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Indirect interaction between an endemic and an invading pathogen: A case study of *Plasmodium* and Usutu virus dynamics in a shared bird host population

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ABSTRACT

Infectious disease agents can influence each other's dynamics in shared host populations. We consider such influence for two mosquito-borne infections where one pathogen is endemic at the time that a second pathogen invades. We regard a setting where the vector has a bias towards biting host individuals infected with the endemic pathogen and where there is a cost to co-infected hosts. As a motivating case study, we regard *Plasmodium* spp., that cause avian malaria, as the endemic pathogen, and Usutu virus (USUV) as the invading pathogen. Hosts with malaria attract more mosquitoes compared to susceptible hosts, a phenomenon named vector bias. The possible trade-off between the vector-bias effect and the co-infection mortality is studied using a compartmental epidemic model. We focus first on the basic reproduction number R_0 for Usutu virus invading into a malaria-endemic population, and then explore the long-term dynamics of both pathogens once Usutu virus has become established. We find that the vector bias facilitates the introduction of malaria into a susceptible population, as well as the introduction of Usutu in a malaria-endemic population. In the long term, however, both a vector bias and co-infection mortality lead to a decrease in the number of individuals infected with either pathogen, suggesting that avian malaria is unlikely to be a promoter of Usutu invasion. This proposed approach is general and allows for new insights into other negative associations between endemic and invading vector-borne pathogens.

1. Introduction

When a pathogen invades a community of its host species, other pathogens may already be in circulation. The interaction between resident and invading pathogens could influence invasion success of the emerging pathogen and the subsequent combined dynamics. For vector-borne pathogens, there is evidence that previous infections of Zika or Dengue viruses can facilitate further infections of both diseases due to T cell cross-reactivity (Rothan et al., 2018). In tick-borne diseases, it was observed that co-infections of up to six strains of *Borrelia afzelii* may more easily evade the host immune response than a single infection (Cutler et al., 2021).

Co-infections are possible when different infections in an ecological community share the same reservoir host species. In the context of vector-borne diseases, the vectors also play a role in establishing multiple infections in the hosts they feed on. The co-circulation of pathogens between vectors and hosts in an ecosystem can make prediction and control more difficult (Vogels et al., 2019). This is further complicated when such pathogens interact in a synergistic way, leading to facilitation, or in a competitive way, leading to attenuation. An example of facilitation is the case of the tick-borne pathogen responsible for babesiosis promoting further infections with the pathogen that causes Lyme disease (Dunn et al., 2014). An example of attenuation occurs for different malaria strains participating in direct or immune-mediated competition with one another (de Roode et al., 2005). In some cases, relationships between pathogens can be observed without the exact mechanisms behind them being clear, such as the observation of a negative association between hosts infected with malaria parasites and with West Nile virus (Medeiros et al., 2014).

Some relationships between pathogens can manifest themselves in indirect ways, such as when one of the infections influences host choice by the vectors (Gandon, 2018). For instance, birds infected with the malaria parasite were shown to be more attractive to mosquitoes (Cornet et al., 2013a) - an effect called *vector bias*. This bias is independent

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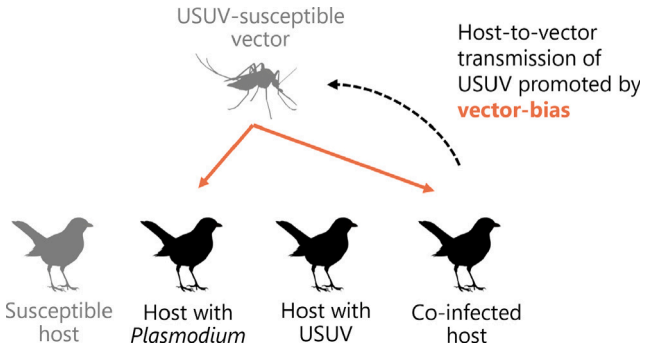

Fig. 1. Hypothesized additional route for USUV transmission in a population where *Plasmodium* is endemic. Vectors may become infected with USUV if the vector bias caused by *Plasmodium* shifts bites from naive hosts to co-infected hosts. Red arrows indicate increased attraction and the dashed arrow indicates a gained transmission opportunity.

of the infection state of the mosquitoes, that is, *Plasmodium*-infected hosts equally attract uninfected and *Plasmodium*-infected vectors (Cornet et al., 2013a). By altering the host's body odours, the parasite ensures its further transmission to other hosts (Puente et al., 2020). From an evolutionary standpoint this could make sense: a feeding preference towards infected hosts increases the chances that the pathogen keeps getting transmitted in a given population. If this vector-bias effect is significant towards any host that carries malaria, we hypothesized that any other pathogens co-infecting hosts and utilizing the same vector species might also benefit. It is relevant, then, to further investigate if the malaria-induced mosquito attractiveness could facilitate the invasion of other diseases in a population.

In 2021, co-infections of *Plasmodium* spp. and Usutu virus (USUV) were detected in many ($n = 67/119$) dead Eurasian blackbirds (*Turdus merula*) in the Netherlands (Giglia et al., 2021). Similar observations were recorded earlier in Belgium (Rouffaer et al., 2018). Both *Plasmodium* and USUV have vector and host species in common, making co-infections more likely. *Plasmodium*, the genus of parasite species responsible for avian malaria, is endemic in Europe (Bentz et al., 2006), while USUV is expanding its range, invading into new areas (Ashraf et al., 2015). Often, a host infected with two pathogens displays additional symptoms or faster mortality rates than single-infected hosts. The effect where the death rate caused by multiple infections is worse than the sum of its parts is also known as *synergistic mortality* (Seabloom et al., 2015). There is evidence that hosts co-infected with *Plasmodium* and USUV suffer from more severe lesions (Giglia et al., 2021), and this co-infection has been suggested to increase the likeliness of mortality in infected blackbirds (Rijks et al., 2016), however the exact scale of this effect remains unknown (Giglia et al., 2021). Perhaps due to this synergistic mortality, in Giglia et al. (2021) more than half of the dead Eurasian blackbirds were co-infected. It is still unclear, however, if this is a result of a high co-infection prevalence in live birds, or due to the co-infected birds being more likely to die.

We are interested in understanding how the vector bias and the consequences of co-infection affect the transmission of co-circulating pathogens such as USUV. The increased attraction caused by the vector bias may influence how new viruses emerge and spread in populations where *Plasmodium* is endemic (Fig. 1), hence *Plasmodium* could indirectly act as a 'wingman pathogen' of USUV (Young and Fefferman, 2022). This potential interaction was also hinted at in Höfle et al. (2022), where the bias towards *Plasmodium* infected red-legged partridges (*Alectoris rufa*) could influence the transmission of Bagaza virus, also from the *Flavivirus* genus like West Nile virus and USUV.

Interaction effects increase the difficulty of outbreak prediction for both malaria and USUV. It is then of interest to explore them in a modelling context to understand how relevant they are for the dynamics of both diseases. We look at the initial risk of an outbreak by studying the dependence of R_0 on key parameters and at the long-term population level consequences of the co-circulation and interaction.

There are several models in the literature focused on vector-borne disease co-infections (Barley et al., 2007; Lawi et al., 2011), and others that look into the effects of feeding preferences or vector bias (Chamchod and Britton, 2010; Kim et al., 2017). These have contributed to our understanding of dynamics between different infections, such as how a HIV-related susceptibility to malaria does not increase single infections of either pathogen (Barley et al., 2007), or how a vector bias affects the endemicity, and hence the control, of malaria (Kim et al., 2017). But to the best of our knowledge, no study has looked at both factors simultaneously. To investigate the interplay of these two factors, we propose a general model that allows the study of the trade-off between co-infections and the vector-bias effect.

In our study, we assume that one pathogen, in our case *Plasmodium* spp. infecting birds, has invaded at some time in the past and has become established in an endemic steady state of the (bird) host and (mosquito) vector populations. The endemic prevalence is determined by the specifics of the *Plasmodium*-only system, including a vector bias for biting *Plasmodium*-infected host individuals. We introduce a second pathogen (USUV) into that endemic steady state, transmitted in the same host population by the same vector species. We first study, in Section 2, the *Plasmodium*-only system, to determine the endemic prevalence in terms of the model ingredients. This then sets the stage for invasion of USUV. In Section 3, we study the invasion success of USUV by characterizing the basic reproduction number R_0 for USUV in a *Plasmodium*-endemic state and we numerically explore the long-term population dynamics of both pathogens.

