Modelling the evolutionary dynamics of an infectious disease with an initial asymptomatic infection stage with recovery

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Abstract. The study of infectious disease dynamics is an ongoing challenge, particularly due to the varied life-history strategies that pathogens exhibit. The ongoing COVID-19 pandemic has emphasised the importance of studying the dynamics of pathogens that allow for an asymptomatic stage (termed latency in this paper) and direct recovery from said asymptomatic stage. Here, we expand on a simple epidemiological model, introduced by Saad-Roy et al. (2020), in order to understand the evolutionary dynamics of allowing for direct recovery of infected, latent individuals. In this model, there are two infectious stages; in the first infectious stage, hosts are fully or partially asymptomatic, and there is a trade-off between transmission and progression. We consider arbitrary trade-offs and the specific case of power-law trade-offs. Through introducing the added parameter of direct recovery from latent infection (hence termed r), we show that there are 4 possible evolutionary stable strategies (ESSs) a pathogen can adopt, depending on the values of other parameters. However, when direct recovery is fast (i.e. at high values of r), the ESSs eventually collapse into one where there is zero latency (i.e. no asymptomatic stage). Overall, our findings suggest that more importance should be given to studying the role of asymptomatic individuals in infectious disease outbreaks and the rate at which they can recover without developing any symptoms.

1. Introduction.

Understanding disease dynamics has and continues to remain a challenge, particularly as various pathogens can take on different life-history strategies. These life-history strategies are shaped by the selection pressures pathogens are under, and can result in pathogens being able to switch to a new host species, and/or evolve to form new strains in current host species [18][8], which in turn can give rise to epidemics or pandemics, such as the ongoing Coronavirus Disease 2019 (COVID-19) pandemic.

One life-history strategy a pathogen could take involves a latent stage before the main infectious period, where the latent stage is defined as the period from when a host is first infectious to when they first start showing symptoms. These latent stages can potentially provide selective advantages to pathogens by increasing the likelihood of spreading among more hosts, particularly since hosts will exhibit no to few symptoms (thus reducing symptom avoidance behaviours and increasing contact with other susceptible individuals) [12]. However, latency itself is also subject to trade-offs with other factors like viral load and transmission; for example, it is likely that asymptomatic and/or less symptomatic individuals would transmit a lower viral load and/or with a lower transmission rate [18]. Therefore, understanding the evolutionarily stable strategies (ESSs) and the role of trade-offs in evolutionary outcomes of pathogens can provide insights into disease dynamics and control, so that future outbreaks of infectious disease could be better understood and controlled [1][11].

Compartmental modelling has been used extensively to study and predict disease dynamics since its conception by Kermack and Mckendrick in 1927 [10]. These models, known as the

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Susceptible-Infectious-Recovered (SIR) models, are typically a deterministic system of non-linear ordinary differential equations that have been useful in not only predicting how a disease can spread and the relevant epidemiological parameters, but also in informing public health action in curbing the spread of infectious diseases [14].

Saad-Roy et al. (2020) had previously formulated an epidemiological model and studied the evolutionary stable strategies (ESS) of latency based on trade-offs between transmission and progression, and found that there were 4 possible ESSs: fully asymptomatic, less symptomatic, fully symptomatic or bistability between fully symptomatic and fully asymptomatic first stages [18]. However, this model did not consider cases in which patients in the latent stage could directly recover from the infection and how that would affect the evolutionary pathway taken by a pathogenic agent with respect to latency. This is especially pertinent in light of the COVID-19 pandemic, where asymptomatic and mildly symptomatic patients have been found to not only be infectious, but also recovery directly from being infectious but asymptomatic [13]. Here, we define symptoms as those that would be recognised by a host without the need for detection. As there are diseases like COVID-19, where "asymptomatic" patients might nevertheless incur physiological problems that can only be detected upon further diagnostic scans [3], there is a need for this definition to be specified.

That hosts can recover directly from being infectious but asymptomatic is a plausible stage in the natural history of SARS-CoV-2 has meant that controlling the spread of the disease outbreak has been particularly challenging and required the usage of strong mitigation measures like contact tracing and so-called lockdowns [17], which refer to a set of restrictive, government-imposed non-pharmaceutical interventions such as stay-at-home orders and movement restrictions. Furthermore, variants have been developing at a comparable rate since the first emergence of the initial SARS-CoV-2 variant in Wuhan, China, [6][7], and these variants in turn have been characterised to be more transmissible and resulting in more severe disease [4]. As various public health measures continue to be imposed and vaccination programmes are underway in several countries, this has led to concerns about what needs to be done in response to the new variants and the potentially different disease dynamics they can bring about. Therefore, understanding the role of asymptomatic individuals and what happens when they can recover without developing symptoms could be essential for informing subsequent disease control strategies in response to future outbreaks.

Here, we investigate how the rate of direct recovery from an asymptomatic stage affects the evolutionary dynamics of an infectious disease, as well as ESSs of latency, directly building on the model developed by Saad-Roy et al. (2020) [18]. We show that while the 4 ESS outcomes presented by Saad-Roy et al. can be attained in our model, this is only possible when direct recovery from asymptomatic infection occurs at very low rates. At higher rates of direct recovery, we observe that the ESS is more likely to be that of a no initial asymptomatic stage.

2. Model.

Our model is based on the model formulated by Saad-Roy et al. (2020), where they studied the evolutionary dynamics of a disease with an initial asymptomatic stage where all hosts eventually progressed to a fully symptomatic second stage [18]. Our goal in this study is to study how these evolutionary dynamics are affected when some hosts are able to recover directly from the initial asymptomatic infectious stage and hence, bypass progression to the fully symptomatic second infectious stage [19].

