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Running title: How do toxicants affect epidemiological dynamics?

# How do toxicants affect epidemiological dynamics?

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# Abstract

Populations are formed of their constituent interacting individuals, each with their own respective within-host biological processes. Infection not only spreads within the host organism but also spreads between individuals. Here we propose and study a multilevel model which links the within-host statuses of immunity and parasite density to population epidemiology under sublethal and lethal toxicant exposure. We analyse this nested model in order to better understand how toxicants impact the spread of disease within populations. We demonstrate that outbreak of infection within a population is completely determined by the level of toxicant exposure, and that it is maximised by intermediate toxicant dosage. We classify the population epidemiology into 5 phases of increasing toxicant exposure and calculate the conditions under which disease will spread, showing that there exists a threshold toxicant level under which epidemics will not occur. In general, higher toxicant load results in either extinction of the population or outbreak of infection. The within-host statuses of the individual host also determine the outcome of the epidemic at the population level. We discuss applications of our model in the context of environmental epidemiology, predicting that increased exposure to toxicants could result in greater risk of epidemics within ecological systems. We predict that reducing sublethal toxicant exposure below our predicted safe threshold could contribute to controlling population level disease and infection.

**Keywords**: epidemiology; host-parasite interactions; immunity; nested model; population dynamics; toxicant stress

# Introduction

The spread of infectious disease within populations occurs at various scales of organisation. Population-scale processes are determined by the interacting individuals within such populations, each with their own respective individual within-host biological processes. Between-host epidemiological dynamics are determined primarily by host demography and transmission (Grenfell and Harwood 1997), while transmission is determined by the level of disease in infected individuals within the population (Mideo et al. 2008). Furthermore, the dynamics of diseased individuals are entirely dependent on their corresponding within-host parasite load and host defence mechanisms (Mideo et al. 2008). Infectious diseases such as host-parasite interactions depend upon two processes; both the immunological host-parasite interaction and the subsequent population level epidemiology (Feng et al. 2012).

Individual organisms are exposed to a wide variety of stressors. These stressors can be broadly defined as either abiotic (anthropogenic or climatic) or biotic (parasites or predation). These stressors either act alone, or in combination which can result in a higher than expected overall effect when synergistic interactions occur between them (Holmstrup et al. 2010). One such anthropogenic stressor is toxicant exposure; chemicals released into the environment which damage or have other detrimental effects on the host. Examples of such chemical stressors include pesticides in freshwater systems (Relyea and Hoverman 2006), neonicotinoid insecticides in honey bee colonies (Goulson et al. 2015), various environmental pollutants in rotifers (Snell and Janssen 1995) and *Daphnia* (Buratini et al. 2004) and polychlorinated dibenzo-p-dioxins (PCDDs), biphenyls (PCBs) and dibenzofurans (PCDFs) in animals and humans (Van Den Berg et al. 1998). Indeed, toxicants affect a wide range of non-target species, including birds, mammals (Eason et al. 2002), aquatic species (Phipps and Holcombe 1985), and insects (Pisa et al. 2015).

In general, toxicants have lethal effects (Martin and Holdich 1986, Suchail et al. 2001, Iwasa et al. 2004, Blacquière et al. 2012, Pan et al. 2014, Wang et al. 2017), where the direct chronic lethality of toxicant exposure occurs at high doses (Suchail et al. 2001, Pan et al. 2014, Wang et al. 2017). Toxicants often have other effects on behaviour, learning, feeding, memory and fecundity (Warner et al. 1966, Davies et al. 1994, Decourtye et al. 2003, Han et al. 2010, Williamson and Wright 2013, Williams et al. 2015). Individuals exposed to toxicants can face other stressors such as parasite infections which, when combined can cause further damage to the host. For example, the combination of parasite infection and toxicant exposure can increase the initial parasite load (Pettis et al. 2012, Doublet et al. 2015), increase virulence (Coors et al. 2008) and increase mortality (Alaux et al. 2010, Vidau et al. 2011) in the host. These interactions between toxicants and parasites are observed in a multitude of organisms (Holmstrup et al. 2010). In addition to the effects of toxicants on the functionality of the host, toxicants also sublethally damage or inhibit the individual immune response of the host (James and Xu 2012). There are a wide range of immunosuppressive effects which occur as a result of sublethal or field realistic levels of toxicant exposure (Bols et al. 2001, Gilbertson et al. 2003, James and Xu 2012, Mason 2013, Brandt et al. 2016). Throughout this manuscript we will focus on these two simultaneous effects of toxicant damage to the host, and refer to them as follows: lethal exposure reduces the functionality of the host, while sublethal exposure causes a reduction in the functionality of the host immune response.

The individual impacts of stressors on host level processes are well studied, but the subsequent impact on higher scales of organisation such as populations are often not fully understood (Kohler and Triebskorn 2013). Toxicant research tends to focus either on the molecular, physiological or cellular levels, or on merely observing population decline, with the causal link between scales (within-host and population) rarely investigated (Kohler and Triebskorn 2013). For example, lethal and sublethal thresholds of toxicants are determined through experiments with individuals, leading to uncertainty as to what consequence this has for the population level (Gergs et al. 2013). Furthermore, interactions between multiple stressors lead to effects which are not predictable from understanding the individual effects of each stressor (Coors et al. 2008). For example, the chemical stressor cadmium, in combination with other abiotic stressors can affect the population growth rate and life-history parameters of *Daphnia magna* (Heugens et al. 2006). Uncertainty in quantifying toxic effects can be explained through their interaction with other stressors at the individual level, which in turn alter the population dynamics (Heugens et al. 2006). In another study with *Daphnia magna*, pesticide exposure has been shown to enhance the virulence of endoparasites (Coors et al. 2008).

Many mathematical models either consider the within-host dynamics independent of the population (Booton et al. 2018), the epidemiological population dynamics independent of the within-host parasite dynamics (Anderson and May 1992, Nowak and May 2000), or model stressors as general population level processes (Bryden et al. 2013, Booton et al. 2017, Henry et al. 2012). Bridging multi-scale biological processes can be achieved using nested (also called embedded) mathematical models (Gilchrist and Sasaki 2002, Mideo et al. 2008). Nested approaches embed models of within-host dynamics into the epidemiological population scale. This allows epidemiological parameters such as the basic reproduction number $R_0$ to be determined by the dynamics of within-host parameters such as parasite load, immune status and cellular health. This approach is particularly useful when the effects of within-host processes on determining population epidemiology are unknown (Mideo et al. 2008), and as such, parameter relationships can be determined from the subsequent analysis of the nested model, providing important biological mechanistic predictions (Gilchrist and Sasaki 2002, Alizon and van Baalen 2005, Gilchrist and Coombs 2006, Feng et al. 2012; 2013; 2015). For example, the model by Bhattacharya and Martcheva (2016) relates the immune response of a species infected by a pathogen to population epidemiological parameters, using a nested within- and between-host approach. This study however focusses on ecological competition between species, rather than additional sources of stressors such as toxicants.

