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A mathematical model for assessing control strategies against West Nile virus

C. Bowman[a,b], A.B. Gumel[c,*], P. van den Driessche[d], J. Wu[e], H. Zhu[e]

[a] *Institute for Biodiagnostics, National Research Council Canada, Winnipeg, Manitoba, R3B 1Y6, Canada*
[b] *Department of Electrical and Computer Engineering, University of Manitoba, Winnipeg, Manitoba, R3T 5V6, Canada*
[c] *Department of Mathematics, University of Manitoba, 342 Machray Hall, Winnipeg, Manitoba, R3T 2N2, Canada*
[d] *Department of Mathematics and Statistics, University of Victoria, Victoria, British Columbia, V8W 3P4, Canada*
[e] *Laboratory for Industrial and Applied Mathematics, Department of Mathematics and Statistics, York University, Toronto, M3J 1P3, Canada*

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Abstract

Since its incursion into North America in 1999, West Nile virus (WNV) has spread rapidly across the continent resulting in numerous human infections and deaths. Owing to the absence of an effective diagnostic test and therapeutic treatment against WNV, public health officials have focussed on the use of preventive measures in an attempt to halt the spread of WNV in humans. The aim of this paper is to use mathematical modelling and analysis to assess two main anti-WNV preventive strategies, namely: mosquito reduction strategies and personal protection. We propose a single-season ordinary differential equation model for the transmission dynamics of WNV in a mosquito–bird–human community, with birds as reservoir hosts and culicine mosquitoes as vectors. The model exhibits two equilibria; namely the disease-free equilibrium and a unique endemic equilibrium. Stability analysis of the model shows that the disease-free equilibrium is globally asymptotically stable if a certain threshold quantity ($\mathcal{R}_0$), which depends solely on parameters associated with the mosquito–bird cycle, is less than unity. The public health implication of this is that WNV can be eradicated from the mosquito–bird cycle (and, consequently, from the human

* Corresponding author. Tel.: +1 204 474 7486; fax: +1 204 474 7611.
E-mail address: gumelab@cc.umanitoba.ca (A.B. Gumel).

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population) if the adopted mosquito reduction strategy (or strategies) can make $\mathcal{R}_0 < 1$. On the other hand, it is shown, using a novel and robust technique that is based on the theory of monotone dynamical systems coupled with a regular perturbation argument and a Liapunov function, that if $\mathcal{R}_0 > 1$, then the unique endemic equilibrium is globally stable for small WNV-induced avian mortality. Thus, in this case, WNV persists in the mosquito–bird population.

1. Introduction

West Nile virus (WNV) is an arbovirus and a single-stranded RNA virus of the genus *Flavivirus* and the family *Flaviviridae* first isolated in the West Nile district of Uganda in 1937 (Smithburn et al., 1940). The virus, which is transmitted to humans and other animals by female mosquitoes that have fed from the blood of infected birds, has spread in Africa, Europe, the Middle East, west and central Asia, Oceania (subtype Kunjin), and most recently, North America (Campbell et al., 2002; Centers for Disease Control and Prevention, 2002a; Chowers et al., 2001; Nash et al., 2001; Petersen and Marfin, 2002).

Since its first incursion into North America in 1999 (Nash et al., 2001), numerous cases of WNV infections in humans have been recorded in the USA (62 cases in 1999, 21 cases in 2000, 66 cases in 2001 and 4000 cases in 2002) (Centers for Disease Control and Prevention, 2002c; Petersen et al., 2003). The large outbreak in 2002, which occurred in the Ohio and Mississippi River basins, resulted in 284 deaths (Centers for Disease Control and Prevention, 2002b). In Canada, following the first detection of WNV in birds in Ontario in the year 2001, 400 human cases of WNV were reported in Ontario and Quebec in 2002 (Drebot et al., 2003; Petersen et al., 2003). In 2003, WNV accounted for at least 7021 human infections (probable and/or confirmed cases) and 152 deaths in the USA (Centers for Disease Control and Prevention, 2003c) and 1240 infections and 10 deaths in Canada (Health Canada, 2003c). The West Nile virus is sustained and amplified in an enzootic cycle involving birds as reservoir hosts and female mosquitoes primarily of the genus *Culex* as the vectors.

WNV is known to be predominantly spread to humans and other animals via mosquito bites. However, there is now evidence showing WNV transmission through blood transfusions, organ/tissue transplants, needle stick injury, exposure to infected laboratory specimen and mother-to-child transmission (Bender and Thompson, 2003; Centers for Disease Control and Prevention, 2002d,e,f; Health Canada, 2003a; Nosal and Pellizzari, 2003). Fortunately, there is no evidence suggesting human infection by touching or kissing a WNV-infected individual, or from being around a health-care worker who has treated an infected person. Likewise, there is no evidence to date that the virus can pass from infected animals (horses, pets, etc.) to humans (Health Canada, 2003a).

Although many WNV-infected people ($\approx$80%) remain asymptomatic, and some ($\approx$20%) show mild flu-like symptoms such as fever, headache, body aches, nausea, vomiting etc., 1 in 150 infected individuals (mostly immuno-compromised and/or the elderly) develop severe illness. Such severe symptoms, which typically last for several weeks, include high fever, headache, meningitis, encephalitis, disorientation, coma,

tremors, convulsions, muscle weakness, vision loss, numbness and paralysis (Centers for Disease Control and Prevention, 2003a; Health Canada, 2003b).

Unfortunately, a specific treatment for WNV infection is yet to be found. People with mild symptoms often recover on their own. In more severe cases, people usually need to go to hospital where they can receive supportive treatment including intravenous fluids, help with breathing and nursing care. Owing to its global spread and the associated morbidity and mortality it inflicts (Chowers et al., 2001; Nash et al., 2001; Pepperell et al., 2003; Petersen and Marfin, 2002), much attention has been focussed on devising methods for controlling the spread of WNV in humans.

In the absence of effective anti-WNV therapeutic treatment and vaccine, WNV control strategies are based on taking appropriate preventive measures. These measures include mosquito reduction mechanisms and personal protection against exposure to mosquitoes. Mosquito reduction mechanisms entail the elimination of mosquito breeding sites (such as clearing culverts, roadside ditches etc., eliminating standing water), larvaciding (killing of larvae before they become adults) and adulticiding (killing of adult mosquitoes by spraying). On the other hand, personal protection is based on preventing vector mosquitoes from biting humans (by using mosquito repellents, avoiding locations where mosquitoes are biting and using barrier methods such as window screens and long-sleeved clothing) (Nosal and Pellizzari, 2003; Petersen et al., 2003).

The literature on the mathematical modelling of the transmission of WNV is rather scant; we cite two papers. Thomas and Urena (2001) formulate a difference equation model for WNV targeting its effects on New York City, and determine the amount of spraying (killing the mosquitoes) needed to eliminate the virus. Wonham et al. (2004) present a single-season ordinary differential equation model for WNV transmission in the mosquito–bird population. Their study, using local stability results and simulations, shows that while mosquito control decreases WNV outbreak threshold, bird control increases it. The aim of our study is to use mathematical modelling to gain some insights into the transmission dynamics of WNV in the mosquito–bird–human population within a single WNV season (from spring to fall) and to assess the aforementioned preventive strategies. Details of the transmission cycle of WNV are given in Section 2. These guide in the formulation in Section 3 of a deterministic ordinary differential equation model, which monitors the interaction of various mosquitoes, birds and human subpopulations. By investigating the qualitative features of this model, an important epidemiological threshold, known as the basic reproduction number (Anderson and May, 1991), is determined in Section 4. Global stability analyses of the associated equilibria are carried out in Section 4 and Appendix C. Simulation results are presented in Section 5, and Section 6 contains a summary.

2. Transmission of West Nile virus

WNV is transmitted from bird to bird by mosquitoes, which become carriers when they bite infected birds (Bender and Thompson, 2003; Centers for Disease Control and Prevention, 2003b; Petersen et al., 2003). Infected mosquitoes carry the virus in their salivary glands and infect susceptible bird species when taking a blood meal. The infected

birds sustain a significant level of virus in the bloodstream for one to four days after infection, during which time they may transmit the virus to subsequent feeding mosquitoes, continuing the life cycle. After about four days, the bird hosts develop life-long immunity to further West Nile infection (although a small number will succumb to the disease and die). The virus has been found in more than 110 bird species (Bender and Thompson, 2003). Although some of these species may have no obvious signs of illness when infected, others, such as crows, blue and grey jays, magpies and ravens, get sick more often and can die (Health Canada, 2003a). For this reason, the sightings of dead crows have been used in Canada as a marker for WNV activity, and the testing of dead crows for WNV remains a crucial part of the WNV surveillance system (Nosal and Pellizzari, 2003). When infected with WNV, many of the aforementioned avian species develop transient high-titre viremias that should allow transmission of the virus to feeding mosquitoes (Work et al., 1955).

Although WNV infection has been recorded in at least 29 different species of mosquitoes in North America (Bender and Thompson, 2003), it is most common in species that feed on birds. Examples include mosquitoes from the *Culex* genus (the principal maintenance and amplifying vectors of WNV) such as *Culex pipiens*, *Culex restuans* and *Culex tarsalis* (Bender and Thompson, 2003; Health Canada, 2003a; Petersen et al., 2003). Different types of mosquitoes are responsible for WNV infection in humans. These include the "bridging" species which feed on both birds and humans (such as *Coquillettidia perturbans*) and human biters (such as *Aedes vexans*) (Petersen et al., 2003).

In temperate regions, adult mosquitoes begin to emerge in the spring after undergoing the three aquatic stages (egg, larva, pupa). The ensuing viral replication in the mosquito–bird–mosquito cycle, which continues until early fall, is affected by environmental factors such as climate, host and vector predators and parasites, and host immune status (Petersen et al., 2003). In the tropics, the incidence of WNV infections is greatest during the rainy season when mosquitoes are most abundant (Campbell et al., 2002).

In the USA, nine mammalian species (humans, horses, cats, rabbits, skunks, squirrels, chipmunks and two species of bats) were found to be naturally infected with WNV (Komar, 2000; Marfin et al., 2001). Furthermore, nearly all human infections with WNV result from mosquito bites. It is known that WNV-infected humans and horses do not often develop an infectious level of viremia, and are likely dead-end hosts (Campbell et al., 2002; Centers for Disease Control and Prevention, 2003b). Human-to-human or non-human-vertebrate-to-human transmission of WNV has not been documented.

