 153, 154]. Whilst *Wolbachia* is not naturally present in *Aedes aegypti*, it can be introduced via stable transinfections using microinjections [159, 40].

The *Wolbachia*-based control strategy is carried out by infecting mosquitoes with a strain of *Wolbachia* and then releasing them into wild mosquito populations in the hopes of replacing the vector transmitting agent *Aedes aegypti* with one that is incapable of transmission [204, 159, 40]. Infecting an *Aedes* mosquito with *Wolbachia* can change some of the *Aedes* characteristic features. In practice, *Wolbachia* can reduce the life-span of mosquitoes by half producing a deleterous fitness effect [186]. Another feature is cytoplasmic incompatibility (CI) [187, 151, 188, 242] which occurs when a *Wolbachia* infected male mates with an incompatible female mosquito (usually *Wolbachia* uninfected) producing no offspring [205]. Other features of *Wolbachia* which serve as liabilities in mosquitoes include: imperfect maternal transmission (IMT) [197, 40] and loss of *Wolbachia* infection (LWI). LWI impedes the establishment of *Wolbachia*-infected mosquitoes and is a result of mosquito vulnerability to high temperature [196, 48].

However, a novel strain of *Wolbachia*: *w*Au, has shown to produce high viral blockage whilst maintaining *Wolbachia* infection in *Aedes* mosquitoes at higher temperature [162]. Moreover, *w*Au allows superinfection to occur when *w*Au and other strains of *Wolbachia* co-exist in the vector host [162]. Despite these favourable features, *w*Au does not induce CI [162]. Although CI absence does not establish *Wolbachia* infected mosquitoes, the effect

could be outweighed by LWI and IMT [197].

The difference in the common *Wolbachia* strain features are described in Table 4.1 below:

Table 4.1: Characteristics of different *Wolbachia* strains in *Aedes* mosquitoes. As defined in [151], the percentages (%) of the effects of these features are: High⟶ above 90, Medium⟶ 20 to 90, Low⟶ less than 20 and None⟶ 0 (features not detected).

Features	***w*Au**	***w*Mel**	***w*MelPop**	***w*AlbA**	***w*AlbB**
Viral blockage	High[162]	Medium[165, 308]	High[308, 159, 47, 166]	Medium[162]	High[309]
Maternal transmission	High[162]	High[40]	High[186, 167]	High[162]	High[310]
Loss of *Wolbachia* infection at higher hemperature	Low[162]	High[162]	High[162]	Medium[162]	Medium[162]
Fitness cost	Medium[162]	Medium[162]	High[311, 211]	High[162]	Medium[151]
Cytoplasmic incompatibility	None[162]	High[40]	High[186, 167]	High[162]	High[310]

In general, the introduction of mathematical models to understand infection dynamics of diseases has long been helpful in the area of disease control [51]. A number mathematical models of *Wolbachia* dynamics in a mosquito population have been formulated [55, 312, 54, 56, 58, 216, 217, 57, 218, 197]. Some of these models introduced *Wolbachia* strain(s) into a mosquito population and classified them into age-sturctured *Wolbachia*-infected and -uninfected mosquito compartments [56, 58, 57, 197]. Ndii et al., 2012 [56], formulated a mathematical model for the *Wolbachia* interaction between the immature stages (aquatic stage), adult male and female mosquito populations to investigate the persistence of mosquitoes infected with *Wolbachia* when competing with the uninfected ones. They derived the steady state solutions and showed that parameters such as maternal transmission, reproductive, death and maturation rates drive the persistence of the *Wolbachia*-infected mosquito population. A similar model developed by Xue et al, considered the *Wolbachia*-induced fitness change and the CI effect [57]. They showed that if the basic reproduction number (R_0) of the *Wolbachia*-infected mosquitoes is less than one, an endemic *Wolbachia* infection can still occur via backward bifurcation if a sufficient number of the mosquitoes are introduced into the population. A mathematical model of *Wolbachia* to control dengue fever transmission [54] was developed by Hughes et al. The model showed that the use of *Wolbachia* has high potential to control dengue where the R_0 due to *Wolbachia*-infected

Aedes mosquitoes is not too large in endemic areas. Another study of a *Wolbachia* invasive model incorporated IMT and LWI and showed that CI does not guarantee the establishment of *Wolbachia*-infected mosquitoes as the disadvantages derived from IMT and LWI in the production of *Wolbachia*-infected mosquitoes could outweigh CI [197].

Additionally, a study conducted by O'Reilly et al combining multiple modeling methods, was used to estimate the burden of dengue and map its distribution across Indonesia [44]. They predicted that there was a reduction in dengue transmission after a nationwide release of *w*Mel-*Wolbachia*-infected mosquitoes. In addition, they predicted about 86% of the estimated 7.8 million annual cases of symptomatic dengue in Indonesia could be averted following a complete nationwide rollout of *Wolbachia*-infected mosquitoes. Recently, a modeling study presented a dengue transmission model in the presence of female wild-type and *w*MelPop *Wolbachia*-infected *Aedes aegypti* mosquitoes. They concluded that although the *w*MelPop strain reduces the lifespan of infected mosquitoes, which could be challenging to achieve replacement of wild-type mosquitoes, its optimal release ensured the replacement of wild-type mosquitoes and also reduced dengue burden in the human population [312]. A mosquito-*Wolbachia* model was developed by Xue et al, to compare the potential effectiveness of two *Wolbachia* strains (*w*Mel and *w*AlbB) to control arboviral spread [313]. They observed that each of the two different strains of *Wolbachia* can effectively decrease the rate of arboviral transmission.

Here, we develop a general *Wolbachia* model capable of faithfully replicating all of the strain features described in Table 4.1. The general transmission model is an extention of the *Wolbachia* transmission model introduced in Adekunle et al., 2019 [197], which described the competitive dynamics between (*w*Mel-like) *Wolbachia*-infected and uninfected mosquitoes. Despite the non-induction of CI in *w*Au-*Wolbachia*-infected mosquitoes, *w*Au infection is retained and able to block viral transmission efficiently compared to other strains even at high temperature. Therefore, we incorporated this feature to determine if the advantages (*Wolbachia* retainment) of the *w*Au strain outweigh the ineffectiveness of CI. This feature

has not been considered in previous models. Furthermore, we incorporate imperfect maternal transmission into the model. By analysing the system via computing the basic reproduction number(s) and investigating the stability properties of the equilibrium points, the potential of the *w*Au strain as a viable strategy to control *Aedes*-borne infections can be established. The aim of this modeling approach is to support future *Aedes*-borne viral control programs, particularly with the introduction of new *Wolbachia* variants.

4.2 Methods

4.2.1 Model Formation

In this section, we investigate a modified *Wolbachia* transmission model studied in Adekunle et al., 2019 [197], focusing on a novel *Wolbachia* strain, *wAu*, which has high retainment, high viral blockage and does not induce CI. The mosquito population is subdivided into two groups: the uninfected mosquitoes $(.)_u$ and the *Wolbachia* infected mosquitoes $(.)_w$. The term $(.)$ can be aquatic/immature (eggs, larvae and pupae) A, male M or female F mosquitoes. In addition, we denote the aquatic/immature stages, mature male and mature female uninfected mosquitoes as A_u, M_u, F_u, and *Wolbachia*-infected mosquitoes as A_w, M_w, F_w respectively. As in Adekunle et al., 2019 [197] the model also incorporates the IMT of *w*Au-*Wolbachia*.

There are four possible mosquitoes' mating pairs: F_uM_u, F_uM_w, F_wM_u and F_wM_w. As *Wolbachia* infection is maternally transmitted, F_uM_u and F_uM_w will produce uninfected offspring while F_wM_u and F_wM_w will typically produce infected offspring. However if there is imperfect maternal transmission, the two latter strategies could produce some proportions of uninfected offspring [162].

To mathematically write the system of differential equations governing the *Wolbachia* transmission dynamics, we express the feasible mating strategies of uninfected and *Wolbachia* infected mosquito populations together with their per capita egg laying rates as equations (4.1)-(4.6):

Table 4.2: Mosquito-*Wolbachia* Model Notations.

Parameters	**Description**	**Values** (wMel)	**Values** (wAu)	**Dimension**	**References**
ρ_{uu}	Reproduction rate (egg laying rate) from mating between F_u and M_u/M_w mosquitoes	13	13	eggs/day	[314, 186, 197]
ρ_{ww}	Reproduction rate (egg laying rate) from mating between F_w and M_u/M_w mosquitoes	10	10	eggs/day	[314, 40, 197]
δ	The proportion of *Wolbachia* infected eggs resulting from mating between M_uF_w mosquitoes	0.95	0.95	dimensionless	[40]
ν	The proportion of *Wolbachia* infected eggs resulting from mating between M_wF_w mosquitoes	1	1	dimensionless	[197]
ϕ	The CI induction	1	0	dimensionless	[162]
ψ	Fraction of eggs that are male	0.5	0.5	dimensionless	[315, 197]
K	Carrying capacity of the aquatic stage A	10^6	10^6	aquatic mosquitoes	[197]
σ	Loss of *Wolbachia* infection (LWI)	0.04	0	day^{-1}	Assumed
τ_u	Maturation rate of A_u aquatic stage into adulthood (per capita)	0.11	0.11	day^{-1}	[40, 314]
τ_w	Maturation rate of A_w aquatic stage into adulthood (per capita)	0.11	0.11	day^{-1}	[40, 314]
μ_{Au}	A_u aquatic stage mortality rate (per capita)	0.02	0.02	day^{-1}	[57]
μ_{Aw}	A_w aquatic stage mortality rate (per capita)	0.02	0.02	day^{-1}	[57]
μ_u	F_u adult mortality rate (per capita)	0.061	0.04316	day^{-1}	[162, 197]
μ_w	F_w adult mortality rate (per capita)	0.068	0.08079	day^{-1}	[162, 197]

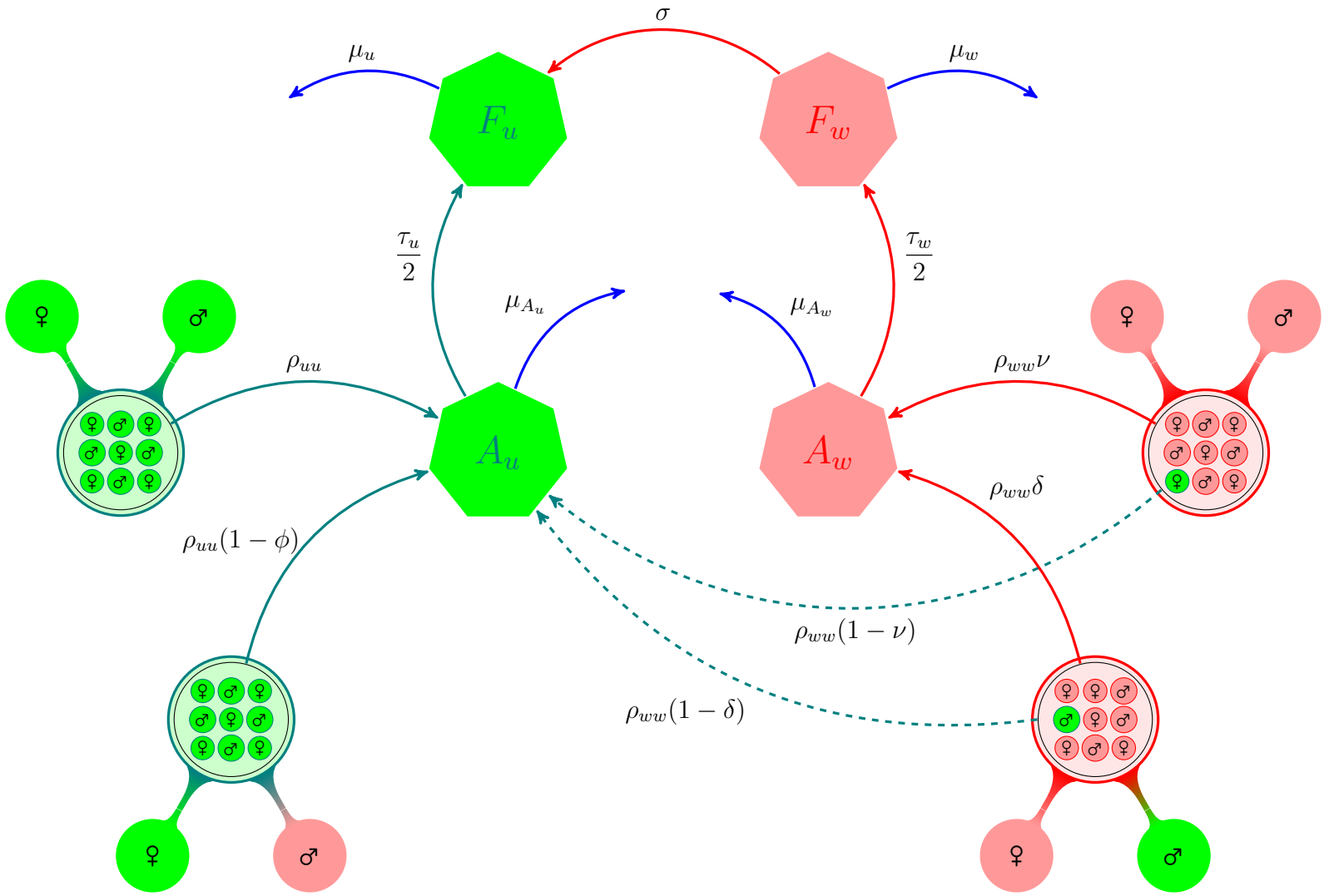

Figure 4.1: General model showing the *Wolbachia* infection dynamics in mosquitoes as M has been set equal to F. The green and red compartmental polygons represent wild-type and *Wolbachia*-infected mosquitoes respectively. A_u and F_u represent the aquatic (eggs, larvae and pupae) and adult female mosquitoes for the uninfected mosquito population respectively while A_w and F_w represent their *Wolbachia* infected counterparts. The teal and red arrows illustrate the population progression of uninfected and *Wolbachia*-infected mosquitoes respectively. The four large circles (each enclosing nine smaller circles) represent the mosquito mating outcomes between a female (♀) and male (♂) mosquitoes. The effect of cytoplasmic incompatibility (ϕ), i.e. for wAu and wMel strains, $\phi = 0$ and $\phi = 1$ respectively, is illustrated by mating between uninfected female and *Wolbachia*-infected male mosquitoes. The dashed lines represent the proportion of uninfected offspring caused by imperfect maternal transmission (IMT). The blue lines depict mosquito mortality. If there is loss of *Wolbachia* infection (LWI), $\sigma > 0$. But if there is no LWI as in wAu-*Wolbachia* strain, then $\sigma = 0$.

$$\frac{dA_u}{dt} = \left[\frac{\rho_{uu}(F_uM_u + (1-\phi)F_uM_w) + \rho_{ww}((1-\delta)F_wM_u + (1-\nu)F_wM_w)}{M}\right]\left(1-\frac{A}{K}\right) - (\tau_u + \mu_{Au})A_u, \tag{4.1}$$

$$\frac{dF_u}{dt} = (1-\psi)\tau_u A_u + \sigma F_w - \mu_u F_u, \tag{4.2}$$

$$\frac{dM_u}{dt} = \psi\tau_u A_u + \sigma M_w - \mu_u M_u, \tag{4.3}$$

$$\frac{dA_w}{dt} = \left[\frac{\rho_{ww}(\nu F_wM_w + \delta F_wM_u)}{M}\right]\left(1-\frac{A}{K}\right) - (\tau_w + \mu_{Aw})A_w, \tag{4.4}$$

$$\frac{dF_w}{dt} = (1-\psi)\tau_w A_w - \sigma F_w - \mu_w F_w, \tag{4.5}$$

$$\frac{dM_w}{dt} = \psi\tau_w A_w - \sigma M_w - \mu_w M_w, \tag{4.6}$$

where $F = F_u + F_w$, $M = M_u + M_w$, $A = A_u + A_w$.

Here, ϕ represents the CI effect which can be either 0 if there is no CI, or 1 if CI is present. σ is the effect of LWI, such that it can either be 0, if there is no *Wolbachia* loss or greater than zero otherwise. In Adekunle et al., 2019 [197] where CI is assumed and LWI is considered, these quantities are set to $\phi = 1$ and $\sigma \geq 0$. In our modified model, considering different strains with the exception of wAu strain, $\phi = 1$ and σ could vary from values greater than zero onwards. However, for the wAu-*Wolbachia* strain, CI is ineffective and high retainment of wAu-*Wolbachia* infection even at high temperatures [162] is established, therefore we set $\phi = 0$ and $\sigma = 0$. Our model also incorporates imperfect maternal transmission generating a proportion of infected and uninfected offspring from mating of both F_wM_u and F_wM_w mosquitoes. To simplify the system, we assume that $M = F$ in accordance with the observed ratio of male to female mosquitoes of 1.02:1 [315]. That is, we set $\psi = 1/2$ (Figure 4.1). By this, it follows that the system of ordinary differential equations (ODEs) in equations (4.1) - (4.6) can be reduced to (4.7) - (4.10) which is the governing *Wolbachia* infection dynamics.

To mathematically express the above schematics, we have that, the feasible mating strategies of uninfected and *Wolbachia* infected mosquito populations together with their per capita

egg laying rates are given by the following differential system:

$$\begin{aligned}
\frac{dA_u}{dt} &= \left[\frac{\rho_{uu}(F_u^2+(1-\phi)F_uF_w)+\rho_{ww}((1-\nu)F_w^2+(1-\delta)F_wF_u)}{F}\right]\left(1-\frac{A}{K}\right) \\
&\quad -(\tau_u+\mu_{Au})A_u, \qquad (4.7)\\
\frac{dF_u}{dt} &= \frac{\tau_u}{2}A_u+\sigma F_w-\mu_uF_u, \qquad (4.8)\\
\frac{dA_w}{dt} &= \left[\frac{\rho_{ww}(\nu F_w^2+\delta F_wF_u)}{F}\right]\left(1-\frac{A}{K}\right)-(\tau_w+\mu_{Aw})A_w, \qquad (4.9)\\
\frac{dF_w}{dt} &= \frac{\tau_w}{2}A_w-\sigma F_w-\mu_wF_w, \qquad (4.10)
\end{aligned}$$

where $F = F_u + F_w$ and $A = A_u + A_w$. Before proceeding, we rescale each of our state variables according to the maximum total population size, which by Adekunle et al. [197] is set by

$$\begin{aligned}
A_u(t)+F_u(t)+A_w(t)+F_w(t) &\leq K+\frac{\tau_uK}{2\mu_u}+\frac{\sigma\tau_wK}{2\mu_u(\mu_w+\sigma)}+\frac{\tau_wK}{2(\mu_w+\sigma)}\\
&\leq K\left(1+\frac{1}{2}\left(\frac{\tau_u}{\mu_u}+\frac{\tau_w}{(\mu_w+\sigma)}\left(1+\frac{\sigma}{\mu_u}\right)\right)\right)\\
&\leq \alpha K
\end{aligned}$$

where $\alpha = 1+\frac{1}{2}\left(\frac{\tau_u}{\mu_u}+\frac{\tau_w}{(\mu_w+\sigma)}\left(1+\frac{\sigma}{\mu_u}\right)\right)$.

The closed set

$$\Omega = \left\{(A_u, F_u, A_w, F_w) \in \mathbb{R}_+^4 \mid A_u + F_u + A_w + F_w \leq \alpha K\right\}$$

which is a feasible region for the above system dynamics is positively invariant [197].

Hence, we let $\bar{A}_u = \frac{A_u}{\alpha K}$, $\bar{A}_w = \frac{A_w}{\alpha K}$, $\bar{F}_u = \frac{F_u}{\alpha K}$, $\bar{F}_w = \frac{F_w}{\alpha K}$, $\bar{A} = \bar{A}_u + \bar{A}_w$ and $\bar{F} = \bar{F}_u + \bar{F}_w$. Also, letting $\nu = 1$, we assume a perfect maternal transmission for the reproduction outcome of $\bar{F}_w\bar{M}_w$ mating. Therefore, the general *Wolbachia* model in terms of population proportions is given by equations (4.11)-(4.14). Hereafter it is clear that

we refer to the scaled values of each state variable and as such drop the overbar from our notation. The scaled model below now evolves in the feasible region $\bar{\Omega}$, where $\bar{\Omega} = \left\{(\bar{A}_u, \bar{F}_u, \bar{A}_w, \bar{F}_w) \in \mathbb{R}^4_+ \mid \bar{A}_u + \bar{F}_u + \bar{A}_w + \bar{F}_w \leq 1\right\}$.

$$\frac{d\bar{A}_u}{dt} = \left[\frac{\rho_{uu}(\bar{F}_u^2 + (1-\phi)\bar{F}_u\bar{F}_w) + \rho_{ww}(1-\delta)\bar{F}_w\bar{F}_u}{\bar{F}}\right]\left(1-\alpha\bar{A}\right) - (\tau_u + \mu_{Au})\bar{A}_u, \quad (4.11)$$

$$\frac{d\bar{F}_u}{dt} = \frac{\tau_u}{2}\bar{A}_u + \sigma\bar{F}_w - \mu_u\bar{F}_u, \quad (4.12)$$

$$\frac{d\bar{A}_w}{dt} = \left[\frac{\rho_{ww}(\bar{F}_w^2 + \delta\bar{F}_w\bar{F}_u)}{\bar{F}}\right]\left(1-\alpha\bar{A}\right) - (\tau_w + \mu_{Aw})\bar{A}_w, \quad (4.13)$$

$$\frac{d\bar{F}_w}{dt} = \frac{\tau_w}{2}\bar{A}_w - \sigma\bar{F}_w - \mu_w\bar{F}_w. \quad (4.14)$$

The modeling of wAu-*Wolbachia* transmission dynamics has not been done as this a distinction from other *Wolbachia* transmission models. Unlike the modeling work in Adekunle et al. [197], apart from the non-induction of CI, we considered the loss of *Wolbachia* infections due to seasonal fluctuation in temperature, a key dynamics that is absent in wAu strain.

4.3 Results

4.3.1 Analysis of the Model

The above general model (4.11)-(4.14) is parametrically adjusted to simultaneously accommodate wAu and wMel *Wolbachia* strains. For the wAu-*Wolbachia* model, we set $\phi = \sigma = 0$ and for the wMel-*Wolbachia* model, we set $\phi = 1$, $\sigma > 0$. The wMel-*Wolbachia* model parameter adjustments correspond to the model studied in [197].

Here, we want to analyse the general model(4.11)-(4.14) with arbitrary values of ϕ and σ to enable comparison with wAu-*Wolbachia* and Adekunle et al. [197] models. Analysing the model for wAu, we have four steady states. The first steady state $e_1 = (0, 0, 0, 0)$ indicates non-existence of mosquitoes. The second $e_2 = (A_u^*, F_u^*, 0, 0)$ signifies the steady

state for the uninfected mosquito population only. The third $e_3 = (0, 0, A_w^*, F_w^*)$ describes the equilibrium point for wAu-infected mosquitoes only. Lastly, the $e_4 = (A_u^*, F_u^*, A_w^*, F_w^*)$ is the equilibrium point for the co-existence of both uninfected and wAu-*Wolbachia*-infected mosquito populations.

Non-existence of mosquito population, e_1

The equilibrium point e_1 is trivial and is not biologically realistic. However, we can gain some insights into the competitive model dynamics by examining the case where there is no interaction between the uninfected and *Wolbachia*-infected mosquitoes. In other words, we want to investigate how each population would behave in the absence of the other. In particular, we derive the reproduction number of the uninfected R_{0u} and *Wolbachia*-infected R_{0w} mosquito populations when they do not interact:

$$R_{0u} = \frac{\rho_{uu}\tau_u}{2\mu_u(\mu_{Au} + \tau_u)}, \tag{4.15}$$

$$R_{0w} = \frac{\rho_{ww}\tau_w}{2\mu_w(\mu_{Aw} + \tau_w)}, \tag{4.16}$$

where the factor of $\frac{1}{2}$ in R_{0u} and R_{0w} stems from the choice to set M = F [315], i.e. $\psi = \frac{1}{2}$ (see Appendices A.1.4).

The probability that an uninfected/ *Wolbachia*-infected juvenile mosquito will mature and become an uninfected/ *Wolbachia*-infected adult mosquito is $\frac{\tau_u}{\mu_{Au}+\tau_u}$ / $\frac{\tau_w}{\mu_{Aw}+\tau_w}$ respectively. The expression $\frac{1}{\mu_u}$ / $\frac{1}{\mu_w}$ measures the average life span of an uninfected/ *Wolbachia*-infected adult mosquito, while $\frac{\rho_{uu}}{\mu_u}$ / $\frac{\rho_{ww}}{\mu_w}$ describes the rate at which uninfected/ *Wolbachia*-infected mosquitoes will grow respectively over time.

These reproductive numbers determine if the uninfected and *Wolbachia*-infected mosquito populations will die out or persist when there is no interaction. Specifically, if $R_{0u} < 1$ and $R_{0w} < 1$, then the two populations will die out (Figure 2(a)). We observed in the decoupled case, the expressions for R_{0u} and R_{0w} are independent of the effects of CI (ϕ) and LWI (σ)

and are therefore equivalent for both the wAu and wMel-*Wolbachia* strains (Figure 4.2) [197].

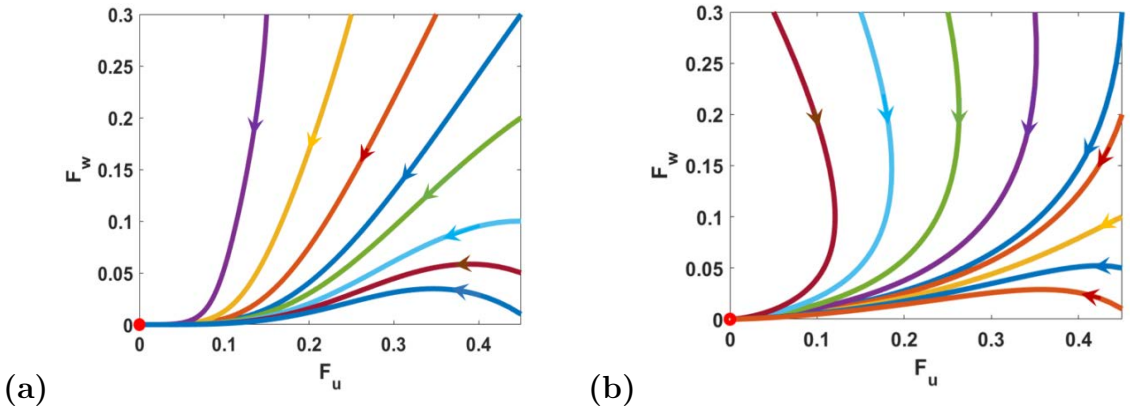

Figure 4.2: Graphs showing the system trajectories in the (F_u, F_w) plane for **(a)** wAu ($\phi = \sigma = 0$) and **(b)** wMel ($\phi = 1$, $\sigma = 0.04$) *Wolbachia* models when $\max[R_{0u}, R_{0w}] < 1$. The red ball point indicates the point of stability, that is $(F_u, F_w) = (0, 0)$ representing mosquito extinction. We set $\rho_{uu} = 0.01$ and $\rho_{ww} = 0.1$. Other parameters used for these model simulations are provided in Table 4.2.

Uninfected mosquito population, e_2

The uninfected-mosquito-only equilibrium point or *Wolbachia*-free equilibrium is

$$e_2 = \left(\frac{1}{\alpha}\left[1 - \frac{1}{R_{0u}}\right], \frac{\tau_u}{2\mu_u\alpha}\left[1 - \frac{1}{R_{0u}}\right], 0, 0\right).$$

For e_2 to exist, we require $R_{0u} > 1$. In addition to the uncoupled reproduction numbers (R_{0u} and R_{0w}) we also define the invasive reproduction number $R_{0w|u}$ which describes the average number of secondary offspring that will become *Wolbachia*-infected adults after introducing a single adult *Wolbachia*-infected mosquito into an established *Wolbachia* uninfected mosquito population.

To compute $R_{0w|u}$, we use the next generation matrix method [215] to obtain

$$R_{0w|u} = \frac{\delta R_{0w}}{R_{0u}}, \tag{4.17}$$

where we have substituted in the definition of R_{0w} from equation (4.16). The invasive repro-

duction number $R_{0w|u}$ is the same for both wAu and wMel-*Wolbachia* strains as that derived in Adekunle et al., 2019 [197]. This is because, the expression (4.17) clearly shows that the invasive reproductive number $R_{0w|u}$ is not dependent on the CI effect, ϕ or LWI, σ.

