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**Author for correspondence:**

Chadi M. Saad-Roy

e-mail: [csaadroy@berkeley.edu](mailto:csaadroy@berkeley.edu)

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# Epidemiological impacts of post-infection mortality

Chadi M. Saad-Roy<sup>1,2</sup>, Simon A. Levin<sup>3</sup>, Bryan T. Grenfell<sup>3,4</sup> and Mike Boots<sup>2,5</sup>

<sup>1</sup>Miller Institute for Basic Research in Science, and <sup>2</sup>Department of Integrative Biology, University of California, Berkeley, CA, USA

<sup>3</sup>Department of Ecology and Evolutionary Biology, and <sup>4</sup>School of Public and International Affairs, Princeton University, Princeton, NJ, USA

<sup>5</sup>Department of Biosciences, University of Exeter, Penryn, UK

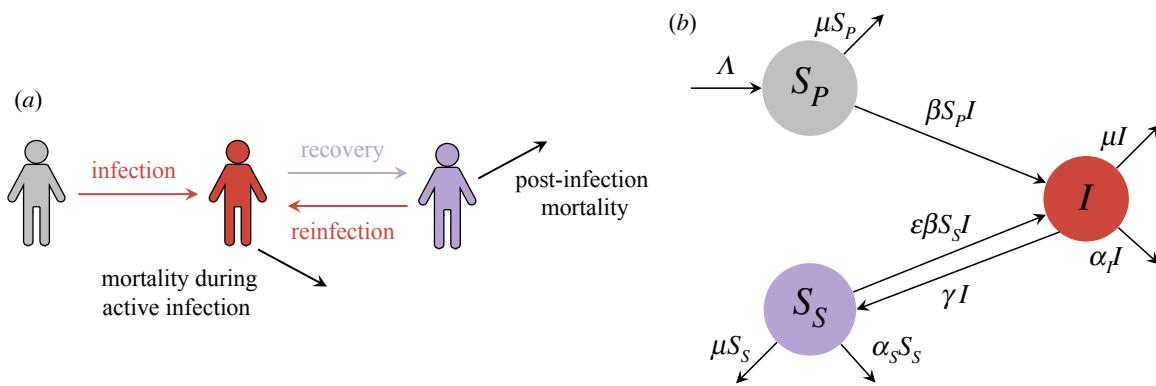
CMS-R, 0000-0002-2217-3071; SAL, 0000-0002-8216-5639; MB, 0000-0003-3763-6136

Infectious diseases may cause some long-term damage to their host, leading to elevated mortality even after recovery. Mortality due to complications from so-called 'long COVID' is a stark illustration of this potential, but the impacts of such post-infection mortality (PIM) on epidemic dynamics are not known. Using an epidemiological model that incorporates PIM, we examine the importance of this effect. We find that in contrast to mortality during infection, PIM can induce epidemic cycling. The effect is due to interference between elevated mortality and reinfection through the previously infected susceptible pool. In particular, robust immunity (via decreased susceptibility to reinfection) reduces the likelihood of cycling; on the other hand, disease-induced mortality can interact with weak PIM to generate periodicity. In the absence of PIM, we prove that the unique endemic equilibrium is stable and therefore our key result is that PIM is an overlooked phenomenon that is likely to be destabilizing. Overall, given potentially widespread effects, our findings highlight the importance of characterizing heterogeneity in susceptibility (via both PIM and robustness of host immunity) for accurate epidemiological predictions. In particular, for diseases without robust immunity, such as SARS-CoV-2, PIM may underlie complex epidemiological dynamics especially in the context of seasonal forcing.

## 1. Introduction

The ongoing SARS-CoV-2 pandemic starkly illustrates the potential of infectious diseases to continue to cause significant infections and mortality across the world. It has also focused attention on the importance of pathogen-induced mortality after active infection (e.g. [1–5]), i.e. post-infection mortality (hereafter referred to as 'PIM'). Thus, to understand the potential future dynamics of SARS-CoV-2, it is important to characterize the effects of PIM on epidemic dynamics. In a broader context, this current observation of PIM for SARS-CoV-2 is part of a wider body of work that examines the long-term impact of infections on hosts. For example, historical findings suggest elevated later-life mortality due to airborne pathogens encountered early in life [6]. Additionally, studies link inflammation due to infectious diseases (early in life) with an increase in later-life mortality [7,8]. Despite these effects being widespread, epidemiological models typically only include virulence during the infectious stage and ignore PIM.

