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Modelling the transmission dynamics of dengue in the presence of *Wolbachia*

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ABSTRACT

Use of the bacterium *Wolbachia* is an innovative new strategy designed to break the cycle of dengue transmission. There are two main mechanisms by which *Wolbachia* could achieve this: by reducing the level of dengue virus in the mosquito and/or by shortening the host mosquito's lifespan. However, although *Wolbachia* shortens the lifespan, it also gives a breeding advantage which results in complex population dynamics. This study focuses on the development of a mathematical model to quantify the effect on human dengue cases of introducing *Wolbachia* into the mosquito population. The model consists of a compartment-based system of first-order differential equations; seasonal forcing in the mosquito population is introduced through the adult mosquito death rate. The analysis focuses on a single dengue outbreak typical of a region with a strong seasonally-varying mosquito population. We found that a significant reduction in human dengue cases can be obtained provided that *Wolbachia*-carrying mosquitoes persist when competing with mosquitoes without *Wolbachia*. Furthermore, using the *Wolbachia* strain *WMel* reduces the mosquito lifespan by at most 10% and allows them to persist in competition with non-*Wolbachia*-carrying mosquitoes. Mosquitoes carrying the *WMelPop* strain, however, are not likely to persist as it reduces the mosquito lifespan by up to 50%. When all other effects of Wolbachia on the mosquito physiology are ignored, cytoplasmic incompatibility alone results in a reduction in the number of human dengue cases. A sensitivity analysis of the parameters in the model shows that the transmission probability, the biting rate and the average adult mosquito death rate are the most important parameters for the outcome of the cumulative proportion of human individuals infected with dengue.

1. Introduction

Dengue is a viral vector-borne disease which is a major public health concern in many tropical and subtropical regions worldwide. It is estimated that around two-thirds of the world's population lives in dengue-endemic regions, and approximately 50–100 million cases occur each year [1]. Due to a high rate of asymptomatic cases, this is an underestimate of the actual number of cases, with a recent estimate being approximately three times this number [2]. Individuals with non-haemorrhagic dengue show symptoms such as high fever, severe headache and vomiting, which last for 2–7 days [1]. If they have the more severe form, dengue haemorrhagic fever (DHF), those symptoms above are followed, after 3–7 days by rapid breathing, bleeding gums and fatigue [1].

Historically, four serotypes of virus that cause dengue have been identified, namely DEN1, DEN2, DEN3, DEN4, although recently potential fifth strain has been discovered [3]. An infected individual gains lifelong immunity to the serotype they are exposed to, but only temporary immunity to the other strains. If they are reinfected with a different serotype, they then have a higher chance of developing the more severe forms of dengue, dengue haemorrhagic fever or dengue shock syndrome. This effect is related to the "antibody dependent enhancement" [4]. This makes the development of vaccines against dengue very challenging as they must protect against all five strains simultaneously, however some progress is being made [5,6].

Dengue is transmitted to humans via the bite of an infectious mosquito. When dengue infects a mosquito, it requires a period of time to replicate and disseminate throughout the insect before it can be transmitted to susceptible humans: this period is called the extrinsic incubation period (EIP), and ranges between 5 and 15 days

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[7]. The closer the mosquito lifespan is to the EIP, the smaller the chance that dengue will be transmitted. There are two mosquito species responsible for the transmission of dengue, *Aedes aegypti* and *Aedes albopictus*. Of these, *Aedes aegypti* is the most competent vector. It is highly anthropophilic, preferring to obtain its blood meals from humans, and prefers artificial water containers such as pots, rain-water containers and discarded tyres for breeding sites, which are most available in areas where humans live. The lifespan of *Aedes aegypti* varies depending on environmental factors such as temperature, humidity and rainfall [8], which leads to fluctuations of the mosquito population in regions where these factors are seasonal.

In the past, a number of strategies for controlling dengue by reducing the mosquito population have been implemented, but they are largely unsustainable [9–12]. For example, the use of insecticides becomes ineffective as mosquitoes develop resistance to particular insecticides [9,10]. The removal of mosquito breeding sites has also been carried out but is often unsustainable since it has to be repeated often, as has been found in Cairns and Singapore [11,12]. These problems highlight a critical need for a novel and sustainable strategy to break the cycle of dengue transmission.

An innovative approach for controlling dengue is introducing the *Wolbachia* bacterium into *Aedes aegypti* mosquitoes [13–17]. *Wolbachia* naturally infects an estimated 66% of insects [18], including *Aedes albopictus*, but is not endemic in *Aedes aegypti*. There are two strains of *Wolbachia* that can be introduced into *Aedes aegypti*, *WMel* and *WMelPop* [15,16], with different effects that are further discussed in Section 2.2.2. *Wolbachia* can reduce dengue transmission via two mechanisms. First, *Wolbachia* inhibits viral replication and dissemination in the dengue vector [13], and, consequently, the ability of *Wolbachia*-carrying mosquitoes to transmit dengue viruses is reduced. Secondly, *Wolbachia* reduces the lifespan of the mosquitoes [14,15] and as a result this may be close to, or less than, the EIP, and so there is less time for the mosquito to transmit dengue to susceptible humans.

This strategy will only be effective against dengue if the *Wolbachia*-carrying mosquitoes can compete successfully with *Wolbachia*-free ones and therefore persist in the wild. Cytoplasmic incompatibility (CI) is a feature of *Wolbachia* infection that is important for population invasion and persistence, since it gives *Wolbachia*-carrying females a reproductive advantage [19,20]. CI results in *Wolbachia*-carrying females being able to reproduce successfully when mating with either *Wolbachia*-free or *Wolbachia*-carrying males, whereas non-*Wolbachia*-carrying females can only reproduce successfully when mating with non-*Wolbachia*-carrying males. Moreover, non-*Wolbachia*-carrying females produce an embryo upon mating with *Wolbachia*-carrying males, but the embryo is not viable and dies, thereby effectively blocking reproduction. CI therefore leads to complex dynamics for the mosquito population in the presence of *Wolbachia*, and so also affects the dynamics of dengue transmission.