To check if the equilibrium point e_2 is stable, we compute the Jacobian of the system and evaluate it at e_2. In particular, letting $z_1 = (\mu_{Au} + \tau_u)$ and $z_2 = (\mu_{Aw} + \tau_w)$, yields

$$J_{e_2}=\begin{pmatrix} -z_1R_{0u} & \frac{\rho_{uu}}{R_{0u}} & z_1(1-R_{0u}) & \frac{(1-\delta)\rho_{ww}}{R_{0u}} \\ \frac{\tau_u}{2} & -\mu_u & 0 & 0 \\ 0 & 0 & -z_2 & \frac{\delta\rho_{ww}}{R_{0u}} \\ 0 & 0 & \frac{\tau_w}{2} & -\mu_w \end{pmatrix}.$$

To obtain the characteristic equation of J_{e_2}, we have

$$|J_{e_2} - \lambda I| \ = 0,$$

which becomes

$$(\lambda^2 + k_1\lambda + k_2)(\lambda^2 + l_1\lambda + l_2) \ = 0,$$

where

$$\begin{aligned} k_1 &= \mu_u + z_1R_{0u}, \\ k_2 &= \mu_u z_1(R_{0u} - 1), \\ l_1 &= \mu_w + z_2, \\ l_2 &= \mu_w z_2(1 - R_{0w|u}). \end{aligned}$$

Therefore, e_2 is locally asymptotically stable if and only if $R_{0w|u} < 1$ and $R_{0u} > 1$ (Figure 4.4). This is also consistent with the study in [197] (See Table 5.1).

***Wolbachia*-infected mosquito population,** e_3

The wAu-infected-only equilibrium point is $e_3 = \left(0, 0, \frac{1}{\alpha}\left[1 - \frac{1}{R_{0w}}\right], \frac{\tau_w}{2\mu_w\alpha}\left[1 - \frac{1}{R_{0w}}\right]\right)$. This again is consistent with Adekunle et al., 2019 [197].

For e_3 to exist we require $R_{0w} > 1$. By computation, the invasive reproductive number $R_{0u|w}$ with respect to uninfected mosquitoes is given as,

$$R_{0u|w} = \frac{R_{0u}}{R_{0w}}\left[(1-\phi) + \frac{\rho_{ww}}{\rho_{uu}}(1-\delta)\right] = \frac{cR_{0u}}{R_{0w}}, \tag{4.18}$$

where $c = (1-\phi) + \frac{\rho_{ww}}{\rho_{uu}}(1-\delta)$. Clearly, $R_{0u|w}$ is dependent on ϕ. For the wMel-*Wolbachia* strain, i.e. $\phi = 1$, $c = \frac{\rho_{ww}}{\rho_{uu}}(1-\delta)$ which is equivalent to that of Adekunle et al., 2019 [197]. However, for the wAu-*Wolbachia* strain, i.e. $\phi = 0$, we have a modified expression of $c = 1 + \frac{\rho_{ww}}{\rho_{uu}}(1-\delta)$ in equation (4.18) because we do not assume CI. Therefore, $c \geq 1$ for wAu-*Wolbachia* strain. Computing the Jacobian at e_3, we have:

$$J_{e_3} = \begin{pmatrix} -z_1 & \frac{\rho_{uu}+(1-\delta)\rho_{ww}}{R_{0w}} & 0 & 0 \\ \frac{\tau_u}{2} & -\mu_u & 0 & 0 \\ z_2(1-R_{0w}) & \frac{-(1-\delta)\rho_{ww}}{R_{0w}} & -z_2R_{0w} & \frac{\rho_{ww}}{R_{0w}} \\ 0 & 0 & \frac{\tau_w}{2} & -\mu_w \end{pmatrix}.$$

The characteristic equation of J_{e_3} is then

$$|J_{e_3} - \lambda I| = (\lambda^2 + m_1\lambda + m_2)(\lambda^2 + n_1\lambda + n_2) = 0,$$

where

$$\begin{aligned} m_1 &= \mu_u + z_1, \\ m_2 &= \mu_u z_1(1 - R_{0u|w}), \\ n_1 &= \mu_w + z_2R_{0w}, \\ n_2 &= \mu_w z_2(R_{0w} - 1). \end{aligned}$$

Therefore, e_3 is locally asymptotically stable if and only if $R_{0u|w} < 1$ and $R_{0w} > 1$ (See Figure

4.4). The condition is equivalent to that found in [197] with generalized expressions for $R_{0u|w}$ used in place of the reduced version presented there (See Table 5.1).

Coexistent mosquito populations, e_4

The equilibrium point for which both the uninfected and *Wolbachia*-infected populations coexist is

$e_4 = (\frac{2\mu_u\beta F_w^*}{\tau_u}, \beta F_w^*, \frac{2\mu_w F_w^*}{\tau_w}, F_w^*)$ where

$$F_w^* = \frac{1}{2\alpha}\left[\frac{\left(1-\frac{\xi}{R_{0w}}\right)\tau_u\tau_w}{(\mu_w\tau_u + \beta\mu_u\tau_w)}\right],$$

$\beta = \dfrac{R_{0w}(R_{0u|w}-1)}{R_{0u}(R_{0w|u}-1)}$ and $\xi = \dfrac{(\beta+1)}{(\delta\beta+1)}$. For e_4 to exist, we require $R_{0w} > \xi > 1$ and

(i) $R_{0w|u}, R_{0u|w} > 1$ or

(ii) $R_{0w|u}, R_{0u|w} < 1$.

The above conditions (i) and (ii) correspond to the cases for $\delta > \dfrac{1}{c}$ and $\delta < \dfrac{1}{c}$ respectively. Comparing these existence conditions with those found above for e_2 and e_3, we see that condition (ii) for the existence of e_4 matches the combined existence and local asymptotic stability condition for e_2 and e_3. In other words, e_2, e_3 and e_4 can coexist, while e_1 always exists (see Figure 4.4).

To establish whether e_4 is stable or not, we compute the Jacobian J_{e_4} evaluated at e_4 to obtain the following characteristic equation:

$$|J_{e_4} - \lambda I| := \lambda^4 + s_1\lambda^3 + s_2\lambda^2 + s_3\lambda + s_4 = 0. \tag{4.19}$$

Let

$z_3 = (\mu_u + \mu_w)$, $z_4 = (\beta\rho_{uu} + \rho_{ww})$, $z_5 = (\beta+1)\rho_{uu} + (1-\delta)\rho_{ww}$, $z_6 = 1 + \beta(2+\beta\delta)$,

$z_7 = (\beta+1)^2\rho_{uu} + (1-\delta)\rho_{ww}$, $z_8 = (1+\beta(2+\beta\delta))\rho_{uu} + (1-\delta)\rho_{ww}$,

then we have:

$$
\begin{aligned}
s_1 &= z_1 + z_2 + z_3 + \alpha z_4 F_w^*, \\
s_2 &= \mu_u\mu_w + z_3(z_1 + z_2 + \alpha z_4 F_w^*) - \frac{\xi}{2R_{0w}(\beta+1)^2}(z_6\rho_{ww}\tau_w + z_7\tau_u), \\
s_3 &= \mu_u\mu_w(z_1 + z_2 + \alpha z_4 F_w^*) + z_3\left[z_1 z_2 + \frac{\alpha}{\beta+1}(z_1(1+\beta\delta)\rho_{ww} + \beta z_2 z_5)F_w^*\right] \\
&- \frac{\xi}{2R_{0w}(\beta+1)^3}\{[(\mu_u + z_1)z_6 + z_8\alpha\beta F_w^*](\beta+1)\rho_{ww}\tau_w \\
&+ [\alpha\beta(1-\delta)z_5\rho_{ww}F_w^* + z_7(\alpha(1+\beta\delta)\rho_{ww}F_w^* + (\mu_w + z_2)(\beta+1))]\tau_u\}, \\
s_4 &= \mu_u\mu_w\left[z_1 z_2 + \frac{\alpha}{\beta+1}(z_1(1+\beta\delta)\rho_{ww} + \beta z_2 z_5)F_w^*\right] - \frac{\xi}{2R_{0w}(\beta+1)^2}\{[z_2 z_6 \\
&+ z_8\alpha\beta F_w^*]\mu_u\rho_{ww}\tau_w + [\alpha\beta(1-\delta)z_5\rho_{ww}F_w^* + z_7(\alpha(1+\beta\delta)\rho_{ww}F_w^* + z_2(\beta+1))]\mu_w\tau_u \\
&- \frac{\xi}{2R_{0w}}[z_8\rho_{ww}]\}.
\end{aligned}
$$

In order to establish the nature of the equilibrium point e_4, we performed numerical testing using the Monte Carlo method in [55] to verify the conditions (i) and (ii) by computing the real part of the eigenvalues of the Jacobian matrix, evaluated at e_4. Simulation results are illustrated in Figure 4.3.

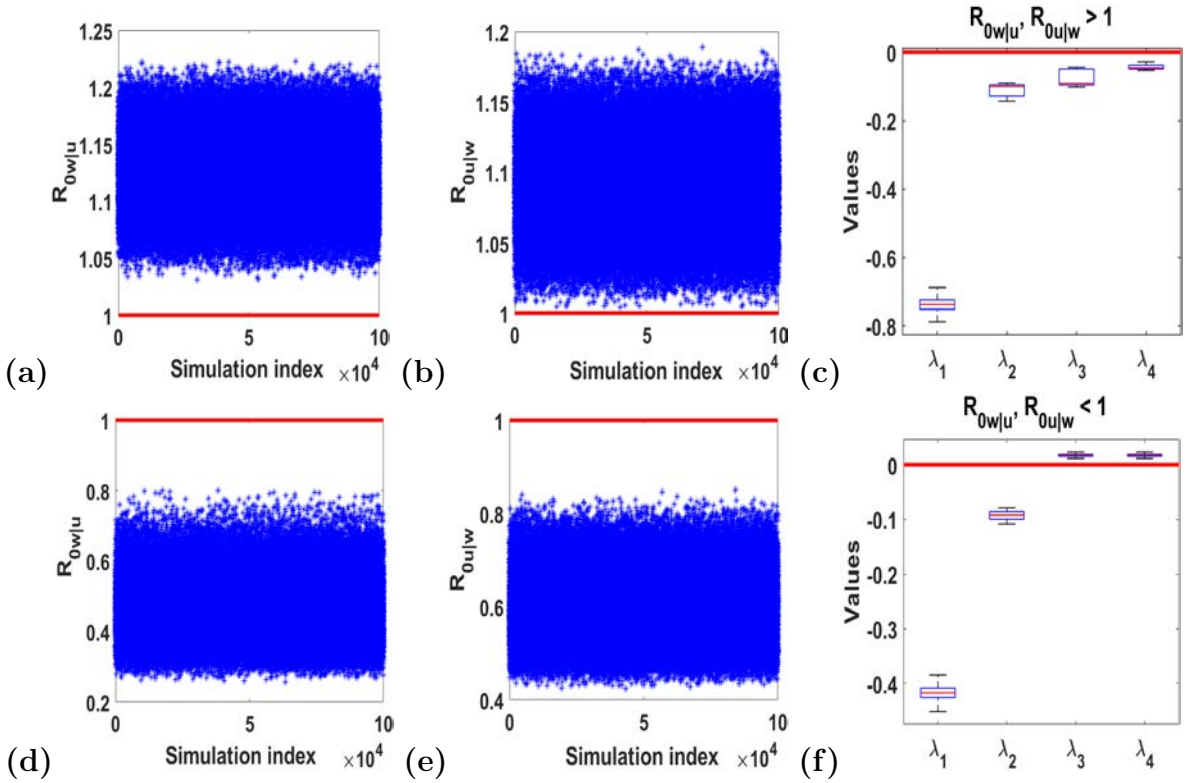

Figure 4.3: Graphs showing the numerical testing for the stability conditions (i) and (ii) and the real part of the eigenvalues' distribution ($\lambda_1, \lambda_2, \lambda_3$ and λ_4) for e_4: (a) and (b) show that $R_{0w|u}, R_{0u|w} > 1$ always hold. (c) shows the related distribution of the real part of the eigenvalues for condition (i). (d) and (e) show the condition $R_{0w|u}, R_{0u|w} < 1$ always hold while (f) shows the corresponding distribution of the real part of the eigenvalues for condition (ii).

Although the conditions (i) and (ii) indicated the existence of e_4, Figure 4.3(c) showed that e_4 is locally stable for condition (i) as all the eigenvalues (real part) are negative ($\lambda_1, \lambda_2, \lambda_3, \lambda_4 < 0$). Whilst Figure 4.3(f) showed that e_4 is unstable for condition (ii) as two of the eigenvalues (real part) are positive i.e. $\lambda_3, \lambda_4 > 0$.

Numerically, we illustrated the existence and stability regions for e_4 in Figure 4.4 for the two conditions (i) and (ii) relating to CI and maternal transmission (MT).

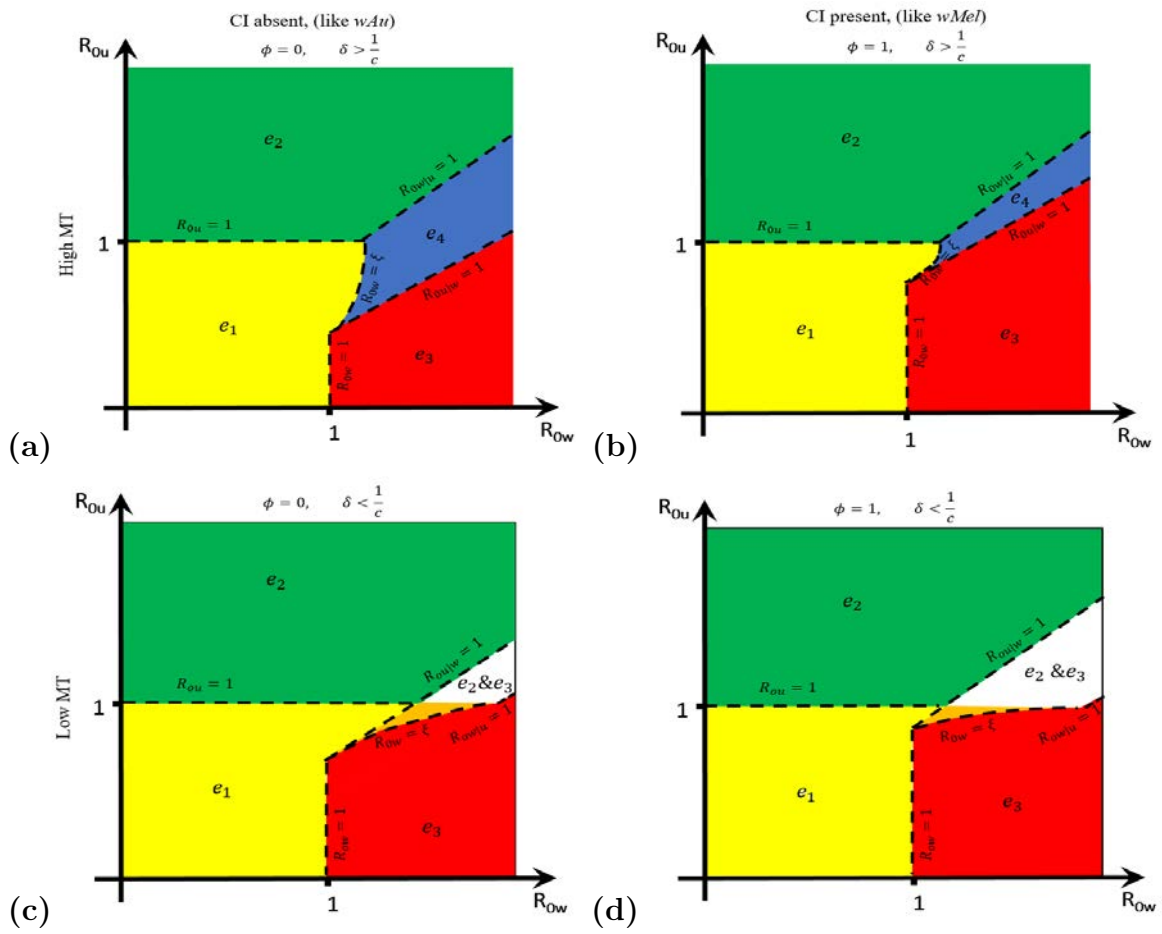

Figure 4.4: This graph shows the existence and local stability regions for the equilibrium points e_1 - e_4 for the *Wolbachia* model (4.11)-(4.14) as a function of the R_{0u} and R_{0w} relating to the cytoplasmic incompatibility (CI), ϕ and maternal transmission (MT), i.e. magnitude of δ and $\frac{1}{c}$. The yellow shaded region indicates the local stability of e_1 equilibrium. The green shaded area illustrates the local stability for the *Wolbachia*-free equilibrium point (e_2). e_3 is locally stable at the red shaded part. The blue region indicates the coexistence local stability e_4. The white region shows the existence of e_2, e_3 and e_4 and local stability of e_2 and e_3 equilibrium points. And the orange region describes the existence and local stability of e_1 and e_3. For $\delta > \frac{1}{c}$; **(a)** describes $\phi = 0$ as the boundary $R_{0w|u} = 1$ sits above the boundary $R_{0u|w} = 1$ and the arc $R_{0w} = \xi$. The co-existent equilibrium e_4 (blue), always sits in the region between these three boundaries because $R_{0w|u} > 1$, $R_{0u|w} > 1$ and $R_{0w} > \xi$. If $R_{0w} < \xi$, then e_1 becomes stable (yellow). **(b)** describes similar conditions as in (a) but for $\phi = 1$. We observed that the boundary $R_{0u|w} = 1$ shifts up while $R_{0w|u} = 1$ remained stationary to accommodate more e_3. For $\delta < \frac{1}{c}$; **(c)** describes $\phi = 0$ as the relative position of e_4 boundaries in (a) flips so that boundary $R_{0u|w} = 1$ sits above boundary $R_{0w|u} = 1$ and the arc $R_{0w} = \xi$. Then, $R_{0w|u} < 1$ and $R_{0u|w} < 1$ and $R_{0w} > \xi$ shows the co-existence of e_2 and e_3 (white). However, e_2 and e_3 are locally stable in the white region as $R_{0w} > 1$ and $R_{01} > 1$. For $R_{0u} < 1$, e_2 and e_4 do not exist, only e_1 and e_3 do and if $R_{0w} > \xi$, e_1 and e_3 are locally stable (orange) and if $R_{0w} < \xi$, only e_3 becomes stable (red). **(d)** describes similar conditions as in (c) but for $\phi = 1$. It was observed that the boundary $R_{0u|w} = 1$ shifts up reducing the region of stability for e_2.

Following a modeling study of *Aedes aegypti* mosquitoes and normal *Wolbachia* (in the presence of CI only) interaction analyzed by Ferreira et al. 2020 [316], three equilibrium points: trivial (q_1); uninfected only (q_2); and coexistence (q_3), were obtained. However, the *Wolbachia*-only equilibrium point was not computed. The established local stability conditions for q_1 and q_2 correspond to that of the wMel-like *Wolbachia* conditions for e_1 and e_2 respectively. For coexistent populations to persist, the reproductive number for infected mosquitoes only, R_i must be greater than 1 and $R_i > R_u$, where R_u is the reproductive number for wild-type mosquitoes only. The model [316] also described the fitness parameter space between R_u and R_i, showing the change in extinction and persistence of the three equilibria when there is an increase in the initial population proportion of the *Wolbachia*-infected mosquitoes. Our model showed the changes in the no-mosquito, wild-type only, *Wolbachia*-only and coexistence population persistence and extinction in the presence and absence of CI with high and low maternal transmission (MT).

Figure 4.4 illustrates the existence and local stability regions for the equilibrium points e_1, e_2, e_3 and e_4 with respect to the reproduction numbers R_{0u} and R_{0w} as well as the relative magnitude of δ and $\frac{1}{c}$. For $\delta > \frac{1}{c}$ (high MT), Figures 4.4**(a)** and **(b)** describe the dynamics for $\phi = 0$ (CI absent) and $\phi = 1$ (CI present) respectively. Within the subset of the yellow region of these figures bounded by $R_{0u} = 1, R_{0w} = 1$, and $R_{0w} = \xi$ we find that only e_1 and e_3 exist. Since e_3 is unstable in this region, we expect the system trajectories to tend to the no-mosquito equilibrium e_1. This was confirmed through numerical simulations shown in Figure 4.5**(a)**. For the existence of e_4 we require $R_{0u|w} > 1$, $R_{0w|u} > 1$ and $R_{0w} > \xi$ for stability (within the blue region). But if $R_{0w} < \xi$, e_1 is stable (yellow).

For $\delta < \frac{1}{c}$ (low MT), Figures 4.4**(c)** and **(d)** portrayed the regions of stability for $\phi = 0$ and $\phi = 1$ respectively. The conditions $R_{0u} < 1, R_{0w} > 1$, and $R_{0u|w} > 1$ project the trajectiory to tend to e_1 (See Figure 4.5(**b**)). In the orange region, e_1 and e_3 exist and are simultaneously locally stable as $R_{0u|w} > 1$ and $R_{0w} > \xi$. In addition, we have that e_4 exists where $R_{0u|w} < 1$ and $R_{0w|u} < 1$ (condition (ii)). With these conditions, e_4 exists together with e_2 and e_3

(white region). In this white region, e_2 and e_3 are locally stable even as $R_{0u} > 1, R_{0w} > 1$ but e_4 is unstable. Also, e_1 exists when $R_{0w} > 1$ and $R_{0u} < 1$ because the local stability of other equilibrium points is violated with these conditions. When $R_{0u|w} > 1$ but $R_{0u} < 1$ and $R_{0w} > 1$, the only stable outcome is the mosquito-free (no-mosquito) equilibrium e_1. This occurs when R_{0u} is less than but still close to one. In this region, uninfected mosquitoes are capable of dominating initially when introduced into a *Wolbachia* saturated equilibrium because imperfect maternal transmission achieves $R_{0u|w} > 1$. This competitive advantage drives out the *Wolbachia* infected mosquitoes leaving uninfected mosquitoes only, which then are unable to sustain their population because $R_{0u} < 1$ (Figure 4.5).

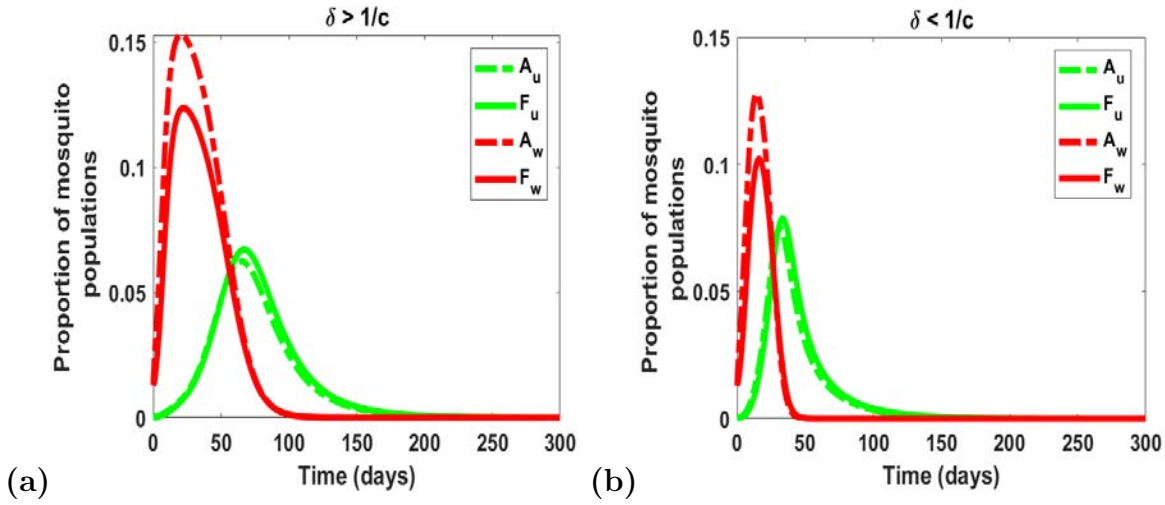

Figure 4.5: Graphs showing the local stability for e_1 relating to the magnitude of δ and $\frac{1}{c}$. The initial conditions for the state variables are $A_u(0) = 0.00015$, $F_u(0) = 0.00013$, $A_w(0) = 0.013$, $F_w(0) = 0.013$. We set $\rho_{uu} = 1, \rho_{ww} = 2.8571, \tau_u = \tau_w = 1, \mu_{Au} = \mu_{Aw} = 0.2, \mu_u = 0.4630, \mu_w = 0.6161$. **(a)** For $\delta > \frac{1}{c}$, where $\delta = 0.4, c = 2.7143, R_{0u} = 0.8999, R_{0w} = 1.9322, R_{0u|w} = 1.2641, R_{0w|u} = 0.8588$. **(b)** For $\delta < \frac{1}{c}$, where $\delta = 0.2, c = 3.2857, R_{0u} = 0.8999, R_{0w} = 1.9322, R_{0u|w} = 1.5303, R_{0w|u} = 0.4294$. The equilibrium point e_1 is locally stable if $R_{0u} < 1, R_{0w} > 1$, $R_{0w|u} < 1$ and $R_{0u|w} > 1$.

With the rate of high maternal transmission (MT) in the absence of CI (like-wAu), the reproductive advantage favours the production of uninfected mosquito offspring as it tends to accommodate more coexistent mosquito populations with wild-type than wMel-like strain (presence of CI) due to the presence of CI (Figure 4.4(a) and (b)). Whilst, with a low MT

rate, the CI presence or absence would favour *Wolbachia*-infected mosquitoes or uninfected mosquitoes respectively. In other words, the coexistent equilibrium point is unstable for the two mosquito populations as these conditions are equivalent to the local stabilities of both *Wolbachia*-free and *Wolbachia*-only equilibrium points (Figure 4.4(c) and (d)). If $R_{0w} < \xi$, the system trajectories tend to the no mosquito equilibrium e_1.

The conditions for the local stability of all equilibrium points are shown in Table 4.3 below.

Table 4.3: Expressions for the condition for stability associated with the equilibrium points.

Equilibrium points	**Conditions for stability**	
	***w*Mel[197]**	***w*Au**
(i) No mosquitoes (e_1)	$R_{0u} < 1$ and $R_{0w} < 1$	$R_{0u} < 1$ and $R_{0w} < 1$
(ii) Uninfected mosquitoes only (e_2)	$R_{0w\|u} < 1$ and $R_{0u} > 1$	$R_{0w\|u} < 1$ and $R_{0u} > 1$
(iii) *Wolbachia*-infected mosquitoes only (e_3)	$R_{0u\|w} < 1$ and $R_{0w} > 1$	$R_{0u\|w} < 1$ and $R_{0w} > 1$
(iv) Both mosquitoes (e_4)	$\delta < 1$, $\mu_u < \delta\mu_w$, $R_{0w} > 1$ and $R_{0u} > 1$	$R_{0w\|u} > 1$, $R_{0u\|w} > 1$, $R_{0w} > 1$ and $R_{0u} > 1$

4.3.2 Sensitivity Analysis of *Wolbachia* model

To carry out the sensitivity analysis we investigate the model robustness due to uncertainties associated with parameter value estimations. In other words, we examine how sensitive the invasive reproductive numbers are with respect to these parameters. This in turn, gives insight on influential parameters and their impact in reducing (or increasing) mosquito-type populations. To carry out this, we compute the normalized sensitivity indices of the invasive reproduction numbers with respect to the parameters used in the model.

Definition

The normalized forward sensitivity index of a variable v with respect to parameter w is defined as:

$$\Lambda_w = \frac{\partial v}{\partial w} \times \frac{w}{v}. \tag{4.20}$$

Using the above formular (4.20), we contruct the following plots in Figure 4.6.

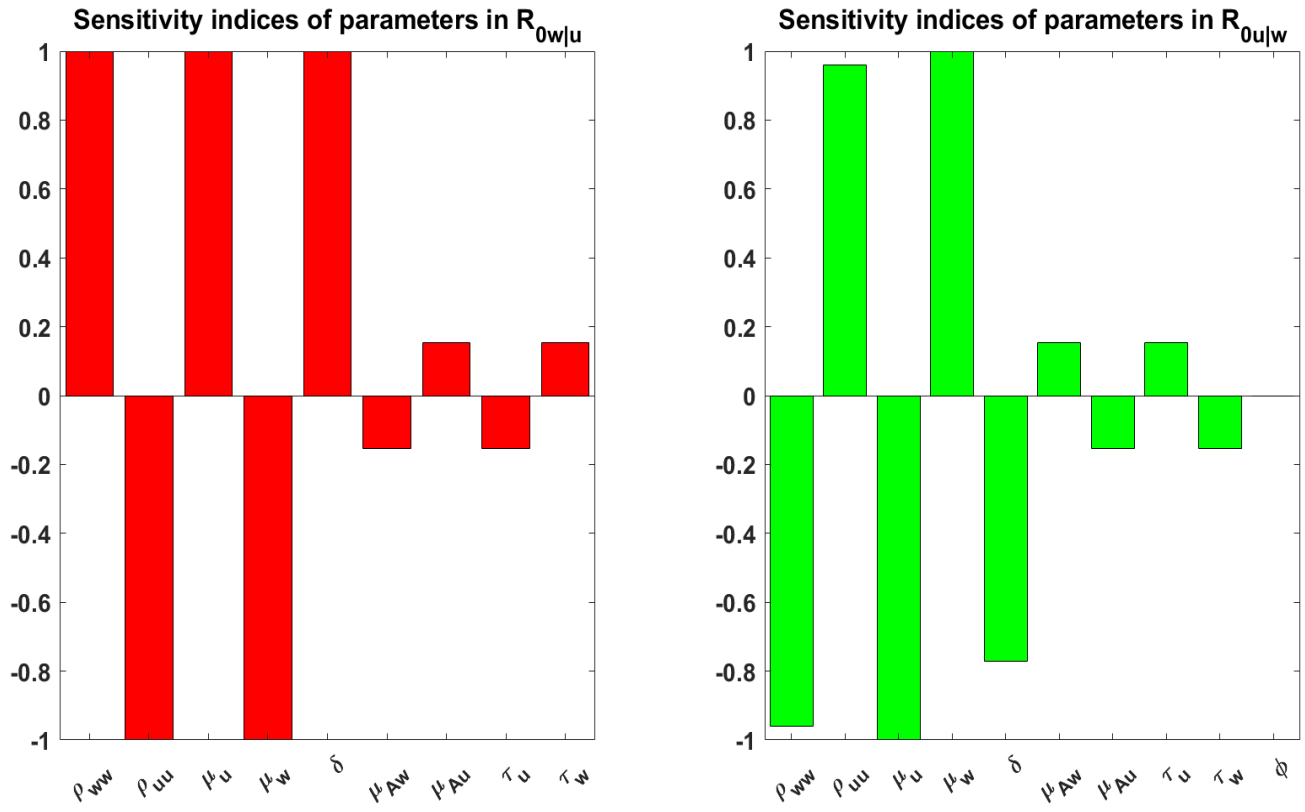

Figure 4.6: Plots showing the sensitivity indices of $R_{0w|u}$ and $R_{0u|w}$ the model parameters.

