

Oikos

**OIK-05654**

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## Appendix 1



## Mathematical supplementary information

### *Derivation of non-dimensional model*

We use the simple modelling framework provided in Booton et al. 2018 to describe the within-host infection dynamics under toxicant exposure in an individual.  $X$ ,  $Y$  and  $Z$  represent the total within-host cells, parasite density and immune function, respectively. Toxicant exposure  $Q$  both reduces the functionality of the immune system at rate  $h$  (sub-lethal) and damages the functionality of the host at rate  $r$  (lethal).  $\lambda$  sets the rate of production for new healthy cells,  $\beta$  the rate of infection,  $d$  the death of healthy cells,  $a$  the death of parasites,  $p$  the immune suppression,  $c$  the production of immunity and  $b$  the removal of immunity. This model is given by the below equations

$$\begin{aligned}\frac{dX}{dt} &= \lambda - \beta Y X - dX - rQ \\ \frac{dY}{dt} &= \beta Y X - aY - pYZ \\ \frac{dZ}{dt} &= c - bZ - hQ\end{aligned}$$

In order to significantly reduce the analysis we non-dimensionalise this model.

We write these differential equations in terms of the new variables:  $\mathcal{X} = \hat{X}X$ ,  $\mathcal{Y} = \hat{Y}Y$ ,  $\mathcal{Z} = \hat{Z}Z$  and

$$\mathbf{t} = \hat{t}t$$

, where the quantities  $\hat{X}$ ,  $\hat{Y}$ ,  $\hat{Z}$  and  $\hat{t}$  will be chosen later. By the chain rule,

$$\begin{aligned}
\frac{d\mathcal{X}}{dt} &= \frac{\hat{X}}{\hat{t}} \frac{dX}{dt} \\
&= \frac{\lambda\hat{X}}{\hat{t}} - \frac{\beta\mathcal{X}\mathcal{Y}}{\hat{t}\hat{Y}} - \frac{d\mathcal{X}}{\hat{t}} - \frac{rQ\hat{X}}{\hat{t}} \\
\frac{d\mathcal{Y}}{dt} &= \frac{\hat{Y}}{\hat{t}} \frac{dY}{dt} \\
&= \frac{\beta\mathcal{X}\mathcal{Y}}{\hat{t}\hat{X}} - \frac{a\mathcal{Y}}{\hat{t}} - \frac{p\mathcal{Y}\mathcal{Z}}{\hat{t}\hat{Z}} \\
\frac{d\mathcal{Z}}{dt} &= \frac{\hat{Z}}{\hat{t}} \frac{dZ}{dt} \\
&= \frac{c\hat{Z}}{\hat{t}} - \frac{b\mathcal{Z}}{\hat{t}} - \frac{hQ\hat{Z}}{\hat{t}}
\end{aligned}$$

Let  $\hat{t} = b$ ,  $\hat{X} = \frac{b}{\lambda}$ ,  $\hat{Y} = \frac{\beta}{b}$ ,  $\hat{Z} = \frac{\hat{t}}{c} = \frac{b}{c}$ ,  $\xi_1 = \frac{r}{\lambda}$ ,  $\xi_2 = \frac{h}{c}$ , which gives

$$\begin{aligned}
\frac{d\mathcal{X}}{dt} &= 1 - \mathcal{X}\mathcal{Y} - \frac{d}{b}\mathcal{X} - \xi_1 Q \\
\frac{d\mathcal{Y}}{dt} &= \frac{\beta\lambda}{b^2}\mathcal{X}\mathcal{Y} - \frac{a}{b}\mathcal{Y} - \frac{pc}{b^2}\mathcal{Y}\mathcal{Z} \\
\frac{d\mathcal{Z}}{dt} &= 1 - \mathcal{Z} - \xi_2 Q
\end{aligned}$$

Then we let  $\phi = \frac{d}{b}$ ,  $\gamma = \frac{a}{b}$ ,  $\epsilon = \frac{\beta\lambda}{b^2}$  and  $\omega = \frac{pc}{b^2}$  which gives the final simplified set of equations

$$\begin{aligned}\frac{d\mathcal{X}}{d\mathfrak{t}} &= (1 - \xi_1 Q) - \mathcal{X}(\phi + \mathcal{Y}) \\ \frac{d\mathcal{Y}}{d\mathfrak{t}} &= \mathcal{Y}(\epsilon\mathcal{X} - \gamma - \omega\mathcal{Z}) \\ \frac{d\mathcal{Z}}{d\mathfrak{t}} &= (1 - \xi_2 Q) - \mathcal{Z}\end{aligned}$$

For convenience in the main text and for the remainder of the supplementary information we replace the above  $\mathcal{X}$  with  $X$  and likewise for  $\mathcal{Y}$ ,  $\mathcal{Z}$  and  $\mathfrak{t}$  with  $Y$ ,  $Z$  and  $t$ .