To study the population dynamics of *Wolbachia*-carrying mosquitoes, several mathematical models have been developed [21–24]. Hancock et al. [21] developed a mathematical model to explore the host population dynamics and *Wolbachia* infection frequency with both single and multiple introductions ("seeding") of *Wolbachia*-carrying mosquitoes. The same authors also developed a metapopulation model to explore the spatial dynamics and found that spatial variation in the density-dependent competition has an effect on the spread of *Wolbachia* infection [22]. Chan and Kim [23] developed a mathematical model incorporating both slow and fast dispersal situations. They found that temperature affects the speed of *Wolbachia* invasion and that the death rate of *Wolbachia*-carrying mosquitoes influences their persistence. Ndii et al. [24] developed a mathematical model of mosquito population dynamics by including the effect of CI in the mating function and competition for resources in the aquatic stage. They found parameter ranges where *Wolbachia*-carrying mosquitoes persist, and showed that the steady state where *Wolbachia*-carrying mosquitoes alone persist only exists when maternal transmission is perfect. They showed that there is a stable steady state where *Wolbachia*-free and *Wolbachia*-carrying mosquito populations can coexist, and this was also found by Chan and Kim [23]. Therefore, throughout the paper we refer to 'absence' and 'presence' of *Wolbachia*, wherein non-*Wolbachia*-carrying mosquitoes persist in both cases. The body of research above suggests that it is possible for *Wolbachia*-carrying mosquitoes to persist in competition with non-*Wolbachia*-carrying mosquitoes, and hence to reduce the transmission of dengue to humans. The question that then arises is to what extent *Wolbachia* infection can reduce human dengue cases. In this paper, a mathematical model for dengue transmission between mosquitoes and humans with underlying *Wolbachia* mosquito population dynamics is developed to quantify the effect of *Wolbachia* on dengue transmission in a human population. We determine the possible effectiveness of using *Wolbachia* as a dengue intervention, but not its relative worth compared to other control measures.

A number of mathematical models have been developed to understand the transmission dynamics of dengue (for example, see [25–33]) and a review of different dengue models was conducted by Andraud et al. [34]. However, only a few mathematical models for dengue transmission with an underlying *Wolbachia*-carrying mosquito population exist [32,33]. Hughes and Britton [32] analysed dengue reduction for situations when only non-*Wolbachia*-carrying mosquitoes persist and when only *Wolbachia*-carrying mosquitoes persist, and did not present the situations when both populations persist. Hancock et al. [33] developed a model for vector-borne pathogen dynamics in the presence of *Wolbachia*-carrying mosquitoes. However, this model was not specifically developed for dengue transmission dynamics and its aim was to investigate the effect of releasing more *Wolbachia*-carrying male mosquitoes. In this paper, we develop a mathematical model for dengue with underlying seasonal mosquito population dynamics in the presence of *Wolbachia*-carrying mosquitoes. Unlike the model of Hughes and Britton [32] and Hancock et al. [33], here we consider seasonality using a sinusoidal forcing function and we also include competition for resources in the aquatic stage. Seasonal effects are included because they are appropriate for regions with a strong seasonal climate, such as Far North Queensland in Australia, which has distinct wet and dry periods: this is where the *Wolbachia* field trials are being conducted [16]. We study a single dengue outbreak over the course of 31 weeks, using data from 2008 [35]. This allows us to make a number of simplifying assumptions, including having only a single strain of dengue and ignoring human migration and demographics. An exploration of key parameter ranges is conducted to quantify the level of dengue reduction obtained from a *Wolbachia* intervention and to study the persistence of *Wolbachia*-carrying mosquitoes over possible parameter ranges.

The remainder of this paper is organised as follows. In Section 2 we describe the model in the absence of *Wolbachia*, the model in the presence of *Wolbachia* and the sensitivity analysis methodology. The results are presented in Section 3. Finally, discussion and conclusions are given in Section 4.

2. Methods

In this section methods are presented that are later used to investigate the *Wolbachia* intervention. Firstly, a model of dengue transmission with humans and a seasonal mosquito population is constructed. Secondly, the model is adapted to include a *Wolbachia*-carrying mosquito population complete with the impact of cytoplasmic incompatibility on the population dynamics. Thirdly, the methodology for the parameter sensitivity analysis is presented, which is used to determine which parameters most influence the cumulative number of human infections.

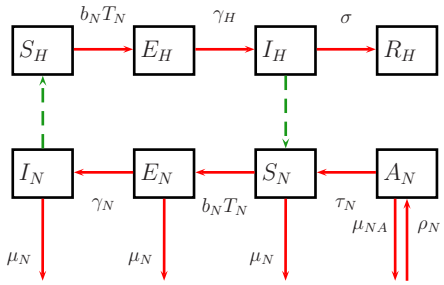

Fig. 1. Schematic of the model in the absence of *Wolbachia*-carrying mosquitoes, Eqs. (1)–(8). Solid lines are population progression lines and dashed lines are disease transmission lines. The subscript H is for the human population and N is for the non-*Wolbachia* mosquito population. The compartments are 'S' for susceptible, 'E' for exposed to dengue but not yet infectious, 'I' for infectious, 'R' for recovered, and 'A' for the aquatic phase of the mosquito life cycle. The transition rates between compartments are shown next to the progression lines and are described in the text.

2.1. Model in the absence of Wolbachia

2.1.1. Model formulation

A mathematical model for the transmission dynamics of dengue between humans and mosquitoes in the absence of *Wolbachia* is developed. This model assumes homogeneous and well-mixed populations and is for one dengue strain only. The model comprises human and vector (mosquito) populations, with births and seasonally-forced deaths for the mosquito population. Since we are considering only a single outbreak with a duration of less than 1 year, human migration and demographics are not influential and hence omitted. As the ratio between male and female mosquitoes is approximately 1.02:1 [36], the number of male and female mosquitoes are taken to be the same. This model only explicitly considers female mosquitoes as they are responsible for dengue transmission, since only the female mosquito takes a blood meal from humans as part of their reproductive cycle. Male mosquitoes are implicitly included, since only half of the aquatic mosquitoes mature to be adult female susceptible mosquitoes. A schematic representation of the model is given in Fig. 1, with the subscript H for the human population and N for the non-*Wolbachia*-carrying mosquito population.

The human population is divided into four subpopulations, namely Susceptible ($\hat{S}_H$), Exposed ($\hat{E}_H$), Infectious ($\hat{I}_H$) and Recovered ($\hat{R}_H$), where the hat is used to denote fully dimensional state variables. Furthermore, since we only consider a single outbreak with a time span on the order of a year, a constant human population size is assumed $N_H = \hat{S}_H + \hat{E}_H + \hat{I}_H + \hat{R}_H$, with no demography. The mosquito population is divided into subpopulations of Aquatic ($\hat{A}_N$, combining the egg, larval and pupal stages), Susceptible ($\hat{S}_N$), Exposed ($\hat{E}_N$) and Infectious ($\hat{I}_N$). The total adult female mosquito population is $\hat{F}_N = \hat{S}_N + \hat{E}_N + \hat{I}_N$. The subscript N is to denote non-*Wolbachia*-carrying mosquitoes and is used here for consistency and to differentiate from *Wolbachia*-carrying mosquitoes in later sections. We group eggs, larvae and pupae into one compartment as they are not involved in the transmission of dengue. Without loss of generality, they can be represented by a single death rate and a single maturation rate for the purpose of modelling the dengue transmission dynamics. No "recovered" class is required for mosquitoes as they remain infected for the rest of their life. The populations of both human and mosquitoes are converted to proportions by letting $S_H = \hat{S}_H/N_H$, $E_H = \hat{E}_H/N_H$, $I_H = \hat{I}_H/N_H$, $R_H = \hat{R}_H/N_H$ and $A_N = \hat{A}_N/K$, $S_N = \hat{S}_N/K$, $E_N = \hat{E}_N/K$, and $I_N = \hat{I}_N/K$. Since the carrying capacity, K, is related to the number of available breeding sites, which depends on the number of humans, we have $K \propto N_H$, and hence $K = LN_H$, where L is the ratio of the carrying capacity to the total human population. The model, with populations as proportions, is then governed by the system of differential equations,

