COMPARATIVE DYNAMICS OF MONOVALENT AND BIVALENT VACCINATION FOR IMMUNOLOGICALLY UNRELATED PATHOGENS

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Multivalent vaccines are designed to immunize against two or more pathogens in a single dose vaccination. A challenge for wide spread use of these vaccines is their lower protection efficacy compared to monovalent vaccines that immunize individuals against a single pathogen. We sought, for the first time, to evaluate the outcomes of bivalent and monovalent vaccines in terms of the reduction in the number of infections over time. For this evaluation, we developed epidemiological models governing the transmission dynamics of two immunologically unrelated pathogens, where immunity conferred by vaccination or natural infection of one pathogen does not provide any cross-protection against the other pathogen. We assumed that a monovalent vaccine provides full, but temporary, protection against a particular pathogen. While protecting against both pathogens requires two pathogen-specific monovalent vaccines, a single dose of the bivalent vaccine provides partial protection against both pathogens. We analyzed the two models to investigate the impact of vaccination. In addition to examining global behaviours and disease persistence of the models, we performed simulations to show the existence of a biologically feasible region for the bivalent vaccine to outperform monovalent vaccines for prevention of disease transmission using a lower number of vaccines.

Keywords: Bivalent Vaccination; Epidemic Modelling; Basic Reproduction Number; Stability Analysis; Persistence; Simulations

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1. Introduction

Vaccination has proven as the most effective and economical measure against many communicable diseases.[1–3] The aim of vaccination is to provide active acquired immunity against a particular pathogen, thereby preventing infection and related outcomes upon exposure to the pathogen. Since the discovery of the polysaccharide conjugate vaccines in the late 1980s,[4] the impact of vaccination on the pathogen-population landscape has dramatically changed. Haemophilus influenzae serotype b (Hib) is the first infection against which a polysaccharide conjugate vaccine was developed and implemented as part of the infant immunization programs in several affected populations.[4] Since then, a number of multivalent combined or unimolecular vaccines have been produced to protect individuals against different pathogens or different serotypes of a pathogen using a single vaccine dose.[5–7] A particular example is the DTaP-IPV-Hib combined vaccine that protects individuals against diphtheria, tetanus, pertussis, polio and Hib.[8]

Multivalent vaccines have the advantage of providing protection against two or more diseases in a single dose, and therefore eliminate a number of logistical and administrative challenges associated with vaccination using monovalent vaccines. However, the protection efficacy of multivalent vaccines may be lower than that provided by individual monovalent vaccines. For instance, several studies have demonstrated lower immunogenicity to the Hib component of the DTaP-IPV-Hib combined vaccine products that include Hib antigens when compared with individually administered Hib polysaccharide conjugate vaccine.[9–12] In addition to the lower protection efficacy conferred by such multivalent vaccines, waning immunity and deferral of boosting may be a cause for the resurgence of some severe infections, such as invasive Hib disease.[13]

In this study, we develop vaccination models to investigate, the effect of monovalent and bivalent vaccines, and compare the outcomes in terms of the vaccine-induced protection and vaccine coverage. We consider these models for two pathogens (referred to as pathogen A and pathogen B), and assume that no cross-protection is conferred through vaccination or natural infection. In the monovalent model, vaccines are assumed to provide full protection against each pathogen for a certain period of time. In the bivalent model, we assume that the vaccine is imperfect, providing only partial protection against each pathogen. While investigating theoretical aspects of these models, we simulate them to illustrate the time profiles of infection spread in the population. By means of simulations, we also show the importance of the durations of vaccine-induced protection and naturally acquired immunity when comparing the outcomes of these models.

2. Vaccination models

To develop vaccination models, we divide a homogeneously mixing population of size N into classes of susceptibles (S), infected individuals with pathogen A (I_A), infected individuals with pathogen B (I_B), recovered individuals from infection with

pathogen A (T_A), recovered individuals from infection with pathogen B (T_B), infected individuals with pathogen B after recovery from infection with pathogen A (J_B), infected individuals with pathogen A after recovery from infection with pathogen B (J_A), and recovered individuals after subsequent infections with both pathogens (R). We assume that recovery from infection with one pathogen does not provide any cross-protection against the other pathogen. We exclude the occurrence of co-infection with both pathogens A and B from our models. Vaccination models include other subpopulations based on the type of vaccine being implemented. In the absence of vaccination, the model (2.3) is expressed as the following system of differential equations

$$\begin{aligned}
S' &= \Lambda - (F_A + F_B)S - dS + \theta(T_A + T_B + R),\\
I'_A &= F_A S - \gamma_A I_A - dI_A,\\
I'_B &= F_B S - \gamma_B I_B - dI_B,\\
T'_A &= \gamma_A I_A - F_B T_A - dT_A - \theta T_A,\\
T'_B &= \gamma_B I_B - F_A T_B - dT_B - \theta T_B,\\
J'_A &= F_A T_B - \gamma_A J_A - dJ_A,\\
J'_B &= F_B T_A - \gamma_B J_B - dJ_B,\\
R' &= \gamma_A J_A + \gamma_B J_B - dR - \theta R,
\end{aligned} \tag{2.1}$$

where

$$F_A = \beta_A \frac{I_A + J_A}{N}, \quad F_B = \beta_B \frac{I_B + J_B}{N}.$$

Parameters of this system are described in Table 2.1. This system will be used as a basic framework for the development of monovalent and bivalent vaccination models.

2.1. *The monovalent vaccine model (MVM)*

In this model, susceptible individuals may be vaccinated against pathogen A (W_A) only, pathogen (W_B) only, or both pathogen (W_{AB}). Vaccination against each pathogen is assumed to provide full protection for a certain period of time. After the vaccine-induced protection has waned, individuals will become susceptible to the infection again. We assume that the durations of vaccine-induced protection and naturally acquired immunity (through natural infection) are the same for both pathogens A and B. Considering the basic framework in (2.1), the MVM is

expressed by

$$\begin{aligned}
S' &= (1-p_m)\Lambda - (F_A + F_B)S - dS + \theta(T_A + T_B + W_A + W_B + W_{AB} + R),\\
I'_A &= F_A S - \gamma_A I_A - dI_A,\\
I'_B &= F_B S - \gamma_B I_B - dI_B,\\
T'_A &= \gamma_A I_A - F_B T_A - dT_A - \theta T_A,\\
T'_B &= \gamma_B I_B - F_A T_B - dT_B - \theta T_B,\\
J'_A &= F_A T_B - \gamma_A J_A - dJ_A,\\
J'_B &= F_B T_A - \gamma_B J_B - dJ_B,\\
W'_A &= p_m r_A \Lambda - F_B W_A - dW_A - \theta W_A,\\
W'_B &= p_m r_B \Lambda - F_A W_B - dW_B - \theta W_B,\\
X'_A &= F_A W_B - \gamma_A X_A - dX_A,\\
X'_B &= F_B W_A - \gamma_B X_B - dX_B,\\
W'_{AB} &= p_m r_{AB} \Lambda - dW_{AB} - \theta W_{AB},\\
R' &= \gamma_A J_A + \gamma_B J_B + \gamma_A X_A + \gamma_B X_B - dR - \theta R,
\end{aligned} \tag{2.3}$$

where

$$F_A = \beta_A \frac{I_A + J_A + X_A}{N}, \quad F_B = \beta_B \frac{I_B + J_B + X_B}{N}.$$

In this model, X_A represents the class of individuals who are infected with pathogen A after being vaccinated only against pathogen B. Similarly, X_B represents the class of individuals who are infected with pathogen B after being vaccinated only against pathogen A. The overall vaccination coverage is given by p_m (where $0 \leq p_m \leq 1$). The parameters r_A, r_B, and r_{AB} represent respectively the fractions of this coverage considered for vaccination against pathogen A, against pathogen B, and against both pathogens, giving $r_A + r_B + r_{AB} = 1$. Other parameters of this model are described in Table 2.1.

2.2. *The bivalent vaccination model (BVM)*

In this model, we assume that a single dose of the vaccine provides protection against both pathogens A and B. In contract to the monovalent vaccine, we assume that the bivalent vaccine confers only partial protection against each pathogen, which reduces susceptibility to infection. Therefore, vaccinated individuals (V_{AB}) may encounter infection with pathogen A or pathogen B at reduced transmission rates. Recovered individuals from infection with pathogen A (Q_A) and pathogen B (Q_B) following vaccination may respectively acquire infection with pathogen B (Y_B) and pathogen A (Y_A). Inclusion of these subpopulations to the basic framework

Table 1. Description of parameters and their values (ranges) used in simulations of the monovalent and bivalent vaccination models.

Model parameters	Description	Values/Range
Λ	recruitment rate	10 yr^{-1}
d	natural death rate	1/70 yr^{-1}
β_A, β_B	transmission rates	0.12, 0.13 $\text{yr}^{-1}\text{people}^{-1}$
γ_A, γ_B	recovery rates from infection	1/10 days^{-1}
θ	rate of waning immunity	varied
p_m	vaccination coverage	varied: [0, 1]
r_A	fraction vaccinated against pathogen A only	0.2
r_B	fraction vaccinated against pathogen B only	0.2
r_{AB}	fraction vaccinated against both pathogens	$1-(r_A+r_B)$
$p_m(r_A+r_{AB})$	vaccination coverage against pathogen A	varied
$p_m(r_B+r_{AB})$	vaccination coverage against pathogen B	varied
p_b	vaccination coverage	varied: [0, 1]
κ_A, κ_B	transmission reduction factors due to vaccine	0.2

gives the following system of differential equations:

$$
\begin{aligned}
S' &= (1-p_b)\Lambda - (F_A+F_B)S - dS + \theta(T_A+T_B+Q_A+Q_B+R+V_{AB}),\\
I'_A &= F_A S - \gamma_A I_A - dI_A,\\
I'_B &= F_B S - \gamma_B I_B - dI_B,\\
T'_A &= \gamma_A I_A - F_B T_A - dT_A - \theta T_A,\\
T'_B &= \gamma_B I_B - F_A T_B - dT_B - \theta T_B,\\
J'_A &= F_A T_B - \gamma_A J_A - dJ_A,\\
J'_B &= F_B T_A - \gamma_B J_B - dJ_B,\\
V'_{AB} &= p_b\Lambda - (\kappa_A F_A + \kappa_B F_B)V_{AB} - dV_{AB} - \theta V_{AB},\\
X'_A &= (\kappa_A F_A)V_{AB} - \gamma_A X_A - dX_A,\\
X'_B &= (\kappa_B F_B)V_{AB} - \gamma_B X_B - dX_B,\\
Q'_A &= \gamma_A X_A - (\kappa_B F_B)Q_A - dQ_A - \theta Q_A,\\
Q'_B &= \gamma_B X_B - (\kappa_A F_A)Q_B - dQ_B - \theta Q_B,\\
Y'_A &= (\kappa_A F_A)Q_B - \gamma_A Y_A - dY_A,\\
Y'_B &= (\kappa_B F_B)Q_A - \gamma_B Y_B - dY_B,\\
R' &= \gamma_A J_A + \gamma_B J_B + \gamma_A Y_A + \gamma_B Y_B - dR - \theta R,
\end{aligned}
\tag{2.5}
$$

where

$$
F_A = \beta_A \frac{I_A + J_A + X_A + Y_A}{N}, \quad F_B = \beta_B \frac{I_B + J_B + X_B + Y_B}{N}.
$$

In this model, p_b represents the vaccination coverage with $0 \le p_b \le 1$. Other parameters are described in Table 2.1.