In general, PIM can emerge via (at least) two biological mechanisms. First, pathogens may cause damage that does not lead to host death during active infection, but that eventually results in other impacts that shorten host lifespan (compared to never-infected susceptible individuals). For instance, a number of other long-term complications from SARS-CoV-2 infections, such as cardiovascular issues [9], indicate potential mechanisms for increased mortality following recovery. Other examples of pathogens that result in long-term effects following recovery from infection range from human papilloma virus (HPV) causing



**Figure 1.** Formulation of epidemiological model with PIM. (a) Schematic illustration of epidemiological processes that are encompassed in the model framework. (b) Model flow diagram with rates into/out of each compartment.

cancer [10], to Epstein–Barr virus potentially causing multiple sclerosis [11]. Additionally, recent work has shown that immunomodulation due to measles infection increases subsequent susceptibility to other diseases [12,13]. In very recent work, Levine *et al.* [14] examined the impact of multiple viruses on neurodegeneration and found multiple positive associations. In turn, these consequences increase the likelihood of PIM.

Second, to successfully clear an infecting pathogen, hosts may disproportionately allocate resources to mount a robust immune response. This could then lead to other consequences that increase mortality after infection, in contrast to those susceptible individuals that have never been infected. For example, a parasitic nematode infection can trigger the release of interleukin 33 (IL-33) as a defence mechanism [15]; in turn, IL-33 might contribute to inflammatory bowel disease [16], which might lead to a decreased lifespan [17]. Related trade-offs have also been invoked to understand the evolutionary emergence of immune systems (e.g. [18]). Both of these mechanisms are very general and there is therefore considerable potential for PIM to be the common outcome of infection.

While there exists a significant body of epidemiological modelling literature that includes host mortality during active infection (often referred to as ‘virulence’) (see, e.g. [19–22]) dynamic impacts of PIM has generally been overlooked. Busenberg & van den Driessche [23] formulated and analysed a model with additional mortality in the infectious and recovered (fully immune) states, where individuals return to complete susceptibility with no additional mortality once host immunity has waned. However, the epidemiological dynamics that result from PIM coupled with a return to (potentially partial) susceptibility is unknown. Recent models that include buffered susceptibility have shown that the strength of immunity can crucially shape epidemic dynamics [24–27]. In particular, simple epidemiological models have revealed that the relative susceptibility to subsequent infection (once a period of complete natural or vaccinal immunity has waned) can govern medium-term epidemic trajectories [25]. Therefore, a key question is to determine the epidemiological impacts of potential interactions between PIM and host immunity via a reduced susceptibility to reinfection.

Here, we study the impact of PIM on epidemic dynamics. We also examine the interplay that emerges if either host immune responses (that reduce the likelihood of reinfection upon recovery) are present or if there is disease-induced mortality during active infection. To accomplish this, we leverage a simple model embedded with PIM, buffered susceptibility and disease-induced mortality during active infection. We

show that PIM has strong destabilizing effects both on its own and in combination with virulence during infection unless acquired immunity is very robust.

## 2. Model framework

To distill the effect of PIM on epidemiological dynamics, we use a mathematical model that distinguishes between never-infected susceptibles and those susceptible individuals that were previously infected (figure 1a).

In our model, recruited individuals (via birth and immigration, at constant rate  $\Lambda$ ) are first never-infected (and fully) susceptible ( $S_P$ ). By successful infection, they become infectious ( $I$ ), and recover to the ‘secondary’ susceptible class ( $S_S$ ) at rate  $\gamma$ . In this stage, PIM occurs at rate  $\alpha_S$ . After recovery, individuals’ relative susceptibility to (re)infection is  $\varepsilon$ , where  $0 \leq \varepsilon \leq 1$ . Thus, if infection confers some immunity against reinfection, then  $\varepsilon < 1$ . On the other hand, if immune responses are absent after recovery, then  $\varepsilon = 1$ . Furthermore,  $\alpha_I$  denotes the rate of infection-induced mortality during active infection. Finally,  $\mu$  denotes the rate of demographic death. Our model is depicted in figure 1b and formulated as follows:

$$\frac{dS_P}{dt} = \Lambda - \beta S_P I - \mu S_P \quad (2.1a)$$

$$\frac{dI}{dt} = \beta I (S_P + \varepsilon S_S) - (\gamma + \mu + \alpha_I) I \quad (2.1b)$$

$$\text{and } \frac{dS_S}{dt} = \gamma I - \varepsilon \beta S_S I - \mu S_S - \alpha_S S_S. \quad (2.1c)$$

Since the total population  $N = S_P + I + S_S$ , it follows that

$$\frac{dN}{dt} = \Lambda - \mu N - \alpha_I I - \alpha_S S_S, \quad (2.2)$$

and any three of the  $S_P$ ,  $I$ ,  $S_S$  and  $N$  equations determine the dynamics in this system.

## 3. Epidemiological dynamics

In Model (2.1), it is clear that there is a disease-free equilibrium  $P_0$  with  $S_{P,0} = \Lambda/\mu$  and  $I_0 = S_{S,0} = 0$ . Since there is only one infected compartment, rearranging  $(\partial/\partial I)(dI/dt)|_{P_0} > 0$  gives that the basic reproduction number  $\mathcal{R}_0$  is

$$\mathcal{R}_0 = \frac{\beta(\Lambda/\mu)}{\gamma + \mu + \alpha_I}. \quad (3.1)$$

Biologically, since  $\Lambda/\mu$  is the size of the population when there is no disease,  $\beta(\Lambda/\mu)$  represents the number of new infections per time in a fully susceptible population. Furthermore,  $1/(\gamma + \alpha_l + \mu)$  is the average time an infectious individual spends in the  $I$  class. Thus,  $\beta(\Lambda/\mu)/(\gamma + \mu + \alpha_l)$  is the average number of new infections in a fully susceptible population. Note that  $\mathcal{R}_0$  in this model does not depend on PIM ( $\alpha_S$ ).