To date, little work addresses the interface between population epidemiology and toxicant stress (Lundin et al. 2015, Bhattacharya and Martcheva 2016). In this study, we examine how toxicants impact the spread of disease within populations, and how the subsequent epidemiology is formed from their respective within- and between-host processes. We introduce and analyse a nested model linking epidemiological between-host processes to those of a previously studied within-host model (Booton et al. 2018). This previous model examined interacting within-host processes: host immunity, host parasite load and host cellular health, and the effects of sublethal and lethal toxicant exposure. This previous study by Booton et al. (2018) showed that within-host parasite density is maximised by intermediate doses of toxicant exposure, but they did not consider the subsequent effects of their results on population level epidemiology. Here, we investigate the change in the basic reproduction number of the epidemic as the toxicant load is increased from zero to extremely high exposure (causing host mortality) and classify the resulting epidemiology into five distinct phases of infection. These phases are determined by the interplay between both within-host and between-host dynamics and processes.

## Methods

Here we consider two scales of biological organisation, both the within-host immuno-infection dynamics and between-host population dynamics. We assume that the within-host dynamics are fast relative to a slower population level timescale, a commonly used method for linking multi-level scales (Gilchrist and Coombs 2006, Mideo et al. 2008, Feng et al. 2013). Therefore, each individual has equal average status of infection at the within-host level, dependent upon the individual's sub-class of infection (susceptible or infected). This significantly reduces the complexity of such nested models, and allows a substitution of within-host steady state values into the between-host system. The separation of time scales through slow-fast dynamics is justified through assuming that each individual belongs to a sub-group of infection, which we characterise below as either susceptible or infected.

### Within-host 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 uninfected within-host cells, parasite density and immune function, respectively. The within-host cells $X$ represent the total number of uninfected cells within the host and $Y$ represents the total number of parasite-infected cells as a measure of parasite density. Here the term uninfected implies that these cells could be potentially infected by a parasite. To simplify the analysis significantly we use a non-dimensionalised version of the original model published in Booton et al. (2018). The full derivation of this model can be found in the electronic supplement, and this model has the same qualitative dynamics, but with fewer parameters.

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

$$\frac{dY}{dt} = Y(\epsilon X - \gamma - \omega Z) \tag{1b}$$

$$\frac{dZ}{dt} = (1 - \xi_2 Q) - Z \tag{1c}$$

Toxicant exposure $Q$ both reduces the functionality of the immune system at rate $\xi_2$ (sublethal) relative to the production of immunity and damages the functionality of the host at rate $\xi_1$ (lethal) relative to the production of new cells. This relationship is the simplest possible assumption regarding the effects of the toxicant on the host, and other such assumptions (such as density-dependence) reproduce qualitatively equivalent results to the model presented here (Booton et al. 2018). Therefore, we assume a constant rate of sublethal and lethal effects on the host, as this the simplest way of reproducing within-host toxicant dynamics. Within the model for any given level of exposure we will consider the simultaneous lethal (i.e. on host function) and sublethal (i.e. on host immunity) effects of the toxicant. The non-dimensionalisation process scaled the remaining parameters relative to the removal of immunity: $\phi$ sets the rate at which healthy cells are removed from the system, $\epsilon$ represents transmission of parasites and production of cells, $\gamma$ sets the death rate of the parasites, and $\omega$ represents the immune suppression and production of immunity (all relative to the removal of immunity). Details on within-host parameter relationships and their substitutions can be found in the electronic supplement.

This model assumes to begin with that $1 - \xi_1 Q > 0$ and $1 - \xi_2 Q > 0$. At the point when $Z = 0$, equation (1c) is removed and the model becomes the system of equations (1a) and (1b) without the term $-\omega YZ$ (as $Z = 0$). In general, throughout this paper we assume $\xi_2 > \xi_1$, which ensures sensible behaviour of the model. If the alternative assumption $\xi_2 < \xi_1$ holds true, the model predicts a healthy immune function even after the parasite and healthy cells are dead (representing host mortality). The effects of this alternative assumption can be found in the electronic supplement. However we focus on the case $\xi_2 > \xi_1$ and argue that this case is biologically valid since the direct lethality of toxicants generally occur at higher doses (Suchail et al. 2001, Pan et al. 2014, Wang et al. 2017), and various types of immunosuppressive damage occur at sublethal or field realistic levels of toxicant (Bols et al. 2001, James and Xu 2012, Brandt et al. 2016). Hence the assumption $\xi_2 > \xi_1$ ensures that the relative effect of sublethal damage is stronger than that of the lethal toxicant damage at lower doses. Similarly, after $Y = 0$, the model becomes equation (1a) but without the term $-XY$. The assumption that $Z = 0$ before $Y = 0$ ensures that we can investigate both the sublethal immunosuppressive effect and direct lethality (reducing host function) of the toxicant before the death of the host at higher levels of $Q$.

We define $X'$ to be the equilibrium state of within-host cells in an uninfected individual in the absence of infection, $X^*$ to be the equilibrium state of within-host cells in an infected individual, and $Y^*$ to be the equilibrium state of parasite density in an infected individual, given by the expressions (derivations of which can be found in the electronic supplement):

$$X' = \begin{cases} \dfrac{1-\xi_1 Q}{\phi} & \text{if } 1-\ \xi_2 Q > 0 \\ 0 & \text{otherwise} \end{cases} \tag{2a}$$

$$X^* = \begin{cases} \dfrac{\gamma\ -\xi_2 Q\omega + \omega}{\epsilon} & \text{if } 1-\ \xi_2 Q > 0 \\ \dfrac{\gamma}{\epsilon} & \text{if } 1-\ \xi_2 Q \le 0\ \&\ Y^* > 0 \\ X' & \text{if } 1-\ \xi_2 Q \le 0\ \&\ Y^* = 0 \end{cases} \tag{2b}$$

$$Y^* = \begin{cases} \dfrac{\epsilon - \xi_1 Q\epsilon}{\gamma - \xi_2 Q\omega + \omega} - \phi & \text{if } 1-\ \xi_2 Q > 0 \\ \dfrac{-\gamma\phi\ -\xi_1\epsilon + \epsilon}{\gamma} & \text{if } 1-\ \xi_2 Q \le 0\ \&\ \dfrac{-\gamma\phi\ -\xi_1\epsilon + \epsilon}{\gamma} > 0 \\ 0 & \text{if } \dfrac{-\gamma\phi\ -\xi_1\epsilon + \epsilon}{\gamma} \le 0 \end{cases} \tag{2c}$$

## Between-host model

The dynamics of an infected population follow those of a simple susceptible - infected (S-I) model framework. Each individual can be classified into either healthy susceptible $S$ or infected $I$ and therefore the total population $N$ is represented by $S + I$. We assume that new individuals enter the population at rate $\Lambda$. Transmission from a healthy susceptible individual to an infected individual occurs at rate $\theta$proportional to the equilibrium status of within-host infection $Y^*$. We assume that the per capita mortality function $u$ is the same for each class with rates $\frac{u}{1+kX'}$ and $\frac{u}{1+kX^*}$ for uninfected and infected individuals respectively, where $k$ sets the strength of the mortality function with respect to the numbers of within-host cells. This ensures that cell depletion at the within-host level causes mortality at the level of the individual hosts, where the mortality function increases as the cell count decreases, up to a maximum value of $u$.

