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Characteristics of immunity and disease-induced mortality synergistically complicate epidemiological dynamics

Chadi M. Saad-Roy[1,2,3,4]*, **Mike Boots**[2,5], **P. van den Driessche**[6]

1 Miller Institute for Basic Research in Science, University of California, Berkeley, California, United States of America, **2** Department of Integrative Biology, University of California, Berkeley, California, United States of America, **3** Department of Mathematics, University of British Columbia, Vancouver, British Columbia, Canada, **4** Department of Microbiology and Immunology, University of British Columbia, Vancouver, British Columbia, Canada, **5** Department of Biosciences, University of Exeter, England, United Kingdom, **6** Department of Mathematics and Statistics, University of Victoria, Victoria, British Columbia, Canada

* chadi.saadroy@ubc.ca

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Abstract

Disease-induced mortality and immunity are two key pathogen-specific drivers of epidemiological dynamics. As highlighted by the COVID-19 pandemic, disease-induced mortality can occur not only during active infection, but also following recovery during a period of immunity or after returning to susceptibility. In parallel, this period of immunity can vary in its average duration and, importantly, in its distribution. While these uncertainties underlie the dynamics of many pathogens, their combined effects remain unknown. To address this gap, we formulate a general framework where individuals return to (potentially partial) susceptibility after one or more recovery classes. We show analytically that disease-induced mortality either during infection or while fully-immune has no qualitative effects if there are two or fewer recovered compartments and individuals return to complete susceptibility. However, with four, five, or six recovered compartments, we numerically find that disease-induced mortality during infection or while immune can be either stabilizing or destabilizing, and that the presence of post-infection mortality while susceptible can enable three switches in stability. Thus, our models reveal that immunity combined with disease-induced mortality can have important epidemiological effects. Our findings therefore illustrate the need to include these effects in pathogen-specific models, and for immuno-epidemiological cohort studies.

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Author summary

Pathogens can cause host mortality during infection, but potentially also after recovery during a period of immunity and a return to (potentially partial) susceptibility once immunity has waned. A classic study revealed that a change in the distribution of the immune period can destabilize endemic dynamics and lead to sustained epidemiological oscillations. Recent work has highlighted that mortality after recovery (accompanied by a return to potentially partial susceptibility) can also be destabilizing. However, the combined impacts of the distribution of a fully-immune period and pathogen-induced mortality (during infection or after recovery) remains unknown. We address this gap here using a mathematical model where, after recovery, individuals flow through multiple fully-immune classes before entering a (potentially partial) susceptible state. We prove that if there are 1 or 2 recovery compartments and individuals return to complete susceptibility after waning, the unique endemic equilibrium is locally stable. With more recovery compartments, we show that disease-induced mortality, either during infection or afterwards, can be stabilizing or destabilizing. Overall, our work illustrates the importance of considering characteristics of immunity, in addition to disease-induced mortality (during infection and after recovery) in epidemiological models.

Introduction

The COVID-19 pandemic has underlined that infectious diseases are complex socio-ecological systems, and that there are many key factors that can affect their dynamics. The qualitative effects of each of these characteristics on such complex systems can be disentangled with simple mathematical models. Throughout the COVID-19 pandemic and faced with much uncertainty, a number of simple models were used to generate such insights. For example, they revealed the importance of climate [1], and clarified a range of questions on the role of immunity and susceptibility for epidemic dynamics [2–9]. In particular, after emergence, the initial pandemic trajectory of a novel pathogen is dominated by the large fraction of completely susceptible people in combination with the basic reproduction number [1]. Subsequently, medium-term and long-term dynamics hinge on the features of host immune responses [2–5,7,8]. In particular, immune life histories are pathogen-specific and lie on a continuum, from lifelong immunity that fully prevents reinfection, to very transient immunity that leads to a return to complete susceptibility [10]. Intuitively, this degree of 'buffering' shapes the replenishment of the susceptible pool, which is in turn a key determinant of the endemic level of infection [3,10].

In addition to the strength and duration of immunity, other important characteristics include the population-level distribution of the immune period. Otto et al. [11] very recently used a model with multiple recovered compartments to represent population-level waning of antibodies for SARS-CoV-2. With such a model, the distribution of the immune period changes from exponential to one that is increasingly less skewed

as the number of compartments increase. In tandem, it is well-known that such a change can trigger periodicity in simple epidemiological models. This result was first shown by Hethcote, Stech, and van den Driessche [12], and examined multiple times since [11,13,14]. In particular, Rost and Tekeli [14] highlighted how this finding could be generalized to multiple infection classes [14]. If the distribution of immunity can trigger periodicity, prior work [12] suggested that demographic processes are stabilizing. However, the impacts of disease-induced mortality in these settings remain unknown.