Intuitively, and as generally with compartmental models in epidemiology (see [28,29]),  $\mathcal{R}_0 = 1$  is a key epidemiological threshold. If  $\mathcal{R}_0 < 1$ , it follows that  $P_0$  is locally asymptotically stable [29]. On the other hand, if  $\mathcal{R}_0 > 1$ ,  $P_0$  is unstable and there is a unique endemic equilibrium  $\hat{P} = (\hat{S}_P, \hat{I}, \hat{S}_S)$  (theorem 1; electronic supplementary material).

### (a) Endemic equilibrium characteristics

Explicit formulas for the endemic values of  $\hat{S}_P$ ,  $\hat{I}$  and  $\hat{S}_S$  are given in the electronic supplementary material (see proof of theorem 1; electronic supplementary material). To guide our understanding of how PIM affects epidemic dynamics, we examine how the endemic states in our model vary with PIM. We find that the equilibrium value of never-infected susceptibles,  $\hat{S}_P$ , is an increasing function of PIM (theorem 2; electronic supplementary material). By contrast, the equilibrium values of infectious and previously infected susceptible individuals,  $\hat{I}$  and  $\hat{S}_S$ , decrease as PIM increases (theorem 2; electronic supplementary material).

In electronic supplementary material, figure S1, we illustrate how  $\hat{S}_P$ ,  $\hat{I}$  and  $\hat{S}_S$  change as  $\alpha_S$  increases, for different robustness of immunity  $\epsilon$  (electronic supplementary material, figure S1A–S1C), transmission rate (electronic supplementary material, figure S1D–S1F) and disease-induced mortality during active infection (electronic supplementary material, figure S1G–S1I). Across scenarios,  $\hat{S}_P$  increases and eventually decelerates as PIM increases (electronic supplementary material, figure S1A, S1D and S1G). In tandem, while  $\hat{I}$  decreases when PIM increases, it seems to eventually also decelerate (electronic supplementary material, figure S1B, S1E and S1H).

The impact of other host and pathogen characteristics on the dependence of  $\hat{S}_S$  on PIM is less clear, as illustrated by comparisons within and across additional disease parameters (electronic supplementary material, figure S1C, S1F and S1I). Thus, the landscape of susceptibility at the population level crucially depends on the degree of PIM. Additionally, how this susceptibility landscape changes as PIM increases is determined by the robustness of immunity, the level of pathogen transmission and the degree of disease-induced mortality during active infection.

In the absence of PIM, i.e.  $\alpha_S = 0$ , the endemic equilibrium in Model (2.1) is always locally asymptotically stable whenever it exists (theorem 3; electronic supplementary material). Therefore, in the long term, epidemiological trajectories attain this value.

### (b) Post-infection mortality can induce epidemic cycles

If PIM occurs, i.e.  $\alpha_S > 0$ , determining the stability of the endemic equilibrium is more complicated, and the eigenvalues of the Jacobian matrix for the  $S_S$ ,  $I$  and  $N$  equations at the endemic equilibrium can be numerically computed (see remark 1; electronic supplementary material for the Jacobian matrix). To titrate the effect of PIM on epidemic dynamics, we begin our analyses by examining the limiting case with no