This also ensures that the death rate of an infected individual is inversely proportional to the equilibrium state of the within-host cells under parasitisation.

The coupled within-host and population level model is a two-dimensional system of non-linear ordinary differential equations (ODEs):

$$\frac{dS}{dt} = \Lambda - \theta SIY^* - \frac{u}{1 + kX'}S \qquad (3a)$$

$$\frac{dI}{dt} = \theta SIY^* - \frac{u}{1 + kX^*}I \qquad (3b)$$

The model was analysed using standard methods from dynamical systems theory and were numerically solved with Wolfram Mathematica version number *10.0.2.0*. The algebraic equilibria were found using the Mathematica function *Solve* and the numeric equilibria by *NDSolve*. We ran simulations to determine parameter dependence of the two systems of ODEs (which can be found in the electronic supplement). This analysis shows that the between-host dynamics fall into sub-dynamics of the universal behaviour of the model, regardless of parameter choice. For this reason, we chose a set which highlights the typical qualitative behaviour and we examine how this behaviour is modified by changing parameters around this standard set. The parameter set we chose is one such set which highlights the qualitative behaviour of the model, and which demonstrates the universal biological results obtained from the model.

# Results

## States of the population system, general case

System (3) has two solutions; the endemic equilibria (EE) and the disease free equilibria (DFE).

$$(S^{DFE}, I^{DFE}) = \left(\frac{\Lambda + k\Lambda X'}{u}, 0\right) \qquad (4a)$$

$$(S^{EE}, I^{EE}) = \left(\frac{u}{\theta Y^* + k\theta X^* Y^*}, \qquad \frac{\Lambda + k\Lambda X^*}{u} - \frac{u}{\theta Y^* + k\theta X' Y^*}\right) \qquad (4b)$$

Therefore system (3) either converges to the EE or DFE depending upon the basic reproduction number $R_0$, calculated as

$$R_0 = \frac{\theta \Lambda Y^* (1 + kX')(1 + kX^*)}{u^2} \qquad (5)$$

This tells us the threshold at which infection will spread throughout the population causing an epidemic ($R_0 > 1$). Increasing between-host transmission $\theta$ or population birth rate $\Lambda$ increases the chance of outbreak. Increasing the density dependent mortality $u$ decreases the chance of outbreak. The maximal value of $R_0$ here is maximised when the within-host functions $Y^*$, $X^*$ and $X'$ are maximised with respect to Q through the function $Y^*(1 + kX')(1 + kX^*)$. We predict that infection can spread through a population when the parasite load $Y^*$ exceeds the critical threshold

$$Y^* = \frac{u^2}{\theta \Lambda (1 + kX')(1 + kX^*)} \qquad (6)$$

When the toxicant $Q$ is not present in the system, we expect $R_0 = 1$ when $\phi \geq 0,\ \epsilon \geq 0,\ \gamma > 0,\ \omega \geq 0,\ \Lambda > 0,\ u > 0,\ \theta \geq 0,\ k \geq 0$ and

$$0 < \phi < \frac{\epsilon}{\gamma + \omega} \qquad (7a)$$

$$\theta + \frac{u^2 \epsilon \phi (\gamma + \omega)}{\Lambda (k + \phi)(\phi(\gamma + \omega) - \epsilon)(k(\gamma + \omega) + \epsilon)} = 0 \qquad (7b)$$

When the toxicant is at a critical level where immunity is depleted at $Q = \frac{1}{\xi_2}$, we expect $R_0 = 1$ when $\phi > 0,\ \epsilon > 0,\ \gamma \geq 0,\ \omega \geq 0,\ \Lambda > 0,\ u > 0,\ \theta \geq 0,\ k \geq 0$ and

$$0 < \xi_1 < \xi_2 \tag{8a}$$

$$0 < \gamma < \frac{\epsilon(\xi_2 - \xi_1)}{\xi_2 \phi} \tag{8b}$$

$$\theta + \frac{\gamma \xi_2^2 u^2 \epsilon \phi}{\Lambda(\gamma k + \epsilon)(k(\xi_2 - \xi_1) + \xi_2 \phi)(\gamma \xi_2 \phi + \epsilon(\xi_1 - \xi_2))} = 0 \tag{8c}$$

When these conditions are met, the term $1 - \xi_2 Q$, is equal to 0, which corresponds to the point at which immunity is depleted $Z = 0$.

## Response to toxicant exposure, case of no infection

Figure 2 shows the baseline dynamics of the model under the absence of within-host (and consequently between-host) infection. The lethality (reducing host function) of the toxicant linearly kills off the population of individuals in phase $0$. Even though immune function is reduced, there is no parasite present to exploit and infect the population. After a threshold value all individual hosts are dead, and the population is extinct (phase $V$). This figure represents the baseline dynamics of the model under increasing toxicity and no infection.

## Response to toxicant exposure, case of sub-lethal effect dominating lethal effect

Figure 3 shows the predicted stage of the epidemic under increasing toxicant exposure according to the simulations of the model. In general, there are 5 separate phases present in the model, as defined below (outbreak is denoted by $*$).

**Phase $I$: no population epidemic**

For low exposure to toxicant, the basic reproduction number is low ($R_0 < 1$). This means that epidemics cannot occur at the population level. There is a very small within-host infection burden ($Y^*$) which increases as the toxicant exposure increases. In this phase, the individual parasite burden is not large enough to cause between-host transmission and thus the population only declines a relatively small amount from the direct exposure to the toxicant.

**Phase $II^*$: outbreak**

Here, the toxicant level is increased beyond a critical threshold causing $R_0 > 1$ and outbreak at the population level. This threshold is determined by the relationship between the within-host immunity, parasite burden and healthy cell status, and the population rate of transmission (Eq. 5). This phase is characterised by a functioning but declining immune status, caused by the increasing toxicant exposure. Combined with a within-host parasite density reaching a peak at the end of phase $II^*$, we see an outbreak of population level infection, and healthy susceptibles reaching a minimum, while the total population decreases rapidly.

