

Global stability of a multistrain SIS model with superinfection and patch structure

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We study the global stability of a multistrain SIS model with superinfection and patch structure. We establish an iterative procedure to obtain a sequence of threshold parameters. By a repeated application of a result by Takeuchi et al. [*Nonlinear Anal Real World Appl.* 2006;7:235–247], we show that these parameters completely determine the global dynamics of the system: for any number of patches and strains with different infectivities, any subset of the strains can stably coexist depending on the particular choice of the parameters.

KEYWORDS

global asymptotic stability, multigroup epidemic model, multistrain model, patch model

MSC CLASSIFICATION

92D30; 34D23

1 | INTRODUCTION

Several viruses have different genetic variants (subtypes) called strains which may differ in their infectivity and virulence. Stronger strains might superinfect an individual already infected by another strain, and there can be a coexistence of different virus strains with different virulence. Nowak¹ considered a model to provide an analytical understanding of the complexities introduced by superinfection. In our earlier work,² we considered a multistrain SIS model with superinfection with n infectious strains and showed that it is possible to obtain a stable coexistence of any subgroup of the n strains. We established an iterative method for calculating a sequence of reproduction numbers, which determine the strains being present in the globally asymptotically stable coexistence equilibrium.

Recently, there has been an increasing interest in the modelling of the spatial spread of infectious diseases (see, e.g., Arino and Portet,³ Knipf,⁴ Knipf and Röst,⁵ Muroya, Kuniya and Enatsu,⁶ Nakata and Röst⁷). There are several ways to model spatial spread: one might use partial differential equations (see, e.g., Peng and Zhao,⁸ Allen et al.,⁹ Ge et al.¹⁰) or one may apply ordinary or functional differential equations where individuals can travel between different patches (countries, regions, cities etc.).

Marvá et al.¹¹ considered a spatially distributed periodic multistrain SIS epidemic model with patches of periodic migration rates without superinfection. Considering global reproduction numbers in the nonspatialized aggregated system that

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serve to decide the eradication or endemicity of the epidemic in the initial spatially distributed nonautonomous model and comparing these global reproductive numbers with those corresponding to isolated patches, they showed that adequate periodic fast migrations can in many cases reverse local endemicity and get global eradication of the epidemic.

Motivated by our earlier work on multistrain models and by the recent results on spatial spread of diseases, we extend our previous model² to the general case of p patches. In Section 2, we establish a multistrain SIS model with superinfection with n infectious strains and patch structure. In Section 3, we establish an iterative procedure to determine the globally asymptotically stable equilibrium of the multipatch model introduced in Section 2.

2 | THE MODEL

We consider a heterogeneous virus population with n virus strains having different infectivities and virulences. We will assume that superinfection is possible, and more virulent strains outcompete the less virulent ones in an infected individual taking over the host completely, that is, we assume that an infected individual is always infected by only one virus strain. Let n denote the number of strains with different virulences, whereas p stands for the number of patches. On each patch, the population is divided into $n + 1$ compartments depending on the presence of any of the virus strains: the susceptible class of patch ℓ is denoted by $S^\ell(t)$ and on each patch ℓ , there are n infected compartments $T_1^\ell, \dots, T_n^\ell$ where a larger index corresponds to a compartment of individuals infected by a strain with larger virulence, so for $i < j$, T_j individuals superinfect T_i individuals. Let B^ℓ denote the birth rate and b^ℓ the death rate on the ℓ th patch. We denote by β_{kj}^ℓ the transmission rate on patch ℓ by which the k th strain infects those who are infected by the j th strain. The transmission rates from susceptibles to strain k on patch ℓ will be denoted by β_{kk}^ℓ . Recovery rate on patch ℓ among those infected by the k th strain will be denoted by θ_k^ℓ . By $m_{\ell i}$, we denote the travel rate from patch i to ℓ , which, on a given patch is equal for all compartments on that patch. This assumption—which is natural in the case of mild diseases—will be important in the transformation of variables described in the next section. The parameters $B^\ell, b^\ell, m_{\ell i}, \ell, i = 1, \dots, p$ are assumed to be nonnegative.

Using these notations, we consider the following multistrain SIS model with superinfection and patch structure:

$$\begin{aligned} \frac{dS^\ell(t)}{dt} &= B^\ell - b^\ell S^\ell(t) - S^\ell(t) \sum_{k=1}^n \beta_{kk}^\ell T_k^\ell(t) + \sum_{k=1}^n \theta_k^\ell T_k^\ell(t) + \sum_{i=1}^p (1 - \delta_{\ell i}) \{m_{\ell i} S^i(t) - m_{i\ell} S^\ell(t)\}, \\ \frac{dT_k^\ell(t)}{dt} &= S^\ell(t) \beta_{kk}^\ell T_k^\ell(t) + T_k^\ell(t) \sum_{j=1}^n (1 - \delta_{kj}) \beta_{kj}^\ell T_j^\ell(t) - (b^\ell + \theta_k^\ell) T_k^\ell(t) + \sum_{i=1}^p (1 - \delta_{\ell i}) \{m_{\ell i} T_k^i(t) - m_{i\ell} T_k^\ell(t)\}, \\ &k = 1, 2, \dots, n, \ell = 1, 2, \dots, p, \end{aligned} \quad (1)$$