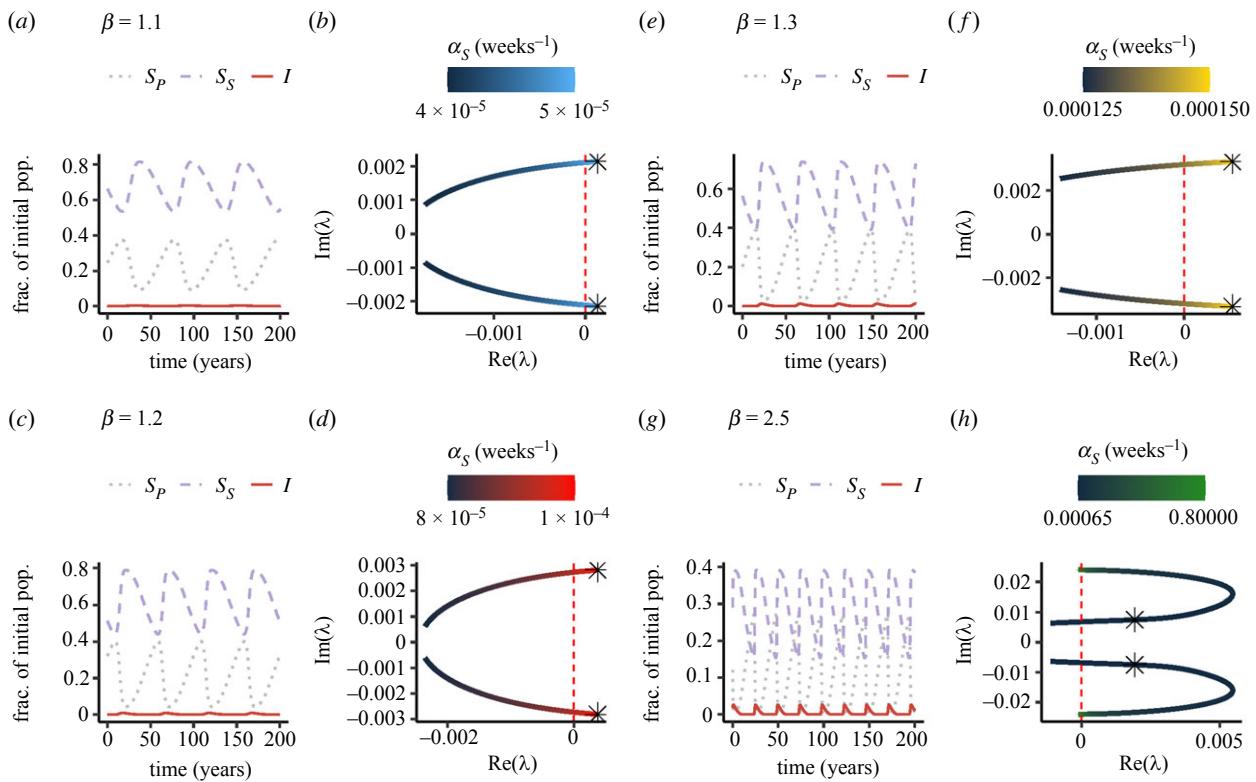
immunity following recovery, i.e.  $\epsilon = 1$ , akin to an SIS model. (In particular, if there is no PIM [i.e.  $\alpha_S = 0$ ], our model reduces to an SIS model [by setting  $S = S_P + S_S$ ].) We also first assume that there is no mortality during active infection ( $\alpha_l = 0$ ). For other parameters, we take the recovery rate  $\gamma = 1 \text{ week}^{-1}$ , i.e. the infection lasts a week, and  $\mu = 0.02 \text{ year}^{-1}$ . Finally, we assume that the magnitude of the recruitment rate  $\Lambda$  is equal to that of  $\mu$ . For interpretation, note that this last assumption means that the state variables  $S_P(t)$ ,  $I(t)$ ,  $S_S(t)$  and  $N(t)$  therefore denote fractions of the population in these classes relative to the initial (disease-free) population size. Thus, the transmission rate  $\beta$  is approximately equal to  $\mathcal{R}_0$  in magnitude.

Figure 2 illustrates potential epidemiological dynamics with PIM for realistic parameter values. As PIM increases, we find that epidemic cycles can appear. As a function of the rate of PIM and for different transmission rates, we plot in figure 2b,d,f,h a pair of eigenvalues (in the complex plane) of the Jacobian matrix (remark 1; electronic supplementary material) whose real parts become eventually positive with large enough PIM ( $\alpha_S$  indicated by the line colour). Since the real parts of a pair of eigenvalues become positive, there is a Hopf bifurcation that gives rise to a limit cycle. Note that, for each plot, we have selected these values of PIM to highlight that PIM can lead to oscillations. In figure 2a,c,e,g, we present corresponding illustrative time series of the epidemiological dynamics for increasing transmission rates with sufficient PIM to trigger periodicity (each star symbol in figure 2b,d,f,h illustrates the value of PIM used for the time series in the previous panel). In these figures, to illustrate the limit cycle and because the cycle period can be long, we plot weeks ( $52 \times 400$ ) + 1 to  $52 \times 600$ .