$$\frac{dS_H}{dt} = -b_N T_N L I_N S_H, \tag{1}$$

$$\frac{dE_H}{dt} = b_N T_N L I_N S_H - \gamma_H E_H, \tag{2}$$

$$\frac{dI_H}{dt} = \gamma_H E_H - \sigma I_H, \tag{3}$$

$$\frac{dR_H}{dt} = \sigma I_H, \tag{4}$$

$$\frac{dA_N}{dt} = \rho_N \frac{F_N}{2}(1 - A_N) - (\tau_N + \mu_{NA}) A_N, \tag{5}$$

$$\frac{dS_N}{dt} = \tau_N \frac{A_N}{2} - \left(b_N T_N I_H + \mu_N(t)\right) S_N, \tag{6}$$

$$\frac{dE_N}{dt} = \left(b_N T_N I_H\right) S_N - \left(\gamma_N + \mu_N(t)\right) E_N \tag{7}$$

and

$$\frac{dI_N}{dt} = \gamma_N E_N - \mu_N(t) I_N, \tag{8}$$

where $S_H + E_H + I_H + R_H = 1$. Since the probability of transmission from a non-*Wolbachia* mosquito to a human is the same as the converse, we also let $T_{HN} = T_{NH} = T_N$. The variation in the adult mosquito death rate is strongly influenced by environmental factors such as temperature, humidity, and rainfall [8] and is therefore sinusoidally forced, according to

$$\mu_N(t) = \mu_{N0}\left(1 - \eta \cos\left(\frac{2\pi(t+\omega)}{365}\right)\right), \tag{9}$$

where η is the strength of seasonal forcing in the adult death rate, and μ_{N0} is the average adult death rate, t is time and ω is the phase shift, which is used to align the cosine function with the seasonal factors in Far North Queensland. Forcing more than one term in this model is unnecessary since the mosquito population is explicitly modelled. The mosquito population size is most sensitive to the death rate, and hence this parameter is chosen for the forcing, resulting in appropriate seasonal fluctuations in the adult mosquito population. Since the mating function is dependent on the population size, this in turn results in appropriate seasonal fluctuations in the aquatic population.

After being bitten by an infectious mosquito, humans become exposed (but not yet infectious) at a rate of $b_N T_N \hat{I}_N/N_H$, which is then non-dimensionalised to $b_N T_N L I_N$ (Eq. (1) and (2)), where b_N is the successful biting rate and T_N is the transmission probability from non-*Wolbachia*-carrying mosquitoes to humans and vice versa. These exposed humans then become infectious at a rate of γ_H and then recover from dengue at a rate of σ.

The aquatic mosquito population increases as the adult mosquitoes mate and breed, but the population is limited by carrying capacity K through the logistic term

$$\rho_N \frac{\hat{F}_N \hat{M}_N}{\hat{M}_N + \hat{F}_N}\left(1 - \frac{\hat{A}_N}{K}\right).$$

Since there are equal numbers of male and female mosquitoes $\hat{M}_N = \hat{F}_N$, and with the scaling this becomes $\rho_N F_N(1 - A_N)/2$ in Eq. (5). The aquatic population dies at a rate of μ_{NA} and mature into susceptible female mosquitoes at a rate of τ_N, where only half of the maturing aquatics are female. Susceptible mosquitoes progress to the exposed class after biting infectious humans at a rate of $b_N T_N \hat{I}_H/N_H$, which non-dimensionalises to $b_N T_N I_H$ in Eqs. (6) and (7). They then become infectious at a rate of γ_N (Eq. (8)), where $1/\gamma_N$ is the extrinsic incubation period.

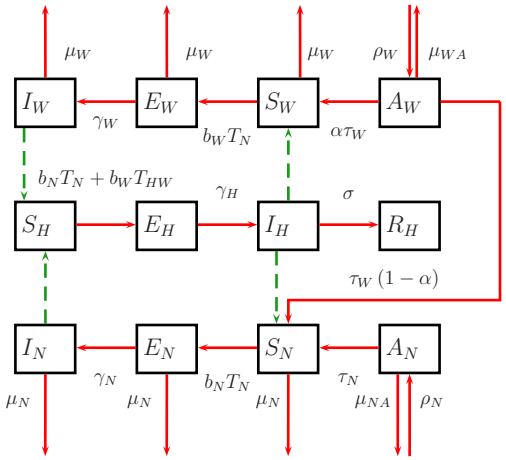

Fig. 2. Schematic of the model in the presence of *Wolbachia*-carrying mosquitoes, Eqs. (11)–(22). Solid lines are population progression lines and dashed lines are disease transmission lines. The subscript H is for the human population, N is for the non-*Wolbachia*-carrying mosquito population and W is for the *Wolbachia*-carrying mosquito population. The compartments are 'S' for susceptible, 'E' for exposed to dengue but not yet infectious, 'I' for infectious, 'R' for recovered, and 'A' for the aquatic phase of the mosquito life cycle. The transition rates between compartments are shown next to the progression lines and are described in the text.

2.1.2. Data and parameter estimation

Cairns is the largest city in the region of Australia where *Aedes aegypti* are present and local dengue transmission occurs there [37,38]. It is also where the *Wolbachia* field trials, which began in 2011, are being conducted [16]. In summer 2008/2009, there was a DEN3 outbreak in Cairns [35] and we use data from this outbreak to estimate the parameter values of transmission probability (T_N), amplitude of seasonality (η) and seasonal phase (ω) for the baseline model, i.e., in the absence of *Wolbachia*, represented by Eqs. (1)–(8). The other parameter values were obtained from the literature and are given in Table 2. The Cairns data covers the period from 2nd November 2008 to 31st May 2009 and was extracted from Fig. 2 of the paper by Ritchie et al. [35]. As our model is formulated as a proportion of the population, each data point is divided by 150,000, which was the approximate population of Cairns in 2008 [39].

We minimise the sum of the squared error between the model and data, which is given by

$$\mathrm{RSS} = \sum_{i=1}^{n} \left(y_i - f_i(x)\right)^2, \tag{10}$$

where y_i is the total proportion of human dengue cases up to the ith week from the observed data, and $f_i(x)$ is the total proportion of human dengue cases up to the ith week from the model simulations. The "lsqnonlin" built-in function in MATLAB is then used to estimate the T_N, η and ω parameter values.

2.2. Model in the presence of Wolbachia

2.2.1. Model formulation

Similarly to the model above, the *Wolbachia*-carrying mosquito population is divided into subpopulations of Aquatic (A_W, again comprised of eggs, larvae and pupae), Susceptible (S_W), Exposed (E_W) and Infectious (I_W) mosquitoes, where $S_W + E_W + I_W = F_W$ and these have been non-dimensionalised by carrying capacity K. The subscript W is to denote *Wolbachia* and to differentiate between *Wolbachia*-free and *Wolbachia*-carrying mosquitoes. The model comprises 12 compartments in total, for the two mosquito and human populations, and a schematic representation is given in Fig. 2.

