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USING WITHIN-HOST MATHEMATICAL MODELLING TO PREDICT THE LONG-TERM OUTCOME OF HUMAN PAPILLOMAVIRUS VACCINES

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ABSTRACT.

The human papillomavirus (HPV) vaccine Gardasil targets both low-risk (non-cancer-causing) and high-risk (cancer-causing) HPV types, while the vaccine Cervarix only targets high-risk types, yet competition between HPV types is not well understood. We develop a within-host mathematical model to examine the long-term outcomes of HPV vaccination. We divide cells into low-risk and high-risk types, and examine the effect of competition for target cells, including the possibility of coinfection. We derive theoretical eradication thresholds for vaccine efficacy and illustrate the outcome for the two existing vaccines. If no vaccination occurs, both viral types coexist, whereas either or both viral types can be eradicated if the vaccine is sufficiently efficacious.

1 Introduction Human Papillomavirus (HPV) is the most common sexually transmitted disease in the world [**9**]. Genital HPVs, which are transmitted sexually, are the central etiologic factor in cervical cancer worldwide [**2, 29**]. Cervical cancer is the second most common form of cancer worldwide and HPV type 16 accounts for about half of all cervical cancer cases in the United States and Europe [**4**]. However, most women infected with HPV, even those infected with the types that are most closely associated with cervical dysplasia (e.g., types 16 and 18), do not develop invasive cervical cancer [**27**]. Low-grade cervical cell abnormalities usually clear spontaneously (60% of cases) and rarely progress to cancer (1%), while high-grade cervical cell abnormalities have lower rates of spontaneous clearance (30–40%) and much higher rates of progression to cancer without treatment (greater than 12%) [**26**].

Keywords: Human papillomavirus, mathematical model, within-host dynamics, cervical cancer, vaccine.

For the most part, HPV infections are cleared by an individual's immune system before they have the chance to develop into a productive infection. For women, 50% of high-risk HPV infections are typically cleared within 8 months of the initial infection, 75% are cleared within 12 months of infection and 97% of women clear the infection within 18 months [**30**]. For men, 70% of high-risk HPV infections are typically cleared within 8 months of the initial infection, 80% are cleared within 12 months and 100% of men clear the infection within 18 months [**11**]. Clearing an infection does not automatically ensure an individual has immunity; in a study by Hernandez et al, many couples became reinfected with the same type of HPV after clearance, likely because there is a new or continuous source of infection [**12**]. This clearance of these persistent HPV infections is probably due to the immune system's $CD4^+$ T-helper cells, since patients who are immunocompromised and have low levels of these T-cells are much more likely to develop persistent HPV infections [**6, 17, 25**]. HPV is able to infect humans with persistent infections, which last an average of 8.4 and 14.0 months for HPV-6 and HPV-16, respectively, which usually present with little to no complications for the host [**13**].

Merck and GlaxoSmithKline have both developed commercial vaccines (Gardasil and Cervarix, respectively), which target HPV types 16 and 18 [**19**]. Merck's vaccine also protects against types 6 and 11, which are responsible for 90% of external genital warts [**1, 19**]. HPV vaccines are composed of virus-like particles, which are empty virus capsids containing the major HPV capsid antigen, but lacking viral DNA [**4**]. Vaccination gives rise to virus-neutralizing antibodies in serum [**1**]. The vaccines showed strong immuno-responses that were several orders of magnitude higher than those observed after natural infections [**1**]. Studies in women have found the vaccine to be nearly 100% effective at preventing diseases caused by the vaccine-specific HPV strains, include precancerous lesions of the cervix, vagina and vulva, as well as genital warts [**21**]. The combination of a successful vaccine and vaccination strategy, then, seems to be the best approach towards preventing cervical cancer [**18**].

It has been speculated that the competition between two HPV types for a similar pool of cellular factors may lead to a deficit in certain cellular factors that could in turn hinder the replication of both viral genomes, or that one viral type could out-compete the other viral type for cellular factors, causing a decrease in the ability of the second viral type to replicate its genome. However, this explanation only applies when two viral types exist in the same cell, not merely in the same

population of cells [**22**]. It is thus unclear whether competition between types not existing in the same cell could result in the exclusion of one type. In general, competition between HPV types is not well understood [**16**].