As we have seen with COVID-19, disease-induced mortality can occur in multiple stages after infection. First, infectious individuals may have elevated mortality during active infection. Due to a variety of causes, post-infection mortality (PIM) can occur after recovery. For example, as illustrated by COVID-19, complications from viral infections could lead to increased cardiovascular damage or neurological damage [15–17], in turn elevating mortality for those previously-infected individuals. Furthermore, immunomodulation, as seen with measles virus [18,19], could result in elevated mortality because of heightened susceptibility to other pathogens. PIM is an emerging area of active research, with an influential recent review on "post-acute infection syndromes" [20], and a major study examining viral exposure and neurodegeneration risk [21]. Clearly, these recent studies underline the importance of understanding the effects of PIM on epidemiological dynamics.

After recovery, an individual may experience a period of immunity before returning to (potentially partial) susceptibility, and post-infection mortality (PIM) could occur in either of these stages. Recent work with a simple susceptible-infected-(potentially susceptible) model showed that PIM can lead to periodicity [22]. In particular, PIM interacts with the previously-infected susceptible pool to cause sustained epidemiological oscillations. The authors also illustrated that lower transmission rates required lower rates of PIM to trigger periodicity, and that the resulting oscillations had longer periods.

However, this work ignored many details of individual immunity, and examined the impact of immunity through only one lens. In particular, these authors incorporated this via a reduction in susceptibility to reinfection, and showed that robust immunity leads to stabilization [22]. In reality, the characteristics of immunity could matter. Additionally, the impact of PIM during a (transient) period of immunity remains unknown. Theoretical research on the population-level effects of PIM is a very useful motivation for data collection to measure PIM, and thus we seek to examine these effects broadly. Such data collection endeavours would require large cohort studies (see *e.g.* [23]).

In this paper, we examine the interactive impacts of immunity and disease-induced mortality on epidemic dynamics. To test for and untangle these effects, we first formulate a general framework and present theoretical preliminaries. We then numerically examine each kind of disease-induced mortality, *i.e.*, during infection, while immune, and while susceptible again after immunity has waned, both on their own and when there is a combination of these sources of disease-induced mortality.

Model framework

To examine the potential interplay between disease-induced mortality and the characteristics of immunity, we extend the ordinary differential equations SIS-like model of [22] (see also [3,10]). In that model, individuals are either fully susceptible (denoted S_P), infectious (denoted I), or previously-infected susceptibles (S_S). To expand this model, we consider multiple (*i.e.* n) fully immune compartments R_i, each with their own potentially elevated mortality α_{R_i}. We also assume that the flow between these compartments occurs at rate σ_i, *i.e.* $\frac{1}{\sigma_i}$ is the average time an individual spends in the R_i compartment. Since previously-infected susceptibles may have decreased susceptibility to reinfection (due to some immunity) after the period of complete immunity wanes, the relative susceptibility of these individuals is denoted as $0 \leq \varepsilon \leq 1$. Furthermore, the transmission rate is denoted by β, the recruitment rate by Λ, the recovery rate by γ, and the demographic mortality rate by μ. Finally, the rate of disease-induced mortality during active infection is denoted as α_I, and the rate of PIM after recovery (and return to susceptibility) as α_S.

Our general model is depicted in Fig 1, and the flows between compartments are governed by the following equations:

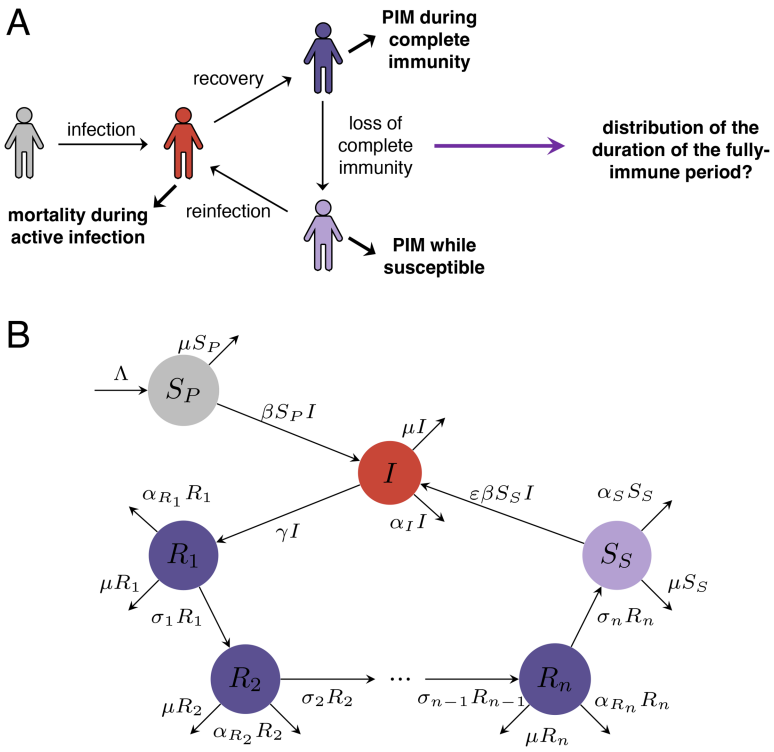

Fig 1. Schematic illustration of the immuno-epidemiological model that encompasses characteristics of immunity and disease-induced mortality (adapted from [22] for the model without a fully-immune period). (*A*) Illustrative representation of an individual trajectory through infection, recovery, loss of immunity, and reinfection, with potential elevated mortality due to disease highlighted. (*B*) Model flow diagram, with arbitrary *n* classes of immune individuals, so that the distribution of the fully-immune period is variable.