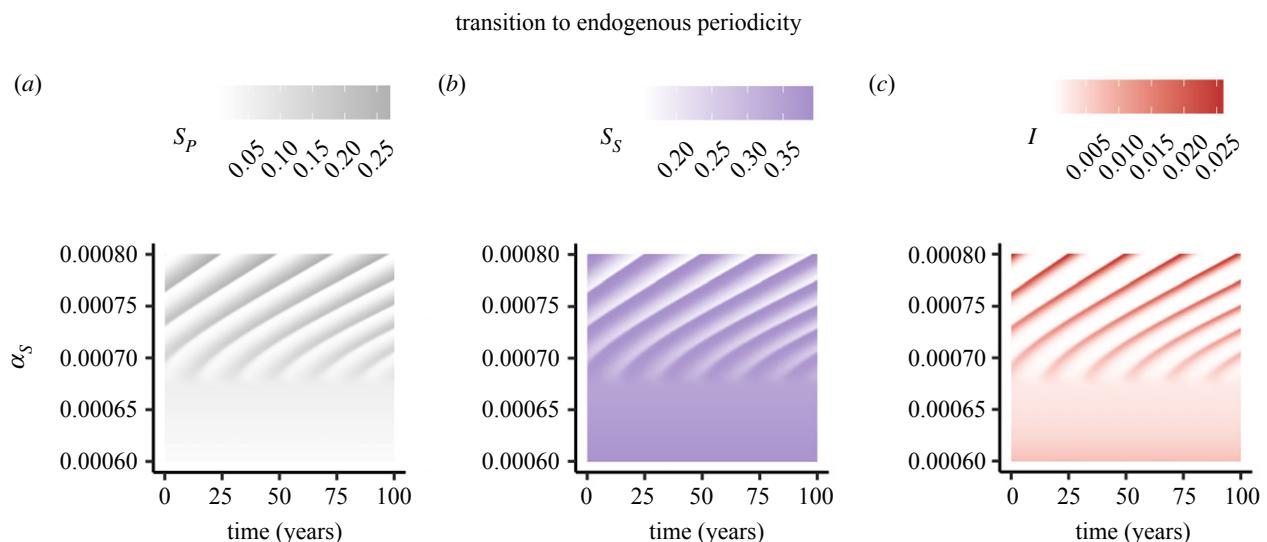
As highlighted by figure 2, low values of PIM are sufficient to trigger periodicity, particularly for low  $\mathcal{R}_0$ . As the transmission rate increases in the examples of figure 2, larger values of PIM are necessary for epidemic cycling; and the resulting cycles have shorter periods. If PIM is very strong, the real part of the pair of eigenvalues becomes negative again (figure 2h). Intuitively, very high PIM means that the contribution of previously infected individuals to the susceptible pool is substantially reduced and eventually is negligible. In the limit of  $\alpha_S \rightarrow \infty$ , i.e. individuals die immediately upon ‘recovery’, our model is akin to an SI epidemiological model. In an SI model, the endemic equilibrium is locally asymptotically stable whenever it exists.

In figure 3, we illustrate the transition from a stable endemic equilibrium to periodicity as PIM increases. Since the resulting cycle is shorter for these parameter values than for those in figure 2a,c,e, we plot weeks ( $52 \times 400$ ) + 1 to  $52 \times 500$  instead. As seen in figure 3c, the periodic behaviour can lead to large changes in  $I(t)$  compared with the endemic equilibrium values for smaller values of  $\alpha_S$  that do not lead to cycles. Interestingly, the infection peak of the cycle appears to be higher for larger PIM (figure 3c). In electronic supplementary material, figure S2, we also highlight a limit cycle example in the  $S_S$ – $S_P$  phase plane (note that in electronic supplementary material, figure S2, we plot weeks ( $52 \times 300$ ) + 1 to  $52 \times 500$  to illustrate the behaviour in the  $S_S$ – $S_P$  phase plane prior to (and including) that visualized in figure 3).

Since disease transmission can often be seasonal, we examine in electronic supplementary material, figure S3 the impact of an annually forced transmission rate, i.e.  $\beta(t) =$



**Figure 2.** Illustrative examples of time series of  $S_P(t)$ ,  $I(t)$  and  $S_S(t)$  for the periodic behaviour that can arise due to PIM, for different transmission rates  $\beta$  and different PIM rates  $\alpha_S$ . Since  $\gamma = 1$  and  $\Lambda = \mu = \frac{1}{50(52)}$ ,  $\mathcal{R}_0 = \beta/(1 + \mu) \approx \beta$ . For (a,c,e) and (g), we simulate 600 years with the first week having  $I(t_0) = 10^{-9}$ ,  $S_P(t_0) = 1 - I(t_0)$  and  $S_S(t_0) = 0$ , and we plot weeks 400(52) + 1 to 600(52). Panels (b,d,f) and (h) present the values of the complex-conjugate pair of eigenvalues of the Jacobian matrix of the  $S_S$ ,  $I$  and  $N$  equations about the endemic equilibrium, for different values of PIM  $\alpha_S$ . The 'star' symbol in each of these plots corresponds to the value of  $\alpha_S$  used for the corresponding previous plot. In all four panels,  $\alpha_I = 0$  and  $\varepsilon = 1$ .