with initial conditions

$$\begin{aligned} S^\ell(0) &= \varphi_0^\ell, T_k^\ell(0) = \varphi_k^\ell, k = 1, 2, \dots, n, \ell = 1, 2, \dots, p, \\ (\varphi_0^1, \varphi_1^1, \varphi_2^1, \dots, \varphi_n^1, \varphi_0^2, \varphi_1^2, \varphi_2^2, \dots, \varphi_n^2, \dots, \varphi_0^p, \varphi_1^p, \varphi_2^p, \dots, \varphi_n^p) &\in \mathbb{R}_+^{(n+1)p} =: \Gamma, \end{aligned} \quad (2)$$

where δ_{kj} denotes the Kronecker delta such that $\delta_{kj} = 1$ if $k = j$ and $\delta_{kj} = 0$ otherwise, and where

$$\begin{aligned} \beta_{kj}^\ell &= \beta_{kk}^\ell, 1 \leq j \leq k, \text{ and} \\ \beta_{kj}^\ell &= -\beta_{jj}^\ell, k + 1 \leq j \leq n, k = 1, 2, \dots, n, \ell = 1, 2, \dots, p. \end{aligned} \quad (3)$$

Note that for $n = 2$ and $p = 1$, (1) corresponds to the model by A. Dénes and G. Röst describing the spread of ectoparasites and ectoparasite-borne diseases,^{12,13} whereas for $p = 1$, it corresponds to the multistrain SIS model by A. Dénes, Y. Muroya and G. Röst.²

3 | MAIN RESULT

Let us introduce the notation

$$N_n^\ell(t) = S^\ell(t) + \sum_{j=1}^n T_j^\ell(t), \ell = 1, 2, \dots, p. \quad (4)$$

Then, by (3), we have $\beta_{kj}^\ell = -\beta_{jk}^\ell$ for $k \neq j$ and hence,

$$\sum_{k=1}^n T_k^\ell(t) \sum_{j=1}^n (1 - \delta_{kj}) \beta_{kj}^\ell T_j^\ell(t) = 0, \quad \ell = 1, 2, \dots, p.$$

Thus, (1) is equivalent to

$$\begin{aligned} \frac{dT_k^\ell(t)}{dt} &= \left(N_n^\ell(t) - \sum_{j=1}^n T_j^\ell(t) \right) \beta_{kk}^\ell T_k^\ell(t) + T_k^\ell(t) \sum_{j=1}^n (1 - \delta_{kj}) \beta_{kj}^\ell T_j^\ell(t) - (b^\ell + \theta_k^\ell) T_k^\ell(t) \\ &\quad + \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} T_k^i(t) - m_{i\ell} T_k^\ell(t) \}, \quad k = 1, 2, \dots, n-1, \end{aligned} \quad (5a)$$

$$\begin{aligned} \frac{dT_n^\ell(t)}{dt} &= \left(N_n^\ell(t) - \sum_{j=1}^n T_j^\ell(t) \right) \beta_{nn}^\ell T_n^\ell(t) + T_n^\ell(t) \sum_{j=1}^n (1 - \delta_{nj}) \beta_{nj}^\ell T_j^\ell(t) \\ &\quad - (b^\ell + \theta_n^\ell) T_n^\ell(t) + \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} T_n^i(t) - m_{i\ell} T_n^\ell(t) \} \end{aligned} \quad (5b)$$

$$= T_n^\ell(t) \left(\beta_{nn}^\ell N_n^\ell(t) - \sum_{j=1}^n \{ \beta_{nn}^\ell - (1 - \delta_{nj}) \beta_{nj}^\ell \} T_j^\ell(t) - (b^\ell + \theta_n^\ell) \right) + \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} T_n^i(t) - m_{i\ell} T_n^\ell(t) \},$$

$$= T_n^\ell(t) (\beta_{nn}^\ell N_n^\ell(t) - \beta_{nn}^\ell T_n^\ell(t) - (b^\ell + \theta_n^\ell)) + \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} T_n^i(t) - m_{i\ell} T_n^\ell(t) \},$$

$$\frac{dN_n^\ell(t)}{dt} = B^\ell - b^\ell N_n^\ell(t) + \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} N_n^i(t) - m_{i\ell} N_n^\ell(t) \}, \quad (5c)$$

$$\ell = 1, 2, \dots, p.$$

Equations (5b) and (5c) are clearly independent from the rest of the equations. In particular, Equation (5c) are also independent from Equation (5b). As the coefficient matrix A of the linear system of equations

$$\begin{pmatrix} B^1 \\ \vdots \\ B^p \end{pmatrix} = \begin{pmatrix} b^1 + \sum_{i=1}^p (1 - \delta_{1i}) m_{i1} & -m_{12} & \dots & -m_{1p} \\ -m_{21} & b^2 + \sum_{i=1}^p (1 - \delta_{2i}) m_{i2} & \dots & -m_{2p} \\ \vdots & \vdots & \ddots & \vdots \\ -m_{p1} & -m_{p2} & \dots & b^p + \sum_{i=1}^p (1 - \delta_{pi}) m_{ip} \end{pmatrix} \begin{pmatrix} N_n^1 \\ \vdots \\ N_n^p \end{pmatrix}$$

is a strictly diagonally dominant Z -matrix, it is nonsingular, and its inverse is nonnegative (because of the nonnegativity of the parameters), hence, this algebraic system has a unique, positive solution

$$\begin{pmatrix} N_n^{1*} \\ \vdots \\ N_n^{p*} \end{pmatrix} = A^{-1} \begin{pmatrix} B^1 \\ \vdots \\ B^p \end{pmatrix}.$$