3. Analysis of the MVM

The system is at an equilibrium if the time derivatives of its variables are zero. The equation

$$N' = \Lambda - dN \tag{3.1}$$

describes the dynamics of the total population. At the equilibrium for the total population we have $N^* = \Lambda/d$, which is globally attracting. From the system specifications, it follows that nonnegative initial values give rise to nonnegative solutions. It is thus meaningful to define the phase space Γ for model (2.3), as

$$\Gamma = \{x = (S, I_A, \ldots, R) \in \mathbb{R}^{13}_+ : N \leq N^*\}.$$

The space Γ is positively invariant with respect to the model (2.3). The solutions are bounded, and remain nonnegative for nonnegative initial values. There is a unique disease-free equilibrium (DFE) given by

$$\begin{aligned} &S^0 = (1-p_m)\frac{\Lambda}{d} + \frac{p_m \Lambda\theta}{(d+\theta)d}, \\ &I^0_A = 0, \quad J^0_A = 0, \quad X^0_A = 0, \quad I^0_B = 0, \quad J^0_B = 0, \quad X^0_B = 0, \\ &T^0_A = 0, \quad T^0_B = 0, \quad R^0 = 0, \\ &W^0_A = \frac{p_m\, r_A \Lambda}{d+\theta}, \quad W^0_B = \frac{p_m\, r_B \Lambda}{d+\theta}, \quad W^0_{AB} = \frac{(p_m\, r_{AB})\Lambda}{d+\theta}. \end{aligned} \tag{3.3}$$

The disease-free subspace is defined as

$$\Gamma_0 = \{x \in \Gamma : I_A = J_A = X_A = I_B = J_B = X_B = 0\}.$$

In Γ_0, model (2.3) reduces to a linear system, and it is easy to obtain that the DFE is globally asymptotically stable in the disease-free subspace Γ_0.

We define the corresponding reproduction numbers for pathogens A and B in model (2.3), as we introduce an individual infected with pathogen A or B, into a completely susceptible population:

$$\begin{aligned} \mathcal{R}_{Am} &= \frac{\beta_A}{(\gamma_A + d)N^*}(S^0 + W^0_B) = \frac{\beta_A}{(\gamma_A + d)}\left(1 - \frac{p_m(1-r_B)d}{d+\theta}\right), \\ \mathcal{R}_{Bm} &= \frac{\beta_B}{(\gamma_B + d)N^*}(S^0 + W^0_A) = \frac{\beta_B}{(\gamma_B + d)}\left(1 - \frac{p_m(1-r_A)d}{d+\theta}\right). \end{aligned} \tag{3.5}$$

Theorem 3.1 *The DFE of model* (2.3) *is locally asymptotically stable if* $\max\{\mathcal{R}_{Am}, \mathcal{R}_{Bm}\} < 1$, *and unstable if* $\max\{\mathcal{R}_{Am}, \mathcal{R}_{Bm}\} > 1$.

A Proof of the theorem is provided in Appendix A. We performed theoretical analysis to investigate the local and global dynamics of the MVM. In particular, after establishing the existence of a unique DFE and describing its local stability, the existence of endemic equilibria are also investigated. Various threshold quantities–reproduction numbers–are defined to describe local and global stability, and we give

sufficient conditions for disease persistence in the MVM. These analyses provide rich dynamics of the model, and we refer the reader to Appendix A for their derivations and proofs.

4. Analysis of the BVM

The steady state $N^* = \Lambda/d$ for the total population is globally attracting in model (2.5). Furthermore, nonnegative initial conditions give rise to nonnegative solutions. The phase space for model (2.5) is defined as

$$\Gamma = \{x = (S, I_{_A}, \ldots, R) \in \mathbb{R}^{15}_{+} : N \leq N^*\},$$

where for simplicity we use the same notation as for model (2.3). The space Γ is positively invariant with respect to model (2.5). The solutions are bounded, and remain nonnegative for nonnegative initial values.

There is a unique DFE given by

$$\begin{aligned} S^0 &= (1-p_b)N^* + \frac{\theta p_b N^*}{(d+\theta)}, \\ V^0_{_{AB}} &= \frac{dp_b N^*}{d+\theta}, \\ I^0_{_A} &= 0, \quad J^0_{_A} = 0, \quad X^0_{_A} = 0, \quad Y^0_{_A} = 0, \\ I^0_{_B} &= 0, \quad J^0_{_B} = 0, \quad X^0_{_B} = 0, \quad Y^0_{_B} = 0, \\ T^0_{_A} &= 0, \quad T^0_{_B} = 0, \quad Q^0_{_A} = 0, \quad Q^0_{_B} = 0, \quad R^0 = 0. \end{aligned} \tag{4.2}$$

In the disease-free subspace $\Gamma_0 = \{x \in \Gamma : I_{_A} = J_{_A} = X_{_A} = Y_{_A} = 0, I_{_B} = J_{_B} = X_{_B} = Y_{_B} = 0\}$ the DFE is globally asymptotically stable in model (2.5). We define the reproduction numbers for pathogens A and B as:

$$\begin{aligned} \mathcal{R}_{Ab} &= \frac{\beta_{_A}}{(\gamma_{_A}+d)N^*}(S^0 + \kappa_{_A} V^0_{_{AB}}) = \frac{\beta_{_A}}{(\gamma_{_A}+d)}\left(1 - \frac{p_b(1-\kappa_{_A})d}{d+\theta}\right), \\ \mathcal{R}_{Bb} &= \frac{\beta_{_B}}{(\gamma_{_B}+d)N^*}(S^0 + \kappa_{_B} V^0_{_{AB}}) = \frac{\beta_{_B}}{(\gamma_{_B}+d)}\left(1 - \frac{p_b(1-\kappa_{_B})d}{d+\theta}\right). \end{aligned} \tag{4.3}$$

Theorem 4.1 *In model* (2.5)*, the DFE is locally asymptotically stable if* $\max\{\mathcal{R}_{Ab}, \mathcal{R}_{Bb}\} < 1$*, and unstable if* $\max\{\mathcal{R}_{Ab}, \mathcal{R}_{Bb}\} > 1$*.*

The proof of this theorem is similar to Theorem 3.1, and we omit it. One can also show the persistence of the disease, and investigate the local and global behaviour of the BVM. Details of such dynamics are provided in Appendix B. Proofs and detailed explanations are omitted where they are similar to those obtained for the MVM.

5. Simulation results

The theoretical analyses of the MVM and BVM (see Appendices A and B) provide rich dynamics of these systems with respect to their local and global behaviours.

The purpose of our simulations here is to compare these models to determine the conditions under which a bivalent vaccine could outcompete monovalent vaccines in preventing infection spread by both pathogens. This comparison is associated with two key parameters including the level of vaccine-induced protection and vaccination coverage of individuals in the population. In the BVM, the number of vaccines is the same as the vaccination coverage; however, in the MVM, protecting individuals against both pathogens with the same coverage as in the BVM requires twice as many vaccinations.

In the MVM, the number of individuals vaccinated per unit time is $p_m\Lambda$. A fraction $r_A + r_B$ of vaccinated newborns receives vaccine against one pathogen only, and the remaining fraction r_{AB} receives vaccines against both pathogens A and B. Since $r_A + r_B + r_{AB} = 1$, the total number of vaccines administered per unit time is $(r_A + r_B)\, p_m\Lambda + 2\, r_{AB}\, p_m\Lambda = p_m\Lambda(1 + r_{AB})$. In the BVM, the number of newborns vaccinated per unit time is $p_b\Lambda$, and each vaccinee receives a single dose of vaccine against both pathogens. Hence, the total number of vaccines is $p_b\Lambda$. It is therefore meaningful to compare the total vaccine doses $(1 + r_{AB})\, p_m\Lambda$ and $p_b\Lambda$ per unit time in the two models. We performed numerical simulations to reveal whether it is possible to reduce the incidence of infections through a bivalent vaccine without increasing the total number of vaccines in the population compared with the MVM.

Heatmaps presented in Figure 1 show the difference in the cumulative number of infections for each pathogen in the two models over twenty years following the start of vaccination. The simulations were run when p_m and p_b vary in their respective ranges between 0 (in the absence of vaccination) and 1 (full vaccination coverage of newborns). In our simulations, four values were considered for the average time period of protection following vaccination or recovery from infection. Figure 1 shows the results for lifetime protection, i.e., $\theta = 0$ (A,E); $\theta^{-1} = 5$ years (B,F); $\theta^{-1} = 10$ years (C,G); and $\theta^{-1} = 15$ years (D,H) protection. Other parameter values are provided in Table 2.1. First and second rows in Figure 1 correspond to the difference in the cumulative number of infections between the two models for pathogens A and B, respectively, with the magnitude of difference indicated by colour bars. The red line indicates the same cumulative number of infections in the two models. The black dashed-line corresponds to the same number of vaccine doses in both models (i.e., $p_b = (1 + r_{AB})p_m$). Colours corresponding to positive numbers above the red line identify the areas in the heatmaps where the cumulative number of infections in the MVM is higher than that in the BVM. Any point below the black dashed-line corresponds to a lower vaccine doses in the BVM compared with the MVM (that is, $p_b < p_m(1 + r_{AB})$). We observed that the red line is below the black dashed-line for values of θ (inverse of the duration of protection) used for simulations, implying that it is possible to reduce the cumulative number of infections for each pathogen by implementing a bivalent vaccine while using a lower number of vaccines compared to the MVM. However, as the length of the duration of protection following vaccination or recovery from natural infection increases, the difference in the cumulative number of infections between the two vaccination models decreases.