Only a handful of mathematical models have addressed the within-host dynamics of HPV and none involve ordinary differential equations (ODEs). Myers *et al.* [**24**] constructed a Markov model that incorporated states for HPV infection, low- and high-grade squamous intraepithelial lesions, and cervical cancer stages I–IV to simulate the natural history of HPV infection in a cohort of women from ages 15 to 85 years. A sensitivity analysis found that lifetime risk of cancer was most sensitive to the incidence of HPV and the probability of rapid HPV progression to high-grade lesions. Motta *et al.* [**23**] used a Lattice Gas Automata model to describe, in a defined space, the immune system entities with their different biological states and the interactions between different entities in two-dimensional physical space generated from the interactions and diffusion of the different entities. They found that, applying the vaccination scheme used with *in vivo* experiments, the number of vaccine injections could be reduced by roughly 30%. Goldhaber-Fiebert *et al.* [**10**] developed a stochastic microsimulation model of cervical cancer that distinguished different HPV types by their incidence, clearance, persistence and progression. They found that the expected reductions in lifetime risk of cancer with annual screening were 76% and with biennial screening were 69%. David *et al.* [**7**] develop three statistical models in order to estimate the long-term persistence of anti-HPV-16/18 antibodies in a cohort of vaccinated women and determine antibody decay rates. Finally, Carter *et al.* [**5**] used statistical estimates to determine whether women can forego invasive treatment in the absence of gold standard diagnoses.

This paper presents the first compartment model to describe the within-host dynamics of HPV vaccination. We develop a competition model between aggregated low-risk types and aggregated high-risk types. Cells may be inhibited by either type or both types simultaneously. The results are illustrated with numerical simulations and the implications addressed in Section 4.

2 Methods The theoretical model consists of susceptible target cells (T_S), low-risk virus V_L (consisting of viral types that do not lead to cervical cancer), high-risk virus V_H (consisting of viral types that may lead to cervical cancer), cells infected with low-risk HPV types (T_L),

cells infected with high-risk HPV types (T_H), and cells coinfected with both low- and high-risk types (T_{LH}). The system of ordinary differential equations models competition between low-risk HPV types and high-risk HPV types. We assume that cells infected with low-risk HPV types do not progress to cancer cells, whereas cells infected with high-risk HPV types (whether or not they are also infected with low-risk types) have the potential to become cancerous.

In our model, we have aggregated the viral types. Hence high-risk types consist of all HPV viral types that may lead to cervical cancer, whether or not they can be vaccinated against. Thus even a perfectly efficacious vaccine against HPV types 11 and 16 will not be 100% efficacious against the pool of high-risk types if there are other high-risk viral types present. Similarly, low-risk types consist of HPV viral types that do not lead to cervical cancer, whether they can be vaccinated against or not. However, we restrict our modelling to cells that compete for a common set of target cells.

The model is described in the appendix and illustrated in Figure 1.

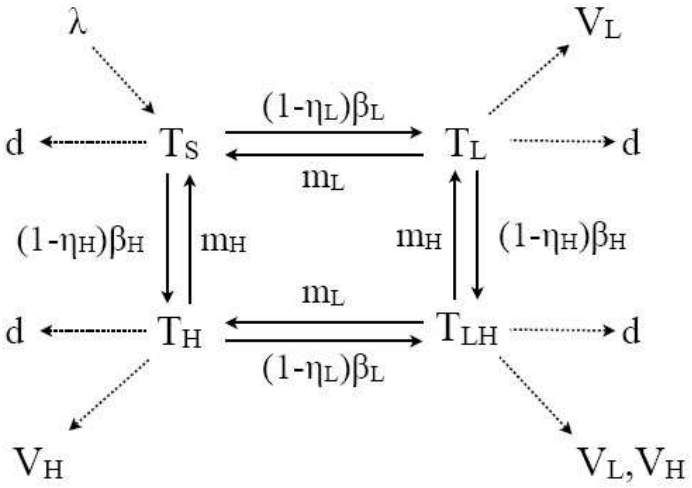

FIGURE 1: Schematic representation of the mathematical model.

It is assumed that target cells are produced at a constant rate λ; these cells can become T_L or T_H cells, once the relevant protein binding

has occurred. Similarly, T_L cells can become T_{LH} cells if subsequently infected by high-risk types and vice versa for T_H cells.

The probability that low-risk virus binds to a target cell is β_L and the probability that high-risk virus binds to a target cell is β_H. Infection is cleared at rates m_L and m_H, respectively.

We assume that low-risk virions V_L are produced at a rate of p_L proportional to the size of the low-risk HPV cells T_L and the co-infected cells T_{LH}; and that high-risk virions V_H are produced at a rate of p_H proportional to the size of the high-risk HPV cells T_H and the co-infected cells T_{LH}. They are both cleared at a rate of d_V.

We model the vaccine's effect as inhibiting binding of virus to target cells and preventing the release of infectious virus from already-infected cells. Thus the inhibition of high-risk virus is $(1 - \eta_H)$; if $\eta_H = 0$, the vaccine has no inhibitory effect, while if $\eta_H = 1$, then the vaccine completely inhibits the relevant strain from binding to target cells. The inhibition of low-risk virus is defined similarly.

The two vaccines may provide different levels of cross-reactivity to other high-risk strains not explicity targeted [**15**]. This is reflected in our parameter η_H, which represents the overall protection against high-risk viral types. For example, a vaccine that provided 99% protection against types 16 and 18, but only 40% protecton against types 31 and 45, may only result in an overall protection of (say) 95%, depending on the prevalence of the various types.