From Figure 4.6 and using the baseline parameter values for the wAu-*Wolbachia* strain in Table 4.2, it is clear that the reproductive and mortality rates for both wild-type (ρ_{uu}, μ_u) and wAu-*Wolbachia*-infected (ρ_{ww}, μ_w) mosquitoes and the proportion of wAu-*Wolbachia*-infected offspring (δ) have the most sensitivity in the invasive reproductive numbers $R_{0w|u}$. Whilst for $R_{0u|w}$, μ_u and μ_w are the most sensitive parameters. Hence for both invasive reproductive numbers, the most sensitive parameters are μ_u and μ_w. This demonstrates that an increase (or decrease) in the mortality rate of wAu-*Wolbachia*-infected mosquitoes by 10% will decrease (or increase) $R_{0w|u}$ by 10%.

4.3.3 Does CI (ϕ) outweigh the LWI (σ)?

For most *Wolbachia* strains except wAu, the mating between uninfected female and *Wolbachia*-infected male mosquito crosses generates no viable offspring. However, *Wolbachia*-

infected mosquitoes tend to lose their *Wolbachia* infection and lower their maternal transmission rate at high temperature $(27 - 37^0C)$ [162]. With the effect of climate change gradually increasing the temperature by the day, *Wolbachia* strains with moderate or high temperature sensitivity such as wMel may not be able to fully maintain a sufficient frequency level to invade the mosquito population.

In our general *Wolbachia* mathematical model, we describe a modified version of Adekunle et al., 2019 [197]. This modification accommodates parameter adjustments for novel wAu and wMel-*Wolbachia* strains. For wAu, our mathematical model showed that despite the production of mosquito offspring due to CI absence, the invasive reproduction number due to infected mosquitoes $R_{0w|u}$ remains unchanged compared to the case where CI is present, as with the wMel-like strain [197]. This further strengthened the fact that CI (inclusion or exclusion) does not guarantee *Wolbachia* mosquitoes' persistence. Also, the invasive reproduction number due to uninfected mosquitoes expression $R_{0u|w}$ for wAu is similar to wMel, except that the expression depends on CI the effect. This is because, the mosquito gender crosses due to non-induction of CI for wAu, i.e. $F_u M_w$, generates uninfected offspring with perfect maternal transmission while wMel does not. The chances of establishing *Wolbachia* infected mosquitoes are lower when CI is ineffective compared to when it is induced. That is, for cytoplasmic inducing wMel-*Wolbachia* mosquitoes, the effect of LWI outweighs CI effect as mosquitoes still lose their infections (Figure 4.7). However, wAu-*Wolbachia* infection retainment (no LWI) in mosquitoes has shown high level of maintaining the *Wolbachia* frequency in the absence of CI in mosquitoes (Figure 4.7). This suggests that the LWI effect outweighs CI.

The LWI rate $\sigma(t)$ which is dependent on the seasons of the year can be modeled by a sinusoidal equation:

$$\sigma(t) = \frac{\sigma_{max}}{2}\left[1 + \cos\left(\frac{2\pi t}{365} - \mathcal{C}\right)\right] \tag{4.21}$$

where σ_{max} is the maximum value of the seasonal variation in LWI, and $\mathcal{C}$ is the phase shift which aligns the model with the seasonal change.

The effects of CI (ϕ) and LWI ($\sigma(t)$) as features of wAu and wMel *Wolbachia* strains are shown in Figure 4.7. For the total mosquito population, wAu-infected mosquitoes ($\phi = 0, \sigma_{max} = 0$) reach the maximum frequency after approximately 250 days. To see the effect of CI induction and slight LWI i.e. $\phi = 1$, $\mathcal{C} = 0.25$, for $\sigma_{max} = 0.02$ and $\sigma_{max} = 0.04$, the *Wolbachia* frequency level oscillates between (0.8 and 1) and (0.6 and 1) respectively. That is, there is a 20% and 40% drop in the frequency level of *Wolbachia* when $\sigma(t)$ is at $\sigma_{max} = 0.02$ and $\sigma_{max} = 0.04$ respectively.

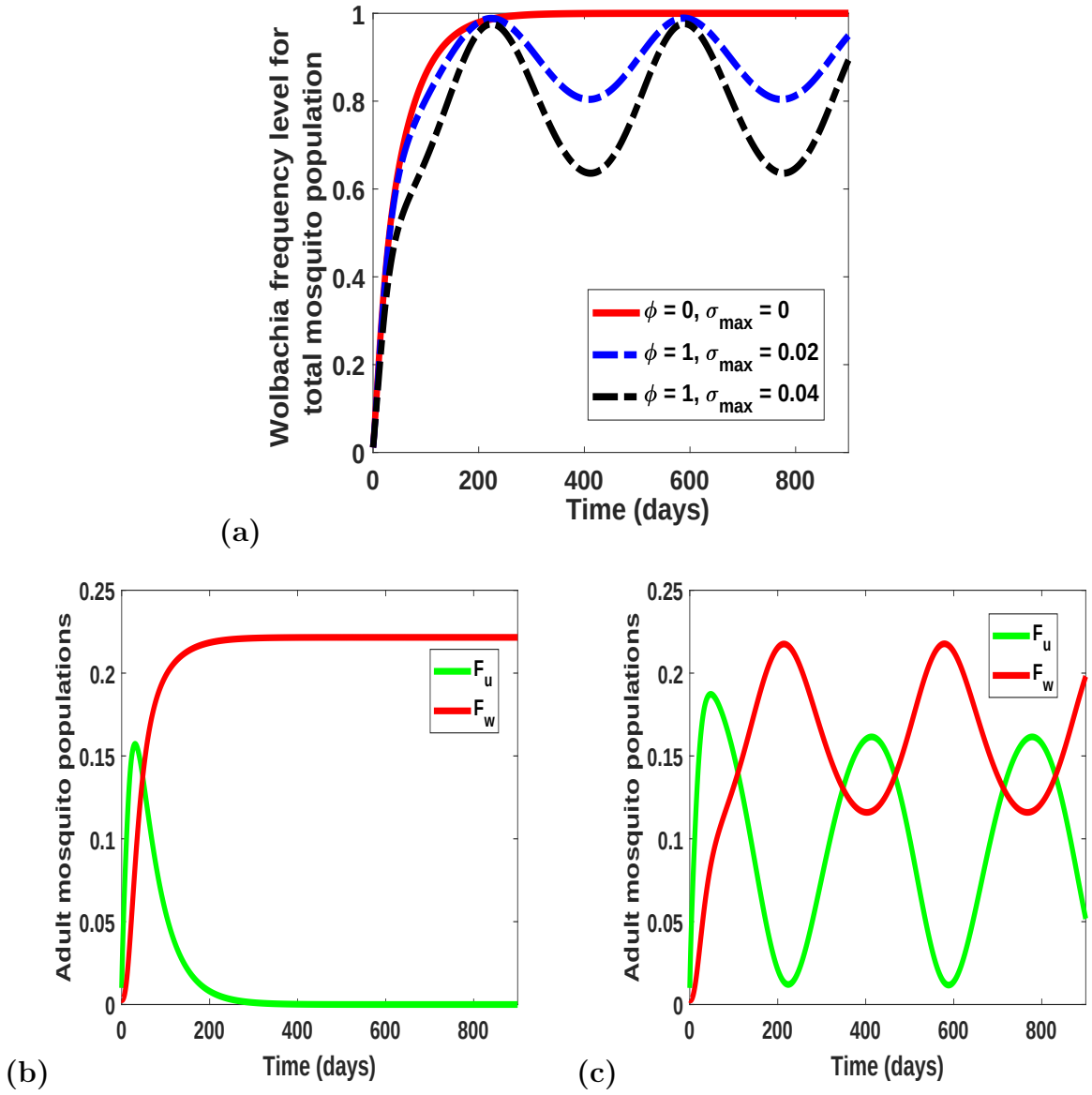

Figure 4.7: **(a)** Effect of CI induction ϕ and LWI $\sigma(t)$ on the *Wolbachia* frequency level. The initial conditions for the state variables are $A_u(0) = 0.25$, $F_u(0) = 0.01$, $A_w(0) = 0$, $F_w(0) = 0.003$. The red line indicates *Wolbachia* retainment as $\phi = 0$ (no CI induction) and $\sigma_{max} = 0$ (no LWI) which are features of wAu-*Wolbachia* strain. The blue and black dashed lines (for wMel-*Wolbachia* strain) illustrate CI induction and LWI i.e $\phi = 1$ for $\sigma_{max} = 0.02$ and $\sigma_{max} = 0.04$ respectively. Parameters for e_3 were used in these simulations. **(b)** Shows the dominance of wAu-*Wolbachia* infected F_w to uninfected F_u adult mosquitoes due to the retainment of *Wolbachia* infections (not affected by seasonal varying LWI). The wAu-*Wolbachia*-infected mosquitoes dominates when there is no CI $\phi = 0$ and LWI $\sigma_{max} = 0$ (red line). **(c)** For wMel-*Wolbachia*-infected mosquitoes, the effect of seasonal varying loss of *Wolbachia* infection is shown as infections rise and drop continuously due to LWI $\sigma_{max} = 0.04$ and CI induction $\phi = 1$.

This showed that, despite CI induction, LWI reduced the contribution of CI to the *Wolbachia* invasion (Figure 4.7(a)). Therefore, the LWI gains highly outweigh the CI effect. By this, our analysis suggests that an increase in LWI in the presence of CI results in a drastic decrease in the *Wolbachia* frequency level (Figure 4.7(a)). On the other hand, Figure 4.7(b) showed the effect of LWI $\sigma(t)$ and CI ϕ with respect to the competitiveness between F_u and F_w. We observed that the F_w population dominates the F_u when there was no CI induction and *Wolbachia* infection is retained, that is, $\phi = 0, \sigma_{max} = 0$ (Figure 4.7(b)). However, if CI induction occurs with loss of *Wolbachia* infections, then the seasonal varying effect occurs as seen in Figure 4.7(c).

4.4 Discussion

In this work, we modelled and investigated a general *Wolbachia* model that contained the transmission dynamics of wAu and wMel *Wolbachia* strains in *Aedes* mosquitoes as special cases. These transmission dynamics described the competition between the novel wAu-*Wolbachia* infected *Aedes* mosquitoes and wild-type mosquitoes and compared the dynamics with the invasive properties of the popular wMel-*Wolbachia* infected mosquitoes. We first derived the *Wolbachia* infection-status reproduction numbers for our wAu-*Wolbachia* model and used them to establish the conditions for the local stability of the equilibrium points for the wAu-*Wolbachia* invasive model. The reproduction number associated with the uninfected mosquitoes shows the reproductive advantage that the wild type has over the wAu strain. The comparison of the wAu-*Wolbachia* model (CI and LWI absent) and wMel-*Wolbachia* model (CI and LWI present) showed that the wAu strain has the potential of compensating for the undesirable features of the wMel strain.

Additionally, this study has reviewed the main features of different *Wolbachia* strains (Table 4.1) and shown that the wAu *Wolbachia* strain is a promising candidate for efficient *Aedes*-borne arboviral transmission control. Moreover, we analyzed the system dynamics of

a general *Wolbachia* invasion model and determined the regions of local stability for each of the identified equilibrium points, highlighting the regions in parameter for which *Wolbachia*-infected mosquito populations persist or go extinct. This work modelled the general *Wolbachia* dynamics which can accommodate various *Wolbachia* characteristics regarding the presence or absence of CI and seasonal changes, unlike Adekunle et al, 2019 [197], which considers only the presence of CI. We also investigated the advantages gained from CI and LWI. This study has demonstrated that despite the absence of CI, the *Wolbachia* frequency level will drop as much as tenfold of the percentage of *Wolbachia* infection lost. We showed that the advantage of *Wolbachia* retainment in mosquitoes strongly outweighed the negative impact of CI indicating *w*Au *Wolbachia* strains may be suitable for arboviral control. Therefore, this modeling work contributes to the previous studies [197, 298, 57, 58, 316] and helps close the gap between ways of maintaining the *Wolbachia* frequency levels in the absence of LWI and CI.

One implementation question for using the *w*Au strain as a replacement of the *w*Mel strain is whether the *w*Au strain is self-sustaining, given that it does not induce CI. In this work, the equilibrium points for the *w*Au-*Wolbachia* model are the same as that for the *w*Mel-*Wolbachia* model except that stricter conditions are required to satisfy the *w*Au-*Wolbachia* model equilibrium points. These more stringent conditions translate to additional resources such as the continuous introduction of a larger scale of *w*Au-infected mosquitoes to ensure replacement [317]. Thus, the *w*Au strain is a promising alternative strain as it does not suffer from LWI due to high weather temperature and is highly effective in preventing the transmission of the arbovirus [162, 224, 48]. Otherwise, combining the two strains may also be a good strategy.

There are limitations associated with any mathematical modeling work, and this study is not exempted. We first assumed the same mosquito gender ratio and expected this proportion to be constant over time. This assumption may be true in a laboratory setting [315], but not necessarily true in a natural mosquito habitat. However, similar conclusions are expected to

be reached as the *Wolbachia* model reduction accurately reproduces the dynamics of the full system [318]. Secondly, we assumed that the absence of CI implies that cross mating resulted in offspring that are uninfected. This may not be true as a small proportion of the offspring may be *Wolbachia* infected [162]. If that is the case, then it means that lesser resources will be required to use the *w*Au strain as a *Wolbachia*-based control strategy. Lastly, we assumed the seasonality affects the associated parameters for the *w*Mel dynamics. However, for the *w*Au strain, it is not affected by seasonality as *w*Au-*Wolbachia* infections are retained at high temperature.

Although several studies [57, 47, 151, 196] have demonstrated that CI drives the persistence of *Wolbachia*-infected *Aedes* mosquitoes, these studies neglected the impact of *Wolbachia* loss in mosquitoes. The CI drive has been shown in four mating lines (See Figure 1) involving a *Wolbachia*-transinfected *Aedes* mosqiutoes mating with wild-type mosquitoes. One of the mating lines for which *Wolbachia*-infected male and uninfected female mosquitoes produced no viable offspring (via CI) truncates the uninfected offspring from being produced as infection is maternally transmitted. With the exception of the mating between the uninfected male and female mosquito line, all other mating lines produce *Wolbachia*-infected offspring leading to persistence. In addition, high temperature affects these *Wolbachia*-infected mosquitoes as they lose their infection due to the unfavourable weather conditions. However, mosquitoes infected with the *w*Au-*Wolbachia* strain have been shown to not only block arboviral transmission efficiently, but also retain the *Wolbachia* infection at typically unfavourable high temperatures. This retainment of infection in mosquitoes strongly outweighed the absence of CI for the *w*Au strain in the establishment and dominance of *w*Au-*Wolbachia* infected mosquitoes.

While vaccine implementation may have been highly effective on dengue seropositive persons in high transmission areas [227, 226], the introduction of *Wolbachia*-infected mosquitoes in low and moderate arboviral endemic areas has also effectively shown successful reduction in dengue burden [44, 312, 248, 166]. Given that these two strategies could reduce the

transmission of *Aedes*-borne diseases, in particular, dengue depending on the transmission level, a modeling study by Ndii, 2020 [319] proposed the use of these combined strategies and compared their effectiveness. The author showed that, *Wolbachia* performs better in the presence of low vaccine efficacy, but is outperformed otherwise [319]. Therefore combining the two strategies may be useful, however understanding both the temperature and seasonality effects on *Wolbachia* intervention programs, and serotypic differences relating to cross-protective immunity to investigate vaccine efficacy is necessary for the reduction and control of *Aedes*-borne arboviral disease transmission.

In conclusion, we have shown that the *w*Au-*Wolbachia* strain could be effective in controlling arbovirus transmission, as its advantages in terms of *Wolbachia* infection retention in mosquitoes may outweigh the absence of CI. This could prove even more promising, especially as the temperature increases due to climate change. Although *w*Mel and *w*AlbB-*Wolbachia* strains only have been rolled out in natural mosquito habitats in replacement programs, combining these strains with *w*Au is worth exploring.

In the next chapter (Chapter 5), I will extend the *Wolbachia* model to capture the introduction of two different *Wolbachia* strains into the wild-type mosquito population and investigate the potential requirement for coexistence. Further, I will examine if releasing two different *Wolbachia* strains is better than one.

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Chapter 5

Modelling ecological dynamics of mosquito populations with multiple co-circulating *Wolbachia* strains

Chapter publication:

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Contrbutions:

Ogunlade, S. T. wrote the manuscript presented in this chapter. Ogunlade, S. T. developed the model, analysed the differential system describing the disease dynamics and the results and wrote the simulation codes for the two *Wolbachia* strains' disease model.
Ogunlade, S. T. conceived the project work described in this chapter. Adekunle, A. I. assisted with the model dynamic formation. Adekunle, A. I. and Meehan, M. T. assisted with the analysis of the results. Meehan, M. T. meticulously reviewing the manuscript while McBryde, E. S. and Adekunle, A. I. contributed to the manuscript draft proof-reading.

Summary

In Section 5.1 of the present chapter, I introduce how *Wolbachia* intracellular bacteria successfully reduce the transmissibility of arthropod-borne viruses (arboviruses) when introduced into virus-carrying vectors such as mosquitoes. Despite the progress made by introducing *Wolbachia* bacteria into the *Aedes aegypti* wild-type population to control arboviral infections, reports suggest that heat-induced loss-of-*Wolbachia*-infection as a result of climate change may reverse these gains. Novel, supplemental *Wolbachia* strains that are more resilient to increased temperatures may circumvent these concerns, and could potentially act synergistically with existing variants. In the next section (Section 5.2), I model the ecological dynamics among three distinct mosquito (sub)populations: a wild-type population free of any *Wolbachia* infection; an invading population infected with a particular *Wolbachia* strain; and a second invading population infected with a distinct *Wolbachia* strain from that of the first invader. The following session (Session 5.3) explores how the range of possible characteristics of each *Wolbachia* strain impacts mosquito prevalence. Further, I analyse the differential system governing the mosquito populations and the *Wolbachia* infection dynamics by computing the full set of basic and invasive reproduction numbers and use these to establish stability of identified equilibria. Section 5.4 investigates the trade off between one and two *Wolbachia* strains. Our results show that releasing mosquitoes with two different strains of *Wolbachia* did not increase their prevalence, compared with a single-strain *Wolbachia*-infected mosquito introduction and only delayed *Wolbachia* dominance (Section 5.5).

Keywords: *Aedes* mosquitoes, *Wolbachia strains*, Stability, Control

5.1 Introduction

Wolbachia infection in arthropods, in particular, *Aedes aeqypti* mosquitoes is capable of inhibiting the transmission of arboviruses such as Zika (ZIKV), Chikungunya (CHIKV) and dengue viruses (DENV) [313, 40, 162, 151]. These arboviruses have been estimated to infect over 390 million people annually causing significant global health problems [16, 313, 320, 321].

Aedes aegypti mosquitoes do not naturally host the intracellular biosymbiotic *Wolbachia* bacteria, but can be infected through microinfection [162]. The *Wolbachia*-based technique of arboviral vector control is predominantly aimed at two mechanisms: distrupting arboviral transmission between vectors and hosts; and suppressing the vector population [39]. Some *Wolbachia* features regulating the success of these mechanisms include immune system pre-activation in the vectors, induction of cytoplasmic incompatibility (CI) rendering offspring unviable, imperfect maternal transmission of *Wolbachia*, loss of *Wolbachia* infection (LWI) due to high temperature, and superinfection by a second *Wolbachia* strain [45, 46, 47, 48]. Based on these features, there are some tradeoffs exhibited by different *Wolbachia* strains, i.e., some strains induce CI (which is good) but also have LWI due to high temperature (which is bad) and vice versa [49, 50].

Presently, the *w*Mel-*Wolbachia* strain is commonly used in the field, with releases in Australia [317], Indonesia [44], Brazil [322], Colombia [323], the United States of America and China [324]. The *w*AlbB *Wolbachia* strain was later introduced in Malaysia [43], Thailand [141], Taiwan [325], India [50] and *w*MelPop in Vietnam [164], while other strains are yet to be field-tested. Single-strain *Wolbachia* experimental studies have shown that most crosses between *Wolbachia*-infected arthropods and wild-type mosquitoes induce unidirectional CI, that is, loss of fertility of a wild-type female mating with a *Wolbachia*-infected male mosquito, but not the reverse [40, 326, 191, 41]. In addition, most *Wolbachia*-infected mosquitoes greatly lose their infection under high temperatures [196, 48] except those infected with the CI-inducing *w*AlbB and *w*Au-*Wolbachia* strains, which does not induce CI [162, 46, 50]. For double-strain *Wolbachia* experimental studies, CI is typically bidirectional, that is, any

mismatch in *Wolbachia* strain among mating vectors results in infertility; however, CI does not affect crosses involving *w*Au-*Wolbachia*-infected males with other *Wolbachia*-infected females [162, 327, 217, 320], opening up a tantalising possibility of two different strains of *Wolbachia*-infected mosquitoes co-existing (Figure 5.1).

Most existing *Wolbachia* modelling studies have only analysed single-strain *Wolbachia* dynamics in arthropod vectors [197, 57, 47, 54, 248, 298, 55, 328, 329, 330]. Meanwhile, those studies that have modelled, discussed or compared the existence of multiple *Wolbachia* subpopulations [327, 320, 331, 151, 313], only consider *Wolbachia* strains with the same CI induction and heat-susceptibility characteristics (e.g. *w*Mel and *w*MelPop strains). Some recent studies compared two different and separate *Wolbachia* strains: *w*Au and *w*Mel [332], *w*AlbB and *w*Mel [313], and *w*AlbB/*w*MelCS and *w*Mel [320]. The authors in [332] investigated the use of vaccination and two *Wolbachia* strains (*w*Au and *w*Mel) to reduce dengue incidence and showed that although both strains can be used to mitigate dengue, *w*Au performed better than *w*Mel. Flores *et al.* [320], showed that the transmission potential of *Wolbachia*-infected mosquitoes was greatly reduced for *w*MelCS and *w*AlbB compared to *w*Mel. In addition, Xue *et al.* [313], showed that *w*Mel, *w*AlbB and *w*MelPop *Wolbachia* strains can effectively reduce arboviral transmission. However, of the three, *w*MelPop has the highest fitness cost to the mosquito and would require a sufficiently large number of *w*MelPop-infecfed mosquitoes to be introduced in order to establish themselves in the *Wolbachia*-free mosquito population [313].

Keeling *et al* developed continuous-time models that captured the dynamics of mosquitoes with both one and two co-circulating *Wolbachia* strains [327]. They showed that in a single-strain model, a *Wolbachia*-infected population cannot invade a wild-type mosquito population unless the proportion of infected mosquitoes is high enough to break through the critical infection threshold — an example of the Allee effect [333]. For two strains, they showed that the models exhibit the founder control effect [327]: either of the strains could invade from low density levels if the other strain is present. Further, in a mixed mosquito population

with two *Wolbachia* strains, the authors showed the coexistent equilibrium is unstable as one strain will knock out the other depending on the parameters and densities defining the strains. That is, a *Wolbachia* dominant strain defined by *Wolbachia*-favourable parameters will outperform the other [327]. However, moving from a homogeneous to a spatially heterogeneous system, the two *Wolbachia* strains may coexist locally. This could be established only by the inflow of two different *Wolbachia* strains in the areas defined between bounded regions of different patches of *Wolbachia*-infected mosquito habitats [327]. Similar studies investigated the introduction of *Wolbachia*-infected mosquitoes with different mortality and fertility rates and showed that *Wolbachia*-infected mosquitoes will not dominate the wild-mosquito population if the efficacy of the vertical (maternal) transmission is less than 75% [334]. In addition, *Wolbachia* infection was predicted to easily spread among the wild-type population for higher transmission rates [335]. Two recent modelling studies [336, 337] considered the spread of *Wolbachia* infection in mosquitoes via delay differential equations. They showed that *Wolbachia* infection will established itself and dominate the wild-type mosquito population if the *Wolbachia* release level surpasses the basic reproductive number of the *Wolbachia*-infected mosquitoes [336, 337]. Another recent modelling study [331] showed that the introduction of multiple *Wolbachia* strains could be more efficient than a single-strain introduction depending on the number, frequency and fitness cost of *Wolbachia* introductions. For low fitness cost imposed by *Wolbachia*, the single-strain introduction is efficient in achieving *Wolbachia* dominance with more frequent introductions of the same strain. In this work, we want to assess whether two-*Wolbachia*-strain introduction is better than one with respect to the *Wolbachia* loss and CI attributes of each strain.

As mentioned above, the *w*Au and *w*AlbB strains are heat-resistant however, *w*Au does not induce CI. On the other hand, the *w*Mel strain does induce CI but is more heat sensitive. The *w*Mel strain is effective at reducing transmission potential (quantified by the presence or absence of dengue virus in saliva-inoculated mosquitoes) but not as effective as *w*AlbB and *w*MelCS [162, 320]. Therefore, the two-strain model involving different CI and heat loss

features of *Wolbachia* strains such as wAu and wMel, wAu and wAlbB or wAlbB and wMel has the potential to demonstrate synergies of these strains. Such two-strain models have to the authors knowledge not previously been developed.

In this study, we develop a general two-strain *Wolbachia* model that could account for any two particular *Wolbachia* strains. We then adjust the model to capture two particular *Wolbachia* strains with contrasting high temperature and CI induction behaviours (Figure 5.1). The general *Wolbachia* model is an extension of the single-strain *Wolbachia* transmission model considered in [49], which explored the dynamics between crosses of wAu and wild-type, and wMel and wild-type mosquitoes. The results in [49] showed that despite a lack of CI-induction, the single wAu strain could be more effective than wMel in sustaining *Wolbachia* infection as its *Wolbachia* infection retention feature could outweigh that of CI-inducing strains such as wMel, which is susceptible to high temperature. In our adjusted two-strain *Wolbachia* model, we consider both uni-and bi-directional CI together with temperature-induced *Wolbachia* loss where necessary. We also consider the effect of imperfect maternal transmission in the model. We analyse the resulting differential system by computing the basic and invasive reproductive numbers and explore the two-strain *Wolbachia* model's practicality for *Wolbachia* dominance.

5.2 Model Formation

In this study, we formulate a general two-strain *Wolbachia* model which accommodates the combined interaction of two *Wolbachia* strains with arbitrary characteristics. The total mosquito population is categorised into three subpopulations namely the wild-type, uninfected mosquitoes (u), mosquitoes infected with the first *Wolbachia* strain (w_1) (e.g., wAu), and mosquitoes infected with the second *Wolbachia* strain (w_2) (e.g., wMel/wAlbB) (see Appendix A section Figure A.1). Figure A.1 shows the population progression from matings of male and female adult mosquitoes (from nine possible mating pairs) to offspring, regulated

by CI effects, imperfect maternal transmission (IMT) and *Wolbachia* infection loss for a general two-strain *Wolbachia* model. As a particular example, that includes the effects of both uni and bidirectional CI and IMT, Figure 5.1 depicts the population progression following the feasible matings between *w*Au-like and *w*Mel-like adult mosquitoes. Other schematics showing the two-strain *Wolbachia* combinations of *w*Au and *w*AlbB, and *w*Mel and *w*AlbB are shown in the Appendix A section (Figures A.2 and A.3).