The model is governed by the following system of differential equations.

$$\frac{dS_H}{dt} = -b_N T_N L I_N S_H - b_W T_{HW} L I_W S_H, \tag{11}$$

$$\frac{dE_H}{dt} = b_N T_N L I_N S_H + b_W T_{HW} L I_W S_H - \gamma_H E_H, \tag{12}$$

$$\frac{dI_H}{dt} = \gamma_H E_H - \sigma I_H, \tag{13}$$

$$\frac{dR_H}{dt} = \sigma I_H, \tag{14}$$

$$\frac{dA_N}{dt} = \rho_N \frac{F_N^2}{2(F_N + F_W)}(1 - (A_N + A_W)) - (\tau_N + \mu_{NA})A_N, \tag{15}$$

$$\frac{dS_N}{dt} = \tau_N \frac{A_N}{2} + (1-\alpha)\tau_W \frac{A_W}{2} - (b_N T_N I_H + \mu_N(t))S_N, \tag{16}$$

$$\frac{dE_N}{dt} = b_N T_N I_H S_N - (\gamma_N + \mu_N(t))E_N, \tag{17}$$

$$\frac{dI_N}{dt} = \gamma_N E_N - \mu_N(t) I_N, \tag{18}$$

$$\frac{dA_W}{dt} = \rho_W \frac{F_W}{2}(1 - (A_N + A_W)) - (\tau_W + \mu_{WA})A_W, \tag{19}$$

$$\frac{dS_W}{dt} = \tau_W \alpha \frac{A_W}{2} - (b_W T_N I_H + \mu_W(t))S_W, \tag{20}$$

$$\frac{dE_W}{dt} = b_W T_N I_H S_W - (\gamma_W + \mu_W(t))E_W \tag{21}$$

and

$$\frac{dI_W}{dt} = \gamma_W E_W - \mu_W(t) I_W. \tag{22}$$

In this model, the rates at which a human becomes exposed are now different to the model in the absence of *Wolbachia*, as seen in Eq. (1). Here, a susceptible human becomes exposed after being bitten by either non-*Wolbachia* or *Wolbachia*-carrying infectious mosquitoes at a rate of $b_N T_N L I_N$ and $b_W T_{HW} L I_W$, respectively (see Eqs. (11) and (12)), where b_W is the successful biting rate of *Wolbachia*-carrying mosquitoes and T_{HW} is the transmission probability from *Wolbachia*-carrying mosquitoes to humans. Note that the transmission probability from humans to *Wolbachia*-carrying mosquitoes is assumed to be equal to that of humans to non-*Wolbachia* mosquitoes, so that $T_{WH} = T_N$, while the transmission probability of dengue from mosquitoes to human differs between *Wolbachia*- and non-*Wolbachia*-carrying mosquitoes (see Section 2.2.2 for explanation).

For the mosquito populations, the effects of cytoplasmic incompatibility and imperfect maternal transmission are included. The effect of CI is included by considering different mating functions, i.e., the non-*Wolbachia*-carrying females can only reproduce when mating with *Wolbachia*-carrying males, giving $\rho_N F_N M_N / P$, where $P = F_N + M_N + F_W + M_W$. Since the ratio of male to female mosquitoes is taken to be 1:1, this is reduced to $\rho_N F_N^2/(2(F_N + F_W))$ (see Eq. (15)). Aquatic *Wolbachia*-carrying mosquitoes are produced when *Wolbachia*-carrying females mate with both *Wolbachia*-free and *Wolbachia*-carrying males, giving $\rho_W F_W (M_N + M_W)/P$, which simplifies to $\rho_W F_W/2$ (Eq. (19)). *Wolbachia*-carrying aquatic mosquitoes mature into *Wolbachia*-carrying adults at a rate of τ_W, with a proportion, α, of them becoming *Wolbachia*-carrying adults and $(1-\alpha)$ becoming non-*Wolbachia*-carrying adults (see Eqs. (16) and (20)), to capture the effect of imperfect maternal transmission of *Wolbachia* [15,40]. As with the non-*Wolbachia*-carrying mosquitoes, the death rate of *Wolbachia*-carrying adult mosquitoes varies seasonally according to Eq. (9).

Table 1
Relationships between non-*Wolbachia* and *Wolbachia* related parameters. c, d, f and g are the ratios of the reproductive rate, transmission probability, death rate and the biting rate of *Wolbachia*-carrying mosquitoes to non-*Wolbachia* rates, respectively.

Parameter	Relationship
ρ_W	$c\rho_N$
T_{HW}	dT_N
μ_W	$f\mu_N$
b_W	gb_N

2.2.2. Wolbachia parameters

In this section, model parameters relating to *Wolbachia* are presented and discussed. Most of these are given in terms of non-*Wolbachia* ones, following the conventions in the literature. The relationships between *Wolbachia* and non-*Wolbachia* parameters are given in Table 1.

The reproductive rate of *Wolbachia*-carrying mosquitoes is generally lower than for non-*Wolbachia*-carrying ones ($c < 1$), significantly so for *WMelPop* and marginally so for the *WMel* strain. This is because *WMelPop* decreases the viability of eggs [20,41], whereas *WMel* does not have a significant effect on them [15]. The death rate of *Wolbachia*-carrying mosquitoes is higher than non-*Wolbachia* ones ($f > 1$) because *Wolbachia* reduces the mosquito lifespan [15,20]. *WMel* and *WMelPop* reduce the lifespan of mosquitoes up to 10% and 50% respectively [15,20]. *Wolbachia* also inhibits viral replication and dissemination in the mosquitoes [13,15]. This results in a lower dengue viral load in the *Wolbachia*-carrying mosquitoes, and to reflect this, we set the transmission probability from infectious *Wolbachia*-carrying mosquitoes to humans to less than that for *Wolbachia*-free mosquitoes ($d < 1$). Additionally, *Wolbachia* causes a condition known as bendy proboscis [42], which inhibits feeding and lowers the successful biting rate ($g < 1$). This lower biting rate also captures the effect that due to the viral replication inhibition, some *Wolbachia*-carrying mosquitoes are effectively not infected with dengue, and so the overall transmission rate from humans is lower (that is, $b_W T_N < b_N T_N$).

For the parameter values used in this paper, there are only two realistic stable states, which are that only non-*Wolbachia*-carrying mosquitoes persist, and that both populations persist (Fig. 3). An additional stable state does exist where only the *Wolbachia*-carrying mosquitoes persist, but this requires perfect maternal transmission of *Wolbachia*, which may not be realistic [15]. This state was also found by Ndii et al. [24] for an autonomous system. When both populations persist, the proportion of *Wolbachia*-carrying mosquitoes is around 86%, which compares well with the 90% observed in Hoffmann et al. [16].