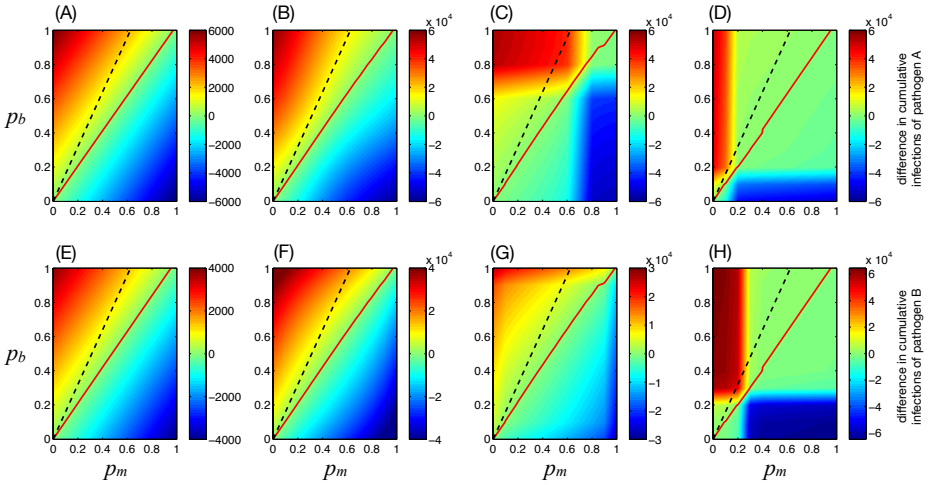

Fig. 1. Comparison of the cumulative number of infections caused by each pathogen in the two models over twenty years, with varying vaccine coverages. In figures A and E, the duration of immunity is lifetime ($\theta = 0$). In other figures, the duration of immunity is $\theta^{-1} = 5$ years (B,F), $\theta^{-1} = 10$ years (C,G), and $\theta^{-1} = 15$ years (D,H). Colour bars show the difference between the cumulative number of infections in the MVM and BVM. Positive values indicate a lower number of infections using a bivalent vaccine. The red line corresponds to scenarios where the difference in the cumulative number of infections is zero. In the area below the black dashed-line, the total number of vaccines in the BVM is lower than that in the MVM. Other parameter values are provided in Table 2.1.

For comparison purposes, we also simulated the time profiles of infection caused by each pathogen in the two models. For these simulations we fixed a pair of (p_m, p_b) in the area between the red and black dashed lines in the heatmaps. Figures 2 and 3 show these time profiles, where red, blue, and green curves correspond to the classes I_A, J_A, and X_A in each model, and magenta curves in Figure 3 correspond to the class Y_A in the BVM. Parameter values are provided in Table 2.1 with $p_m = 0.6$ and $p_b = 0.8$. These simulations show a similar qualitative behaviour of infection curves when the difference in the cumulative number of infections between the two models is small. However, for large differences (Figure 1C), the corresponding infection curves render different long-term behaviour (Figures 2-C,G and 3-C,G).

Remark. For the simulations presented here, we assumed the same duration of immune protection following vaccination and recovery from natural infection. However, for many diseases, natural infection may induce stronger and longer-lasting immunity than vaccination. We therefore carried out further simulations with a longer protection period for immunity induced by natural infection compared to that conferred by vaccination. We observed (Figure 4) that the effect of naturally acquired immunity transcends the effect of vaccine-induced immunity.

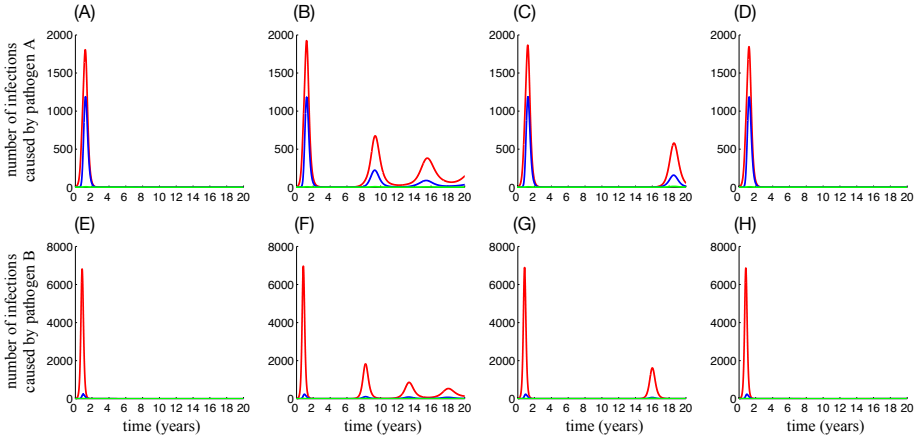

Fig. 2. Time profiles of infections caused by each pathogen in the MVM (2.3), where the duration of immunity is (A,E): lifetime ($\theta = 0$); (B,F): 5 years ($\theta^{-1} = 5$); (C,G): 10 years ($\theta^{-1} = 10$); and (D,H): 15 years ($\theta^{-1} = 15$). Red, blue, and green curves correspond to the classes I_A, J_A, and X_A. Vaccination coverages are $p_m = 0.6$ and $p_b = 0.8$. Other parameter values are provided in Table 2.1.

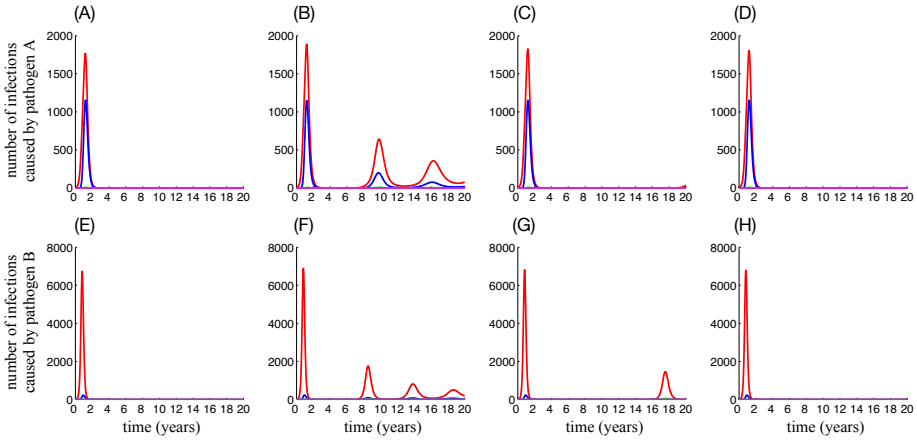

Fig. 3. Time profiles of infections caused by each pathogen in the BVM (2.5), where the duration of immunity is (A,E): lifetime ($\theta = 0$); (B,F): 5 years ($\theta^{-1} = 5$); (C,G): 10 years ($\theta^{-1} = 10$); and (D,H): 15 years ($\theta^{-1} = 15$). Red, blue, green, and magenta curves correspond to the classes I_A, J_A, X_A, and Y_A. Vaccination coverages are $p_m = 0.6$ and $p_b = 0.8$. Other parameter values are provided in Table 2.1.

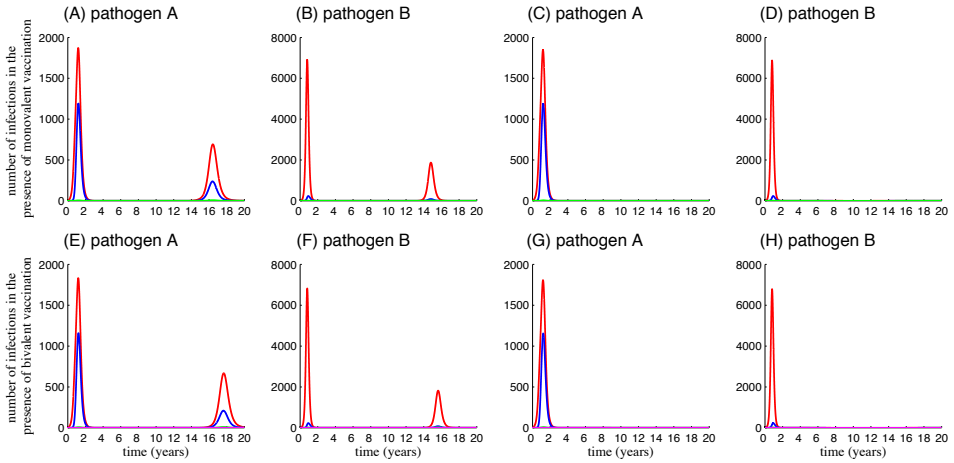

Fig. 4. Time profiles of infections caused by each pathogen in the BVM (2.5), where the duration of vaccine-induced immunity is (A,B,E,F): 5 years; (C,D,G,H): 10 years; and the duration of naturally acquired immunity is (A,B,E,F): 10 years; (C,D,G,H): 15 years. Red, blue, green, and magenta curves correspond to the classes I_A, J_A, X_A, and Y_A. Vaccination coverages are $p_m = 0.6$ and $p_b = 0.8$. Other parameter values are provided in Table 2.1.

Discussion

Bivalent vaccines have the advantage of providing immunity against two or more pathogens in a single-dose vaccination. These vaccines can potentially reduce costs associated with the administration of single-dose vaccines for different diseases, in addition to providing the uniform vaccination coverage of each disease. However, the protection efficacy of such vaccines may not be as good as that provided by individually administered monovalent vaccines against different pathogens. A number of bivalent vaccines are currently being used in many countries,[5–8] however an important question is whether these vaccines could reduce the morbidity caused by different pathogens in the population without increasing vaccine doses compared to monovalent vaccines.

To address this question, we developed, for the first time, epidemiological models for transmission dynamics of two immunologically unrelated pathogens, where immunity conferred by vaccination or natural infection of one pathogen does not provide any cross-protection against the other pathogen. These models have the same basic framework in the absence of vaccination, but they are structurally different when monovalent and bivalent vaccines are incorporated. We carried out the theoretical analysis to show global behaviours and persistence. While the vaccine-induced immunity wanes over time in both models, our main assumption is that monovalent vaccines provide full protection against each pathogen, but the bivalent vaccine provides only partial protection against both pathogens.

We compared the outcomes of vaccination in each model by means of numerical

simulations. For this evaluation, we considered the cumulative number of infections caused by each pathogen in the two models overtime, while changing the time duration of the vaccine-induced protection. Our simulation results (Figure 1) suggest that, within biologically feasible range of model parameters, it is possible to reduce the total number of infections using a bivalent vaccine with a lower number of vaccines compared to the MVM. This is illustrated by the region between red and dashed-black lines in Figure 1. We observed that the reduction in the total number of infections over a certain period of time depends significantly on the duration of the vaccine-induced protection (i.e., the parameter $1/\theta$). We also note that our results are quantitatively subject to variations in the parameter space; however, we expect that qualitative signatures of the models remain intact in epidemiologically feasible spectra.