*Piecewise equilibria for the within-host model*

The equilibria for the non-dimensional model are

$$(X_{DFE}, Y_{DFE}, Z_{DFE}) = \left( \frac{1 - \xi_1 Q}{\phi}, 0, 1 - \xi_2 Q \right)$$

and

$$(X_{EE}, Y_{EE}, Z_{EE}) = \left( \frac{\gamma - \xi_2 Q \omega + \omega}{\epsilon}, \frac{\epsilon - \xi_1 Q \epsilon}{\gamma - \xi_2 Q \omega + \omega} - \phi, 1 - \xi_2 Q \right)$$

We define  $X'$  to be the equilibrium state of within-host cells in an uninfected individual in the absence of infection. Under increasing  $Q$ , the solution for  $X'$  is defined until  $\frac{1 - \xi_1 Q}{\phi} = 0$  (after which the solution would be negative) and hence we set the value equal to zero after this point:

$$X' = \begin{cases} \frac{1 - \xi_1 Q}{\phi}, & \text{if } 1 - \xi_1 Q > 0 \\ 0, & \text{otherwise} \end{cases}$$

We define  $X^*$  to be the equilibrium state of within-host cells in an infected individual. The solution depends on whether or not the infection is present within the host, and whether or not the immune system has been depleted to zero. If the immune system  $Z$  is nonzero ( $1 - \xi_2 Q > 0$ ),  $X^*$  is the solution defined by  $X_{EE}$ . However, once the immune system is depleted, then the

ODEs become

$$\begin{aligned}\frac{dX}{dt} &= (1 - \xi_1 Q) - X(\phi + Y) \\ \frac{dY}{dt} &= Y(\epsilon X - \gamma)\end{aligned}$$

which has a solution at

$$(X_{EE2}, Y_{EE2}) = \left(\frac{\gamma}{\epsilon}, \frac{-\gamma\phi - \xi_1 Q\epsilon + \epsilon}{\gamma}\right)$$

Hence if  $Z = 0$  at  $1 - \xi_2 Q = 0$  and the parasite density is above zero, then  $X^*$  is the solution defined by  $X_{EE2}$ . However, once the infection is removed from the system by the toxicant, the ODE system becomes

$$\frac{dX}{dt} = (1 - \xi_1 Q) - \phi X$$

which has a solution at

$$X_{DFE} = \frac{1 - \xi_1 Q}{\phi}$$

After  $Y^* = 0$  the solution for  $X^*$  becomes identical to  $X'$ . Collecting these three conditions together yields the piecewise equilibria defined as:

$$X^* = \begin{cases} \frac{\gamma - \xi_2 Q \omega + \omega}{\epsilon}, & \text{if } 1 - \xi_2 Q > 0 \\ \frac{\gamma}{\epsilon}, & \text{if } 1 - \xi_2 Q \leq 0 \text{ \& } Y^* > 0 \\ X', & \text{if } 1 - \xi_2 Q \leq 0 \text{ \& } Y^* = 0 \end{cases}$$

Similarly  $Y^*$  is the equilibrium state of parasite density in an infected individual. This is determined by the status of immunity and by the point at which the infection is removed from the system. If  $Z > 0$  at  $1 - \xi_2 Q > 0$  then  $Y^*$  is defined by  $Y_{EE1}$ . However if the immune system is depleted then the ODE system becomes 2 dimensional and the solution for  $Y^*$  becomes  $Y_{EE2}$ . This solution is defined until  $Y_{EE2} = 0$ , at which point the infection is completely removed from the host and remains at 0 indefinitely. Collecting these conditions together yields the piecewise equilibria for the parasite density:

$$Y^* = \begin{cases} \frac{\epsilon - \xi_1 Q \epsilon}{\gamma - \xi_2 Q \omega + \omega} - \phi, & \text{if } 1 - \xi_2 Q > 0 \\ \frac{-\gamma \phi - \xi_1 \epsilon + \epsilon}{\gamma}, & \text{if } 1 - \xi_2 Q \leq 0 \text{ \& } \frac{-\gamma \phi - \xi_1 \epsilon + \epsilon}{\gamma} > 0 \\ 0, & \frac{-\gamma \phi - \xi_1 \epsilon + \epsilon}{\gamma} \leq 0 \end{cases}$$