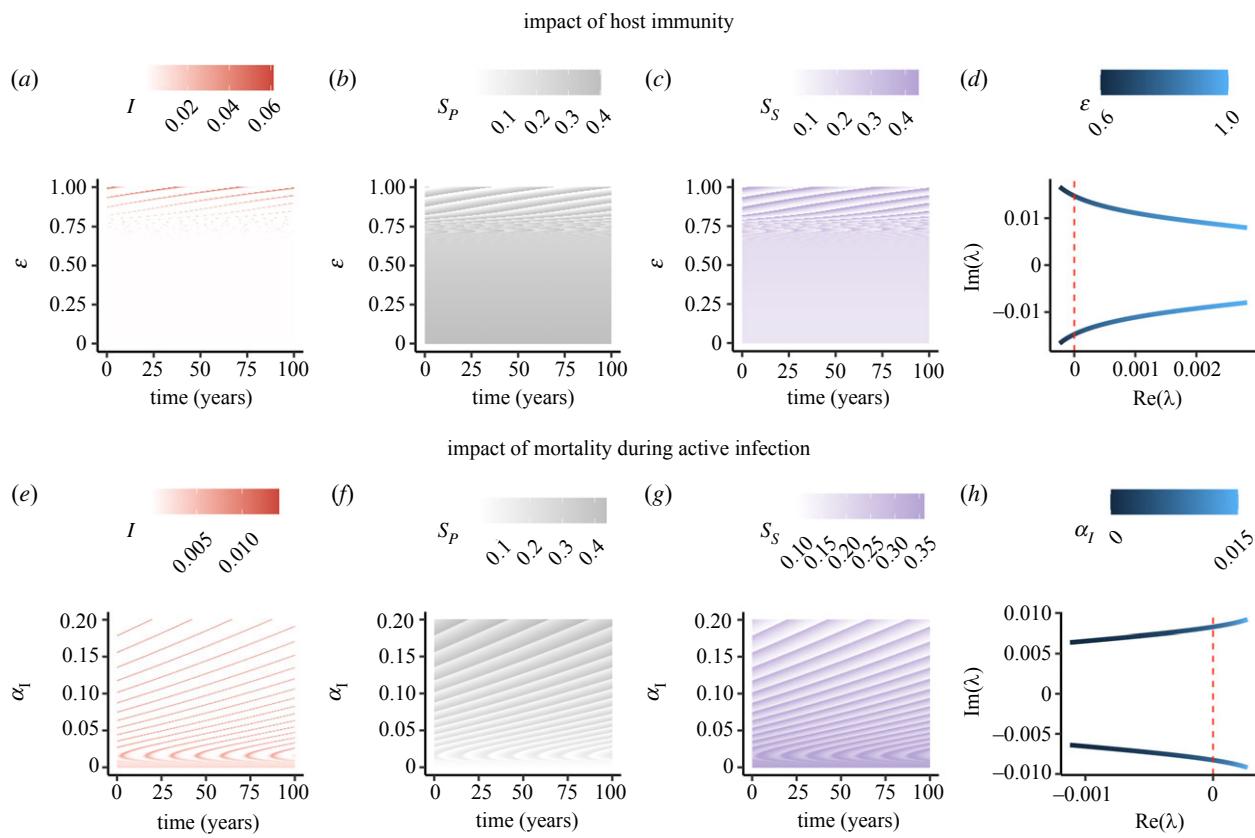


**Figure 3.** Illustrative examples of PIM triggering endogenous periodicity. Heat maps of time series of (a)  $S_P$ , (b)  $S_S$  and (c)  $I$  as PIM is varied. In all panels,  $\beta = 2.5$ ,  $\gamma = 1$ ,  $\alpha_I = 0$ ,  $\mu = \frac{1}{50(52)}$  and  $\varepsilon = 1$ . To obtain these heat maps, we simulate 500 years with initial conditions (at the first week) of  $I(t_0) = 10^{-9}$ ,  $S_P(t_0) = 1 - I(t_0)$  and  $S_S(t_0) = 0$ . For the heat maps, we discard the first 400 years and plot weeks 400(52) + 1 to 500(52).

$\beta_0(1 + \delta \sin(2\pi t/52))$ . When PIM is weak and the endemic equilibrium is stable, seasonal variations in transmission lead to annual cycles (e.g. electronic supplementary material, figure S3A). However, when PIM enables cycles, we find that adding a seasonal transmission rate can lead to complex dynamics (electronic supplementary material, figure S3B–S3D). In particular, small outbreaks are first immediately followed by larger ones; these then abate, slowly decreasing to very low levels of infection. During this time, the susceptible pool builds up, thus enabling this process to repeat.

### (c) Impacts of other characteristics on epidemic dynamics with post-infection mortality

To determine the impact of PIM on epidemic dynamics, we have focused on the simplest SIS-like model that includes PIM but no disease-induced mortality during active infection nor immunity following recovery. However, directly transmitted diseases often deviate from these basic assumptions, and increased model complexity can lead to subtle effects on epidemic dynamics. In particular, these