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$$\frac{dS_P}{dt} = \Lambda - \beta S_P I - \mu S_P, \tag{1a}$$

$$\frac{dI}{dt} = \beta I(S_P + \varepsilon S_S) - (\gamma + \mu + \alpha_I)I, \tag{1b}$$

$$\frac{dR_1}{dt} = \gamma I - (\mu + \alpha_{R_1} + \sigma_1)R_1, \tag{1c}$$

$$\frac{dR_2}{dt} = \sigma_1 R_1 - (\mu + \alpha_{R_2} + \sigma_2)R_2, \tag{1d}$$

$$\vdots \tag{1e}$$

$$\frac{dR_n}{dt} = \sigma_{n-1} R_{n-1} - (\mu + \alpha_{R_n} + \sigma_n)R_n, \tag{1f}$$

$$\frac{dS_S}{dt} = \sigma_n R_n - \varepsilon\beta S_S I - (\mu + \alpha_S)S_S. \tag{1g}$$

Thus, the total population $N = S_P + I + R_1 + \cdots + R_n + S_S$ follows

$$\frac{dN}{dt} = \Lambda - \alpha_I I - \alpha_S S_S - \sum_{i=1}^{n} \alpha_{R_i} R_i - \mu N. \tag{2}$$

Our model contains special cases that were studied in detail in previous work. First, if $\alpha_I = 0$, $\alpha_{R_i} = 0$ for $i = 1, ..., n$, $\alpha_S = 0$, $\varepsilon = 1$, and in the absence of recruitment or demographic mortality (*i.e.* $\Lambda = \mu = 0$), we recover the classic $SIR_1R_2...R_nS$ model of [12], where $S = S_P + S_S$ (see also the base epidemiological model of [11] used for SARS-CoV-2 dynamics). Second, if $n = 1$ and if $\sigma_1 \to \infty$, our model reduces to the simple SIS-like model used to examine the impacts of PIM on epidemiological dynamics [22].

In their paper that showed that immune progression via multiple recovered compartments could lead to endogenous periodicity, Hethcote, Stech & van den Driessche [12] indicated that recruitment and (demographic) mortality are likely to stabilize the endemic equilibrium. However, the qualitative effects of mortality as a result of infection on epidemiological dynamics remain unknown. Here, we study the impacts of disease-induced mortality during infection or after recovery, the latter of which can occur while immune or after immunity has waned.

Results and discussion

In our model, the disease-free equilibrium has $S_P^{(0)} = \frac{\Lambda}{\mu}$ with all other variables zero. Furthermore, since our model has a unique infected compartment, the basic reproduction number can be calculated directly using the I equation, giving

$$\mathcal{R}_0 = \frac{\beta \frac{\Lambda}{\mu}}{\gamma + \alpha_I + \mu}, \tag{3}$$

which is the same $\mathcal{R}_0$ as in [22]. Thus, the addition of fully immune compartments has no impact on the basic reproduction number. This is intuitive, as population-level immunity is only generated via infection and is thus absent before the disease is introduced. In Theorem 1 (S1 Appendix), we prove that our model has a unique endemic equilibrium if $\mathcal{R}_0 > 1$, whereas the only equilibrium when $\mathcal{R}_0 < 1$ is disease-free. Furthermore, for the endemic equilibrium, we give the Jacobian matrix that determines its local stability for general n in Remark 1 (S1 Appendix).

We first examine the SIRS exponentially-distributed immune period case with no PIM after immunity wanes (*i.e.* $n = 1$, $\varepsilon = 1$ and $\alpha_S = 0$). In this model, we prove in Theorem 3 (S1 Appendix) that additional mortality during active infection or during recovery does not affect the stability of the endemic equilibrium, *i.e.* the endemic equilibrium is locally stable when $\mathcal{R}_0 > 1$. This latter result (on additional mortality during recovery) is analogous to previous findings with a different SIRS model [24].

Furthermore, when $n = 2$, we prove that the endemic equilibrium of this 4-dimensional model is also locally stable if $\mathcal{R}_0 > 1$, irrespective of the rates of PIM in R_1 or R_2 (Theorem 4, S1 Appendix, using the appropriate Routh-Hurwitz conditions [25]). Thus, when the immune period distribution cannot destabilize the endemic equilibrium on its own, PIM during this period has no qualitative dynamical effect. This is a sharp contrast to PIM in previously-infected susceptible individuals, which can cause periodicity in the SIS case [22]. Intuitively, while PIM when susceptible affects the effective reproduction number (*i.e.* $\mathcal{R}_E(t) = \mathcal{R}_0(S_P(t) + \varepsilon S_S(t))$ for a general ε), PIM while immune has no effect on this quantity. Our theoretical results are in line with previous findings of Hethcote et al. [12], where, with no vital dynamics nor disease-induced mortality, the endemic equilibrium is locally stable when $n = 1$ or $n = 2$, but the model with $n = 3$ can lead to periodic solutions.

