INTRODUCTION

Reduced-host movement due to infection, known as lethargy, is a commonly observed disease manifestation, which can affect the parasite transmission rate and disease spread (Eames et al., 2010; Perkins et al., 2016). Many parasites, including those responsible for common illnesses in humans such as measles and the flu, can alter host movement behaviour and induce lethargy, which can prevent infected individuals from socializing and going to work and school (Eames et al., 2010; Hart, 1988; Holmstad et al., 2006; McKay et al., 2020; Van Kerckhove et al., 2013). Like parasite-induced host mortality, parasite-induced host lethargy can be a direct or an indirect consequence of the rate a parasite produces infectious stages using host resources and/or the clearance rate of the parasite by the immune system of the host (Belser et al., 2013; Zitzow et al., 2002).

The severity of lethargy can affect the transmission of a parasite from one host to another because a lethargic host may be less likely to make a direct contact with a susceptible host than a moving host (Day, 2001; Ewald, 1983, 1994). Thus, a trade-off can emerge between the rate of host lethargy and the rate of parasite replication within a host.

Previous studies investigated the role of population spatial structure, due to host dispersal, migration and metapopulation dynamics, in virulence evolution (Cressler et al., 2016; Messinger & Ostling, 2009; Nørgaard et al., 2021; Thrall & Burdon, 1997). Spatially structured host populations can promote the evolution of
intermediate and low virulence due to local genetic structuring or local availability of susceptible hosts (Berrangruber et al., 2015; Lion et al., 2011; Lion & Gandon, 2015; Osnas et al., 2015). In this paper, we consider the effect of reduced-host movement due to infection on virulence evolution using a model with two infective classes: moving and resting (or lethargic), which have distinct epidemiological characteristics due to distinct movement behaviours. A number of previous studies have proposed similar epidemic models with coupled behaviour-disease classes and transitions from one class to another (Fenichel et al., 2011; Piera et al., 2011; Verelst et al., 2016; Wang et al., 2015), and recent works highlight the need to combine modelling frameworks from the epidemiological and animal movement literatures (Dougherty et al., 2017; Fofana & Hurford, 2017; Scherer et al., 2020; White et al., 2018).

We formulate a mathematical model to investigate the role of host movement as an underlying process for an evolutionary trade-off between the rate of parasite transmission and the rate of parasite replication within a host, which determines the level of virulence a parasite causes in its host. The adaptive virulence hypothesis, commonly known as the trade-off hypothesis, states that high virulence or slow host recovery rates are the consequence of high parasite replication rate within the host (Acevedo et al., 2019; Alizon & van Baalen, 2005; Anderson & May, 1982; Antia et al., 1994; Gilchrist & Sasaki, 2002). When virulence and transmission are linked by an evolutionary trade-off, then high virulence will be maintained because it is beneficial for parasite transmission (Alizon et al., 2009; Alizon & Michalakis, 2015; Bull, 1994; Cressler et al., 2016; Ebert & Herre, 1996; Frank, 1996; Lipsitch & Moxon, 1997; Read, 1994).