In models considered here, we assumed no cross-protection between the two pathogens. When considering bivalent vaccines for different strains of the same pathogen in the presence of cross-protection, the dynamics of disease spread and prevention become more complex. In this case, recovery from infection with one strain may provide partial protection against infection with another strain. Complexity of disease dynamics when using this type of bivalent vaccines merits further investigation. Additional study of the frameworks developed here for specific vaccines and scenarios is proceeding.

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Appendix A. Persistence and global behaviour of the MVM

Proof of Theorem 3.1. To derive the stability of the DFE, it is sufficient to investigate the Jacobian of the infection subsystem around the DFE. The linear system

$$[I'_A, J'_A, X'_A, I'_B, J'_B, X'_B]^T = J \cdot [I_A, J_A, X_A, I_B, J_B, X_B]^T$$

approximates the dynamics of the infection classes in the initial phase of the epidemic, where J is a 6×6 matrix, defined as

$$J = \begin{bmatrix} J_1 & 0 \\ 0 & J_2 \end{bmatrix}$$

with $J_1, J_2 \in \mathbb{R}^{3\times 3}$,

$$J_1 = \begin{bmatrix} \beta_A \frac{S^0}{N^*} - (\gamma_A + d) & \beta_A \frac{S^0}{N^*} & \beta_A \frac{S^0}{N^*} \\ \beta_A \frac{T_B^0}{N^*} & \beta_A \frac{T_B^0}{N^*} - (\gamma_A + d) & \beta_A \frac{T_B^0}{N^*} \\ \beta_A \frac{W_B^0}{N^*} & \beta_A \frac{W_B^0}{N^*} & \beta_A \frac{W_B^0}{N^*} - (\gamma_A + d) \end{bmatrix},$$

$$J_2 = \begin{bmatrix} \beta_B \frac{S^0}{N^*} - (\gamma_B + d) & \beta_B \frac{S^0}{N^*} & \beta_B \frac{S^0}{N^*} \\ \beta_B \frac{T_A^0}{N^*} & \beta_B \frac{T_A^0}{N^*} - (\gamma_B + d) & \beta_B \frac{T_A^0}{N^*} \\ \beta_B \frac{W_A^0}{N^*} & \beta_B \frac{W_A^0}{N^*} & \beta_B \frac{W_A^0}{N^*} - (\gamma_B + d) \end{bmatrix}.$$

Let $s(J)$ denote the maximum real part of the eigenvalues of J. For stability of the DFE, we require $s(J) < 0$. It follows from the block diagonal structure of J that the six eigenvalues of the matrix arise pairwise as the eigenvalues of the diagonal blocks, which are

$$\lambda_1 = \beta_A \frac{S^0 + T_B^0 + W_B^0}{N^*} - (\gamma_A + d), \quad \lambda_2 = -(\gamma_A + d), \quad \lambda_3 = -(\gamma_A + d),$$
$$\lambda_4 = \beta_B \frac{S^0 + T_A^0 + W_A^0}{N^*} - (\gamma_B + d), \quad \lambda_5 = -(\gamma_B + d), \quad \lambda_6 = -(\gamma_B + d).$$

We note that $\lambda_2, \lambda_3, \lambda_5, \lambda_6 < 0$; moreover $\lambda_1 < 0$ (> 0) if and only if $\mathcal{R}_{Am} < 1$ (> 1), and $\lambda_4 < 0$ (> 0) if and only if $\mathcal{R}_{Bm} < 1$ (> 1). These imply the local stability of the DFE. □

We define four subspaces as follows:

$$\Upsilon_A = \{x \in \Gamma : I_A = 0,\, J_A = 0,\, X_A = 0\},$$
$$\Upsilon_B = \{x \in \Gamma : I_B = 0,\, J_B = 0,\, X_B = 0\},$$
$$\Omega_A = \{x \in \Gamma : I_A + J_A + X_A > 0\},$$
$$\Omega_B = \{x \in \Gamma : I_B + J_B + X_B > 0\}.$$

Υ_A and Υ_B are the extinction spaces of pathogens A and B, respectively. Note that $\Omega_A = \Gamma \setminus \Upsilon_A$, and Ω_A is the subspace where pathogen A is present. Similarly, Ω_B is the subspace where pathogen B is present, and it holds true that $\Omega_B = \Gamma \setminus \Upsilon_B$. It is easy to see that all four subspaces are invariant with respect to model (2.3).

A.1. *Behaviour in the presence of a single pathogen*

We now investigate the behaviour of model (2.3) in the special case, where one of the pathogens (say, without loss of generality, pathogen B) is absent. This confines

the analysis to the subspace Υ_B. For the special case where pathogen A is absent, one can obtain similar results to those presented below.

In Υ_B, the equations for I_B, J_B, and X_B can be eliminated from model (2.3), as $I_B = J_B = X_B \equiv 0$ implies $I_B' = J_B' = X_B' \equiv 0$. We introduce new variables by $\hat{S} = S + T_B + W_B$, $\hat{V} = W_A + W_{AB}$, $\hat{I} = I_A + J_A + X_A$, $\hat{R} = T_A + R$, and obtain the system

$$\begin{aligned}
\hat{S}' &= (1 - p_m(r_A + r_{AB}))\Lambda - \beta_A \frac{\hat{I}}{N}\hat{S} - d\hat{S} + \theta(\hat{V} + \hat{R}),\\
\hat{V}' &= p_m(r_A + r_{AB})\Lambda - d\hat{V} - \theta\hat{V},\\
\hat{I}' &= \beta_A \frac{\hat{I}}{N}\hat{S} - \gamma_A\hat{I} - d\hat{I},\\
\hat{R}' &= \gamma_A\hat{I} - d\hat{R} - \theta\hat{R},
\end{aligned} \tag{A.6}$$

where we used $\hat{S} + \hat{V} + \hat{I} + \hat{R} = N$, $F_B \equiv 0$, and $1 - p_m + p_m r_B = 1 - p_m(r_A + r_{AB})$. With $\hat{V}^0 = \frac{p_m(r_A + r_{AB})\Lambda}{d+\theta}$ and $\hat{S}^0 = (1 - p_m(r_A + r_{AB}))\frac{\Lambda}{d} + \frac{\theta}{d}\hat{V}^0$, the reproduction number of system (A.6) is calculated as

$$\frac{\beta_A}{(\gamma_A + d)N^*}\hat{S}^0 = \frac{\beta_A}{(\gamma_A + d)}\left(1 - \frac{p_m(r_A + r_{AB})d}{d + \theta}\right),$$

and using $r_A + r_{AB} = 1 - r_B$ we note that this formula is the same as that of $\mathcal{R}_{Am}$ in (3.5). Hence, $\mathcal{R}_{Am}$ can be used to describe the reproduction number of system (A.6).

The system (A.6) gives a special case of the system (2) in Ref. 14. Therefore, $\mathcal{R}_{Am}$ gives the reproduction number associated with the system (2) in Ref. 14. Following the analysis in Ref. 14, we define

$$\hat{\mathcal{D}}_1 = \left\{(\hat{S}, \hat{V}, \hat{I}, \hat{R}) \in \mathbb{R}^4_+ : N = N^*\right\}, \quad \hat{\mathcal{D}}_0 = \left\{(\hat{S}, \hat{V}, \hat{I}, \hat{R}) \in \hat{\mathcal{D}}_1 : \hat{I} = 0\right\}.$$

Theorem Appendix A.1 *Consider the system* (A.6). *There is a unique endemic equilibrium* $\hat{\mathcal{E}}_1$ *if and only if* $\mathcal{R}_{Am} > 1$. *The endemic equilibrium* $\hat{\mathcal{E}}_1$ *is globally asymptotically stable in the subspace* $\hat{\mathcal{D}}_1 \setminus \hat{\mathcal{D}}_0$ *whenever* $\mathcal{R}_{Am} > 1$. *For any* $\mathcal{R}_{Am} \geq 0$ *there is a unique DFE, denoted by* $\hat{\mathcal{E}}_0$, *which is globally asymptotically stable in* $\hat{\mathcal{D}}_1$ *whenever* $\mathcal{R}_{Am} \leq 1$.

Proof. We recall from the equation (3.1) that there is a unique equilibrium N^* for the total population, hence every equilibrium of (A.6) lies in $\hat{\mathcal{D}}_1$. It follows from the non-negativity of solutions that $\hat{\mathcal{D}}_1$ is invariant with respect to (A.6). The dynamics of system (A.6) restricted to $\hat{\mathcal{D}}_1$ is equivalent to that of system (15) in Ref. 14. Using Theorems 1, 3, and 4, and Lemmas 3 and 5 of Ref. 14, we establish the assertion of the theorem. □

It is worth mentioning that system (2) in Ref. 14 allows for the forward and backward bifurcations at the DFE. However, the analysis of system (2) in Ref. 14

shows that the backward bifurcation is impossible with a fully protective vaccine, which excludes the possibility of a backward bifurcation in our system (A.6).

For system (A.6), we obtained that $\hat{S}, \hat{V}, \hat{I}$, and $\hat{R}$ converge to one of the two attractors $\hat{\mathcal{E}}_0$ and $\hat{\mathcal{E}}_1$. Let $(\hat{S}, \hat{V}, \hat{I}, \hat{R}) \to (\hat{S}^*, \hat{V}^*, \hat{I}^*, \hat{R}^*)$ where $(\hat{S}^*, \hat{V}^*, \hat{I}^*, \hat{R}^*) \in \{\hat{\mathcal{E}}_0, \hat{\mathcal{E}}_1\}$, and let $F_{_A}^* = \beta_{_A} \hat{I}^*/N^*$. We show that in model (2.3) there is a unique equilibrium $x^* = (S^*, I_{_A}^*, \ldots, R^*)$ associated with each of $\hat{\mathcal{E}}_0$ and $\hat{\mathcal{E}}_1$.