Parameter	Definition
δ	natural demographic birth and death rate
ω	loss of immunity rate
β_1	rate of infectivity from first infectious stage
β_2	rate of infectivity from second infectious stage
v_1	rate of progression from first infectious stage to second infectious stage
r	recovery rate, from first infectious stage only
v_2	recovery rate, from second infectious stage

Table 1: Model parameters and their definitions. Refer to Figure 1 for a schematic of the model. Adapted from Saad-Roy et al. (2020).

Our model is formulated in terms of fractions, such that all of the compartments add up to 1, which represents the total population. For simplicity, we do not consider death due to disease and therefore assume that the population is at demographic equilibrium [18]. The host population is partitioned into four classes, where we denote the fraction of individuals susceptible to the disease by S, infectious hosts in the initial asymptomatic stage by I_1 and in the fully symptomatic stage by I_2, and the recovered fraction by R.

We assume the natural demographic rate (birth and death) to be $\delta > 0$ and the rate of loss of immunity to be $\omega \geq 0$, meaning that a host is immune for time $\frac{1}{\omega}$ when $\omega > 0$. We also assume that a host in I_1 transmits at rate β_1, progresses to I_2 at rate v_1, and progresses to R at rate r. When a host is fully symptomatic and at compartment I_2, we assume that the host stays in it on average $\frac{1}{v_2}$ and transmits at rate β_2. We formulate the epidemiological model, also visualised in Figure 1, known as the Susceptible-Infectious(I_1, less symptomatic)-Infectious(I_2, fully symptomatic)-Recovered (SIIRS) model, as such [16][18]:

$$\frac{dS}{dt} = \delta - \delta S - \beta_1 S I_1 - \beta_2 S I_2 + \omega R \tag{2.1a}$$

$$\frac{dI_1}{dt} = \beta_1 S I_1 + \beta_2 S I_2 - (v_1 + r + \delta) I_1 \tag{2.1b}$$

$$\frac{dI_2}{dt} = v_1 I_1 - (v_2 + \delta) I_2 \tag{2.1c}$$

$$\frac{dR}{dt} = v_2 I_2 + r I_1 - (\omega + \delta) R \tag{2.1d}$$

3. Epidemiological and Evolutionary Dynamics of the Model.

3.1. Epidemiological Dynamics of the model. The basic reproduction number, R_0, of a disease is defined as the average number of secondary cases that arise from a single primary case in a completely susceptible population. R_0 is often an important indicator in determining epidemiological dynamics, and has been used as a reference for informing public health responses to infectious diseases. $R_0 = 1$ serves as a threshold, where $R_0 < 1$ normally implies that a disease will die out and $R_0 > 1$ implies persistence. However, in some cases $R_0 < 1$ can lead to a coexistence of equilibria (one unstable, one locally stable) with disease and the disease-free equilibrium [19].

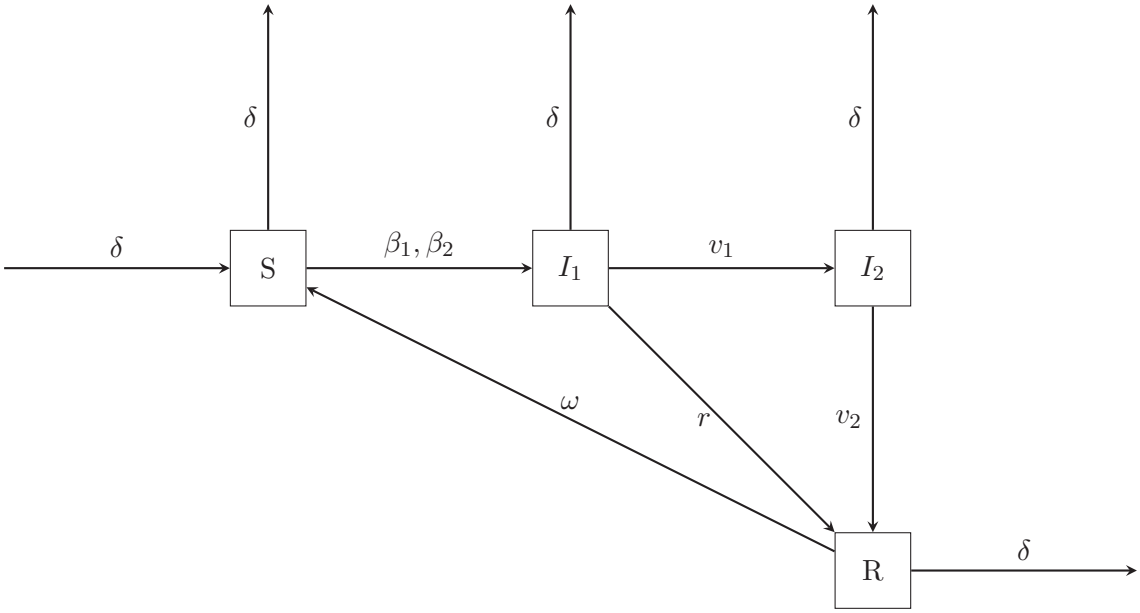

Figure 1: Schematic of the SIIRS model and its compartments, where S = susceptible individuals, I_1 = infectious but asymptomatic/less symptomatic individuals, I_2 = infectious and fully symptomatic individuals, R = recovered individuals. Refer to Table 1 for the definition of model parameters.