**Phase $III^*$: disease reduced**

Increasing the toxicant exposure further results in a complete depletion of the within-host immune status. The basic reproduction number of the infection begins to drop resulting in fewer infected cases and therefore an increase in healthy individuals. Infected individuals are killed off by the mortality induced by the epidemic. This higher level of toxicant exposure causes the parasite density to drop below the minimum required for an infection to spread at the population level (determined by Eq. 6). This means that the total population is able to recover marginally due to the infection being removed.

### Phase $IV$: disease controlled

At the start of phase $IV$, the population epidemic is over ($R_0 < 1$). As the toxicant exposure is increased again, the within-host parasite density decreases to 0. At these very high levels of exposure, the individuals are killed by the direct mortality inducing toxicant causing the population to decline once again.

### Phase $V$: host dead

At extremely high levels of exposure the host is killed due to the lethality of the toxicant. All within-host functions are depleted. This results in the population reaching extinction.

## Response to toxicant exposure, case of lethal effect dominating sub-lethal effect and case of no lethal effect

We explore the case of the absence of toxicant exposure ($\xi_1 = 0$) in Fig. ES1, and also the case of aggressive toxicant exposure ($\xi_1$ larger than $\xi_2$) in Fig. ES2. Both of these figures can be found in the electronic supplementary information.

Setting the lethal toxicant exposure $\xi_1 = 0$ (Fig. ES1) results in similar phase based dynamics observed in Fig. 3. Under this condition, the first stages of the epidemic can be divided into phases $I$ and $II^*$, qualitatively identical to those found in Fig. 3. However, after the host immune function is destroyed, a new phase $III^*b$ occurs for any increasing value of toxicant. This results in a persistent epidemic caused by the lack of any lethal effects of the toxicant. In this case, the basic reproduction number remains constant for all further toxicant exposure. Therefore, the low toxicant behaviour of the model is similar to the original, even after removing this lethal toxicant effect $\xi_1 = 0$.

We set the lethal toxicant effect higher than the sublethal effect in Fig. ES2. This is in order to examine the effect of reversing the assumption used throughout this paper ($\xi_2 < \xi_1$). We see that this alternative assumption predicts three phases of the epidemic which are broadly similar to those found in Fig. 3. The individual is highly infective to begin with and then the lethal toxicant effect begins to remove the within-host parasite density. After this, the population level infection is removed from the system, and the model returns back to phases $IV$ and $V$ seen in the original dynamical behaviour of the model.

Both of these figures highlight similar epidemiological phases of the model under different assumptions and are sub-dynamics of the original dynamics found in Fig. 3.

## Within-host parameter phase dependence

Here, we outline the behaviour of the model for a wider range of pairwise parameters. We do this in order to investigate the effects of slight changes to our original parameter set, and to see how the trade-offs between important within- and between-host functions determine the subsequent population epidemic. We define the phases as above, with phase $0$ representing the region where there is no feasible within-host or between-host disease.

**Direct lethal effect $\xi_1$ and sublethal $\xi_2$ toxicant effect**

Figure 4 shows the predicted phase of the population epidemic for 3 different levels of toxicant exposure, and for a range of lethal toxicant effect (relative to the production of new within-host cells) and sublethal toxicant effect (relative to the production of immunity). The white regions in Fig. 4 show the space in which the assumption ($\xi_2 < \xi_1$) is broken. First, the absence of toxicant exposure ($Q = 0$) results in no such epidemic for any value of lethal and sublethal toxicant effect. Second, as the toxicant exposure is increased to an intermediate value ($Q = 0.50$), outbreak (phase $II^*$) occurs when the toxicant has both sufficiently high lethal and high sublethal effect. Third, as the toxicant reaches high levels ($Q = 1.50$), the outcome of the outbreak can fall into any of the phases of epidemiology ($0 - V$), dependent upon the respective lethal and sublethal properties of the toxicant. Higher lethal and sublethal toxicant stress can result in the extinction of the population, whereas lower lethality and higher sublethal effects are required for outbreak (phases $II^*$ and $III^*$).

**Within-host transmission and production of cells (relative to removal of immunity) $\boldsymbol{\epsilon}$ and between-host transmission $\boldsymbol{\theta}$.**

Figure 5 likewise shows the predicted phase for a range of different levels of $\epsilon$ and $\theta$. In the absence of toxicant ($Q = 0$), outbreak can only occur ($II^*$) if the within-host transmission and production of cells $\epsilon$ is sufficiently high. Otherwise, no epidemic can occur for any value of between-host transmission. Secondly as the toxicant is increased to an intermediate value ($Q = 1.00$), the epidemic occurs ($III^*$) if both parameters are sufficiently large. Third, at extremely high levels of exposure ($Q = 2.00$), the population becomes extinct.

**Birth rate $\Lambda$ and mortality rate $u$**

Figure 6 shows the relationship between the between-host birth and death rates and the predicted stage of the epidemic. In the absence of toxicant exposure ($Q = 0$), there are 2 possible outcomes. A low death rate is required to see the outbreak of the disease. Otherwise between-host disease is not possible for any choice of $\Lambda$ and $u$. Increasing the toxicant exposure to higher levels ($Q = 1.00$) results in a complete switch to either the reduction or control of the disease. Finally, increasing the exposure to an extremely high level ($Q = 2.00$) results in host death and the extinction of the population.

# Discussion

We have studied and analysed a nested multi-level model of within and between-host processes to understand how toxicants impact epidemiological dynamics. A key finding is that population epidemics are dependent upon the level of toxicant exposure. In general, infection prevalence is maximised by intermediate levels of toxicant. We classify this population epidemic into 5 phases showing that any outbreak is dependent on the toxicant's sublethal and lethal properties. Higher toxicant exposure results in either outbreak of infection or death of the population. In particular, the stress-mediated within-host statuses of immune function and parasite load also determine the outcome of the epidemic at the population level.

Importantly our model predicts that epidemics may not occur until reaching an intermediate threshold exposure of toxicant. At low levels of exposure, the parasite density is able to increase but between-host infection is equal to zero within the population until reaching a critical threshold (at the start of phase $II^*$). Sub-lethal toxicant exposure can have dramatic consequences for population epidemiology, causing widespread outbreak. These results support the body of work on synergistic interactions between environmental chemicals and natural stressors (Holmstrup et al. 2010), and highlight the effects of toxicants on higher scales of organisation such as population dynamics, which are often not understood (Kohler and Triebskorn 2013) or difficult to experimentally test (Gergs et al. 2013).