3 Results The model predicts that there is a threshold of vaccine efficacy against aggregated low-risk and aggregated high-risk HPV types. If the vaccine does not satisfy (A.2) or (A.3), then both low-risk and high-risk types will coexist. If (A.3) is satisfied but (A.2) is not, then high-risk types will be eradicated, whether or not target cells are also coinfected with low-risk types. If both (A.2) and (A.3) hold, then the vaccine will eradicate both low-risk and high-risk types. (The case where (A.2) holds but (A.3) does not is not realistic.) The results are summarised in Table 2.

Figure 2 demonstrates the phase-portrait of the four possible outcomes. Figure 2A is the result of insufficient vaccination against either low-risk or high-risk HPV types. In this case, the disease-free equilibrium, the low-risk equilibrium and the high-risk equilibrium are all unstable, so we expect coexistence of low- and high-risk types. Figure 2B is the result of successfully vaccinating against high-risk but not low-risk types (e.g., Cervarix). In this case, high-risk types are eradicated, while

Parameter	Value	Units	Reference	Notes
λ	21.84	cells/day (per 1000)	[**14**]	
d	1/730	days^{-1}	[**33**]	
β_L	0.32	$\text{cells}^{-1}\text{days}^{-1}$	[**20**]	The estimated viral load was 7.5 log copies, so we converted to transmission probability [**32**].
β_H	0.235	$\text{cells}^{-1}\text{days}^{-1}$	[**8**]	The estimated viral load was 10^6 copies/μg, which is in line with the viral load during preliminary infection for HIV [**32**], so we used the same transmission probability.
η_L	0.9	days^{-1}	[**19**]	
η_H	0.9	days^{-1}	[**19**]	
p_H	4.11	days^{-1}	[**34**]	The estimated figure was "several thousand" virions per cell [**34**], so we chose 3000 and divided by the lifespan.
p_L	4.11	days^{-1}	–	Assumed identical to p_H.
d_V	$(\ln 2)/3$	days^{-1}	[**28**]	Calculated from the half-life of virions.
m_L	1/252	days^{-1}	[**13**]	
m_H	1/420	days^{-1}	[**13**]	

TABLE 1: Parameter values

low-risk types persist. Figure 2C is the result of successfully vaccinating against low-risk types, but not high-risk types. In this case, the high-risk types persist. This case is included for completeness; we do not expect this to occur in reality. Figure 2D is the result of successfully vaccinating against both low-risk and high-risk types (e.g., Gardasil). In this case, the disease-free equilibrium is stable and infection is eradicated.

To illustrate the theoretical results, the effects of vaccinating with both Gardasil and Cervarix were simulated and compared to the effects

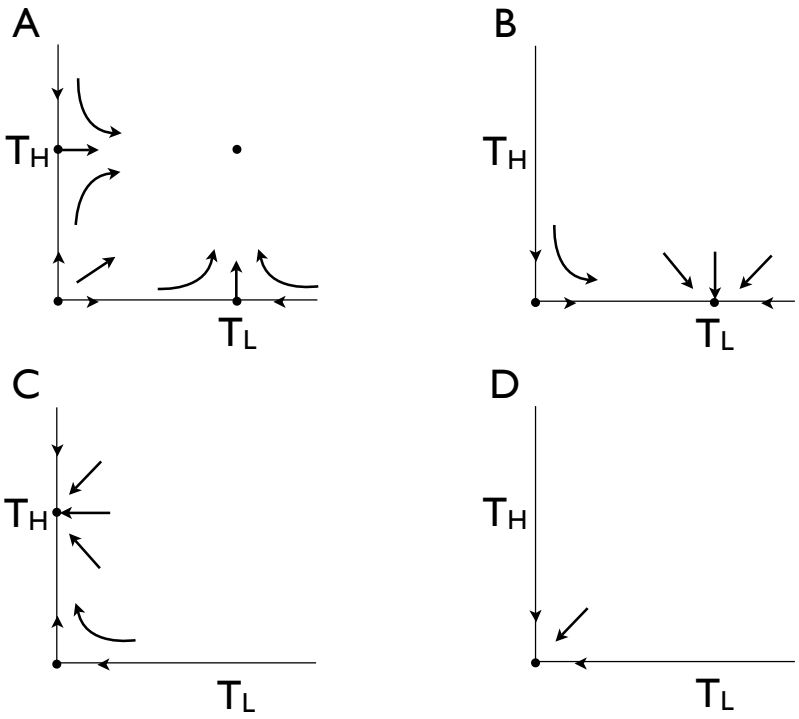

FIGURE 2: Phase-portrait representation of the four possible outcomes. A: The results of insufficient vaccination against either low-risk or high-risk HPV types. B: The results of successfully vaccinating against high-risk but not low-risk types (e.g., Cervarix). C: The results of successfully vaccinating against low-risk types, but not high-risk types. This case is included for completeness; we do not expect this to occur in reality. D: The results of successfully vaccinating against both low-risk and high-risk types (e.g., Gardasil). All axes have units of cells.

of not vaccinating. Figure 3 demonstrates the effect of insufficient vaccination with parameters $\eta_L = 0$, $\eta_H = 0$. In this case, both low-risk and high-risk viral types persist in large numbers. Parameters used are listed in Table 1.