We compute R_0 using the next-generation matrix approach [19], which gives

$$R_0 = \frac{\beta_1}{v_1 + r + \delta} + \frac{v_1 \beta_2}{(v_1 + r + \delta)(v_2 + \delta)}$$

where $\frac{\beta_1}{v_1+r+\delta}$ and $\frac{\beta_2}{(v_2+\delta)}$ represent the average number of infections arising from a host in I_1 and I_2 respectively, and $\frac{v_1}{(v_1+r+\delta)}$ represents the probability of a host progressing from I_1 to I_2.

In this SIIRS model, when there are no cases or when $R_0 < 1$, a disease-free equilibrium exists such that all the population falls under S, i.e. S=1. When $R_0 > 1$, a unique endemic equilibrium $\hat{E}$ with a positive fraction of infections exists where

$\hat{S} = \frac{1}{R_0}$,

$\hat{I_1} = \frac{(1-\frac{1}{R_0})}{1+\frac{v_1}{v_2+\delta}+\frac{r}{\mu+\delta}+(\frac{v_2}{\omega+\delta})(\frac{v_1}{v_2+\delta})}$,

$\hat{I_2} = \frac{v_1}{v_2+\delta}\hat{I_1}$, and

$\hat{R} = ((\frac{v_2}{\omega+\delta})(\frac{v_1}{v_2+\delta}) + \frac{r}{\omega+\delta})\hat{I_1}$.

3.2. Evolutionary Dynamics of the model. Having established the epidemiological dynamics of our model, in this section, we study the evolutionary dynamics of our model with

respect to latency, λ. $\lambda = 0$ denotes that the first stage of infection is fully symptomatic, that is I_1 and I_2 are indistinguishable, and $\lambda \to \infty$ means that the first stage is fully asymptomatic. Similar to Saad-Roy et al., we study the conditions under which an initial asymptomatic or mildly symptomatic stage is advantageous to an infectious pathogen, particularly when there is an additional parameter r, the rate of transition from I_1 to R (in other words, some mildly asymptomatic or asymptomatic patients recover without becoming fully symptomatic).

As in Saad-Roy et al. (2020), the following assumptions hold in this model: a host currently infected with an existing pathogen cannot be coinfected with the invading mutant, and a host resistant to the endemic pathogen is also resistant to the mutant pathogen. Additionally, it is assumed throughout the section that $R_0 > 1$ and that the population is at the equilibrium $\hat{E}$. Given all these assumptions, in our model, maximising fitness would be equivalent to achieving a maximum value of R_0, since R_0 is a measure of the number of successful infections by an infectious host. This would be equivalent to achieving a minimum fraction of susceptibles (S) at endemic equilibrium as $\hat{S} = \frac{1}{R_0}$. Thus, for a mutant pathogen (with strategy λ) to successfully invade and replace the resident pathogen (with strategy $\bar{\lambda}$), the mutant pathogen strategy must lead to a lower number of susceptibles than the resident pathogen strategy, i.e. a higher value of R_0.

At the I_1 stage, we consider a trade-off between progression to stage I_2 and transmission, due to both traits being functions of λ. For instance, a lower pathogenic load could mean having an initial stage with decreased transmissibility, but could also result in having an initial stage where there are fewer or no symptoms but a longer infectious period (potentially allowing for a larger number of infections).

Hence, R_0 can be represented as a strategy of λ as such:

$$R_0[\lambda] = \frac{\beta_1[\lambda]}{v_1[\lambda] + r + \delta} + \frac{\beta_2 v_1[\lambda]}{(v_2 + \delta)(v_1[\lambda] + r + \delta)} \tag{3.1}$$

where β_1 and v_1 are functions of λ.

3.3. General Forms of Trade-offs. Here, we consider general forms of trade-off between transmission and progression, and simply assume that transmission and progression approach a fixed value as $\lambda \to \infty$ [i.e. $\beta_1[\infty]$ and $v_1[\infty]$ are fixed constants] (see Appendix A.1 for detailed calculations). We consider a general trade-off form in order to elucidate what conditions would give rise to different evolutionarily stable strategies and use this to explore specific trade-off functions, such as that of Subsection 3.4, as well as the effect of r on the evolutionary dynamics of the model.

Let $R_0[0]$ represent R_0 when there is no latency and $R_0[\infty]$ represent R_0 when there is full latency.

If

$$R_0[0] > R_0[\infty]$$

and

$$\beta_1'[0] > \frac{v_1'[0]}{v_1[0] + r + \delta}(\beta_1[0] - \frac{\beta_2}{v_2 + \delta}(r + \delta))$$

there exists at least one local fitness maximum, which is representative of an evolutionary stable strategy, λ^*. Note that the condition on $\beta_1^{'}[0]$ above corresponds to the case where R_0 is increasing in λ at $\lambda = 0$.

Else, for

$$\beta_1^{'}[0] > \frac{v_1^{'}[0]}{v_1[0] + r + \delta}(\beta_1[0] - \frac{\beta_2}{v_2 + \delta}(r + \delta)),$$

and

$$R_0[0] < R_0[\infty]$$

$R_0[0]$ is not an ESS, and if $\beta_1^{'}[0]$ is additionally positive for all λ between 0 and ∞, then $R_0[\lambda]$ is a strictly increasing function with ESS $\lambda^* \to \infty$.

Conversely, if

$$\beta_1^{'}[0] < \frac{v_1^{'}[0]}{v_1[0] + r + \delta}(\beta_1[0] - \frac{\beta_2}{v_2 + \delta}(r + \delta))$$

and

$$R_0[0] < R_0[\infty],$$

there exists at least one local minimum (unstable evolutionary singular strategy), resulting in bistability between $\lambda = 0$ and some/full latency.