Our model also predicts that population epidemics follow phase-based transitions dependent on the level of toxicant exposure. Within our model, 5 such phases are present. First, the parasite burden is too small within individuals to have any impact on the population level. Only when the parasite density crosses a minimum threshold (Eq. 6) do we see any population level impact. The immunosuppressive toxicant effect causes the parasite density to rapidly multiply and spread between individuals. Under increasing exposure, prevalence only subsides when the parasite is reduced by the lethal toxicant effect. The sublethal immunosuppressive effect of the toxicant only impacts the population if the toxicant exposure is low. Otherwise the lethality of the toxicant takes over and kills the host, causing extinction of the population. These complicated phase-based epidemics show that the effect of toxicant exposure upon population disease outbreak is non-linear. Interestingly, when considering the population density under increasing toxicant exposure we see a rapid decrease in the population in the early and late stages of this exposure. However, in phase $III^*$, we see a marginal increase in the density which represents population recovery. This is caused by a significant reduction in the epidemiological dynamics and means that the healthy population is able to recover. This has implications for environmental assessors, where often the indicator of an ecosystem's healthy state is population density, rather than the individual clinical states of a system. Our results suggest that by only monitoring population density the underlying dynamics may go unnoticed, especially in the predicted mid-range toxicant phase $III^*$.

A further prediction the model makes is that trade-offs between within- and between-host functions determine the subsequent population epidemiology (Fig. 4, Fig. 5 and Fig. 6). We show that outbreak will occur when the individual sublethal toxicant effect is relatively higher than that of the lethal effect. Although we also predict that higher exposure to toxicants can result in any of the defined epidemiological phases. This suggests that population epidemiology can be completely determined by the relative sublethal and lethal properties of the toxicant. In addition, we also show that the sublethal toxicant effect determines whether the population will become extinct at high toxicant exposure. This further suggests that the individual properties of toxicants are important in determining outbreak. The trade-off between different scales of transmission also determine these phase-based epidemics. In general, higher levels of both within- and between-host transmission result in outbreak. Another implication of these phase-based plots are that slight increases in parameters can result in sudden epidemiological switches. For example, the third panel in Fig. 4 shows all of the phases in our system. A slight increase in the sublethal effect $\xi_2$ at this high toxicant exposure $Q = 1.50$ can result in abrupt transitions between phase $0$ or $I$ to phase $IV$. These kind of transitions show that these phases of epidemiology are sensitive to slight perturbations in the effects of sublethal and lethal toxicant exposure. Introducing a new toxicant into a healthy population with only a slightly stronger sublethal effect on the host could cause a dramatic regime shift and ultimately high mortality rates (shift from phase $I$ to phase $IV$).

The results in the main text of this paper depend entirely upon the relative sublethal and lethal effects of the toxicant, particularly on the assumption that $\xi_2 > \xi_1$. We focussed on this assumption for multiple reasons. If this assumption were reversed, the within-host model predicts unrealistically that the immune function will be present even after the host is dead. In Fig. ES2 we show that under this reverse assumption, the results still fall into the phase-based transitions seen under the normal assumption and are sub-dynamics of the original phases shown in Fig 3. Another reason we focus on the case of $\xi_2 > \xi_1$ is because direct chronic lethality often occurs at higher doses of toxicant (Suchail et al. 2001, Pan et al. 2014, Wang et al. 2017) and immunosuppressive damage occurs at various levels of lower dose toxicant exposure (Bols et al. 2001, James and Xu 2012, Brandt et al. 2016). Therefore, we argue that focussing on the case in which host mortality occurs at higher toxicant exposure and immunosuppressive damage occurs at lower, sublethal levels is biologically realistic.

A previous study, Booton et al. (2018) used a simple modelling framework to describe the within-host infection dynamics under toxicant exposure in an individual. This work demonstrated that an intermediate exposure of toxicant maximised within-host parasite density. In this paper, we introduced a nested modelling framework based on the within-host model used in Booton et al. (2018), which extends the previous model to the epidemiological between-host population level. We did this in order to examine how epidemiological parameters interact with within-host processes, showing that population epidemics are determined by the level of toxicant exposure, which can be divided into 5 such phases. Few studies examine the interaction between toxicant stress and within-host processes, and even fewer then relate this to the population scale (Lundin et al. 2015, Bhattacharya and Martcheva 2016). The novelty therefore in this paper is the consideration of both within- and between-host scales, as opposed to the singular scale examined in Booton et al. (2018). By relating these scales with toxicant exposure, we were able to classify the complicated relationship between increasing toxicant exposure and the spread of disease at the population level. We show how $R_0$ changes with respect to between-host parameters, showing that an increase in between-host transmission or birth rate, a decrease in mortality, or an increase in the relative effect of host mortality (Fig. ES3) increases the chance of outbreak. In addition, the maximal value of $R_0$ is determined by the trade-off between the within-host functions, as shown in Eq. (5). This maximal value is equivalent to the point at which the within-host cells in infected individuals level out and where the within-host parasite density is maximised, for all parameters. Therefore, the value of Q which maximises the within-host parasite density is equal to the value which maximises the spread of infection at the population level. This is an interesting result, and can be explained through the identical 'turning point' found for all within-host processes (as demonstrated for example in Fig. 3, at $Q = 0.5$). This results from the depletion of the immune system, whereby the total population level risk of infection is maximised when those individuals within the population have weakened immune responses as a result of sublethal toxicant exposure.

These results have a number of applications, one such application being motivated by the impacts that toxicants have on a wide range non-target species (Phipps and Holcombe 1985, Snell and Janssen 1995, Van Den Berg et al. 1998, Eason et al. 2002, Buratini et al. 2004, Relyea and Hoverman 2006, Goulson et al. 2015, Pisa et al. 2015). For example, the recent and widespread losses in worldwide bee populations (Goulson et al. 2015) are thought to be caused by multifactorial synergistic stressors (Alaux et al. 2010, Neumann and Carreck 2010, Potts et al. 2010, Ratnieks and Carreck 2010, Vanbergen 2013). Within this setting, this work fills a previously identified research gap (Lundin et al. 2015) by outlining the complicated relationship between toxicant stress and population epidemics. In general, increased exposure to toxicants should result in more colony epidemics and therefore greater population losses. Intermediate exposure to toxicants could result in dramatic decreases in overall colony health. Reducing the sublethal toxicant exposure below the predicted safe phase $I$ threshold (to ensure $R_0 < 1$ in Eq. 5) ensures that no colony epidemic can occur. These results highlight the nonlinear relationship between pesticide exposure and population epidemiology. Indeed, the very general nature of this model means that these results may be applied to any enviro-epidemiological system exposed to disease.