3. Model formulation

The model is based on monitoring the temporal dynamics of the populations of uninfected female mosquitoes $M_u(t)$, infected female mosquitoes $M_i(t)$, uninfected birds $B_u(t)$, infected birds $B_i(t)$, susceptible humans $S(t)$, asymptomatically infected humans $E(t)$, symptomatically infected humans $I(t)$, hospitalized WNV-infected humans $H(t)$ and recovered humans $R(t)$ as described in the following subsections. Here, $N_M = M_u(t) + M_i(t)$ is the total population of female mosquitoes in the community, $N_B = B_u(t) + B_i(t)$ is the total population of birds in the community and $N_H = S(t) + E(t) + I(t) + H(t) + R(t)$ is the total human population. A schematic description of the model is depicted in Fig. 1.

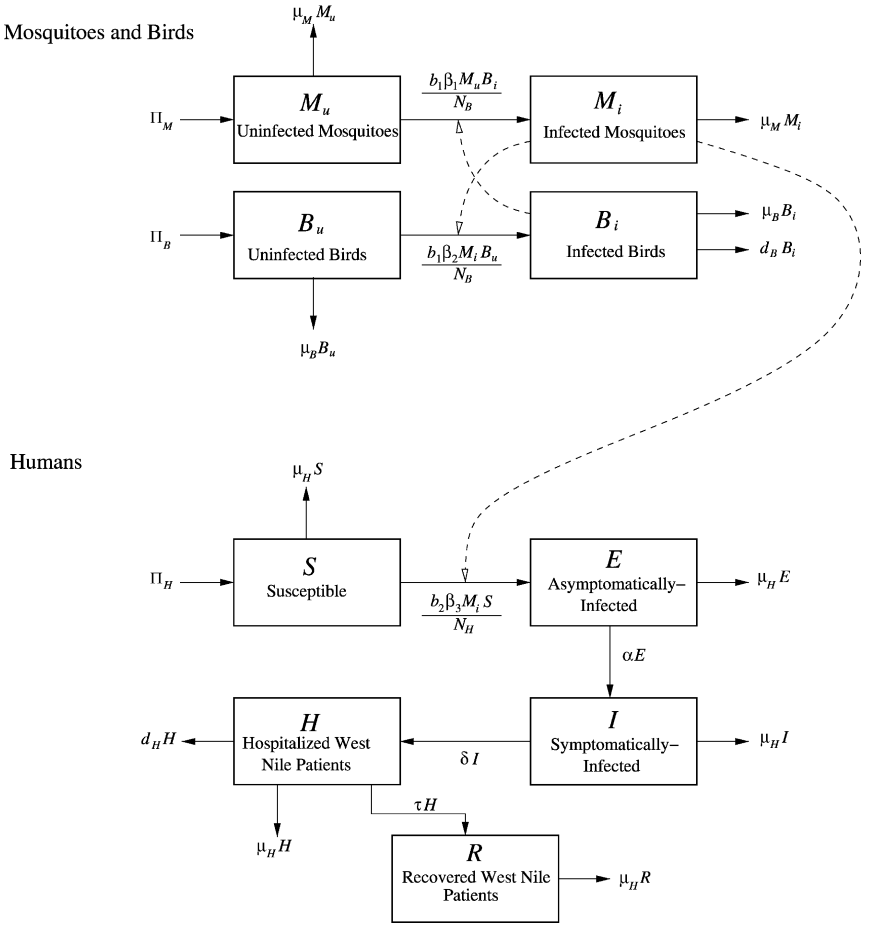

Fig. 1. Flow chart of the model.

3.1. *Uninfected and infected female mosquitoes*

The uninfected female mosquito population is increased via the birth or immigration of uninfected (susceptible) mosquitoes at a constant rate Π_M. It is diminished by infection, which may be acquired when uninfected mosquitoes feed from the blood of infected birds, and by natural death (due to their finite lifespan) at a rate μ_M. The flow can be represented using the differential equation

$$\frac{\mathrm{d}M_u}{\mathrm{d}t} = \Pi_M - \frac{b_1(N_M, N_B, N_H)\beta_1 M_u B_i}{N_B} - \mu_M M_u, \tag{1}$$

where $b_1(N_M, N_B, N_H)$ is the per capita biting rate of mosquitoes on the primary host (birds), β_1 is the probability of West Nile transmission from infected birds to uninfected mosquitoes. Since mosquitoes bite both birds and humans, it is plausible to assume

that the average number of mosquito bites received by birds and humans depends on the total sizes of the populations of mosquitoes, birds and humans in the community. Consequently, we define the mosquito biting rate to be a function of these total populations (that is, $b_1 = b_1(N_M, N_B, N_H)$). Here, cross-infection between birds and mosquitoes is modeled using mass action incidence (Brauer and Castillo-Chavez, 2000; Hethcote, 2000) normalized by total bird population (see also Wonham et al., 2004; Anderson and May, 1991, pp. 394–395).

The infected female mosquito population is generated via the infection of uninfected mosquitoes by infected birds and diminished by natural death (at rate μ_M). It is assumed that infected mosquitoes do not recover before they die naturally, and that these mosquitoes do not die of WNV. Furthermore, it is assumed that vertical transmission in mosquitoes is negligible (and therefore omitted). Thus,

$$\frac{\mathrm{d}M_i}{\mathrm{d}t} = \frac{b_1(N_M, N_B, N_H)\beta_1 M_u B_i}{N_B} - \mu_M M_i. \tag{2}$$

3.2. Uninfected and infected birds

The population of uninfected birds is increased via the recruitment of uninfected birds (either by birth or immigration) at a rate Π_B. It is reduced by infection acquired when uninfected birds are bitten by a WNV-carrying mosquito, and natural death (at a rate μ_B). Thus,

$$\frac{\mathrm{d}B_u}{\mathrm{d}t} = \Pi_B - \frac{b_1(N_M, N_B, N_H)\beta_2 M_i B_u}{N_B} - \mu_B B_u, \tag{3}$$

where β_2 is the probability of WNV transmission from mosquitoes to birds.

The population of infected birds is generated by infection of uninfected birds following contact with infected mosquitoes. It is diminished by natural death (at rate μ_B) and by WNV-induced death (at a rate d_B). This model assumes horizontal transmission from infected birds to susceptible birds is negligible (Langevin et al., 2001; MClean et al., 2001; Nasci et al., 2001; Turell et al., 2001; Wonham et al., 2004). This gives

$$\frac{\mathrm{d}B_i}{\mathrm{d}t} = \frac{b_1(N_M, N_B, N_H)\beta_2 M_i B_u}{N_B} - \mu_B B_i - d_B B_i. \tag{4}$$

3.3. Susceptible and infected humans

The population of susceptible humans is increased via recruitment of humans (by birth or immigration) into the community at a constant rate Π_H. It is decreased infection (acquired via contact with infected mosquitoes) and by natural death (at a rate μ_H). This gives

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \Pi_H - \frac{b_2(N_M, N_B, N_H)\beta_3 M_i S}{N_H} - \mu_H S, \tag{5}$$

where $b_2(N_M, N_B, N_H)$ is the per capita rate of biting of humans by mosquitoes and β_3 is the probability of WNV transmission from mosquitoes to humans. Here, it is assumed that new human infections are acquired at a rate that depends on the average number of

mosquito bites per unit time and on the transmission probability normalized by total human population (see also Anderson and May, 1991, pp. 394–395).

It is assumed that all newly WNV-infected humans are in the asymptomatic phase. The population of asymptotically infected humans is decreased due to natural death (at rate μ_H) and development of symptoms (at a rate α). Thus,

$$\frac{\mathrm{d}E}{\mathrm{d}t} = \frac{b_2(N_M, N_B, N_H)\beta_3 M_i S}{N_H} - \mu_H E - \alpha E. \tag{6}$$

Asymptomatically infected individuals are assumed to develop symptoms (and move into the $I(t)$ population) following the typical 2–14 days of incubation (Campbell et al., 2002; Petersen et al., 2003). The symptomatic population is decreased by natural death (at rate μ_H) and hospitalization (at a rate δ). This gives

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \alpha E - \mu_H I - \delta I. \tag{7}$$

The population of hospitalized individuals is generated via the hospitalization of symptomatic individuals (at rate δ). It is diminished by natural death (at rate μ_H), disease-induced death (at a rate d_H) and recovery (at a rate τ). The case-fatality rates range from 4% to 18% (Chowers et al., 2001; Nash et al., 2001; Pepperell et al., 2003; Petersen et al., 2003; Tsai et al., 1998) and between 15% to 29% in persons older than 70 years (Chowers et al., 2001; Petersen et al., 2003; Tsai et al., 1998). It should be noted that, although no specific anti-WNV treatment exists, these hospitalized individuals are offered supportive treatment (notably intravenous fluids). The above assumptions give

$$\frac{\mathrm{d}H}{\mathrm{d}t} = \delta I - \mu_H H - d_H H - \tau H. \tag{8}$$

Hospitalized individuals who recover move into the recovered population (at rate τ). The recovered population is diminished by natural death (at rate μ_H). It is assumed that WNV infection induces life-long immunity in humans, so that recovered humans do not acquire further WNV infection in the future (see Health Canada, 2003d; State of Wisconsin, 2003). This gives

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \tau H - \mu_H R. \tag{9}$$

3.4. Basic properties

It is easy to see from (1)–(9) that the equations for the rate of change of the total populations of mosquitoes, birds and humans are given by

$$\frac{\mathrm{d}N_M}{\mathrm{d}t} = \Pi_M - \mu_M N_M, \tag{10}$$

$$\frac{\mathrm{d}N_B}{\mathrm{d}t} = \Pi_B - \mu_B N_B - d_B B_i, \tag{11}$$

$$\frac{\mathrm{d}N_H}{\mathrm{d}t} = \Pi_H - \mu_H N_H - d_H H, \tag{12}$$

respectively. All parameters of the model are assumed to be non-negative, with the death rates μ_M, μ_B, μ_H, recruitment terms Π_M, Π_B, Π_H and transmission coefficients $\beta_1, \beta_2, \beta_3$ together with the biting rates $b_1(N_M, N_B, N_H)$ and $b_2(N_M, N_B, N_H)$ positive. Furthermore, each of the total subpopulations ($N_M(t)$, $N_B(t)$ and $N_H(t)$) is assumed to be positive for $t = 0$. Consider the region

$$\mathcal{D} = \{(M_u, M_i, B_u, B_i, S, E, I, H, R) \in \mathbb{R}_+^9 : N_M \leq \Pi_M/\mu_M, \\ N_B \leq \Pi_B/\mu_B, N_H \leq \Pi_H/\mu_H\}.$$

It can be shown that all solutions of the system starting in $\mathcal{D}$ remain in $\mathcal{D}$ for all $t \geq 0$. Thus, $\mathcal{D}$ is positively invariant and it is sufficient to consider solutions in $\mathcal{D}$. In this region, the usual existence, uniqueness and continuation results hold for the system.