The trade-off hypothesis has received some empirical support, but has also been criticized for its restrictive definition of the term virulence (Alizon et al., 2009; Alizon & Michalakis, 2015; Blanquart et al., 2016; Cressler et al., 2016; de Roode et al., 2008; Doumayrou et al., 2013; Fraser et al., 2007; Fraser et al., 2014; Williams et al., 2014). Theoretical analyses of the evolution of virulence frequently define virulence as parasite-induced host mortality and ignore non-lethal effects due to parasite infection (Alizon et al., 2009; Anderson & May, 1982; Frank, 1996). Notable mathematical formulations that have investigated non-lethal parasite virulence have considered parasite-induced host sterility (Abbate et al., 2015; Best et al., 2017; Bonds, 2006; Lively, 2006; O’Keefe & Antonovics, 2002), parasite-induced reduced-host growth (Schjørring & Koella, 2003) and reduced-host movement due to infection has gained more interest recently where some studies showed that different levels of virulence evolve at the front and the tail of the epidemic wave (Griette et al., 2015; Lion & Gandon, 2016; Osnas et al., 2015). The aim of this paper is to explicitly represent parasite-induced effects on host movement as a process underlying the transmission-virulence trade-off. Notably, we consider that infected hosts can shift between two discrete movement states: moving and resting, and we justify this formulation based on studies from the animal movement literature (Dougherty et al., 2017; Edelhoff et al., 2016; Fofana & Hurford, 2017; Teimouri et al., 2018). Reduced-host movement (host lethargy) is a complex phenomenon and could be an adaptive defence mechanism of the host to infection (Binning et al., 2017). In this paper, we focus on the case where lethargy is caused by pathogen replication rate within the host. We investigate the evolution of the rate of parasite replication within a host when the infection is lethal and non-lethal. We find that the main drivers of the evolutionary dynamics are lethargy and disease-induced mortality costs to the parasite, and when the disease-induced mortality or the lethargy cost is high, then evolution converges towards a parasite strain that induces moderate virulence. For a range of parameter values, where the lethargy and the disease-induced mortality costs are not high, a bistable evolutionary equilibrium occurs. As such, depending on the initial virulence and the magnitude of the effect of mutation, either a parasite strain that induces moderate virulence or a parasite strain that induces high virulence in the host population can evolve. Finally, we discuss how our results can aid in understanding the transient coexistence of parasite strains with different virulence in avian influenza viruses.

2 | EPIDEMIOLOGICAL MODEL

To formalize the epidemic model, we modified a simple susceptible-infected-susceptible (SIS) model to include two discrete movement states (moving and resting). Figure 1 describes the epidemic model,
and definitions for all the parameters and notations used in this paper are provided in Table 1.

We assume that susceptible hosts are always in the moving state, and infected hosts are in the moving state before lethargy and in the resting state during lethargy. Let $S_M$, $I_M$, and $I_R$ denote the numbers of susceptible hosts in the moving state, infected hosts in the moving state and infected hosts in the resting state respectively. The epidemiological dynamics of the host population are described by,

\[ \frac{dS_M}{dt} = \theta + \gamma (I_M + I_R) - S_M (\Lambda + d) \]  \hspace{1cm} (1)

\[ \frac{dI_M}{dt} = \Lambda S_M - I_M [d + \gamma + \psi(a)] \]  \hspace{1cm} (2)

\[ \frac{dI_R}{dt} = \psi(a) I_M - I_R [d + \gamma + \nu(a)] \]  \hspace{1cm} (3)

where $\Lambda = \alpha (c_m I_M + c_r I_R)$ is the force of infection.

We assume that a susceptible host becomes infected by making a direct contact with an infected host that is either in the moving or the resting state. We formulate these two infection events separately because a lethargic host in the resting state is less likely to make a direct contact than a non-lethargic host in the moving state. In order to capture this idea, we decompose the transmission coefficient frequently denoted $\beta$ into two components: the probability of making a direct contact and the probability of disease transmission given a contact between a susceptible host and an infected host (Day, 2001). The first component depends on the movement state of the host, and we assume that an infected host is less likely to make a direct contact in the resting state compared with the moving state ($c_r < c_m$) (Day, 2001; Ewald, 1983, 1994; Lloyd-Smith et al., 2004). The second component depends on parasite properties only, and we assume that the probability of disease transmission given an infectious contact is proportional to within-host parasite replication rate $\alpha$ (Brauer, 2008; Diekmann et al., 2012). The parameter $\alpha$ can be seen as the difference between parasite replication rate and parasite clearance rate by the immune system of the host (Lipsitch & Moxon, 1997). To formulate the infection process we apply the mass-action law, thus the number of new infections per unit time due to one infected host in the moving state is $\alpha c_m S_M$ and in the resting state is $\alpha c_r S_M$. We assume that an infected host is immediately infectious.