*The basic reproduction number*

We will use the next generation matrix method to derive the basic reproduction number. The disease free equilibrium for the between-host model is

$$(S^{DFE}, I^{DFE}) = \left( \frac{\Lambda + k\Lambda X'}{u}, 0 \right)$$

The next generation matrix  $G$  is comprised of two parts:  $F$  and  $V^{-1}$  where  $F$  represents the new infections and  $V$  represents the transfer of individuals between compartments:

$$F = \begin{pmatrix} 0 & 0 \\ IY^*\theta & SY^*\theta \end{pmatrix}$$

$$V = \begin{pmatrix} \frac{u}{kX'+1} + IY^*\theta & SY^*\theta \\ 0 & \frac{u}{kX^*+1} \end{pmatrix}$$

$$V^{-1} = \begin{pmatrix} \frac{kX'+1}{u+I(kX'+1)Y^*\theta} & -\frac{S(kX'+1)(kX^*+1)Y^*\theta}{u(u+I(kX'+1)Y^*\theta)} \\ 0 & \frac{kX^*+1}{u} \end{pmatrix}$$

so that

$$G = FV^{-1} = \begin{pmatrix} 0 & 0 \\ IY^*\theta & SY^*\theta \end{pmatrix} \begin{pmatrix} \frac{kX'+1}{u+I(kX'+1)Y^*\theta} & -\frac{S(kX'+1)(kX^*+1)Y^*\theta}{u(u+I(kX'+1)Y^*\theta)} \\ 0 & \frac{kX^*+1}{u} \end{pmatrix}$$

$$G = \begin{pmatrix} 0 & 0 \\ 1 - \frac{u}{u+I(kX'+1)Y^*\theta} & \frac{S(kX^*+1)Y^*\theta}{u+I(kX'+1)Y^*\theta} \end{pmatrix}$$

The eigenvalues of  $G$  are

$$\left(0, \frac{\theta SY^*(kX^* + 1)}{\theta IY^*(kX' + 1) + u}\right)$$

The largest eigenvalue of  $G$  evaluated at the DFE is the basic reproduction number.  $\frac{\theta SY^*(kX^*+1)}{\theta IY^*(kX'+1)+u}$  evaluated at  $(S^{DFE}, I^{DFE}) = (\frac{\Lambda+k\Lambda X'}{u}, 0)$  gives the basic reproduction number:

$$R_0 = \frac{\theta \Lambda Y^*(1 + kX')(1 + kX^*)}{u^2}$$

## Additional figures

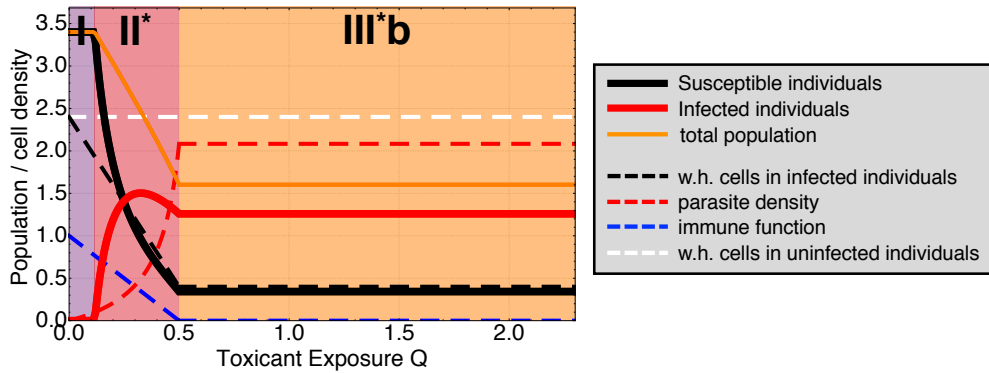
### *Absence of toxicant lethality ( $r = 0$ )*