Theorem Appendix A.2 *In model* (2.3)*, there is a unique endemic equilibrium* E_m^A *in* $\Upsilon_{_B}$ *if and only if* $\mathcal{R}_{Am} > 1$*. The equilibrium* E_m^A *is globally asymptotically stable in the subspace* $\Omega_{_A} \cap \Upsilon_{_B} \cap \{x \in \Gamma : N = N^*\}$ *whenever* $\mathcal{R}_{Am} > 1$*. For any* $\mathcal{R}_{Am} \geq 0$*, the unique DFE is globally asymptotically stable in* $\Upsilon_{_B} \cap \{x \in \Gamma : N = N^*\}$ *whenever* $\mathcal{R}_{Am} \leq 1$*.*
In model (2.3)*, there is a unique endemic equilibrium* E_m^B *in* $\Upsilon_{_A}$ *if and only if* $\mathcal{R}_{Bm} > 1$*. The equilibrium* E_m^B *is globally asymptotically stable in the subspace* $\Omega_{_B} \cap \Upsilon_{_A} \cap \{x \in \Gamma : N = N^*\}$ *whenever* $\mathcal{R}_{Bm} > 1$*. For any* $\mathcal{R}_{Bm} \geq 0$ *the unique DFE is globally asymptotically stable in* $\Upsilon_{_A} \cap \{x \in \Gamma : N = N^*\}$ *whenever* $\mathcal{R}_{Bm} \leq 1$*.*

Proof. We prove the first part of the theorem. It is obvious that $T_{_B} \to 0$, $W_{_{AB}} \to W_{_{AB}}^0$, and $W_{_A} \to W_{_A}^0$ in model (2.3) in the subspace $\Upsilon_{_B}$, so let $T_{_B}^* = 0$, $W_{_{AB}}^* = W_{_{AB}}^0$, and $W_{_A}^* = W_{_A}^0$. We also note that $W_{_B} \to W_{_B}^*$ where $W_{_B}^* = p_m r_{_B} \Lambda/(d+\theta+F_{_A}^*) \neq 0$; thus $S \to S^*$ where $S^* = ((1-p_m)\Lambda + \theta(\hat{V}^* + \hat{R}^* + W_{_B}^*))/(F_{_A}^* + d) \neq 0$. Therefore, the components $I_{_A}^*$, $J_{_A}^*$, and $X_{_A}^*$ of the equilibrium must satisfy

$$\begin{aligned} F_{_A}^* S^* &= (\gamma_{_A} + d) I_{_A}^*, \\ F_{_A}^* T_{_B}^* &= (\gamma_{_A} + d) J_{_A}^*, \\ F_{_A}^* W_{_B}^* &= (\gamma_{_A} + d) X_{_A}^*, \\ \hat{I}^* &= I_{_A}^* + J_{_A}^* + X_{_A}^*. \end{aligned}$$

Note that $\hat{I}^* = 0$ and $F_{_A}^* = 0$ in $\hat{\mathcal{E}}_0$, which implies $I_{_A}^* = J_{_A}^* = X_{_A}^* = 0$. Furthermore, we have $\hat{I}^* > 0$, $F_{_A}^* > 0$ in $\hat{\mathcal{E}}_1$, which implies $I_{_A}^* = F_{_A}^* S^*/(\gamma_{_A} + d) > 0$, $J_{_A}^* = 0$, and $X_{_A}^* = F_{_A}^* W_{_B}^*/(\gamma_{_A} + d) > 0$ (note that we used $T_{_B}^* = 0$). In both cases, $I_{_A} \to I_{_A}^*$, $J_{_A} \to J_{_A}^*$, and $X_{_A} \to X_{_A}^*$. Lastly, it is easy to see that $T_{_A} \to T_{_A}^*$ where $T_{_A}^* = \gamma_{_A} I_{_A}^*/(\theta + d)$, and $R \to R^*$ where $R^* = \gamma_{_A} X_{_A}^*/(\theta + d)$.

In the subspace $\Upsilon_{_B}$, the classes $I_{_B}$, $J_{_B}$, and $X_{_B}$ are at zero state. Let $I_{_B}^* = J_{_B}^* = X_{_B}^* = 0$ at any equilibrium. The equilibrium associated with $\hat{\mathcal{E}}_0$ is a DFE of model (2.3), and by uniqueness, it follows that it is the DFE given in (3.3). At the equilibrium of the model (2.3) that is associated with $\hat{\mathcal{E}}_1$, we have $I_{_A}^*, X_{_A}^* > 0$. We denote this equilibrium by E_m^A, which is an endemic equilibrium with respect to pathogen A and disease-free equilibrium with respect to pathogen B. We refer to E_m^A as the boundary endemic equilibrium of model (2.3) in the presence of pathogen A and in the absence of pathogen B. □

A.2. *Persistence and global behavior*

We recall from the equation (3.1) that the total population converges to the equilibrium N^*. We consider model (2.3) as a non-autonomous system with nonautonomous term $N(t)$, which is governed by (3.1). By $\lim_{t\to\infty} N(t) = N^*$, model (2.3) is asymptotically autonomous with the limiting system which arises from (2.3) by replacing $N(t)$ with N^*. In this section our analysis is restricted to the case when the total population is at its steady state, that is, $N = N^*$. By the theory of asymptotically autonomous systems (see Refs. 15–17) the dynamics of the limiting system is qualitatively equivalent to that of the original model (2.3).

Note that the equation for W_{AB} in model (2.3) is independent from other equations, and $\lim_{t\to\infty} W_{AB} = W^0_{AB} = (p_m\, r_{AB})\Lambda/(d+\theta)$. This means that $\lim_{t\to\infty}(N - W_{AB}) = \Lambda/d - (p_m\, r_{AB})\Lambda/(d+\theta)$. We define the quantities

$$\mathcal{R}^c_{Am} = \frac{\beta_A}{(\gamma_A + d)}\left(1 - \frac{d\, p_m\, r_{AB}}{d+\theta}\right),$$

$$\mathcal{R}^c_{Bm} = \frac{\beta_B}{(\gamma_B + d)}\left(1 - \frac{d\, p_m\, r_{AB}}{d+\theta}\right).$$

Note that $\mathcal{R}_{Am} \le \mathcal{R}^c_{Am}$ and $\mathcal{R}_{Bm} \le \mathcal{R}^c_{Bm}$.

Theorem Appendix A.3 *In the subspace* $\Gamma^W = \{x \in \Gamma : W_{AB} \ge (p_m\, r_{AB})\Lambda/(d+\theta)\}$ *each solution converges to the subspace* $\Upsilon_A \cap \Gamma^W$ *(to the subspace* $\Upsilon_B \cap \Gamma^W$*) if* $\mathcal{R}^c_{Am} \le 1$ *(*$\mathcal{R}^c_{Bm} \le 1$*).*

Proof. Suppose $\mathcal{R}^c_{Am} \le 1$, and consider the Lyapunov function $V_1(x) = I_A + J_A + X_A$. The derivative of V_1 along the solutions of the system is

$$\dot V_1 = (I_A + J_A + X_A)(\gamma_A + d)\left(\frac{\beta_A}{(\gamma_A + d)N^*}(S + T_B + W_B) - 1\right).$$

In the subspace Γ^W, we have $S + T_B + W_B \le N^* - (p\, r_{AB})\Lambda/(d+\theta)$, hence

$$\dot V_1 \le (I_A + J_A + X_A)(\gamma_A + d)\left(\frac{\beta_A}{(\gamma_A + d)N^*}\left(N^* - \frac{(p_m\, r_{AB})\Lambda}{d+\theta}\right) - 1\right).$$

The derivative $\dot V_1 \le 0$ if $\mathcal{R}^c_{Am} \le 1$. Note that $\dot V_1 = 0$ if and only if $I_A + J_A + X_A = 0$ or $S + T_B + W_B = N^* - (p_m\, r_{AB})\Lambda/(d+\theta)$, although the latter is only possible if $I_A = J_A = X_A = 0$. Thus, the subspace where $\dot V_1 = 0$ is Υ_A. It follows from LaSalle's invariance principle that $\lim_{t\to\infty}(I_A + J_A + X_A) = 0$ holds for each solution, implying that pathogen A dies out. One can show similarly the result for pathogen B by using the Lyapunov function $V_2(x) = I_B + J_B + X_B$. □

Theorem Appendix A.4 *The DFE is globally asymptotically stable in the subspace* $\Gamma^W = \{x \in \Gamma : W_{AB} \ge (p\, r_{AB})\Lambda/(d+\theta)\}$ *if* $\mathcal{R}^c_{Am} \le 1$ *and* $\mathcal{R}_{Bm} \le 1$*, or if* $\mathcal{R}^c_{Bm} \le 1$ *and* $\mathcal{R}_{Am} \le 1$*.*

Proof. Suppose $\mathcal{R}^c_{Am} \le 1$ and $\mathcal{R}_{Bm} \le 1$, and consider the Lyapunov function V_1 as defined in the previous theorem. Therefore $\dot V_1 \le 0$, and the largest invariant

set in $V_1 = 0$ is the DFE. Thus, by Theorem Appendix A.1, the DFE is globally asymptotically stable in Υ_{A}.

Similarly, when $\mathcal{R}^c_{Bm} \leq 1$ and $\mathcal{R}_{Am} \leq 1$, we obtain for $V_2(x) = I_{B} + J_{B} + X_{B}$ that $\dot{V}_2 \leq 0$. Moreover the largest invariant set in $V_2 = 0$ is the DFE. Thus, in both cases, the limit set of each solution is the DFE, which proves the theorem. □

Theorem Appendix A.5 *In the subspace* $\Gamma^W \cap \Omega_{B}$, E^B_m *is globally asymptotically stable if* $\mathcal{R}^c_{Am} \leq 1$ *and* $\mathcal{R}_{Bm} > 1$. *In the subspace* $\Gamma^W \cap \Omega_{A}$, E^A_m *is globally asymptotically stable if* $\mathcal{R}^c_{Bm} \leq 1$ *and* $\mathcal{R}_{Am} > 1$.

Proof. Suppose $\mathcal{R}^c_{Am} \leq 1$ and $\mathcal{R}_{Bm} > 1$, and consider the Lyapunov function V_1 as defined above. It can be shown that $\dot{V}_1 \leq 0$, and the largest invariant set in $V_1 = 0$ is E^B_m; thus by Theorem Appendix A.1, the DFE is globally asymptotically stable in $\Upsilon_{A} \cap \Omega_{B}$.

Similarly, when $\mathcal{R}^c_{Bm} \leq 1$ and $\mathcal{R}_{Am} > 1$ we obtain for $V_2(x) = I_{B} + J_{B} + X_{B}$ that $\dot{V}_2 \leq 0$. Moreover the largest invariant set in $V_2 = 0$ is the E^A_m. Hence, the results follow from LaSalle's invariance principle. □

We continue our analysis with investigating persistence in model (2.3). We introduce two new quantities. Let $\mathcal{R}^*_{Am}$ be the expected number of new infections with pathogen A when an individual infected with pathogen A is introduced into the population that is at the steady state E^B_m. Let $\mathcal{R}^*_{Bm}$ be the expected number of new infections with pathogen B when an individual infected with pathogen B is introduced into the population that is at the steady state E^A_m. The expressions for $\mathcal{R}^*_{Am}$ and $\mathcal{R}^*_{Bm}$ read

$$\mathcal{R}^*_{Am} = \frac{\beta_{A}}{N^*(\gamma_{A} + d)}(S^* + T^*_{B} + W^*_{B}),$$
$$\mathcal{R}^*_{Bm} = \frac{\beta_{A}}{N^*(\gamma_{A} + d)}(S^* + T^*_{A} + W^*_{A}),$$

where S^*, T^*_{B}, and W^*_{B} are the states of the corresponding classes at the equilibrium E^B_m, and S^*, T^*_{A}, and W^*_{A} are the states of the corresponding classes at the equilibrium E^A_m.