Figure 4 demonstrates the effects of vaccinating with Cervarix, assuming sufficient vaccine efficacy against high-risk types with parameters $\eta_L = 0$, $\eta_H = 1$, but all other parameters as in Figure 3. In this

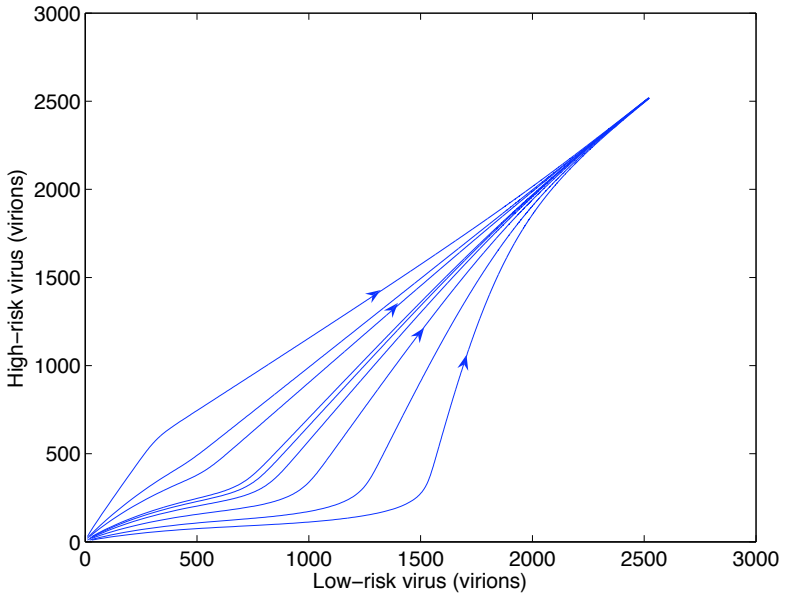

FIGURE 3: The effect of insufficient vaccination. Both low-risk and high-risk viral types persist in large numbers. Parameters were as in Table 1 except $\eta_H = \eta_L = 0$.

	$\eta_L < \eta_L^*$	$\eta_L > \eta_L^*$
$\eta_H < \eta_H^*$	Coexistence of both types	High-risk types only (unrealistic)
$\eta_H > \eta_H^*$	Low-risk types only	Eradication of both types

TABLE 2: The outcome depends upon the vaccine efficacy.

case, high-risk viral types are driven to extinction, while low-risk cells persist in high numbers.

Figure 5 demonstrates the effects of vaccinating with Gardasil, assuming sufficient vaccine efficacy against both high-risk and low-risk types with parameters $\eta_L = 1$, $\eta_H = 1$, but all other parameters as in Figure 3. In this case, both high-risk and low-risk viral types are driven to extinction.

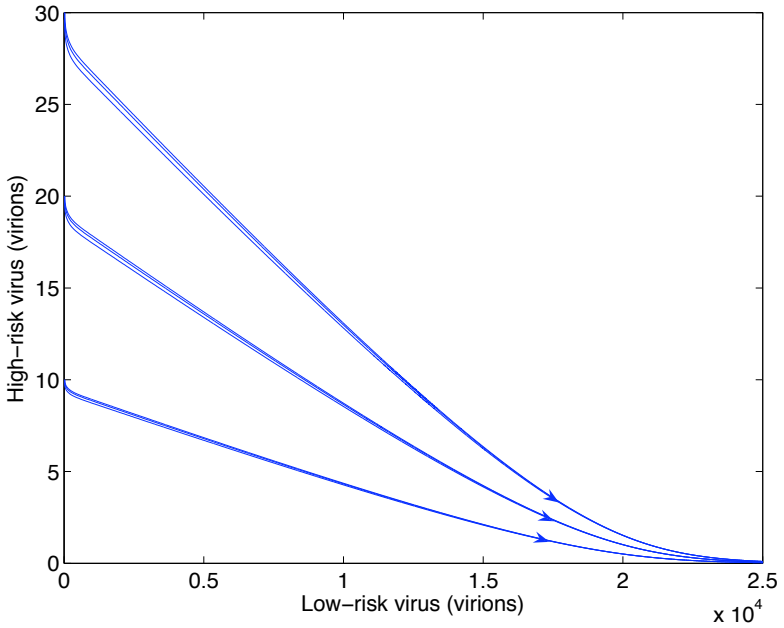

FIGURE 4: The effects of vaccinating with Cervarix, assuming perfect vaccine efficacy against high-risk types. High-risk viral types are driven to extinction, while low-risk cells persist in high numbers. Parameters were identical to Figure 3, except $\eta_H = 1$.