Let us define $P_\ell(t) := N_n^\ell(t) - N_n^{\ell*}$, $\ell = 1, \dots, p$, then for $P_\ell(t)$, we have the equation

$$\frac{d}{dt} \begin{pmatrix} P_1(t) \\ \vdots \\ P_p(t) \end{pmatrix} = -A \begin{pmatrix} P_1(t) \\ \vdots \\ P_p(t) \end{pmatrix}. \quad (6)$$

From the properties of the matrix $-A$, applying the Gershgorin circle theorem, we obtain that $P_\ell(t) \rightarrow 0$ exponentially as $t \rightarrow \infty$, $\ell = 1, \dots, p$. Hence, for Equation (5c), there exist positive constants $N_n^{\ell*}$, $\ell = 1, 2, \dots, p$ such that

$$\lim_{t \rightarrow +\infty} N_n^\ell(t) = N_n^{\ell*}, \quad \ell = 1, 2, \dots, p, \quad (7)$$

exponentially and (5b) has the following limit system:

$$\frac{dT_n^\ell(t)}{dt} = T_n^\ell(t) (\beta_{nn}^\ell N_n^{\ell*} - (b^\ell + \theta_n^\ell) - \beta_{nn}^\ell T_n^\ell(t)) + \sum_{i=1}^p (1 - \delta_{i\ell}) \{m_{\ell i} T_n^i(t) - m_{i\ell} T_n^\ell(t)\}, \quad \ell = 1, 2, \dots, p, \quad (8)$$

which is a p -dimensional Lotka–Volterra system with patch structure, in the form as Equation (2.1) in Takeuchi et al.¹⁴

We introduce the notation

$$\tilde{m}_{ii} = \sum_{\ell=1}^p (1 - \delta_{i\ell}) m_{i\ell}, \quad i = 1, 2, \dots, p,$$

and define the connectivity matrix

$$M = \begin{bmatrix} -\tilde{m}_{11} & m_{12} & \dots & m_{1p} \\ m_{21} & -\tilde{m}_{22} & \dots & m_{2p} \\ \vdots & \vdots & \ddots & \vdots \\ m_{p1} & m_{p2} & \dots & -\tilde{m}_{pp} \end{bmatrix}.$$

Now, we define

$$c_n^\ell = \beta_{nn}^\ell N_n^{\ell*} - (b^\ell + \theta_n^\ell), \quad \ell = 1, 2, \dots, p,$$

and

$$M_n = \begin{bmatrix} c_n^1 - \tilde{m}_{11} & m_{12} & \dots & m_{1p} \\ m_{21} & c_n^2 - \tilde{m}_{22} & \dots & m_{2p} \\ \vdots & \vdots & \ddots & \vdots \\ m_{p1} & m_{p2} & \dots & c_n^p - \tilde{m}_{pp} \end{bmatrix}.$$

Let us denote by $s(L)$ the stability modulus of a $p \times p$ matrix L , defined by $s(L) := \max\{\operatorname{Re} \lambda : \lambda \text{ is an eigenvalue of } L\}$. If L has nonnegative off-diagonal elements and is irreducible, then $s(L)$ is a simple eigenvalue of L with a (componentwise) positive eigenvector (see, e.g., Theorem A.5 in Smith¹⁵).

Proposition 1 (see Theorem 2.1 in Takeuchi et al.¹⁴). *Suppose that M_n is irreducible. Then, Equation (8) has a positive equilibrium which is globally asymptotically stable if $s(M_n) > 0$. If $s(M_n) \leq 0$, then 0 is a globally asymptotically stable equilibrium, and the populations go extinct in every patch.*

Note that we may take that the populations go extinct in every patch not only if $s(M_n) < 0$ but also if $s(M_n) = 0$ (see Theorem 2.2 of Faria¹⁶).

Let $E_n^* = (T_n^{1*}, T_n^{2*}, \dots, T_n^{p*})$ be the unique equilibrium of (8) which is globally asymptotically stable. Then, $E_n^* = (0, 0, \dots, 0)$ if $s(M_n) \leq 0$, and $E_n^* = (T_n^{1*}, T_n^{2*}, \dots, T_n^{p*})$ satisfies $T_n^{\ell*} > 0$, $\ell = 1, 2, \dots, p$, if $s(M_n) > 0$. Therefore, in the first case, the unique equilibrium of (8), is globally asymptotically stable on $\{(T_n^1, T_n^2, \dots, T_n^p) \in \mathbb{R}_+^p\}$, whereas in the second case, the unique positive equilibrium $E_n^* = (T_n^{1*}, T_n^{2*}, \dots, T_n^{p*})$ with $T_n^{\ell*} > 0$, $\ell = 1, 2, \dots, p$ is globally asymptotically stable with respect to $\{(T_n^1, T_n^2, \dots, T_n^p) \in \mathbb{R}_+^p\} \setminus \{(0, 0, \dots, 0)\}$. Let us introduce the notations

$$N_{n-1}^\ell(t) = S^\ell(t) + \sum_{j=1}^{n-1} T_j^\ell(t), \quad \ell = 1, 2, \dots, p,$$

and

$$b_{(1)}^\ell = b^\ell - \beta_{kn}^\ell T_n^{\ell*} = b^\ell + \beta_{nn}^\ell T_n^{\ell*}, \quad k = 1, 2, \dots, n-1, \quad \ell = 1, 2, \dots, p,$$

and

$$B_{(1)}^\ell = B^\ell + \theta_n^\ell T_n^{\ell*}, \quad \ell = 1, 2, \dots, p,$$

where $(T_n^{1*}, \dots, T_n^{p*})$ is either equal to $(0, \dots, 0)$ (if $s(M_n) \leq 0$) or it is equal to the unique positive equilibrium of (8) (if $s(M_n) > 0$). This way, substituting T_n^{i*} , $i = 1, \dots, p$ into the place of $T_n^i(t)$ in (4) and (5), we may consider the following reduced system of (5) for the global stability of (1):