Else, if

$$\beta_1^{'}[0] < \frac{v_1^{'}[0]}{v_1[0] + r + \delta}(\beta_1[0] - \frac{\beta_2}{v_2 + \delta}(r + \delta))$$

and

$$R_0[0] > R_0[\infty],$$

then $\lambda^* = 0$ is an ESS. If $R_0[\lambda]$ is strictly decreasing, then $\lambda^* = 0$ is the only ESS.

3.4. Specific Trade-Offs. In this case, we assume that the rates of change of transmission rates $(\beta_1[\lambda], v_1[\lambda])$ increase as latency decreases, and this can be represented by the assumed functional forms below:

$$\beta_1[\lambda] = b_1(\lambda + 1)^{-b_2} + \beta_1[\infty] \tag{3.2}$$

$$v_1[\lambda] = c_1(\lambda + 1)^{-c_2} + v_1[\infty] \tag{3.3}$$

where all coefficients, exponents and constants are positive real numbers.

There are a number of cases to consider, which in turn give rise to a number of possible evolutionary stable strategies depending on the relationships between the parameters (see Appendix A.2 for detailed calculations and explanations).

3.4.1. Case 1: $\frac{\beta_2}{v_2+\delta} - \frac{\beta_{1,\infty}}{r+\delta} \geq 0$. Suppose the average number of infections caused by individuals in the second stage ($\frac{\beta_2}{v_2+\delta}$, which will also be referred to as k (see also Figure 3)) is greater than or equal to the maximally latent rate of transmission times the duration spent in I_1 without progressing to I_2 ($\frac{\beta_{1,\infty}}{r+\delta}$), i.e. the average number of infections caused by individuals in the maximally latent first stage who did not progress to the second stage:

If

$$\frac{b_1 b_2}{c_1 c_2} < \frac{\beta_{1,0} - \frac{\beta_2}{v_2+\delta}(r+\delta)}{v_{1,0}+\delta+r} \tag{3.4}$$

then $R_0[\lambda]$ has a local maximum, i.e. there is a unique positive ESS. Conversely, if (3.4) does not hold, then $R_0[\lambda]$ is strictly decreasing and the ESS is when $\lambda = 0$.

3.4.2. Case 2: $\frac{\beta_2}{v_2+\delta} - \frac{\beta_{1,\infty}}{r+\delta} < 0$. Conversely, supposing that $\frac{\beta_2}{v_2+\delta} - \frac{\beta_{1,\infty}}{r+\delta} < 0$, the evolutionary outcomes are dependent on how fast transmission rate (b_2) and progression rate (c_2) decay relative to each other.

Sub-case 2a: $c_2 > b_2$

In this case, transmission rate decays more slowly than progression rate, and the outcomes are similar to that of Case 1, depending on whether equation (3.4) holds. If (3.4) holds, then there is a unique positive ESS, otherwise, $R_0[\lambda]$ is strictly decreasing and the ESS is when $\lambda = 0$.

Sub-case 2b: $c_2 < b_2$

In this case, progression rate decays more slowly than transmission rate. If equation (3.4) holds, then $R_0[\lambda]$ is strictly increasing, and ESS is $\lambda^* \to \infty$. Conversely, if (3.4) does not hold, then $R_0[\lambda]$ has a local minimum, which is an unstable evolutionary singular strategy. This therefore gives rise to bistable ESSs at zero and maximal latency.

A summary of all possible ESSs described above and the necessary conditions can be found in Figure 2.

	$\frac{\beta_2}{v_2+\delta} - \frac{\beta_{1,\infty}}{r+\delta} \geq 0$	$\frac{\beta_2}{v_2+\delta} - \frac{\beta_{1,\infty}}{r+\delta} < 0$	
		$c_2 > b_2$	$c_2 < b_2$
$\frac{b_1 b_2}{c_1 c_2} < \frac{\beta_{1,0} - \frac{\beta_2}{v_2+\delta}(r+\delta)}{v_{1,0}+\delta+r}$	$0 < \lambda^* < \infty$	$0 < \lambda^* < \infty$	$\lambda^* \to \infty$
$\frac{b_1 b_2}{c_1 c_2} > \frac{\beta_{1,0} - \frac{\beta_2}{v_2+\delta}(r+\delta)}{v_{1,0}+\delta+r}$	$\lambda^* = 0$	$\lambda^* = 0$	Bistable ESSs: $\lambda^* = 0$ and $\lambda^* \to \infty$

Figure 2: A summary table of the possible ESSs with respect to latency and the conditions in which they can be attained, as described in Subsection 3.4. Conditions are summarised in white cells and ESSs are summarised in grey cells.

4. The effect of r on the evolutionary dynamics of the M odel. In the previous sections, we show that the addition of an additional parameter, r (the rate of direct recovery from

the initial latent stage), can still produce the ESS outcomes determined for the various cases and sub-cases determined by Saad-Roy et al. (2020). Here, we further discuss the effect of changing the value of r on ESS outcomes and evolutionary pathways with respect to Specific Trade-Offs.

Figure 3 depicts a pictorial representation of how changing the value of r affects the possible ESS outcomes across different parameter regimes. In general, for the same set of parameters and fixed value of latency, as r increases in value, the value of R_0 decreases, thus suggesting that in the specific trade-off condition (transmission vs latency) of this model, allowing for direct recovery from a latent/less symptomatic stage might have some negative effect on fitness of the infectious agent.