Lemma Appendix A.1 *In model* (2.3), $\mathcal{R}^*_{Am} < \mathcal{R}_{Am}$ *and* $\mathcal{R}^*_{Bm} < \mathcal{R}_{Bm}$.

Proof. We show that $S^* + T^*_{A} + W^*_{A} < S^0 + W^0_{A}$, where S^*, T^*_{A}, and W^*_{A} are the states of the corresponding classes at the equilibrium E^A_m, and S^0 and W^0_{A} are the states of the corresponding classes at the DFE. Hence $\mathcal{R}^*_{Bm} < \mathcal{R}_{Bm}$.

Recall that the pathogen B is absent at both the DFE and E^A_m. Therefore $W^0_{A} = W^*_{A}$ and $W^0_{AB} = W^*_{AB}$. Furthermore, at any equilibrium, the total population is at the steady state N^*, and we obtain

$$S^0 + W^0_{B} = S^* + T^*_{A} + W^*_{B} + I^*_{A} + X^*_{A} + R^*.$$

Equating the right hand sides of the equations in model (2.3) to zero, it is easy to see that $T_A^* = \gamma_A I_A^*/(\theta + d)$ and $R^* = \gamma_A X_A^*/(\theta + d)$; thus we derive from the above equation that

$$S^0 + W_B^0 = S^* + W_B^* + (I_A^* + X_A^*)\left(1 + \frac{\gamma_A}{\theta + d}\right)$$

$$W_B^0 - W_B^* - (I_A^* + X_A^*) - \frac{\gamma_A}{\theta + d} X_A^* = S^* + T_A^* - S^0.$$

Since $W_B^0 = p_m r_B \Lambda(d + \theta)$ and $(d + \theta)W_B^* = p_m r_B \Lambda - \beta_A (I_A^* + X_A^*)W_B^*/N^*$, from the ninth equation of (2.3), we obtain

$$\begin{aligned}
&(W_B^0 - W_B^* - (I_A^* + X_A^*) - \frac{\gamma_A}{\theta + d} X_A^*)(d + \theta) \\
&= (I_A^* + X_A^*)\left(\frac{\beta_A}{N^*} W_B^* - (d + \theta)\right) - \gamma_A X_A^* \\
&= -I_A^*(d + \theta) - \gamma_A X_A^* < 0,
\end{aligned}$$

where for the last equality we used $(I_A^* + X_A^*)\beta_A W_B^*/N^* - X_A^*(d + \theta) = 0$ from the tenth equilibrium equation of (2.3). Hence $S^* + T_A^* < S^0$, which implies $S^* + T_A^* + W_A^* < S^0 + W_A^0$ and $\mathcal{R}_{Bm}^* < \mathcal{R}_{Bm}$. The relation $\mathcal{R}_{Am}^* < \mathcal{R}_{Am}$ can be proven similarly. □

We now recall some definitions and results from Ref. 18.

Definition Appendix A.1 *Let X be an arbitrary nonempty set and $\rho\colon X \to \mathbb{R}_+$.*

A semiflow $\Phi : \mathbb{R}_+ \times X \to X$ is called uniformly weakly ρ-persistent*, if there exists some $\epsilon > 0$ such that*

$$\limsup_{t\to\infty} \rho(\Phi(t, x)) > \epsilon \quad \forall x \in X, \rho(x) > 0.$$

Φ is called uniformly (strongly) ρ-persistent*, if there exists some $\epsilon > 0$ such that*

$$\liminf_{t\to\infty} \rho(\Phi(t, x)) > \epsilon \quad \forall x \in X, \rho(x) > 0.$$

A set M in X is called uniformly weakly ρ-repelling *if there is no $x \in X$ such that $\rho(x) > 0$ and $\Phi(t, x) \to M$ as $t \to \infty$.*

Uniformly weakly ρ-persistence is a property that is weaker than uniformly (strongly) ρ-persistence. However, Theorem 4.5 in Ref. 18 establishes conditions on X and Φ such that uniformly weakly ρ-persistence implies uniformly (strongly) ρ-persistence.

In what follows, we present uniformly persistence results for model (2.3). It is easy to see that the model generates a continuous flow on the phase space. After showing weakly persistence for some choices of ρ, we will consider the conditions of Theorem 4.5 in Ref. 18 to prove uniformly (strongly) persistence. We will also use Theorem 8.17 in Ref. 18 to assert uniformly weakly ρ-persistence, by examining some uniformly weakly ρ-repelling sets.

The ω-limit set of a point $x \in X$ is defined as

$$\omega(x) = \{y \in X : \exists \{t_n\}_{n\geq 1} \text{ such that } t_n \to \infty, \Phi(t_n, x) \to y \text{ as } n \to \infty\}.$$

Theorem Appendix A.6 *$I_A + J_A + X_A$ is uniformly (strongly) persistent in Ω_A if either $\mathcal{R}^*_{Am} > 1$, or $\mathcal{R}_{Am} > 1$ and $\mathcal{R}_{Bm} \leq 1$. $I_B + J_B + X_B$ is uniformly (strongly) persistent in Ω_B if either $\mathcal{R}^*_{Bm} > 1$, or $\mathcal{R}_{Bm} > 1$ and $\mathcal{R}_{Am} \leq 1$.*

Proof. We prove the theorem for the persistence of pathogen A only. The phase space Γ is nonempty, so let $X = \Gamma$ and $x = (S, I_A, \ldots, R) \in \Gamma$ be any state of the model. Consider $\rho(x) = I_A + J_A + X_A$. Then we have

$$\{x \in \Gamma \colon \rho(x) = 0\} = \Upsilon_A,$$

the extinction space of pathogen A. We investigate $\Omega := \cup_{x\in\Upsilon_A} \omega(x)$. From Theorem Appendix A.2, it follows that $\Omega = M_1 \cup M_2$ whenever $\mathcal{R}_{Bm} > 1$, and $\Omega = M_1$ whenever $\mathcal{R}_{Bm} \leq 1$, where M_1 is the DFE and $M_2 = E^B_m$.

First, we show that M_1 is uniformly weakly ρ-repelling if $\mathcal{R}_{Am} > 1$. Suppose there is some x such that $\rho(x) > 0$ and $\Phi(t, x) \to M_1$ as $t \to \infty$; that is, there is a solution such that $I_A(t) + J_A(t) + X_A(t) > 0$ but $\lim_{t\to\infty}(I_A(t) + J_A(t) + X_A(t)) = 0$ and $\lim_{t\to\infty}(S(t) + W_B(t) + T_B(t)) = S^0 + W^0_B + T^0_B$. Thus, for any $\epsilon > 0$ and sufficiently large $t > 0$, we have $S(t) + W_B(t) + T_B(t) > S^0 + W^0_B + T^0_B - \epsilon$. For the derivative of $I_A + J_A + X_A$, we obtain

$$\begin{aligned}(I_A + J_A + X_A)' &= (I_A + J_A + X_A)\left(\beta_A(S + T_B + W_B) - (\gamma_A + d)\right)\\ &> (\gamma_A + d)(I_A + J_A + X_A)\left(\frac{\beta_A}{\gamma_A + d}(S^0 + W^0_B + T^0_B - \epsilon) - 1\right)\\ &= (\gamma_A + d)(I_A + J_A + X_A)\left(\mathcal{R}_{Am} - \epsilon\frac{\beta_A}{\gamma_A + d} - 1\right),\end{aligned}$$

which is positive for small ϵ by $\mathcal{R}_{Am} > 1$, contradicting $\lim_{t\to\infty}(I_A(t) + J_A(t) + X_A(t)) = 0$. Note that this result holds when $\mathcal{R}^*_{Am} > 1$, as $\mathcal{R}^*_{Am} > 1$ implies $\mathcal{R}_{Am} > 1$.

We derive similarly that M_2 is uniformly weakly ρ-repelling if $\mathcal{R}^*_{Am} > 1$. Assume the contrary, there is a solution such that $I_A(t) + J_A(t) + X_A(t) > 0$ but $\lim_{t\to\infty}(I_A(t) + J_A(t) + X_A(t)) = 0$ and $\lim_{t\to\infty}(S(t) + W_B(t) + T_B(t)) = S^* + W^*_B + T^*_B$, where S^*, W^*_B, and T^*_B are the corresponding components of E^B_m. For any $\epsilon > 0$ and sufficiently large $t > 0$, we derive

$$\begin{aligned}(I_A + J_A + X_A)' &= (I_A + J_A + X_A)\left(\beta_A(S + T_B + W_B) - (\gamma_A + d)\right)\\ &> (\gamma_A + d)(I_A + J_A + X_A)\left(\frac{\beta_A}{\gamma_A + d}(S^* + W^*_B + T^*_B - \epsilon) - 1\right)\\ &= (\gamma_A + d)(I_A + J_A + X_A)\left(\mathcal{R}^*_{Am} - \epsilon\frac{\beta_A}{\gamma_A + d} - 1\right) > 0,\end{aligned}$$

where we used $S(t)+W_B(t)+T_B(t) > S^*+W^*_B+T^*_B-\epsilon$. However, $(I_A+J_A+X_A)' > 0$, which contradicts $\lim_{t\to\infty}(I_A(t) + J_A(t) + X_A(t)) = 0$.

Suppose now $\mathcal{R}_{Bm} \leq 1$ and $\mathcal{R}_{Am} > 1$. Then $\Omega \subset M_1$, M_1 is isolated, compact, invariant, acyclic, and weakly ρ-repelling. Therefore, Theorem 8.17 in Ref. 18 implies that $I_A + J_A + X_A$ is weakly ρ-persistent. However, we recall again that $\mathcal{R}^*_{Am} > 1$ implies $\mathcal{R}_{Am} > 1$, hence the last statement also holds when $\mathcal{R}_{Bm} \leq 1$ and $\mathcal{R}^*_{Am} > 1$. If $\mathcal{R}_{Bm} > 1$, then $\Omega \subset (M_1 \cup M_2)$, M_1 and M_2 are invariant, isolated, compact, and weakly ρ-repelling if $\mathcal{R}^*_{Am} > 1$, and $\{M_1, M_2\}$ is acyclic. Thus, by Theorem 8.17 in Ref. 18, we conclude that $I_A + J_A + X_A$ is weakly ρ-persistent if $\mathcal{R}^*_{Am} > 1$ and $\mathcal{R}_{Bm} > 1$.