4 Discussion This is the first within-host compartment model of HPV vaccination. We stress that mathematical models can be a useful tool for predicting future outcomes, but are heavily reliant upon the assumptions that are inherent in the model. Nevertheless, mathematical models have been able to give significant insight into scientific processes over the years and disease models in particular [**3, 31**].

Note that Cervarix only has a reductive effect on HPV types 16 and 18, and allows HPV types 6 and 11 to take hold (Figure 4), whereas Gardasil has a reductive effect on all four types (Figure 5).

Our model has several limitations, which should be acknowledged. We aggregate the infection, waning and protection for all low-risk or all high-risk HPV types. Inclusion of the immune system dynamics would provide a more realistic description of the life cycle of the virus. Further work will include more detailed modelling of the distribution of cells

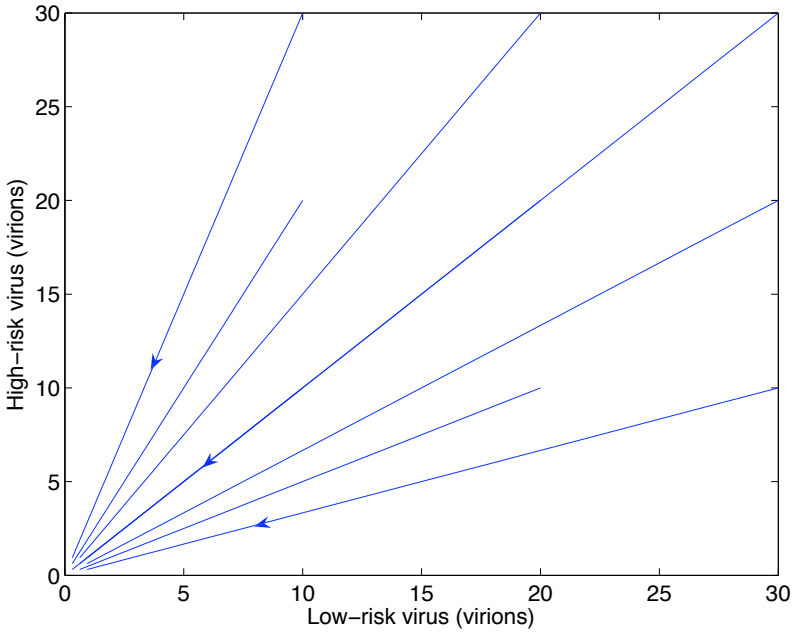

FIGURE 5: The effects of vaccinating with Gardasil, assuming perfect vaccine efficacy against both high-risk and low-risk types. Both are driven to extinction. Parameters were identical to Figure 3, except $\eta_L = \eta_H = 1$.

in the body, as well as intermediate stages between infection and the development of cancer. Finally, it should also be noted that the death rate was assumed identical for susceptible and infected cell types. This is unlikely to be true, but this assumption serves to underestimate the relevant timescale. Thus the reduction caused by the vaccine is likely to be greater in reality than estimated here.

In summary, competition between viral types for target cells results in coexistence of competing viral strains without sufficiently efficacious vaccination. Vaccines that target high-risk HPV types, whether or not they also target low-risk HPV types, have the potential to eradicate high-risk HPV types, assuming sufficient efficacy against the virus.

Appendix: mathematical details

A.1 The model The mathematical model consists of six ordinary differential equations:

$$\begin{aligned}
\frac{dT_S}{dt} &= \lambda - (1-\eta_L)\beta_L T_S V_L - (1-\eta_H)\beta_H T_S V_H \\
&\quad - dT_S + m_L T_L + m_H T_H \\
\frac{dT_L}{dt} &= (1-\eta_L)\beta_L T_S V_L - dT_L - m_L T_L \\
&\quad - (1-\eta_H)\beta_H T_L V_H + m_H T_{LH} \\
\frac{dT_H}{dt} &= (1-\eta_H)\beta_H T_S V_H - dT_H - m_H T_H \\
&\quad - (1-\eta_L)\beta_L T_H V_L + m_L T_{LH} \\
\frac{dV_L}{dt} &= p_L T_L + p_L T_{LH} - d_V V_L \\
\frac{dV_H}{dt} &= p_H T_H + p_H T_{LH} - d_V V_H \\
\frac{dT_{LH}}{dt} &= (1-\eta_L)\beta_L T_H V_L + (1-\eta_H)\beta_H T_L V_H \\
&\quad - (d + m_L + m_H) T_{LH}.
\end{aligned} \tag{A.1}$$

Initial conditions are $T_S(0) = \lambda/d$ (the level of target cells without infection), $T_L(0) = T_H(0) = T_{LH}(0) = 0$, $V_L(0) \geq 0$ and $V_H(0) \geq 0$. These initial conditions represent the earliest stage of infection.