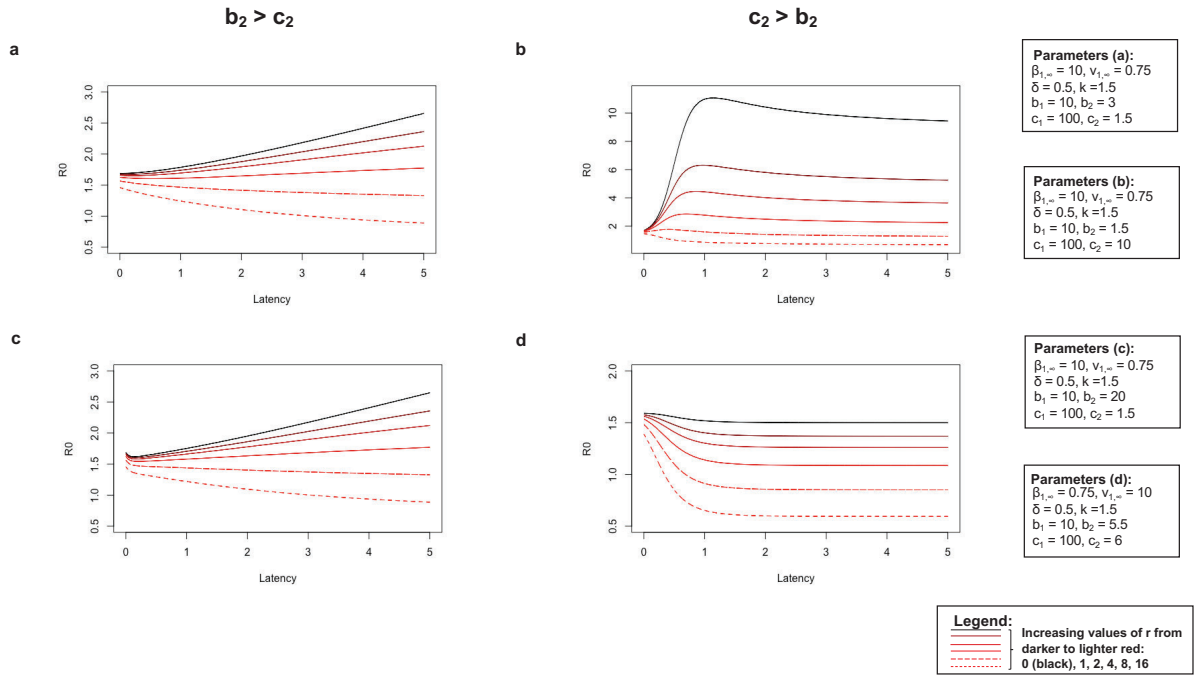

Figure 3: Pictorial representation of how, under specific trade-off conditions, different values of r affect the evolutionary pathways of $R_0[\lambda]$; the left column (a, c) show cases where $b_2 > c_2$, the right column (b, d) where $c_2 > b_2$. Here, the term $\frac{\beta_2}{v_2+\delta}$ will be represented by the parameter, k. Values of r used = 0 (black), 1 (darkest red), 2, 4, 8 (long dashed line), 16 (lightest red, short dashed line). For a, values of other parameters used: $\beta_{1,\infty} = 1$, $v_{1,\infty} = 0.75$, $\delta = 0.5$, $k = 1.5$, $b_1 = 0.2$, $b_2 = 3$, $c_1 = 100$, $c_2 = 1.5$. For b, values of other parameters used: $\beta_{1,\infty} = 1$, $v_{1,\infty} = 0.75$, $\delta = 0.5$, $k = 1.5$, $b_1 = 0.2$, $b_2 = 1.5$, $c_1 = 100$, $c_2 = 3$. For c, values of other parameters used: $\beta_{1,\infty} = 10$, $v_{1,\infty} = 0.75$, $\delta = 0.5$, $k = 1.5$, $b_1 = 10$, $b_2 = 1.5$, $c_1 = 100$, $c_2 = 1.5$. For d, values of other parameters used: $\beta_{1,\infty} = 0.5$, $v_{1,\infty} = 0.75$, $\delta = 0.5$, $k = 1.5$, $b_1 = 10$, $b_2 = 1.5$, $c_1 = 100$, $c_2 = 10$.

There are a number of possible pathways on how ESS might shift as r increases:

1. If the initial ESS is $\lambda^* \to \infty$, the ESS will eventually shift to bistable ESSs at zero and

maximal latency and then eventually to $\lambda = 0$ (Fig. 2a),

2. If there are initially bistable ESSs at zero and maximal latency, the ESS will eventually shift to $\lambda = 0$ (Fig. 2c),

3. If there is a unique positive ESS when $r = 0$ initially, the ESS will shift to $\lambda = 0$ as the value of r increases (Fig. 2b),

and finally,

4. If the initial ESS is $\lambda = 0$ when $r = 0$, the ESS will remain at $\lambda = 0$ (Fig. 2d).

In other words, as r increases, (3.4) is less likely to hold true and Case 1 is more likely to hold true, resulting in the ESS eventually shifting to $\lambda = 0$ beyond certain values of r. This seems to hold true regardless of the parameter regime and the initial ESS when $r = 0$. The model would effectively reduce to an SIRS epidemiological model, and r would be incorporated into the rate of recovery from the (single) infectious stage.