2. Methods

To set the scene for our analysis, we first specify the dynamics of *Plasmodium* in the host/vector populations, including a bias of vectors for malaria-infected hosts. We establish the endemic state for *Plasmodium* in our model and explore how this state depends on selected ingredients, especially the strength of the vector bias. After that, we specify the next-generation matrix (Diekmann et al., 2010) for USUV governing the introduction of USUV into a USUV-naive, *Plasmodium*-endemic, steady state. We explore how R_0 for USUV depends on the strength of the vector bias and the additional death rate for co-infected hosts.

2.1. Model for Plasmodium with vector bias

We describe the *Plasmodium*-only system by an Susceptible-Infected-type model given by the following set of ordinary differential equations:

$$\begin{aligned} S_v' &= \Delta_v - \frac{kI_{hp}}{kI_{hp}+S_h} S_v\alpha_p - \mu_v S_v \\ S_h' &= \Delta_h - \frac{S_h}{kI_{hp}+S_h} I_{vp}\beta_p - \mu_h S_h \\ I_{vp}' &= \frac{kI_{hp}}{kI_{hp}+S_h} S_v\alpha_p - \mu_v I_{vp} \\ I_{hp}' &= \frac{S_h}{kI_{hp}+S_h} I_{vp}\beta_p - (\mu_h+\delta_p) I_{hp} \end{aligned} \tag{1}$$

where S_i and I_i are the susceptible and the infectious individuals. The subscript p refers to infection with *Plasmodium*, and the subscripts v refer to the vector and h refer to the host. See Table 1 for all parameters and their default values. We make the following assumptions:

- Constant recruitment and death rates, given by Δ_v, Δ_h and μ_v, μ_h, respectively.

Table 1
Default parameter values for the *Plasmodium* and co-infection models. All rates are given per day.

	Parameter	Value	Source
Δ_v	Vector recruitment rate	500	Villela et al. (2017)
μ_v	Vector death rate	0.067	Hartemink et al. (2007)
Δ_h	Host recruitment rate	10	Blayneh et al. (2009)
μ_h	Host mortality rate	0.0012	Rubel et al. (2008)
b	Biting rate	0.2	Cruz-Pacheco et al. (2005)
r_p	Transmission probability of *Plasmodium* (host to vector)	0.95	Woodworth et al. (2005)[a]
q_p	Transmission probability of *Plasmodium* (vector to host)	0.98	Samuel et al. (2011)[a]
α_p	Transmission rate of *Plasmodium* (host to vector)	0.19	–
β_p	Transmission rate of *Plasmodium* (vector to host)	0.196	–
δ_p	Additional death rate caused by *Plasmodium*	0.07	Atkinson et al. (1995)[a]
r_u	Transmission probability of USUV (host to vector)	0.125	Rubel et al. (2008)
q_u	Transmission probability of USUV (vector to host)	1	Rubel et al. (2008)
α_u	Transmission rate of USUV (host to vector)	0.025	–
β_u	Transmission rate of USUV (vector to host)	0.2	–
r_c	Co-transmission probability (host to vector)	0.0396	[b]
q_c	Co-transmission probability (vector to host)	0.3267	[b]
α_c	Co-transmission rate (host to vector)	0.0015	–
β_c	Co-transmission rate (vector to host)	0.013	–
δ_u	Additional death rate caused by USUV	0.06	Rubel et al. (2008)

[a] Estimate from Hawaiian bird species — values could differ for blackbirds.
[b] Assumption.

- Individuals follow Susceptible-Infectious dynamics, i.e., we ignore the latency period and recovery from infection. We partially explored, in Section S4 of the Supporting Information, the effect of introducing a latency period in the vector and the effect of introducing recovery in the host. Since these mechanisms did not impact the effect of vector bias or disease mortalities on transmission we decided it was a fair assumption to keep them out of the model.
- Transmission of the pathogen is host-frequency dependent (Wonham et al., 2006), which we consider a fair assumption when the hosts are present at such numbers that their abundances are not limiting to the vectors.
- The transmission rate from host to vector is given by $\alpha_p = br_p$ and the transmission rate from vector to host is given by $\beta_p = bq_p$. Both are characterized by fixed biting rates and fixed probabilities per bite that the pathogen is successfully transmitted.
- The biting behaviour is made heterogeneous through the coefficient k as in Chamchod and Britton (2010), representing a vector bias.

The vector bias gives the feeding preference of a vector towards *Plasmodium*-infected host individuals. It acts as a weight in the expressions for the force of infection, increasing the biting to some hosts. We assume that mosquitoes arrive randomly at each host and then the biting rate is influenced by the infection status of the host, as in Chamchod and Britton (2010), Mojeeb and Li (2019). In this case, the vector bias k can be defined as the ratio of the probability that a vector bites a *Plasmodium*-infected host, w, and the complementary probability that a vector bites a susceptible host, $1-w$. If $w > 1-w \Leftrightarrow k > 1$ then the vector preferentially bites infected hosts, while if $w < 1-w \Leftrightarrow k < 1$ the vector prefers to bite susceptible hosts. Unlike the probabilities w and $1-w$, k can theoretically take any value between $(0, \infty)$, but we restrict our analysis to the range $[1, 10]$. This parameter has a straightforward interpretation: for example, if $k = 2$ then the probability of a mosquito choosing to bite an infected host is twice that of choosing a susceptible host. The probabilities w, and consequently $1 - w$ and the ratio k, are derived in the following way. Assume that A is the event that a vector bites the host, and that B is the event that a vector arrives at a *Plasmodium*-infected host. Then $P(B) = \frac{I_{hp}}{N_h}$, and $P(\overline{B}) = \frac{S_h}{N_h} = 1 - \frac{I_{hp}}{N_h}$. So, $w = P(A|B)$ and hence $1 - w = P(A|\overline{B})$. We are interested in the probability that a host is infected with *Plasmodium* knowing that it was bitten by a vector. That is given, according to Bayes' theorem, by

$$P(B|A) = \frac{P(A|B)P(B)}{P(A|B)P(B) + P(A|\overline{B})P(\overline{B})}$$

$$= \frac{wI_{hp}/N_h}{wI_{hp}/N_h + (1-w)(1-I_{hp}/N_h)} = \frac{kI_{hp}}{kI_{hp} + S_h}$$

and, likewise, the probability of a susceptible host being bitten by a vector is given by

$$P(\overline{B}|A) = \frac{P(A|\overline{B})P(\overline{B})}{P(A|B)P(B) + P(A|\overline{B})P(\overline{B})} = \frac{S_h}{kI_{hp} + S_h}$$

Later in Section 2.2 this will be extended to include the feeding preferences in the presence of multiple host classes, where besides the completely susceptible hosts and *Plasmodium*-carrying hosts, there are also hosts infected with USUV, and co-infected hosts.

The *Plasmodium*-free steady state with both vector and host present is given by $S_v^* = K_v = \Delta_v/\mu_v$ and $S_h^* = K_h = \Delta_h/\mu_h$, where K_v and K_h are the carrying capacities for vectors and hosts.

The next-generation matrix $\boldsymbol{K_p}$ (Diekmann et al., 2010) for this system is given by

$$\boldsymbol{K_p} = \begin{pmatrix} 0 & \frac{\alpha_p k K_v}{(\mu_h+\delta_p)K_h} \\ \frac{\beta_p}{\mu_v} & 0 \end{pmatrix}$$

The spectral radius of $\boldsymbol{K_p}$ evaluated at the *Plasmodium*-free steady state corresponds to the basic reproduction number $R_0(\mathrm{P})$ and is given by

$$R_0(\mathrm{P}) = \sqrt{\frac{\alpha_p \beta_p k K_v}{(\mu_h + \delta_p)\mu_v K_h}} \tag{2}$$

In the Supporting Information we show that the *Plasmodium*-only system reaches a unique endemic steady state with susceptible and infectious sub-populations of both vector and host positive.