$$\begin{aligned} \frac{dT_k^\ell(t)}{dt} &= \left(N_{n-1}^\ell(t) - \sum_{j=1}^{n-1} T_j^\ell(t) \right) \beta_{kk}^\ell T_k^\ell(t) + T_k^\ell(t) \sum_{j=1}^{n-1} (1 - \delta_{kj}) \beta_{kj}^\ell T_j^\ell(t) - \left(b_{(1)}^\ell + \theta_k^\ell \right) T_k^\ell(t) \\ &+ \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} T_k^i(t) - m_{i\ell} T_k^\ell(t) \}, \quad k = 1, 2, \dots, n-2, \end{aligned} \quad (9a)$$

$$\begin{aligned} \frac{dT_{n-1}^\ell(t)}{dt} &= \left(N_{n-1}^\ell(t) - \sum_{j=1}^{n-1} T_j^\ell(t) \right) \beta_{n-1, n-1}^\ell T_{n-1}^\ell(t) + T_{n-1}^\ell(t) \sum_{j=1}^{n-1} (1 - \delta_{n-1, j}) \beta_{n-1, j}^\ell T_j^\ell(t) - \left(b_{(1)}^\ell + \theta_{n-1}^\ell \right) T_{n-1}^\ell(t) \\ &+ \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} T_{n-1}^i(t) - m_{i\ell} T_{n-1}^\ell(t) \} \\ &= T_{n-1}^\ell(t) \left(\beta_{n-1, n-1}^\ell N_{n-1}^\ell(t) - \beta_{n-1, n-1}^\ell T_{n-1}^\ell(t) - \left(b_{(1)}^\ell + \theta_{n-1}^\ell \right) \right) \\ &+ \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} T_{n-1}^i(t) - m_{i\ell} T_{n-1}^\ell(t) \}, \end{aligned} \quad (9b)$$

$$\begin{aligned} \frac{dN_{n-1}^\ell(t)}{dt} &= B_{(1)}^\ell - b_{(1)}^\ell N_{n-1}^\ell(t) + \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} N_{n-1}^i(t) - m_{i\ell} N_{n-1}^\ell(t) \}, \\ &\ell = 1, 2, \dots, p. \end{aligned} \quad (9c)$$

It is easy to see that (9) is of similar structure as (5), but with dimension pn . The positivity of the new parameters follows from the conditions (3). This means that by repeating the above steps, namely, substituting the limit of the total populations in the patches and then substituting the limit of the Lotka–Volterra system for the strongest strain, we can further reduce the dimension by substituting the values of the equilibrium which is globally asymptotically stable, of the decoupled p dimensional Lotka–Volterra system into the remaining equations.

We proceed repeating the same steps for the newly arising reduced system, decreasing the dimension of our system in each round of the procedure by p . In each round, for q decreasing from $n-1$ to 1, we introduce the respective limits $N_q^{\ell*}$ and $T_q^{\ell*}$, as well as the matrices M_q corresponding to the reduced system in an analogous way as it was presented in the case of the original system. In the end, we arrive at a p dimensional Lotka–Volterra system, the dynamics of which can be determined in a similar way as in the above case. This final system will give us an equilibrium value for $S^1(t)$ and $(T_1^1(t), T_2^1(t), \dots, T_p^1(t))$. Thus, by the above discussion, we can reach a conclusion by induction to the global dynamics of the model (1) and we formulate the following theorem.

Theorem 1. *Assume that the connectivity matrix M is irreducible. Then the global dynamics of the multistrain, multipatch SIS model (1) is completely determined by the threshold parameters $(s(M_1), s(M_2), \dots, s(M_n))$ which can be obtained iteratively. There exists an equilibrium in Γ which is globally asymptotically stable with respect to the region Γ_0 , where Γ_0 is the interior of Γ .*

Proof of Theorem 1. The main part of the proof consists of the above description of the steps of the procedure. There is one point left to be shown: we have to prove that in each step, when we substitute the limits $N_k^{\ell*}$ and $T_k^{\ell*}$, respectively, into the remaining equations, the dynamics of the resulting system is indeed equivalent to that of the preceding one.

We summarize the steps of the procedure in the following.

1. We obtain $N_n^{\ell*}$ ($\ell = 1, \dots, p$) from the linear system (6).
2. We substitute the limits $N_n^{\ell*}$ ($\ell = 1, \dots, p$) into Equation (5b) to obtain Equation (8).

3. We obtain the limits $T_n^{\ell*}$ ($\ell = 1, \dots, p$) of the Lotka–Volterra system (8).
4. We create the new variables $N_{n-1}^{\ell}(t)$, $\ell = 1, \dots, p$ and parameters $b_{(1)}^{\ell}, B_{(1)}^{\ell}$, $\ell = 1, \dots, p$.
5. We substitute the limits $T_n^{\ell*}$ ($\ell = 1, \dots, p$) into Equation (5a) to obtain the reduced system (9) which has the same structure as the original one (5).
6. We repeat this cycle $n - 1$ times, with the indices decreased by 1 every time.

For the validity of Step 3 in the q th cycle, we need to verify that M_{n-q} is irreducible. Because $M_{n-q} = M + \text{diag}[c_{n-q}^1, \dots, c_{n-q}^p]$ and we assumed that M is irreducible, M_{n-q} is also irreducible.