Figure ES1 shows the predicted outcome of the model in the absence of toxicant lethality for increasing toxicant exposure  $Q$ . Setting the parameter  $\xi_1 = 0$  means that there is no direct lethality-causing toxicant effect. Under this condition, the first stages of the epidemic are similar to those observed in the original analysis (Fig. 3). However in this scenario, after the host immune function is destroyed, a new phase *III\*b* occurs for all values of toxicant higher than a critical value. This results in a persistent epidemic caused by the lack of direct lethality within the toxicant, and increasing the toxicant further has no effect on the epidemic. In this case the basic reproduction number increases to a maximum value and remains constant for all further exposure.

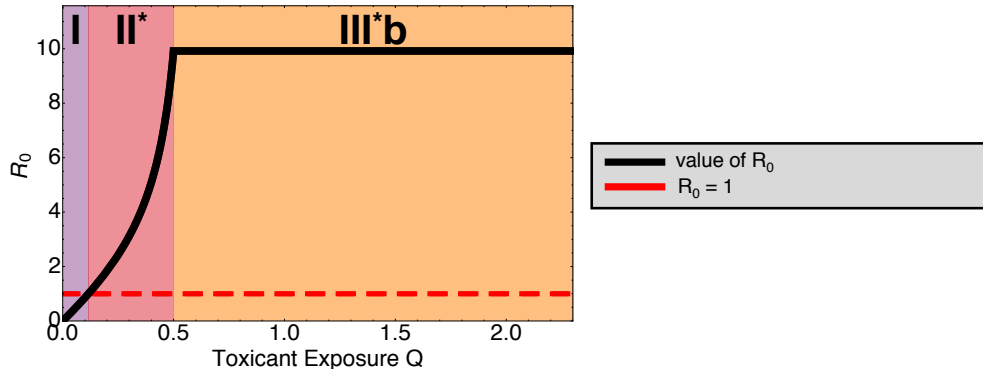
### *Aggressive toxicant lethality ( $\xi_1$ relatively larger than $\xi_2$ )*

Figure ES2 shows the stages of the epidemic for increasing toxicant exposure  $Q$ , but for a relatively greater lethality effect compared to that of the sub-lethal immunosuppressive effect. This condition results in the population becoming highly infected even at low values of toxicant exposure. This occurs because of the aggressive lethality of the toxicant causing the within-host parasite density to reduce before the immune function. These later phases of the epidemic (*III\**, *IV* and *V*) all correspond to the phases in the previous simulation (Fig. 3), so we can think about these results as sub-dynamics of

the original phases. This shows that in general the infective phases of the population dynamics increase as the toxicant exposure increases, regardless of the parameter conditions.

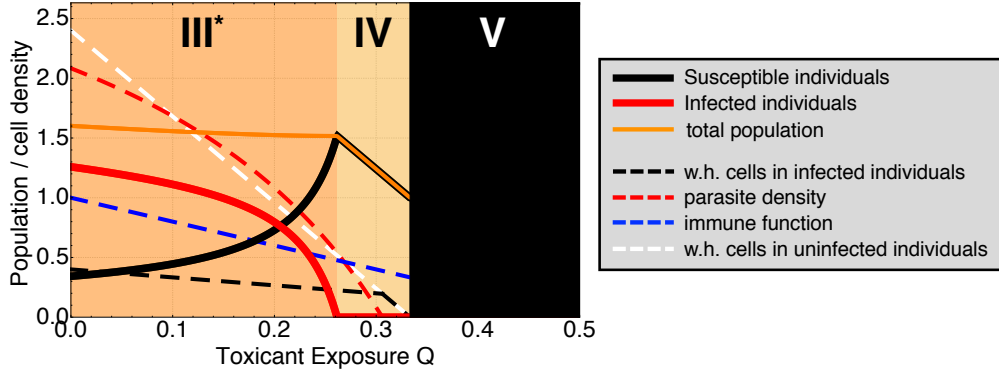


(a)