2.2. Model for USUV in a Plasmodium endemic state

We now regard a system consisting of a vector species, a host species, and two pathogens: *Plasmodium* and USUV. For this, we model the dynamics and interactions with the following ODE-system

$$\begin{aligned}
N_v' &= \Delta_v - \mu_v N_v \\
N_h' &= \Delta_h - \mu_h N_h - \delta_p I_{hp} - \delta_u I_{hu} - \delta_c I_{hc} \\
I_{vp}' &= \alpha_p \frac{kI_{hp} + kI_{hc}}{N_k} S_v - \alpha_u \frac{I_{hu} + kI_{hc}}{N_k} I_{vp} - \mu_v I_{vp} \\
I_{vu}' &= \alpha_u \frac{I_{hu} + kI_{hc}}{N_k} S_v - \alpha_p \frac{kI_{hp} + kI_{hc}}{N_k} I_{vu} - \mu_v I_{vu} \\
I_{vc}' &= \alpha_c \frac{kI_{hc}}{N_k} S_v + \alpha_p \frac{kI_{hp} + kI_{hc}}{N_k} I_{vu} + \alpha_u \frac{I_{hu} + kI_{hc}}{N_k} I_{vp} - \mu_v I_{vc}
\end{aligned} \tag{3}$$

$$I'_{hp} = \beta_p \frac{S_h}{N_k}(I_{vp} + I_{vc}) - \beta_u \frac{kI_{hp}}{N_k}(I_{vu} + I_{vc}) - (\mu_h + \delta_p)I_{hp}$$
$$I'_{hu} = \beta_u \frac{S_h}{N_k}(I_{vu} + I_{vc}) - \beta_p \frac{I_{hu}}{N_k}(I_{vp} + I_{vc}) - (\mu_h + \delta_u)I_{hu}$$
$$I'_{hc} = \beta_c \frac{S_h}{N_k} I_{vc} + \beta_u \frac{kI_{hp}}{N_k}(I_{vu} + I_{vc}) + \beta_p \frac{I_{hu}}{N_k}(I_{vp} + I_{vc}) - (\mu_h + \delta_c)I_{hc}$$

where the indexes p, u, and c stand for infection of *Plasmodium*, USUV, and co-infection by both, respectively. $N_v = S_v + I_{vp} + I_{vu} + I_{vc}$ and $N_h = S_h + I_{hp} + I_{hu} + I_{hc}$ are the total vector and host abundances, respectively, and N_k is the total host abundance weighted by k, i.e., $N_k = N_h + (k-1)(I_{hp} + I_{hc})$. This term expresses the frequency dependence in the presence of vector bias towards *Plasmodium*-infected hosts. This virtual number of hosts as experienced by the vector, with vector bias k, is $S_h + kI_{hp} + I_{hu} + kI_{hc}$. If we then substitute the actual number of naive hosts $S_h = N_h - I_{hp} - I_{hu} - I_{hc}$, we obtain N_k as above. Similar to Section 2.1, the transmission rates of USUV from host to vector are given by $\alpha_u = br_u$, and from vector to host by $\beta_u = bq_u$. On top of the assumptions made for system 2.1 we also assume that:

- The two pathogens do not directly interact with each other within host (for example, there is no competition, nor an influence on transmission success per bite) except for the additional death rate in co-infected hosts.
- *Plasmodium* and USUV are transmitted independently from and to co-infected individuals during feeding. From the literature data we found, the transmission probabilities for *Plasmodium* and USUV are high (i.e., near 1, see Table 1). If we simply assume that the two diseases are independently transmitted from co-infected individuals, that means that the introduction of a co-infected individual, however rare, into a completely susceptible population will lead to a decrease in the susceptibles that is three times larger than the biting rate. So, to avoid this, we adjust the co-transmission probabilities to be three times lower, that is $r_c = r_p r_u/3$ and $q_c = q_p q_u/3$, for host to vector and vector to host transmission respectively.
- Neither vectors nor hosts acquire immunity, and the vectors do not die from either infection. The death rates of the hosts are increased by an additional quantity δ_p if infected with *Plasmodium*; δ_u if infected with USUV; or δ_c if they are co-infected. The death rate of co-infection is assumed to be at least as severe as the sum of both individual disease death rates, $\delta_c \geq \delta_p + \delta_u$. That is, we will explore a range of values for $\delta_c \geq 0.13$.
- Co-infected hosts attract vectors in the same way as hosts infected only with *Plasmodium*.

The force of infection from a vector infected only with *Plasmodium* to a susceptible host is equal to $\beta_p I_{vp}/N_k$. This represents the probability per unit of time that an infected vector with *Plasmodium* infects a susceptible host if there is a preference towards biting hosts that are already infected with *Plasmodium*. Like in system (1), the transmission rates from host to vector α_i and from vector to host β_i are given by the product of the biting rate b with the probability of successful transmission from host to vector r_i or from vector to host q_i. The default values of additional parameters can be found in Table 1; Fig. 2 describes the model schematically.

For consistency, we check that the interpretation of the vector bias parameter k still holds in the presence of more host classes, namely those infected with USUV only, I_{hu}, and those co-infected, I_{hc}. The auxiliary parameter w, and hence $1-w$, have the same interpretation as before since we assume that USUV has no influence on the vector bias. Here w gives the probability that a vector bites a *Plasmodium*-infected host (either single or co-infected), and $1-w$ gives the probability that a vector bites a host susceptible for *Plasmodium* (either in a completely naive state or infected with USUV only). Again $w = P(A|B)$ and $1-w = P(A|\overline{B})$. Assume that A is the event that a vector bites the host, and that B is the event that a vector arrives at a host already infected with *Plasmodium*, regardless of whether it is single or co-infected. We have $P(B) = \frac{I_{hp}+I_{hc}}{N_h}$, and $P(\overline{B}) = \frac{S_h+I_{hu}}{N_h} = 1 - \frac{I_{hp}+I_{hc}}{N_h}$. The probability of a host being infected with *Plasmodium* knowing that it was bitten by a vector is now given by

$$P(B|A) = \frac{w(I_{hp} + I_{hc})}{w(I_{hp} + I_{hc}) + (1-w)(S_h + I_{hu})} = \frac{k(I_{hp} + I_{hc})}{k(I_{hp} + I_{hc}) + S_h + I_{hu}}$$
$$= \frac{k(I_{hp} + I_{hc})}{N_k}$$

Later we will explore the long-term dynamics of the system (3), for the case that USUV successfully invaded into a *Plasmodium*-endemic steady state. First, we need to establish the conditions under which such USUV invasion is successful, i.e., we need to characterize R_0 for invasion of USUV into a vector-host population where *Plasmodium* is in an endemic steady state. We consider the situation where all abundances are positive. For the characterization of R_0 for USUV in that context, we consider the ODE-system, linearized around the {USUV-free, *Plasmodium*-endemic}-steady state where the values of the steady state abundances for the total number of vectors and hosts and for the *Plasmodium*-infected vectors and host, $(N_v^*, N_h^*, I_{vp}^*, I_{hp}^*)$, are given in Section 2.1, for the case with vector bias. All other states involve USUV-infected individuals and these are therefore zero in the USUV-free steady state, $I_{vu} = I_{vc} = I_{hu} = I_{hc} = 0$.

Starting from system (3), the standard approach to characterize R_0 distinguishes four states-at-infection (Diekmann et al., 2010) from the USUV point of view. An individual vector can start 'USUV-infected life' in one of two ways: a naive vector individual acquires USUV ('U-vector', state-at-infection 1) or a vector that is already infected by *Plasmodium* acquires USUV ('PU-vector', 2). Similarly, for host individuals we distinguish naive hosts acquiring USUV ('U-host', 3) or a host already infected with *Plasmodium* acquires USUV ('PU-host', 4). Hence, the next-generation matrix is four-dimensional.

From system (3), with *Plasmodium* in its pre-USUV steady state, we can write the partial Jacobian matrix for the four states-at-infection as

$$\boldsymbol{J} = \begin{pmatrix} -\mu_v - \frac{\alpha_p k I_{hp}^*}{N_k^*} & 0 & \frac{\alpha_u(N_v^* - I_{vp}^*)}{N_k^*} & \frac{\alpha_u k(N_v^* - I_{vp}^*)}{N_k^*} \\ \frac{\alpha_p k I_{hp}^*}{N_k^*} & -\mu_v & \frac{\alpha_u I_{vp}^*}{N_k^*} & \frac{\alpha_u k I_{vp}^* + \alpha_c k(N_v^* - I_{vp}^*)}{N_k^*} \\ \frac{\beta_u(N_h^* - I_{hp}^*)}{N_k^*} & \frac{\beta_u(N_h^* - I_{hp}^*)}{N_k^*} & -\mu_h - \delta_u - \frac{\beta_p I_{vp}}{N_k^*} & 0 \\ \frac{\beta_u k I_{hp}^*}{N_k^*} & \frac{\beta_u k I_{hp}^* + \beta_c(N_h^* - I_{hp}^*)}{N_k^*} & \frac{\beta_p I_{vp}^*}{N_k^*} & -\mu_h - \delta_c \end{pmatrix}$$