4. Existence and stability of equilibria

4.1. Disease-free equilibrium (DFE)

4.1.1. Local stability

The model (1)–(9) has a DFE, obtained by setting the right hand sides of (1)–(9) to zero, given by

$$E_0 : (M_u^*, M_i^*, B_u^*, B_i^*, S^*, E^*, I^*, H^*, R^*) \\ = \left(\frac{\Pi_M}{\mu_M}, 0, \frac{\Pi_B}{\mu_B}, 0, \frac{\Pi_H}{\mu_H}, 0, 0, 0, 0\right). \tag{13}$$

It can be seen that E_0 attracts the region

$$\mathcal{D}_0 = \{(M_u, M_i, B_u, B_i, S, E, I, H, R) \in \mathcal{D} : M_i = B_i = E = I = H = R = 0\}.$$

The linear stability of E_0 is governed by the basic reproduction number $\mathcal{R}_0$ (Anderson and May, 1991; Brauer and Castillo-Chavez, 2000; Hethcote, 2000), which can be found from the next generation matrix for the system (1)–(9). Noting that the model has five infected populations, namely M_i, B_i, E, I and H, it follows that, using the notation of van den Driessche and Watmough (2002), the matrices F and V, for the new infection terms and the remaining transfer terms respectively, are given in partitioned form by

$$F = \begin{pmatrix} F_1 & 0 \\ F_2 & 0 \end{pmatrix}, \qquad V = \begin{pmatrix} V_1 & 0 \\ 0 & V_2 \end{pmatrix}$$

where

$$F_1 = \begin{pmatrix} 0 & \dfrac{b_1(N_B^*, N_M^*, N_H^*)\beta_1 N_M^*}{N_B^*} \\ b_1(N_B^*, N_M^*, N_H^*)\beta_2 & 0 \end{pmatrix}, \; V_1 = \begin{pmatrix} \mu_M & 0 \\ 0 & \mu_B + d_B \end{pmatrix}.$$

Here, F is a non-negative matrix of rank 2 and V is non-singular. It is easy to show that at steady state, the spectral radius (dominant eigenvalue) of the non-negative matrix FV^{-1}, denoted by $\rho(FV^{-1})$, is equal to $\rho(F_1V_1^{-1})$; hence, we do not need to explicitly give F_2

and V_2. Thus,

$$\mathcal{R}_0 = \rho(FV^{-1}) = \sqrt{\frac{b_1^2(N_M^*, N_B^*, N_H^*)\beta_1\beta_2\mu_B\Pi_M}{\mu_M^2(\mu_B + d_B)\Pi_B}}. \tag{14}$$

The quantity $\mathcal{R}_0$ is the basic reproduction number of infection. Theorem 2 of van den Driessche and Watmough (2002) gives the following stability result with $\mathcal{R}_0$ given by (14).

Lemma 1. *For system* (1)–(9)*, the disease-free equilibrium* E_0*, given by* (13)*, is locally asymptotically stable if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$.

It should be noted that the Jacobian for the populations M_i, B_i, E, I, H at E_0 is given by $F - V$, and that $\rho(FV^{-1}) < 1$ if and only if all eigenvalues of $F - V$ have negative real parts (i.e., $F - V$ is a stable matrix); see Theorem 2 in van den Driessche and Watmough (2002). Since the eigenvalues of $F - V$ are those of $F_1 - V_1$ and $-V_2$ (which has negative eigenvalues $-(\mu_H + \alpha)$, $-(\mu_H + \delta)$ and $-(\mu_H + d_H + \tau)$), it follows that $F_1 - V_1$ has all its eigenvalues with negative real parts if and only if $\mathcal{R}_0 < 1$.

Near the DFE, E_0, each infective bird produces $\frac{b_1(N_M^*, N_B^*, N_H^*)\beta_1\mu_B\Pi_M}{\mu_M(\mu_B+d_B)\Pi_B}$ new infected mosquitoes over its expected infectious period. Similarly, each infective mosquito produces $\frac{b_1(N_M^*, N_B^*, N_H^*)\beta_2}{\mu_M}$ new infected birds over its expected infectious period. The square root in $\mathcal{R}_0$ represents a geometric mean, and gives the expected number of new infections produced by a single infective (mosquito or bird) when introduced into a susceptible population. Note that since humans are dead-end hosts, the parameters associated with the human dynamics only contribute into $\mathcal{R}_0$ through the dependence of $b_1(N_M, N_B, N_H)$ on the total human population (N_H).

Biologically speaking, Lemma 1 implies that West Nile virus can be eradicated from the mosquito–bird–human populations (when $\mathcal{R}_0 < 1$) if the initial sizes of the subpopulations of the model are in the basin of attraction of E_0. To ensure that the virus eradication is independent of the initial sizes of the subpopulations of the model, it is imperative to show that the DFE is globally asymptotically stable as follows.

4.1.2. Global stability

In order to establish the global stability of the DFE, some assumptions are introduced for deriving the functional forms of $b_1(N_M, N_B, N_H)$ and $b_2(N_M, N_B, N_H)$. This is primarily based on the malaria model considered in Anderson and May (1991). It is assumed that each mosquito bites at a certain average rate, b, and that hosts are always sufficiently in abundance so that it is reasonable to assume that b is constant. The rate at which birds contract WNV infection is given by the product of the average biting rate (b), the number of mosquitoes that are currently infected (M_i), the probability that a bite will be infectious (β_2) and the fraction of bites that go to susceptible birds, which is given by the ratio of susceptible birds to the total number of hosts ($\frac{B_u}{N_B+N_H}$). Thus, the force of infection term in (3) is given by

$$\frac{b_1(N_M, N_B, N_H)\beta_2 M_i B_u}{N_B} = \frac{b\beta_2 B_u M_i}{N_H + N_B},$$

from which it follows that

$$b_1(N_M, N_B, N_H) = \frac{bN_B}{N_B + N_H}.$$

Similarly,

$$b_2(N_M, N_B, N_H) = \frac{bN_H}{N_B + N_H}.$$

From now on, it will be assumed that the biting rates b_1 and b_2 are constants. This is justified as follows. WNV-induced mortality in humans is negligible (Chowers et al., 2001), so d_H is assumed to be small. Recent studies (see, for instance, Komar et al., 2003) have shown that bird mortality is quite variable; it is not entirely clear how significant WNV-related mortality is in selected bird populations (whilst it is quite high in some species like corvid, it is minimal in others (Eidson et al., 2001)). Thus, in line with Wonham et al. (2004), we assume that WNV-induced mortality does not significantly impact bird populations, i.e., d_B is small.

It should be mentioned that, even with small WNV-induced mortality rates, variability in the total population of humans and birds is still possible due to transient relaxation to population carrying capacity. We are more interested in long term behaviour than transient dynamics. Using Eqs. (10) and (11), it can be shown that the total bird and human populations will, after some transition, lie in the intervals $[\Pi_B/(\mu_B + d_B), \Pi_B/\mu_B]$ and $[\Pi_H/(\mu_H + d_H), \Pi_H/\mu_H]$, respectively. Thus, their variations will be quite small if d_B and d_H are small. Numerical simulations of the model with small d_B and d_H and initial conditions close to the DFE confirm this. Thus, we choose to ignore the transient variation, and set

$$b_1(N_M, N_B, N_H) = \frac{bN_B^*}{N_B^* + N_H^*}, \qquad b_2(N_M, N_B, N_H) = \frac{bN_H^*}{N_B^* + N_H^*}.$$

It has been shown in Lemma 1 that the model has a locally asymptotically stable disease-free equilibrium (E_0) whenever $\mathcal{R}_0 < 1$. We claim the following global stability result.

Theorem 1. *If $\mathcal{R}_0 < 1$, then the disease-free equilibrium, E_0 given by (13), is globally asymptotically stable (GAS) in $\mathcal{D}$.*

Proof. It is clear from Appendix A that E_0 is the only equilibrium of the model whenever $\mathcal{R}_0 < 1$. Since all solutions remain in the positively invariant region $\mathcal{D}$, it follows that

$$M_u(t) \leq \frac{\Pi_M}{\mu_M}, \qquad B_u(t) \leq \frac{\Pi_B}{\mu_B} \tag{15}$$

for all $t \geq 0$. Since E_0 is locally asymptotically stable (Lemma 1), it suffices to show that any solution of (1)–(9) in the ω-limit set of an orbit in $\mathcal{D}$ converges to the disease-free equilibrium. Let (M_u, M_i, B_u, B_i) be the corresponding components of such a solution. It follows, using (11), that

$$N_B(t) = \mathrm{e}^{-\mu_B(t-s)} N_B(s) + \int_s^t \mathrm{e}^{-\mu_B(t-\theta)} [\Pi_B - d_B B_i(\theta)] \mathrm{d}\theta. \tag{16}$$

Setting $s \to -\infty$ in (16) gives

$$N_B(t) = \frac{\Pi_B}{\mu_B} - d_B X_B(t), \tag{17}$$

where

$$X_B(t) = \int_{-\infty}^{t} \mathrm{e}^{-\mu_B(t-\theta)} B_i(\theta)\mathrm{d}\theta. \tag{18}$$

Since $N_B(t) > 0$, it follows that $d_B X_B(t) < \Pi_B/\mu_B$ so that (from Eqs. (2), (4), (17) and (18))

$$\frac{\mathrm{d}X_B}{\mathrm{d}t} = -\mu_B X_B + B_i,$$

$$\frac{\mathrm{d}M_i}{\mathrm{d}t} \le -\mu_M M_i + \frac{b_1\beta_1\Pi_M}{\mu_M\left(\frac{\Pi_B}{\mu_B} - d_B X_B\right)} B_i,$$

$$\frac{\mathrm{d}B_i}{\mathrm{d}t} \le b_1\beta_2 M_i - (\mu_B + d_B) B_i.$$

Using a standard comparison argument (see Lakshmikantham and Leela, 1969), we only need to show that every solution of the system

$$\frac{\mathrm{d}X_B}{\mathrm{d}t} = -\mu_B X_B + B_i, \tag{19}$$

$$\frac{\mathrm{d}M_i}{\mathrm{d}t} = -\mu_M M_i + \frac{b_1\beta_1\Pi_M}{\mu_M\left(\frac{\Pi_B}{\mu_B} - d_B X_B\right)} B_i, \tag{20}$$

$$\frac{\mathrm{d}B_i}{\mathrm{d}t} = b_1\beta_2 M_i - (\mu_B + d_B) B_i, \tag{21}$$

converges to zero as $t \to \infty$.