To obtain that in each case, the limit of the solutions of the resulting system after the substitution will be the same equilibrium as the limit of the solutions of the original system, we will apply Theorem 4.1 of Hirsch and Smith.¹⁷ To apply this theorem, we recall the quasimonotone condition¹⁷ for a differential equation $x'(t) = f(t, x(t))$: we say that the time-dependent vector field $f : J \times D \rightarrow \mathbb{R}^n$ (where $J \subset \mathbb{R}$ and $D \subset \mathbb{R}^n$) satisfies the quasimonotone condition in D if for all $(t, y), (t, z) \in J \times D$, we have

$$y \leq z \text{ and } y_i = z_i \text{ implies } f_i(t, y) \leq f_i(t, z).$$

According to Theorem 4.1 of Hirsch and Smith,¹⁷ if $f, g : J \times D \rightarrow \mathbb{R}^n$ are continuous, Lipschitz on each compact subset of D , at least one of them satisfies the quasimonotone condition, and $f(t, y) \leq g(t, y)$ for all $(t, y) \in J \times D$, then

$$y, z \in \mathbb{R}^n, y \leq z \text{ implies } x(t; t_0, y) \leq x(t; t_0, z) \text{ for all } t > t_0,$$

where $x(t; t_0, y)$ denotes the solution of $x'(t) = f(t, x(t))$ started from y at $t = t_0$.

To show that the limits $T_{\kappa}^{\ell*}$ obtained during the procedure by substituting the limits of (8) into (5a) are the same as the limit of the variables T_{κ}^{ℓ} , $\kappa = 1, \dots, n$, $\ell = 1, \dots, p$ in the original system, we will use an induction argument. It is clear from the above that the claim is true for $\kappa = n$. Let now $1 \leq r \leq n - 1$ and let us suppose that the claim holds for all $T_{\kappa}^{\ell}(t)$ for $r < \kappa \leq n$. The limits $T_r^{\ell*}$ are obtained by first substituting the limits $T_{r+1}^{\ell*}$ into the equations for $T_j^{\ell}(t)$, $1 \leq j \leq r$ and then substituting the limits $N_r^{\ell*}$ into the equations for $T_r^{\ell}(t)$, hence, we have to compare the limits of the two systems

$$\begin{aligned} \frac{dT_r^{\ell}(t)}{dt} &= (N_{r+1}^{\ell}(t) - 2T_{r+1}^{\ell}(t) - T_r^{\ell}(t)) \beta_{rr}^{\ell} T_r^{\ell}(t) - \left(b_{(n-r+1)}^{\ell} + \theta_r^{\ell} \right) T_r^{\ell}(t) + \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} T_r^i(t) - m_{i\ell} T_r^{\ell}(t) \} \\ &= (N_r^{\ell}(t) - T_{r+1}^{\ell}(t) - T_r^{\ell}(t)) \beta_{rr}^{\ell} T_r^{\ell}(t) - \left(b_{(n-r+1)}^{\ell} + \theta_r^{\ell} \right) T_r^{\ell}(t) + \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} T_r^i(t) - m_{i\ell} T_r^{\ell}(t) \} \end{aligned} \quad (10)$$

and

$$\begin{aligned} \frac{dT_r^{\ell}(t)}{dt} &= (N_r^{\ell*} - T_r^{\ell}(t)) \beta_{rr}^{\ell} T_r^{\ell}(t) - \left(b_{(n-r)}^{\ell} + \theta_r^{\ell} \right) T_r^{\ell}(t) + \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} T_r^i(t) - m_{i\ell} T_r^{\ell}(t) \}, \\ &\ell = 1, 2, \dots, p. \end{aligned} \quad (11)$$

We know that $N_r^{\ell}(t)$ ($\ell = 1, \dots, p$) converge to $N_r^{\ell*}$ ($\ell = 1, \dots, p$), whereas from the definition of r , we have that $T_{r+1}^{\ell}(t)$ ($\ell = 1, \dots, p$) converge to $T_{r+1}^{\ell*}$ ($\ell = 1, \dots, p$). Then, for any $\varepsilon > 0$, there exists a $\bar{t} > 0$ such that $|N_r^{\ell}(t) - N_r^{\ell*}| < \varepsilon$ and $|T_{r+1}^{\ell}(t) - T_{r+1}^{\ell*}| < \varepsilon$ for all $t > \bar{t}$, $\ell = 1, \dots, p$. If we substitute $T_{r+1}^{1*} + \varepsilon, \dots, T_{r+1}^{p*} + \varepsilon, N_r^{1*} - \varepsilon, \dots, N_{n-q}^{p*} - \varepsilon$, resp. $T_{r+1}^{1*} - \varepsilon, \dots, T_{r+1}^{p*} - \varepsilon, N_r^{1*} + \varepsilon, \dots, N_{n-q}^{p*} + \varepsilon$ into (10), we obtain two systems of the same structure as (11), and one of them is a lower, the other is an upper estimate of (10), and each has a globally asymptotically stable equilibrium $(\underline{T}_r^1(\varepsilon), \dots, \underline{T}_r^p(\varepsilon))$ and $(\bar{T}_r^1(\varepsilon), \dots, \bar{T}_r^p(\varepsilon))$, respectively, because of Proposition 1. It is easy to see that the original system (10), considered as a nonautonomous system with time-dependent coefficients $T_{r+1}^1(t), \dots, T_{r+1}^p(t), N_r^1(t), \dots, N_r^p(t)$, satisfies the quasimonotone condition, as well as the systems obtained after the substitution. Hence, we can apply Theorem 4.1 of Hirsch and Smith¹⁷ to obtain that for any solution $(T_r^1(t), \dots, T_r^p(t))$ of (10),

$$\underline{T}_r^{\ell}(\varepsilon) \leq \liminf_{t \rightarrow \infty} T_r^{\ell}(t) \leq \limsup_{t \rightarrow \infty} T_r^{\ell}(t) \leq \bar{T}_r^{\ell}(\varepsilon), \quad \ell = 1, \dots, p. \quad (12)$$

Solutions of limit Eq. (11) converge to a globally asymptotically stable equilibrium by Proposition 1, and by letting $\varepsilon \rightarrow 0$, we find that this limit is the same as that of (10).