from which we separate the transmission terms into a matrix $\boldsymbol{T}$ and the transition terms into a matrix $\boldsymbol{\Sigma}$:

$$\boldsymbol{T} = \begin{pmatrix} 0 & 0 & \frac{\alpha_u(N_v^* - I_{vp}^*)}{N_k^*} & \frac{\alpha_u k(N_v^* - I_{vp}^*)}{N_k^*} \\ 0 & 0 & \frac{\alpha_u I_{vp}^*}{N_k^*} & \frac{\alpha_u k I_{vp}^* + \alpha_c k(N_v^* - I_{vp}^*)}{N_k^*} \\ \frac{\beta_u(N_h^* - I_{hp}^*)}{N_k^*} & \frac{\beta_u(N_h^* - I_{hp}^*)}{N_k^*} & 0 & 0 \\ \frac{\beta_u k I_{hp}^*}{N_k^*} & \frac{\beta_u k I_{hp}^* + \beta_c(N_h^* - I_{hp}^*)}{N_k^*} & 0 & 0 \end{pmatrix}$$

$$\boldsymbol{\Sigma} = \begin{pmatrix} -\mu_v - \frac{\alpha_p k I_{hp}^*}{N_k^*} & 0 & 0 & 0 \\ \frac{\alpha_p k I_{hp}^*}{N_k^*} & -\mu_v & 0 & 0 \\ 0 & 0 & -\mu_h - \delta_u - \frac{\beta_p I_{vp}}{N_k^*} & 0 \\ 0 & 0 & \frac{\beta_p I_{vp}^*}{N_k^*} & -\mu_h - \delta_c \end{pmatrix}$$

The next-generation matrix, $\boldsymbol{K} = -\boldsymbol{T}\boldsymbol{\Sigma}^{-1}$, then has the following form (denoted with subscript 'u' to indicate the fact that we are regarding USUV-invasion):

$$\boldsymbol{K_u} = \begin{pmatrix} 0 & 0 & k_{13} & k_{14} \\ 0 & 0 & k_{23} & k_{24} \\ k_{31} & k_{32} & 0 & 0 \\ k_{41} & k_{42} & 0 & 0 \end{pmatrix} \tag{4}$$

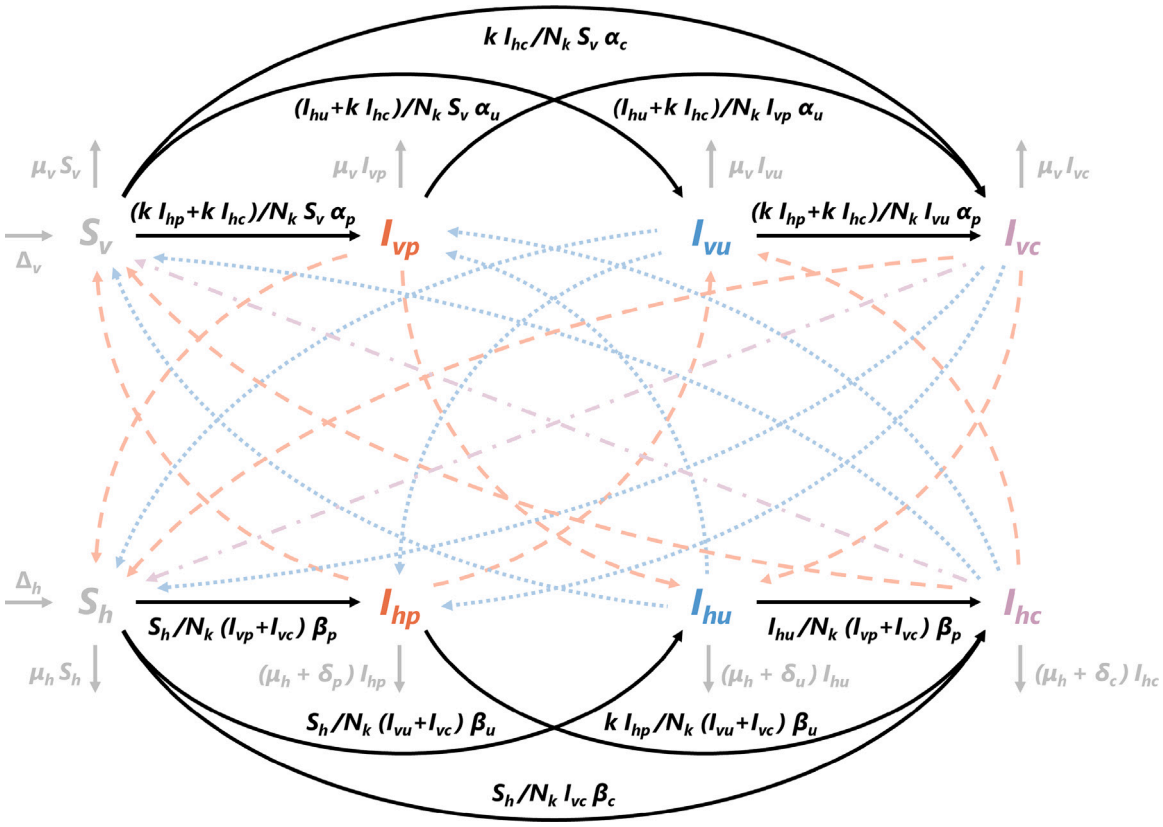

Fig. 2. Flow diagram of the population dynamics in the full model (3). Transitions between compartments are given by solid black arrows and recruitment and death related transitions in solid grey arrows. The different types of pathogen transmissions are given by orange dashed arrows for *Plasmodium* transmission, blue dotted arrows for USUV transmission, and purple dash-dotted arrows for co-transmission. S_v, I_{vp}, I_{vu}, and I_{vc} are vectors that are susceptible, infected with *Plasmodium*, infected with USUV, and co-infected, and S_v, I_{vp}, I_{vu}, and I_{vc} represent the same but for the hosts. The total host population weighted by the vector bias is given by $N_k = S_h + kI_{hp} + I_{hu} + kI_{hc}$.

The non-zero elements k_{ij}, are the expected number of new infections with state-at-infection i caused by one individual which has just become infected as type j, during its entire infectious period. Apart from deriving expressions for the k_{ij} from the Jacobian at the USUV-free steady state, these can also be found by reasoning from the epidemiological interpretation (see Diekmann et al. (2010)). This reasoning is insightful for the interpretation of the k_{ij} terms. In the setting of system (3), they are the product of (i) the number of contacts per unit of time between individuals of type j and USUV-susceptibles that can become type i upon infection; (ii) the probability of successful transmission per contact; (iii) the duration of the period that an infected individual is of type j. For example, to get state-at-infection 1, a naive vector can either have contact with a U-host (leading to k_{13}) or with a 'PU-host' (leading to k_{14}). The situation is more complicated for individuals starting infected life in state-at-infection 2. Here, there are three possibilities. A *Plasmodium*-infected vector can acquire USUV from a U-host (leading to k_{23}), or from a 'PU-host' when only USUV is transmitted (contributing to k_{24}), or a naive vector can acquire USUV and *Plasmodium* from a 'PU-host' (also contributing to k_{24}). Similar reasoning applies for states-at-infection 3 and 4.

There are two subtleties to consider, related to changes in the current state of individuals that have a state-at-infection where they are not infected with *Plasmodium*. The state-at-infection is a label that is fixed to the individual at the moment it gets infected with USUV. In the *Plasmodium* transmission dynamics running in the background in steady state, individuals with state-at-infection 1 (U-vector) and 3 (U-host) can become infected with *Plasmodium* during their USUV-infectious period. The USUV-infectious period of 'PU-vectors' (state 2) ends by death of the individual and the expected duration is $1/\mu_v$. The USUV-infectious period of 'PU-hosts' (state 4) ends by death of the individual and the expected duration is $1/(\mu_h + \delta_c)$. The subtlety is in the duration of state-at-infection 1 and 3. These individuals also end their USUV-infectious period with death, but can, in addition, leave their state by becoming infected with *Plasmodium*. For a U-host, this happens with exponential rate $\beta_p I^*_{vp}/N^*_k$ in the steady state at which we assess USUV-invasion. The duration of the period spent in state 3 therefore is $1/(\mu_h + \delta_u + \beta_p I^*_{vp}/N^*_k)$. For a U-vector, similar reasoning leads to a duration $1/(\mu_v + k\alpha_p I^*_{hp}/N^*_k)$. The second subtlety arises from this change in current state. The individuals that change their current state from U-vector to 'PU-vector' (or U-host to 'PU-host'), instead of dying as U-vector (or U-host), can continue to make new cases, but with the different rates that characterize the 'PU-state'. Therefore, additional transmission terms arise for elements $k_{13}, k_{23}, k_{31}, k_{41}$. For example,

$$k_{31} = \beta_u \frac{N^*_h - I^*_{hp}}{\mu_v N^*_k + k\alpha_p I^*_{hp}} + \beta_u \frac{(N^*_h - I^*_{hp})k\alpha_p I^*_{hp}}{\mu_v N^*_k(\mu_v N^*_k + k\alpha_p I^*_{hp})} = \beta_u \frac{N^*_h - I^*_{hp}}{\mu_v N^*_k}$$