Table 5.1: Mosquito-*Wolbachia* Model Parameters

Parameters	Description	Values	Dimension
Population size			
A_i	Number of aquatic stage (egg, larvae, pupae) mosquitoes with infection status i		-
F_i	Number of adult female mosquitoes with infection status i		-
M_i	Number of adult male mosquitoes with infection status i		-
K	Carrying capacity of the aquatic stage mosquitoes		aquatic mosquitoes
Proportions			
η_{ij}	Proportion of eggs (offspring) with infection i produced from female parent with infection i mating with male parent with infection j	0-1 [197, 40]	-
$1-\eta_{ij}$	Proportion of uninfected eggs (offspring) produced from female parent with infection i mating with male parent with infection j	0-1 [49, 40]	-
ϕ_{ij}	Uni- or bidirectional CI effectiveness for adult female mosquito with infection i mating with adult male mosquito with infection j	0 or 1 [162, 46]	-
Per-capita rates			
ρ_u	Egg-laying rate of uninfected female mosquitoes	13 [197, 314]	Eggs/day
ρ_i	Egg-laying rate of female mosquitoes with infection status i	10-11 [197, 314]	Eggs/day
σ_i	Rate of *Wolbachia* infection loss for mosquitoes with infection status i	0-0.02 [49]	day^{-1}
τ_i	Maturation rate for aquatic stage mosquitoes of i into adulthood	0.11 [314, 40]	day^{-1}
μ_{A_i}	Mortality rate for aquatic stage mosquitoes of infection type i	0.02 [57]	day^{-1}
μ_i	Mortality rate for reproductively mature (adult) mosquitoes with infection status i	0.043-0.082 [338, 46, 162]	day^{-1}

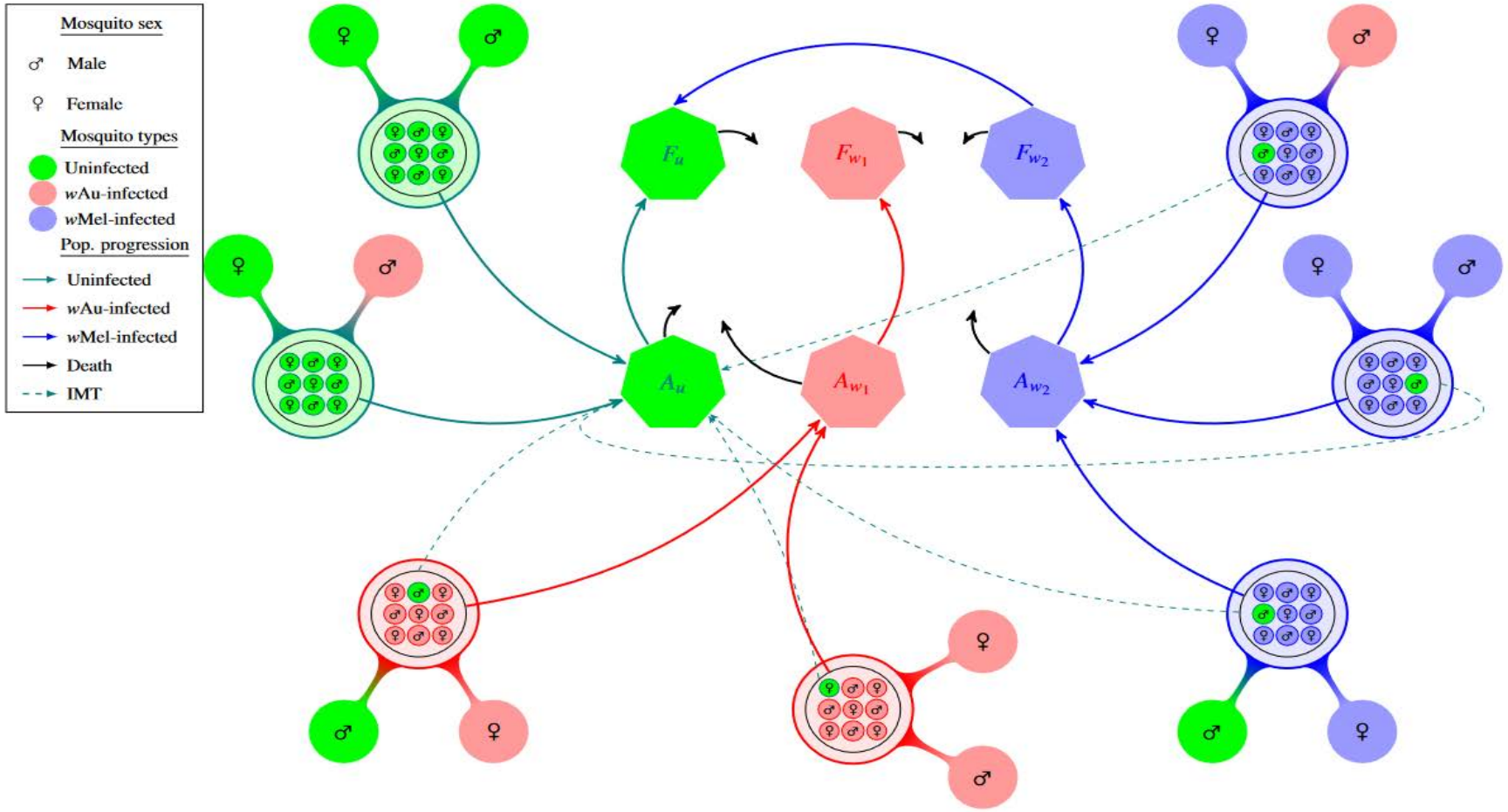

Figure 5.1: Model schematic of Mosquito-*Wolbachia* dynamics between uninfected mosquitoes u and *Wolbachia*-infected mosquitoes with strains $\mathbf{w_1}$ (wAu-like) and $\mathbf{w_2}$ (wMel-like). The green, red, and blue represent the uninfected, wAu-*Wolbachia*-infected and wMel-*Wolbachia* infected mosquito populations respectively. The lines (solid and dashed) represent the population progression where the dashed lines indicate the imperfect maternal transmission (IMT). The black arrows represent deaths. The cytoplasmic incompatibility (CI) induction which inhibits the production of offspring has been adjusted where required. $A \longrightarrow$ Aquatic (eggs, larvae and pupae) mosquitoes and $F \longrightarrow$ Adult mosquitoes.

Let F, M and A be the total number of female, male and aquatic mosquitoes respectively:

$$F = \sum_{k\epsilon\{u,w_1,w_2\}} F_k, \quad M = \sum_{k\epsilon\{u,w_1,w_2\}} M_k, \quad A = \sum_{k\epsilon\{u,w_1,w_2\}} A_k \tag{5.1}$$

where subscripts denote the infection status of each subpopulation. Equation (5.1) describes the total sum of uninfected, w_1-*Wolbachia*-infected and w_2-*Wolbachia*-infected mosquitoes for adult female, male and aquatic individuals. In what follows, we assume $M = F$ so as to simplify the system following observational studies that recorded no significant difference in male to female (*Aedes aegypti* and *Aedes albopictus*) mosquito ratio [339, 340]. The mathematical equations describing the two-strain *Wolbachia* transmission dynamics together with the mosquitoes' reproductive rates for the general case are written as:

$$\begin{aligned}
\frac{dA_u}{dt} &= \xi_u\left(1-\frac{A}{K}\right) - (\tau_u + \mu_{A_u})A_u, \\
\frac{dF_u}{dt} &= \frac{\tau_u}{2}A_u + \sum_{j\epsilon\{w_1,w_2\}} \sigma_j F_j - \mu_u F_u, \\
\frac{dA_i}{dt} &= \xi_i\left(1-\frac{A}{K}\right) - (\tau_i + \mu_{A_i})A_i, \\
\frac{dF_i}{dt} &= \frac{\tau_i}{2}A_i - (\mu_i + \sigma_i)F_i,
\end{aligned} \tag{5.2}$$

where, $i\epsilon\{w_1, w_2\}$ represents the infection status/type, the carrying capacity (K) is a derived parameter quantifying the availability of the mosquito ovipositional breeding sites in a given location where aquatic stage mosquitoes would mature into adulthood. For our purposes, K provides an upper bound on the size of the aquatic stage mosquito population in a particular location. The differential equations in (5.2) represent the dynamics of the compartments for the A_u, F_u, A_i, F_i which yield the number of uninfected aquatic stage, uninfected adult,

i-infected aquatic stage and i-infected adult mosquitoes respectively. Therefore,

$$\begin{aligned}
\xi_u &= \frac{\rho_u F_u \sum_{k\epsilon\{u,w_1,w_2\}} ([1-\phi_{uk}]F_k) + \sum_{j\epsilon\{w_1,w_2\}} \left(\rho_j F_j \sum_{k\epsilon\{u,w_1,w_2\}} ([1-\eta_{jk}][1-\phi_{jk}]F_k)\right)}{F}, \\
&= \frac{\rho_u F_u(F_u+F_{w_1}) + \rho_{w_1} F_{w_1} ([1-\eta_{w_1 u}]F_u + [1-\eta_{w_1 w_1}]F_{w_1}) + \rho_{w_2} F_{w_2} ([1-\eta_{w_2 u}]F_u + [1-\eta_{w_2 w_2}]F_{w_2} +}{F} \\
\xi_i &= \frac{\rho_i F_i \sum_{k\epsilon\{u,w_1,w_2\}} (\eta_{ik}[1-\phi_{ik}]F_k)}{F}, \\
&= \begin{cases} \xi_{w_1} = \frac{\rho_{w_1} F_{w_1}(\eta_{w_1 w_1} F_{w_1} + \eta_{w_1 u} F_u)}{F} \\ \xi_{w_2} = \frac{\rho_{w_2} F_{w_2}(\eta_{w_2 w_2} F_{w_2} + \eta_{w_2 u} F_u + \eta_{w_2 w_1} F_{w_1})}{F}, \end{cases}
\end{aligned}$$

where $\rho_j F_j \sum_{k\epsilon\{u,w_1,w_2\}} ([1-\eta_{jk}][1-\phi_{jk}]F_k)$ is the proportion of mosquito offspring that are generated from the mating combination of a female mosquito with infection status i and any other (infected or uninfected) male mosquito and accounting for CI as necessary. The ξ_u and ξ_i in equation (5.3) represent the total reproductive rates (measured as eggs per day) across all breeding combinations for uninfected and i-infected aquatic mosquitoes respectively.

Each of the model parameters appearing in equations (5.2) and (5.3) are described in Table 1. To rescale the above differential system with respect to the total population size using K, we have that $\sum_k A_k$, the sum of the aquatic stage mosquitoes with infection $k\epsilon\{u, w_1, w_2\}$ is less than or equal to the carrying capacity, which yields

$$\sum_k A_k \leq K.$$

This implies that

$$A_i \leq K.$$

From system (2), we also have the constraints $F_i \leq \frac{\tau_i K}{2(\sigma_i+\mu_i)}$, and $F_u \leq \frac{K}{2\mu_u}\left(\tau_u + \sum_j \frac{\sigma_j \tau_j}{\sigma_j+\mu_j}\right)$. Combining the above results yields

$$\sum_{k\in\{u,w_1,w_2\}} (A_k(t)+F_k(t)) \leq K\left(1+\frac{1}{2}\left(\frac{\tau_u}{\mu_u} + \sum_{j\in\{w_1,w_2\}} \frac{\tau_j}{(\mu_j+\sigma_j)}\left(1+\frac{\sigma_j}{\mu_u}\right)\right)\right) = \alpha K$$

where $\alpha = 1 + \frac{1}{2}\left(\frac{\tau_u}{\mu_u} + \sum_j \frac{\tau_j}{(\mu_j + \sigma_j)}\left(1 + \frac{\sigma_j}{\mu_u}\right)\right)$.

Given the above, it is straightforward to show that the closed set

$$\Omega = \left\{ (A_u, F_u, A_{w_1}, F_{w_1}, A_{w_2}, F_{w_2}) \in \mathbb{R}^6_+ \mid \sum_k (A_k(t) + F_k(t)) \leq \alpha K \right\}$$

is the feasible region for the system dynamics and is positively invariant [197].

Rescaling each of the state variables in terms of the quantity αK gives

$$\begin{aligned}
\frac{dA_u}{dt} &= \xi_u (1 - \alpha A) - (\tau_u + \mu_{A_u}) A_u, \\
\frac{dF_u}{dt} &= \frac{\tau_u}{2} A_u + \sum_{j \epsilon \{w_1, w_2\}} \sigma_j F_j - \mu_u F_u, \\
\frac{dA_i}{dt} &= \xi_i (1 - \alpha A) - (\tau_i + \mu_{A_i}) A_i, \\
\frac{dF_i}{dt} &= \frac{\tau_i}{2} A_i - (\mu_i + \sigma_i) F_i.
\end{aligned} \tag{5.4}$$

Therefore, the general *Wolbachia* model in equation (5.2) in terms of population proportion becomes equation (5.4). Hence, in the scaled system (5.4), the sum of the state variables has an upper bound of 1. That is,

$$\sum_{k \epsilon \{u, w_1, w_2\}} (A_k + F_k) \leq 1.$$

5.3 Model equilibria

The main three features of our general, two-strain *Wolbachia* model (5.4) are: (i) loss of infection at high temperatures; (ii) cytoplasmic incompatability; and (iii) imperfect maternal transmission. With these *Wolbachia* characteristics, we want to calculate the system equilibria and determine the conditions for their stability. Theoretically, we investigate six possible equilibrium points: a mosquito-free equilibrium; a wild-type (infection-free) mosquito-only equilibrium; a single-strain *Wolbachia*-only equilibrium; a coexistent wild-type and single-

strain *Wolbachia*-infected equilibrium; a coexistent two different *Wolbachia* strains equilibrium; and finally, a multi-strain equilibrium where all three mosquito subpopulations coexist. We find that the first four of these are possible, but the last two are not.

To facilitate our equilibrium analysis, we first calculate a set of basic and invasive reproductive numbers for each mosquito subpopulation, both in the presence and absence of other mosquitoes. The set of invasive reproductive numbers represent the number of new mosquitoes of a particular type (specified by the first index, prior to the — separator) that would be generated by a single mosquito of that type when introduced into various mosquito population backgrounds (specified by the second index, following the — separator). For example, the quantity $R_{0i|u}$ is the average number of new mosquitoes with infection i that would be produced by a single i-infected mosquito throughout its lifespan, when it is introduced into a background of uninfected mosquitoes. Whereas, $R_{0u|i}$ is the average number of new uninfected mosquitoes generated by the introduction of an uninfected mosquito into an endemic mosquito population with infection status i, throughout its lifetime. An exception to this convention are the quantities R_{0u} and R_{0i} which respectively give the number of the new uninfected and infected mosquitoes generated (per index) when no (or few) background mosquitoes are present. Following this definition we see that each of the R_0 terms represent ratios and are therefore dimensionless. Hence, R_{0u} and R_{0i} are derived (see Appendices A.1.4) as:

$$\begin{aligned} R_{0u} &= \frac{\rho_u(1-\phi_{uu})\tau_u}{2\mu_u(\mu_{A_u}+\tau_u)} = \frac{\rho_u\tau_u}{2\mu_u(\mu_{A_u}+\tau_u)}, \\ R_{0i} &= \frac{\rho_i\eta_{ii}(1-\phi_{ii})\tau_i}{2(\mu_i+\sigma_i)(\mu_{A_i}+\tau_i)} = \frac{\rho_i\eta_{ii}\tau_i}{2(\mu_i+\sigma_i)(\mu_{A_i}+\tau_i)}, \end{aligned}$$

where we have substituted in the values $\phi_{uu} = \phi_{ii} = 0$. This is because CI does not affect the matings between mosquitoes with the same infection status. In the event of perfect maternal transmission (i.e., $\eta_{ii} = 1$) and infection retention ($\sigma_i = 0$), the basic reproductive numbers of the *Wolbachia* strains (R_{0i}) become analogous to the simpler expression given

for the wild-type subpopulation (R_{0u}). The uninfected/i-infected juvenile mosquito will mature and become an uninfected/i-infected adult mosquito with a probability of $\frac{\tau_u}{\mu_{A_u}+\tau_u}$ / $\frac{\tau_i}{\mu_{A_i}+\tau_i}$ respectively. In addition $\frac{1}{\mu_u}$ / $\frac{1}{\mu_i}$ measures the average life span of an uninfected/i-infected adult mosquito, while $\frac{\rho_u}{\mu_u}$ / $\frac{\rho_i}{\mu_i}$ describes how fast the uninfected/i-infected mosquito population increases or decreases over time respectively.

5.3.1 Mosquito-free equilibrium

Here, we want to establish the mosquito-free equilibrium point is $e_0 = \{0, 0, 0, 0, 0, 0\}$. For this equilibrium, we find that it is ecologically unrealistic, however, considering the mathematically feasible case where there is no interactive competition between the mosquito populations and then investigating the populations separately, we numerically showed that if $\max[R_{0u}, R_{0i}] < 1$ the mosquito populations will go extinct, otherwise, they will persist (Figure 5.2).

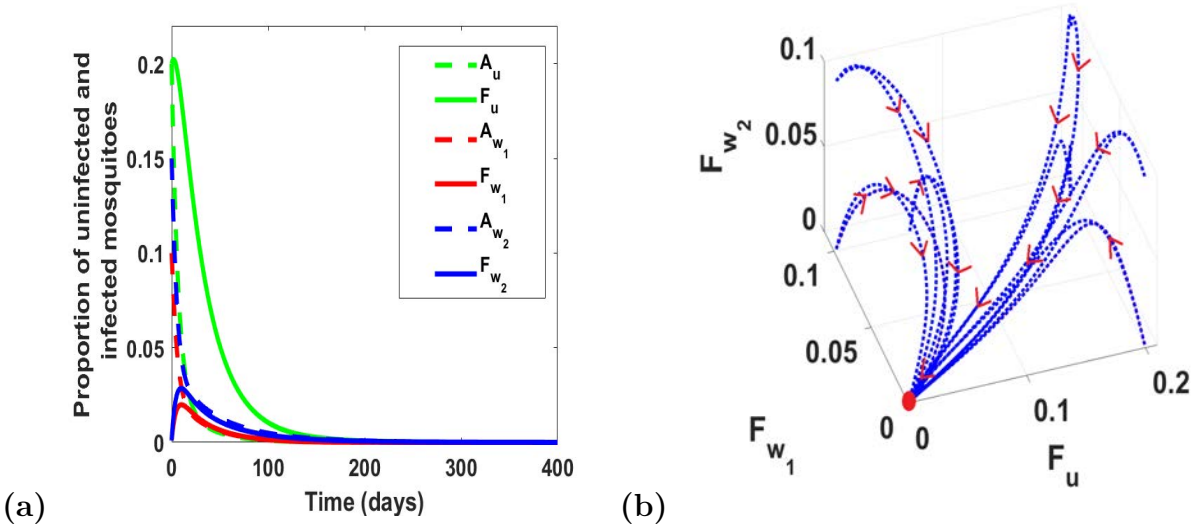

Figure 5.2: No mosquito equilibrium point. (a) Shows the stability of e_0. We set $\rho_u = 0.01$, $\rho_{w_1} = 0.12$, $\rho_{w_2} = 0.15$ and $R_{0u} = 0.098$, $R_{0w_1} = 0.6080$, $R_{0w_2} = 0.6995$. (b) Numerical simulations showing the trajectories (in blue dashed curves with red arrows) in the (F_u, F_{w_1}, F_{w_2}) coordinates for when $\max[R_{0u}, R_{0w1}, R_{0w2} < 1]$. The red ball point represents the stability point, i.e. $(F_u, F_{w_1}, F_{w_2}) = (0, 0, 0)$

Next, we will establish the single (infection-free and *Wolbachia*-infected) mosquito popu-

lation equilibrium points and determine the conditions under which they are stable.

5.3.2 *Wolbachia*-free mosquitoes only

For the two-strain model (5.4), we first consider the existence and stability conditions for the persistence of *Wolbachia*-free mosquitoes only. We find that the infection-free equilibrium point is

$$e_u = (\bar{A}_u^u, \bar{F}_u^u, \bar{A}_{w_1}^u, \bar{F}_{w_1}^u, \bar{A}_{w_2}^u, \bar{F}_{w_2}^u) = \left(\frac{1}{\alpha}\left[1 - \frac{1}{R_{0u}}\right], \frac{\tau_u}{2\alpha\mu_u}\left[1 - \frac{1}{R_{0u}}\right], 0, 0, 0, 0\right)$$

where the overbar and superscript denote that these state variables are equilibrium values. The equilibrium point e_u exists if and only if $R_{0u} > 1$.

Using the next generation matrix method, we obtain the invasive reproductive numbers $R_{0i|u}$ which are the average number of offspring that will be $i\epsilon\{w_1, w_2\}$ *Wolbachia*-infected after introducing a single infected adult into a completely susceptible (wild-type) mosquito population. We find that for any two competing strains $\phi_{iu} = \phi_{ii} = 0$ (no CI induction between F_iM_u and F_iM_i), such that $\xi_u \to \rho_u(1 - \phi_{uu})F_u = \rho_u F_u$ and $\xi_i \to 0$. In this case, we find

$$R_{0i|u} = \frac{R_{0i}\eta_{iu}}{R_{0u}\eta_{ii}}, \tag{5.5}$$

where $R_{0i|u}$ in equation (5.5) is the invasive reproductive number with respect to infected mosquitoes with infection i. To establish the stability of e_u, we evaluate the Jacobian at this equilibrium point, (J^{e_u}), and then calculate the characteristic equation $|J^{e_u} - \lambda I| = 0$, which gives:

$$(\lambda^2 + a_1\lambda + a_2)(\lambda^2 + a_3\lambda + a_4)(\lambda^2 + a_5\lambda + a_6) = 0$$

where

$$
\begin{aligned}
a_1 &= \mu_u + (\mu_{Au} + \tau_u)R_{0u} \\
a_2 &= \mu_u(\mu_{Au} + \tau_u)(R_{0u} - 1) \\
a_3 &= (\mu_{w_1} + \sigma_1) + (\mu_{Aw_1} + \tau_{w_1}) \\
a_4 &= (\mu_{w_1} + \sigma_1)(\mu_{Aw_1} + \tau_{w_1})(1 - R_{0w_1|u}) \\
a_5 &= (\mu_{w_2} + \sigma_2) + (\mu_{Aw_2} + \tau_{w_2}) \\
a_6 &= (\mu_{w_2} + \sigma_2)(\mu_{Aw_2} + \tau_{w_2})(1 - R_{0w_2|u}).
\end{aligned}
$$

Therefore, e_u is locally asymptotically stable if and only if $R_{0u} > 1$, $R_{0w_1|u} < 1$ and $R_{0w_2|u} < 1$ (see Figure 5.3).

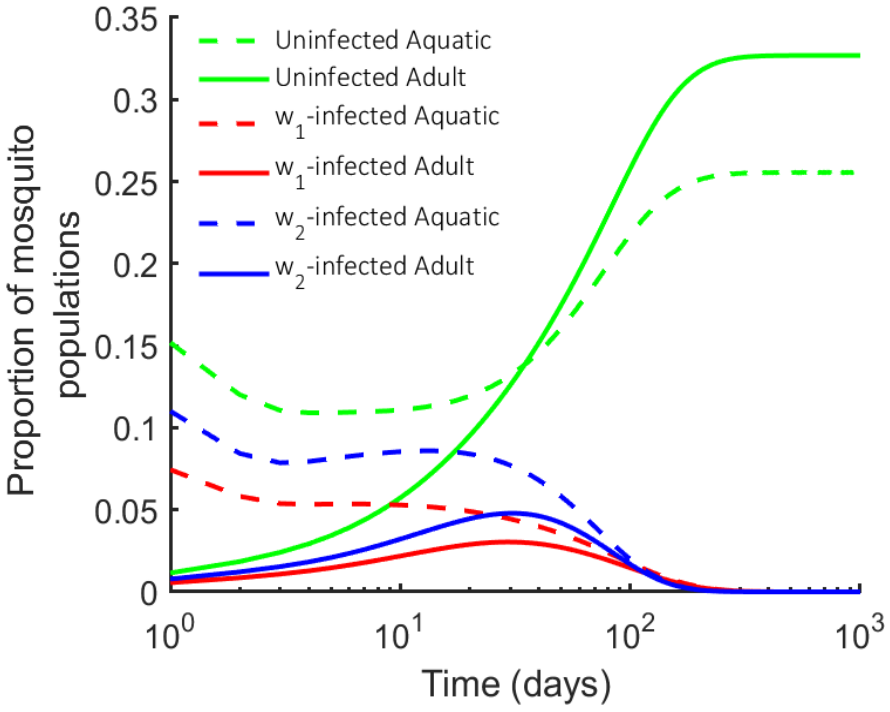

Figure 5.3: *Wolbachia*-free mosquito equilibrium point e_u: The stability conditions for the numerical simulations using $\rho_u = 10$, $\rho_{w_1} = 13$, and $\rho_{w_2} = 11$, leading to $R_{0u} > 1$, $R_{0w_1|u} < 1$ and $R_{0w_2|u} < 1$. Other parameters used are consistent with Table 5.1.

5.3.3 *i-Wolbachia*-infected mosquito population only

Here, we consider the stability conditions for the persistence of a single strain of *i-Wolbachia*-infected mosquitoes, and the extinction of all other subpopulations (*j- Wolbachia*-infected mosquitoes where $j \neq i$). For the equilibrium point e_i, $i\epsilon\{w_1, w_2\}$ to exist, there must be no loss of *Wolbachia* infection ($\sigma_i = 0$) and the maternal transmission of *Wolbachia* infection to offspring must be perfect ($\eta_{ii} = 1$). From the two-strain *Wolbachia* model (5.4), the equilibrium point e_i, $i\epsilon\{w_1, w_2\}$ is obtained as

$$e_i = \left(0, 0, \frac{1}{\alpha}\left[1 - \frac{1}{R_{0i}}\right], \frac{\psi\tau_i}{\alpha\mu_i}\left[1 - \frac{1}{R_{0i}}\right], 0, 0\right)$$

where we require $R_{0i} > 1$. Once again we can use the Jacobian method to calculate the invasive reproductive number for the wild-type mosquito population against a background of type $i\epsilon\{w_1, w_2\}$-infected mosquitoes; this yields:

$$R_{0u|i} = \frac{R_{0u}}{R_{0i}}\left[(1 - \phi_{ui}) + \frac{\rho_i}{\rho_u}(1 - \eta_{iu})\right], \tag{5.6}$$

where $R_{0u|i}$ in equation (5.6) is the invasive reproductive number due to uninfected mosquitoes and ϕ_{ui} represents the effect of unidirectional CI between an i-infected male and an uninfected female.

We can also derive the invasive reproduction number of the other *Wolbachia* strain $j \neq i$ in equation (5.7) as

$$R_{0j|i} = \frac{R_{0j}\eta_{ji}}{R_{0i}\eta_{jj}}(1 - \phi_{ji}), \tag{5.7}$$

where ϕ_{ji} represents the bidirectional CI effect between a j-infected female and an i-infected male. η_{ji} and η_{jj} denote the proportion of mosquito offspring with j infection produced from a j-infected female mosquito mating with either an i-infected or j-infected male mosquito respectively.

Each of the *Wolbachia* strains $i\epsilon\{w_1 \text{ or } w_2\}$ can establish itself when introduced separately (single *Wolbachia*-infected mosquito introduction) as their equilibrium points are stable [49]. However, for the introduction of two mosquitoes, each with different *Wolbachia* strains (co-circulating i and j, $i \neq j$), into the wild-type mosquito population, unlike the establishment of *Wolbachia*-infected mosquitoes in the single-strain introduction in [49], we want to establish the stability of either of the strains (i or j) in the total (two different *Wolbachia*-infected and wild-type) mosquito population.

To establish the stability of the i-*Wolbachia*-infected population equilibrium point e_i, we evaluate the Jacobian J of the system at e_i and compute the characteristic equation in equation (5.8) as follows:

$$|J^{e_i} - \lambda I| = (\lambda^2 + b_1\lambda + b_2)(\lambda^2 + b_3\lambda + b_4)(\lambda^2 + b_5\lambda + b_6) = 0 \tag{5.8}$$

where,

$$\begin{aligned}
b_1 &= \mu_i + (\mu_{A_i} + \tau_i)R_{0i} \\
b_2 &= \mu_i(\mu_{A_i} + \tau_i)(R_{0i} - 1) \\
b_3 &= \mu_u + (\mu_{A_u} + \tau_u) \\
b_4 &= \mu_u(\mu_{A_u} + \tau_u)(1 - R_{0u|i}) \\
b_5 &= (\mu_j + \sigma_j) + (\mu_{A_j} + \tau_j) \\
b_6 &= (\mu_j + \sigma_j)(\mu_{A_j} + \tau_j)(1 - R_{0j|i}).
\end{aligned}$$

Therefore, the conditions for stability of e_i are: $R_{0i} > 1$, $R_{0u|i} < 1$, $R_{0j|i} < 1$ $(i \neq j)$. Hence, the equilibrium point e_i is locally and asymptotically stable provided that $\sigma_i = 0$ and $\eta_{ii} = 1$. To demonstrate the e_i stability conditions for two specific *Wolbachia* strains, let $i\epsilon\{w_1 = w\text{Au}\}$ and $j\epsilon\{w_2 = w\text{Mel}\}$ describe the properties of wAu and wMel *Wolbachia*

strains respectively. These two *Wolbachia* strains differ in their *Wolbachia* infection retention and CI effect. Therefore, accounting for these differences, the conditions for stability of the wAu *Wolbachia*-infected population equilibrium point (e_{w_1}) are given as $R_{0w_1} > 1$, $R_{0u|w_1} < 1$, $R_{0w_2|w_1} < 1$ (see Figure 5.4(a)).