It remains to show that weakly ρ-persistence implies uniformly (strong) ρ-persistence. The phase space X is compact, hence there exists a compact attractor. Moreover our flow is continuous, and therefore we can apply Theorem 4.5 in Ref. 18 to assert uniformly (strongly) persistence. □

The question of whether $I_A + J_A + X_A$ is uniformly persistent in Ω_A when $\mathcal{R}^*_{Am} \leq 1 < \mathcal{R}_{Am}$ and $\mathcal{R}_{Bm} > 1$ remains unaddressed. However, based on numerical experiments, we conjecture that this assertion holds true. If so, this result, together with Theorem Appendix A.6 means that $I_A + J_A + X_A$ is uniformly persistent in Ω_A when $\mathcal{R}_{Am} > 1$. Similar conjecture is proposed for the uniform persistence of $I_B + J_B + X_B$ in Ω_B when $\mathcal{R}_{Bm} > 1$.

Theorem Appendix A.7 *In the subspace* $\Omega_A \cap \Omega_B$, $I_A + J_A + X_A + I_B + J_B + X_B$ *is uniformly (strongly) persistent if* $\min\{\mathcal{R}_{Am}, \mathcal{R}_{Bm}\} > 1$.

Proof. For $X = \Gamma$ and $x = (S, I_A, \ldots, R) \in \Gamma$, we consider $\rho(x) = I_A + J_A + X_A + I_B + J_B + X_B$. Then, the disease-free subspace is

$$\{x \in \Gamma \colon \rho(x) = 0\} = \{(S, I_A, \ldots, R) : I_A = J_A = X_A = I_B = J_B = X_B = 0\}.$$

In the absence of both pathogens, the system is linear and the DFE is globally asymptotically stable. Let $\Omega := M_1$ where M_1 is the DFE. We show that M_1 is uniformly weakly ρ-repelling if $\mathcal{R}_{Am} > 1$ and $\mathcal{R}_{Bm} > 1$. Suppose there exists a solution such that $I_A(t) + J_A(t) + X_A(t) > 0$ and $I_B(t) + J_B(t) + X_B(t) > 0$ but $\lim_{t\to\infty}(I_A(t)+J_A(t)+X_A(t)+I_B(t)+J_B(t)+X_B(t)) = 0$ and $\lim_{t\to\infty}(S(t)+W_B(t)+T_B(t)) = S^0 + W^0_B + T^0_B$. Then, for any $\epsilon > 0$ and sufficiently large $t > 0$, we have $S(t)+W_B(t)+T_B(t) > S^0+W^0_B+T^0_B-\epsilon$ and $S(t)+W_A(t)+T_A(t) > S^0+W^0_A+T^0_A-\epsilon$. We obtain

$$
\begin{aligned}
&(I_A + J_A + X_A + I_B + J_B + X_B)' \\
&\quad = (I_A + J_A + X_A)\,(\beta_A(S + T_B + W_B) - (\gamma_A + d)) \\
&\quad + (I_B + J_B + X_B)\,(\beta_B(S + T_A + W_A) - (\gamma_B + d)) \\
&\quad > (\gamma_A + d)(I_A + J_A + X_A)\left(\frac{\beta_A}{\gamma_A + d}(S^0 + W_B^0 + T_B^0 - \epsilon) - 1\right) \\
&\quad + (\gamma_B + d)(I_B + J_B + X_B)\left(\frac{\beta_B}{\gamma_B + d}(S^0 + W_A^0 + T_A^0 - \epsilon) - 1\right) \\
&\quad = (\gamma_A + d)(I_A + J_A + X_A)\left(\mathcal{R}_{Am} - \epsilon\frac{\beta_A}{\gamma_A + d} - 1\right) \\
&\quad + (\gamma_B + d)(I_B + J_B + X_B)\left(\mathcal{R}_{Bm} - \epsilon\frac{\beta_B}{\gamma_B + d} - 1\right),
\end{aligned}
$$

which is positive for small ϵ since $\mathcal{R}_{Am} > 1$ and $\mathcal{R}_{Bm} > 1$, contradicting $\lim_{t\to\infty}(I_A(t) + J_A(t) + X_A(t) + I_B(t) + J_B(t) + X_B(t)) = 0$.

We apply Theorem 8.17 in Ref. 18 to derive that $I_A + X_A + I_B + X_B$ is weakly ρ-persistent. We note that $\Omega \subset M_1$, M_1 is isolated, compact, invariant, acyclic, and weakly ρ-repelling. The phase space X is compact, and hence there exists a compact attractor. Furthermore, the flow is continuous, and thus Theorem 4.5 in Ref. 18 implies uniformly (strongly) persistence. □

The above theorem can be extended by noting that $I_A + J_A + X_A$ persists if $\mathcal{R}_{Am} > 1$ and $\mathcal{R}_{Bm} \le 1$, and $I_B + J_B + X_B$ persists if $\mathcal{R}_{Bm} > 1$ and $\mathcal{R}_{Am} \le 1$.

Corollary Appendix A.1 *In the subspace* $\Omega_A \cap \Omega_B$, $I_A + J_A + X_A + I_B + J_B + X_B$ *is uniformly (strongly) persistent if* $\max\{\mathcal{R}_{Am}, \mathcal{R}_{Bm}\} > 1$.

Appendix B. Persistence and global behaviour of the BVM

B.1. *Behavior in the presence of a single pathogen*

Similar to model (2.3) (the MVM), we define Υ_A and Υ_B in the BVM as the extinction spaces of pathogens A and B, respectively, and Ω_A (Ω_B) as the subspace where only pathogen A (only pathogen B) is present:

$$
\begin{aligned}
\Upsilon_A &= \{x \in \Gamma : I_A = 0, J_A = 0, X_A = 0, Y_A = 0\}, \\
\Upsilon_B &= \{x \in \Gamma : I_B = 0, J_B = 0, X_B = 0, Y_B = 0\}, \\
\Omega_A &= \{x \in \Gamma : I_A + J_A + X_A + Y_A > 0\}, \\
\Omega_B &= \{x \in \Gamma : I_B + J_B + X_B + Y_B > 0\}.
\end{aligned}
$$

It is easy to see that all four subspaces are invariant with respect to model (2.5).

We investigate the model (2.5) in the special case where one of the pathogens (say, without loss of generality, pathogen B) is absent. The analysis in this subsection is therefore restricted to the subspace Υ_B. For the special case where pathogen A is absent, one can obtain similar results to those presented here.

In the subspace $\Upsilon_{_B}$, the equations for $I_{_B}$, $J_{_B}$, $X_{_B}$, and $Y_{_B}$ can be eliminated from model (2.5), as $I_{_B} = J_{_B} = X_{_B} = Y_{_B} \equiv 0$ implies $I'_{_B} = J'_{_B} = X'_{_B} = Y'_{_B} \equiv 0$. We introduce new variables: $\breve{S} = S + T_{_B}$, $\breve{V} = V_{_{AB}} + Q_{_B}$, $\breve{I} = I_{_A} + J_{_A} + X_{_A} + Y_{_A}$, $\breve{R} = T_{_A} + Q_{_A} + R$, and obtain the following system

$$\begin{aligned}
\breve{S}' &= (1-p_b)\Lambda - \beta_{_A}\frac{\breve{I}}{N}\breve{S} - d\breve{S} + \theta(\breve{V}+\breve{R}),\\
\breve{V}' &= p_b\,\Lambda - \kappa_{_A}\beta_{_A}\frac{\breve{I}}{N}\breve{V} - d\breve{V} - \theta\breve{V},\\
\breve{I}' &= \beta_{_A}\frac{\breve{I}}{N}\breve{S} + \kappa_{_A}\beta_{_A}\frac{\breve{I}}{N}\breve{V} - \gamma_{_A}\breve{I} - d\breve{I},\\
\breve{R}' &= \gamma_{_A}\breve{I} - d\breve{R} - \theta\breve{R},
\end{aligned} \tag{B.2}$$

where we used $\breve{S} + \breve{V} + \breve{I} + \breve{R} = N$ and $F_{_B} \equiv 0$. With $\breve{V}^0 = \frac{p_b\Lambda}{d+\theta}$ and $\breve{S}^0 = (1-p_b)\frac{\Lambda}{d} + \frac{\theta}{d}\breve{V}^0$, the reproduction number of (B.2) is calculated as

$$\frac{\beta_{_A}}{(\gamma_{_A}+d)N^*}(\breve{S}^0 + \kappa_{_A}\breve{V}^0) = \frac{\beta_{_A}}{(\gamma_{_A}+d)}\left(1 - \frac{p_b(1-\kappa_{_A})d}{d+\theta}\right),$$

and we note that this formula is the same as that of $\mathcal{R}_{Ab}$ in (4.3). Hence, $\mathcal{R}_{Ab}$ can be used to describe the reproduction number of system (B.2).

The system (B.2) gives a special case of system (2) in Ref. 14. Thus, $\mathcal{R}_{Ab}$ gives the reproduction number associated with system (2) in Ref. 14. Following the analysis of Ref. 14, we define

$$\begin{aligned}
\breve{\mathcal{D}}_1 &= \left\{(\breve{S},\breve{V},\breve{I},\breve{R}) \in \mathbb{R}^4_+ : N = N^*\right\},\\
\breve{\mathcal{D}}_0 &= \left\{(\breve{S},\breve{V},\breve{I},\breve{R}) \in \breve{\mathcal{D}}_1 : \breve{I} = 0\right\}.
\end{aligned}$$

The following results are obtained by similar arguments as those in Theorem Appendix A.1.