The second term is the product of three factors: (i) the rate of encountering naive hosts and infecting them with U, $\beta_u(N^*_h - I^*_{hp})/N^*_k$; (ii) the expected time this continues, $1/\mu_v$; and (iii) the probability that the vector individual we are considering from the moment it became infected with U indeed transitions to the 'PU-state' before dying of natural causes. This probability is: (rate of transition from U to UP)/(total rate of leaving U-state):

$$\frac{\frac{k\alpha_p I^*_{hp}}{N^*_k}}{\frac{k\alpha_p I^*_{hp}}{N^*_k} + \mu_v} = \frac{k\alpha_p I^*_{hp}}{k\alpha_p I^*_{hp} + \mu_v N^*_k}$$

The other three elements with such an additional transmission term can be found by similar reasoning.

The epidemiological route and the route via the linearization of system (3), based on the matrices $\boldsymbol{T}$ and $\boldsymbol{\Sigma}$, lead to the following expressions for the k_{ij}:

$$k_{13} = \alpha_u \frac{N_v^* - I_{vp}^*}{(\mu_h + \delta_u)N_k^* + \beta_p I_{vp}^*} + \alpha_u k \frac{(N_v^* - I_{vp}^*)\beta_p I_{vp}^*}{(\mu_h + \delta_c)N_k^* \left((\mu_h + \delta_u)N_k^* + \beta_p I_{vp}^*\right)}$$

$$k_{14} = k\alpha_u \frac{N_v^* - I_{vp}^*}{(\mu_h + \delta_c)N_k^*}$$

$$k_{23} = \alpha_u \frac{I_{vp}^*((\mu_h + \delta_c)N_k^* + k\beta_p I_{vp}^*)}{(\mu_h + \delta_c)N_k^*((\mu_h + \delta_u)N_k^* + \beta_p I_{vp}^*)} + \alpha_c \frac{k\beta_p I_{vp}^*(N_v^* - I_{vp}^*)}{(\mu_h + \delta_c)N_k^*((\mu_h + \delta_u)N_k^* + \beta_p I_{vp}^*)}$$

$$k_{24} = k\alpha_c \frac{N_v^* - I_{vp}^*}{(\mu_h + \delta_c)N_k^*} + k\alpha_u \frac{I_{vp}^*}{(\mu_h + \delta_c)N_k^*}$$

$$k_{31} = \beta_u \frac{N_h^* - I_{hp}^*}{\mu_v N_k^* + k\alpha_p I_{hp}^*} + \beta_u \frac{(N_h^* - I_{hp}^*)k\alpha_p I_{hp}^*}{\mu_v N_k^*(\mu_v N_k^* + k\alpha_p I_{hp}^*)} = \beta_u \frac{N_h^* - I_{hp}^*}{\mu_v N_k^*}$$

$$k_{32} = \beta_u \frac{N_h^* - I_{hp}^*}{\mu_v N_k^*}$$

$$k_{41} = k\beta_u \frac{I_{hp}^*}{\mu_v N_k^* + k\alpha_p I_{hp}^*} + \frac{(k\beta_u I_{hp}^* + \beta_c(N_h^* - I_{hp}^*))k\alpha_p I_{hp}^*}{\mu_v N_k^*(\mu_v N_k^* + k\alpha_p I_{hp}^*)}$$

$$k_{42} = k\beta_u \frac{I_{hp}^*}{\mu_v N_k^*} + \beta_c \frac{N_h^* - I_{hp}^*}{\mu_v N_k^*}$$

The equation for the eigenvalues of (3) is given by

$$\lambda^4 - (k_{13}k_{31} + k_{14}k_{41} + k_{23}k_{32} + k_{24}k_{42})\lambda^2 + (k_{13}k_{24} - k_{14}k_{23})(k_{31}k_{42} - k_{41}k_{32}) = 0$$

Hence, the eigenvalues are given by

$$\lambda^2 = \frac{A}{2}(1 \pm \sqrt{1 - B})$$

with

$$A := k_{13}k_{31} + k_{14}k_{41} + k_{23}k_{32} + k_{24}k_{42} \tag{5}$$

and

$$B := \frac{4(k_{13}k_{24} - k_{14}k_{23})(k_{31}k_{42} - k_{41}k_{32})}{A^2} \tag{6}$$

We see that $A > 0$. Hence, if $B < 1$ all four eigenvalues are real, and the dominant eigenvalue is positive. One can see easily that indeed $B < 1$ by writing

$$\begin{aligned}(k_{13}k_{31} + k_{14}k_{41} + k_{23}k_{32} + k_{24}k_{42})^2 - 4(k_{13}k_{24} - k_{14}k_{23})(k_{31}k_{42} - k_{41}k_{32}) \\ = (k_{13}k_{31} - k_{24}k_{42})^2 + (k_{14}k_{41} - k_{23}k_{32})^2 \\ + 2(k_{13}k_{31} + k_{24}k_{42})(k_{14}k_{41} + k_{23}k_{32}) \\ + 4(k_{14}k_{23}k_{31}k_{42} + k_{13}k_{24}k_{32}k_{41}) > 0.\end{aligned}$$

The basic reproduction number for USUV-invasion into a *Plasmodium*-endemic and USUV-free steady state of system (3) is therefore given by:

$$R_0(\mathrm{U}) = \sqrt{\frac{A}{2}(1 + \sqrt{1 - B})} \tag{7}$$

3. Results

3.1. Impact of vector bias on Plasmodium transmission

Before exploring the effect of the vector bias and disease-related death rates on the invasion of USUV, we first investigate these effects on the invasion risk of *Plasmodium* into a naive population, expressed by $R_0(\mathrm{P})$. We consider for the vector bias the range $k \geq 1$ and for the additional death rate caused by *Plasmodium* the range $\delta_p \geq 0.035$. We vary δ_p since it may be different from the value in Table 1 which was not specific for blackbirds (Himmel et al., 2020). For each particular combination of k and δ_p, the endemic steady state of *Plasmodium* is recalculated if $R_0(\mathrm{P}) > 1$. Fig. 3a shows the impact of k and δ_p, with all other parameters fixed to the values in Table 1. For any δ_p, a vector bias always leads to higher $R_0(\mathrm{P})$ values, and with higher δ_p leading to lower $R_0(\mathrm{P})$ values.

However, in the long term, as shown in Fig. 3b, a higher vector bias leads to a lower prevalence of *Plasmodium* in the hosts. A higher k leads to a slight increase in I_{vp}^*/N_v^* (not shown) and a decrease in I_{hp}^*/N_h^*. Theoretically, in the limit as $k \to \infty$, $S_h^* \to \Delta_h/\mu_h$, that is, if the vector bias is infinitely large, the vectors are essentially ignoring the susceptible hosts and the infection prevalence decreases to zero. As for δ_p, its effect on the endemic prevalence of *Plasmodium* in hosts is the following. For the parameter values in Table 1, and assuming $k = 5$ to guarantee the existence of the endemic steady state, $S_h^* = 7$ and $I_{hp}^* = 140$ when $\delta_p = 0.07$, and $S_h^* = 2$ and $I_{hp}^* = 47$ when $\delta_p = 0.21$. That is, the additional death rate caused by the disease affects not only the endemic prevalence of the infected hosts, but also of the susceptible ones. The higher δ_p is, the faster the infected hosts are being removed. This gives a larger probability that mosquitoes bite susceptible hosts, since the contact is given by $\beta_p I_{vp}/(kI_{hp} + S_h)$. So if the infected hosts are removed faster, this also means a faster conversion of susceptibles into infecteds. This leads to what we observe in Fig. 3(b), where an increase in δ_p for constant k leaves the prevalence I_{hp}^*/N_h^* practically unaffected.