The system (19)–(21) is cooperative and irreducible with a unique equilibrium in the closure of the open set

$$\tilde{\mathcal{D}} = \left\{(X_B, M_i, B_i) : 0 < X_B < \frac{\Pi_B}{\mu_B d_B}, M_i > 0, B_i > 0\right\}.$$

Thus, by Theorem 3.1 in Smith (1995, p. 18),

$$(X_B(t), M_i(t), B_i(t)) \to (0, 0, 0) \qquad \text{as} \qquad t \to \infty. \tag{22}$$

Since $(M_i(t), B_i(t)) \to (0, 0)$ as $t \to \infty$, it follows that $M_i(t) < \epsilon_1$ and $B_i(t) < \epsilon_2$ for large t and sufficiently small ϵ_1, ϵ_2. Thus, (1) and (3) can be expressed as

$$\frac{\mathrm{d}M_u(t)}{\mathrm{d}t} > \Pi_M - b_1\beta_1\epsilon_2\frac{\mu_B}{\Pi_B} M_u - \mu_M M_u, \tag{23}$$

$$\frac{\mathrm{d}B_u(t)}{\mathrm{d}t} > \Pi_B - b_1\beta_2\epsilon_1\frac{\mu_B}{\Pi_B} B_u - \mu_B B_u. \tag{24}$$

Then,

$$\liminf_{t\to\infty} M_u(t) \ge \frac{\Pi_M}{b_1\beta_1\epsilon_2\frac{\mu_B}{\Pi_B} + \mu_M}, \qquad \liminf_{t\to\infty} B_u(t) \ge \frac{\Pi_B}{b_1\beta_2\epsilon_1\frac{\mu_B}{\Pi_B} + \mu_B}. \tag{25}$$

Setting $\epsilon_1 \to 0$ and $\epsilon_2 \to 0$ gives

$$\liminf_{t\to\infty} M_u(t) \geq \frac{\Pi_M}{\mu_M} \qquad \text{and} \qquad \liminf_{t\to\infty} B_u(t) \geq \frac{\Pi_B}{\mu_B}. \tag{26}$$

Combining (15) and (26) shows that if $\mathcal{R}_0 < 1$,

$$\lim_{t\to\infty} M_u(t) = \frac{\Pi_M}{\mu_M} \qquad \text{and} \qquad \lim_{t\to\infty} B_u(t) = \frac{\Pi_B}{\mu_B}. \tag{27}$$

It follows from (27) and (22) that if $\mathcal{R}_0 < 1$, then $(M_u, M_i, B_u, B_i) \to (\frac{\Pi_M}{\mu_M}, 0, \frac{\Pi_B}{\mu_B}, 0)$ as $t \to \infty$. Using (22) in (5)–(9), it can be shown that $S \to \frac{\Pi_H}{\mu_H}$ and $(E, I, H, R) \to (0, 0, 0, 0)$ as $t \to \infty$. Thus, E_0 is globally asymptotically stable in $\mathcal{D}$ whenever $\mathcal{R}_0 < 1$. □

4.2. Endemic equilibria

For (1)–(9) with b_1, b_2 constants, the endemic equilibrium, in which infected compartments are non-zero, cannot easily be expressed in closed form. Details given in Appendix A lead to the following result.

Theorem 2. *The model* (1)–(9) *has a unique positive endemic equilibrium (denoted by* E_1*) if* $\mathcal{R}_0 > 1$ *and no positive endemic equilibrium if* $\mathcal{R}_0 < 1$.

Linearizing Eqs. (1)–(9) around E_1, and applying the Routh–Hurwitz criteria, gives the following result (see Appendix B for proof):

Lemma 2. *If* $\mu_B > d_B$, *then the unique endemic equilibrium* E_1 *of* (1)–(9) *is locally asymptotically stable whenever* $\mathcal{R}_0 > 1$.

Furthermore, the following global stability result can be established (see Appendix C for proof):

Theorem 3. *If* $d_B \in [0, d_0]$ *for some small* $d_0 \in \mathbb{R}_+$ *and* $\mathcal{R}_0 > 1$, *then every solution of* (1)–(9) *starting in* $\mathcal{D} \setminus \mathcal{D}_0$ *converges to* E_1 *as* $t \to \infty$.

5. Assessment of preventive strategies

The two main control strategies against the spread of WNV in humans are mosquito reduction strategies and personal protection against exposure to mosquitoes. Mosquito reduction strategies include the elimination of mosquito breeding sites (through improved drainage and prevention of standing water), larvaciding (killing mosquito larvae before they become adults) and adulticiding (killing adult mosquitoes via fogging) using appropriate biological agents (Nosal and Pellizzari, 2003). Personal protection, on the other hand, entails the use of clothing protection, insect repellents (containing DEET) and avoiding places where mosquitoes bite (Petersen and Marfin, 2002). In order to examine the effects of these two classes of anti-WNV strategies, the model (1)–(9) is simulated using the set of parameter values given in Table 1. It should be mentioned that some of these parameters (e.g. α, δ, τ) are estimated on the basis of some published data

Table 1
Model parameters and their interpretations

Parameter	Description	Estimated value
Π_M	Recruitment rate of uninfected mosquitoes (per day)	Variable
Π_B	Recruitment rate of susceptible birds (per day)	1000
Π_H	Recruitment rate of susceptible humans (per day)	30
$1/\mu_M$	Average lifespan of a mosquito (days)	Variable
$1/\mu_B$	Average lifespan of a bird (days)	1000
$1/\mu_H$	Average lifespan of a human (days)	$70 * 365$
q	Efficacy of the personal protection	$0 \leq q \leq 1$
c	Fraction of community complying with personal protection protocol	$0 \leq c \leq 1$
b_1	Rate of biting of birds by mosquitoes (per day)	0.09
b_2	Rate of biting of humans by mosquitoes (per day)	$0.09(1 - cq)$
β_1	Probability of transmission from bird to mosquito	0.16
β_2	Probability of transmission from mosquito to bird	0.88
β_3	Probability of transmission from mosquito to human	0.88
d_B	WNV-induced death rate for birds (fraction per day)	5×10^{-5}
d_H	WNV-induced death rate for humans (fraction per day)	5×10^{-7}
$1/\alpha$	Incubation period in humans (days)	14
δ	Hospitalization rate for humans (days)	1
$1/\tau$	Recovery rate for humans (days)	14

(such as Campbell et al., 2002; Petersen et al., 2003; Chowers et al., 2001; Pepperell et al., 2003) or knowledge of the approximate lifespan of birds and mosquitoes (thereby enabling the realistic estimation of μ_B, μ_M). The parameter μ_H is taken to be $1/(70 * 365)$ per day, in line with the 70-year average life expectancy of humans in Canada. Following Wonham et al. (2004) and the references therein, the transmission probabilities β_1 and β_2 are assigned the mean values of 0.16 and 0.88 respectively, and the rate of biting of birds by mosquitoes is set at $b_1 = 0.09$ per day. It is, therefore, plausible to set $\beta_3 = 0.88$ and $b_2 = 0.09$ per day. Owing to the absence of data, some of the other parameters associated with the model (1)–(9) (e.g. Π_B, d_B, Π_H and d_H) are estimated (see Table 1). The results obtained are reported in the following subsections.

5.1. *Effect of mosquito reduction strategies*

The effect of larvaciding is incorporated in our model by decreasing the recruiting parameter, Π_M, of uninfected mosquitoes. In other words, a reduction in Π_M serves to reduce the number of mosquitoes being born into the community, and thus can be used to investigate the effects of larvaciding on the epidemic. Similarly, the effects of fogging and other adulticiding methods for eliminating adult mosquitoes is modelled by decreasing $1/\mu_M$. Furthermore, since $\mathcal{R}_0$ is an increasing function of Π_M and a decreasing function of μ_M, the use of any preventive strategy that can reduce Π_M or increase μ_M results in a reduction of WNV infections in the mosquito–bird cycle and, consequently, in humans.

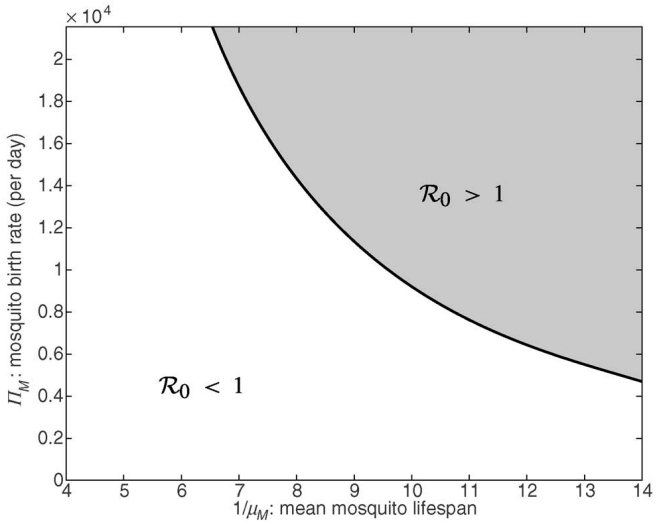

Fig. 2. Basic reproduction number of infections ($\mathcal{R}_0$) as a function of Π_M (representing the effect of larviciding) and mean mosquito lifespan, $1/\mu_M$ (representing the effect of adulticiding). All other parameters are as shown in Table 1.

Numerous simulations were carried out with varying values of Π_M and $1/\mu_M$, and the results obtained are depicted in Fig. 2. It is assumed, here, that the maximum lifespan of a mosquito is 14 days (that is, $1/\mu_M \leq 14$ days) and the maximum number of recruited mosquitoes is 2.2×10^4 per day (that is, $\Pi_M \leq 2.2 \times 10^4$). It is clear from Fig. 2 that low efficacies of larvaciding (corresponding to higher values of mosquito birth rate Π_M) and adulticiding (corresponding to higher mean values of mosquito lifespan $1/\mu_M$) make $\mathcal{R}_0 > 1$. The implication of this is that the disease will persist in the population. This is owing to the fact that the endemic equilibrium is globally stable for a small rate of WNV-induced avian mortality whenever $\mathcal{R}_0 > 1$ (Theorem 2). For instance, a mosquito control strategy that allows the daily birth of 10^4 mosquitoes and mosquito lifespan of at least ten days will fail to eradicate the disease in the mosquito–bird populations (since this strategy results in $\mathcal{R}_0 > 1$ in Fig. 2). On the other hand, if larvaciding can ensure that less than 4×10^3 mosquitoes are born daily, then the disease will be eradicated regardless of the presence or absence of other control measures (in this case, $\mathcal{R}_0 < 1$). Similarly, an adulticiding program that reduces the mean mosquito lifespan to at most six days is sufficient to singly eradicate WNV from the mosquito–bird community. Fig. 3 depicts a three-dimensional plot of the combined effects of larvaciding and adulticiding on the number of asymptomatically infected humans at steady state (E^{**}). As expected, this figure shows that increasing the efficacies of larvaciding and adulticiding results in a decrease in the WNV incidence in the human community (in comparison to the case where these control measures are non-existent). Overall, this study shows that a sufficiently effective mosquito reduction strategy, based on the use of larvaciding or adulticiding (or their combination), can lead to the eradication of WNV in the entire mosquito–bird–human community.