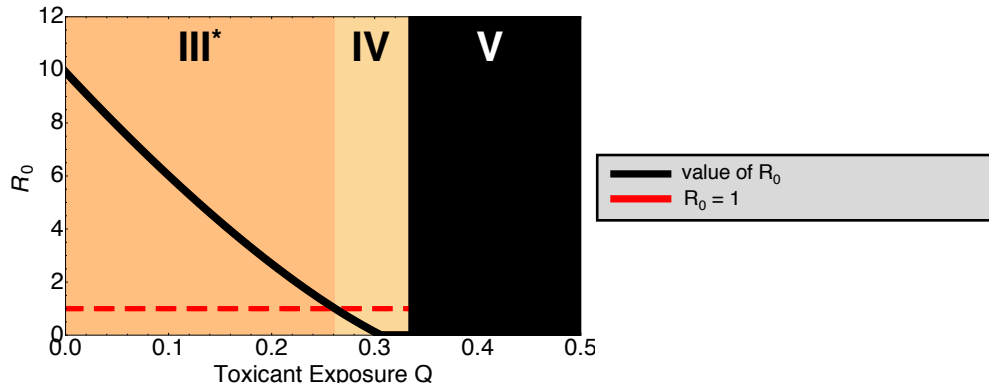


(b)

Figure ES1: The predicted three phases of an infected population under increasing toxicant stress  $Q$  with no direct lethality of the toxicant  $\xi_1 = 0$ . Starred phases ( $II^*$  and  $III^*b$ ) represent the outbreak of infection where  $R_0 > 1$ . The individual remains highly infective in the absence of toxicant lethality. Parameters taken from Table 1 but with  $\xi_1 = 0$ .



(a)



(b)

Figure ES2: The predicted three phases of an infected population under increasing toxicant stress  $Q$  with a relatively aggressive lethal effect of the toxicant  $\xi_1 > \xi_2$ . Starred phase  $III^*$  represents the outbreak of infection where  $R_0 > 1$ . The individual is highly infective to begin with and then the aggressive toxicant effect removes the within-host parasite load which reduces the chance of infection at the population level. Parameters taken from Table 1 but  $\xi_1 = 3$ ,  $\xi_2 = 2$  and  $\epsilon = 3$ .

#### *Dependence of $R_0$ on $Q$ and $k$*

Here we plot the dependence of the basic reproduction number  $R_0$  on  $Q$  and  $k$  (Figure ES3). Since  $k$  sets the sensitivity of the relative effect of host mortality, and appears in the derivation of  $R_0$  twice, we plot the relationship between these parameters in 3D space. Here we see that  $k$  determines the

rate at which  $R_0$  reaches a maximum, and the subsequent rate at which  $R_0$  is reduced. Note that this maximum value also depends on the parasite density  $Y^*$ .

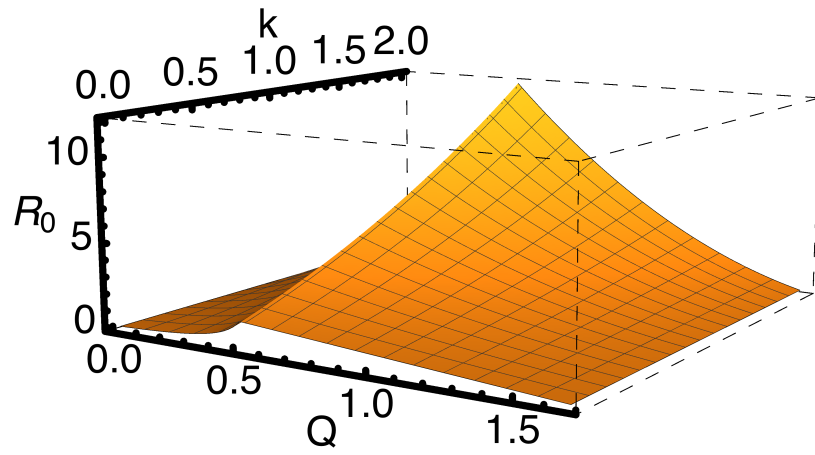


Figure ES3: The dependence of  $R_0$  on toxicant exposure  $Q$  and relative effect of host mortality  $k$