2.2.3. Measurement of Wolbachia effect on dengue

A measure is needed to assess the impact of the *Wolbachia* intervention on dengue transmission, which we do by comparing the total number of human dengue cases in the absence and presence (i.e., persistence) of *Wolbachia*-carrying mosquitoes. The relative effect is expressed as a percentage, given by

$$\kappa = 100 \times \left(\frac{H_A - H_P}{H_A} \right) \%, \tag{23}$$

where H is the final attack proportion of the human population, with subscripts to denote the absence (A) and presence (P) of *Wolbachia*.

2.3. Sensitivity analysis

A global sensitivity analysis is performed using the standard combination of Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficient (PRCC) multivariate analysis [43–45]. LHS is a stratified Monte Carlo sampling method, where the random parameter distributions are divided into N equal probability intervals and samples taken from each [43–45], where N is the sample size. Each interval of each parameter is sampled only once without replacement, and the entire range of each parameter is explored [43–45]. Parameters are sampled from a triangular probability distribution because we expect the values close to the peak of the triangular distribution pattern are those that are more likely to occur. The minimum, maximum and expected values are given in Table 2.

PRCC is an efficient method for measuring the nonlinear but monotonic relationship between inputs and the model outcome of interest [43–45]. In this paper, the inputs are the parameters as well as the

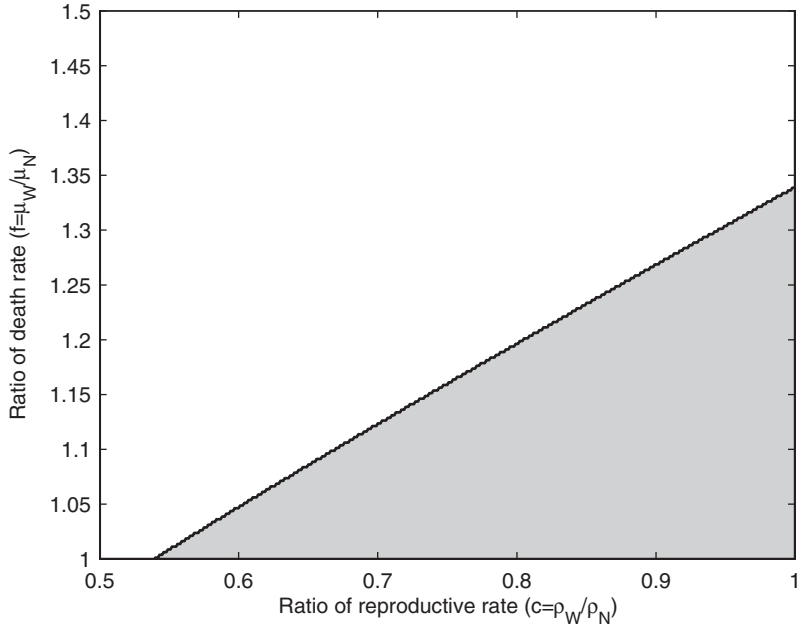

Fig. 3. A plot of the persistence, shown by the shaded region, of the *Wolbachia*-carrying mosquito population, over a range of the *Wolbachia* reproductive and death rates, expressed as ratios of the non-*Wolbachia* rates. In the unshaded region only non-*Wolbachia*-carrying mosquitoes persist.

initial number of exposed humans, while the model outcome is the cumulative proportion of infectious individuals, which is the solution of

$$\frac{dC_{IH}}{dt} = \gamma_H E_H.$$

The ranges of the input parameters are available in the literature and only samples of the parameter values that result in the persistence of mosquitoes are included in the calculation. The PRCC is computed for the full length of 31 weeks. The statistical significance test for each PRCC value is performed according to:

$$t = \text{PRCC}\sqrt{\frac{N-2}{1-\text{PRCC}^2}}.$$

The most significant parameters are those for which a small change in value leads to a significant change in the output, that is the cumulative number of infectious humans.

3. Results

In this section the model simulation and sensitivity analysis results are presented for both models. The governing systems of differential equations are integrated using MATLAB's inbuilt routine "ode45", with the parameter values given in Table 2. We run the model until the mosquito population reaches the periodic stable state, before the infected humans are introduced into the population on 2nd November. That is, the transient dynamics of the introduction of the *Wolbachia* mosquitoes into the system are not considered. In Far North Queensland, dengue is not endemic, hence dengue outbreaks occur as dengue cases are introduced into the population. For both models, the initial conditions for the human population are $E_{H0} = 2/(1.5 \times 10^5)$, $I_{H0} = 0 = R_{H0}$ and $S_{H0} = 1 - E_{H0} - I_{H0} - R_{H0}$.

3.1. Model in the absence of Wolbachia

In this section we consider the model in the absence of *Wolbachia*, Eqs. (1)–(8), as described in Section 2.1, which serves as a baseline model for comparison with the *Wolbachia* intervention. Most of the parameters are obtained from the literature, as per references in Table 2. The remaining three parameters, T_N, η and ω, are optimised using MATLAB's `lsqnonlin` function. We constrain the optimisation by physical limits, that is, between 0 and 1 for T_N since it is a probability, 0 to 365 for seasonal phase ω, and 0 to 1 for η so that the death rate μ_N remains positive at all times. We fit the parameters as follows. The model is run to its periodic stable state and then two exposed humans are introduced. The sum of square errors is calculated using the cumulative 31-week proportional weekly data of Ritchie et al. [35]. The parameters are then optimised using MATLAB's `lsqnonlin` function, with a final sum of squares error equal to 3×10^{-7}; the resulting parameter values T_N, η and ω are given in Table 2. To assess the goodness-of-fit we calculated the χ^2 statistic for the model residuals using MATLAB's `chi2gof` function. This returned a p-value of 0.3713, and so we fail to reject the hypothesis that the residuals are from a normal distribution. There is some systematic bias in the residuals around the start of the outbreak, evident in Fig. 4, where the observed outbreak rises slightly faster than the model. While model embellishments could be added to account for this, here we consider that the standard SEIR model of infectious disease is sufficient for our intended purpose: comparing the outbreak dynamics in the absence and presence of *Wolbachia*.

For the sensitivity analysis, 5200 runs are performed to assess the model's sensitivity to the parameters. The parameter ranges used are given in Table 2. The range of initially-exposed humans is taken to be between one and five individuals. This is realistic as only a small number of initial cases triggers the outbreak [35]. The changes in parameter sensitivity over time are common for SEIR models due to the changes in disease dynamics over time, as seen in Figs. 5 and 6. Fig. 5 shows that, for most of the time period, the most influential parameters are the transmission probability (T_N), the biting rate (b_N) and the average adult death rate (μ_{N0}), where the latter has a negative correlation. The phase, ω, influences the outbreak size by shifting the peaks and troughs of the mosquito population around; an outbreak can take off around the peak. Because of the sinusoidal nature of the seasonality, the correlation between ω and the outbreak size changes sign over time. The parameter γ_H determines the progression rate of humans from the exposed to infectious class. In early times, when introducing exposed individuals, this parameter drives an increase in infectious humans. If this parameter is high, the initial introduced cases will quickly move to the infectious class. As the epidemic takes off, the cumulative number of infectious individuals are determined more by the biting rate b_N, successful transmission probability T_N and so γ_H declines in importance. After the initial introduction of cases in early times, as the epidemic takes off, the dynamics of the mosquito

Table 2
Parameter descriptions, values and sources for both models. The *Wolbachia*-related parameters are for the *WMel* strain. Further explanation of the parameter values is given in the text.