While we have so far analyzed our model in general, we examine in the remainder of this paper settings where the mean duration of complete immunity is fixed across values of n, so that an increase in n only affects the distribution of

the period of complete immunity and does not also increase its average duration. Thus, we focus on the case where $\sigma_i = n\sigma$, giving a period of complete immunity that is Erlang distributed with mean $\frac{1}{\sigma}$. We also set the recovery rate $\gamma = 1$ per week (which means $\mathcal{R}_0 \approx \beta$), and vary the transmission rate β between 1.5 and 2.5 per week, which is within the range for common circulating respiratory infections (see, for example, [2] and [26]).

Disease-induced mortality during active infection. We begin by examining the impact of disease-induced mortality during active infection, (*i.e.*, $\alpha_I > 0$), and set all other additional mortality rates to zero (*i.e.* $\alpha_{R_i} = \alpha_S = 0$). We numerically examine the effects of larger n on the stability of the unique endemic equilibrium. To characterize this, we compute the eigenvalues for the Jacobian matrix about the endemic equilibrium. For different distribution of immune periods (n) and transmission rates (β), we illustrate in Fig 2 the characteristics of this equilibrium as a function of the rate of disease-induced mortality during active infection and of the average duration of immunity. We find that if the duration of immunity is negligible, disease-induced mortality does not destabilize the endemic equilibrium on its own. Intuitively, in these conditions, our model resembles an SIS model (which itself has a stable endemic equilibrium).

On the other hand, if there is a noticeable period of immunity, we surprisingly find that disease-induced mortality can either trigger periodicity or stabilize the endemic equilibrium. First, in settings when the characteristics of immunity do not destabilize the endemic equilibrium on their own, it can act synergistically with disease-induced mortality to change the stability of the equilibrium. Additionally, an increase in the rate of disease-induced mortality causes the range of immune periods for which this occurs to shift to increasingly larger values (of average duration of immunity). Furthermore, this feature persists even if the characteristics of immunity can alone trigger this change in stability.

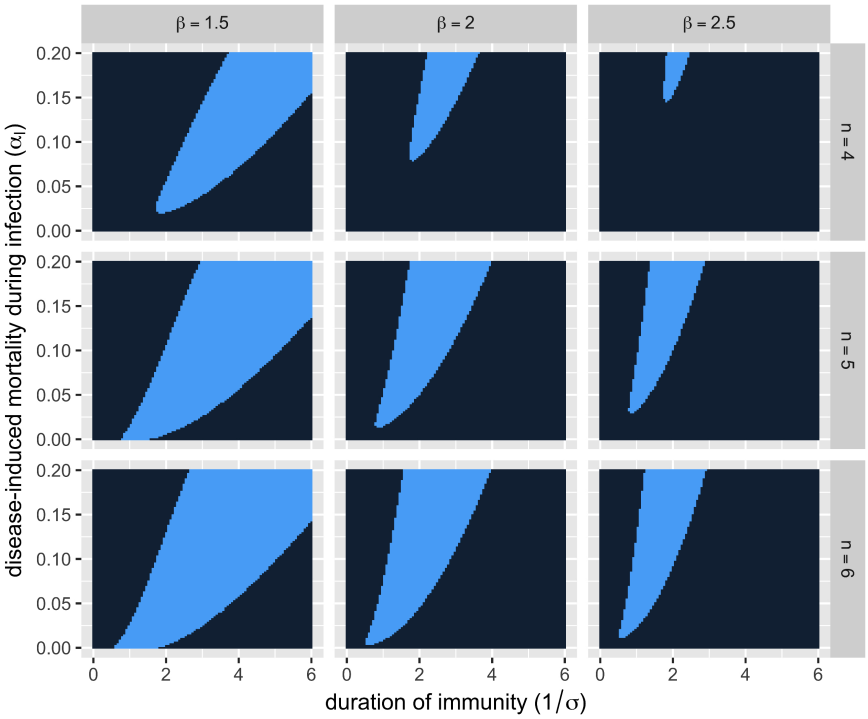

Fig 2. Combined impact of disease-induced mortality during infection and the distribution of the immune period on the characteristics of the endemic equilibrium. Dark blue denotes a region where all the eigenvalues of the endemic equilibrium have negative real parts and thus this equilibrium is locally asymptotically stable. On the other hand, light blue denotes a region where the endemic equilibrium is unstable. The columns denote different values of transmission rate β per week, and the rows are different numbers n of fully immune compartments. Other parameters are: $\gamma = 1$ per week, $\Lambda = \mu = 0.02$ per year, $\varepsilon = 1$, and $\alpha_{R_i} = \alpha_S = 0$.