Thus, while Subsection 3.2 demonstrates the possibility of 4 ESS outcomes (similarly outlined in Saad-Roy et al. (2020)), here, we show that having any one of the 4 ESS outcomes is only possible at low values of r, and the 4 outcomes collapse into 1 ESS outcome (i.e. no latency), at higher values of r.

5. Discussion. Several infectious diseases have a less symptomatic or even completely asymptomatic stage, during which the infected host is still able to transmit the disease before progressing to a fully symptomatic stage or even directly to recovery. Identifying such a stage in infectious diseases is important as it forms an essential part of the natural history of the disease, which in turn is required to designing appropriate intervention and control mechanisms.

Here, we studied how introducing a pathway of direct recovery from a mildly symptomatic/fully asymptomatic stage (represented by the parameter r) in an SIIRS epidemiological model developed by Saad-Roy et al. (2020) could affect the evolutionary stable strategy (ESS) of an infectious disease with respect to latency, λ, i.e. how asymptomatic the initial stage of infection is.

Through the addition of the parameter r, we found that the findings of Saad-Roy et al. are most likely to be applicable only when the value of r is not too large. Instead, at very high values of r, the ESS tends to be $\lambda = 0$ regardless of the values of other parameters. This suggests that there might be some form of evolutionary trade-off between latency and direct progression into recovery from an initial less symptomatic stage. In the epidemiological context of the disease, a higher rate of direct recovery would mean that upon entering the first infectious stage, infected individuals spend a shorter time remaining infectious (and thus being able to infect more susceptibles). Therefore, selection should favour increasing and prolonging the infectiousness of infected individuals and hence increase the number of infections in the population. In the specific example of our specific trade-off case, decreasing the latency would result in an increase in transmission and progression rates (see Equation (3.2) and Equation (3.3)) of I_1 individuals, thus prolonging infectiousness of infected individuals.

Furthermore, viral load and shedding may also be lower in I_1 individuals compared to I_2 individuals [16]. If I_1 individuals are clearing the infection at a faster rate than they are producing secondary infections, it would be evolutionarily advantageous for a pathogen to have to low latency or even no latency at all. However, given the confusion over the

true infectiousness of asymptomatic compared to symptomatic infected individuals and the variation in different pathogens [16][20][15], more needs to be done to understand the true infectivity of asymptomatic infectious carriers and more accurately model their behaviour and interactions. Regardless, the findings of our model highlight the importance of studying asymptomatic carriers and their recovery without further progression to full symptomaticity even at low levels of occurrence, as the evolutionary outcomes of the pathogen can vary and accordingly, the type of public health interventions that are useful and necessary to implement.

Asymptomatic carriers have been understood to significantly propagate the spread of several diseases such as influenza, Ebola virus, community-mediated methicillin-resistant *Staphylococcus aureus* (MRSA), and more recently, COVID-19. Particularly in the context of the ongoing COVID-19 pandemic, studies have estimated the percentage of asymptomatic carriers to be at least 15%, and that the infectiousness of these asymptomatic carriers is similar to that of fully symptomatic patients[20].

However, asymptomatic carriers are often difficult to detect unless they are actively tested. This means that in most cases, only symptomatic cases (or initially asymptomatic/mildly symptomatic cases that later developed all clinical symptoms) are detected, which makes interpreting the natural history of the disease accurately more difficult. Therefore, epidemiological models such as the one we have presented here can be useful in providing predictions about how future strains are likely to evolve, and this information can be used to inform public health decisions to control the spread of infectious diseases. In fact, predicting the parameters of so-called Susceptible-Asymptomatic-Infected-Removed (SAIR) models, such as the one used in this paper, have been able to explain how the course of the COVID-19 pandemic took place across different countries [2]. Additionally, a study by Gumel et al. (2021)[9], which modelled the ongoing COVID-19 pandemic using a similar compartmental model to the one used in this paper showed that the rate at which asymptomatic individuals recovered from infection (i.e. r in our model) was one of the parameters that had the most effect on and was negatively correlated to R_0, similar to what our model suggests.

Nevertheless, there still runs a risk of incorrectly modelling diseases and therefore incorrectly assessing the viability and effectiveness of an intervention in preventing disease outbreaks [5]. All of this makes it all the more important that more data is collected about asymptomatic carriers, and the COVID-19 pandemic is only one such example to illustrate this importance.

5.1. Future Directions. In this model, direct recovery rate from an initial asymptomatic stage (r) was treated as an arbitrary constant; however, it is likely that r itself has some sort of trade-off relationship with respect to latency and other factors. Therefore, it would be interesting to model the effect of r on the evolutionary pathways, where r assumes a functional form demonstrating some trade-off relationship with latency. To understand what sort of relationship r might have with latency, such an extension of this model could also be compared with empirical data from infectious pathogens with a life-history including a latent stage.

Future extensions of our model could also include modelling social behaviours, such as contact tracing and/or quarantine immediately after diagnosis, and studying the effect these behaviours have on r and other parameters, and how that, in turn, affects transmission trade-offs

and evolutionary pathways. It would also be interesting to consider how vaccine or treatment regimes can alter the evolutionary pathways with respect to latency, so that informed public health decisions can be made accordingly in response to future epidemic and/or pandemic outbreaks.

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Appendix A. Evolutionary Dynamics. In all sections, when finding the maxima for R_0, we set the first derivative to 0.