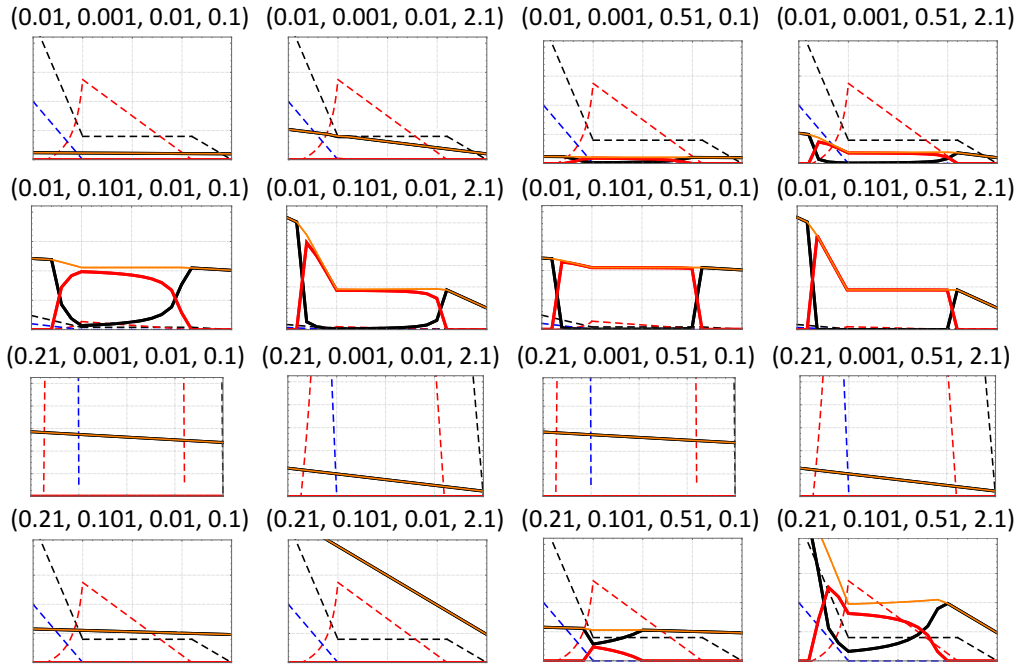
## Parameter dependence

In the within-host system, the parameter set  $(\phi, \epsilon, \gamma, \omega)$  determine the within host dynamics when the immune system is depleted before the host is dead under the assumption  $\xi_2 > \xi_1$ . We ran simulations around this parameter set to determine the universal behaviour of the model. We found that in the within-host system, three such possibilities exist for any combination of parameters:

- The within-host parasite density is maximised at an intermediate level of toxicant  $Q$  and is equal to 0 when  $Q = 0$ . An example of such a parameter set is  $(\phi, \epsilon, \gamma, \omega) = (0.5, 0.5, 0.2, 1)$ .
- At  $Q = 0$ , the within-host parasite density is non zero. An example of such a parameter set close to the above set is  $(\phi, \epsilon, \gamma, \omega) = (0.25, 0.5, 0.2, 1)$ .
- The within-host parasite density is equal to zero when  $Q = 0$  and remains at zero regardless of  $Q$ . This represents the region under which a parasite infection is not feasible. An example of such a parameter set close to the above set is  $(\phi, \epsilon, \gamma, \omega) = (0.75, 0.25, 0.4, 1)$ .

Given these three different possibilities for the within-host dynamics, we run further simulations to examine the effects of parameter dependence on between-host dynamics. For the between-host parameter set  $(u, \Lambda, \theta, k)$  we set the within-host parameter set  $(\phi, \epsilon, \gamma, \omega)$  equal to the above 3 options.