**Figure 4.** Interplay of additional host and pathogen characteristics with PIM. (a–d) Illustrative example for the impact of host immunity on epidemic dynamics with PIM. The heat maps in (a–c) are as in figure 3, but with  $\varepsilon$  varying instead of  $\alpha_S$ . (d) As in figure 2b,d,f,h, but with  $\varepsilon$  varying. In (a–d),  $\beta = 2.5$ ,  $\alpha_S = 0.001$ ,  $\gamma = 1$ ,  $\alpha_I = 0$  and  $\mu = \frac{1}{50(52)}$ . (e–h) Illustrative example for the impact of disease-induced mortality during active infection. Panels (e–g) are as in figure 3, but with  $\alpha_I$  varying instead of  $\alpha_S$ . (h) As in that of (d), but with  $\alpha_I$  varying instead of  $\varepsilon$ . In (e–h),  $\beta = 2.5$ ,  $\varepsilon = 1$ ,  $\alpha_S = 0.00065$ ,  $\mu = \frac{1}{50(52)}$ ,  $\gamma = 1$  and  $\mu = \frac{1}{50(52)}$ . For the heat maps of (a–c) and (e–g), and as in figure 3a, weeks 400(52) + 1 to 500(52) are plotted.

additional biological complexities can interplay with the emergent periodicity driven by PIM. We illustrate these with examples below.

### (i) Host immunity

Many diseases do not exhibit classic SIS-type characteristics, with hosts developing some immunity following recovery. For example, measles elicits very robust immunity following recovery [30]. Other pathogens, such as respiratory syncytial virus or rotavirus, elicit immunity against reinfection, but it is incomplete [31,32]. In these cases,  $\varepsilon < 1$ , i.e. the relative susceptibility to reinfection is *less* than to primary infection. We find that with partial immunity, periodicity can still occur with PIM (figure 4a–d).

In the limiting case where host immunity following infection is ‘perfect’ and no reinfection is possible, i.e.  $\varepsilon = 0$ , then the endemic equilibrium  $\hat{E}$  is locally asymptotically stable (theorem 4; electronic supplementary material). This result implies that for a fixed value of PIM that induces cycling in the SIS case, robust enough host immunity catalyses a collapse of the epidemic cycle to the endemic equilibrium. We illustrate this transition in figure 4a–d. Intuitively, as immunity increases and the critical ‘collapse’ point approaches, more frequent epidemics occur (figure 4a), and the landscapes of susceptibility correspondingly change (figure 4b,c). If PIM is higher, then periodicity can persist with stronger immunity, i.e. for smaller values of  $\varepsilon$  (see electronic supplementary material, figure S4).

### (ii) Pathogen-induced mortality during active infection

So far, we have focused on settings where there is no pathogen-induced mortality during active infection, i.e.  $\alpha_I = 0$ . However, pathogens can cause some infectious individuals to die during infection (see e.g. [19]). Therefore, we next relax this initial assumption and examine the impact of death due to disease during infection, i.e.  $\alpha_I > 0$ , on epidemic dynamics with PIM.

When there is no PIM, we have proved that the endemic equilibrium is locally asymptotically stable if  $\mathcal{R}_0 > 1$  (theorem 3; electronic supplementary material). Surprisingly, we find that, in the presence of some limited PIM not sufficiently strong enough to trigger cycling by itself, disease-induced mortality during active infection can cause a transition from a stable endemic state to periodicity (figure 4e–h). Thus, this analysis illustrates that disease-induced death during infection can heighten the impact of PIM on epidemic dynamics.

## 4. Discussion and conclusion

Finding periodicity in simple epidemiological models has long been a research focus (e.g. [33]). For example, with nonlinear incidence rates to model transmission, Liu *et al.* [34,35] found that a variety of behaviours are possible, including periodic solutions. In other work, Hethcote *et al.* [36] proved that periodicity can occur in SIRS models with three or more recovered classes. In a generalization of this result, Röst & Tekeli [37] showed that cycles can emerge (via Hopf

bifurcation) in SIS models with four or more infected stages. Furthermore, in a simple mathematical model, Tidbury *et al.* [38] found that immune priming can cause periodicity. By contrast, Busenberg & van den Driessche [23] formulated an SIRS model with exponential births and deaths, and with potentially increased mortality in both the infected and the recovered classes. In that model, the unique endemic equilibrium for the proportions of individuals in each compartment is globally asymptotically stable.

Here, we have used a simple mathematical model to show that PIM in combination with a return to (some) susceptibility can lead to periodicity. The intuition that underlies this key result is that PIM interferes with reinfection by impacting the secondary susceptible pool. When periodicity occurs, we have shown that the length of the cycles is partly set by the magnitude of the transmission rate (note that larger rates of PIM are needed for larger transmission rates). Furthermore, we found that disease-induced mortality during active infection can synergistically promote cycling. By contrast, robust host immunity (captured via a low relative susceptibility to reinfection) decreases the impact of the secondary susceptible pool on epidemic dynamics, which can therefore cause the disappearance of the cycling behaviour. Thus, for childhood infections that are fully immunizing or nearly so, such as measles, our results show that PIM does not qualitatively change the dynamics (i.e. no potential periodicity). This may explain why childhood disease dynamics are so well understood with their dynamics well described by seasonally forced SIR models. On the other hand, for the dynamics of infectious diseases that do not elicit sterilizing lifelong immunity after recovery, our work highlights an overlooked but likely very common driver of complexity, with cycles emerging. In particular, our findings reveal that 'hidden' characteristics of (potentially partially) susceptible individuals, beyond their potential susceptibility to reinfection, can destabilize epidemic dynamics. Untangling these characteristics will require simple models (for intuition) in conjunction with careful data collection and analyses (for calibration). Our work particularly highlights the need to quantify PIM in infectious disease systems without robust immunity.