The framework presented in this study focusses on linking two scales of biological organisation under toxicant stress. This toxicant stress affects the within-host dynamics in two ways, acting as an indirect immunosuppressant and directly impacting the vital functionality of individual health. A further improvement to the model could investigate the role of social immunity, a process by which populations prevent infection from spreading. Social insects are known to perform behavioural traits such as removing diseased or dead individuals (Spivak and Gilliam 1998), preventing others from interacting with infected individuals (Waddington and Rothenbuhler 1976), and collectively raising the temperature of the surrounding environment through a process known as social fever (Starks et al. 2000), all in order to prevent further infection. Incorporating these social mechanisms into our nested multilevel modelling framework could shed new light on the way that populations use innate and social immunity to combat disease.

In summary, this work takes a multifactorial approach to model infection at the population level which can be divided into 5 phases dependent upon the level of toxicant stress. We predict that infection within populations is maximised by intermediate toxicant exposure, and that there exists a toxicant threshold below which individual parasite density is controlled and outbreak does not occur. The modelling framework used here presents a starting position to think about how within-host functions such as immunity and parasite density determine population level effects. This work highlights the need for experimental studies which focus on measuring epidemiological traits of populations under increasing toxicant exposure.

# Declarations

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We declare we have no competing interests.

# Figures and tables

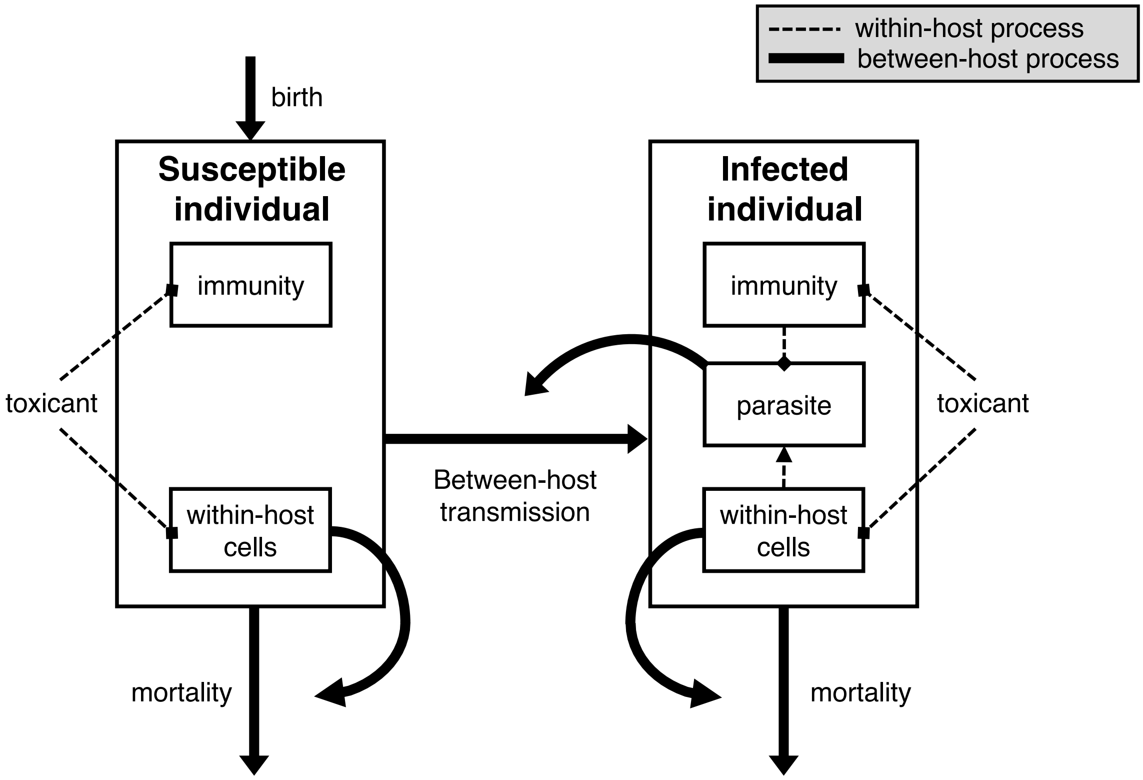



*Figure 1: The outline of the multilevel model. Bold lines show the between-host processes and dashed show the within-host processes. Individuals can either be classified as susceptible or infected. Infection spreads between hosts dependent upon the within-host parasite density. The toxicant impacts immune function and the general functionality of the host. New individuals enter the system via birth and leave via death which is dependent upon the individual within-host cellular health status.*