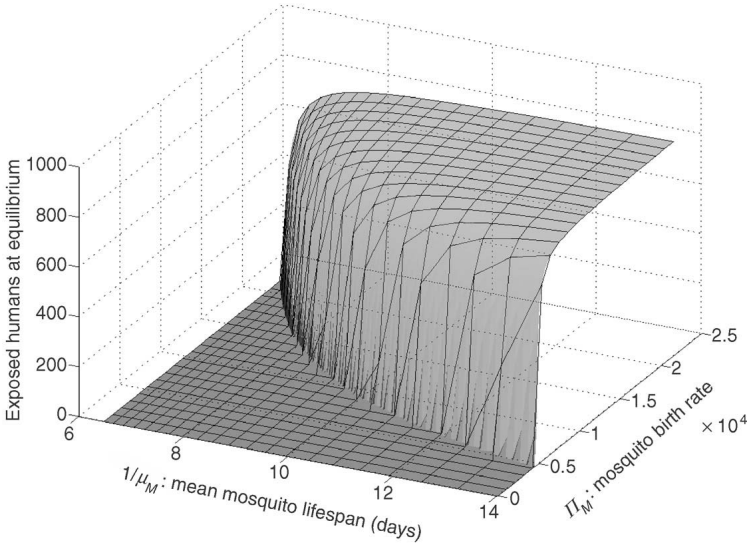

Fig. 3. Total number of asymptomatically infected humans at steady state (E^{**}) as a function of Π_M (representing the effects of larviciding) and mean mosquito lifespan, $1/\mu_M$ (representing the effects of fogging and other adult mosquito control strategies). All other parameters are as shown in Table 1.

5.2. *Effect of personal protection*

The aim here is to assess the impact of using personal protection on the control of WNV spread in humans. Since personal protection is aimed at minimizing exposure to mosquitoes, thereby reducing the risk of infection, it is deemed prudent to model the effect of personal protection by rescaling the transmission coefficient, $b_2\beta_3$, of WNV to humans (following mosquito bites) using $b_2\beta_3 \rightarrow b_2\beta_3(1 - cq)$, where $0 < q \leq 1$ is the efficacy of the personal protection strategy adopted, and $0 \leq c \leq 1$ is the fraction of the community employing it (compliance), where $c = 1$ means 100% compliance and $c = 0$ represents no compliance at all. The effect of personal protection is then assessed by simulating the model in the absence of any mosquito control strategy with varying values of c and q. Although no amount of personal protection can lead to WNV eradication in the mosquito–bird community, higher efficacies and compliance rates of personal protection can significantly reduce WNV incidence in humans.

5.3. *Adulticiding versus personal protection*

Despite the fact that personal protection strategies have no effect on the mosquito–bird amplifying WNV reservoir, they can serve to reduce the number of humans becoming infected. We, consequently, seek to compare the effects of adulticiding (fogging) and personal protection on the control of the spread of West Nile virus in humans. The results, depicted in Fig. 4, show a marked increase in the number of asymptotically infected humans at steady state with increasing non-compliance of personal protection (smaller

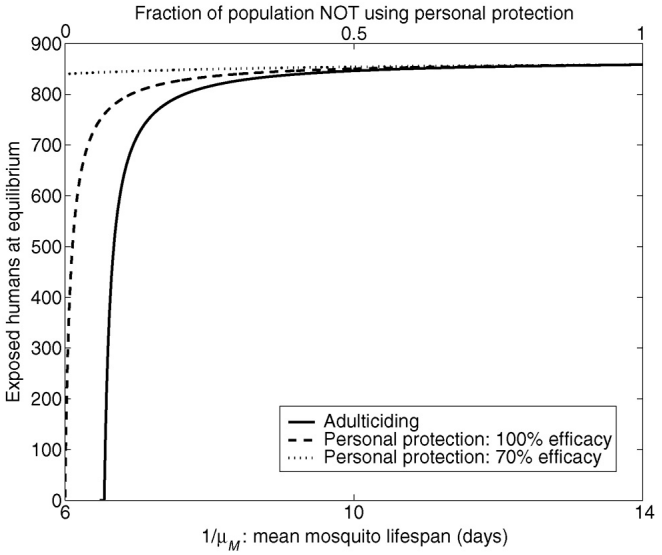

Fig. 4. Total number of exposed, infected and hospitalized humans at steady state ($E^{**}+I^{**}+H^{**}$) as a function of mean mosquito lifespan, $1/\mu_M$. This solid curve represents the effects of adulticiding, which is plotted on the bottom axis, in the absence of personal protection strategies ($c = q = 0$). The dotted and dashed curves represent the fraction of people not using personal protection measures ($1 - c$), as shown on the top axis, at $q = 0.7$ (70% efficacy) and $q = 1$ (100% efficacy) respectively with $1/\mu_M = 14$ days (which represents the absence of adulticiding). All other parameters are as shown in Table 1.

values of c) and mean mosquito lifespan. On the other hand, the use of personal protection with high efficacy reduces the number of cases in humans. For instance, if 90% of the human population use personal protection ($c = 0.9$), then the number of asymptomatically infected humans will be 845 if the personal protection is 70% effective and 792 if the efficacy is 100%. Although this clearly shows that the efficacy of personal protection is important, Fig. 4 also shows that in addition to high efficacy of personal protection strategies, high compliance is necessary for such strategies to make meaningful impact in combatting WNV in humans. Furthermore, this figure shows that adulticiding can be more effective in reducing the number of infections in humans than personal protection.

6. Summary and future refinements

This paper is based on the design and use of a new model for the transmission dynamics of WNV in a mosquito–bird–human community. The model, which incorporates essential elements of WNV transmission, enables the assessment of various anti-WNV preventive strategies. On the basis of the parameter values used in our simulations, our study shows that:

(i) In the absence of recruitment of infected birds or mosquitoes into the community, WNV can be eradicated from the entire mosquito–bird–human community using

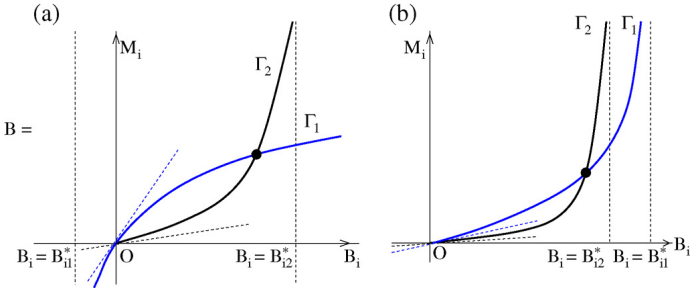

Fig. 5. Graphical representation of the unique endemic equilibrium on the M_i, B_i plane when $\mathcal{R}_0 > 1$. (a) $B^*_{i1} \leq 0$, (b) $B^*_{i1} > 0$.

sufficiently effective mosquito reduction strategies alone. This finding is consistent with the claim in (Wonham et al., 2004) that a 40–70% reduction in the initial population of mosquitoes would have prevented the WNV outbreak in New York in 2000.

(ii) On average, adulticiding is a more effective preventive strategy for controlling WNV spread in humans in comparison to the use of personal protection.

(iii) WNV incidence in humans increases with increasing mean mosquito lifespan, and if the mean mosquito lifespan is large enough, then personal protection is of little significance in combatting WNV spread in humans unless it has very high efficacy and compliance rate.

As more biological facts on WNV become known, our mathematical model should be refined. For instance, it had been thought that WNV was only transmitted through mosquito bites. However, studies from the U.S. Geological Survey (2003) and those in Komar et al. (2001b,a, 2003) show that WNV can be transmitted from bird to bird in a confined laboratory setting. Hence, it is worthwhile to investigate the effect of bird-to-bird transmission of WNV. One other effect is that freshly dead WNV-infected birds may still transmit the virus to mosquitoes that feed on them within the short window (on a timescale of a few hours). These factors could enhance WNV reservoirs in birds and the ability of amplification/transmission of the virus.

Our model considers WNV transmission among mosquitoes, birds and humans, by considering the dynamics in an isolated patch (one single mosquito–bird–human community); the effect of seasonality and migration of birds are not accounted for. These are important factors since, for non-tropical regions, the cold season signals the end of the epidemic season, while the heterogeneity and migration of birds from region to region plays a key role in the viral amplification process. It is feasible that infected birds can migrate from one region to another. This fact can be incorporated in our model by assuming that a proportion (p) of recruited birds (Π_B) are infected. That is, a proportion $\Pi_B(1-p)$ of recruited birds are susceptible whilst the remaining fraction ($\Pi_B p$) is infected. The consequence of this (recruitment of infected birds) is that the disease-free equilibrium (E_0) does not exist any longer. Thus, no amount of preventive measures can eradicate WNV from the mosquito–bird–human community (although these measures can lead to

significant reductions in WNV infections). The effect of seasonality can be incorporated by using time-dependent transmission coefficients.

One other way to extend our study is to relax our assumption of constant biting rates (b_1 and b_2), which relied on simulations around the disease-free equilibrium with small WNV-induced avian and human mortality levels, and carry out a rigorous mathematical analysis of the resulting model (with time varying biting rates b_1 and b_2 as defined in Section 4.1.2).

Overall, in addition to showing that WNV can be controlled in a human population using a mosquito reduction strategy alone, our study establishes the global dynamics of a relatively large non-linear dynamical system.

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Appendix A. Proof for the uniqueness of the endemic equilibrium

In this appendix, a proof for the existence of a unique endemic equilibrium for the model (1)–(9) (with b_1, b_2 constants) is given. First consider the equations for the mosquito–bird–mosquito cycle (1)–(4). Adding Eqs. (1) and (2) gives, at steady state,

$$M_u = \frac{\Pi_M}{\mu_M} - M_i. \tag{A.1}$$

Similarly, adding Eqs. (3) and (4) leads to

$$B_u = \frac{\Pi_B}{\mu_B} - \left(1 + \frac{d_B}{\mu_B}\right) B_i. \tag{A.2}$$

It is clear from (A.1) and (A.2) that $B_u \geq 0$ and $M_u \geq 0$ if $B_i \leq B_{i2}^* = \frac{\Pi_B}{\mu_B + d_B}$ and $M_i \leq M_i^* = \frac{\Pi_M}{\mu_M}$ respectively. Hence, to ensure that all the state variables are non-negative, we restrict to $(B_i, M_i) \in [0, B_{i2}^*] \times [0, M_i^*]$.