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We also find that an increase in transmission rate narrows the region of instability (compare panels of Fig 2 from left to right). This result is partially reminiscent of the finding that higher levels of post-infection mortality are needed to trigger periodicity for higher transmission rates in a simple SIS-like model [22]. Finally, we observe the opposite effect if the distribution of immunity becomes sharper (*i.e.* increasing n). Again, this echoes previous work that showed that including more recovered compartments in an $SIR_1...R_nS$ model was increasingly destabilizing [12].

Post-infection mortality during complete immunity. With other distributions of the immune period, we numerically test the effect of PIM during complete immunity and assume that this rate of PIM is constant across the period of complete immunity, *i.e.* $\alpha_{R_i} = \alpha_R$ for $i = 1, ..., n$. We first assume that disease-induced mortality only occurs during complete immunity, so that $\alpha_I = \alpha_S = 0$. In Fig 3, we examine a range of average durations of immunity and rates of PIM during this period, for different transmission rates and distributions of immune periods. We find that while mortality during the period of complete immunity is not destabilizing on its own (for the parameter ranges we examined), it can have a number of other important effects. First, if the characteristics of immunity are destabilizing on their own, PIM while immune can stabilize this equilibrium. On the other hand, if the distribution of immunity does not destabilize the equilibrium on its own, PIM during the immune period can lead to a switch in stability. In these cases, if this PIM becomes large enough, it triggers another change, so that the equilibrium regains stability. Perhaps most interestingly, we find that neither the characteristics of immunity nor PIM (during the immune period) can destabilize the endemic equilibrium on their own if transmission rates are high enough (at least for the parameter ranges in Fig 3). However, the combination of these features can lead to an unstable endemic equilibrium.

To examine the robustness of our results, we now study them in the context of PIM during complete immunity. If the baseline value of PIM during complete immunity is slightly elevated, the regions of stability with disease-induced mortality

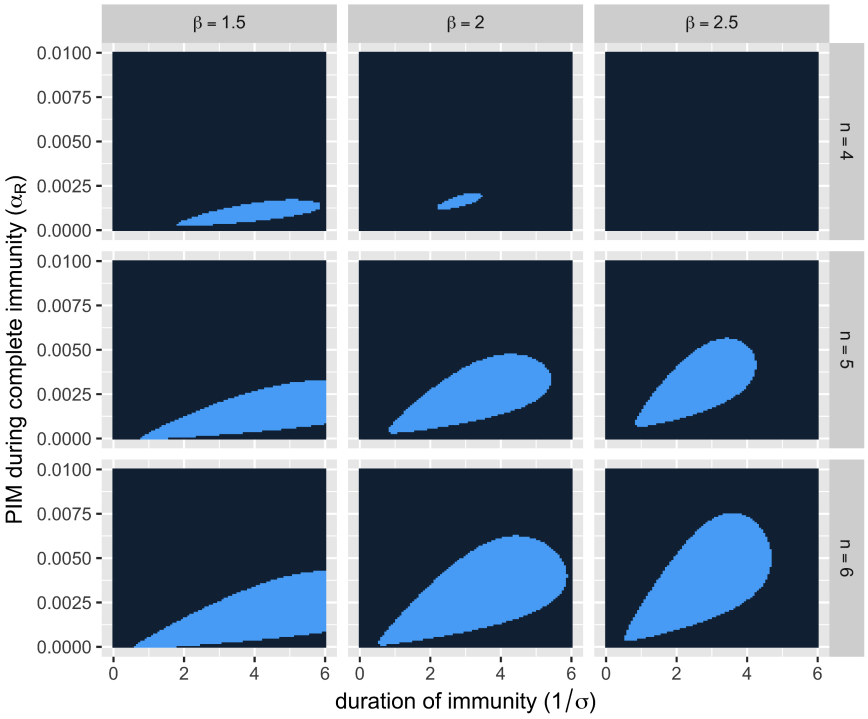

Fig 3. Combined impacts of post-infection mortality while immune and the characteristics of this period. Across all panels, disease-induced mortality during infection and PIM in the secondary susceptible class are set to zero, *i.e.* $\alpha_I = \alpha_S = 0$. Details and other parameter values are as in Fig 2.

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during active infection undergo quantitative changes (compare Fig 2 with S1 Fig in S1 Appendix). More modest changes occur if instead the baseline value of disease-induced mortality during active infection is elevated (compare Fig 3 with S2 Fig in S1 Appendix). However, the appearance of an unstable region for $\beta = 2.5$ and $n = 4$ is a notable contrast. Thus, the combination of different sources of disease-induced mortality can have important implications.

Post-infection mortality after a return to susceptibility. In combination with the distribution of the immune period length, we have so far shown that disease-induced mortality, either during active infection or while immune can have important effects on the stability of the endemic equilibrium. However, in the settings we have examined, these kinds of disease-induced mortality do not on their own destabilize the endemic equilibrium.