A.1. General Trade-Offs. In the case of general trade-offs,

$$R_0[\lambda] = \frac{\beta_1[\lambda]}{v_1[\lambda] + r + \delta} + \frac{\beta_2 v_1[\lambda]}{(v_1[\lambda] + r + \delta)(v_2 + \delta)}$$

$$\frac{dR_0[\lambda]}{d\lambda} = \frac{1}{v_1[\lambda] + r + \delta}(\beta_1'[\lambda] + \frac{\beta_2 v_1'[\lambda]}{v_2 + \delta}) - \frac{v_1'[\lambda]}{(v_1[\lambda] + r + \delta)^2}(\beta_1 + \frac{\beta_2 v_1[\lambda]}{v_2 + \delta})$$

At the evolutionarily stable strategy (ESS) for a particular viral strain, R_0 is a maximum in the evolutionary landscape. For that, $\frac{dR_0[\lambda]}{d\lambda} = 0$ at a particular value(s) of latency, which could be 0, ∞, or a positive real number, denoted as λ^*.

Therefore, for the ESS to exist at a particular value of latency, $\lambda^* > 0$,

$$\frac{dR_0[\lambda]}{d\lambda} = 0$$

and

$$\frac{dR_0[\lambda]}{d\lambda}\Big|_{\lambda=0} > 0$$

This will occur iff

$$\frac{1}{v_1[0]+r+\delta}(\beta_1^{'}[0]+\frac{\beta_2 v_1^{'}[0]}{v_2+\delta}) > \frac{v_1^{'}[0]}{(v_1[0]+r+\delta)^2}(\beta_1[0]+\frac{\beta_2 v_1[0]}{v_2+\delta})$$

which simplifies to:

$$\beta_1^{'}[0] > \frac{v_1^{'}[0]}{v_1[0]+r+\delta}(\beta_1[0]-\frac{\beta_2}{v_2+\delta}(r+\delta))$$

Suppose that $\lim_{\lambda\to\infty}\beta_1^{'}[\lambda]=0$ and $\lim_{\lambda\to\infty}v_1^{'}[\lambda]=0$

if $R_0[0]>R_0[\infty]$ and $\beta_1^{'}[0]>\frac{v_1^{'}[0]}{v_1[0]+r+\delta}(\beta_1[0]-\frac{\beta_2}{v_2+\delta}(r+\delta))$, there exists at least one local maximum, which is representative of an evolutionary stable strategy, λ^*.

Else, for $\beta_1^{'}[0]>\frac{v_1^{'}[0]}{v_1[0]+r+\delta}(\beta_1[0]-\frac{\beta_2}{v_2+\delta}(r+\delta))$, $R_0[\lambda]$ is a strictly increasing function with ESS $\lambda^*\to\infty$.

Conversely, if $\beta_1^{'}[0]<\frac{v_1^{'}[0]}{v_1[0]+r+\delta}(\beta_1[0]-\frac{\beta_2}{v_2+\delta}(r+\delta))$ and $R_0[0]<R_0[\infty]$, there exists at least one local minimum (unstable evolutionary singular strategy), resulting in bistability between $\lambda=0$ and some/full latency.

Else, if $\beta_1^{'}[0]<\frac{v_1^{'}[0]}{v_1[0]+r+\delta}(\beta_1[0]-\frac{\beta_2}{v_2+\delta}(r+\delta))$ and $R_0[0]>R_0[\infty]$, then $R_0[\lambda]$ is a strictly decreasing function with $\lambda^*=0$.

A.2. Specific Trade-Offs. For the specific case where trade-offs take on power-law or exponential functional forms,

$$R_0[\lambda]=\frac{1}{(c_1[\lambda+1]^{-c_2}+v_{1,\infty}+r+\delta)}(b_1[\lambda+1]^{-b_2}+\beta_{1,\infty}+\frac{\beta_2}{v_2+\delta}(c_1[\lambda+1]^{-c_2}+v_{1,\infty}))$$

$$\begin{aligned}\frac{dR_0[\lambda]}{d\lambda} &= -\frac{1}{(c_1[\lambda+1]^{-c_2}+v_{1,\infty}+r+\delta)}(b_1b_2[\lambda+1]^{-b_2-1}+\frac{\beta_2}{v_2+\delta}c_1c_2[\lambda+1]^{-c_2-1})\\ &+\frac{c_1c_2[\lambda+1]^{-c_2-1}}{(c_1[\lambda+1]^{-c_2}+v_{1,\infty}+r+\delta)^2}(b_1[\lambda+1]^{-b_2}+\beta_{1,\infty}+\frac{\beta_2}{v_2+\delta}(c_1[\lambda+1]^{-c_2}+v_{1,\infty}))\end{aligned}$$

which, after multiplying by
$((c_1[\lambda+1]^{-c_2}+v_{1,\infty}+r+\delta)^2\cdot(-\frac{[\lambda+1]^{b_2+c_2+1}}{b_1b_2}))$
and rearranging simplifies to:

$$\begin{aligned}c_1-\frac{c_1c_2}{b_2}+(v_{1,\infty}+r+\delta)[\lambda+1]^{c_2}+\frac{c_1c_2}{b_1b_2}(r+\delta)(\frac{\beta_2}{v_2+\delta}-\frac{\beta_{1,\infty}}{r+\delta})[\lambda+1]^{b_2}\\ =f[\lambda]\end{aligned}$$

$$f[\lambda]=A_0+A_1[\lambda+1]^{c_2}+A_2[\lambda+1]^{b_2}$$

where:

$$A_0 = c_1 - \frac{c_1 c_2}{b_2}, \quad A_1 = v_{1,\infty} + r + \delta, \quad A_2 = \frac{c_1 c_2}{b_1 b_2}(r+\delta)(\frac{\beta_2}{v_2+\delta} - \frac{\beta_{1,\infty}}{r+\delta})$$