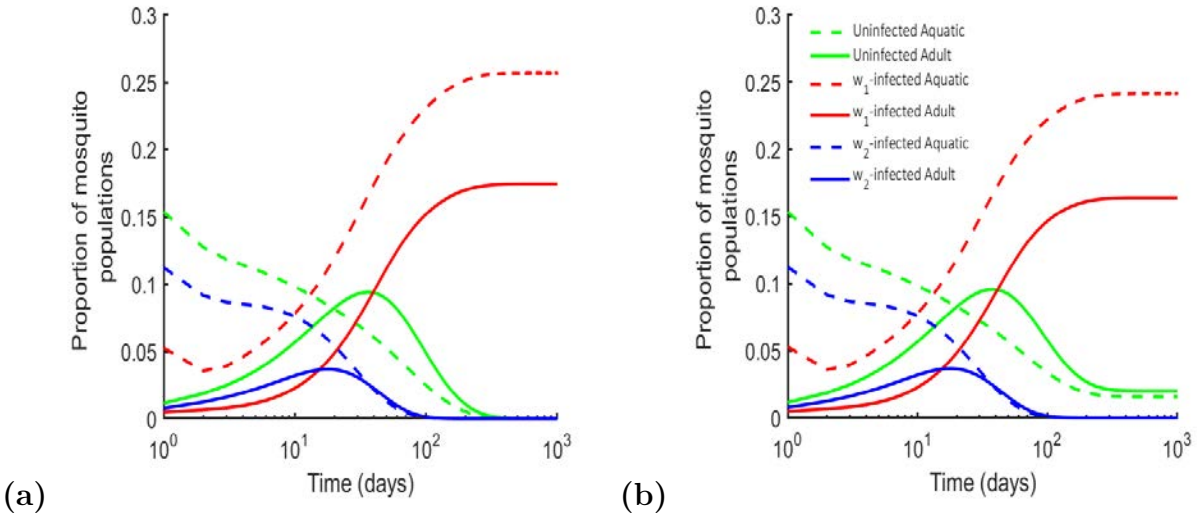

Figure 5.4: $w_1(w\text{Au})$-infected mosquito equilibrium point e_{w_1}: The graphs show the local stability conditions for e_{w_1}. Using $\rho_u = 10$, $\rho_{w_1} = 40$, and $\rho_{w_2} = 11$, **(a)** we set $\eta_{w_1w_1} = 1$, $\sigma_{w_1} = 0$ and the stability conditions $R_{0w_1} > 1$, $R_{0u|w_1} < 1$ and $R_{0w_2|w_1} < 1$ are satisfied. **(b)** On setting $\eta_{w_1w_1} = 0.97$, the e_{w_1} equilibrium point becomes unstable and shifts to e_{uw_1}. Other parameters used are consistent with Table 5.1

Figure 5.4(a) showed the stability of wAu-*Wolbachia*-infected population provided that a perfect maternal transmission ($\eta_{w_1w_1} = 1$) and no *Wolbachia* infection loss ($\sigma_{w_1} = 0$) was observed. But as the maternal transmission becomes imperfect ($\eta_{w_1w_1} < 1$), the equilibrium point becomes unstable due to leakage of uninfected mosquitoes as seen in Figure 5.4(b). Similarly, the same corresponding effect as observed in Figure 5.4(b) is seen if there is an increase in the *Wolbachia* infection loss ($\sigma_{w_1} > 0$).

For the uninfected mosquito population to coexist with *Wolbachia*-infected mosquitoes, one of these two conditions must be satisfied: there must either be a continuous loss of *Wolbachia* infection ($\sigma_i > 0, i\epsilon\{w_1, w_2\}$), or maternal transmission is imperfect ($\eta_{ii} < 1$). Table 5.2 below provides the CI parameters used in this section.

Table 5.2: Table showing the effect of CI parameters for different combination of mosquito crosses (1 = Present, 0 = Absent; UD = unidirectional and BD = bidirectional)

CI Parameters	**Mosquito Crosses**	**CI type**	**CI effect (u =uninfected, w_1 =*w*Au,w_1 =*w*Mel/*w*AlbB)**
ϕ_{uw_1}	$F_uM_{w_1}$	UD	0
ϕ_{uw_2}	$F_uM_{w_2}$	UD	1
$\phi_{w_1w_2}$	$F_{w_1}M_{w_2}$	BD	1
$\phi_{w_2w_1}$	$F_{w_2}M_{w_1}$	BD	0

By these adjustments, we have the coexistence equilibria described below.

5.3.4 Uninfected and single-infected mosquito populations

Here, we consider the general case of model (5.4), and in the subsections that follow, special cases are investigated. The general equilibrium point e_{ui} for coexisting uninfected and one of $i\epsilon\{w_1, w_2\}$ infected mosquito populations is

$$e_{ui} = \left(\frac{2(\beta\mu_u - \sigma_i)F_i^*}{\tau_u}, \beta F_i^*, \frac{2(\mu_i + \sigma_i)F_i^*}{\tau_i}, F_i^*, 0, 0 \right),$$

where

$$F_i^* = \frac{\left(1 - \frac{H}{R_{0i}}\right)\tau_u\tau_i}{2\alpha((\mu_i + \sigma_i)\tau_u + (\beta\mu_u - \sigma_i)\tau_i)}, \tag{5.9}$$

and

$$H = \frac{(1+\beta)}{\left(1 + \frac{\eta_{iu}}{\eta_{ii}}\beta\right)},$$

as

$$a_1\beta^2 + b_1\beta + c_1 = 0, \tag{5.10}$$

where,

$$a_1 = R_{0i|u} - 1 \tag{5.11}$$

$$b_1 = \frac{R_{0i}}{R_{0u}}\left[\left(\frac{R_{0u}}{R_{0i}}\frac{\sigma_i}{\mu_u}R_{0i|u} + R_{0u|i}\right) - 1\right] \tag{5.12}$$

$$c_1 = \frac{\rho_i}{\rho_u}(1 - \eta_{ii}) + \frac{\sigma_i\eta_{ii}}{\eta_{iu}\mu_u}R_{0i|u}. \tag{5.13}$$

Therefore, for e_{ui} to exist for any *i-Wolbachia* strain, $\eta_{ii} < 1$ or $\sigma_i > 0$ given the conditions $\beta\mu_u > \sigma_i$ and for $H \geq 1$, $\eta_{iu} \leq \eta_{ii} \leq 1$. To establish stability, $R_{0i} > H \geq 1$, $R_{0i|u} > 1$, $\left(\frac{R_{0u}}{R_{0i}}\frac{\sigma_i}{\mu_u}R_{0i|u} + R_{0u|i}\right) > 1$ and $\eta_{ii} < 1$ must be satisfied. According to the Routh-Hurwitz criterion for polynomials [341], e_{ui} with equation 5.10 is stable if and only if $\{\frac{b_1}{a_1}, \frac{c_1}{a_1}\} > 0$. Although e_{ui} could exist if $R_{0i|u} < 1$, $\left(\frac{R_{0u}}{R_{0i}}\frac{\sigma_i}{\mu_u}R_{0i|u} + R_{0u|i}\right) < 1$, it is unstable as $\frac{c_1}{a_1} < 0$. Interestingly, e_{ui} will exist if the *Wolbachia*-infected mosquitoes do not go extinct when introduced into a completely susceptible wild-type mosquito population provided that there is either no perfect maternal transmission of *Wolbachia* infection $\eta_{ii} < 1$ or loss of *Wolbachia* infection at high temperature $\sigma_i > 0$ occured.

The demonstration of the uninfected and specific *Wolbachia*-infected mosquitoes' existence has been done by [49], where the authors considered the coexistence of uninfected and wAu-*Wolbachia*-infected mosquitoes. The existence conditions in [49] are consistent with the existent conditions described in this section.

5.3.5 w_1 and w_2 infected mosquito populations

The equilibrium point for coexisting w_1 and w_2 infected mosquito populations in the absence of wild-type does not exist. This is because there is no dynamical link connecting the population progression of both strains. Although our model described that w_1 strain does not induce CI, w_2 does. Therefore, these two strains could not coexist in the absence of wildtype mosquitoes as a result of direct offspring competitive exclusion.

We proceed to investigate the three populations existence equilibrium point.

5.3.6 Uninfected, w_1 and w_2 infected mosquito populations

The equilibrium point for the uninfected, w_1 and w_2 populations is

$$e_{u,w_1,w_2} = \left(\frac{2(\mu_u - \sigma_{w_1}f(F_u^*) - \sigma_{w_2}g(F_u^*))}{\tau_u}, F_u^*, \frac{2(\mu_{w_1} + \sigma_{w_1})f(F_u^*)}{\tau_{w_1}}, f(F_u^*), \frac{2(\mu_{w_2} + \sigma_{w_2})g(F_u^*)}{\tau_{w_2}}, g(F_u^*)\right).$$

In the presence of any two competing strains $i\epsilon\{w_1\ (w\text{Au}),\ w_2\ (w\text{Mel}/w\text{AlbB})\}$, the effect of CI is absent between crosses F_iM_u and F_iM_i (i.e. $\phi_{iu} = \phi_{ii} = 0$). In the case of the uninfected and $i\epsilon\{w_1, w_2\}$ different *Wolbachia*-infected mosquito populations, we would like to consider two contrasting *Wolbachia* strains, say wAu and wMel together with the uninfected mosquito populations. Apart from wAu, which has no CI effect, most (if not all) *Wolbachia* strains, have similar characteristics but may differ in *Wolbachia* infection retention at high temperature. As such, we consider the parameters guiding the wAu as $\sigma_{w_1} = 0$ and for wMel we use σ_{w_2} to adjust for the differences in the other strains relating to wMel such as wAlbB/wMelPop/wPip. The effect of unidirectional and bidirectional CI are also defined by $\phi_{uw_1} = \phi_{w_2w_1} = 0$ and $\phi_{uw_2} = \phi_{w_1w_2} = 1$.

On solving the $i\epsilon\{w_1, w_2\}$ infected compartments in (2), we have

$$F_u^* = \frac{F_{w_1}^* R_{0w_1}(R_{w_2|w_1} - 1) + F_{w_2}^* R_{0w_2}}{R_{0u}(R_{0w_1|u} - R_{0w_2|u})} = m(F_{w_1}^*, F_{w_2}^*). \tag{5.14}$$

For $F_{w_1}^*$ and $F_{w_2}^*$, we have that, on solving the uninfected and w_1 infected compartments in equations (2),

$$F_{w_2}^* = \frac{F_u^* \left(F_u^* \mu_u R_{0u}(R_{w_1|u} - 1) - F_{w_1}^* \mu_u R_{0w_1}(R_{0u|w_1} - 1)\right)}{F_u^* \left(\sigma_{w_2} R_{0w_1|u} + \frac{\rho_{w_2}}{\rho_u}(1 - \eta_{w_2u})\mu_u\right) R_{0u} + F_{w_1}^* \left(\sigma_{w_2} R_{0w_1} + \frac{\rho_{w_2}}{\rho_u}(1 - \eta_{w_2w_1})\mu_u R_{0u}\right)} = n(F_u^*, F_{w_1}^*). \tag{5.15}$$

Rearrange (5.14) to make $F_{w_2}^*$ the subject and equate to (5.15), we obtain:

$$F_{w_1}^* = \frac{F_u^* R_{0u}\left((R_{w_1|u} - R_{0w_2|u}) - F_u^* R_{0w_2}\mu_u(R_{0w_1|u} - 1)\right)}{F_u^* R_{0w_1}\left(R_{0w_2}(1 - R_{0u|w_1})\mu_u + R_{0u}(R_{0w_2|w_1} - 1)\left(\frac{\rho_{w_2}}{\rho_u}(1 - \eta_{w_2u})\mu_u + \sigma_{w_2} R_{0w_1|u}\right)\right) - \sigma_{w_2} R_{0w_1} - \frac{\rho_{w_2}}{\rho_u}(1 - \eta_{w_2w_1})\mu_u R_{0u}} = f(F_u^*) \tag{5.16}$$

Now, solving the uninfected and w_2 infected compartments in equations (2), we obtain

$$aF_{w_1}^{*2} + bF_{w_1}^* + c = 0 \tag{5.17}$$

where

$$\begin{aligned} a &= \left(\mu_u F_u^* R_{0u|w_1} R_{0w_1} + F_{w_2}^*(1-\eta_{w_2w_1})\frac{\rho_{w_2}}{\rho_u} R_{0u}\right) \\ b &= F_u^* R_{0u}\left(\mu_u F_u^* + (1-\eta_{w_2u})\frac{\rho_{w_2}}{\rho_u} F_{w_2}^*\right) + \eta_{w_2w_1}\frac{\rho_{w_2}}{\rho_{w_1}} F_{w_2}^* R_{0w_1}\left(\sigma_{w_2} F_{w_2}^* - \mu_u F_u^*\right) \\ c &= \left(F_{w_2}^* + \eta_{w_2u} F_u^*\right)\left(\sigma_{w_2} F_{w_2}^* - \mu_u F_u^*\right) F_{w_2}^* \end{aligned}$$

Rearrange (5.14) to make $F_{w_1}^*$ the subject and substitute into (5.17), we obtain a real solution

$$F_{w_2}^* = F_u^* \frac{R_{0u|w_1} R_{0w_1} R_{0w_2} \mu_u \rho_u}{(R_{0w_2|w_1} R_{0w_1} - R_{0w_2}) R_{0u} \rho_{w_2}} = g(F_u^*) \tag{5.18}$$

Substitute (5.16) and (5.18) into (5.14), we obtain:

$$F_u^* = h(f(F_u^*), g(F_u^*)). \tag{5.19}$$

Therefore, making F_u^* the subject, we obtain:

$$F_u^* = \frac{P}{Q}. \tag{5.20}$$

Where,

$$
\begin{aligned}
P &= \rho_{w_2} R_{0u}(1-\eta_{w_2w_1})(p_1+p_2)+p_3 \\
Q &= R_{0w_1}\left(\rho_{w_2}R_{0u}^2(1-\eta_{w_2w_1})(q_1+q_2+q_3)+\mu_u\rho_u R_{0w_1}R_{0w_2}R_{0u|w_1}(q_4+q_5)\right) \\
p_1 &= \mu_u\rho_{w_2}(1-\eta_{w_2w_1})R_{0u}^2(R_{0w_1|u}-R_{0w_2|u}) \\
p_2 &= \rho_u R_{0w_1}(\mu_u^2 R_{0u|w_1}R_{0w_2}+R_{0u}(R_{0w_1|u}-R_{0w_2|u})(\sigma_{w_2}+(R_{0w_2|w_1}-1))) \\
p_3 &= \mu_u\rho_u^2\sigma_{w_2}R_{0w_1}^2R_{0w_2}R_{0u|w_1} \\
q_1 &= \mu_u\rho_u R_{0w_2}(1-R_{0u|w_1}(R_{0w_1|u}-R_{0w_2|u})) \\
q_2 &= \mu_u\rho_u R_{0w_2}(R_{0w_2|w_1}(R_{0w_1|u}-1)-R_{0w_2}) \\
q_3 &= R_{0u}(R_{0w_1|u}-R_{0w_2|u})(R_{0w_2|w_1}-1)(\mu_u\rho_{w_2}(1-\eta_{w_2u})+\rho_u\sigma_{w_2}R_{0w_1|u}) \\
q_4 &= \mu_u\rho_u R_{0w_2}(1-R_{0u|w_1}) \\
q_5 &= R_{0u}(R_{0w_2|w_1}-1)(\mu_u\rho_{w_2}(1-\eta_{w_2u})+\rho_u\sigma_{w_2}R_{0w_1|u}).
\end{aligned}
$$

The equilibrium point for the uninfected, w_1 and w_2 populations will only exist if $R_{0w_1|u} > 1$, $R_{0u|w_1} < 1$, $R_{0w1|u} > R_{0w2|u}$, $R_{0w_2|w_1} > 1$. The last two conditions are incompatible if the maximum proportion of offspring generated via maternal transmission is perfect, i.e., $\max\{\eta_{ij} = 1\}$. This show that there is no biological stable equilibrium, only a temporary coexistence can be demonstrated numerically and this has potential advantages.

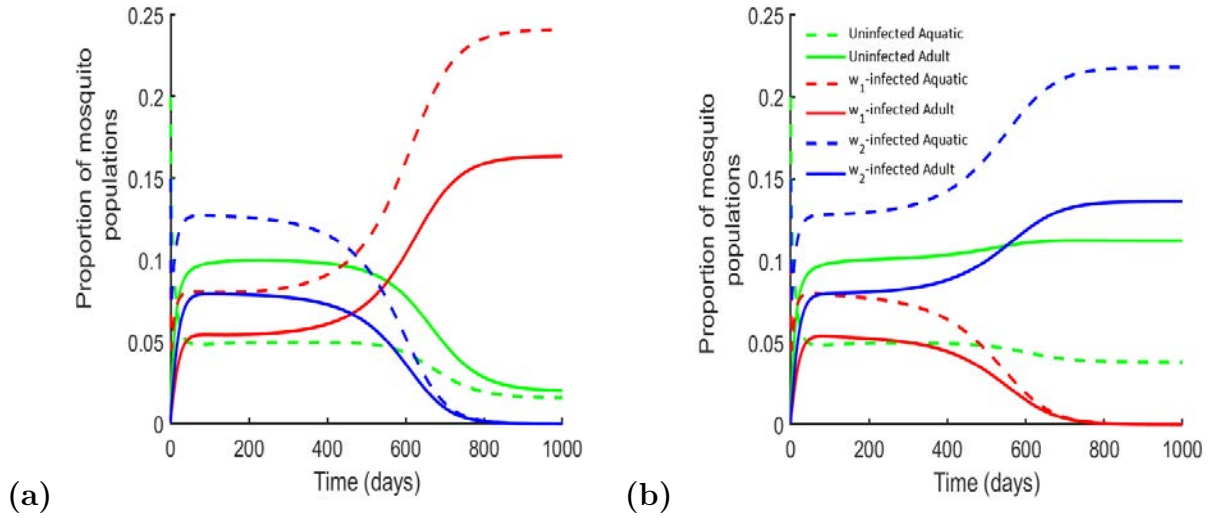

Figure 5.5: The numerical simulations showing pseudo existence of $e_{uw_1w_2}$. For $R_{0u}, R_{0w_1}, R_{0w_2} > 1$, using $\rho_u = 10$, $\rho_{w_1} = 41.5$ and $\rho_{w_2} = 30$. (a) Showed that mosquitoes with strains wAu (with maternal transmission of $\eta_{w_1w_1} = 0.97$), wMel ($\eta_{w_2w_2} = 0.97$) and wild-type exist for a time and then one of the *Wolbachia* infected mosquitoes-wMel is eliminated by the other dominating wAu-infected mosquito population showing instability. (b) Showed that an infinitesimal decrease in the reproductive rate of wAu-infected mosquitoes, i.e. ($\rho_{w_1} = 41.4$), eliminates wAu-infected mosquito population and allows for the coexistence of uninfected and wMel-infected mosquitoes. Other parameters are consistent with Table5.1

For the three (uninfected, wAu-infected, wMel-infected) mosquito populations to temporarily exist, we require $R_{0u}, R_{0w_1}, R_{0w_2} > 1$ (see Figure 5.5). It is observed that, the populations can only exist at most for some time (1-2 years) in this case, however, the dominating *Wolbachia* strain will eventually knock out the other depending on parameters contributing to its invading force or characteristics such as maternal transmission of *Wolbachia* infection, reproductive and loss of *Wolbachia* infection rates (Figure 5.5). This is called the founder control as established in [327]. Interestingly, some mathematical and biological implications could be derived between the pseudo-stable times prior to the founder control effect. These implications are elaborated in the next section (Section 5) outlining the tradeoffs between using one and two strains of *Wolbachia* infected mosquitoes to control arboviral infections.

5.4 The trade off between one and two *Wolbachia* strains

The competitiveness between the uninfected mosquitoes together with their one or two strain *Wolbachia* infected counterparts varies between strains. These differences could be accounted for based on the CI types (ϕ_{ii}), the per capita reproductive rate (ρ_i) and the loss of *Wolbachia* infection rate (σ_i) corresponding to the *Wolbachia* strains used. First, in the absence of loss of *Wolbachia* infection, two different *Wolbachia* infected mosquitoes that each possess CI (i.e. four out of nine possible mating combinations will induce CI) could be advantageous compared to other paired combinations. In addition, this advantage could also outweigh that of a CI-inducing single *Wolbachia* strain (one out of four possible mating combinations only induce CI). Figure 4.1 depicts the generation of offspring from crosses of double *Wolbachia* strain combinations with contrasting CI induction.

This suggests that the combination could drive *Wolbachia* infections to establish faster than others in an ideal situation where there is absence of *Wolbachia* infection loss due to high temperature.

However, considering the effect of heat, we model the σ_i (the loss of *Wolbachia* infection rates for the $i\epsilon\{w_1, w_2\}$ *Wolbachia* infection) as a function of seasonal variations (with time) for *Wolbachia* loss in equation (5.21)

$$\sigma_i(t) = \frac{\sigma_{m_i}}{2}\left(\cos\left(\frac{2\pi t}{365} - \Omega\right) + 1\right), \tag{5.21}$$

where σ_{m_i} describes the maximum value of the seasonal fluctuation in the *Wolbachia* loss for the corresponding strains $i\epsilon\{w_1, w_2\}$. Ω represents the phase shift of the transcedental function that positions the model with the seasonal variation. Figure 5.6 (a) shows the *Wolbachia* frequency levels for a single-strain (wAu, wMel and wAlbB) and a combination of double-strain (wAu with wMel, wAu with wAlbB and wMel with wAlbB) *Wolbachia*-infected mosquitoes in the presence/absence of CI and *Wolbachia* infection loss properties. The Figure 5.6 (a) is disintegrated into Figures (b), (c), (d), (e), (f) and (g). Figure 5.6 (b)

describes the single-strain wAu-*Wolbachia*-infected mosquito dominance after 7-8 months in the absence of *Wolbachia* heat loss and CI induction. On the other hand, Figure 5.6 (c) visualises the effect of LWI on single-strain wMel-*Wolbachia*-infected mosquitoes seasonally over the years despite lack of CI. Figure 5.6 (d) shows similar dynamics as in Figure 5.6 (b) but had a decreased number of wild type mosquitoes wand as a result, increased number of wAlbB mosquitoes due to lack of CI. For the double-strain (wAu with wMel), *Wolbachia*-infected mosquitoes, Figure 5.6 (e) shows that the two strains could be maintained before exhibiting the founder control and as such, a gradual dominating strain (wAu in this case) knocks out the other (wMel) after 1.4 years. This occured as wMel-mosquitoes with CI continually lose their *Wolbachia* infection due to heat while the non CI-inducing wAu-mosquitoes do not, therefore strengthening the fact that the gains from not losing *Wolbachia* infection outweigh those of CI [49]. Further, Figure 5.6 (f) shows that the combination of the two (wAu and wMel) *Wolbachia* strains would lead to a longer time for dominance to occur as seen in Figure 5.6 (a).

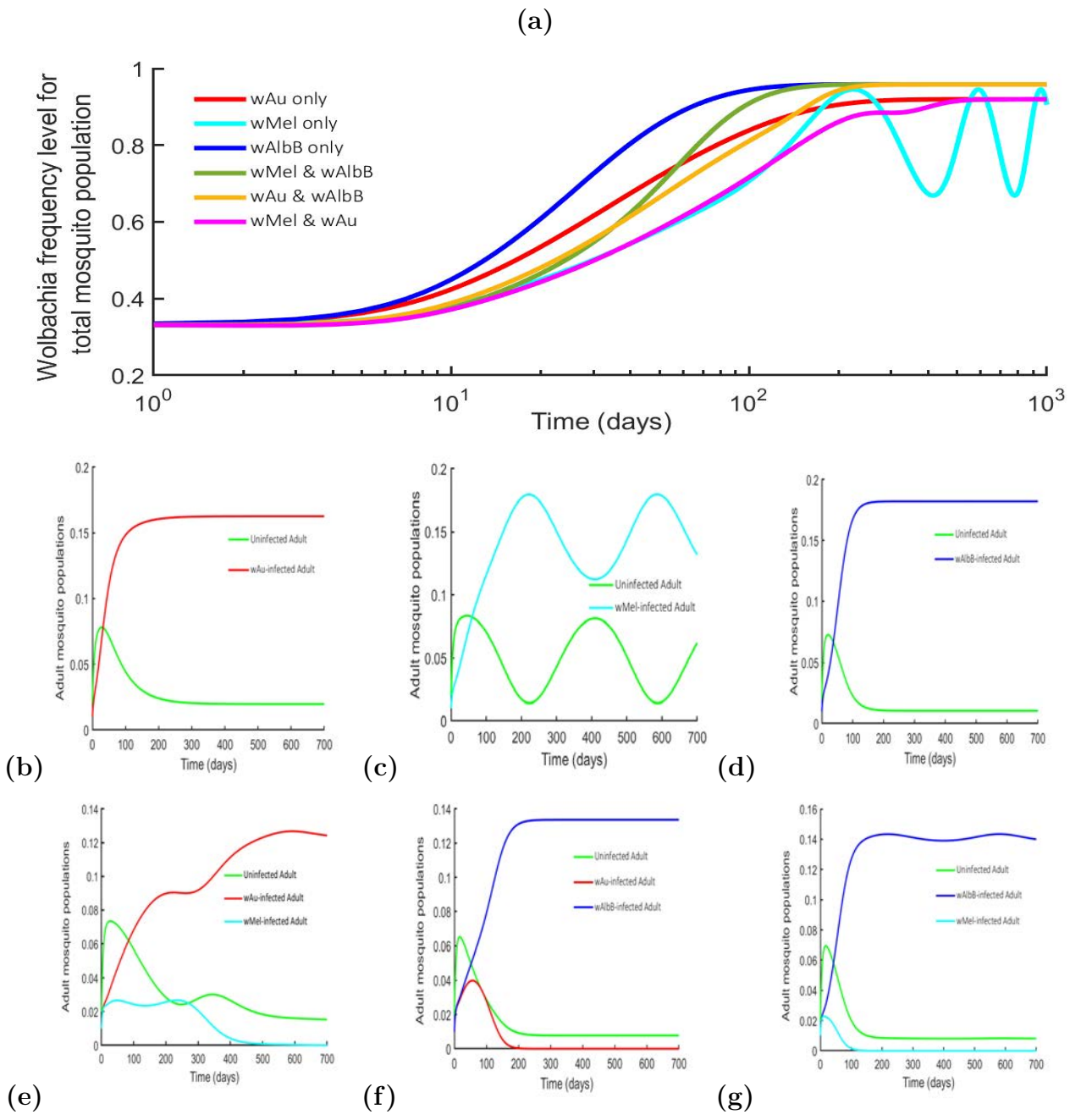

Figure 5.6: *Wolbachia* frequency levels for both single and double-strain *Wolbachia*-infected mosquitoes in the presence/absence of CI and *Wolbachia* infection loss. **(a)** Showed the *Wolbachia* frequency levels of both one-strain – wAu; wMel; wAlbB, and two-strain – wAu & wAlbB; wAu & wMel; and wMel & wAlbB *Wolbachia*-infected mosquitoes, accounting for the effects of uni- and bidirectional CIs and the LWI (parameters used can be found in Table 5.3). **(b)** Showed the adult mosquitoes for wAu-*Wolbachia* only competition with the wild type mosquitoes as in wAu only *Wolbachia* frequency in **(a)**. **(c)** Showed the adult mosquitoes for wMel-*Wolbachia* competitio onlyn with uninfected mosquitoes as in wMel only in **(a)**. **(d)** Showed the adult mosquitoes for wAlbB-*Wolbachia* competition only with uninfected mosquitoes as shown in **(a)**. **(e)** Showed the adult mosquito population of the two strain competition of wAu and wMel together with wild-type mosquitoes for the *Wolbachia* frequency of wAu and wMel in **(a)**. **(f)** Showed the adult populations for uninfected, wAu- and wAlbB-infected mosquitoes for the *Wolbachia* frequency in **(a)**. **(g)** Showed the adult populations for wAlbB- and wMel-infected mosquitoes for the *Wolbachia* frequency in **(a)**.

For the other two-strain combinations i.e wAu and wAlbB and wMel and wAlbB (Figure 5.6 (f) & (g)), there is an increase in the frequency levels of *Wolbachia* compared to wAu- and wMel-only strain (as seen in Figure 5.6 (a)). However, it was observed that wAlbB-only *Wolbachia* strain were able to dominate faster and performed best in all comparison in terms of having higher affinity to retain *Wolbachia* infections in mosquitoes at high weather temperatures in the absence of CI (Figure 5.6 (a)).