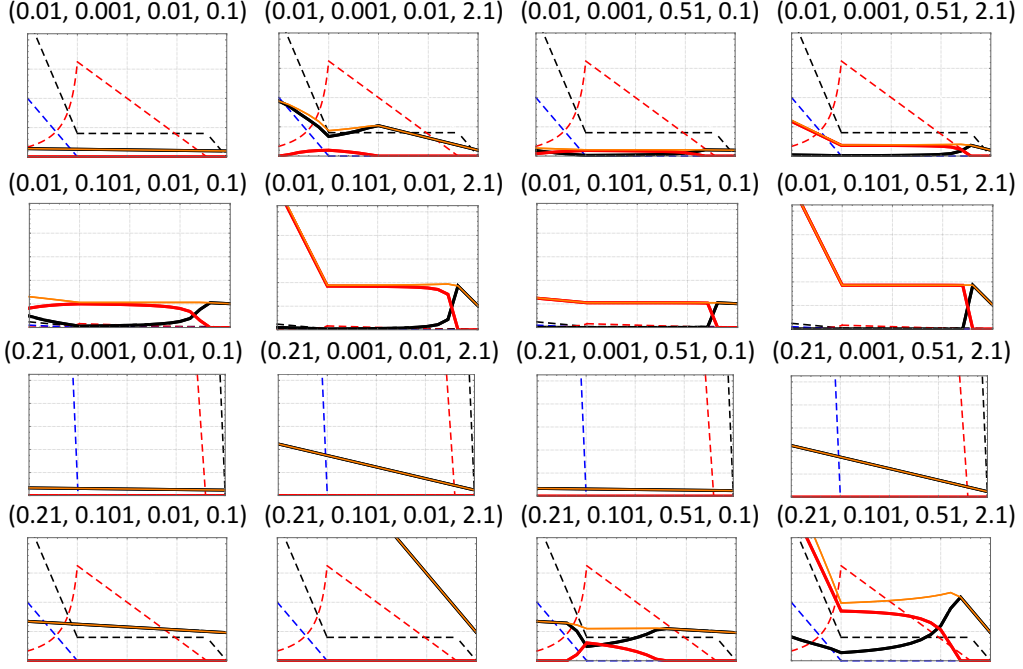
This ensures that we examine each possibility for a range of parameter space. We vary  $u \in (0.01, 0.21)$ ,  $\Lambda \in (0.001, 0.101)$ ,  $\theta \in (0.01, 0.51)$  and  $k \in (0.1, 2.1)$ . This ensures we see the different dynamical behaviour of the model under different parameter combinations.



The sensitivity of the between-host system with respect to the parameter set  $(\phi, \epsilon, \gamma, \omega) = (0.5, 0.5, 0.2, 1)$ , for varying  $(u, \Lambda, \theta, k)$ .

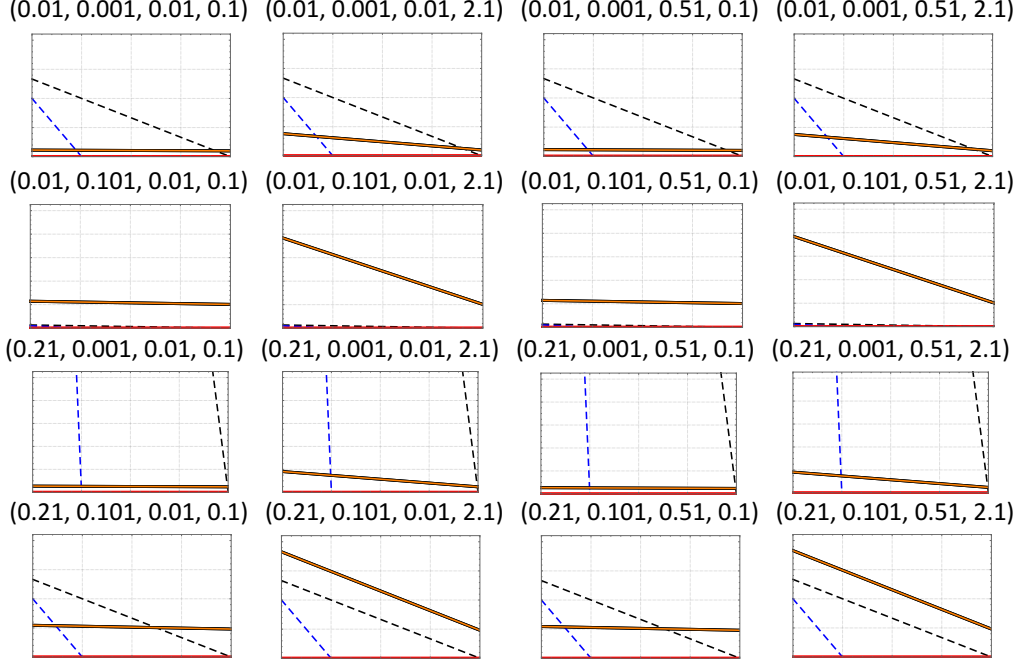
As in the main text,  $Q$  is on the x axis, and the density is on the y axis. Each figure has identical within-host dynamics and are scaled according to the between-host dynamics. In the case of intermediate within-host parasite density at  $(\phi, \epsilon, \gamma, \omega) = (0.5, 0.5, 0.2, 1)$ , the only possible between-host dynamics are either no between-host infection, or the usual 5 phase epidemic we see in the main text, where the epidemic is maximised at an intermediate

$Q$ .