Remark. This model includes both Gardasil (with $\eta_L, \eta_H \neq 0$) and Cervarix (with $\eta_L = 0$ and $\eta_H \neq 0$). However, it also generalises to vaccination against either low-risk or high-risk types.

A.2 Analysis The disease-free equilibrium (DFE) is given by

$$(T_S, T_L, T_H, V_L, V_H, T_{LH}) = (\lambda/d, 0, 0, 0, 0, 0)\ .$$

There is a low-risk equilibrium, given by

$$(\overline{T}_S, \overline{T}_L, 0, \overline{V}_L, 0, 0) = \left(\frac{d_V(d+m_L)}{p_L\beta_L(1-\eta_L)}, \overline{T}_L, 0, \frac{p_L}{d_V}\overline{T}_L, 0, 0 \right),$$

where

$$\overline{T}_L = \frac{\lambda(1-\eta_L)\beta_L p_L - dd_V(d+m_L)}{dp_L\beta_L(1-\eta_L)}.$$

Note that

$$\overline{T}_L = \frac{\lambda}{d} - \overline{T}_S.$$

There is a high-risk equilibrium, given by

$$(\widetilde{T}_S, 0, \widetilde{T}_H, 0, \widetilde{V}_H, 0) = \left(\frac{d_V(d+m_H)}{p_H\beta_H(1-\eta_H)}, 0, \widetilde{T}_H, 0, \frac{p_H}{d_V}\widetilde{T}_H, 0\right),$$

where

$$\begin{aligned}\widetilde{T}_H &= \frac{\lambda(1-\eta_H)\beta_H p_H - dd_V(d+m_H)}{dp_H\beta_H(1-\eta_H)} \\ &= \frac{\lambda}{d} - \widetilde{T}_S.\end{aligned}$$

There is also a coexistence equilibrium,

$$(\widehat{T}_S, \widehat{T}_L, \widehat{T}_H, \widehat{V}_L, \widehat{V}_H, \widehat{T}_{LH})$$

with the property that

$$\widehat{T}_{LH} = \frac{(1-\eta_L)\beta_L p_L + (1-\eta_H)\beta_H p_H}{d_V(d+m_L+m_H) - (1-\eta_L)\beta_L p_L\widehat{T}_H - (1-\eta_H)\beta_H p_H\widehat{T}_L}\widehat{T}_L\widehat{T}_H.$$

The Jacobian matrix is $J = [J_1 \mid J_2]$ where

$$J_1 = \begin{bmatrix} -(1-\eta_L)\beta_L V_L \\ -(1-\eta_H)\beta_H V_H - d & m_L & m_H \\ (1-\eta_L)\beta_L V_L & \begin{matrix}-d-m_L \\ -(1-\eta_H)\beta_H V_H\end{matrix} & 0 \\ (1-\eta_H)\beta_H V_H & 0 & \begin{matrix}-d-m_H \\ -(1-\eta_L)\beta_L V_L\end{matrix} \\ 0 & p_L & 0 \\ 0 & 0 & p_H \\ 0 & (1-\eta_H)\beta_H V_H & (1-\eta_L)\beta_L V_L \end{bmatrix}$$

and

$$J_2 = \begin{bmatrix} -(1-\eta_L)\beta_L T_S & -(1-\eta_H)\beta_H T_S & 0 \\ (1-\eta_L)\beta_L T_S & -(1-\eta_H)\beta_H T_L & m_H \\ -(1-\eta_L)\beta_L T_H & (1-\eta_H)\beta_H T_S & m_L \\ -d_V & 0 & p_L \\ 0 & -d_V & p_H \\ (1-\eta_L)\beta_L T_H & (1-\eta_H)\beta_H T_L & -d-m_L-m_H \end{bmatrix}.$$

A.3 The disease-free equilibrium At the DFE, we have

$$J = \begin{bmatrix} d & m_L & m_H & -(1-\eta_L) \times \beta_L T_S & -(1-\eta_H) \times \beta_H T_S & 0 \\ 0 & -d-m_L & 0 & (1-\eta_L)\beta_L T_S & 0 & m_H \\ 0 & 0 & -d-m_H & 0 & (1-\eta_H)\beta_H T_S & m_L \\ 0 & p_L & 0 & -d_V & 0 & p_L \\ 0 & 0 & p_H & 0 & -d_V & p_H \\ 0 & 0 & 0 & 0 & 0 & -d-m_L \\ & & & & & -m_H \end{bmatrix}.$$