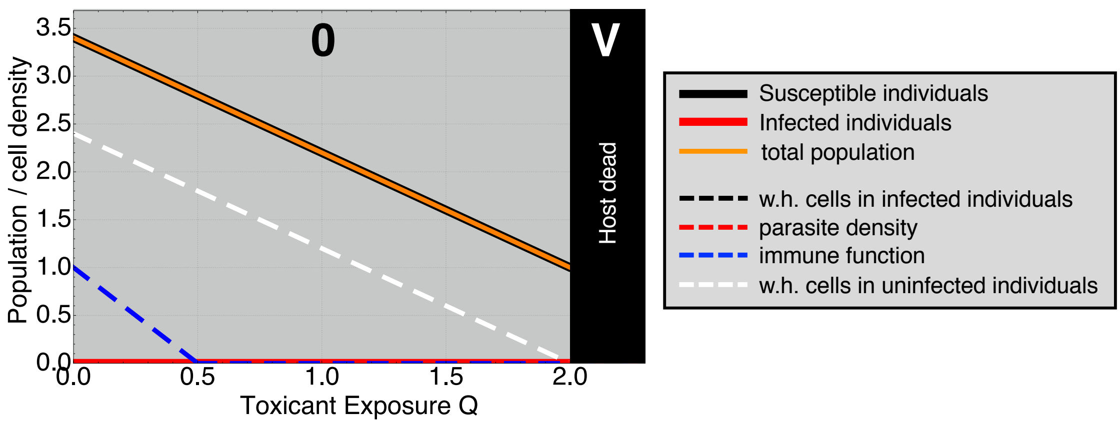
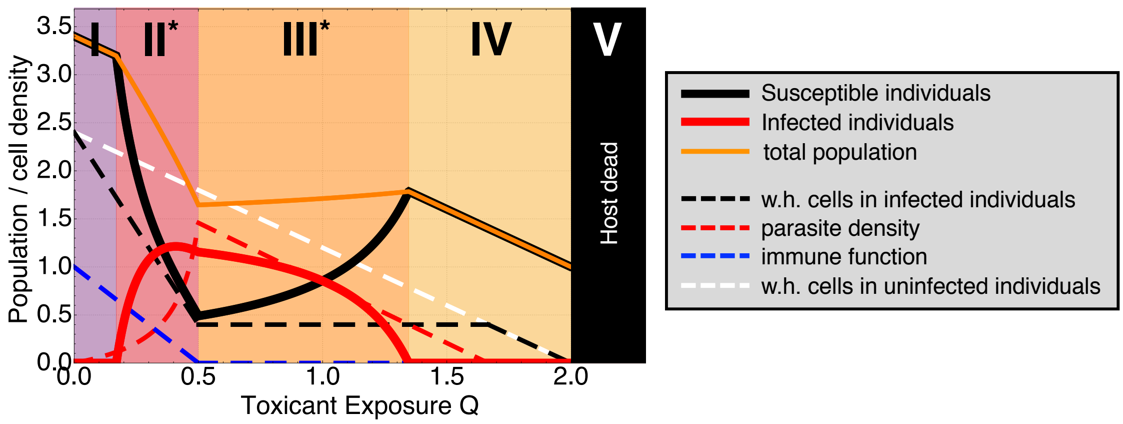
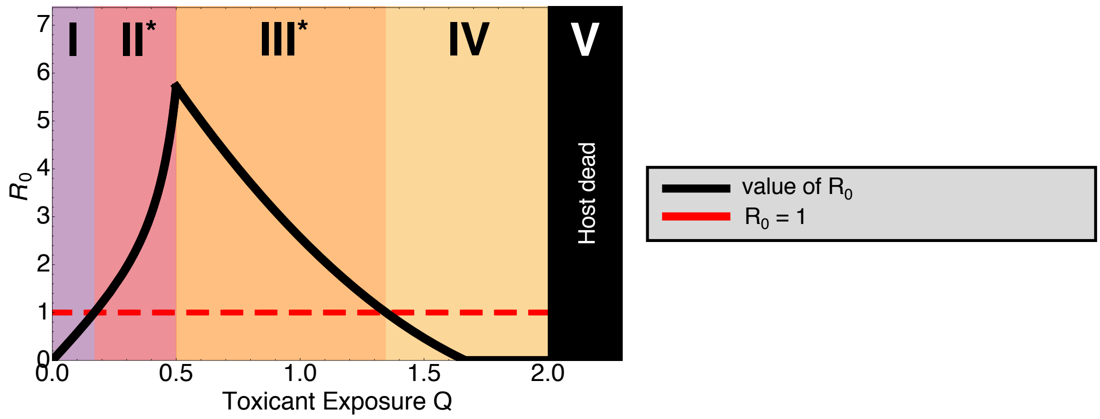



*Figure 2: The baseline dynamics of the model without initial within-host infection. The absence of the within-host infection means that the infection cannot spread to the population level. Phase* $0$ *corresponds to the region of no feasible infection and phase* $V$ *corresponds to the death of all individuals within the population. Parameters as in Table 1, but with the initial parasite density* $Y^* = 0$.




*(a)*




*(b)*

*Figure 3: The predicted five phases of an infected population under increasing toxicant stress $Q$. Starred phases ($II^*$ and $III^*$) represent the outbreak of infection where $R_0 > 1$. In (a) solid lines represent the population dynamics and dashed lines the within-host dynamics. In (b) the black line shows the value of $R_0$ and the dashed red line shows the threshold at which $R_0 = 1$ and above which outbreak will occur within the population. Parameters taken from Table 1.*

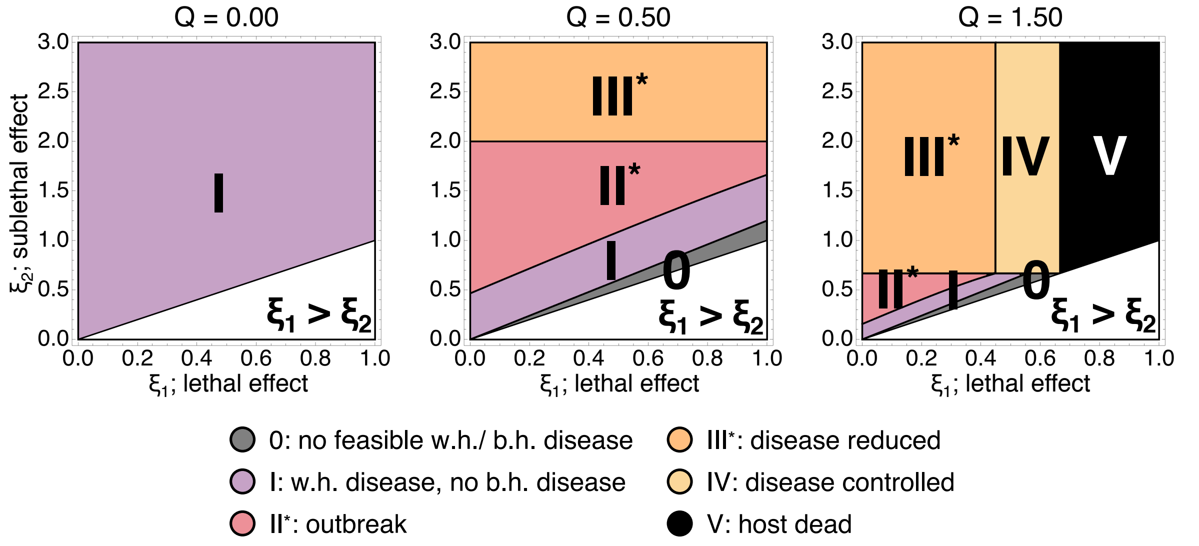



*Figure 4: The predicted phase $(0 - V)$ epidemiological outcome of the population level dynamics for 3 levels of toxicant exposure and varying direct lethal toxicant effect (relative to the production of new within-host cells) $\xi_1$ and sublethal effect (relative to the production of immunity) $\xi_2$. Note that the white region represents the phase space under which the assumption $\xi_2 > \xi_1$ is no longer valid. Starred phases ($II^*$ and $III^*$) represent the outbreak of infection within the population. For the absence of toxicant exposure $Q = 0$, outbreak cannot occur for any value of $\xi_1$ and $\xi_2$. For intermediate $Q = 0.50$, outbreak occurs if the values of $\xi_1$ and $\xi_2$ are sufficiently large. For lethal $Q = 1.50$, any of the phases can occur dependent upon the choice of $\xi_1$ and $\xi_2$. High values of $\xi_1$ and $\xi_2$ result in extinction of the population. Parameters as in Table 1, but for varying $\xi_1$ and $\xi_2$ as above.*