Substituting (A.1) into (2) with N_B from (11) gives the following curve:

$$M_i = \frac{\frac{b_1\beta_1\Pi_M}{\mu_M} B_i}{\frac{\Pi_B}{\mu_B}\mu_M + \left(b_1\beta_1 - \mu_M\frac{d_B}{\mu_B}\right) B_i} = \Gamma_1(B_i). \tag{A.3}$$

Clearly, $\Gamma_1(0) = 0$ and the slope of Γ_1 at $(M_i, B_i) = (0, 0)$ is $m_{\Gamma_1} = \frac{b_1\beta_1\mu_B\Pi_M}{\mu_M^2\Pi_B}$. Furthermore, from (A.3), if $\mu_M d_B \neq b_1\beta_1\mu_B$, Γ_1 has a vertical asymptote given by

$B_i = B_{i1}^*$, where $B_{i1}^* = \frac{\mu_M \Pi_B}{\mu_M d_B - b_1\beta_1\mu_B}$, and B_{i1}^* can be positive or negative (see Fig. 5). If $\mu_M d_B = b_1\beta_1\mu_B$, Γ_1 is reduced to a straight line through the origin with slope m_{Γ_1}, the case included in the scenario $B_{i1}^* < 0$.

Substituting (A.2) into (4) with N_B from (11) gives

$$M_i = \frac{(\Pi_B - d_B B_i)B_i}{b_1\beta_2\left(\frac{\Pi_B}{\mu_B+d_B} - B_i\right)} = \Gamma_2(B_i). \tag{A.4}$$

Note that Γ_2 has a vertical asymptote at $B_i = B_{i2}^*$. Although the curve Γ_2 has two branches, only the branch situated to the left of B_{i2}^* is of interest. Furthermore, the slope of Γ_2 at the origin is $m_{\Gamma_2} = \frac{\mu_B+d_B}{b_1\beta_2}$. For the cases $B_{i1}^* \le 0$ and $B_{i1}^* > 0$, it follows from Fig. 5(a) and (b) that a unique endemic equilibrium exists if and only if $m_{\Gamma_1} > m_{\Gamma_2}$. Hence, a unique endemic equilibrium exists if and only if $\mathcal{R}_0 > 1$.

To ensure that the unique intersection of the curves Γ_1 and Γ_2 leads to a positive equilibrium, we only need to verify $M_i \le M_i^*$. Clearly, since $B_i < B_{i2}^*$, it follows that $B_i < \frac{\Pi_B}{\mu_B+d_B} < \frac{\Pi_B}{d_B}$. Therefore it follows from (A.3) that

$$M_i = \frac{b_1\beta_1\frac{\Pi_M}{\mu_M}B_i}{b_1\beta_1 B_i + \frac{\mu_M d_B}{\mu_B}\left(\frac{\Pi_B}{d_B} - B_i\right)} < \frac{b_1\beta_1\frac{\Pi_M}{\mu_M}B_i}{b_1\beta_1 B_i} = \frac{\Pi_M}{\mu_M}. \tag{A.5}$$

Thus, the subsystem (1)–(4) has a unique endemic equilibrium with $B_i = B_i^{**} \in (0, B_{i2}^*)$. This value can now be obtained in closed form as follows. Equating the right hand sides of (A.3) and (A.4) and simplifying gives (for $B_i \neq 0$) the following quadratic:

$$a_2(B_i^{**})^2 + a_1 B_i^{**} + a_0 = 0, \tag{A.6}$$

where

$$a_2 = \frac{d_B(\mu_M d_B - b_1\beta_1\mu_B)}{b_1\beta_2\mu_B}, \tag{A.7}$$

$$a_1 = \frac{b_1\beta_1\Pi_M}{\mu_M} - \frac{(2\mu_M d_B - b_1\beta_1\mu_B)}{b_1\beta_2\mu_B}\Pi_B, \tag{A.8}$$

$$a_0 = \frac{\mu_M \Pi_B^2(1-\mathcal{R}_0^2)}{b_1\beta_2\mu_B}. \tag{A.9}$$

Solving for B_i^{**} from (A.6) enables the other variables (M_i^{**}, B_u^{**} and M_u^{**}) to be computed from (A.3), (A.2) and (A.1), respectively. From (5)–(9) at an equilibrium, the variables S, I, H, and R (and thus N_H) can be expressed in terms of the variable E. Substituting these into (2) and using the unique value of M_i^{**}, results in a quadratic for E, which has exactly one root E^{**} in the biologically meaningful range $0 < E^{**} < \Pi_H/(\mu_H+\alpha)$. This gives a unique value for each of the other human components, giving a unique endemic equilibrium for the full system:

$$E_1 := (M_u^{**}, M_i^{**}, B_u^{**}, B_i^{**}, S^{**}, E^{**}, I^{**}, H^{**}, R^{**}).$$

Appendix B. Proof for the local stability of the endemic equilibrium

Since humans do not feed back into the mosquito–bird cycle, the Jacobian of the whole system is reducible, with eigenvalues given by those of the subsystem (1)–(4) together with those of the human subsystem (5)–(9). Evaluating the Jacobian of (1)–(4) at E_1 gives

$$J = \begin{bmatrix} -\frac{b_1\beta_1 B_i^{**}}{B_i^{**}+B_u^{**}} - \mu_M & 0 & \frac{b_1\beta_1 M_u^{**} B_i^{**}}{(B_i^{**}+B_u^{**})^2} & \frac{b_1\beta_1 M_u^{**} B_i^{**}}{(B_i^{**}+B_u^{**})^2} - \frac{b_1\beta_1 M_u^{**}}{B_i^{**}+B_u^{**}} \\ \frac{b_1\beta_1 B_i^{**}}{B_i^{**}+B_u^{**}} & -\mu_M & -\frac{b_1\beta_1 M_u^{**} B_i^{**}}{(B_i^{**}+B_u^{**})^2} & -\frac{b_1\beta_1 M_u^{**} B_i^{**}}{(B_i^{**}+B_u^{**})^2} + \frac{b_1\beta_1 M_u^{**}}{B_i^{**}+B_u^{**}} \\ 0 & -\frac{b_1\beta_2 B_u^{**}}{B_i^{**}+B_u^{**}} & \frac{b_1\beta_2 M_i^{**} B_u^{**}}{(B_i^{**}+B_u^{**})^2} - \frac{b_1\beta_2 M_i^{**}}{B_i^{**}+B_u^{**}} - \mu_B & \frac{b_1\beta_2 M_i^{**} B_u^{**}}{(B_i^{**}+B_u^{**})^2} \\ 0 & \frac{b_1\beta_2 B_u^{**}}{B_i^{**}+B_u^{**}} & -\frac{b_1\beta_2 M_i^{**} B_u^{**}}{(B_i^{**}+B_u^{**})^2} + \frac{b_1\beta_2 M_i^{**}}{B_i^{**}+B_u^{**}} & -\frac{b_1\beta_2 M_i^{**} B_u^{**}}{(B_i^{**}+B_u^{**})^2} - \mu_B - d_B \end{bmatrix},$$

from which it follows that the eigenvalues of J are $-\mu_M$ and the roots of

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$$

where

$$a_1 = \frac{b_1\beta_1 B_i^{**} + \mu_M B_i^{**} + 2\mu_B B_i^{**} + d_B B_i^{**} + b_1\beta_2 M_i^{**} + d_B B_u^{**} + 2\mu_B B_u^{**} + \mu_M B_u^{**}}{B_i^{**}+B_u^{**}}$$

$$\begin{aligned} a_2 = {} & \frac{1}{(B_i^{**}+B_u^{**})^2}[(\mu_M d_B + b_1\beta_1 d_B + 2b_1\beta_1\mu_B + \mu_B d_B + 2\mu_B\mu_M + \mu_B^2) \\ & \times (B_i^{**})^2 + (4\mu_B\mu_M + 2\mu_B^2 + 2\mu_B d_B + b_1\beta_1 d_B + 2b_1\beta_1\mu_B + 2\mu_M d_B) \\ & \times B_u^{**} B_i^{**} + b_1\beta_2(b_1\beta_1 + \mu_B + \mu_M + d_B) M_i^{**} B_i^{**} + (\mu_M d_B + 2\mu_B\mu_M \\ & + \mu_B^2 + \mu_B d_B)(B_u^{**})^2 + (-b^2\beta_2\beta_1 M_u^{**} + b_1\beta_2(\mu_B + \mu_M) M_i^{**}) B_u^{**}] \end{aligned}$$

$$\begin{aligned} a_3 = {} & \frac{1}{(B_i^{**}+B_u^{**})^3}[\beta_1\beta_2(d_B B_i^{**} + \mu_B B_i^{**} + \mu_B B_u^{**})(M_i^{**} B_i^{**} - B_u^{**} M_u^{**}) b_1^2 \\ & + ((B_i^{**}+B_u^{**})\mu_M\beta_2(d_B B_i^{**} + \mu_B B_i^{**} + \mu_B B_u^{**}))b_1 M_i^{**} \\ & + (B_i^{**}+B_u^{**})^2\beta_1 B_i^{**}\mu_B(\mu_B + d_B)b_1 + \mu_M\mu_B(B_i^{**}+B_u^{**})^3(\mu_B + d_B)]. \end{aligned}$$

Clearly, $a_1 > 0$. The next task is to determine the signs of a_2 and a_3. It is easy to see that Eq. (14) can be rewritten in terms of β_2 as

$$\beta_2 = \frac{\mathcal{R}_0^2\mu_M^2(\mu_B + d_B)\Pi_B}{\Pi_M\mu_B b^2\beta_1}. \tag{B.1}$$

Solving the quadratic equation (A.6) for $\mathcal{R}_0^2$ in terms of B_i^{**} gives

$$\mathcal{R}_0^2 = \frac{\mu_M(\Pi_B - d_b B_i^{**})^2 + \mu_B b_1\beta_1 B_i^{**}(\Pi_B - d_B B_i^{**})}{\mu_M\Pi_B(\Pi_B - (\mu_B + d_B)B_i^{**})}. \tag{B.2}$$

Substituting the expressions for the model variables ((A.1)–(A.3)) at the endemic equilibrium and (B.1) and (B.2) into the expressions for a_2 and a_3 and collecting terms

in b_1 and β_1 respectively gives

$$a_2 = \frac{b_1 B_i^{**}\beta_1\mu_B[(\mu_B+d_B)(\Pi_B-(\mu_B+d_B)B_i^{**})+\Pi_B\mu_B]}{(\Pi_B-d_B B_i^{**})(\Pi_B-(\mu_B+d_B)B_i^{**})} + \frac{\mu_B[\Pi_B(\Pi_B-d_B B_i^{**})\mu_M+(\mu_B+d_B)((\Pi_B-d_B B_i^{**})^2+(B_i^{**})^2\mu_B d_B)]}{(\Pi_B-d_B B_i^{**})(\Pi_B-(\mu_B+d_B)B_i^{**})}$$

$$a_3 = \frac{b_1\beta_1\mu_B^2(\mu_B+d_B)B_i^{**}((\Pi_B-d_B(B_i^{**})^2+(B_i^{**})^2\mu_B d_B))}{(\Pi_B-d_B B_i^{**})^2(\Pi_B-(\mu_B+d_B)B_i^{**})} + \frac{(\Pi_B(\mu_B-d_B)+d_B^2 B_i^{**}+B_i^{**}\mu_B d_B)\mu_M\mu_B(\mu_B+d_B)B_i^{**}}{(\Pi_B-(\mu_B+d_B)B_i^{**})(\Pi_B-d_B B_i^{**})}.$$

It is easy to see that a_2 and a_3 are both positive if

$$B_i^{**} < \frac{\Pi_B}{(\mu_B+d_B)} < \frac{\Pi_B}{d_B}, \qquad \mu_B > d_B. \tag{B.3}$$

The first of these conditions is required for the positivity of B_u. The second is biologically reasonable.