As we have assumed that for all larger indices, the limits of the compartments of the original system (5) are equal to the limits obtained during the procedure, using the equations for $T_r^1(t), \dots, T_r^p(t)$ after $n - r + 1$ cycles of the procedure satisfy the quasimonotone condition and the comparison (12), the limits obtained for these have to coincide with those of the original system (for $r = n$, the statement follows directly).

To prove that not only attractivity but also global asymptotic stability holds, we will again use induction. Let $E = (\bar{S}^1, \bar{T}_1^1, \dots, \bar{T}_n^1, \dots, \bar{S}^p, \bar{T}_1^p, \dots, \bar{T}_n^p)$ denote the equilibrium obtained at the end of the procedure, where $\bar{T}_i^j = 0$ or $\bar{T}_i^j > 0$ depending on the stability moduli $(s(M_1), s(M_2), \dots, s(M_n))$ and let $E_\kappa = (\bar{S}^1, \bar{T}_1^1, \dots, \bar{T}_\kappa^1, \dots, \bar{S}^p, \bar{T}_1^p, \dots, \bar{T}_\kappa^p)$ be the equilibrium of the $p(\kappa + 1)$ -dimensional system

$$\begin{aligned} \frac{dT_k^\ell(t)}{dt} &= \left(N_k^\ell(t) - \sum_{j=1}^{\kappa} T_j^\ell(t) \right) \beta_{kk}^\ell T_k^\ell(t) + T_k^\ell(t) \sum_{j=1}^{\kappa} (1 - \delta_{kj}) \beta_{kj}^\ell T_j^\ell(t) - \left(b_{(n-\kappa)}^\ell + \theta_k^\ell \right) T_k^\ell(t) \\ &\quad + \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} T_k^i(t) - m_{i\ell} T_k^\ell(t) \}, \\ k &= 1, 2, \dots, \kappa - 1, \ell = 1, 2, \dots, p, \end{aligned} \quad (13a)$$

$$\begin{aligned} \frac{dT_\kappa^\ell(t)}{dt} &= T_\kappa^\ell(t) \left(\beta_{\kappa,\kappa}^\ell N_\kappa^\ell(t) - \left(b_{(n-\kappa)}^\ell + \theta_\kappa^\ell \right) - \beta_{\kappa,\kappa}^\ell T_\kappa^\ell(t) \right) \\ &\quad + \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} T_\kappa^i(t) - m_{i\ell} T_\kappa^\ell(t) \}, \\ \ell &= 1, 2, \dots, p, \end{aligned} \quad (13b)$$

$$\begin{aligned} \frac{dN_\kappa^\ell(t)}{dt} &= B_{(n-\kappa)}^\ell - b_{(n-\kappa)}^\ell N_\kappa^\ell(t) + \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} N_\kappa^i(t) - m_{i\ell} N_\kappa^\ell(t) \}, \\ \ell &= 1, 2, \dots, p, \end{aligned} \quad (13c)$$

obtained during the procedure with E_κ consisting of the first $p(\kappa + 1)$ coordinates of E . Let us suppose that E_κ is a stable equilibrium of the $p(\kappa + 1)$ -dimensional reduced system for some $\kappa \leq n$. We will show that in each step, $E_{\kappa+1}$ is a stable equilibrium of the $p(\kappa + 2)$ -dimensional reduced system

$$\begin{aligned} \frac{dT_k^\ell(t)}{dt} &= \left(N_{\kappa+1}^\ell(t) - \sum_{j=1}^{\kappa+1} T_j^\ell(t) \right) \beta_{kk}^\ell T_k^\ell(t) + T_k^\ell(t) \sum_{j=1}^{\kappa+1} (1 - \delta_{kj}) \beta_{kj}^\ell T_j^\ell(t) \\ &\quad - \left(b_{(n-\kappa-1)}^\ell + \theta_k^\ell \right) T_k^\ell(t) + \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} T_k^i(t) - m_{i\ell} T_k^\ell(t) \}, \\ k &= 1, 2, \dots, \kappa, \end{aligned} \quad (14a)$$

$$\begin{aligned} \frac{dT_{\kappa+1}^\ell(t)}{dt} &= \left(N_{\kappa+1}^\ell(t) - \sum_{j=1}^{\kappa+1} T_j^\ell(t) \right) \beta_{\kappa+1,\kappa+1}^\ell T_{\kappa+1}^\ell(t) + T_{\kappa+1}^\ell(t) \sum_{j=1}^{\kappa+1} (1 - \delta_{\kappa+1,j}) \beta_{\kappa+1,j}^\ell T_j^\ell(t) \\ &\quad - \left(b_{(n-\kappa-1)}^\ell + \theta_{\kappa+1}^\ell \right) T_{\kappa+1}^\ell(t) + \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} T_{\kappa+1}^i(t) - m_{i\ell} T_{\kappa+1}^\ell(t) \}, \\ &= T_{\kappa+1}^\ell(t) \left(\beta_{\kappa+1,\kappa+1}^\ell N_{\kappa+1}^\ell(t) - \beta_{\kappa+1,\kappa+1}^\ell T_{\kappa+1}^\ell(t) - \left(b_{(n-\kappa-1)}^\ell + \theta_{\kappa+1}^\ell \right) \right) \\ &\quad + \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} T_{\kappa+1}^i(t) - m_{i\ell} T_{\kappa+1}^\ell(t) \}, \end{aligned} \quad (14b)$$