Once a period of complete immunity wanes, individuals may become susceptible again. To test the effects of PIM in this stage, we illustrate in Fig 4 the dynamical impacts of such PIM in conjunction with the duration of immunity, for different distributions of immune periods and different transmission rates. We surprisingly find that if PIM in previously-infected susceptibles destabilizes the endemic equilibrium on its own, an increasingly longer period of immunity can first stabilize this equilibrium, then destabilize it again, and then potentially eventually re-stabilize it. Thus, PIM in previously-infected susceptibles can lead to three switches in stability of the endemic equilibrium (*e.g.* $\beta = 2$ and $\alpha_S = 0.0075$), whereas the settings we examined with other forms of disease-induced mortality resulted in at most two switches.

On the other hand, for a fixed duration of immunity, we also find that an increase in PIM can either destabilize or stabilize the endemic equilibrium. For example, if the characteristics of immunity (both the duration and distribution) destabilize the endemic equilibrium on their own, PIM can stabilize and then potentially also destabilize it (bottom left panel of Fig 4, where $\beta = 1.5$). Finally, we observe that the combination of PIM and immunity can destabilize the endemic equilibrium in regions where the absence of one of these features leads to a stable equilibrium, and this is particularly evident for higher transmission rates.

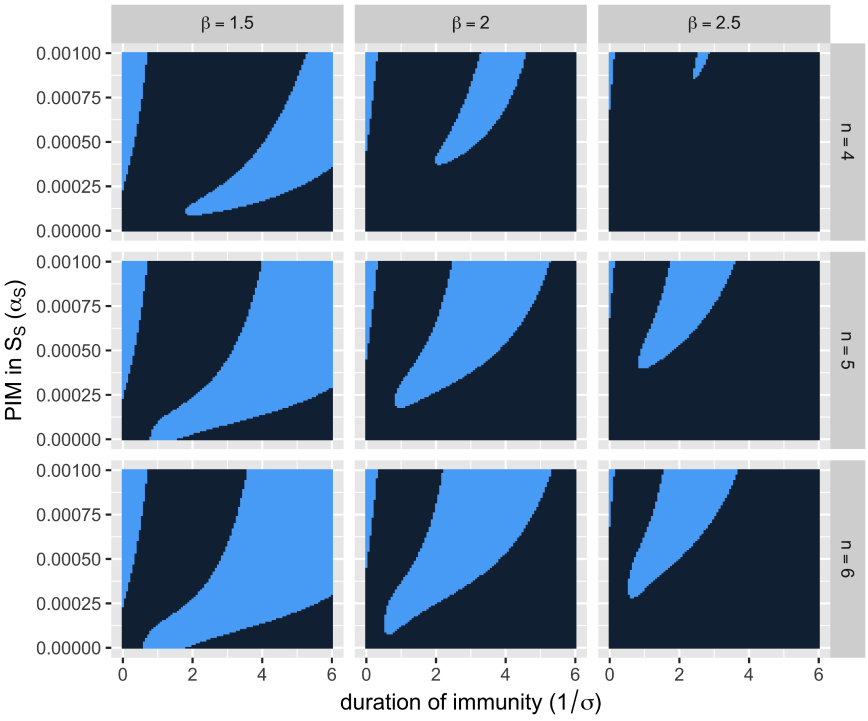

Fig 4. Effects of PIM after immune waning with distributions of immunity. Throughout all panels, there is no disease-induced mortality during active infection or while immune, *i.e.* $\alpha_I = \alpha_R = 0$. All details and other parameter values are as in Fig 2.

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Finally, as before, we examine the robustness of our results by varying the remaining disease-induced mortality parameters in a series of supplementary figures. Importantly, we find that an elevated baseline of disease-induced mortality during either complete immunity (S3 Fig in S1 Appendix), active infection (S4 Fig in S1 Appendix), or both stages (S5 Fig in S1 Appendix) can have important effects. These additional sources of disease-induced mortality can be either stabilizing or destabilizing, and which occurs will depend on the distribution and the average duration of the immune period, the transmission rate, and the level of PIM in secondarily susceptible individuals. If this level is instead elevated at baseline, the regions of instability with disease-induced mortality during active infection change. For example, they seem to become larger for higher transmission rates and narrower for lower transmission rates (compare Fig 2 and S6 Fig in S1 Appendix). Combined with PIM during complete immunity, these effects appear compounded (S7 Fig in S1 Appendix). Furthermore, an elevated baseline of PIM while susceptible has very marginal effects on the regions of instability with PIM during complete immunity (S8 and S9 Figs in S1 Appendix).

Return to partial susceptibility after immunity has waned. So far in our numerical explorations we have assumed that after immunity wanes, individuals return to complete susceptibility ($\varepsilon = 1$). Thus, the likelihood of infection once immunity has waned is identical to that for never-infected susceptible individuals. In reality, however, the relative susceptibility after immune waning compared to that for never-infected susceptibles (ε) could range from unity to zero, with the latter case denoting a fully immunizing infection.