The characteristic polynomial is thus

$$\det(J-\Lambda I) = (-d-\Lambda)(-d-m_L-m_H-\Lambda)\det M_1 \det M_2,$$

where

$$M_1 = \begin{bmatrix} -d-m_L-\Lambda & (1-\eta_L)\beta_L T_S \\ p_L & -d_V-\Lambda \end{bmatrix},$$

$$M_2 = \begin{bmatrix} -d-m_H-\Lambda & (1-\eta_H)\beta_H T_S \\ p_H & -d_V-\Lambda \end{bmatrix}.$$

Thus we have stability if

$$\eta_L > \eta_L^* \equiv 1 - \frac{dd_V(d+m_L)}{p_L\beta_L\lambda} \tag{A.2}$$

and

$$\eta_H > \eta_H^* \equiv 1 - \frac{dd_V(d+m_H)}{p_H\beta_H\lambda}. \tag{A.3}$$

Note that if (A.2) holds, then $\overline{T}_L < 0$, while if (A.3) holds, then $\widetilde{T}_H < 0$. In these cases, the relevant strain is eliminated, due to the invariance of first quadrant, so the negative steady state is never reached.

A.4 The low-risk equilibrium At the low-risk equilibrium, the Jacobian matrix is $J = [J_3 \mid J_4]$ where

$$J_3 = \begin{bmatrix} -(1-\eta_L)\beta_L\overline{V}_L - d & m_L & m_H \\ (1-\eta_L)\beta_L\overline{V}_L & -d-m_L & 0 \\ 0 & 0 & -d-m_H-(1-\eta_L)\beta_L\overline{V}_L \\ 0 & p_L & 0 \\ 0 & 0 & p_H \\ 0 & 0 & (1-\eta_L)\beta_L\overline{V}_L \end{bmatrix}$$

and

$$J_4 = \begin{bmatrix} -(1-\eta_L)\beta_L\overline{T}_S & -(1-\eta_H)\beta_H\overline{T}_S & 0 \\ (1-\eta_L)\beta_L\overline{T}_S & -(1-\eta_H)\beta_H\overline{T}_L & m_H \\ 0 & (1-\eta_H)\beta_H\overline{T}_S & m_L \\ -d_V & 0 & p_L \\ 0 & -d_V & p_H \\ 0 & (1-\eta_H)\beta_H\overline{T}_L & -d-m_L-m_H \end{bmatrix}.$$

The characteristic polynomial satisfies

$$\det(J-\Lambda I) = \det A \det B,$$

where

$$A = \begin{bmatrix} -(1-\eta_L)\beta_L\overline{V}_L - d - \Lambda & m_L & -(1-\eta_L)\beta_L\overline{T}_S \\ (1-\eta_L)\beta_L\overline{V}_L & -d-m_L-\Lambda & (1-\eta_L)\beta_L\overline{T}_S \\ 0 & p_L & -d_V-\Lambda \end{bmatrix},$$

$$B = \begin{bmatrix} -d-m_H & & \\ -(1-\eta_L)\beta_L\overline{V}_L - \Lambda & (1-\eta_H)\beta_H\overline{T}_S & m_L \\ p_H & -d_V-\Lambda & p_H \\ & & \\ (1-\eta_L)\beta_L\overline{V}_L & (1-\eta_H)\beta_H\overline{T}_L & \begin{matrix} -d-m_L \\ -m_H-\Lambda \end{matrix} \end{bmatrix}.$$

We can write

$$\det A = -\Lambda^3 - a_2\Lambda^2 - a_1\Lambda - a_0,$$

where

$$\begin{aligned}
a_2 &= (1-\eta_L)\beta_L\overline{V}_L + 2d + m_L + d_V > 0,\\
a_1 &= [(1-\eta_L)\beta_L\overline{V}_L + d](d+d_V) + m_L d > 0,\\
a_0 &= (1-\eta_L)\beta_L d d_V \overline{V}_L > 0.
\end{aligned}$$

We have

$$\det B = -\Lambda^3 - b_2\Lambda^2 - b_1\Lambda + b_0, \tag{A.4}$$

where

$$\begin{aligned}
b_2 &= 2d + 2m_H + (1-\eta_L)\beta_L\overline{V}_L + d_V + m_L > 0\\
b_1 &= (d + m_H + (1-\eta_L)\beta_L\overline{V}_L)d_V\\
&\quad + (d + m_H + (1-\eta_L)\beta_L\overline{V}_L)(d + m_L + m_H)\\
&\quad + d_V(d + m_L + m_H) - m_L(1-\eta_L)\beta_L\overline{V}_L\\
&\quad - p_H(1-\eta_H)\beta_H(\overline{T}_L + \overline{T}_S)\\
&= (d+m_H)(d_V + d + m_L + m_H)\\
&\quad + (1-\eta_L)\beta_L\overline{V}_L(d_V + d + m_H)\\
&\quad + d_V(d + m_L + m_H) - p_H(1-\eta_H)\beta_H\frac{\lambda}{d}.
\end{aligned}$$