3.2. Impact of vector bias on USUV transmission

We investigate the potential trade-off between the vector bias and the additional death rate caused by the co-infection. Fig. 4a shows how the context of a co-infection matters for the introduction of USUV in a population where *Plasmodium* is already endemic.

We observe from Fig. 4a that $R_0(\mathrm{U})$ is hardly affected by k for the ranges shown, in contrast to the case of $R_0(\mathrm{P})$ in Fig. 3a. From (2) one can see that $R_0(\mathrm{P})$ scales with $\sqrt{k}$. In $R_0(\mathrm{U})$ given by (7) the relationship with k is not at all straightforward. Fig. 4a shows, however, that for values of $k < 10$, a vector bias hardly influences USUV invasion potential.

In the long term, system (3) starts from the {*Plasmodium*-endemic, USUV-free} steady state, with R_0 for USUV larger than 1. We focus on the prevalence of infected hosts with USUV, both in the single- and co-infected forms, $(I_{hu} + I_{hc})/N_h$. Since we cannot derive analytic expressions for the endemic steady state as in Section 2.1, we take the prevalence of USUV-infected hosts after 500 days from numerical simulations. After such point in time the prevalence stays constant, given the parameters in Table 1 (see also Section 3 of the Supporting Information for further numerical explorations). Fig. 4b shows this prevalence for different values of the vector bias k and the additional death rate caused by the co-infection δ_c. The simulations start at the *Plasmodium*-endemic steady state and an additional vector infected with only USUV. That is, the starting conditions of the full model are $\{S_v, S_h, I_{vp}, I_{vu}, I_{vc}, I_{hp}, I_{hu}, I_{hc}\} = \{S_v^*, S_h^*, I_{vp}^*, 1, 0, I_{hp}^*, 0, 0\}$, and the remaining parameters are fixed at the values shown in Table 1. For these parameter values, $R_0(\mathrm{U}) > 1$, so USUV is able to invade. The long-term dynamics show that a stronger vector bias leads to a lower prevalence of USUV (slightly more hosts with USUV-only but substantially fewer with USUV and *Plasmodium*). In Fig. 4b we can see that there is no trade-off between the vector bias and the additional death rate from co-infection in the ranges considered here. Both parameters lead to a decrease in USUV prevalence in the long term.

The impacts of a latency period in vectors and recovery from infection in hosts were studied in Section S4 of the Supporting Information. They do not qualitatively affect the patterns of the vector bias and co-infection mortality on the invasion risk of USUV, so they may be omitted for simplicity.

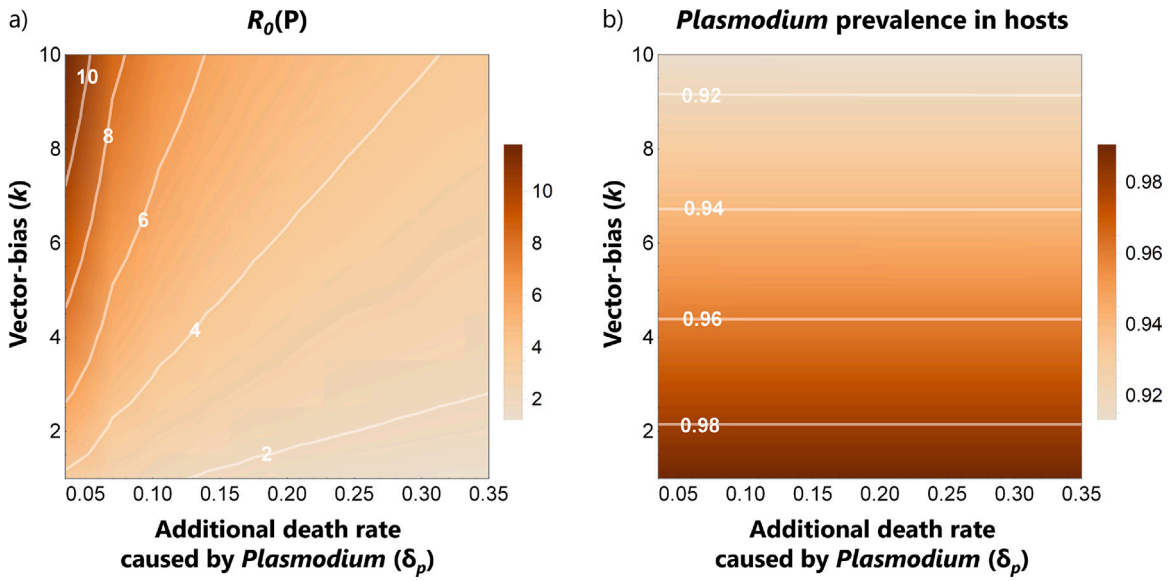

Fig. 3. The vector bias increases the invasion risk of *Plasmodium*, but leads to a decrease of its endemic prevalence in hosts. (a) Impact of vector bias k and *Plasmodium*-induced death rate δ_p on *Plasmodium*-invasion risk R_0(P). (b) Endemic steady state prevalence of *Plasmodium* in hosts (see Section 1 of the Supporting Information) for values where *Plasmodium* invaded the population. The ranges considered are $[1, 10]$ for k and $[0.035, 0.35]$ for δ_p.

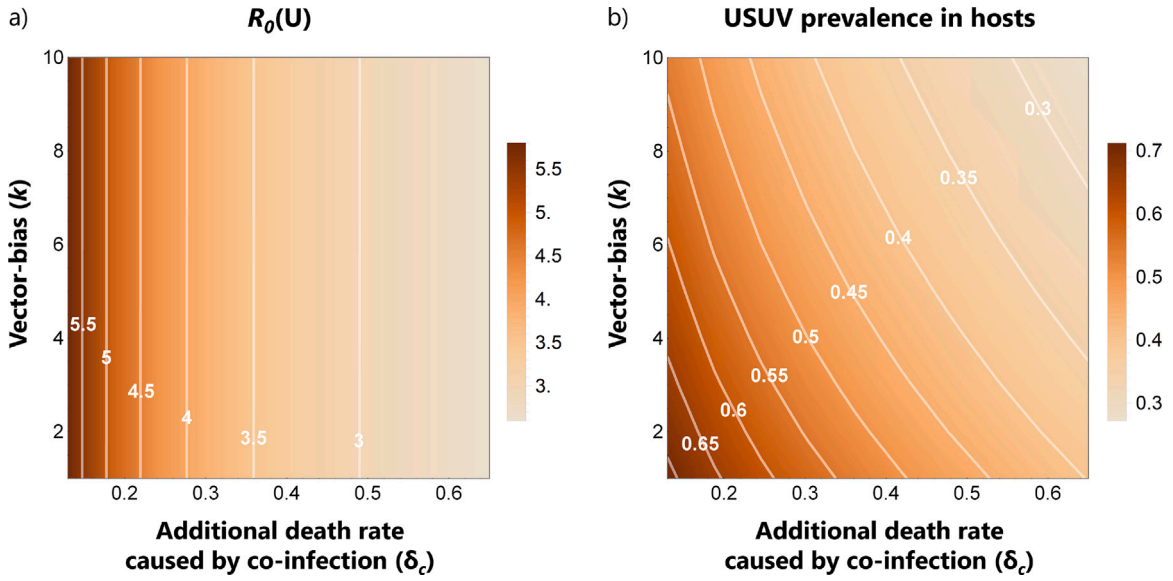

Fig. 4. A vector bias does not facilitate the invasion of USUV into a *Plasmodium* endemic steady state, and leads to a decrease of its long-term prevalence in hosts. (a) Impact of vector bias k and the additional co-infection-induced death rate δ_c on USUV invasion risk R_0(U). (b) Prevalence of USUV in hosts (single or co-infected) close to an endemic steady state ($t = 500$ days).

4. Discussion

Pathogen transmission dynamics are influenced by many factors, including direct or indirect interaction with other pathogens. There has been a substantial amount of work in modelling the population dynamics with co-infections. Examples of such analyses relate to interaction between Zika-dengue (Bonyah et al., 2019), malaria-meningitis (Lawi et al., 2011), malaria-typhoid fever (Mutua et al., 2015), malaria-cholera (Okosun and Makinde, 2014; Egeonu et al., 2021), malaria-lymphatic filariasis (Slater et al., 2013), malaria-Zika (Amoah-Mensah et al., 2018), malaria-rotavirus (Omondi et al.), malaria-HIV (Barley et al., 2007; Mukandavire et al., 2009; Pinto and Rocha, 2012; Mohammed-Awel and Numfor, 2017), HIV-tuberculosis (Naresh and Tripathi, 2005). Most of these studies focus on the long-term dynamics of the interaction between the two pathogens/parasites. They generally start by introducing both infectious agents into the population simultaneously and then study the situation where both invade and where, after a while, the precise nature of the introduction no longer influences the dynamics of the agents and their interaction. We, in contrast, were interested in the common situation where a pathogen invades into an area where other pathogens already established. In this study, we considered that one pathogen has become endemic in a vector and host community, and then another pathogen invades. Here we investigated two indirect mechanisms of interaction in the context of vector-borne pathogens in a joint host population. The existence of mechanisms such as an additional death rate in co-infected hosts or vector bias induced by one pathogen, opens up non-trivial epidemiological outcomes.