The remaining task associated with the Routh–Hurwitz criteria is to show that $a_1a_2 - a_3 > 0$. It can be shown, following extensive manipulations, that $a_1a_2 - a_3$ can be written in terms of the following quadratic:

$$D_2 b_1^2 + D_1 b_1 + D_0, \tag{B.4}$$

with

$$D_2 = \frac{\left((\Pi_B-(\mu_B+d_B)B_i^{**})(d_B+\mu_B)+\Pi_B\mu_B\right)\beta_1^2(B_i^{**})^2\mu_B^2}{(\Pi_B-d_B B_i^{**})^2(\Pi_B-(\mu_B+d_B)B_i^{**})}$$

$$D_1 = \frac{\mu_B\beta_1 B_i^{**}\mu_M\left((d_B+\mu_B)\left(\Pi_B-(d_B+\mu_B)B_i^{**}\right)+2\,\Pi_B\mu_B\right)}{\left(\Pi_B-d_B B_i^{**}\right)\left(\Pi_B-(d_B+\mu_B)B_i\right)} + \frac{\mu_B\beta_1 B_i^{**}\left((d_B+\mu_B)\left(\Pi_B-(d_B+\mu_B)B_i^{**}\right)+\Pi_B\mu_B\right)^2}{\left(\Pi_B-d_B B_i^{**}\right)\left(\Pi_B-(d_B+\mu_B)B_i^{**}\right)^2}$$

$$D_0 = \frac{\mu_M^2\mu_B\Pi_B}{\Pi_B-(d_B+\mu_B)B_i^{**}}\mu_M^2 + \frac{\left((\mu_B+2d_B)\left(\Pi_B-(\mu_B+d_B)B_i^{**}\right)^2+2\mu_B\Pi_B\left(\Pi_B-(\mu_B+d_B)B_i^{**}\right)+\Pi_B\mu_B^2 B_i^{**}\right)\Pi_B\mu_B}{\left(\Pi_B-d_B B_i^{**}\right)\left(\Pi_B-(\mu_B+d_B)B_i^{**}\right)^2} \times\mu_M\frac{\mu_B(d_B+\mu_B)\left((d_B+\mu_B)\left(\Pi_B-(d_B+\mu_B)B_i^{**}\right)+\Pi_B\mu_B\right)\left((\Pi_B-d_B B_i)^2+B_i^{**2}\mu_B d_B\right)}{\left(\Pi_B-d_B B_i^{**}\right)\left(\Pi_B-(d_B+\mu_B)B_i^{**}\right)^2}.$$

Eq. (B.4) is clearly positive provided the inequalities in (B.3) are satisfied. Thus, $a_1a_2 - a_3 > 0$ provided (B.3) hold.

For the human subsystem, taking variables S, I, H, R and N_H, the eigenvalues are $-\mu_H$ and the roots of the polynomial

$$(\lambda+\mu_H+d_H+\tau)(\lambda+\mu_H+\delta)(\lambda+\mu_H+\alpha)(\lambda+\mu_H+b_2\beta_3 M_i^{**}/N_H^{**}) - d_H\delta\alpha b_2\beta_3 M_i^{**}S^{**}/N_H^{**} = 0.$$

The constant term in the above polynomial is positive, and the Routh–Hurwitz conditions show that all eigenvalues have negative real parts, completing the proof that E_1 is locally asymptotically stable provided that $\mu_B > d_B$ and $\mathcal{R}_0 > 1$.

Appendix C. Proof for the global stability of the endemic equilibrium

It is easy to show that each of the variables $M_u(t)$, $M_i(t)$, $B_u(t)$ and $B_i(t)$ remains positive for all $t > 0$ as long as $0 \leq N_M(0) \leq \frac{\Pi_M}{\mu_M}$, $0 \leq N_B(0) \leq \frac{\Pi_B}{\mu_B}$ and $(M_i(0), B_i(0)) \neq 0$.

Firstly, consider the case with $d_B = 0$. Eqs. (10) and (11) now become

$$\frac{\mathrm{d}N_M(t)}{\mathrm{d}t} = \Pi_M - \mu_M N_M,$$
$$\frac{\mathrm{d}N_B(t)}{\mathrm{d}t} = \Pi_B - \mu_B N_B.$$

We want to show that a solution in the ω-limit set of a given trajectory of (1)–(4) converges to $\tilde{E}_1$, the component of E_1 associated with the subsystem (1)–(4) with $d_B = 0$, as $t \to \infty$. Let $X(t) = (M_u(t), M_i(t), B_u(t), B_i(t))$ be such a solution. Then it is defined for all $t \in \mathbb{R}$ and is bounded for all $t \in \mathbb{R}$. Integrating the above equations from s to t and letting $s \to -\infty$ gives

$$M_i = \frac{\Pi_M}{\mu_M} - M_u \qquad \text{and} \qquad B_i = \frac{\Pi_B}{\mu_B} - B_u. \tag{C.1}$$

We emphasize that (C.1) holds only for the solutions that are defined and bounded for all $t \in \mathbb{R}$. In particular, (C.1) holds for solutions that pass through the ω-limit set of every given bounded solution of (1)–(4). For these solutions that are defined and bounded for all $t \in \mathbb{R}$, we can then substitute (C.1) into (2) and (4) to obtain

$$\begin{cases} \dfrac{\mathrm{d}M_i(t)}{\mathrm{d}t} = b_1\beta_1\dfrac{\mu_B}{\Pi_B}\left(\dfrac{\Pi_M}{\mu_M} - M_i\right)B_i - \mu_M M_i, \\ \dfrac{\mathrm{d}B_i(t)}{\mathrm{d}t} = b_1\beta_2\dfrac{\mu_B}{\Pi_B}\left(\dfrac{\Pi_B}{\mu_B} - B_i\right)M_i - \mu_B B_i. \end{cases} \tag{C.2}$$

$\Gamma = \{(M_i, B_i) : 0 \leq M_i \leq \frac{\Pi_M}{\mu_M}, 0 \leq B_i \leq \frac{\Pi_B}{\mu_B}\}$. Inside this region, the system (C.2) generates a strongly order-preserving flow and has two equilibria, namely (0, 0) and $(M_i^{**}, B_i^{**})|_{d_B=0}$. Since (0, 0) is unstable and $(M_i^{**}, B_i^{**})|_{d_B=0}$ is locally asymptotically stable, the theory of monotone dynamical systems (see Smith, 1995, Theorem 2.2, p. 17) then ensures that $M_i(t) \to M_i^{**}|_{d_B=0}$ and $B_i(t) \to B_i^{**}|_{d_B=0}$ as $t \to \infty$ provided $(M_i(0), B_i(0)) \neq (0, 0)$.

We now claim that if $d_B = 0$, then it is impossible for $X(t) \to \tilde{E}_0$ (where $\tilde{E}_0$ represents the components of E_0 associated with (1)–(4) with $d_B = 0$) as $t \to \infty$. If $X(t) \to \tilde{E}_0$, then for small $\epsilon > 0$, there exists $T > 0$ such that

$$\frac{\Pi_M}{\mu_M} - \epsilon \leq M_u(t) \leq \frac{\Pi_M}{\mu_M}$$

$$\frac{\Pi_B}{\mu_B} - \epsilon \leq B_u(t) \leq \frac{\Pi_B}{\mu_B}$$

for all $t \geq T$. Therefore, Eqs. (2) and (4) can now be expressed in the matrix–vector inequality form:

$$\begin{bmatrix} \frac{dM_i(t)}{dt} \\ \frac{dB_i(t)}{dt} \end{bmatrix} \geq Q \begin{bmatrix} M_i \\ B_i \end{bmatrix} \text{ with } Q = \begin{pmatrix} -\mu_M & \frac{b_1\beta_1\mu_B}{\Pi_B}\left(\frac{\Pi_M}{\mu_M} - \epsilon\right) \\ \frac{b_1\beta_2\mu_B}{\Pi_B}\left(\frac{\Pi_B}{\mu_B} - \epsilon\right) & -\mu_B \end{pmatrix}.$$

Since $\mathcal{R}_0 > 1$ (needed for the existence and local stability of E_1), it follows that for sufficiently small $\epsilon > 0$, the matrix Q has a positive real eigenvalue, say α, with associated eigenvector $\mathbf{u} \in \mathbb{R}^2$ that has both components positive. Since $M_i(T) > 0$ and $B_i(T) > 0$, there exists $\epsilon > 0$ small so that $M_i(T) > \epsilon u_1$ and $B_i(T) > \epsilon u_2$. Thus, a standard comparison argument (Lakshmikantham and Leela, 1969) leads to

$$(M_i(t), B_i(t))^T \geq \epsilon e^{\alpha(t-T)}(u_1, u_2)^T \to \infty. \tag{C.3}$$

Clearly, the inequality (C.3) contradicts $(M_i(t), B_i(t)) \to 0$ as $t \to \infty$. Thus, $X(t)$ cannot approach $\tilde{E}_0$ as $t \to \infty$ for $d_B = 0$.

We can now show that if $d_B = 0$, then $X(t) \to \tilde{E}_1$ as $t \to \infty$ if $0 \leq N_M(0) \leq \frac{\Pi_M}{\mu_M}$, $0 \leq N_B(0) \leq \frac{\Pi_B}{\mu_B}$ and $M_i(0) + B_i(0) \neq 0$. This is because the above discussions show that there must be a full trajectory, in the ω-limit set of $X(t)$, that is not the equilibrium $\tilde{E}_0$ and must converge to $\tilde{E}_1$ as $t \to \infty$. Note that $\tilde{E}_1$ is asymptotically stable and the above trajectory must enter the basin of attraction of $\tilde{E}_1$. Using the continuity of solutions with respect to initial values, we conclude that $X(t)$ must enter the domain of attraction of $\tilde{E}_1$ and hence $X(t)$ converges to $\tilde{E}_1$ as $t \to \infty$.