Next, we have

$$\begin{aligned}
b_0 &= -(d + m_H + (1-\eta_L)\beta_L\overline{V}_L)d_V(d + m_L + m_H)\\
&\quad + (1-\eta_H)\beta_H\overline{T}_S p_H(1-\eta_L)\beta_L\overline{V}_L + m_L p_H(1-\eta_H)\beta_H T_L\\
&\quad + d_V m_L(1-\eta_L)\beta_L\overline{V}_L\\
&\quad + (d + m_H + (1-\eta_L)\beta_L\overline{V}_L)p_H(1-\eta_H)\beta_H\overline{T}_L\\
&\quad + (d + m_L + m_H)p_H(1-\eta_H)\beta_H\overline{T}_S\\
&= -(d+m_H)d_V(d + m_L + m_H) - (1-\eta_L)\beta_L p_L\overline{T}_L(d + m_L + m_H)
\end{aligned}$$

$$
\begin{aligned}
&+ m_L p_H (1-\eta_H)\beta_H \overline{T}_L + m_L(1-\eta_L)\beta_L p_L \overline{T}_L \\
&+ (1-\eta_H)\beta_H p_H \left(d + m_L + m_H + (1-\eta_L)\beta_L \frac{p_L}{d_V}\overline{T}_L\right)\left(\frac{\lambda}{d} - \overline{T}_L\right) \\
&+ \left(d + m_H + (1-\eta_L)\beta_L \frac{p_L}{d_V}\overline{T}_L\right)(1-\eta_H)\beta_H p_H \overline{T}_L \\
= &-(d+m_H)d_V(d+m_L+m_H) - (1-\eta_L)\beta_L p_L \overline{T}_L (d+m_H) \\
&+ (1-\eta_H)\beta_H p_H \left(d + m_L + m_H + (1-\eta_L)\beta_L \frac{p_L}{d_V}\overline{T}_L\right)\frac{\lambda}{d}.
\end{aligned}
$$

A.5 Conditional stability Suppose that

$$p_H \beta_H (1-\eta_H) - d_V(d+m_H) = -\epsilon < 0$$

so that (A.3) holds. It follows immediately that the high-risk equilibrium does not exist. Suppose further that (A.2) does not hold, so that the low-risk equilibrium exists.

Then we have

$$
\begin{aligned}
b_1 &> (d+m_H)(d_V + d + m_L + m_H) \\
&\quad + (1-\eta_L)\beta_L \overline{V}_L (d_V + d + m_H) \\
&\quad + d_V(d + m_L + m_H) - d_V(d+m_H) > 0 \\
b_0 &= -\epsilon\left(d + m_L + m_H + (1-\eta_L)\beta_L \frac{p_L}{d_V}\overline{T}_L\right) < 0 \\
b_2 b_1 - b_0 &> (2d + 2m_H + (1-\eta_L)\beta_L \overline{V}_L + d_V + m_L) \\
&\quad \times \big[(d+m_H)(d_V + d + m_L + m_H) \\
&\quad + (1-\eta_L)\beta_L \overline{V}_L (d_V + d + m_H) \\
&\quad + d_V(d + m_L + m_H) - d_V(d+m_H)\big] \\
&\quad - \epsilon\left(d + m_L + m_H + (1-\eta_L)\beta_L \frac{p_L}{d_V}\overline{T}_L\right) > 0
\end{aligned}
$$

if ϵ is small. Thus, by the Routh–Hurwitz Criterion, the low-risk equilibrium is stable if (A.3) holds but (A.2) does not.

Conversely, if (A.3) does not hold, then $b_0 > 0$ and the characteristic polynomial (A.4) has a root with positive real part.

By symmetry, the high-risk equilibrium will be stable if (A.2) holds and (A.3) does not. Finally, if neither (A.3) nor (A.2) hold, then both the low-risk and high-risk equilibria will be unstable.

A.6 Summary In summary, if neither (A.2) nor (A.3) hold, then the DFE is unstable, $\overline{T}_L > 0$ and $\widetilde{T}_H > 0$. See Figure 3.

If (A.3) holds, but (A.2) does not hold, then the DFE is unstable, $\overline{T}_L > 0$ and $\widetilde{T}_H < 0$. In this case, the low-risk equilibrium is stable. See Figure 4. If (A.2) holds, but (A.3) does not hold, then the DFE is unstable, $\overline{T}_L < 0$ and $\widetilde{T}_H > 0$. (Note that we do not expect this case to arise in reality.)

If (A.2) and (A.3) both hold, then the DFE is asymptotically stable, while $\overline{T}_L < 0$ and $\widetilde{T}_H < 0$. See Figure 5.

The local stability results are summarised in Table 2 and Figure 2.

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