In Theorem 2 (S1 Appendix), we show theoretically that when immunity is lifelong (*i.e.* $\varepsilon = 0$) and $\mathcal{R}_0 > 1$, the endemic equilibrium is locally asymptotically stable. Thus, the endemic equilibrium is stabilized as ε decreases, and any region of instability eventually disappears for small enough ε. Intuitively, this result is due to an increasingly diminished contribution of the previously-infected susceptible pool to the effective reproduction number (*i.e.* $\mathcal{R}_E(t) = \mathcal{R}_0(S_P(t) + \varepsilon S_S(t))$) as ε decreases, which is as in the SIS-like case (see [22]). Thus, the qualitative epidemiological effects of the uncertainties in the characteristics of the immune period and in the features of disease-induced mortality hinge on individuals eventually returning to susceptibility after recovery. To quantify these unknowns, a combination of immunological and epidemiological studies are needed, including large immuno-epidemiological cohort studies across ages as suggested by Saad-Roy et al. [23].

Caveats and future directions

In our model, we have made a number of simplifying assumptions that should be examined further in future work. First, we have ignored multiple sources of potential heterogeneities, such as age (*e.g.* [4]), space (*e.g.* [27–29]), transmission (*e.g.* [30–32]), and individual-level variations in immune responses [33], and these may complicate the characteristics of immunity. For example, children may develop more robust immune responses than adults, and the shape of the immune period distribution could itself vary with age cohorts. Furthermore, age-structure could also affect disease-induced mortality, both during infection and afterwards, and this should be examined in future work. Additionally, untangling the effects or mortality, immunity, and age via refined models is thus a fruitful avenue for future research. Relatedly, space is an important source of heterogeneity that we have ignored for tractability. As more data are collected on disease-induced mortality and immunity, the role of space in shaping immuno-epidemiological trajectories could be studied further. With refined models and methods developed for ecological systems (see *e.g.* [34]), the effects of all these factors on epidemiological dynamics could potentially be disentangled.

Second, we have ignored explicit pathogen evolutionary dynamics in our model, and assumed that waning immunity could be due to either host or pathogen characteristics. In reality, pathogen evolutionary dynamics could be explicitly considered, and its interplay with epidemiological and immunological dynamics studied in a more granular fashion [35]. Furthermore, pathogen evolution may result in changes in model parameters, such as a change in transmission, or a change in disease-induced mortality (either during or after infection). The evolution of disease-induced mortality during infection has been the subject of a large body of literature (see *e.g.* [36–39]). Additionally, a recent article focuses on the evolution

of post-infection mortality [40], and it would thus be very valuable to study the evolution of disease-induced mortality within our mathematical framework.

Third, individuals may change their behavior to decrease their likelihood of infection (see *e.g.* [41]), and these social dynamics can then affect epidemiological dynamics, which would then feedback into individual decision-making (see *e.g.* [42–46]). While we have ignored these coupled dynamics here, future work should examine the effects of coupled socio-epidemiological models with disease-induced mortality during and after infection with different characteristics of immunity.

Fourth, since we have focused on the distribution of the fully-immune period, we have assumed that once complete immunity wanes the relative susceptibility to reinfection is ε, which remains constant while individuals are in S_S. In reality, this relative susceptibility could change over time. Thus, an important future avenue is to consider multiple partially susceptible compartments, each with their own relative susceptibility, through which individuals progress (as long as they remain uninfected).

Fifth, from a more mathematical standpoint, we have proved that our general model has a unique endemic equilibrium and we have investigated its stability. However, we have not examined the possibility of an additional limit cycle when the endemic equilibrium is locally asymptotically stable (as was shown numerically for certain parameter values in [12]). If such a limit cycle were to exist and be bistable with the endemic equilibrium, epidemiological dynamics would hinge on the initial conditions, and this should be examined in detail. Furthermore, in our numerical examples, the onset of a destabilized endemic equilibrium are characterized by two complex eigenvalues crossing into the non-negative half-plane. This is a hallmark of a Hopf bifurcation, which gives rise to periodic solutions (*e.g.* see [22] for the simple case). While we have not examined this in detail in our current model, it is possible that this relatively complex system has a stable limit cycle. Periodicity in epidemic models has been the subject of much research, and has been shown to emerge due to a variety of factors, including the distribution of immunity [12] (see also [11,13,14]), post-infection mortality [22], immune priming [47], and immune boosting after waning [48]. Thus, other important future directions are to extend our model to consider such characteristics that we have so far ignored but that can lead to periodicity on their own.