Table 5.3: Table showing the parameter values used for the effect of CI and LWI on seasonal variation for one and two *Wolbachia* strains

***Wolbachia* Strain(s)**	ϕ_{uw_1}	ϕ_{uw_2}	$\phi_{w_1w_2}$	$\phi_{w_2w_1}$	σ_{m_1}	σ_{m_2}
One Strain						
wAu	0	-	-	-	0	-
wMel	1	-	-	-	0.025	-
wAlbB	1	-	-	-	0	-
Two Strains						
wAu & wMel	0	1	1	0	0	0.025
wAu & wAlbB	0	1	1	0	0	0
wAlbB & wMel	1	1	1	1	0	0.025

Therefore, starting a *Wolbachia* rollout with two strains simultaneously may not be advantageous as the time to dominate the population could be reached faster using a single strain with high *Wolbachia* retention at high temperature in the absense of CI (Figure 5.6). The parameter values used for the seasonal variation effects for one and two *Wolbachia* strain simulations are described in Table 5.3.

5.5 Discussion

In this work we set out to explore the impact of introducing two *Wolbachia* strains simultaneously. Using information on the ecological dynamics of multiple *Wolbachia* strains with various characteristics [313, 320, 327, 217, 331], we were interested in exploring stable co-existence and synergistic effects. We found neither of these. Specifically, we found that the fitter *Wolbachia*-infected mosquito strain would dominate and eliminate the other strain meaning that co-existence would always be temporary. Furthermore, the temporary co-existence did not increase prevalence of *Wolbachia* strains, and either had no impact or reduced prevalence.

Our motivation for examining co-existence was based on the recognition that some studies have shown that a *Wolbachia* strain: *w*Au, does not exhibit either unidirectional or bidirectional cytoplasmic incompatibility (CI) [162, 46]. That is, when a *w*Au-infected *Wolbachia* male mosquito is crossed with another strain *Wolbachia*-infected female, they produce offspring with the other *Wolbachia* strain. For this reason, we believed that combining *w*Au with other strains may not interfere with the dynamics of the other strain and could potentially be synergistic. This is particularly so because *w*Au has the positive feature of high heat tolerance, which plausibly may outweigh the lack of CI [197, 49]. Therefore, we developed a two-strain general model (5.4) and tuned the parameters to reflect properties of *w*Au, *w*Mel and *w*AlbB in turn.

Our two-strain general model described the transmission dynamics of uninfected and *Wolbachia*-infected mosquitoes with two different strains (Appendix A2 Figure A.1). We derived the general mosquito-free reproduction numbers and further established the *Wolbachia* invasive reproduction numbers singly for the two strains using the *Wolbachia*-infection free equilibrium point. These invasive reproduction numbers were used to establish the local stability conditions of the equilibrium points and were in line with results from single strain models reported previously [49]. In the general model, we specifically examined *w*Au: with absent CI and good *Wolbachia* retention in heat and we combined this (in our *in silico*

model) with wMel & wAlbB: CI present in both and loses/retains *Wolbachia* infection in heat, respectively. Considering the transmission dynamics involving these single strains, we established that there was local stability for each of wAu-infected and wAlbB-infected mosquitoes and that they would dominate uninfected mosquitoes provided there was no loss of *Wolbachia* infections due to high temperature and a complete maternal transmission is exhibited from male and female mosquito crosses with similar strains. However, a single population of only wMel-infected mosquitoes does not exist indefinitely, as uninfected mosquitoes emerge because of loss of infection in this strain at high temperatures.

For each of the strains wAlbB and wAu-infected mosquitoes, we assume perfect maternal transmission and no heat loss. Under these circumstances there is no stable equilibrium with uninfected mosquitoes. The system dynamically converges to a single-population equilibrium i.e either uninfected or wAu/wAlbB-only-infected population. This is because, the perfect maternal transmission blocks any leakage of uninfected offspring making the steady state of zero uninfected mosquitoes and 100% wAu-infected mosquitoes stable provided its invasive reproduction number is greater than one. In contrast, the coexistence of the uninfected and the CI-inducing wMel-infected mosquitoes exists as the wMel-infected mosquitoes are continuously losing their infections due to high temperature. Under these circumstances, the coexistence with uninfected mosquitoes will continue to exist provided there is *Wolbachia* infection loss. For all three strains, there is a potential uninfected-mosquito only equilibrium if the *Wolbachia*-infected mosquitoes are unable to invade an existing uninfected population (when the invasive reproduction number for *Wolbachia* infected mosquitoes is less than one).

While co-existence of a single strain of wMel and uninfected mosquitoes is stable (via loss of *Wolbachia* infection in mosquitoes), we found no such stability point for two different strains of *Wolbachia*-infected mosquitoes. Nevertheless, we showed through numerical simulation that under plausible parameter ranges, *Wolbachia* strains may coexist for a year or two. However, this co-existence is always temporary and cannot attain stability as one strain will dominate the other to exclusion. Once a population of mosquitoes is present in

the population, it becomes harder for species to invade, and the founder strain will exclude any competing strain [327]. We showed numerically that before hitting founder control, the two different *Wolbachia*-infected mosquito populations coexisted for some time, providing some hope of establishing a synergistic effect. However, our study showed that introducing two strains of *Wolbachia* simultaneously could neither fast track the time to *Wolbachia* dominance in the wild-population nor increase the *Wolbachia* prevalence compared to a single *Wolbachia* strain release of the fitter strain (in our context *w*AlbB). This was also true for the combination of *w*Au and *w*Mel, with *w*Au as a single strain out-performing the introduction of both strains simultaneously.

Our work therefore leads to the recommendation of rolling out one-strain of *Wolbachia*-infected mosquitoes with optimal characteristics (high *Wolbachia* infection retention at high temperature, high maternal transmission and complete CI) rather than attempting mixed strain rollouts.

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Chapter 6

Quantifying the impact of *Wolbachia* releases on dengue infection in Townsville, Australia

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Contrbutions:

Ogunlade, S. T. wrote the manuscript presented in this chapter. Ogunlade, S. T. developed the model, analysed the differential system governing the human-vector disease dynamics of dengue infection in the presence of *Wolbachia* bacteria and the results' interpretation. Ogunlade, S. T. and Adekunle, A. I. conceived the project work described in this chapter. Adekunle, A. I. assisted with the model dynamics formation and data analysis. Adekunle, A. I. and Meehan, M. T. assisted with the interpretation of the results. McBryde, E. S. and Adekunle, A. I. and Meehan, M. T. contributed to proof-reading the manuscript.

Summary

In Section 6.1 of the present chapter, I describe dengue viral infection as a life-threatening and most wide-spread *Aedes*-borne arboviral infection globally. A unique strategy to halt the propagation of dengue virus transmission in areas with moderate and low endemicity, involves the introduction of *Wolbachia* bacteria into the arthropod vectors (*Wolbachia*-based biological control). Further, I investigate the impact of the *Wolbachia* introduction on dengue transmission dynamics in Townsville: a North Queensland city where dengue outbreaks occur every year during the wet season due to the importation of frequent entry of dengue-positive people. In Section 6.2, I describe the data and its source and present a mathematical model that governs the dengue transmission dynamics both in human and mosquito population in the presence of *Wolbachia* infection. Following this section is Section 6.3, where the results are discussed. In this section, we computed the basic reproductive number in the presence and absence of *Wolbachia*-infected mosquitoes, introduce seasonality into the model and carry out the data analysis and model simulations, which include parameter estimation. Section 6.4 discusses the summary of the results, which show that after *Wolbachia* introduction, predicted dengue incidence would decrease by 80–90% provided that the dengue infection transmission probability from *Wolbachia*-infected mosquitoes is a quarter of that from non-*Wolbachia* mosquitoes.

Keywords: Dengue, *Aedes* mosquitoes, *Wolbachia*, Transmission probability, Townsvile.

6.1 Introduction

Viral infections such as dengue, which are transmitted by *Aedes* mosquitoes have received global attention recently due to their rise and re-emergence [41, 342, 317]. Of all the *Aedes*-borne diseases, dengue has the most widespread geographical distribution with around 4 billion people at risk and approximately 400 million annual infections [343, 16]. Dengue transmission dynamics are influenced by seasonal variations in temperature and rainfall and dengue epidemiological outbreaks are typically caused by the importation of dengue patients and occur seasonally in locations where the climate is significantly seasonal [268]. The importation of dengue cases has led to the development and reemergence of dengue in a number of nations [344, 345]. The global target set by leaders and other partners involved in dengue control programmes such as The World Health Organisation (WHO), research and funding agencies, for dengue infection is to reduce morbidity and mortality by a quarter and a half respectively [346]. This has prompted the development of new control strategies such as *Wolbachia*-based control in the fight against dengue and other *Aedes*-borne diseases such as Zika, chikungunya and yellow fever [342, 317, 346, 347, 348].

Wolbachia, an intracellular bacterium, which exists in more than half of all insect species, has been shown to successfully suppress the transmission of dengue viruses in blood-feeding arthropods such as mosquitoes [41, 164]. *Wolbachia* could exist in different strains such as *w*Mel, *w*AlbB and *w*MelPop [162, 43, 44]. Some of these strains have been released in the field but the most common is *w*Mel [317, 43, 44, 324, 164]. While the *w*Mel *Wolbachia* rollout method has demonstrated highly positive results in reducing dengue-carrying vectors, it is not without risk due to the problem of its potency, degrading under high temperature conditions [162, 48].

The *w*Mel strain of *Wolbachia* was released in Townsville from October 2014 for close to two and half years [317]. This strategy saw dengue incidence reduced significantly (around 95% reduction) with very few records of local transmission following the high prevalence of *Wolbachia*-infected mosquitoes [317]. Similar success report was reported in nearby Cairns,

Northern Queensland where *w*Mel-infected mosquitoes significantly dominated wild type *Aedes aegypti* population (the main vector agent for dengue transmission) [41]. Other countries such as Brazil, Indonesia and Vietnam have rolled out *Wolbachia*-infected mosquitoes for large scale fight against *Aedes*-borne diseases and have recorded high success rates in mitigating dengue burden [347, 348, 164].

Despite the observed success of *Wolbachia* release programs in reducing dengue burden, some studies have shown that *w*Mel *Wolbachia*-infected mosquitoes may lose their *Wolbachia* infections as a result of seasonal fluctuations [162, 50], or fail to dominate wild-type mosquitoes especially in high endemic settings [163]. A study [349], which conducted a huge *w*Mel-*Wolbachia* release program for a 29-month period (from August 2017 to December 2019), across various locations in Rio de Janeiro, Brazil and estimated the impact on the incidence of dengue and chikungunya, found that *w*Mel did not dominate the wild type as only 38% reduction in dengue incidence and 10% reduction in chikungunya incidence were observed [349]. Despite numerous releases, it is unknown why *w*Mel failed to establish itself immediately in Rio de Janeiro. Townsville, a city in Northern Queensland with population of about 187,500 residents, has seasonal fluctuations [350]. As such, prior to and after rolling out *Wolbachia* in Townsville, there may be need to consider the seasonality on the transmission dynamics of dengue and examine the impact of *Wolbachia*-infected mosquito release on dengue transmission dynamics. This leads to investigating the sustainability of the *Wolbachia*-based strategies in controlling arboviral infections.

In this study, we describe the analysis of the 'before' and 'after' *Wolbachia* mosquito introductions (i.e., pre- and post-*Wolbachia* respectively) in Townsville and account for the impact on dengue diseases. Additionally, we model both the human dengue transmission dynamics alongside the mosquito population dynamics in the presence of *Wolbachia* infection. Other models have described the ecological dynamics of *Wolbachia*-infected mosquito population only in [49, 351]. Here, we extend these *Wolbachia*-mosquito models via incorporating human populations and dengue infection dynamics. This model estimates the transmission

probabilities between humans and non-*Wolbachia*, and *Wolbachia*-infected mosquitoes and in turn provides insight on the impact of *Wolbachia* introduction of dengue incidence.

6.2 Methods

6.2.1 Data source and description

The data used for this analysis were extracted from O'Neill et al [317]. These data described the *Wolbachia* field trials in 32 suburbs in the city of Townsville, which is one of the largest cities in North Queensland, Australia with a population of 187,500 [350]. Mosquitoes such as *Aedes aegypti* are endemic and the monthly incidence of locally acquired dengue and imported cases was reported [317].

6.2.2 *Wolbachia* data

From October 2014, *w*Mel-*Wolbachia*-infected mosquitoes were continually released for a 28-month period across 32 suburbs in the city of Townsville, Australia. Releases were carried out using the mosquito release containers (Mozzie boxes) and biogents sentinel mosquito traps were set up for subsequent mosquito capture [317]. These traps were monitored and collected weekly prior to February 2016, after which a fortnight collection ensued. In each release location, *Wolbachia* rollout continued until the *Wolbachia*-frequency proportion in the trapped mosquitoes exceeded 50% for a fortnight. Details on rollout description and method used can be found in [3]. The data information included the 32 suburbs in which the *Wolbachia* release occurred, the release period, the date and total number of trapped mosquitoes caught and the proportion of *Wolbachia*-infected mosquitoes from the total mosquitoes caught. This data was formatted into monthly data to capture the proportion of *Wolbachia*-infected mosquitoes in Townsville.

6.2.3 Dengue data

Observed Townsville dengue data for locally acquired and imported dengue cases from 2001 to 2019 were extracted from O'Neill et al [317]. Given that the *Wolbachia* rollout began in October 2014, these dengue cases were stratified into "pre-*Wolbachia*" and "post-*Wolbachia*" period which translated to cases from January 2001 to September 2014 and October 2014 to February 2019 respectively. Further, the incidence was aggregated into monthly cases and the monthly rate of importation (human infected with dengue arriving from outside Australia into Townsville) for pre- and post-*Wolbachia* period (0.4 and 1 case/month respectively) were estimated using the Poisson distribution rate i.e., the average monthly rate.

6.2.4 Mathematical model of Dengue

Here, a mathematical model is presented, describing the system of differential equations governing the dengue infection dynamics both in the human alongside mosquito population dynamics in the presence of *Wolbachia* infection. The total human population (N_h) is divided into subpopulations of susceptible individuals (S_h), individuals exposed to dengue locally (E_{h_L}) and from importation (E_{h_I}), individuals infected with dengue locally (I_{h_I}) and from importation (I_{h_I}), and Recovered humans (R_h). The flow chart representation is illustrated in Figure 6.1. To account for the contribution of the mosquito vectors and the *Wolbachia* introduction and efficacy, the subpopulation of non-*Wolbachia* mosquitoes is defined as: susceptible mosquitoes (S_u), exposed mosquitoes (E_u), and infected mosquitoes (I_u) with dengue, while *Wolbachia*-infected mosquito counterparts are correspondingly subdivided into S_w, E_w, and I_w (Figure 6.1).

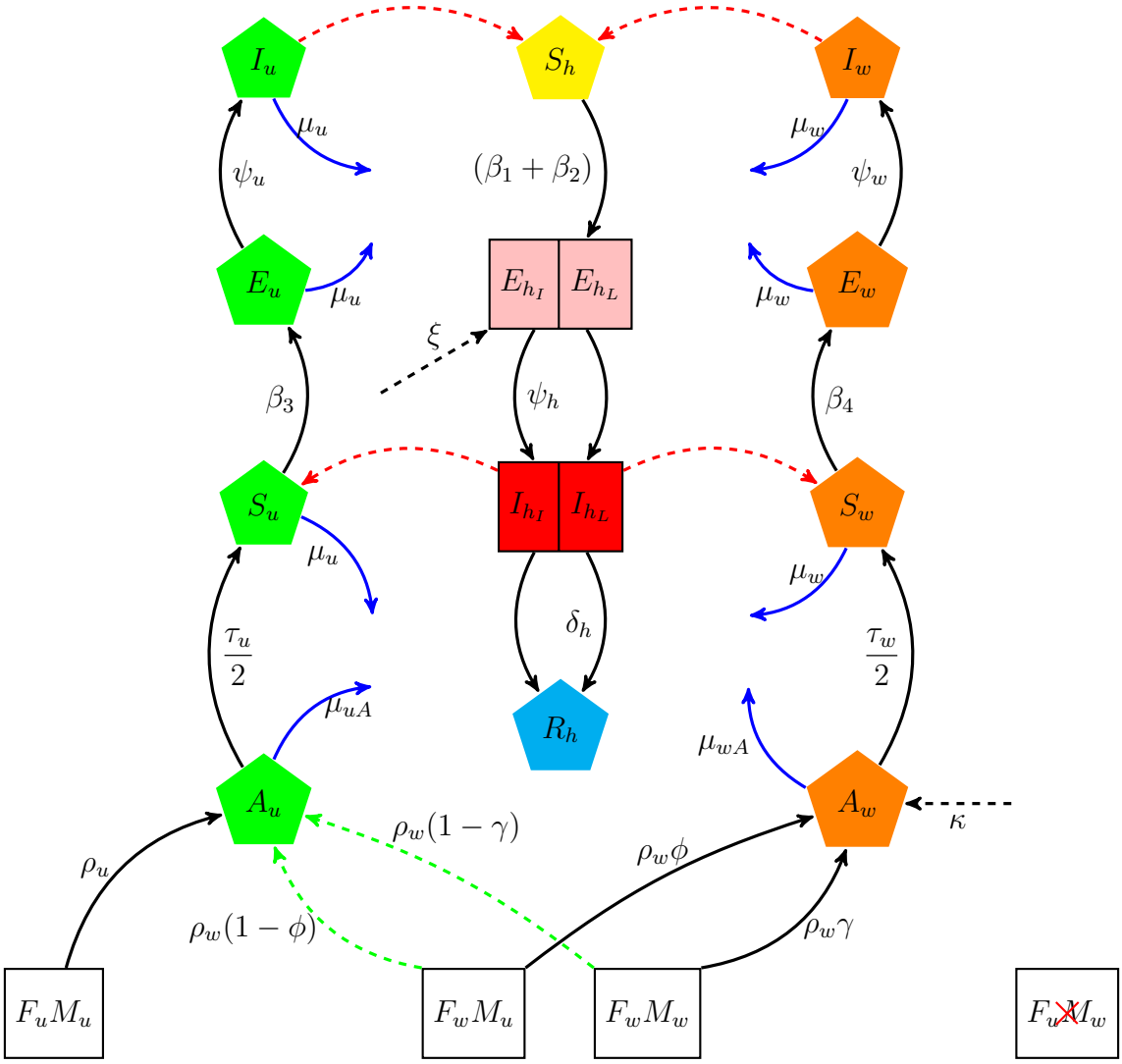

Figure 6.1: Model formation schematic of dengue infection dynamics between human population and mosquitoes, which include the *Wolbachia*-infected mosquitoes. The black solid lines represent the population progression i.e., movement of individuals from a state to the other, while the blue solid lines indicate death. In addition, the dashed red lines signify the transmission of dengue infection either from dengue-infected mosquitoes to susceptible humans or vice versa. The dashed green lines are the proportion of uninfected offspring due to imperfect maternal transmisson of *Wolbachia* infection. The dashed black lines represent importations of dengue-infected humans (ξ) or *Wolbachia* mosquitoes' importation (κ). The $F_{u(w)}$ and $M_{u(w)}$ combinations represent the possible mating pairs and generation of offspring from non-*Wolbachia* (*Wolbachia*-infected) mosquitoes respectively. Of these combinations, F_uM_w do not produce viable offspring due to cytoplasmic incompatibility.

The mosquito activation rates (i.e., the rate at which dengue-exposed mosquitoes become infected) and maturation rates for both *Wolbachia*-infected and uninfected mosquitoes are assumed to be the same. Further, the cytoplasmic incompatibility (CI) effect was considered as the mating pair of uninfected female and *Wolbachia*-infected male mosquitoes (F_uM_w) do not produce viable offspring. The imperfect maternal transmission described in [49, 351] was also incorporated as a small proportion ($[1-\gamma]$ and $[1-\phi]$) of uninfected eggs (aquatic stage mosquitoes) that are produced from *Wolbachia*-infected females.

The differential system governing the dengue transmission dynamics in humans and mosquito vectors in the presence of *Wolbachia* is given below as:

$$
\begin{aligned}
\frac{dS_h}{dt} &= -(\beta_1+\beta_2)S_h,\\
\frac{dE_{h_I}}{dt} &= -\psi_h E_{h_I}+\xi(t),\\
\frac{dE_{h_L}}{dt} &= (\beta_1+\beta_2)S_h-\psi_h E_{h_L},\\
\frac{dI_{h_I}}{dt} &= \psi_h E_{h_I}-\delta_h I_{h_I},\\
\frac{dI_{h_L}}{dt} &= \psi_h E_{h_L}-\delta_h I_{h_L},\\
\frac{dR_h}{dt} &= \delta_h(I_{h_I}+I_{h_L}),\\
\frac{dA_u}{dt} &= \left[\frac{\rho_u F_u^2+\rho_w[(1-\gamma)F_w^2+(1-\phi)F_wF_u]}{F}\right]\left(1-\frac{A}{K}\right)-(\tau_u+\mu_{uA})A_u, \qquad (6.1)\\
\frac{dS_u}{dt} &= \frac{\tau_u}{2}A_u-(\beta_3+\mu_u)S_u,\\
\frac{dE_u}{dt} &= \beta_3 S_u-(\psi_u+\mu_u)E_u,\\
\frac{dI_u}{dt} &= \psi_u E_u-\mu_u I_u,\\
\frac{dA_w}{dt} &= \left[\frac{\rho_w[\gamma F_w^2+\phi F_wF_u]}{F}\right]\left(1-\frac{A}{K}\right)-(\tau_w+\mu_{wA})A_w,\\
\frac{dS_w}{dt} &= \frac{\tau_w}{2}A_w-(\beta_4+\mu_w)S_w,\\
\frac{dE_w}{dt} &= \beta_4 S_w-(\psi_w+\mu_w)E_w,\\
\frac{dI_w}{dt} &= \psi_w E_w-\mu_w I_w,
\end{aligned}
$$

where $N_h = S_h + E_{h_I} + E_{h_L} + I_{h_I} + I_{h_L} + R_h$, $A = A_u + A_w$,

$\beta_1 = \frac{b_u \alpha_u L I_u}{N_h}$, $\beta_2 = \frac{b_w \alpha_{wh} L I_w}{N_h}$, $\beta_3 = \frac{b_u \alpha_u I_h}{N_h}$, $\beta_4 = \frac{b_w \alpha_w I_h}{N_h}$, $\alpha_w = \alpha_u$, $I_h = I_{h_I} + I_{h_L}$.

Furthermore, the transmission rate is defined as the multiplication of two parameters (mosquito biting rate × transmission probability). There are four transmission probabilities with respect to dengue infection in equation (6.1). They are (a) transmission probability from dengue-infected humans to dengue-susceptible non-*Wolbachia* mosquitoes; (b) transmission probability from dengue-infected humans to dengue-susceptible *Wolbachia*-infected mosquitoes; (c) transmission probability from dengue-infected non-*Wolbachia* mosquitoes to dengue-susceptible humans; and (d) transmission probability from dengue-infected *Wolbachia*-infected mosquitoes to dengue-susceptible humans. The transmission probabilities (a), (b) and (c) are assumed to be same, however transmission probability (d) is different to others as *Wolbachia* inhibit dengue virus replication in mosquitoes thereby mitigating transmission. We further calibrate the model to achieve the *Wolbachia*-infected mosquito frequency $\geq 80\%$ after *Wolbachia* introduction (see Figure 6.2), and then use the dengue local incidence to calibrate the transmission parameters.

6.3 Results

6.3.1 R_0 computation

Here, we derive the basic reproductive number R_0, which is the number of new dengue cases generated by a typical infected person in a completely susceptible human population. At the dengue infection-free steady state, $E_{h_I} = E_{h_L} = I_{h_I} = I_{h_L} = R_h = 0$, $E_u = I_u = 0$, $E_w = I_w = 0$. Therefore, $N_h = S_h$. To compute the basic reproductive number R_0 with or without *Wolbachia*-infected mosquitoes, we use the next generation matrix method such that we divide the Exposed and Infected local humans and vector compartments into the appearance rate of new dengue infections, f, and progression rates from exposed to infectious compartments and death rates, v.

Let $F_{ij} = \dfrac{\partial f_i}{\partial x_j}$ and $V_{ij} = \dfrac{\partial v_i}{\partial x_j}$, where x_j's are the exposed and infected compartments respectively. Therefore,

$$F = \begin{pmatrix} 0 & 0 & 0 & Lb_u\alpha_u & 0 & Lb_w\alpha_w \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & b_uS_u\alpha_u & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & b_wS_w\alpha_w & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} \psi_h & 0 & 0 & 0 & 0 & 0 \\ -\psi_h & \delta_h & 0 & 0 & 0 & 0 \\ 0 & 0 & \mu_u + \psi_u & 0 & 0 & 0 \\ 0 & 0 & -\psi_u & \mu_u & 0 & 0 \\ 0 & 0 & 0 & 0 & \mu_w + \psi_w & 0 \\ 0 & 0 & 0 & 0 & -\psi_w & \mu_w \end{pmatrix}.$$

Hence, the reproductive number R_0 is given as:

$$R_0 = \rho(FV^{-1}) = \sqrt{R_{0u}^2 + R_{0w}^2},$$

where $R_{0u} = \sqrt{\dfrac{b_u^2\alpha_u^2 L\psi_u S_u}{(\mu_u + \psi_u)\delta_h\mu_u}}$ and $R_{0w} = \sqrt{\dfrac{b_w^2\alpha_{wh}\alpha_u L\psi_w S_w}{(\mu_w + \psi_w)\delta_h\mu_w}}$.

R_{0u} is defined as the instantaneous basic reproductive number which is dependent on changes in the mosquito population in the absence of *Wolbachia*-infected mosquitoes, while R_{0w} is *Wolbachia*-infected mosquito only counterpart. The reproductive number R_0 represents the spectral radius of the matrix FV^{-1} denoted by $\rho(FV^{-1})$. The square roots in the R_{0u} and R_{0w} represent the geometric mean that takes the average number of secondary dengue infections produced by an individual infected with dengue in the absence and presence of *Wolbachia*-infected mosquitoes.

6.3.2 Seasonal forcing

Further, we adjusted the mosquito carrying capacity (equation (6.2)) to account for the seasonal variations in the model as mosquito population fluctuates with climate [298].

The carrying capacity (K) is given as:

$$K = \frac{LN_h}{2}\left[\cos\left(\frac{2\pi(t-t_0)}{365.25}\right)+1\right] \tag{6.2}$$

where L is the ratio of the carrying capacity to the total human population, defined by $L = \frac{K}{N_h}$. The t_0 is the phase shift which is responsible to adjust the model simulation with the study location's seasonal fluctuations. The model is parameterized for Townsville dengue data, however, it can be used for other dengue-endemic regions where local dengue outbreaks had occurred as a result of importation of cases. The parameters ξ and κ, which are defined as

$$\xi(t) = \begin{cases} \dfrac{4.8}{365.25} \text{ per day}, & t < T \\ \dfrac{12}{365.25} \text{ per day}, & t \geq T \end{cases} \text{ and } \kappa(t) = \begin{cases} 0, & t < T \\ 5,000, & t \geq T \end{cases},$$

represent the daily dengue and *Wolbachia* importation rates respectively, where T is the start time for *Wolbachia* rollout program in Townsville i.e., $T = 1^{st}$ October, 2014. Remaining model parameters are described in Table 6.1.

Table 6.1: Model parameter descriptions

Parameters	Description	Values	Dimension	Reference
b_u	Biting rate of non-*Wolbachia* mosquitoes	0.3	day^{-1}	[352]
b_w	Biting rates of *Wolbachia*-infected mosquitoes	0.95 b_u	day^{-1}	[268]
ψ_h	Progression rate from exposed to infectious human	$\frac{1}{5.5}$	day^{-1}	[268]
ψ_u	Progression rate from exposed to infectious non-*Wolbachia* mosquitoes	0.1	day^{-1}	[268, 353]
ψ_w	Progression rate from exposed to infectious *Wolbachia* mosquitoes	0.1	day^{-1}	[268, 353]
μ_{uA}	Death rate of aquatic non-*Wolbachia* mosquitoes	0.02	day^{-1}	[57]
μ_{wA}	Death rate of aquatic *Wolbachia* mosquitoes	0.02	day^{-1}	[57]
μ_u	Death rate of non-*Wolbachia* adult mosquitoes	0.043	day^{-1}	[162, 49]
μ_w	Death rate of *Wolbachia*-carrying adult mosquitoes	0.068	day^{-1}	[162, 49]
N_h	Total human population	180000	humans	[354]
K	Carrying capacity of the aquatic stage mosquitoes	2 N_h	aquatic mosquitoes	
ρ_u	Reproductive rate of non-*Wolbachia* mosquitoes	13	Eggs/day	[49, 197]
ρ_w	Reproductive rate of *Wolbachia*-carrying mosquitoes	10	Eggs/day	[49, 197]
δ_h	Recovery rate	0.2	day^{-1}	[268]
α_u	Transmission probability between humans and non-*Wolbachia* mosquitoes	0.23	-	Estimated
α_w	Transmission probability from humans to *Wolbachia*-carrying mosquitoes	α_u	-	Estimated
α_{wh}	Transmission probability from *Wolbachia*-carrying mosquitoes to humans	0.06	-	Estimated
τ_u	Maturation rate of non-*Wolbachia* mosquitoes	0.11	day^{-1}	[314, 40]
τ_w	Maturation rate of *Wolbachia*-carrying mosquitoes	0.11	day^{-1}	[314, 40]
γ	The proportion of *Wolbachia*-infected eggs resulting from mating between *Wolbachia*-infected moaquitoes	0.95	-	[351]
ϕ	The proportion of *Wolbachia* infected eggs resulting from mating between *Wolbachia*-infected female and non-Wolbachia male mosquitoes	0.95	-	[49, 40]

6.3.3 Data analysis and model simulations

The Townsville *Wolbachia* data which includes the release period, mosquitoes' collection date, number of mosquitoes collected, proportion of *Wolbachia* positive mosquitoes and the rollout location (suburbs) [317] were compiled into monthly data to show the monthly distribution of *Wolbachia*-infected mosquitoes from the total captured mosquitoes (Figure 6.2). It is observed that there was an increasing trend in the *Wolbachia* positive mosquitoes indicating increased establishment of *Wolbachia*-infected mosquitoes, however, there is a sinusoidal behaviour in the *Wolbachia* frequency. This may be due to several factors such as the effect of high temperature, or abundance of wild-type mosquitoes which could hamper dominance of *Wolbachia*-infected mosquitoes due to Allee effect [327].