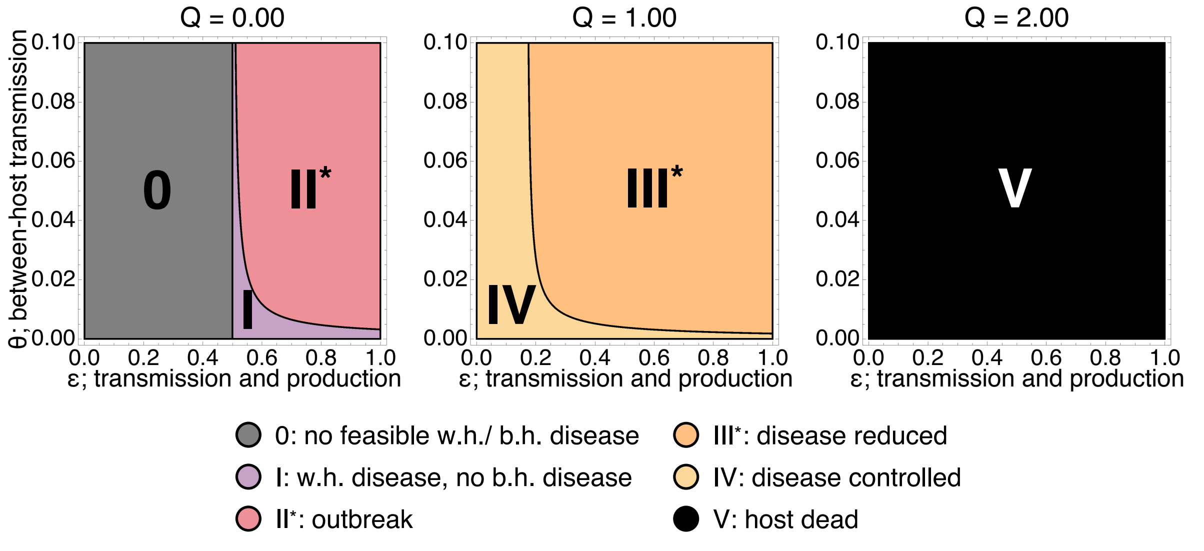



*Figure 5: The dynamical phase $(0 - V)$ for a range of within-host transmission and production of cells (relative to the removal of immunity) $\epsilon$ and between-host transmission $\theta$. Starred phases ($II^*$ and $III^*$) represent the outbreak of infection within the population. For $Q = 0$, outbreak will occur ($II^*$) if $\epsilon$ is sufficiently large, otherwise phase $0$ will occur for any value of $\theta$. For $Q = 1.00$, phase $III^*$ occurs only if both $\epsilon$ and $\theta$ are large enough. For high $Q = 2.00$, population extinction occurs for any chosen values of $\epsilon$ and $\theta$. Parameters as in Table 1, but for varying $\epsilon$ and $\theta$.*

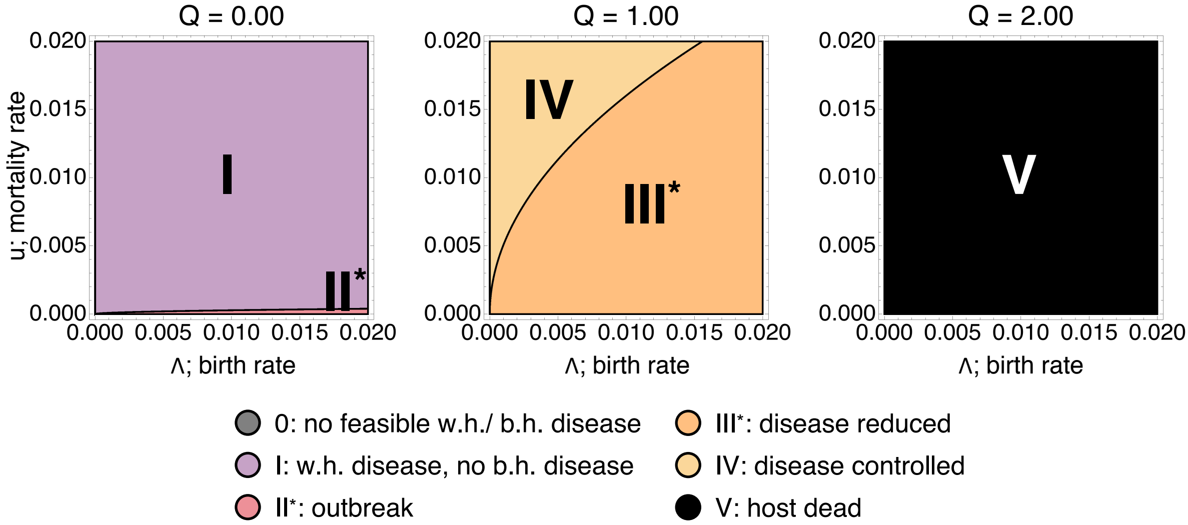



*Figure 6: The predicted phase $(0-V)$ for a range of between-host birth rate $\Lambda$ and between-host mortality $u$. Starred phases ($II^*$ and $III^*$) represent the outbreak of infection within the population. For $Q=0$, outbreak will occur ($II^*$) if $u$ is sufficiently low. For $Q=1.00$, either outbreak $III^*$ occurs or phase $IV$ occurs depending on the choice of $\Lambda$ and $u$. For $Q=2.00$, all hosts are dead and extinction of the population occurs. Parameters as in Table 1, but for varying transmission parameters $\Lambda$ and $u$.*

| *Parameter/ variable description* | *Symbol* | *Value* | *Units* |
|---|---|---|---|
| **Within-host** | | | |
| Within-host uninfected cells | $X$ | | No dimension |
| Parasite density | $Y$ | | No dimension |
| Immune function | $Z$ | | No dimension |
| Lethal toxicant effect relative to production of new cells | $\xi_1$ | 0.5 | No dimension |
| Sublethal toxicant effect relative to production of immunity | $\xi_2$ | 2 | No dimension |
| Mortality of cells relative to removal of immunity | $\phi$ | 0.4166 | No dimension |
| Mortality of parasite relative to removal of immunity | $\gamma$ | 0.2 | No dimension |
| Within-host transmission and production of cells relative to removal of immunity | $\epsilon$ | 0.5 | No dimension |
| Suppression and production of immunity relative to removal of immunity | $\omega$ | 1 | No dimension |
| **Between-host** | | | |
| Susceptible individuals | $S$ | | Individuals |
| Infected individuals | $I$ | | Individuals |
| Birth rate | $\Lambda$ | 0.01 | Individuals time$^{-1}$ |
| Between-host transmission rate | $\theta$ | 0.01 | Individuals$^{-1}$ time$^{-1}$ |
| Mortality rate | $u$ | 0.01 | Time$^{-1}$ |
| Relative effect of host mortality | $k$ | 1 | No dimension |

*Table 1: The between and within-host parameters used in the analysis and simulations of the model, and their respective units. For the within-host parameters and their units used in Booton et al. 2018, please see the electronic supplementary information.*

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