Since there is already evidence that SARS-CoV-2 infections can lead to elevated mortality after recovery, our results show that it is important to determine the value of  $\alpha_S$  for predictions of future SARS-CoV-2 dynamics. Furthermore, given that low amounts of PIM can trigger periodicity, this phenomenon may be widespread for circulating endemic diseases that potentially contribute to early mortality. To measure PIM, large cohort studies designed to study immuno-epidemiology and evolution for SARS-CoV-2 and beyond (as discussed in [39] for SARS-CoV-2) could include explicit longer-term morbidity and mortality.

Building on our work, there are a number of other potential future avenues that should be investigated. In particular, we have assumed SIS-like dynamics, where individuals are either immune for life, or are immediately (potentially partially) re-susceptible to infection upon recovery. However, the impact of a period of 'perfect immunity', e.g. strain-transcending immunity for influenza [40], before a return to (partial) susceptibility (akin to the SIR(S) model [24,25]) should be determined. Similarly, we have ignored the possibility of a short recovery period after acute infection with no (or little) risk of additional mortality, with a subsequent increase in PIM. We have also considered a homogeneous

population and ignored age heterogeneities. Since transmission patterns could be different across and among different age groups (e.g. older individuals may participate less in transmission), future work should examine the confluence of PIM and age structure. Since periodicity emerges in our model due to the interaction between elevated mortality and reinfections, we conjecture that either a period of complete immunity, a short recovery period with decreased PIM followed by increased mortality, or age structure (where older, or both younger and older, individuals have an elevated risk of PIM) would still result in cycles, provided that this interaction remains present.

Perhaps more importantly, vaccination can have important epidemiological (e.g. [41]) and evolutionary effects (e.g. [42,43]) on pathogen dynamics. Vaccination can prevent (or decrease the likelihood of) infection via host immune responses. Additionally, as highlighted by SARS-CoV-2, vaccines may also potentially decrease the likelihood of long-term symptoms (i.e. 'long COVID') after infection [44–46], and may even decrease long-term symptoms for those that were infected before vaccination [47]. Such a decrease of longer-term symptoms could represent a decrease in PIM. Thus, the impacts of vaccination on epidemic dynamics with PIM should be investigated.

In terms of the host response to infection, we have taken the simplifying assumption that a secondary and beyond infection is equivalent to a primary infection. However, the transmissibility and duration of infection may be different. In particular, if host immunity is present, it is possible that a reinfection is both less transmissible and shorter in duration than a primary infection. Future work should examine the impact of these other forms of immunity on epidemic dynamics with PIM. Relatedly, we have assumed that susceptibility after recovery from secondary infections and beyond is identical to susceptibility after recovery to primary infections. In reality, however, their characteristics may differ. First, due to prolonged damage from multiple infections, PIM could increase with the number of infections. Second, immunity may increasingly become more robust as a host experiences multiple infections. Thus, incorporating multiple classes of susceptibility, with potentially different degrees of PIM, is a fruitful avenue for future research.

While we have formulated a population-level model, a key future direction is to take a cross-scale modelling approach with within-host kinetics (e.g. [48]). For example, such a model may be able to untangle the underlying mechanisms that shape PIM, disease-induced mortality during active infection, and immunity following recovery. A within-host model could also reveal how pathogen loads affect the combination of these characteristics. Other interesting avenues would be to study the potential interplay between PIM and different functional forms for births, or dynamic births as in wildlife populations, and to examine the impact of stochasticity (both as a potential driver and in local extinction). Finally, while we have focused on the long-term behaviour in our model, it would be useful to characterize the transient dynamics (see e.g. [49,50] for transient dynamics in ecology) that emerge due to PIM.

Overall, our results underline the importance of characterizing different degrees of susceptibility in populations in conjunction with the life-history trajectories of individuals as their susceptibility changes. In particular, we have illustrated that small changes in the characteristics of susceptible individuals after they recover (i.e. increased mortality) can result in surprising population-level effects. More

generally, our work underlines the use of simple epidemiological models to obtain qualitative insights. Since the inclusion of PIM induces cycles in the simplest model formulation, our work stresses the importance of investigating the impact of PIM in larger, less tractable models of epidemic dynamics. In tandem, our results suggest that empirical studies to quantify PIM are key for predictability.

**Data accessibility.** Codes are available as electronic supplementary material [51].

**Authors' contributions.** C.M.S.-R: conceptualization, investigation, writing—original draft, writing—review and editing; S.A.L.: investigation, writing—review and editing; B.T.G.: investigation, writing—review and editing; M.B.: investigation, writing—review and editing.

All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

**Conflict of interest declaration.** We declare we have no competing interests.

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