Now consider the general case with $d_B > 0$ but small. For this case, the analysis will be based on using a regular perturbation argument together with Liapunov function theory as follows. Let $X(t)$ be as above, namely a solution of (1)–(4) with $d_B = 0$, and let $Y(t) = (M_u(t), M_i(t), B_u(t), B_i(t))$ be a solution of (1)–(4) with $d_B > 0$ and $(M_i(0), B_i(0)) \neq 0$. Furthermore, let $X(0) = Y(0)$, let $F(X)$ denote the vector field of (1)–(4) with $d_B = 0$ and $g(M_u, M_i, B_u, B_i) = (0, 0, 0, B_i)$. Let $J(X)$ be the Jacobian of F evaluated at X. Note that $F(X)$ and $J(X)$ are bounded in the region $0 \leq N_M \leq \Pi_M/\mu_M$ and $0 \leq N_B \leq \Pi_B/\mu_B$. Then,

$$\frac{dX}{dt} = F(X),$$
$$\frac{dY}{dt} = F(Y) - d_B g(Y).$$

We want to show that $|X(t) - Y(t)|$ can be made arbitrarily small uniformly for all $t \geq 0$ if d_B is small.

Let $Y = X + d_B Z$ with $Z(0) = 0$ and $d_B > 0$. Then,

$$\begin{aligned} \frac{dX(t)}{dt} + d_B\frac{dZ(t)}{dt} &= F(X + d_B Z) - d_B g(X + d_B Z) \\ &= F(X) + \int_0^1 J(X + \theta d_B Z) d_B Z \, d\theta - d_B g(X + d_B Z). \end{aligned} \tag{C.4}$$

So, since $d_B > 0$,

$$\frac{\mathrm{d}Z(t)}{\mathrm{d}t} = \int_0^1 J(X + \theta d_B Z)Z\mathrm{d}\theta - g(X + d_B Z). \tag{C.5}$$

Thus,

$$\begin{aligned}\frac{\mathrm{d}Z(t)}{\mathrm{d}t} &= \int_0^1 [J(X) + J(X + \theta d_B Z) - J(X)]Z\mathrm{d}\theta - g(X + d_B Z)\\ &= J(X)Z + \int_0^1 [J(X + \theta d_B Z) - J(X)]Z\mathrm{d}\theta - g(X + d_B Z)\\ &= J(\tilde{E}_1)Z + [J(X) - J(\tilde{E}_1)]Z\\ &\quad + \int_0^1 [J(X + \theta d_B Z) - J(X)]Z\mathrm{d}\theta - g(X + d_B Z).\end{aligned} \tag{C.6}$$

Since $\tilde{E}_1$ is asymptotically stable for the system (1)–(4), there exists a positive definite matrix C such that

$$CJ(\tilde{E}_1) + (J(\tilde{E}_1))^T C = -I_{4\times 4}. \tag{C.7}$$

Therefore, $L(Z) = Z^T C Z$ is a Liapunov function for the linearized system of (1)–(4) at $\tilde{E}_1$ when $d_B = 0$. Choose constants $\alpha_2 \geq \alpha_1 > 0$ so that $\alpha_1 Z^T Z \leq L(Z) \leq \alpha_2 Z^T Z$. Note that $X(t) \to \tilde{E}_1$ as $t \to \infty$, and that $J(X)$ is uniformly Lipschitz and $g(X)$ is bounded in the region where $0 \leq N_M \leq \Pi_M/\mu_M$ and $0 \leq N_B \leq \Pi_B/\mu_B$. Therefore, there exist $T \geq 0$ and constants $k_1, k_2, d_0 > 0$ so that for $t \geq T$ and for all $d_B \in [0, d_0]$,

$$\begin{aligned}\frac{\mathrm{d}L(Z(t))}{\mathrm{d}t} &\leq -\frac{1}{2}Z^T Z + d_B k_1 Z^T Z + k_2\sqrt{Z^T Z}\\ &\leq -\frac{1}{2}Z^T Z + \frac{d_B k_1}{\alpha_1}L(Z) + \frac{k_2}{\sqrt{\alpha_1}}\sqrt{L(Z)}\\ &\leq -\left(\frac{1}{2\alpha_2} - \frac{d_B k_1}{\alpha_1}\right)L(Z) + \frac{k_2}{\sqrt{\alpha_1}}\sqrt{L(Z)}\\ &= \sqrt{L(Z)}\left[-\left(\frac{1}{2\alpha_2} - \frac{d_B k_1}{\alpha_1}\right)\sqrt{L(Z)} + \frac{k_2}{\sqrt{\alpha_1}}\right].\end{aligned} \tag{C.8}$$

Thus,

$$L(Z(t)) \leq \max\left\{L(Z(T)), \left[\frac{k_2}{\sqrt{\alpha_1}\left(\frac{1}{2\alpha_2} - \frac{d_B k_1}{\alpha_1}\right)}\right]^2\right\}. \tag{C.9}$$

It is easy to show from (C.5) that $L(Z(T))$ is uniformly bounded for all small $d_B > 0$. Therefore, if d_0 is small, then $\sup_{t\geq 0} Z(t)$ is uniformly bounded for all $d_B \in [0, d_0]$.

We now complete the proof for the subsystem (1)–(4) by first noting that if we write $\mathcal{R}_0 = \mathcal{R}_0(d_B)$, then $\mathcal{R}_0(d_B) > 1$ for small d_B if and only if $\mathcal{R}_0(0) > 1$ (this follows since $\mathcal{R}_0$ is a decreasing function of d_B). Using the standard argument for linearized stability (see Verhulst, 1990, pp. 88–90), if d_B is small, then there exists a $\delta_0 > 0$ (independent of $d_B \in [0, d_0]$) so that if $|Y(0) - \hat{E}_1| < \delta_0$, where $\hat{E}_1$ is the corresponding component

of E_1, then $Y(t) \to \hat{E}_1$ as $t \to \infty$. Recall if $M_i(0) + B_i(0) \neq 0$, then $X(t) \to \tilde{E}_1$ as $t \to \infty$. Let $T^* > 0$ be given so that $|X(T^*) - \tilde{E}_1| < \frac{1}{2}\delta_0$, and choose $d_0 > 0$ so small that $d_B \sup_{t\geq 0} |Z(t)| < \frac{1}{4}\delta_0$ and $|\hat{E}_1 - \tilde{E}_1| < \frac{1}{4}\delta_0$ if $d_B \in [0, d_0]$. Then

$$|Y(T^*) - \hat{E}_1| \leq |Y(T^*) - X(T^*)| + |X(T^*) - \tilde{E}_1| + |\hat{E}_1 - \tilde{E}_1| < \delta_0.$$

Hence, for the subsystem (1)–(4), $Y(t) \to \hat{E}_1$ as $t \to \infty$.

To establish global stability of E_1, we need to also consider the human components of E_1. We provide a technique for doing so as follows. Using the change of variables $X_H = N_H + \frac{d_H}{\tau} R$, $X_1 = S + E$ and $X_2 = S + E + I = X_1 + I$, Eqs. (5)–(9) with (12) can now be written as

$$\frac{\mathrm{d}X_H}{\mathrm{d}t} = \Pi_H - \mu_H X_H \tag{C.10}$$

$$\frac{\mathrm{d}X_1}{\mathrm{d}t} = \Pi_H - (\mu_H + \alpha)X_1 + \alpha S \tag{C.11}$$

$$\frac{\mathrm{d}X_2}{\mathrm{d}t} = \Pi_H - (\mu_H + \delta)X_2 + \delta X_1 \tag{C.12}$$

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \Pi_H - \frac{b_2\beta_2 M_i S}{N_H} - \mu_H S \tag{C.13}$$

$$\frac{\mathrm{d}N_H}{\mathrm{d}t} = \Pi_H - (\mu_H + d_H + \tau)N_H + d_H X_2 + \tau X_H. \tag{C.14}$$

Let $(\tilde{X_H}, \tilde{X}_1, \tilde{S}, \tilde{N}_H, \tilde{X}_2)$ be a solution of (C.10)–(C.14) in the ω-limit set of a given solution of (X_H, X_1, S, N_H, X_2). Since $M_i(t) \to M_i^{**}$ and $X_H(t) \to \frac{\Pi_H}{\mu_H}$ as $t \to \infty$, it follows that

$$\frac{\mathrm{d}\tilde{X}_1}{\mathrm{d}t} = \Pi_H - (\mu_H + \alpha)\tilde{X}_1 + \alpha\tilde{S} \tag{C.15}$$

$$\frac{\mathrm{d}\tilde{S}}{\mathrm{d}t} = \Pi_H - \frac{b_2\beta_2 M_i^{**}\tilde{S}}{\tilde{N}_H} - \mu_H\tilde{S} \tag{C.16}$$

$$\frac{\mathrm{d}\tilde{N}_H}{\mathrm{d}t} = \Pi_H - (\mu_H + d_H + \tau)\tilde{N}_H + d_H\tilde{X}_2 + \tau\frac{\Pi_H}{\mu_H} \tag{C.17}$$

$$\frac{\mathrm{d}\tilde{X}_2}{\mathrm{d}t} = \Pi_H - (\mu_H + \delta)\tilde{X}_2 + \delta\tilde{X}_1. \tag{C.18}$$

The system (C.15)–(C.18) is a cooperative irreducible system (see Smith, 1995) in the region

$$\mathbb{R}^4_+ = \{(\tilde{X}_1, \tilde{S}, \tilde{N}_H, \tilde{X}_2)^T : \tilde{X}_1, \tilde{S}, \tilde{N}_H, \tilde{X}_2 > 0\}$$

and its closure $\overline{\mathbb{R}^4_+}$ has only one equilibrium $(\tilde{X}_1^*, \tilde{S}^*, \tilde{N}_H^*, \tilde{X}_2^*) = (S^{**} + E^{**}, S^{**}, N_H^*, S^{**} + E^{**} + I^{**})$. Therefore, by Theorem 3.1 in Smith (1995, p. 18) we conclude that

$$(\tilde{X}_1(t), \tilde{S}(t), \tilde{N}_H(t), \tilde{X}_2(t)) \to (\tilde{X}_1^*, \tilde{S}^{**}, \tilde{N}_H^*, \tilde{X}_2^*) \qquad \text{as } t \to \infty.$$

This, together with the local asymptotic stability of $(\tilde{X}_1^*, \tilde{S}^{**}, \tilde{N}_H^*, \tilde{X}_2^*)$, then implies that

$$(X_H(t), X_1(t), S(t), N_H(t), X_2(t)) \to (X_H^*, X_1^*, S^{**}, N_H^*, X_2^*) \qquad \text{as } t \to \infty,$$

completing the proof.

Unfortunately, our proof does not yield an explicit estimation for the minimal d_B for which the global stability of E_1 holds. In fact, we believe the global stability of E_1 holds for all $d_B > 0$.

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