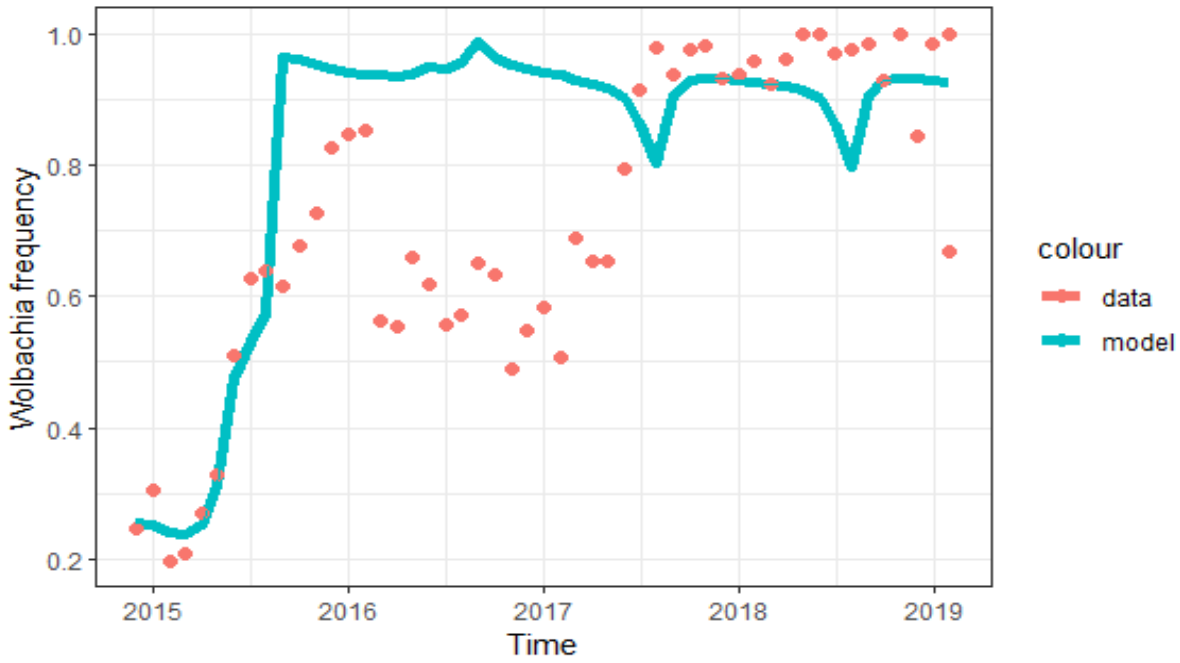

Figure 6.2: Plot of the proportion of monthly *Wolbachia*-positive mosquitoes along the model calibration to achieve the required *Wolbachia* frequency.

The Townsville dengue data from [317] were used to parameterize the model. We used the dengue data to investigate whether there was a trend in the number of imported cases. We found that the number of imported cases increased over the study period, as shown in Figure

6.3 (left panel). The importation rates for the pre- and post-*Wolbachia* were estimated from the observed imported dengue cases using the Poisson distribution rate. As a consequence of this finding, we allowed importations to reflect pre-*Wolbachia* (approx. 4.8 per year) and post-*Wolbachia* (approx. 12 per year) time periods.

The model simulations were carried out in R using the general solver for ordinary differential equations "ode" that comes in the "deSolve" package. The initial total population was given as $N_h = 180,000$ (Townsville population) while other initial populations were $S_h = N_h - (E_{h_I} + E_{h_L} + I_{h_I} + I_{h_L} + R_h)$, $I_{h_I} = I_{h_L} = 1$, and other populations are set to zero ($E_{h_I} = E_{h_L} = R_h = 0$).

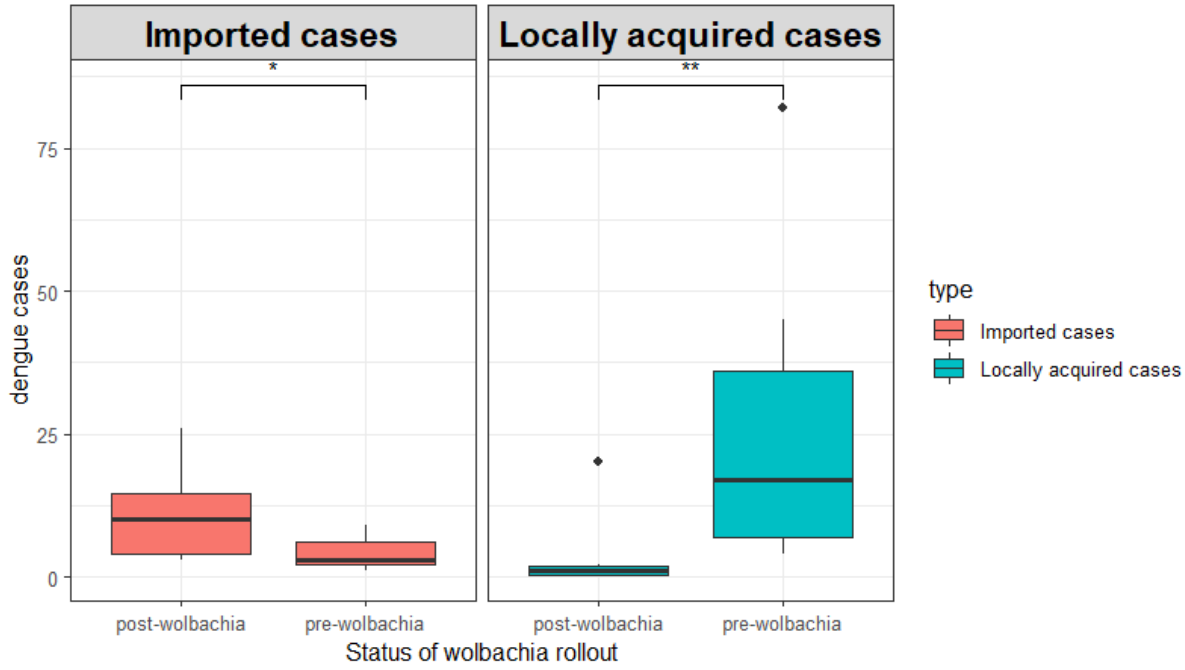

Figure 6.3: Box plot showing the difference between pre-*Wolbachia* and post-*Wolbachia* status for both imported and locally acquired dengue cases.

6.3.4 Parameter estimation

We fit the data using the maximum likelihood method (MLE) for Poisson distribution in R (version 3.6.1) via estimating two free parameters: the transmission probabilities from

dengue-infected *Wolbachia*-uninfected mosquito to susceptible humans (α_u = 0.2727, CI = 0.2707 - 0.2747) and from dengue-infected *Wolbachia*-infected mosquito to susceptible humans (α_{wh}= 0.0756, CI = 0.0179 – 0.3184) (Figure 6.4). This estimate is consistent with the modelling study estimate in [268] carried out in Cairns.

Figure 6.4 showed that dengue infections occur mostly in the summer and usually dies out in the winter following the seasonal forcing of the model, with peak transmission at $t_0 = 15^{th}$ January. Further, there is an increase in local cases with the highest number recorded in early 2009. However, when *Wolbachia* was introduced in the last quarter of 2014, there was a drastic reduction in dengue cases. The corresponding reduction in dengue cases via *Wolbachia* intervention (ψ), which was computed using equation (6.3) is around 89% (CI: 78–91%).

$$\psi = \left[\frac{C_u - C_w}{C_w}\right] \times 100\% \tag{6.3}$$

where C_u and C_w represent the model cumulative dengue incidence in the absence (u) and presence (w) of *Wolbachia* mosquitoes respectively from the time *Wolbachia* was introduced.

Similar to the reduction in the Cairns study [268], which is a tropical region, the transmission probabilities in Townsville, a sub-tropical may have influenced the lower reduction in dengue cases as *Wolbachia* strategy typically works best when the strength of seasonality is weak [298]. The *Wolbachia* efficacy may decline due to an increased likelihood of transmission as this might allow for a potential dengue return.

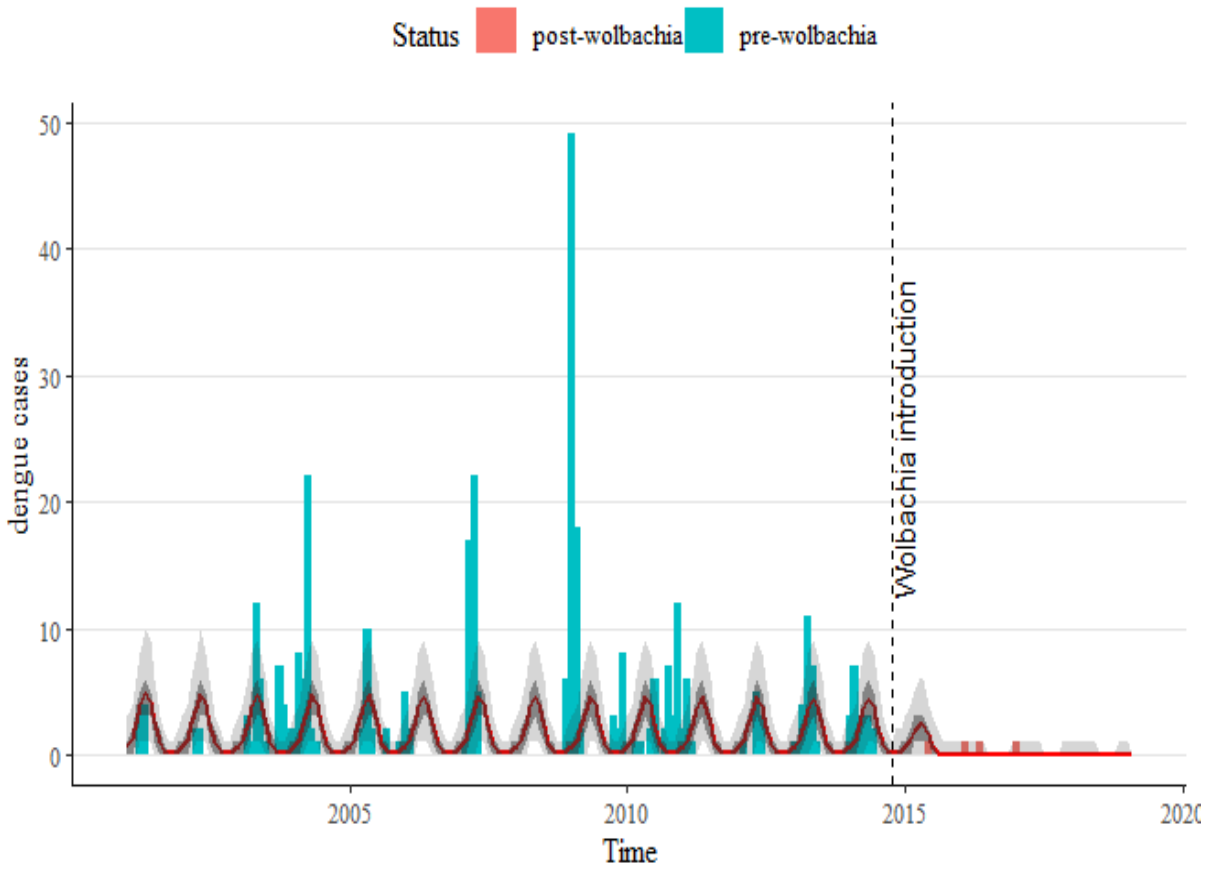

Figure 6.4: Plot of the data fitting of the number of Townsville dengue cases from 2001-2019 using the model (6.1).

To account for the impact of *Wolbachia* introduction on dengue infection, we further computed the reproductive number (R_0) in the presence of *Wolbachia* mosquitoes using the estimated transmission probabilities (Figure 6.5).

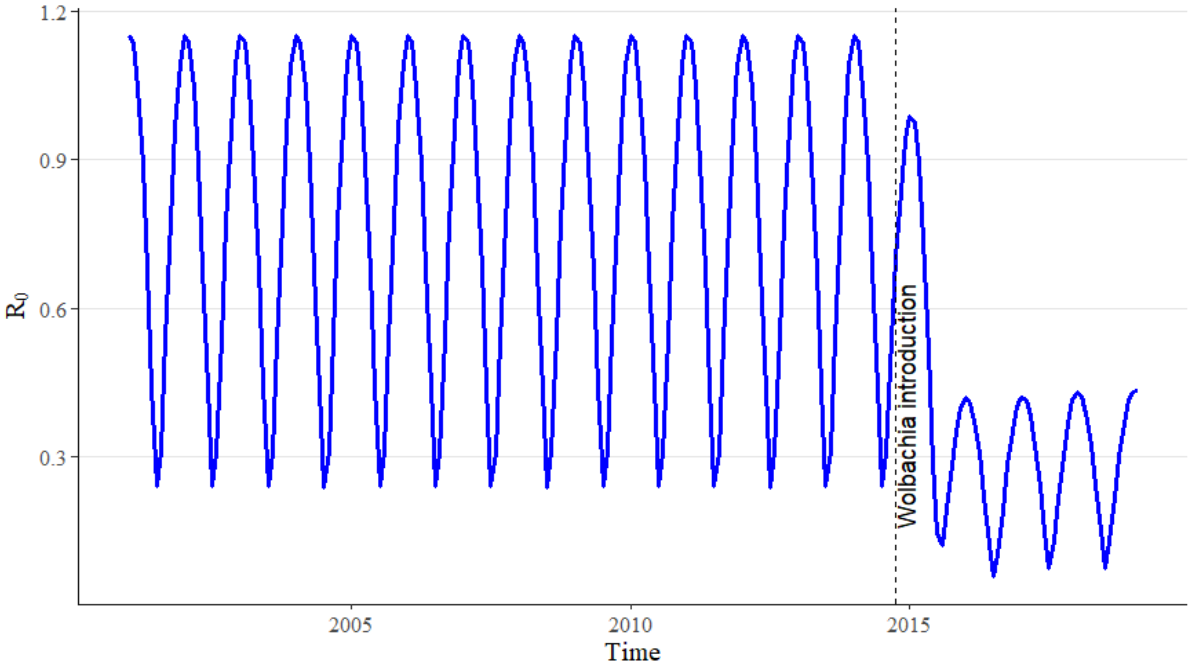

Figure 6.5: Time-varying reproductive number (R_0).

Prior to *Wolbachia* introduction in Figure 6.5, the peak R_0 is approximately 1.15, however, the average R_0 is less than 1. This indicates that although the dengue infection is supposed to die out, dengue through the years still persists as a result of the continual influx of dengue imported cases (so long as $R_0 > 0$). Further, after *Wolbachia* introduction in October 2014, within two years, there was a drastic decrease in the peak R_0, which becomes 0.4. In practice, the dengue infection gradually dies out as shown in Figure 6.4, bringing the number of cases to nearly zero.

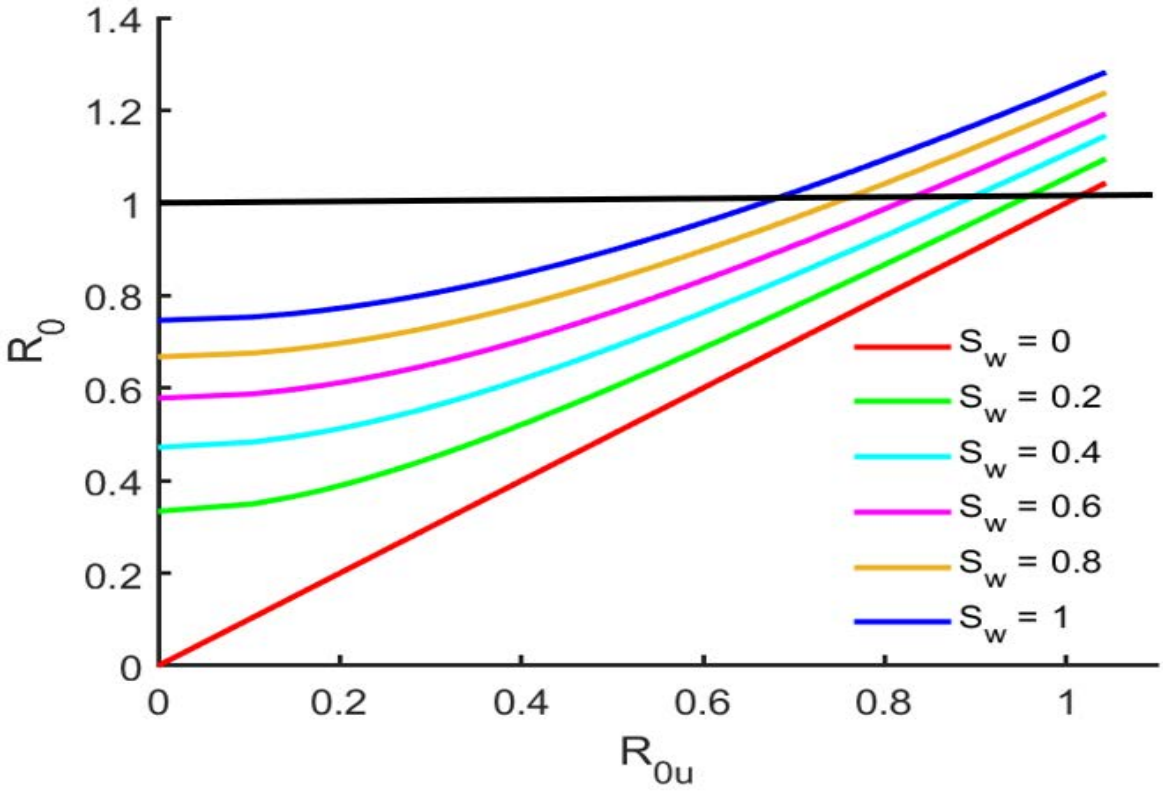

Figure 6.6: Shows the relationship between the reproductive number in the presence and absence of *Wolbachia*-mosquitoes' introduction. The black horizontal line represents $R_0 = 1$.

Figure 6.6 showed the changing R_0 with time based on the proportion of *Wolbachia*-infected mosquitoes introduced. It can be seen that as the proportion of *Wolbachia*-infected mosquitoes (S_w) increase, the peak R_{0u} decreases. However, if R_{0u} is high enough, R_0 at the maximum S_w (that is, $S_w = 1$), can still be above 1 (Figure 6.6). This indicated that *Wolbachia*-infected mosquitoes may fail to dominate the wild-type at $S_w = 1$ for high R_0 as this in turn will not decrease the dengue incidence. In low endemic settings such as Townsville, the average reproductive number in the absence of *Wolbachia* (i.e., R_{0u}) is 0.65 (Figure 6.5). It was observed that, for all values of S_w, and for $R_{0u} = 0.65$, R_0 is less than one. This indicated that the *Wolbachia* rollout reduced dengue incidence. Although, dengue may still persist scantily over the years, this may be due to continual importation of dengue cases provided that $R_0 > 0$. This usually occur in low or moderate dengue endemic settings. In

the case of higher dengue endemicity, i.e., where R_0 is high, introducing *Wolbachia*-infected mosquitoes (that is, for all proportion values of S_w) may still not reduce R_0 below one. This described why *Wolbachia* rollout may not work as expected in some high dengue endemic settings as experimented by [349].

6.4 Discussion

In this study, we developed a mathematical model and investigated the pre- and post-*Wolbachia* effects on the transmission dynamics of dengue together with imported dengue-infected individuals. We observed that for the imported dengue data, dengue cases were significantly lower during the pre-*Wolbachia* times (times prior to *Wolbachia* rollout) than post-*Wolbachia* times. This likely reflects global trends in which there was a resurgence of dengue cases throughout the South-East Asia region – the location of most international importations of dengue into Townsville. Despite higher numbers of dengue introductions, local dengue dropped significantly after *Wolbachia* introduction.

Further, the results of the parameter estimation showed the transmission probability from *Wolbachia* mosquitoes to susceptible humans is a quarter of that from non-*Wolbachia* infected mosquitoes. With the estimated transmission rates, *Wolbachia* was able to reduce dengue burden by approximately 80–90%.

There are some limitations to this study. First, in our model, we did not consider the effect of loss of *Wolbachia* infection due to high temperature having included the seasonality in the mosquito carrying capacity. Second, we have only considered a circulating serotype of dengue in humans and mosquito vectors in the presence of a *Wolbachia* endosymbiont. Further studies may consider factors such as co-circulation of different serotypes of dengue virus in the presence of different *Wolbachia* strains and investigate the impact on the dengue transmission dynamics. Finally, we have made some assumptions based on published research about the parameters employed in this work. This may affect the basic reproductive number.

Additionally, in most climes, if the basic reproductive number is less than one, it means that the infection rate will eventually fall to zero. However, this may not always hold as diseases such as dengue have stochastic transmission dynamics that may be sensitive to random events and as such, the basic reproductive number being less than one does not ensure a complete absence of dengue, as repeated importations may continue to cause stuttering chains of transmission.

The findings from this study have demonstrated consistency with the study in Cairns [268] in terms of the impact of *Wolbachia* introductions in reducing dengue cases. Our results showed that *Wolbachia* intervention may be successful in reducing dengue outbreaks if the dengue transmission probability from *Wolbachia* mosquitoes to susceptible humans is a quarter of that from non-*Wolbachia* mosquitoes. We also showed that *Wolbachia*-mosquito introduction may successfully work or fail to dominate the wild-type mosquitoes depending on the degree of dengue endemicity.

In conclusion, the results of this work showed that *Wolbachia* release can be successful in reducing the incidence of dengue in areas with low or moderate endemicity provided that there is a low chance of transmission (that is, transmission probabilities: $0.0179 — 0.3184$) together with biologically realistic parameters. Our findings suggest that *Wolbachia* introduction in such areas may be successful in reducing dengue outbreaks. This work will contribute to the global effort in drastically mitigating dengue transmission via transmission probabilities.

Acknowledgements

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Chapter 7

Discussion, Future directions and Conclusion

7.1 Discussion of research findings

In this thesis, I have critically reviewed and analysed the mathematical modelling of *Aedes*-borne arboviral transmission dynamics via *Wolbachia* introductions. My work has investigated the changes in *Wolbachia* dominance and persistence that occur based on several of the characteristics which vary by strain, and in doing that I identified the optimal strain/combination of strains for *Wolbachia* persistence. In general, the work presented herein, fills the research gap from previous studies as that was instrumental in developing models that capture the impact of using different *Wolbachia* features and strains.

Aedes-borne aboviral infections continue to pose a public health concern world-wide. In **Chapter 2**, I conducted a narrative study review of arboviral infections, controls and *Wolbachia*-based strategies via an extensive literature search. Here, I discussed some of the most important arboviruses (DENV, ZIKV, CHIKV, and YFV) and how they are transmitted via *Aedes* mosquitoes. Further, I discussed the vector controls as a measure for eliminating or mitigating viral infections. Of the vector controls, I particularly highlighted the *Wolbachia*-

based control as natural and self-sustaining. The *Wolbachia* control method targeted these viral infections by suppressing the vector population or disrupting the viral multiplication in the vector hosts thereby inhibiting feasible transmission. The *Wolbachia* bacterium has been shown to successfully reduce *Aedes*-borne viral infections such as DENV, ZIKV, CHIKV, and YFV in endemic and non-endemic regions. Although promising, the *Wolbachia* control technique is not always guaranteed to succeed as it may encounter the challenge of decreasing potency at unfavourable climatic conditions, lack of cytoplasmic incompatibility (CI), among other limiting factors. Further, the review identified that no modelling work has been done on the introduction of two *Wolbachia* strains with contrasting characteristics to quantify arboviral disease control. This identification clearly revealed the need for insight, understanding and impact of introducing different *Wolbachia* strains into a wild-type mosquito population especially in arboviral endemic areas.

Further, to investigate the mathematical modelling contributions to controlling arboviral infections, in particular, dengue, the most wide-spread and significant arboviral infection, I carried out a systematic review in **Chapter 3**, via an extensive literature search and investigated the role of mathematical models in the transmission of the most transmissible arboviral infection: dengue. In this study, I found that deterministic modelling methods are the main mathematical modelling methods used for analysing dengue vector control. In addition, of the vector control methods, the biological vector controls are the most mathematically modelled, as some of the methods, which include *Wolbachia*-based and sterile insect techniques are self-sustaining and gaining global usage around the world. Further, I observed that all the vector control methods studied are effective, however there are some downsides. For chemical controls, long usage could fuel vector (mosquito) resistance to the chemicides and reduce effectiveness. For biological controls such as *Wolbachia*-based control, high temperature, seasonality and heatwaves tend to diminish their effectiveness. For environmental controls, there are few modelling publications addressing these and, as such, there is a need to further model environmental elements. Environmental management strategies

have a lot of promise but are currently understudied. In order to assess the influence on the eradication or elimination of dengue disease generally, it is imperative to take into account the combination of the three vector control approaches.

In **Chapter 4**, I developed a mathematical model involving the transmission of a novel *Wolbachia* infection (*w*Au) in *Aedes*-mosquitoes. This particular *w*Au-*Wolbachia* strain has a number of advantageous characteristics such as improved viral blocking and maintenance of *Wolbachia* infection at high temperatures but no cytoplasmic incompatibility. This model explains the competitive dynamics between mosquitoes that are infected with *w*Au-*Wolbachia* and those that are not, as well as the significance of poor maternal transmission. Further, I first computed the *Wolbachia*-infection status reproductive numbers for the *w*Au-*Wolbachia* invasive model and used that to define the requirements for the local stability of the equilibrium points. Now, using the *w*Au strain in place of other field-released CI-inducing *Wolbachia* strains such as *w*Mel, one implementation concern is whether or not it is self-sustaining given that it does not induce CI. I found that the *w*Au-*Wolbachia* model's equilibrium points are almost identical to those of the *w*Mel-like *Wolbachia* model, however stricter requirements are needed to satisfy the *w*Au-*Wolbachia* model equilibrium points. The *w*Au strain is a prospective replacement strain since it effectively stops the spread of the arbovirus and does not experience LWI from high temperatures. In addition, I found that sustained maintenance of *Wolbachia* infection in mosquitoes strongly outweighed the lack of CI in the establishment and domination of *w*Au-*Wolbachia* infected mosquitoes. Otherwise, combining the two strains (including *w*Au) might also be an alternative strategy as *w*Au do not induce bidirectional CI.

I next examined the prospect of combining two different strains of *Wolbachia* – each with some favourable and some less favourable features. The prospect of potential stability is improved by the lack of bidirectional CI, which allows the production of offspring, leading to the hypothesis that, when a male and female mosquito with different *Wolbachia* strains (including *w*Au) mate, they generate offspring with the maternal infection status, unlike any

other mosquito pairs with contrasting *Wolbachia* strain, which do not.

In order to investigate the combination of two *Wolbachia* strains as a control strategy, I considered modelling the ecological dynamics of mosquito populations with multiple co-circulating *Wolbachia* strains. Prior to that, some field and simulation-based studies have described the ecological dynamics of multiple *Wolbachia* strains with various characteristics. These studies have shown that unless bidirectional CI (excluding *w*Au strain) occurs in the vectors' zygotes producing unviable offspring, coexistence may be difficult to achieve. Therefore, I assessed the possibility of achieving the coexistence state and investigated its impact in comparison with single-strain *Wolbachia* dynamics. According to recent studies, the *w*Au-*Wolbachia* strain does not exhibit both unidirectional or bidirectional CI. That is, when a *w*Au-infected *Wolbachia* male mosquito is crossed with an uninfected or other *Wolbachia*-infected female, they produce offspring (uninfected or other *Wolbachia*-infected offspring respectively) as opposed to cases of other combined crosses of *Wolbachia* strains. Although CI contributes to the establishment of *Wolbachia*-infected mosquitoes, our simulations in Chapter 4 showed that the *w*Au feature of heat tolerance may outweigh the lack of CI. Additionally, the non-CI features of *w*Au allowed the combination with other strains to produce offspring. Hence, I developed a two-strain general model in the next Chapter (Chapter 5) and tuned the parameters to reflect properties of multiple *Wolbachia* strain combinations.