$$\begin{aligned} \frac{dN_{\kappa+1}^\ell(t)}{dt} &= B_{(n-\kappa-1)}^\ell - b_{(n-\kappa-1)}^\ell N_{\kappa+1}^\ell(t) + \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} N_{\kappa+1}^i(t) - m_{i\ell} N_{\kappa+1}^\ell(t) \}, \\ \ell &= 1, 2, \dots, p. \end{aligned} \quad (14c)$$

Suppose this does not hold, that is, $E_{\kappa+1}$ is unstable. In this case, there exist an $\varepsilon > 0$ and a sequence $\{x_m\} \rightarrow E_{\kappa+1}$, $|x_m - E_{\kappa+1}| < 1/m$ such that the orbits started from the points of the sequence leave $B(E_{\kappa+1}, \varepsilon) := \left\{ x \in \mathbb{R}_+^{(\kappa+2)p} : |x - E_{\kappa+1}| \leq \varepsilon \right\}$. By an exit point from $B(E_{\kappa+1}, \varepsilon)$, we mean a point x such that $|E_{\kappa+1} - x| = \varepsilon$ and for the trajectory through x , there is an open interval $J \ni 0$ such that for all $t \in J$, $xt \in B(E_{\kappa+1}, \varepsilon)$ if $t \leq 0$ and $xt \notin B(E_{\kappa+1}, \varepsilon)$ if $t > 0$. Let us denote by x_m^ε the first exit point from $B(E_{\kappa+1}, \varepsilon)$ of the solution started from x_m , reached at time τ_m . There is a convergent subsequence of the sequence x_m^ε (still denoted by x_m^ε) which tends to a point denoted by $x_\varepsilon^* \in S(E_{\kappa+1}, \varepsilon) := \left\{ x \in \mathbb{R}_+^{(\kappa+2)p} : |x - E_{\kappa+1}| = \varepsilon \right\}$. We will show that $E_{\kappa+1} \in \alpha(x_\varepsilon^*)$. For this end, let us consider the set $S\left(E_{\kappa+1}, \frac{\varepsilon}{2}\right)$. Clearly, all solutions started from the points x_m (we drop the first elements of the sequence, if necessary) will leave the set $B\left(E_{\kappa+1}, \frac{\varepsilon}{2}\right)$. We denote the last exit point of each trajectory from this set before time τ_m , respectively, by $x_m^{\varepsilon/2}$. Also this sequence has a convergent subsequence (still denoted the same way), let us denote its limit by $x_{\varepsilon/2}^*$. We will show that the trajectory started from $x_{\varepsilon/2}^*$ goes through x_ε^* . As $E_{\kappa+1}$ is globally attractive, this trajectory will eventually enter $S\left(E_{\kappa+1}, \frac{\varepsilon}{4}\right)$ at some time $T > 0$. Let us suppose that the trajectory started from $x_{\varepsilon/2}^*$ does not go through x_ε^* and let us denote by $d > 0$ the distance of this trajectory from x_ε^* . For continuity reasons, there is an $N \in \mathbb{N}$ so that for any $m > N$, $|x_{\varepsilon/2}^* t - x_m^{\varepsilon/2} t| < \max\left\{\frac{d}{2}, \frac{\varepsilon}{8}\right\}$ for $0 < t < T$. This means that for m large enough, the trajectory started from $x_m^{\varepsilon/2}$ will enter again $S\left(E_{\kappa+1}, \frac{\varepsilon}{2}\right)$ without getting close to x_ε^* which contradicts either x_m^ε being the first exit point from $B(E_{\kappa+1}, \varepsilon)$ or $x_m^{\varepsilon/2}$ being the last exit point before τ_m from $B\left(E_{\kappa+1}, \frac{\varepsilon}{2}\right)$. Hence, we have shown that the trajectory started from $x_{\varepsilon/2}^*$ goes through x_ε^* . Proceeding like this (taking neighbourhoods of radius $\varepsilon/4, \varepsilon/8$ etc.), we obtain that the backward trajectory of x_ε^* enters any small neighbourhood of $E_{\kappa+1}$. That is, there exists a decreasing sequence $t_n < 0$ such that $|xt_n - E_{\kappa+1}| < \frac{\varepsilon}{2n}$. We have either $t_n \rightarrow t^*$ for some $t^* < 0$ or $t_n \rightarrow -\infty$. In the first case, $xt_n \rightarrow x^* = E_{\kappa+1}$ which contradicts the fact that $E_{\kappa+1}$ is an equilibrium. Hence, $t_n \rightarrow \infty$, and we obtain that $E_{\kappa+1} \in \alpha(x_\varepsilon^*)$, while it follows from the global attractivity of $E_{\kappa+1}$ that the ω -limit set of the trajectory is $\{E_{\kappa+1}\}$. Let us denote this trajectory by $\gamma(x_\varepsilon^*)$.