Symbol	Description	Min	Expected	Max	Unit	Source
T_N	Transmission probability	0	0.2614	1	N/A	Fitted
b_N	Biting rate	0	0.63	1	day^{-1}	[46]
μ_{N0}	Adult mosquito death rate	1/30	1/14	1/10		[8]
$d = T_{HW}/T_N$	Ratio of transmission probability W cf. non-W	0	0.5	1	N/A	[13]
σ	Recovery rate	1/14	1/5	1/3	day^{-1}	[47]
$g = b_W/b_N$	Ratio of biting rates W cf. non-W	0	0.95	1	N/A	[42]
τ_W	Maturation rate of W	1/12	1/10	1/8	day^{-1}	[8]
ω	Phase	0	20.61	365	day	Fitted
$f = \mu_W/\mu_N$	Ratio of death rate W cf. non-W	1	1.1	1.25	N/A	[15,20]
ρ_N	Reproductive rate	1	1.25	2.5	day^{-1}	[24]
α	Maternal transmission	0.85	0.9	1	N/A	[15,24,40]
$c = \rho_W/\rho_N$	Ratio of reproductive rate W cf. non-W	0.7	0.95	1	N/A	[15]
γ_W	Progression rate from exposed to infectious	1/12	1/10	1/8	day^{-1}	[48]
τ_N	Maturation rate	1/17	1/10	1/6	day^{-1}	[8]
μ_{WA}	Aquatic death rate	1/20	1/14	1/7	day^{-1}	[8]
η	Seasonality amplitude	0	0.6228	1	N/A	Fitted
γ_H	Progression rate from exposed to infectious human	1/7	1/5.5	1/4	day^{-1}	[47]
μ_{NA}	Death rate of aquatic non-W	1/20	1/14	1/7	day^{-1}	[8]
γ_N	Progression from exposed to infectious non-W	1/12	1/10	1/8	day^{-1}	[48]
$L = K/N_H$	Ratio of carrying capacity cf. total human population		3		N/A	[48]
E_{H0}	Initial exposed human	1	2	5	N/A	

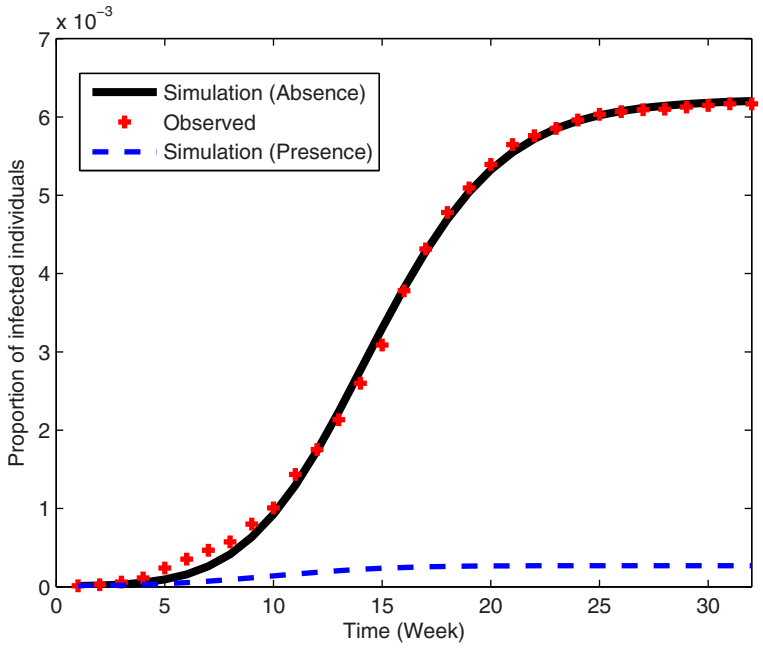

Fig. 4. Plots of observed data and the output of the fitted model (*Wolbachia* absent), Eqs. (1)–(8)), as well as the model in the presence of *Wolbachia* (Eqs. (11)–(22)). The data covers the time period 2nd November 2008 to 31st May 2009, extracted from Fig. 2 of Ritchie et al. [35]. The parameter values are given in Table 2. The initial human subpopulations are $E_{H0} = 2/(1.5 \times 10^5)$, $I_{H0} = R_{H0} = 0$ and $S_{H0} = 1 - E_{H0} - I_{H0} - R_{H0}$, for both models. The initial mosquito subpopulations for the model in the absence of *Wolbachia* are $A_{N0} = 0.8210$, $S_{N0} = 1.2634$ and $E_{M0} = I_{M0} = 0$, and for the model in the presence of *Wolbachia* they are $A_{N0} = 0.0138$, $S_{N0} = 0.1326$, $A_{W0} = 0.7535$, $S_{N0} = 0.9400$ and $E_{M0} = I_{M0} = E_{W0} = I_{W0} = 0$. The initial proportion of exposed individuals are introduced after the mosquito population reaches the stable periodic state.

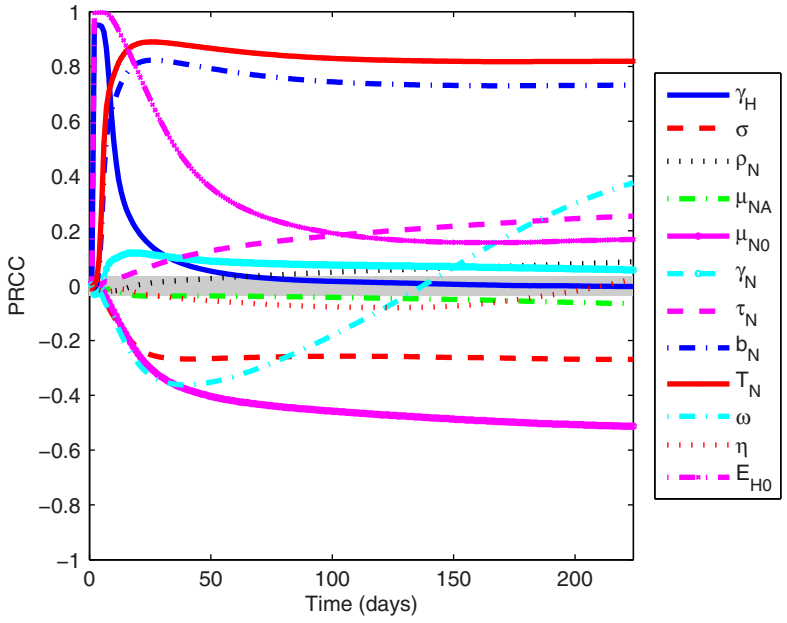

Fig. 5. Plot of the PRCC over time of the model in the absence of *Wolbachia*. The PRCC is calculated with respect to cumulative number of infectious individuals. The grey area indicates the region where the PRCC is not significantly different from zero (significance level 0.01), using 5200 samples.

population have a larger influence on the disease dynamics. When there are many susceptible mosquito in the population, there will be many infectious mosquitoes and hence many infected humans. An increase in the number of susceptible mosquitoes is regulated by the parameter τ_N and so this parameter is impactful in the later period after the epidemic has taken off. As expected, the cumulative number of infectious individuals is most sensitive to the initially-exposed humans (E_{H0}) at early times, since they are immediately added to this output. However, for the range considered, E_{H0} does not change the proportion of dengue reduction due to the introduction of *Wolbachia*-carrying mosquitoes.