$\frac{dR_0[\lambda]}{d\lambda} = -K[\lambda]f[\lambda]$, $K[\lambda] > 0$ for all λ,
where $K[\lambda] = (c_1[\lambda+1]^{-c_2} + v_{1,\infty} + r + \delta)^2 \cdot (-\frac{[\lambda+1]^{b_2+c_2+1}}{b_1 b_2})$
This means that at $\lambda = 0$, $f[0] = A_0 + A_1 + A_2 < 0$ for $\frac{dR_0[\lambda]}{d\lambda} > 0$ to hold true.
There are a number of conditions in which this condition can be satisfied.
Case 1: $\frac{\beta_2}{v_2+\delta} - \frac{\beta_{1,\infty}}{r+\delta} \geq 0$
$A_2 \geq 0$, hence $f[\lambda]$ is strictly increasing from $A_0 + A_1 + A_2$ to ∞. If $f[0] < 0$, then $f[\lambda]$ crosses the λ-axis once, and there is a max R_0 at λ^*, where $0 < \lambda^* < \infty$.

For that, $A_0 + A_1 + A_2 < 0$, which when rearranged, gives rise to the following condition that needs to be satisfied for $0 < \lambda^* < \infty$:

$$\frac{b_1 b_2}{c_1 c_2} < \frac{\beta_{1,0} - \frac{\beta_2}{v_2+\delta}(r+\delta)}{v_{1,0} + \delta + r}$$

Else, if $f[0] = 0$, then $\frac{dR_0[\lambda]}{d\lambda}\Big|_{\lambda=0} = 0$, and $\lambda^* = 0$. Similarly, if $f[0] > 0$, then $\frac{dR_0[\lambda]}{d\lambda}\Big|_{\lambda=0} < 0$ and $R_0[\lambda]$ is a strictly decreasing function, thus $\lambda^* = 0$.
Case 2: $\frac{\beta_2}{v_2+\delta} - \frac{\beta_{1,\infty}}{r+\delta} < 0$
In this case, $A_2 < 0$, so there are additional cases to consider:
Sub-case 2a: $A_0 < 0$, i.e. $c_2 > b_2$
rearranging $f[\lambda] = 0$ and multiplying each side by $[\lambda+1]^{-b_2}$ gives:

$$A_1[\lambda+1]^{c_2-b_2} = -A_0[\lambda+1]^{-b_2} - A_2$$

where $A_1, -A_0, -A_2 > 0$
let

$$g_1[\lambda] = A_1[\lambda+1]^{c_2-b_2}$$

$$g_2[\lambda] = -A_0[\lambda+1]^{-b_2} - A_2$$

$g_1[\lambda]$ is a strictly increasing function from A_1 to ∞, while $g_2[\lambda]$ is a strictly decreasing function from $-(A_0 + A_2)$ to $-A_2$.

If $g_1[0] < g_2[0]$, then both g_1 and $g_2[0]$ will intersect at least once $\Rightarrow$ such an intersection is a root of $f[\lambda] = 0$, and is thus an ESS. $g_1[0] < g_2[0]$ means that $A_1 < -(A_0 + A_2)$, which when rearranged gives $A_0 + A_1 + A_2 < 0$.

Hence, similar to Case 1, a unique λ^* exists only if $A_0 + A_1 + A_2 < 0$, and that λ^* is the ESS; otherwise, $\lambda^* = 0$.

Sub-case 2b: $A_0 > 0$, i.e. $c_2 < b_2$

rearranging $f[\lambda] = 0$ and multiplying each side by $[\lambda + 1]^{-c_2}$ gives:

$$-A_2[\lambda + 1]^{b_2 - c_2} = A_0[\lambda + 1]^{-c_2} + A_1$$

where $A_1, A_0, -A_2 > 0$
let

$$h_1[\lambda] = -A_2[\lambda + 1]^{b_2 - c_2}$$

$$h_2[\lambda] = A_0 + A_2[\lambda + 1]^{-c_2}$$

$h_1[\lambda]$ is a strictly increasing function from $-A_2$ to ∞, while $h_2[\lambda]$ is a strictly decreasing function from $A_0 + A_1$ to A_1.

If $h_2[0] < h_1[0]$, then both h_1 and $h_2[0]$ will intersect at least once to give a unique root $\lambda^* > 0 \Rightarrow h_2[0] < h_1[0]$ means that $-A_2 < A_0 + A_1$, which when rearranged gives $A_0 + A_1 + A_2 > 0$, i.e.

$$\frac{b_1 b_2}{c_1 c_2} > \frac{\beta_{1,0} - \frac{\beta_2}{v_2 + \delta}(r + \delta)}{v_{1,0} + \delta + r}$$

But under these conditions, $\frac{dR_0[\lambda]}{d\lambda}\Big|_{\lambda=0} = -K[0]f[0] < 0$, thus $\lambda^* > 0$ is a local minimum, and hence an unstable evolutionary singular strategy instead $\Rightarrow$ ESS are at the two extremes $\lambda^* = 0$ and $\lambda^* \to \infty$, which are bistable.

Conversely, if $h_2[0] > h_1[0]$ and $A_0 + A_1 + A_2 < 0$, then $h_2[0]$ and $h_1[0]$ do not intersect, resulting in no unique root λ^*. However, $\frac{dR_0[\lambda]}{d\lambda}\Big|_{\lambda=0} = -K[0]f[0] > 0$ and $R_0[\lambda]$ is strictly increasing, thus ESS is $\lambda^* \to \infty$.