The sensitivity of the between-host system with respect to the parameter set  $(\phi, \epsilon, \gamma, \omega) = (0.25, 0.5, 0.2, 1)$ , for varying  $(u, \Lambda, \theta, k)$ .

In the case of a non-zero parasite density at  $Q = 0$  at  $(\phi, \epsilon, \gamma, \omega) = (0.25, 0.5, 0.2, 1)$ , the only possible between-host dynamics are either no between-host infection, or the usual 5 phase epidemic we see in the main text, where the epidemic is maximised at an intermediate  $Q$ . In addition we see a third qualitative outcome where the between-host infection is present at  $Q = 0$ , which corresponds to the figure starting in phase  $III^*$ , and continuing through phases  $IV$  and  $V$ . So we may think of these as sub-dynamics of the original 5 phases.



The sensitivity of the between-host system with respect to the parameter set  $(\phi, \epsilon, \gamma, \omega) = (0.75, 0.25, 0.4, 1)$  for varying  $(u, \Lambda, \theta, k)$ . No between-host epidemic is possible.

Finally we examine the possibility that the within-host parasite density remains at zero regardless of  $Q$  at  $(\phi, \epsilon, \gamma, \omega) = (0.75, 0.25, 0.4, 1)$ . Here we see that the absence of within-host infection corresponds to the absence of between-host infection, regardless of between-host parameter choice.

To summarise, there are three possible outcomes for the between-host dynamics regardless of parameter choice. These are

- No between-host infection ( $R_0 < 1$ ), which depending on the level of immunity are sub-dynamics of the original 5 phases (phases *I* and *IV*).
- Between-host infection is maximised at an intermediate toxicant expo-

sure, with 5 epidemic phases.

- The between-host infection is present at  $Q = 0$ , which represents sub-dynamics of the original 5 phases (phases  $III^*$ ,  $IV$  and  $V$ )

The universal behaviour of the model falls into these 3 categories.

## Units

Here we provide the units for the original parameters and the new derived parameters from the non-dimensionalisation process. For each unit of within-host time (denoted by time' to signify the different timescale) and unit of between-host time (denoted by time) we calculate the units for each parameter as:

Parameter description	Symbol	Units
<b>Within-host (before non-dimensionalisation)</b>		
production of within-host cells	$\lambda$	cells time' <sup>-1</sup>
within-host transmission rate	$\beta$	cells <sup>-1</sup> time' <sup>-1</sup>
mortality of within-host cells	$d$	time' <sup>-1</sup>
direct lethal effect of toxicant	$r$	cells time' <sup>-1</sup>
toxicant exposure	$Q$	no dimension
death rate of parasites	$a$	time' <sup>-1</sup>
immune suppression	$p$	cells <sup>-1</sup> time' <sup>-1</sup>
production of immunity	$c$	cells time' <sup>-1</sup>
removal of immunity	$b$	time' <sup>-1</sup>
indirect sub-lethal effect of toxicant	$h$	cells time' <sup>-1</sup>
<b>Within-host (after non-dimensionalisation)</b>		
lethal toxicant effect relative to production of new cells	$\xi_1$	no dimension
sub-lethal toxicant effect relative to production of immunity	$\xi_2$	no dimension
mortality of cells relative to removal of immunity	$\phi$	no dimension
mortality of parasite relative to removal of immunity	$\gamma$	no dimension
transmission and production of cells relative to removal of immunity	$\epsilon$	no dimension
suppression and production of immunity relative to removal of immunity	$\omega$	no dimension
<b>Between-host</b>		
birth rate	$\Lambda$	individuals time <sup>-1</sup>
between-host transmission rate	$\theta$	individuals <sup>-1</sup> time <sup>-1</sup>
mortality rate	$u$	time <sup>-1</sup>
relative effect of host mortality	$k$	no dimension

Table 1: The units for the between and within-host parameters used in the analysis and simulations of the model.