3.2. Model in the presence of Wolbachia

In this section the effect of *Wolbachia*-carrying mosquitoes on the dengue dynamics is investigated. Variations in parameter values are explored to quantify the persistence of *Wolbachia* and its effects on human dengue cases. The initial conditions for the two mosquito populations are $A_{N0} = 0.0138$, $S_{N0} = 0.1326$, $E_{N0} = I_{N0} = 0$, $A_{W0} = 0.7535$, $S_{W0} = 0.9400$, and $E_{W0} = 0 = I_{W0}$, which are obtained by running the model to the periodic stable state with no dengue. Since the *WMel* strain of *Wolbachia* is used in the Cairns field experiments [16], we use its expected parameter values in our model.

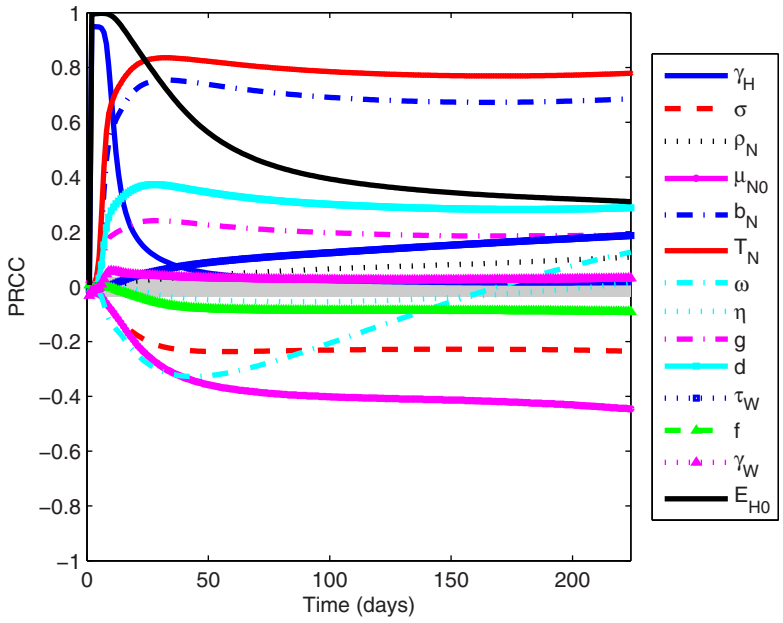

Fig. 6. Plot of PRCC over time for the model in the presence of *Wolbachia*. For clarity we show only those parameters that have a PRCC outside the range (−0.05, 0.05). The grey area indicates the region in which the PRCC is not significantly different from zero (significance level 0.01), using 5190 samples.

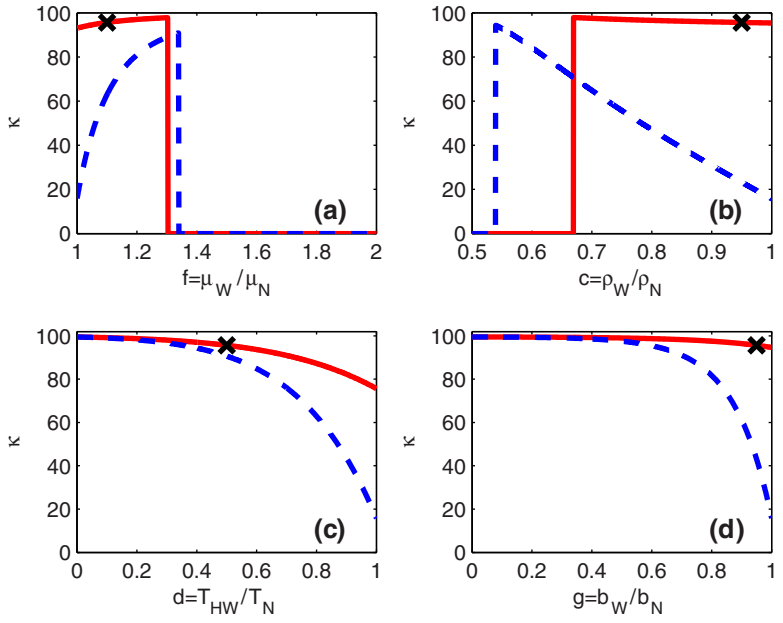

Fig. 7. Plot of the relative effect, κ from Eq. (23), on human dengue cases in the absence and presence of *Wolbachia*-carrying mosquitoes against the ratios of (a) adult death rate ($f = \mu_W/\mu_N$), (b) reproductive rate ($c = \rho_W/\rho_N$), (c) transmission probability ($d = T_{HW}/T_N$) and (d) biting rate ($g = b_W/b_N$). In each case the other ratios are set to the expected values for *WMel* from Table 2 (solid lines), or 1 (dashed lines). Crosses mark the case where all ratios are set to their expected *WMel* values.

3.2.1. Sensitivity analysis

The results of the sensitivity analysis are similar to those of the model in the absence of *Wolbachia*, and are shown in Fig. 6. The transmission probability (T_N), the biting rate (b_N) and the average adult mosquito death rate (μ_{N0}) are the most influential parameters on the model outcome. Furthermore, in early times, the cumulative number of infectious individuals is sensitive to E_{H0} and γ_H. An exploration of the ratios of transmission probability, $d = T_{HW}/T_N$, biting rate, $g = b_W/b_N$, and death rate, $f = \mu_W/\mu_N$, is also carried out, as they relate to the most influential parameters. We also explore the ratio of reproductive rate, $c = \rho_W/\rho_N$, to obtain information regarding its effect on dengue and on the parameter range where *Wolbachia*-carrying mosquitoes persist.