Chapter 5 described the two-strain general model, which examined the transmission dynamics of uninfected and *Wolbachia* infected mosquitoes with two different strains (Appendices Figure A.1). In the model, I used the information on the ecological dynamics of different *Wolbachia* strains with various traits to explore the co-existence stability and synergistic effects. I derived the general mosquito-free reproduction numbers and further established the *Wolbachia* invasve reproduction numbers singly for the two strains using the *Wolbachia*-infection free equilibrium point. These invasive reproduction numbers were used to establish the local stability conditions of the equilibrium points and were in line with

results from single strain models reported previously in Chapter 4. In Chapter 5, we also investigated whether two *Wolbachia*-infected mosquitoes could coexist with their wild-type counterparts and remain stable especially when the two strains exhibit differing characteristics that could either work synergistically or antagonistically. The model results showed that the three mosquito populations may temporarily co-exist under plausible parameter ranges, but can not attain stability as one *Wolbachia*-infected mosquito population with the fitter *Wolbachia* strain will dominate the other thereby, establishing founder control, which is consistent with the lack of stability for multi-*Wolbachia* strain described in previous studies. That is, when mosquitoes with a particular *Wolbachia* strain is already present, no other (different) *Wolbachia*-infected mosquitoes could invade from low population levels in the population dynamics as one *Wolbachia* strain must always dominate the other. In addition, the temporary co-existence did not increase the *Wolbachia* mosquito prevalence and only delayed *Wolbachia* dominance. Prior to establishing the founder control, the mosquito populations may coexist for some time and as such, provide the need to explore the trade-offs between using one and two *Wolbachia* strains for arboviral infection control.

Considering the competitiveness between the three populations (uninfected and the two different *Wolbachia*-infected mosquitoes) using the two-strain *Wolbachia* model in Chapter 5, I explored the trade-offs between one and two-strain *Wolbachia*-infected mosquitoes. The results of this study showed that despite founder control at later times, introducing two different *Wolbachia* strains simultaneously could neither fast-track the time to *Wolbachia* dominance in the wild-type mosquito population nor increase the *Wolbachia* frequency compared to a fitter single *Wolbachia* strain release. Therefore, one *Wolbachia* strain roll-out may perform better than the combination of two different *Wolbachia* strains if one of the two strains does lose its *Wolbachia* infections at high heat (say, in combination with *w*Mel). Although in an ideal situation where *Wolbachia* infection loss due to high temperature is negligible, given that CI drives *Wolbachia*-infected mosquito establishment, the two different *Wolbachia* strains with both CI features only could be better as the overall CI induction

effect of the combined two *Wolbachia* strains is more than one strain (i.e., CI effect ratio for two *Wolbachia* strains to one is 1.78:1 respectively, as four out of nine mating pairs are affected by CI compared to one in four mating pairs in one *Wolbachia* strain rollout). This is not feasible in field studies as temperature can not be negligible when carrying out such research studies. Overall, this work informs the recommendation of releasing a single-strain of *Wolbachia*-infected mosquitoes with optimal properties such as high maternal transmission, complete cytoplasmic incompatibilities, and high *Wolbachia* infection retention and maintenance), rather than attempting multi-strain roll-outs.

In **Chapter 6**, I examined the *Wolbachia* introduction in Townsville, North Queensland; a region where dengue outbreaks occurred yearly due to importation or frequent immigration of people infected with dengue virus, and investigated the influence on the dengue transmission dynamics. I observed that the transmission probability from *Wolbachia* mosquitoes to susceptible humans is a quarter of that from non-*Wolbachia* infected mosquitoes. With the estimated transmission rates, *Wolbachia* was able to reduce dengue burden by 80–90%. This is consistent with the Cairns study in [268].

7.2 Limitations of the studies

The work presented in this thesis has some features that could affect or impact the understanding of the interpretation of results and conclusions. In the narrative and systematic literature review chapters (Chapter 2 and Chapter 3 respectively), the results relied on the experimental and modelling results of articles taken from the extensive database search describing the vector controls of arboviruses and arboviral transmission models. These articles demonstrated several preventive measures for reducing the spread of arboviruses. However, in Chapter 3, the selected articles for the systematic review were not evenly distributed with (yearly) time as over fifty percent of the studies carried out were from 2017. The major dengue outbreaks that occurred between 2018 and 2019 in the Americas and some parts of South

East Asia may have had an impact on the distribution. As a result, interests in vector control modelling studies were aroused. Additionally, in order to prevent oversight, only English-language journal articles that had already been published were taken into account. Other referencing formats such as, book sections, conference proceedings and serials were excluded because they lacked adequate information to evaluate the studies. After deleting duplicates, the other referring formats make up about 3% of the articles that were searched, thus excluding them would have an insignificant effect. In essence, the Assessment for Modelling Studies (AMS) tool relies on the authors' expertise in evaluating the included publications, which could give rise to potential bias. As a result of some publications not being included in the databases used for this research study, there is a potential of information bias.

Every mathematical modelling project has constraints, and this study is not an exception. In the modelling studies in Chapter 4 and 5, I considered the single and multi-strain *Wolbachia* transmission dynamics in *Aedes* mosquitoes respectively and investigated the trade-off between CI and LWI and between strains. While formulating the general *Wolbachia* transmission model, initially, I made the assumption that the mosquito gender ratio would remain the same over time. In a laboratory setting, this assumption might be accurate, but not always in a natural mosquito habitat. However, given that the *Wolbachia* model reduction faithfully reproduces the dynamics of the complete system, comparable outcomes are anticipated. A further assumption I made in Chapter 4 was that the complete absence of unidirectional CI implied that cross-mating produced offspring that were free of the *Wolbachia* infection. This may not always be the case in the natural habitat since a small proportion of the progeny might carry the *Wolbachia* bacteria. However, if that is true, it suggests that using the *w*Au strain as a *Wolbachia*-based control strategy would require less resources. In Chapter 5, I assumed that absence of bidirectional CI suggested that cross-mating would generate offspring with the maternal *Wolbachia* infection status. Finally, I made the assumption that seasonality has an impact on the associated parameters for the *w*Mel dynamics in Chapter 4 and 5. However, for the *w*Au and *w*AlbB strains, they are not affected by seasonal fluctuations

as they both maintain *Wolbachia* infections at high temperature.

7.3 Future directions

To advance the understanding of *Wolbachia*-based control effectiveness in reducing arboviral incidence, a number of potential research directions could be opened. These research directions, which could make use of our work as baseline or guideline include:

- In this thesis, I have assumed the presence or absence of CI to be complete. Future studies could combine modelling the effect of partial CI with experimental data to explore and identify the impact on *Wolbachia* transmission dynamics [49, 351].

- As described in this thesis, I have assumed the sex ratio of adult male to female mosquitoes to be 1:1. This is based on laboratory studies. However, this may not be the case in the field. More experimental field studies need to be conducted to account for a more precise adult mosquito sex ratio [339, 340]. This will not only further the understanding on the precise number of male and female mosquitoes, but also reveal the proportion of eggs that would mature to become either male or female mosquitoes especially for *Wolbachia*-infected mosquitoes in the field.

- In this thesis, I have investigated the *Wolbachia* inter-strain competition (i.e. competition between two vectors carrying different *Wolbachia* strains) and described its trade-offs. It may be of interest for future studies to possibly explore the *Wolbachia* intra-strain competition in a vector (i.e. competition of two different strains in a mosquito) and investigate its impact on the *Wolbachia* transmission dynamics [327, 351].

- While it has been shown that the three mosquito population, which includes the uninfected and two different *Wolbachia*-infected mosquitoes can not attain stability, future studies could explore various modelling approaches such as spatial models to investigate the feasibility of stability of these three mosquito population. Such models could

inform further understanding on the impact of prolonged stability [327].

- One of the crucial factors governing the dynamics of dengue transmission is the biting rate of mosquitoes. In this thesis, I assume a constant mosquito biting rate. It will be interesting to investigate changes in the biting rates of *Wolbachia*-infected and uninfected mosquitoes as mosquitoes tend to feed less when infected with *Wolbachia*, causing weakened proboscis. This will improve the understanding on how the rates of mosquito bites affects arboviral transmission dynamics, in particular, DENV [268, 49].

- The work in this thesis can serve as a guide to field work, particularly in choice of *Wolbachia* strain, and optimal strain characteristics for reducing dengue burden, and sustained prevalence. It also suggests that attempts at strain coexistence are likely to be futile and counter-productive under the circumstances explored in this thesis. Furthermore, this thesis provides a framework for future testing using simulation prior to undertaking expensive and resource intensive field studies [39].

7.4 Concluding remarks

This thesis informs the development of modelling strategies and contributions to the gradually dominating vector control – *Wolbachia*-based strategies. In addition, this thesis provides insights on *Wolbachia*-based modelling approaches and furthered our understanding by describing the trade-offs between cytoplasmic incompatibility and loss of *Wolbachia* infection. Further, the work presented herein, investigates the different *Wolbachia* strains for simulating *Wolbachia* release strategies and explores the synergistic and discordant effects amongst *Wolbachia* strains to control arboviral infections. This thesis also demonstrates new understanding via the combination of mathematical and statistical models to complement experimental data with host-vector mechanism of arboviral (dengue) infection. The findings of this work will boost ongoing and future arboviral control programmes that depend on the introduction of new *Wolbachia* strains.

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Appendix A

A.1 Basic Properties of the model

A.1.1 Positivity

Theorem A.1.2. *For any given non-negative initial conditions, the solution of the wAu-Wolbachia invasive model with $\nu = 1$ are non-negative for all $t \geq 0$ and bounded.*

Proof. Proving by contradiction, such that when a solution converges to a feasible region $\mathbb{R}^4_+$, it stays there forever. Now, considering the four cases below:

(a) There exists a time $t_1 > 0$ such that whenever $A_u(t_1) = 0$, $\frac{dA_u(t_1)}{dt} < 0$, $A_w, F_u, F_w \geq 0$ for $0 \leq t \leq t_1$.

(b) There exists a time $t_2 > 0$ such that whenever $F_u(t_2) = 0$, $\frac{dF_u(t_2)}{dt} < 0$, $A_u, A_w, F_w \geq 0$ for $0 \leq t \leq t_2$.

(c) There exists a time $t_3 > 0$ such that whenever $A_w(t_3) = 0$, $\frac{dA_w(t_3)}{dt} < 0$, $A_u, F_u, F_w \geq 0$ for $0 \leq t \leq t_3$.

(d) There exists a time $t_4 > 0$ such that whenever $F_w(t_4) = 0$, $\frac{dF_w(t_4)}{dt} < 0$, $A_u, A_w, F_u \geq 0$ for $0 \leq t \leq t_4$.

It can be shown that $A(t) \leq K$ provided that $A(0) < K$. For case (a), we have;

$$\frac{dA_u(t_1)}{dt} = \left[\frac{\rho_{uu}(F_u^2(t_1) + F_u(t_1)F_w(t_1)) + \rho_{ww}(1-\delta)F_w(t_1)F_u(t_1)}{F(t_1)}\right]\left(1 - \frac{A_w(t_1)}{K}\right) \geq 0 \quad \text{(A.1)}$$

This equation (A.1) clearly contradicts case (a): $\frac{dA_u(t_1)}{dt} < 0$. For the remaining cases (b), (c) and (d), we have the following;

$$\begin{aligned}
\frac{dF_u(t_2)}{dt} &= \frac{\tau_u}{2}A_u(t_2) \geq 0 \\
\frac{dA_w(t_3)}{dt} &= \left[\frac{\rho_{ww}(F_w^2(t_3) + \delta F_w(t_3)F_u(t_3))}{F(t_3)}\right]\left(1 - \frac{A_u(t_3)}{K}\right) \geq 0 \\
\frac{dF_w(t_4)}{dt} &= \frac{\tau_w}{2}A_w(t_4) \geq 0
\end{aligned}$$

Therefore, the solutions are positive for all the future times provided that the initial conditions are non-negative. □

A.1.3 Boundedness of solution

Corollary 1.1: *Let* $P(t) = A_u(t) + F_u(t) + A_w(t) + F_w(t)$*, there exists a constant* $\tau > 0$ *such that* $\limsup_{t\longrightarrow\infty} P(t) \leq \Upsilon$.

Proof. By adding equations (4.12)-(4.14), we obtain

$$\begin{aligned}
\frac{dP(t)}{dt} &= \left[\frac{\rho_{uu}(F_u^2 + F_uF_w) + \rho_{ww}(F_w^2 + F_wF_u)}{F}\right]\left(1 - \frac{A}{K}\right) - \mu_uF_u - \mu_wF_w \\
&- \frac{1}{2}(A_u\tau_u + A_w\tau_w) - (A_u\mu_{Au} + A_w\mu_{Aw}) \qquad \text{(A.2)}
\end{aligned}$$

Having shown that $A_u < K$ and $A_w < K$, it follows that $F_u \leq \frac{\tau_u K}{2\mu_u}$ and $F_w \leq \frac{\tau_w K}{2\mu_w}$. Let $\mu = min(\mu_u, \mu_w, \mu_{Au}, \mu_{Aw})$ and $\tau = min(\tau_u, \tau_w)$, therefore, equation (A.2) becomes

$$\frac{dP}{dt} \leq \frac{K\tau(\rho_{uu} + \rho_{ww})}{2\mu} - P\mu \qquad \text{(A.3)}$$

From the above inequality, it follows that there exists a constant Υ such that

$$\limsup_{t\longrightarrow\infty} P(t) \leq \Upsilon \qquad \text{(A.4)}$$

□

A.1.4 Reproductive numbers

Here, we derive the reproductive numbers for the scaled model (4.11) - (4.14) as follows:

$$\begin{aligned}
\frac{dA_u}{dt} &= \left[\frac{\rho_{uu}(F_u^2+(1-\phi)F_uF_w)+\rho_{ww}(1-\delta)F_wF_u}{F}\right](1-\alpha A)-(\tau_u+\mu_{Au})A_u,\\
\frac{dF_u}{dt} &= \frac{\tau_u}{2}A_u+\sigma F_w-\mu_uF_u,\\
\frac{dA_w}{dt} &= \left[\frac{\rho_{ww}(F_w^2+\delta F_wF_u)}{F}\right](1-\alpha A)-(\tau_w+\mu_{Aw})A_w,\\
\frac{dF_w}{dt} &= \frac{\tau_w}{2}A_w-\sigma F_w-\mu_wF_w.
\end{aligned}$$

Theorem A.1.5. *The zero equillibrium for mosquito population dynamics is locally and asymptotically stable (LAS) when* $R_{0u}<1$, *where* $R_{0u}=\frac{\rho_{uu}\tau_{A_u}}{2\mu_u(\mu_{A_u}+\tau_{A_u})}$

Proof. Considering the differential system for the uninfected mosquito population, we compute the Jacobian (J_{e_1}) as

$$J_{e_1}=\begin{pmatrix}-\mu_{A_u}-\alpha F_u\rho_{uu}-\tau_{A_u} & (1-\alpha A_u)\rho_{uu}\\ \frac{\tau_u}{2} & -\mu_u\end{pmatrix}.$$

We then evaluate (J_{e_1}) at no mosquito equilibrium. This yields

$$J_{e_1}(0)=\begin{bmatrix}-\mu_{A_u}-\tau_{A_u} & \rho_{uu}\\ \frac{\tau_{A_u}}{2} & -\mu_u\end{bmatrix}.$$

To obtain the characteristic equation of J_{e_1}, we have

$$|J_{e_1}-\lambda I| = 0,$$

which becomes

$$\begin{aligned}(\lambda+\mu_u)(\lambda+\mu_{A_u}+\tau_{A_u})-\frac{\rho_{uu}\tau_{A_u}}{2} &= 0,\\ \lambda^2+\lambda(\mu_u+\mu_{A_u}+\tau_{A_u})+\mu_u(\mu_{A_u}+\tau_{A_u})(1-R_{0u}) &= 0\end{aligned}$$

Therefore, if $R_{0u}<1$, then all the eigenvalues are negative and therefore the no-mosquito equilibrium (e_1) is locally and asymptotically stable. This also applies to the *Wolbachia*-infected mosquito compartments such that if $R_{0w}<1$, then e_1 is locally and asymptotically stable. □

A.2 Two-strain *Wolbachia* schematics

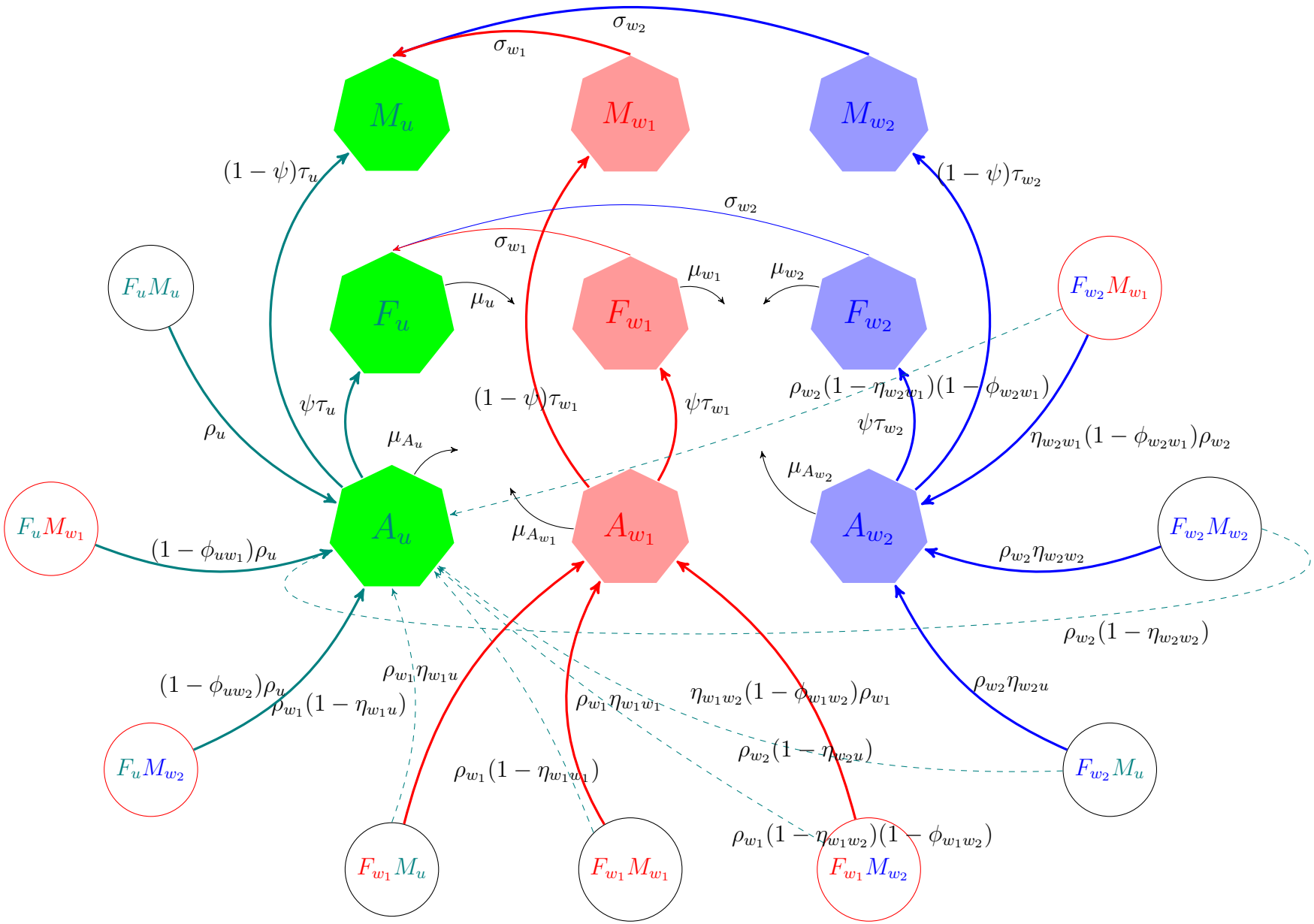

Figure A.1: General model formation schematic of Mosquito-*Wolbachia* dynamics between uninfected mosquitoes and *Wolbachia*-infected mosquitoes with strains w_1 and w_2. The green red and blue represent the uninfected, w1-*Wolbachia*-infected and w2-*Wolbachia* infected mosquito populations respectively. The solid lines describe how the populations progressed and the dashed lines represent the imperfect maternal transmission (IMT). The $\phi_{i,j}, (i = u, w_1, w_2, j = w_1, w_2)$, represent the induction of cytoplasmic incompatibility (CI), inhibiting the production of offspring. See Table 5.1 for the symbols' descriptions

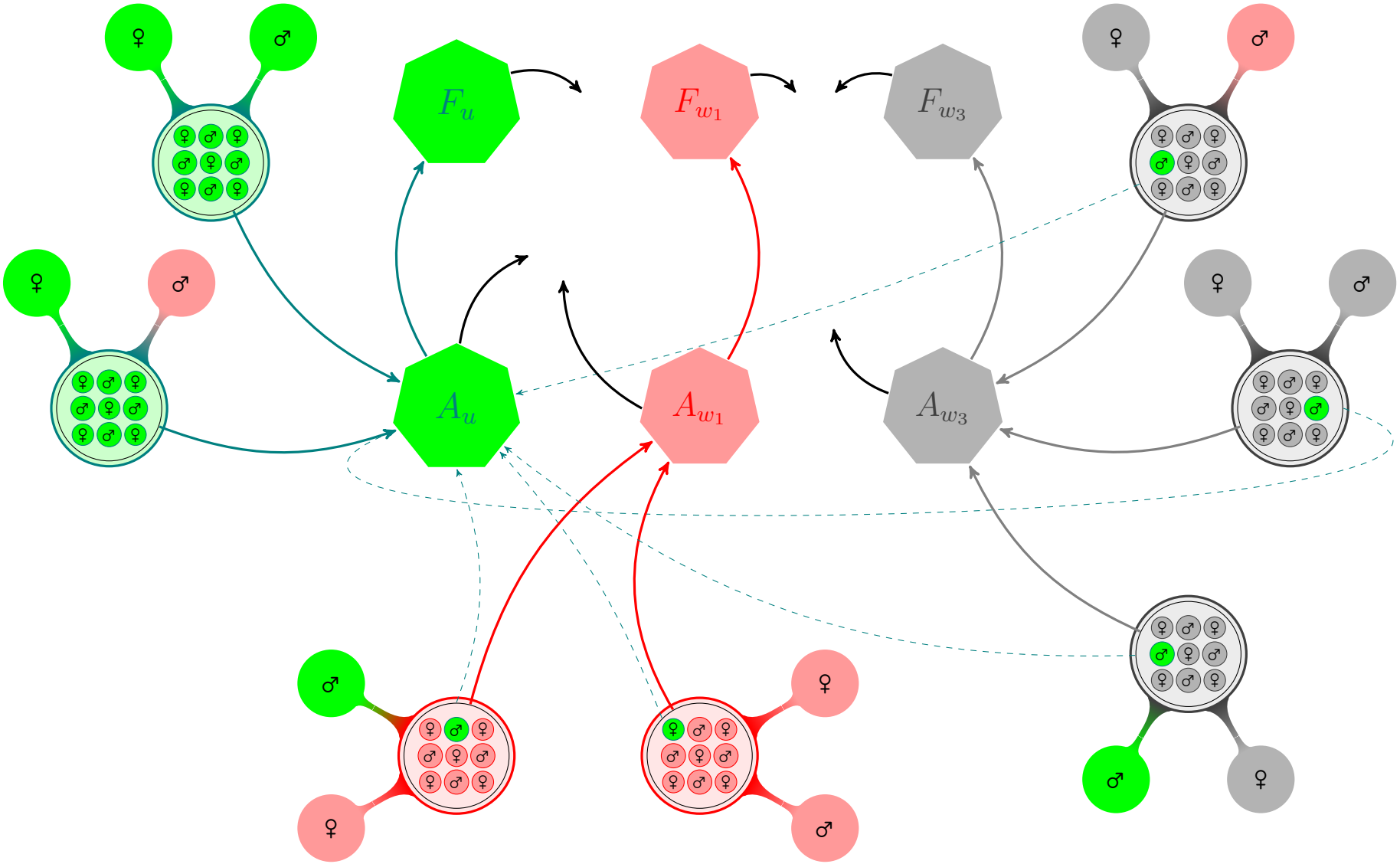

Figure A.2: Reduced ($M = F$) and adjusted model formation schematic of Mosquito-*Wolbachia* dynamics between uninfected mosquitoes and *Wolbachia*-infected mosquitoes with strains w_1 (wAu-like) and w_3 (wAlbB-like). The green, red, and grey represent the uninfected, wAu-*Wolbachia*-infected and wAlbB-*Wolbachia* infected mosquito populations respectively. The solid lines represent the population progression and the dashed lines indicate the imperfect maternal transmission (IMT). The black colour represents deaths. The cytoplasmic incompatibility (CI) induction which inhibits the production of offspring has been adjusted where required.

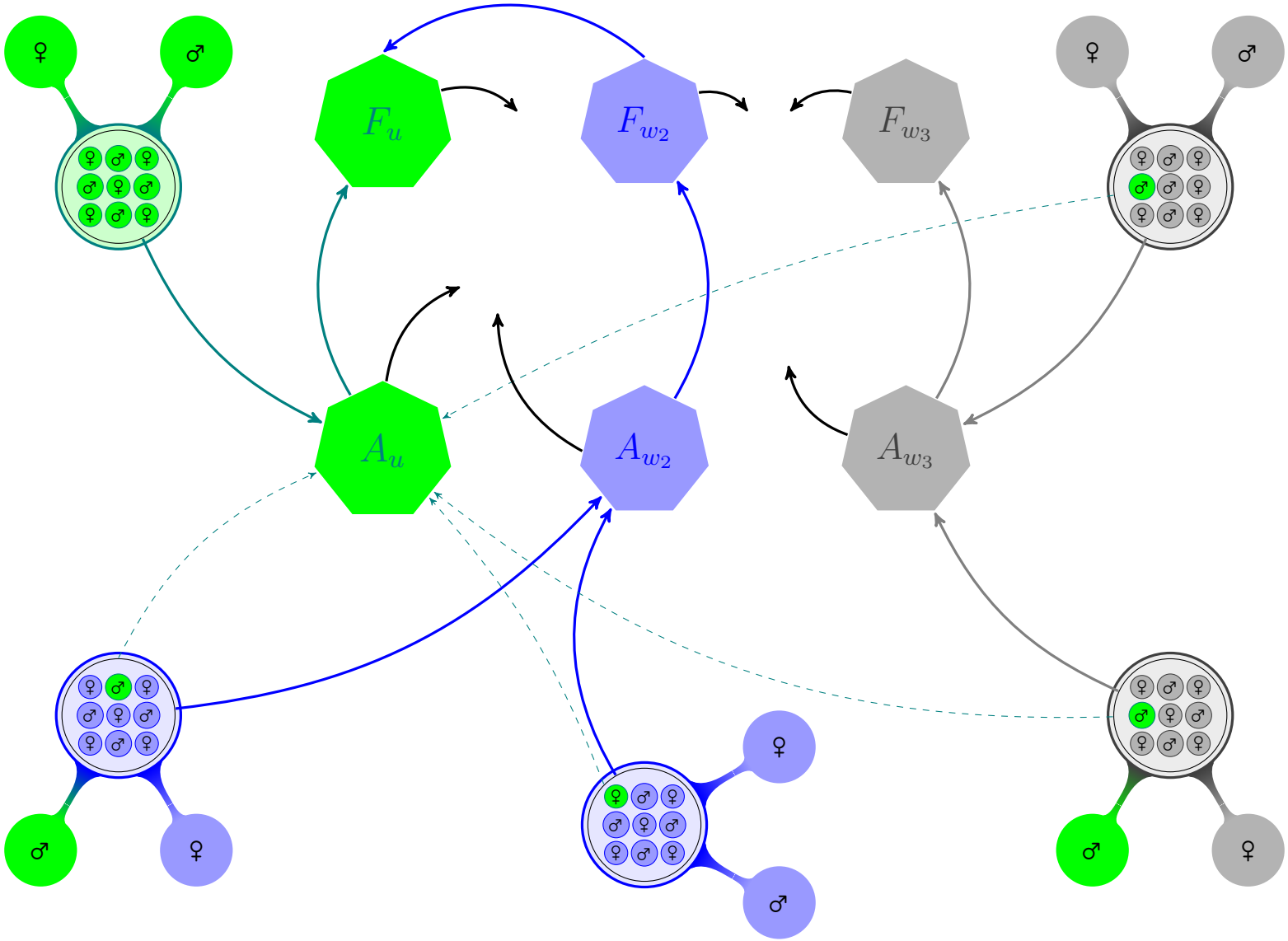

Figure A.3: Reduced ($M = F$) and adjusted model formation schematic of Mosquito-*Wolbachia* dynamics between uninfected mosquitoes and *Wolbachia*-infected mosquitoes with strains w_2 (wMel-like) and w_3 (wAlbB-like). The green, blue, and gray represent the uninfected, wMel-*Wolbachia*-infected and wAlbB-*Wolbachia* infected mosquito populations respectively. The solid lines represent the population progression and the dashed lines indicate the imperfect maternal transmission (IMT). The black colour represents deaths. The cytoplasmic incompatibility (CI) induction which inhibits the production of offspring has been adjusted where required.