For *Plasmodium* and USUV, the additional death rates caused by each infection separately and by the co-infection decrease the invasion risk of both pathogens. A higher *Plasmodium*-related death rate

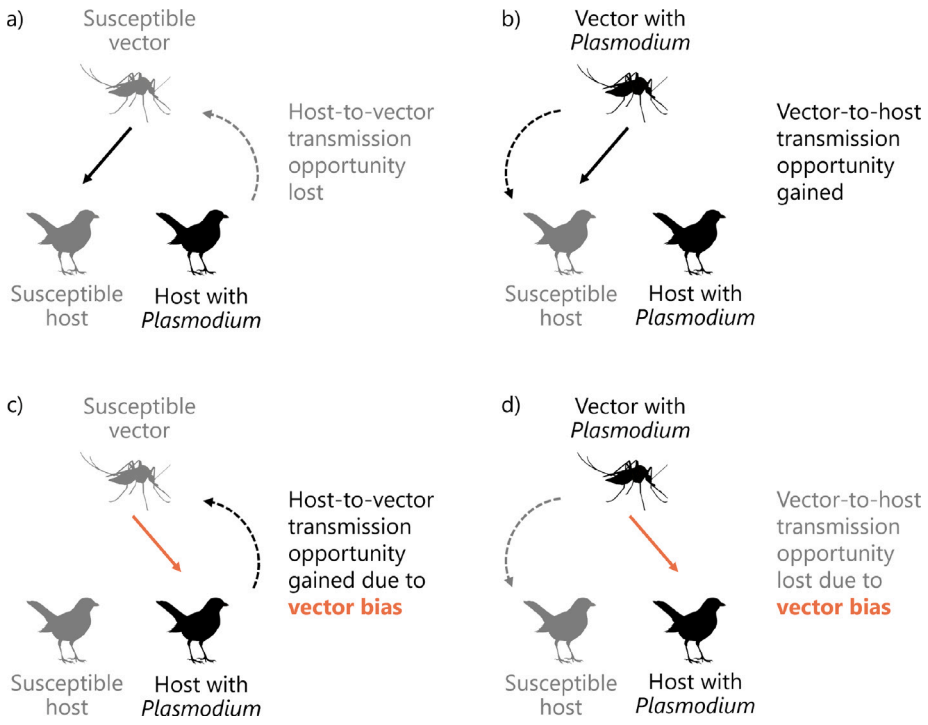

Fig. 5. Understanding the conditions that make the vector bias act as an amplifier or as an attenuator of *Plasmodium* transmission. In scenarios (a) and (b) the vector ends up biting the susceptible host, while in (c) and (d) it bites the infected host, promoted by the vector bias. At the onset of an epidemic, the majority of the hosts are susceptible, so any bias towards the few infected hosts (c) contributes to a higher pathogen invasion risk. At the latter stages, when there is a depletion of the susceptible hosts, a bias towards the infected hosts (d) wastes an opportunity for transmission to a naive host.

was shown to hardly affect the long-term prevalence of hosts with malaria. In the context of multiple circulating infections, an additional death rate of co-infected hosts leads to a decrease of co-infected hosts. We observed that the overall USUV-prevalence in the long term decreases with increasing co-infection death rate, since that leads to fewer USUV-infected hosts to contribute to its transmission.

For the *Plasmodium* parasite, a higher vector bias increases invasion success, but leads to an overall lower long-term malaria prevalence among hosts, consistent with Abboubakar et al. (2016) and Wang and Zhao (2017). A vector bias promotes the invasion of *Plasmodium* into a naive population by increasing the attractiveness of naive vectors towards the initially scarce *Plasmodium*-infected hosts. This can be visualized as a switch from scenario (a) in Fig. 5 towards scenario (c). This early benefit is no longer observed in the long term, since there are now wasted opportunities to transmit *Plasmodium* to the less preferred susceptible hosts. The switch from scenario (b) in Fig. 5 to scenario (d) results in a dilution effect. This split influence of the vector bias at invasion and in the long term is analogous to the differences observed between areas of low and high transmission in Kim et al. (2017). The vector bias was shown to increase the endemic prevalence of infected humans with *Plasmodium* in low transmission areas, but decrease it in high transmission areas.

The relationship between pathogen co-circulation and the presence of a strong vector-bias effect therefore presents trade-offs, with potential epidemiological consequences. From the viral point-of-view, a vector bias towards infected hosts is advantageous if there are more susceptible than infected vectors. If, however, there is a high abundance of infected vectors compared to susceptible ones, and this vector-bias effect persists, then the vectors are wasting bites on already infected hosts. The ideal scenario for the pathogen would be if susceptible vectors were more attracted to infected hosts, and infected vectors to susceptible hosts. This happens in some plant diseases such as the barley yellow dwarf virus, or the potato leaf roll virus (Gandon, 2018) but we do not know of any example in animal or human infections. In the case of malaria, this vector-bias effect simply makes infected hosts more attractive to vectors, regardless if the vectors themselves are susceptible or infected (Cornet et al., 2013a; Gandon, 2018).

The hypothesis that USUV transmission is promoted by the vector bias due to *Plasmodium* in co-infected hosts is also not supported in the long term. In fact, we observe the opposite, with a higher vector bias leading to a lower long-term prevalence of USUV (see Fig. 4b). One might think that this is due to the additional death rate caused by the co-infection, but this is not the case. By setting $\delta_c = \delta_p + \delta_u$ (that is, no additional death rate on top of the increase due to *Plasmodium* and USUV infection), we still observe a decrease in long-term USUV prevalence as vector bias increases. Our explanation for the negative influence of a vector bias on USUV transmission is the following. For the sake of argument, consider a starting population consisting only of uninfected hosts and hosts with *Plasmodium*, and that the vector bias $k \to \infty$. In this extreme scenario, the vectors are exclusively biting hosts already infected with *Plasmodium*. This means that the only new *Plasmodium* infections are in the class of uninfected vectors becoming infected with *Plasmodium*. No new infections in the hosts occur in this case since the vectors never get a chance to bite them. With time, the hosts in the starting population that were infected with *Plasmodium* die out. Now consider the same extreme situation with USUV also in circulation. We start with a population with a certain amount of susceptible, *Plasmodium*-infected, USUV-infected, and co-infected hosts. If $k \to \infty$, then vectors bite only hosts already infected with *Plasmodium* or co-infected. The only way to produce new USUV infections in hosts is in the specific case where a vector infected with USUV (either single- or co-infected) bites a *Plasmodium*-infected host and these decline over time. This is in stark contrast of a scenario where $k \approx 1$, i.e., when there is no vector bias. In this case, there are more opportunities to generate USUV infections in hosts: (i) that are susceptible when bitten by an USUV-infected vector; (ii) that are *Plasmodium*-infected when bitten by an USUV-infected vector. Therefore, in the long term we expect USUV prevalence to be negatively affected by a strong vector