3.2.2. Parameter exploration

Although we are using values for c, d, f and g from the literature, the provided values are generally qualitative descriptions, or from lab trials which may not be representative of what happens in the field, and hence the correct parameter values may differ. Therefore, in this section we vary these parameters one at a time to determine their effects on human dengue cases, as measured by the relative effect given in Eq. (23). Thus, we quantify the effect of introducing *Wolbachia*-carrying mosquitoes on dengue transmission for a range of realistic parameter values. There are two scenarios being considered, and their resulting effects on dengue cases are shown in Fig. 7. The first uses the expected values for *WMel* for the non-varied *Wolbachia* parameters (the solid line in the figure). The second scenario

uses the non-*Wolbachia*-carrying mosquito values (i.e., taking the ratios in Table 1 equal to one), allowing us to explore the effect of cytoplasmic incompatibility on the dengue transmission dynamics, should Wolbachia have no other effect on the mosquito physiology. This second scenario is represented by the dashed line in the figure.

The vertical lines in Fig. 7(a) and (b), for f and c, respectively, denote the boundary between persistence ($\kappa > 0$) and non-persistence ($\kappa = 0$) for the *Wolbachia*-carrying mosquitoes. For f, the ratio of death rates, both scenarios show that as the death rate of *Wolbachia*-carrying mosquitoes increases, the relative effect on dengue also increases up to the point where the *Wolbachia*-carrying mosquitoes no longer persist, around $f = 1.30$ for the solid line and $f = 1.34$ for the dashed line. The default values, with $f = 1.1$, are identified on the figure by a cross, showing that *WMel* should reduce human dengue cases by approximately 96%. Interestingly, in the second scenario, when $c = d = f = g = 1$, we see that even if all of the *Wolbachia* parameters are equal to their non-*Wolbachia* counterparts, the human dengue cases are still reduced by approximately 16%. This occurs due to the combination of CI and competition, with the total female mosquito population ($F_N + F_W$) being reduced. The CI means there is a different mating function for the *Wolbachia*-free and *Wolbachia*-carrying mosquitoes, and in particular that no non-*Wolbachia*-carrying offspring are produced from the combination of a non-*Wolbachia* female and *Wolbachia*-carrying male (there is effectively a $0 \times F_N F_W$ term in Eq. (15)). This difference in the mating functions combined with the competition in the aquatic phase results in a reduced total mosquito population, and hence less dengue. This provides the new insight that CI alone affects the dengue transmission dynamics.

In Fig. 7(b), for the solid line with expected *WMel* values, when the reproductive rate of *Wolbachia*-carrying mosquitoes is too low compared to *Wolbachia*-free mosquitoes, the *Wolbachia*-carrying mosquitoes no longer persist, and hence have no effect on human dengue cases. This occurs at approximately $c = 0.66$ for the expected parameter values (solid line), and $c = 0.52$ for $d = f = g = 1$ (dashed line). When *Wolbachia*-carrying mosquitoes do persist, the effect on human dengue decreases with increasing c since the total number of mosquitoes increases, despite CI. However, this effect is negligible for the expected parameter values (solid line), with over 90% reduction in dengue for all values where *Wolbachia*-carrying mosquitoes persist.

In Fig. 7(c), the results show that even if $d \approx 1$ (transmission is not directly affected by *Wolbachia*), a reduction in human dengue cases of approximately 76% is still obtained, due to the other effects of *Wolbachia* on mosquito physiology. In addition, as shown in Fig. 7(d), a 90% reduction in human dengue cases is obtained even though the biting rate of *Wolbachia*-carrying mosquitoes is close to that of non-*Wolbachia* mosquitoes ($g \approx 1$).

4. Discussion and conclusions

We have developed a mathematical model for the presence of a *Wolbachia*-carrying mosquito population in order to quantify the effects of such an intervention on human dengue cases. Our model incorporates seasonal forcing through the adult mosquito death rate, the effect of cytoplasmic incompatibility, and competition for resources in the aquatic stage. This model considers only a single dengue serotype with the mosquito population in periodic stable state, appropriate to the study of a single dengue outbreak. It is assumed that half of the mosquito population mature into female adults, that a single introduction event occurs, and that there is no initial dengue immunity in the human population. These effects will have an impact on the dengue transmission dynamics, with initial dengue immunity reducing the relative effect of the *Wolbachia* introduction due to smaller outbreak sizes. However, the purpose of this model was to determine an indicative effect of the introduction of *Wolbachia*-carrying mosquitoes on the dengue transmission dynamics. Extensions to the model which consider the effect of immunity in the human population are the subject of future work.

A model without seasonality can only fit the data for far North Queensland in one of two ways. Firstly, nearly all humans need to be previously infected and are now recovered ($R_{H0} \approx 1$), which is not realistic. Secondly, all mosquitoes can die out, which mimics seasonal effects for a single year. However, unlike in a model which includes seasonal effects, the mosquito population cannot re-emerge. Exploration of key parameter ranges was performed to determine the level of dengue reduction due to *Wolbachia* and the persistence of *Wolbachia*-carrying mosquitoes, which is important since definite values are not known. A global sensitivity analysis was used to determine the most influential parameters.

We found that using the Wolbachia strain *WMel*, which reduces the mosquito lifespan by at most 10%, allows *Wolbachia*-carrying mosquitoes to persist. This result is compatible with what has been suggested by Walker et al. [15] and the results from field experiments [16]. Furthermore, Fig. 7 provides the new insight that cytoplasmic incompatibility is an important biological factor. CI not only gives a reproductive advantage to *Wolbachia*-carrying female mosquitoes, but also influences the transmission dynamics of dengue, through a reduced mosquito population. The release of more *Wolbachia*-carrying males than females is being considered by Hancock et al. [33], and their analysis may be important in considering the effect of cytoplasmic incompatibility on dengue transmission dynamics, and the possible feminisation of the *Wolbachia*-carrying mosquito population. However, our results suggest that with equal numbers of males and females, *Wolbachia*-carrying mosquitoes can persist, and hence a reduction in dengue human cases can be obtained. Furthermore, the ratios of transmission probability, $d = T_{HW}/T_N$, and of biting rate, $g = b_W/b_N$, determine the level of reduction in human dengue cases. In contrast, the ratios of death rate, $f = \mu_W/\mu_N$, and of reproductive rate, $c = \rho_W/\rho_N$, determine the persistence of *Wolbachia*-carrying mosquitoes. This result is corroborated by the results of the sensitivity analysis. Additionally, the biting and reproductive rates are linked, since female mosquitoes take blood meals for reproduction. Here we treat them as independent for the purpose of exploring the parameter space and note that the relative effect is consistent.

In conclusion, a one-strain dengue mathematical model incorporating *Wolbachia*-carrying mosquitoes has been developed for a single outbreak. We quantify the effect that *Wolbachia* will have on human dengue cases, once the mosquito populations have reached their periodic stable states. *Wolbachia* comes with a fitness cost to *Aedes aegypti* mosquitoes, and we explore the parameter values for which *Wolbachia* will persist in the mosquito population. Our results show that for realistic *WMel* parameter values, *Wolbachia*-carrying mosquitoes can greatly reduce the transmission of dengue. We also show that in the absence of any other effect on the mosquito physiology by *Wolbachia*, cytoplasmic incompatibility alone affects the transmission of dengue, reducing the human cases.

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