Sixth, while we have focused on the stability of the endemic equilibrium,we have ignored transient dynamics, and these are important in ecological systems (see *e.g.* [49,50]). Future research should clarify these for our model, and how they depend on the characteristics of immunity and disease-induced mortality. Relatedly, we have also ignored explicit strain dynamics and its interplay with transient dynamics (*e.g.* [51]). These are salient features to explore in future work, especially for emerging pathogens, as they transition to endemicity. While this transition has been explored in previous work for SARS-CoV-2, (*e.g.* see [2–4,7,11]), the impacts of disease-induced mortality and of the immune period distribution remain open questions. Additionally, we have omitted external seasonality (*e.g.* [1,3,52]), and examining the interplay between features of immunity, disease-induced mortality, and seasonal cycles should be pursued. Stochasticity could also play an important role in transient and endemic dynamics, especially in the context of the characteristics of immunity and disease-induced mortality. Stochastic persistence and extinctions of variants could be important, and large scale models that build on our framework should investigate this further.

Seventh, we have ignored the distribution of the infection period, and taken it to be exponential. In reality, however, this distribution could also be less skewed, and this could affect epidemiological dynamics. Thus, a valuable future avenue would be to combine our model with the general model of Röst and Tekeli [14]. Additionally, beyond relative susceptibility, we have omitted other characteristics of reinfections, such as their transmissibility, duration, or various sources of disease-induced mortality during and following infection. If the transmissibility or duration of reinfections is decreased, we conjecture that this would stabilize the endemic equilibrium, in line with our results on the stabilizing effect of the relative susceptibility of reinfection. However, future work should examine these questions in detail.

Finally, we have omitted vaccination and the subsequent characteristics of vaccinal immunity. The deployment of vaccines can have important population-level effects [3,5,53,54], and incorporating this into our framework is an important area for future work. In particular, the strength and duration of vaccinal immunity may be different from that induced from infection, and the distribution of the vaccinal immune period could also vary. Furthermore, infections after vaccination

could themselves be different than primary infections or reinfections, and this should be investigated further. Additionally, vaccination coverage can also change over time, and examining varying vaccination rates in the context of immunity and disease-induced mortality would also be valuable.

Conclusions

As perhaps best exemplified by the COVID-19 pandemic, host immune responses are key features that can shape the trajectories of infectious disease dynamics (*e.g.* [3]). For example, upon recovery, a host may be fully immune, before becoming susceptible again to infection. The distribution of this initial period of immunity, in addition to its average duration and to the relative susceptibility (to reinfection) following immune waning, are important characteristics that determine an individual's likelihood for reinfection throughout their life. In tandem, infections can lead to disease-induced mortality both during infection and after recovery. While characteristics of such mortality and immunity have an immediate individual-level impact, the potential combined effects of these factors on population-level dynamics are less clear. In this paper, we investigated these effects and found they can complicate the dynamics at endemicity.

Using a simple immuno-epidemiological model, we titrated the effects of immunity and disease-induced mortality on pathogen dynamics. We first showed that our model has a unique endemic equilibrium when the basic reproduction number is greater than 1. In settings where $\mathcal{R}_0$ exceeds 1, we then focused on whether this endemic state is stable or unstable. In particular, if individuals return to complete susceptibility, we analytically proved that this equilibrium cannot be destabilized by disease-induced mortality during infection or while immune (after recovery) if there are at most two recovered compartments. However, in other settings, the dynamics are more complicated. In particular, we numerically found that disease-induced mortality can both stabilize and destabilize this equilibrium, and which occurs depends on the particular setting. Furthermore, if there is disease-induced mortality after infection and once hosts have returned to susceptibility, we find that larger values of average immune period length can potentially first stabilize, then destabilize, and then (re)stabilize the endemic equilibrium (*i.e.* three changes to stability).

Overall, our model reveals surprisingly complicated effects that can emerge from immunity and disease-induced mortality. Since our model is relatively simple, these findings stress the need to include characteristics of immunity and disease-induced mortality in more complex epidemiological models. While we have focused on a conceptual model to titrate the effects of immunity and disease-induced mortality on epidemic dynamics, refined epidemiological models that move beyond this framework, and are applied to specific diseases and settings, will be needed to examine the potential implications and ensuing recommendations for public health officials. Finally, our work highlights the importance of properly quantifying the characteristics of immunity and disease-induced mortality for epidemiological predictions. To measure rates of disease-induced mortality after recovery, and to characterize the features of immunity (including the distribution of its duration), large-scale cohort immuno-epidemiological studies, as outlined in [23], are required. These will also clarify the impacts of pathogen characteristics (such as novel variants), as well as those of hosts (such as age-structure). With these data, appropriate models (such as multi-group models with group-specific immunity and disease-induced mortality parameters), structured with age and with multiple variants, could be formulated and parameterized.

Supplementary information

S1 Appendix This file is the Supplementary Information that accompanies the main text.
(PDF)

S1 Code This code generates the figures.
(R)

Author contributions

Conceptualization: Chadi M. Saad-Roy.

Formal analysis: Chadi M. Saad-Roy, Pauline van den Driessche.

Investigation: Chadi M. Saad-Roy, Mike Boots, Pauline van den Driessche.

Writing – original draft: Chadi M. Saad-Roy.

Writing – review & editing: Chadi M. Saad-Roy, Mike Boots, Pauline van den Driessche.

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