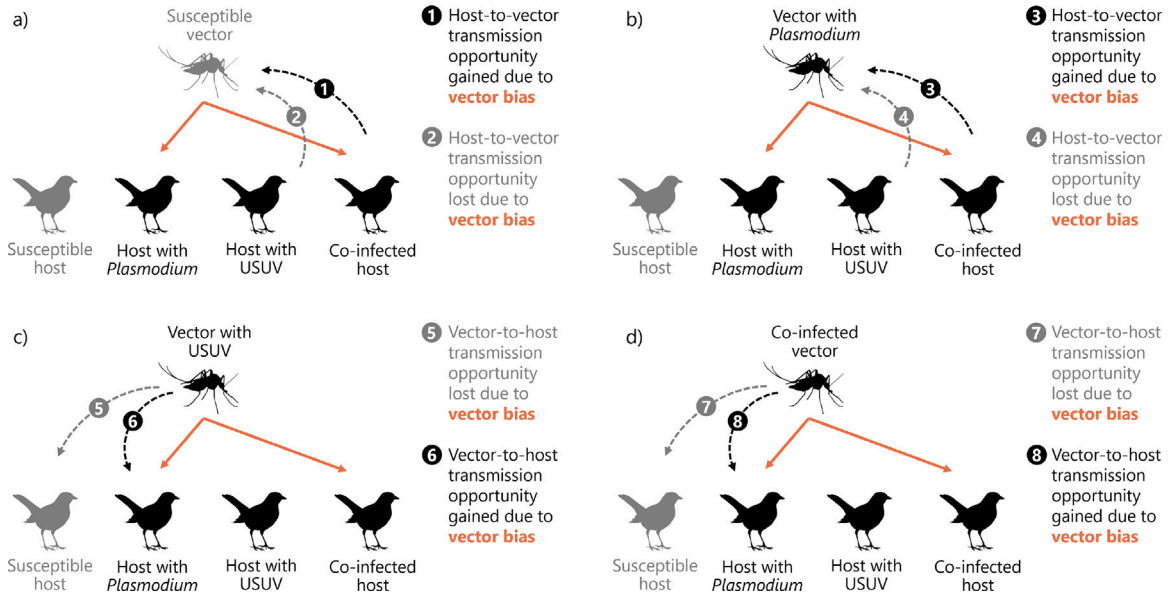

Fig. 6. How the potential promotion of USUV due to the vector bias is self-negated. (a-d) For every biting possibility, an opportunity to transmit USUV happens always at the expense of missing a different opportunity to transmit it. For example, in (a) a susceptible vector may become infected with USUV if the vector bias shifts its preference from a susceptible host, but not if it shifts its preference from a host with USUV. At the onset of an epidemic, co-infected hosts are rare so a vector bias can produce new infections in the case where the mosquito 'wanted' to choose a susceptible host rather than a host carrying USUV. However, a high vector bias also leads to a lower prevalence of *Plasmodium*, making co-infections even more rare to begin with.

preference towards *Plasmodium*-infected hosts. Logically, this extreme scenario is simply an argument we employ to explain the patterns in Fig. 4. In reality, if $k \to \infty$, then before USUV is even introduced, the *Plasmodium* prevalence would already be zero. As explained before, the prevalence of hosts infected with *Plasmodium* would decrease to zero in this scenario, and any questions related to co-infections would no longer apply.

Contact heterogeneity plays a big role in the invasion of vector-borne diseases (Simpson et al., 2012; Miller and Huppert, 2013; Smith et al., 2007). It is also known that contact clustering can, under certain conditions, promote the spread of infections and even co-infections (Hébert-Dufresne and Althouse, 2015; Mann et al., 2021). In the indirect interaction between *Plasmodium* and USUV, the contacts between vectors and hosts are made more clustered, but only transiently. That is, when the hosts become infected with *Plasmodium*, the biting patterns of the vectors are affected by the vector bias and hence the network structure is temporarily changed. Here we showed how changes in contact structure by a vector bias promote the invasion and spread of the pathogen responsible for such bias, but do not further facilitate the invasion and spread of further pathogens that share a similar transmission cycle.

In Fig. 6 we illustrate the transmission possibilities of USUV. Unlike the case of *Plasmodium* invasion into a naive population, the invasion of USUV is not always promoted by a vector bias. Such transmission opportunities are only promoted if the mosquito preference is shifted from hosts not carrying USUV towards co-infected hosts. If that attractiveness for *Plasmodium* single-infected hosts and co-infected hosts competes with the attractiveness towards USUV single-infected, then the vector bias promotion effect is self-negated.

Our model neglects some ecological mechanisms that could be relevant in the transmission of *Plasmodium* and USUV. For example, malaria is caused by several types of *Plasmodium*, while we considered only the one that has the strongest burden on blackbirds as this was our population of interest. Future studies could investigate how the different strains differ in transmission behaviour and burdens on the host and how that in turn can affect co-circulation of other vector-borne diseases. The consequences of *Plasmodium* infection on birds are quite severe, with individuals in some cases suffering from sudden death. This may impede co-infections to ever becoming common, even in the absence of an even stronger effect on mortality caused by both infections occurring at the same time.

Due to lack of information in the literature on the co-transmission rates of these diseases, assumptions had to be made. Given that the transmission rates of each disease were relatively high, there is an argument to be made that the co-transmission rate, under the assumption of independent transmission, would also be unrealistically high. This would mean that co-infected individuals would have the chance to transmit only the first disease, only the second, or both with the same chance, which would also be near the biting rate. To limit this, one could add a penalty in the transmission of each disease or in the co-transmission. Since we had data on the transmission of each disease, but not on the co-transmission, we believe this it is a fair choice to add a penalty to the co-transmission rates. The decision to divide co-transmission rates by 3, rather than independently decreasing the transmission rates of each disease, could introduce a limitation in our model. While the chosen approach simplifies the modelling process, it may not fully capture the nuanced dynamics of individual disease transmissions. Ideally, we would have detailed data on the transmission probabilities for each disease in the appropriate species, but in the absence of that decreasing transmission rates independently could be an alternative strategy, potentially offering a more detailed representation of how each disease contributes to overall transmission. Both options have their merits, and the choice between them depends on the specific goals of the modelling study and the desired level of detail in representing disease interactions.

We only included fitness costs to the hosts, reflected by the additional death rate parameters. There is evidence, however, that vectors also suffer consequences when biting infected hosts. For co-infections between *Plasmodium* and lymphatic filariasis the mosquitoes suffer increased mortality. This has been shown to decrease the long-term prevalence of *Plasmodium* in both hosts and vectors (Slater et al., 2013). Even though there is no study showing a vector disease-induced additional death rate for either *Plasmodium* or USUV, there is a reduction in fecundity when infected with *Plasmodium* (Vézilier et al., 2012). More fine-tuned models could then investigate if this fitness burden

out-weights the facilitation of introduction of USUV (or another vector-borne disease) due to a vector bias. A study (Cornet et al., 2013b) found that a vector bias was detected only during the chronic phase, that is after approximately 24 days post infection in the host. Our model, however, assumes an immediate effect as soon as the host gets infected with malaria. This could lead to overestimation of $R_0(P)$ and accelerated transmission dynamics at the long term for both *Plasmodium* and USUV.

Our formulation did not consider explicitly multiple infections of the same pathogen. In other words, we assume that a host already infected with malaria is indistinguishable from a host that was by chance infected with malaria two or more times. Repeated malaria infections in birds have been reported and carry additive costs (Marzal et al., 2008), which were not accounted for in our model. Alternatively, a co-infection model that allows for repeated infection of the same (van Baalen and Sabelis, 1995) or different strains could be applied (Choisy and de Roode, 2010). The added fitness cost of multiple malaria infections leads to overall fewer hosts that are more attractive to mosquitoes (essentially having a lower vector bias), potentially promoting USUV in the long term.

After co-circulations of *Plasmodium* and West Nile virus were detected in suburban Chicago (Medeiros et al., 2014), it was pointed out how endemic *Plasmodium*, and the heterogeneous biting patterns it causes, may influence WNV transmission (Medeiros et al., 2016). However, as pointed out earlier, a negative association between *Plasmodium* and WNV has been observed (Medeiros et al., 2014). It is unclear whether this is a result of a direct interaction between *Plasmodium* and WNV, or due to the decreased survival of the co-infected hosts. Since WNV and USUV are closely related viruses, one can hypothesize that a negative interaction similar to the one discussed here may happen between *Plasmodium* and USUV. This would make any potential amplification caused by co-infections even less significant. A recent study observed that co-infected blackbirds had lower levels of *Plasmodium* than single-infected ones (Himmel et al., 2020). This all seems to suggest that co-infections are an unlikely major driver for the USUV spread, which is consistent with our results.

The invasion success of a new pathogen depends on a vast array of factors. Our model provided a way to include indirect interactions with an endemic infection and the invading disease. The increased attractiveness caused by the endemic pathogen does not necessarily facilitate the invasion of a new one, nor does it lead to a higher prevalence in the long term. This showed that one needs to take a closer look at community interactions and history of infections when trying to understand the risk of establishment of new vector-borne diseases.

CRediT authorship contribution statement

Afonso Dimas Martins: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Mick Roberts:** Writing – review & editing, Validation, Methodology, Formal analysis. **Quirine ten Bosch:** Writing – review & editing, Visualization, Validation, Supervision. **Hans Heesterbeek:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.tpb.2024.04.002.

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