We know that Equations (14b) for $\frac{d}{dt}T_{\kappa+1}^1(t), \dots, \frac{d}{dt}T_{\kappa+1}^p(t)$ and (14c) for $\frac{d}{dt}N_{\kappa+1}^1(t), \dots, \frac{d}{dt}N_{\kappa+1}^p(t)$ can be decoupled from the rest of the equations and using the exponential stability of the limits

$$\lim_{t \rightarrow +\infty} N_{\kappa+1}^\ell(t) = N_{\kappa+1}^{\ell*}, \ell = 1, 2, \dots, p,$$

and Proposition 1 we obtain that $\overline{T}_{\kappa+1}^1, \dots, \overline{T}_{\kappa+1}^p$ is a stable equilibrium of the system consisting of the system

$$\begin{aligned} \frac{dT_{\kappa+1}^\ell(t)}{dt} &= T_{\kappa+1}^\ell(t) \left(\beta_{\kappa+1, \kappa+1}^\ell N_{\kappa+1}^{\ell*} - (b^\ell + \theta_{\kappa+1}^\ell) - \beta_{\kappa+1, \kappa+1}^\ell T_{\kappa+1}^\ell(t) \right) \\ &+ \sum_{i=1}^p (1 - \delta_{\ell i}) \{ m_{\ell i} T_{\kappa+1}^i(t) - m_{i\ell} T_{\kappa+1}^\ell(t) \}, \ell = 1, 2, \dots, p. \end{aligned}$$

Therefore, the equilibrium $E_{\kappa+1}$ is stable in the coordinates $T_{\kappa+1}^1, \dots, T_{\kappa+1}^p$ in the sense that for any $\tilde{\varepsilon} > 0$ there exists a $\tilde{\delta}(\tilde{\varepsilon}) > 0$ such that for any initial value x with $|x - E_{\kappa+1}| < \tilde{\delta}$, $|T_{\kappa+1}^\ell(t) - \overline{T}_{\kappa+1}^\ell| < \tilde{\varepsilon}$ for all $t > 0$ and $\ell = 1, \dots, p$. Thus, the trajectory $\gamma(x_\varepsilon^*)$ obtained above lies entirely in the subspace $\left\{ T_{\kappa+1}^1 = \overline{T}_{\kappa+1}^1, \dots, T_{\kappa+1}^p = \overline{T}_{\kappa+1}^p \right\}$. On the other hand, the current $p(\kappa + 2)$ -dimensional system coincides with the $p(\kappa + 1)$ -dimensional system on this subspace. For the latter system, stability of the equilibrium E_κ follows from the induction assumption. However, the existence of an orbit $\tilde{\gamma}$ (different from the equilibrium $E_{\kappa+1}$) whose ω -limit set is $\{E_{\kappa+1}\}$ and whose α -limit set contains $E_{\kappa+1}$ contradicts the stability of the equilibrium E_κ . Indeed, let us suppose that E_κ is stable and there exists such an orbit $\tilde{\gamma}$. The stability of E_κ would implies that for any $\hat{\varepsilon} > 0$, there exists a $\hat{\delta}(\hat{\varepsilon})$ such that for any solution started from an initial value P with $|P - E_\kappa| < \hat{\delta}$, we have $|Pt - E_\kappa| < \hat{\varepsilon}$ for all $t > 0$. Hence, this is also true for $\hat{\varepsilon} = |E_\kappa - \tilde{P}|/2$ for any $\tilde{P} \in \tilde{\gamma}$, which is a contradiction, as a solution started from a point of $\tilde{\gamma}$ clearly leaves $S(E_\kappa, \hat{\varepsilon})$. Hence, no such orbit $\tilde{\gamma}$ can exist. This implies the global asymptotic stability of the equilibrium of the $p(\kappa + 2)$ -dimensional system.

For $\kappa = 1$, the assertion holds trivially, hence, repeating the inductive step we obtain global asymptotic stability of the equilibrium E . \square

4 | DISCUSSION

Pathogen genetic diversity is a major obstacle to the design of efficient control strategies for a number of different diseases, including malaria, HIV or TB (Childs et al.¹⁸). It makes rather challenging the preparation for seasonal influenza¹⁹ and the management of drug resistance.²⁰ Any model incorporating multiple pathogen strains has to keep track of people infected with, and immune to different strains, resulting in a high dimensional system. The comprehensive mathematical analysis of such systems is rather challenging; hence, global analysis is typically restricted to models with two or three strains. For a class of multistrain models, Dang et al.²¹ concluded that the competitive exclusion principle holds. A coupling term between strains promoted coexistence in Meehan et al.²² Furthermore, superinfection has important consequences in the evolutionary considerations of host-pathogen interactions, allowing the coexistence of many strains, see Chapter 11 in Nowak.¹

In this paper, we established an SIS model on several patches for a disease with multiple strains. We assumed that more virulent strains can superinfect an individual infected by less virulent strains and outcompete them within the host. We established an iterative procedure which allows us to determine the global dynamics of the system. By applying this procedure, the dimension of the system is gradually decreased and a sequence of reproduction numbers is determined. Arriving at the end of the procedure, the globally asymptotically stable equilibrium of the full system is obtained, where a subset of the strains coexist, depending on the sequence of the reproduction numbers. It is important to note that the procedure not only reveals which of the several strains will persist but also tells us that (in case of a strongly connected network of patches) a particular strain will be present in all or none of the patches.

One real life example of such co-existence is described in Anderson and May,²³ where the authors analysed the myxoma virus infection in Australian rabbit populations and found an equilibrium distribution of virus strains with different levels of virulence. In our previous work² and in the present paper, we established the global asymptotic stability of such equilibrium distributions in an SIS setting with superinfection.

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CONFLICT OF INTEREST

This work does not have any conflicts of interest.

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