Theorem Appendix B.1 *Consider system* (B.2)*. There is a unique endemic equilibrium $\breve{\mathcal{E}}_1$ if and only if $\mathcal{R}_{Ab} > 1$. The endemic equilibrium $\breve{\mathcal{E}}_1$ is globally asymptotically stable in the subspace $\breve{\mathcal{D}}_1 \setminus \breve{\mathcal{D}}_0$ whenever $\mathcal{R}_{Ab} > 1$. For any $\mathcal{R}_{Ab} > 0$, there is a unique DFE $\breve{\mathcal{E}}_0$, that is globally asymptotically stable in $\breve{\mathcal{D}}_1$ whenever $\mathcal{R}_{Ab} \le 1$.*

We obtained that $\breve{S}, \breve{V}, \breve{I}$, and $\breve{R}$ converge in system (B.2). Let $(\breve{S},\breve{V},\breve{I},\breve{R}) \to (\breve{S}^*,\breve{V}^*,\breve{I}^*,\breve{R}^*)$ where $(\breve{S}^*,\breve{V}^*,\breve{I}^*,\breve{R}^*) \in \{\breve{\mathcal{E}}_0, \breve{\mathcal{E}}_1\}$, and let $F^*_{_A} = \beta_{_A}\breve{I}^*/N^*$. We show that in model (2.5) there is a unique equilibrium $x^* = (S^*, I^*_{_A}, \ldots, R^*) \in \mathbb{R}^{15}$ associated with each of $\breve{\mathcal{E}}_0$ and $\breve{\mathcal{E}}_1$.

Theorem Appendix B.2 *In model* (2.5)*, there is a unique endemic equilibrium E^A_b in $\Upsilon_{_B}$ if and only if $\mathcal{R}_{Ab} > 1$. The equilibrium E^A_b is globally asymptotically stable in the subspace $\Omega_{_A} \cap \Upsilon_{_B} \cap \{x \in \Gamma : N = N^*\}$ whenever $\mathcal{R}_{Ab} > 1$. For any $\mathcal{R}_{Ab} \ge 0$, the unique DFE is globally asymptotically stable in $\Upsilon_{_B} \cap \{x \in \Gamma : N = N^*\}$*

whenever $\mathcal{R}_{Ab} \leq 1$.
In model (2.5)*, there is a unique endemic equilibrium* E_b^B *in* Υ_A *if and only if* $\mathcal{R}_{Bb} > 1$. *The equilibrium* E_b^B *is globally asymptotically stable in the subspace* $\Omega_B \cap \Upsilon_A \cap \{x \in \Gamma : N = N^*\}$ *whenever* $\mathcal{R}_{Bb} > 1$. *For any* $\mathcal{R}_{Bb} \geq 0$*, the unique DFE is globally asymptotically stable in* $\Upsilon_A \cap \{x \in \Gamma : N = N^*\}$ *whenever* $\mathcal{R}_{Bb} \leq 1$.

Proof. Indeed, it is obvious that $T_B \to 0$ and $Q_B \to 0$ in the subspace Υ_B. Let $T_B^* = 0$ and $Q_B^* = 0$. Then $S \to \breve{S}^*$ and $V_{AB} \to \breve{V}_{AB}^*$, and we let $S^* = \breve{S}^*$ and $V_{AB}^* = \breve{V}_{AB}^*$. It follows from model (2.5) that the components I_A^*, J_A^*, X_A^* and Y_A^* of the equilibrium need to satisfy

$$\begin{aligned} F_A^* S^* &= (\gamma_A + d) I_A^*, \\ F_A^* T_B^* &= (\gamma_A + d) J_A^*, \\ \kappa_A F_A^* V_{AB}^* &= (\gamma_A + d) X_A^*, \\ F_A^* Q_B^* &= (\gamma_A + d) Y_A^*, \\ I_A^* + J_A^* + X_A^* + Y_A^* &= \breve{I}^*. \end{aligned}$$

However, $T_B \to 0$ and $Q_B \to 0$ imply that $J_A \to J_A^*$ and $Y_A \to Y_A^*$ with $J_A^* = Y_A^* = 0$. Note that $\breve{I}^* = 0$ and $F_A^* = 0$ at $\breve{\mathcal{E}}_0$, which implies $I_A^* = X_A^* = 0$. On the other hand, we have $\breve{I}^* > 0$, $F_A^* > 0$ at $\breve{\mathcal{E}}_1$; hence $I_A^* = F_A^* S^*/(\gamma_A + d) > 0$ and $X_A^* = F_A^* V_{AB}^*/(\gamma_A + d) > 0$. In both cases, $I_A \to I_A^*$ and $X_A \to X_A^*$. Finally, it is easy to see that $T_A \to T_A^*$ and $Q_A \to Q_A^*$ where $T_A^* = (\gamma_A I_A^*)/(\theta + d)$ and $Q_A^* = (\gamma_A X_A^*)/(\theta + d)$ and moreover $R \to 0$, giving $R^* = 0$.

Note that in the subspace Υ_B, the classes I_B, J_B, X_B, and Y_B are at zero state; thus $I_B^* = J_B^* = X_B^* = Y_B^* = 0$ at any equilibrium in Υ_B. The equilibrium associated with $\breve{\mathcal{E}}_0$ is therefore a disease-free equilibrium in model (2.5), and by uniqueness it follows that it is the DFE. At the equilibrium of model (2.5) that is associated with $\breve{\mathcal{E}}_1$, it follows that $I_A^*, X_A^* > 0$. We denote this equilibrium by E_b^A, which is an endemic equilibrium with respect to pathogen A and disease-free with respect to pathogen B. We refer to E_b^A as the boundary endemic equilibrium of model (2.5) in the presence of pathogen A and in the absence of pathogen B. With the above arguments, we have proven the first part of the theorem, and the second part can be shown similarly. □

B.2. *Persistence*

Here, we show sufficient conditions for the persistence of the disease in model (2.5). We again define the reproduction number $\mathcal{R}_{Ab}^*$ ($\mathcal{R}_{Bb}^*$), when the population is at its steady state E_b^B (E_b^A). The expressions for $\mathcal{R}_{Ab}^*$ and $\mathcal{R}_{Bb}^*$ read

$$\begin{aligned} \mathcal{R}_{Ab}^* &= \frac{\beta_A}{(\gamma_A + d)N^*}(S^* + T_B^* + \kappa_A(V_{AB}^* + Q_B^*)), \\ \mathcal{R}_{Bb}^* &= \frac{\beta_B}{(\gamma_B + d)N^*}(S^* + T_A^* + \kappa_B(V_{AB}^* + Q_A^*)), \end{aligned}$$

where S^*, T^*_B, V^*_{AB}, and Q^*_B are the states of the corresponding classes at the equilibrium E^B_b, and S^*, T^*_A, V^*_{AB}, and Q^*_A are the states of the corresponding classes at the equilibrium E^A_b.

Lemma Appendix B.1 *In model* (2.5), $\mathcal{R}^*_{Ab} < \mathcal{R}_{Ab}$ *and* $\mathcal{R}^*_{Bb} < \mathcal{R}_{Bb}$.

Proof. We show that $S^* + T^*_A + \kappa_B(V^*_{AB} + Q^*_A) < S^0 + \kappa_B V^0_{AB}$, where S^0 and V^0_{AB} are the states of the corresponding classes at the DFE. Then, it follows that $\mathcal{R}^*_{Bb} < \mathcal{R}_{Bb}$.

Recall that pathogen B is absent at both equilibria. Equating the right hand sides of the equations for Q_A, V_{AB}, and X_A in model (2.5) to zero, we obtain

$$\begin{aligned}
\kappa_A F^*_A V^*_{AB} &= (\gamma_A + d)X^*_A,\\
V^*_{AB} &= \frac{p_b\Lambda}{d+\theta} - \frac{\kappa_A F^*_A V^*_{AB}}{d+\theta} = \frac{p_b\Lambda}{d+\theta} - \frac{(\gamma_A + d)X^*_A}{d+\theta},\\
V^0_{AB} &= \frac{p_b\Lambda}{d+\theta},\\
Q^*_A &= \frac{\gamma_A X^*_A}{d+\theta}.
\end{aligned}$$

Using these equalities, we derive

$$V^0_{AB} - V^*_{AB} - Q^*_A = \frac{p_b\Lambda}{d+\theta} - \left(\frac{p_b\Lambda}{d+\theta} - \frac{(\gamma_A + d)X^*_A}{d+\theta}\right) - \frac{\gamma_A X^*_A}{d+\theta} \quad = \frac{dX^*_A}{d+\theta}.$$

Since the total population is at the steady state N^* at any equilibrium, we obtain

$$S^* + I^*_A + T^*_A + V^*_{AB} + X^*_A + Q^*_A = S^0 + V^0_{AB},$$

which we use to express $S^* + T^*_A - S^0$, as

$$S^* + T^*_A - S^0 = V^0_{AB} - I^*_A - V^*_{AB} - X^*_A - Q^*_A = -I^*_A - \frac{\theta X^*_A}{d+\theta}.$$

Since $dX^*_A/(d+\theta) > 0$ and $-I^*_A - \theta X^*_A(d+\theta) < 0$, it follows from $\kappa_B \geq 0$ that

$$\begin{aligned}
-I^*_A - \frac{\theta X^*_A}{d+\theta} &< \kappa_B \frac{dX^*_A}{d+\theta},\\
S^* + T^*_A - S^0 &< \kappa_B(V^0_{AB} - V^*_{AB} - Q^*_A),\\
S^* + T^*_A + \kappa_B(V^*_{AB} + Q^*_A) &< S^0 + \kappa_B V^0_{AB},
\end{aligned}$$

which yields $\mathcal{R}^*_{Bb} < \mathcal{R}_{Bb}$. The other inequality $\mathcal{R}^*_{Ab} < \mathcal{R}_{Ab}$ can be proven using a similar argument. □

The results for persistence are obtained by applying analogous arguments to those in Theorems Appendix A.6 and Appendix A.7. For the proofs, one may consider the functions $\rho = I_A + J_A + X_A + Y_A$ and $\rho = I_A + J_A + X_A + Y_A + I_B + J_B + X_B + Y_B$. Without detailing their proofs, we state the following results for model (2.5).

Theorem Appendix B.3 *$I_A + J_A + X_A + Y_A$ is uniformly (strongly) persistent in Ω_A if either $\mathcal{R}^*_{Ab} > 1$, or $\mathcal{R}_{Ab} > 1$ and $\mathcal{R}_{Bb} \leq 1$. $I_B + J_B + X_B + Y_B$ is uniformly (strongly) persistent in Ω_B if either $\mathcal{R}^*_{Bb} > 1$, or $\mathcal{R}_{Bb} > 1$ and $\mathcal{R}_{Ab} \leq 1$.*

Theorem Appendix B.4 *In the subspace $\Omega_A \cap \Omega_B$, $I_A + J_A + X_A + Y_A + I_B + J_B + X_B + Y_B$ is uniformly (strongly) persistent if $\min\{\mathcal{R}_{Ab}, \mathcal{R}_{Bb}\} > 1$ (if $\max\{\mathcal{R}_{Ab}, \mathcal{R}_{Bb}\} > 1$).*