An infected host in the moving state can become lethargic and enter the resting state at the rate $\psi(a)$, which is the parasite-induced host lethargy rate, and the infected host can die from the disease in the resting state at the rate $\nu(a)$, which is the parasite-induced host mortality rate (Figure 2). Both the rate of lethargy and the rate of host death due to infection depend on the within-host parasite net replication

| Symbols | Definitions |
|---------|-------------|
| $\alpha$ | Within-host parasite net replication rate |
| $\psi(a)$ | Parasite-induced host lethargy rate |
| $\nu(a)$ | Parasite-induced host mortality rate |
| $c_m$ | The per capita host–host contact rate in the moving state |
| $c_r$ | The per capita host–host contact rate in the resting state |
| $\gamma$ | Host recovery rate |
| $d$ | Host natural mortality rate |
| $\theta$ | Host immigration rate |
| $R_0$ | The expected number of secondary cases by a primary case in a susceptible population |
| $\rho$ | The fraction of infected hosts that experience lethargy |
| $\sigma$ | Case fatality ratio given lethargy |
| $\chi$ | Case fatality ratio ($\rho \times \sigma$) |

| Symbols | Definitions |
|---------|-------------|
| $\alpha_1$ | Within-host net replication rate of the resident strain |
| $\alpha_2$ | Within-host net replication rate of the mutant strain |
| $\alpha^*$ | Evolutionarily stable or convergence stable net replication rates (ESS or CSS) |
| $\psi(a_1)$ | Parasite-induced host lethargy rate of the resident strain |
| $\psi(a_2)$ | Parasite-induced host lethargy rate of the mutant strain |
| $\nu(a_1)$ | Parasite-induced host mortality rate of the resident strain |
| $\nu(a_2)$ | Parasite-induced host mortality rate of the mutant strain |

TABLE 1 List of notations and definitions
rate, and we ignore the details of the dynamics between the parasite replication rate and the immune system within the host for simplicity. We assume that an infected host can recover either in the moving or the resting state at a constant rate \( r \) and become susceptible again. A host can be reinfected multiple times during the course of its life; thus, this type of model is appropriate for infectious diseases that confer no immunity such as rhinoviruses responsible for the common cold in humans (Brauer, 2008; May, 1986). Finally, we assume that susceptible and infected hosts can die naturally at a constant rate \( d \), and new susceptible hosts are recruited through immigration at the rate \( \theta \).

The system of Equations 1–3 exhibits two equilibria: one disease-free and one endemic equilibrium. We use the next-generation matrix approach (see van den Driessche & Watmough, 2002) to derive the basic reproduction number which is given by,

\[
R_0 = \left[ \frac{ac_m S_m^*}{d + \gamma + \psi(a)} + \frac{ac_r S_r^*}{d + \gamma + \nu(a)} \right] S_m^*,
\]

where \( S_m^* = \theta / d \) represents the number of susceptible hosts in the absence of the disease (see Appendix S1.1 of supporting information for the derivation of \( R_0 \)). Equation (4) is the expected number of secondary cases generated by a primary case in a completely susceptible host population, and it informs the outcome of the disease when rare in the host population (Diekmann et al., 2012). If Equation (4) is less than one, then no outbreak occurs, and if Equation (4) is greater than one, then an epidemic occurs and the system reaches a stable endemic equilibrium as long as the input of susceptible hosts through immigration and recovery is permanent (Brauer, 2008). Equation (4) is the sum of the expected number of new infections generated by an infected host in the moving state,

\[
\frac{ac_m S_m^*}{d + \gamma + \psi(a)},
\]

and the resting state multiplied by the probability of entering the resting state,

\[
\frac{ac_r S_r^*}{d + \gamma + \nu(a)} \times \frac{\psi(a)}{d + \gamma + \psi(a)}.
\]

To characterize the degree of non-lethal and lethal virulence associated with within-host parasite replication rate \( \alpha \), we define:

\[
\rho = \frac{\psi(a)}{d + \gamma + \psi(a)},
\]

\[
\sigma = \frac{\nu(a)}{d + \gamma + \nu(a)},
\]

and

\[
\chi = \frac{\psi(a)}{d + \gamma + \psi(a)} \times \frac{\nu(a)}{d + \gamma + \nu(a)}.
\]

where Equations 5–7 are the fraction of hosts that become lethargic, the case fatality ratio given lethargy and the case fatality ratio, respectively. We consider Equation (5) as a measure of non-lethal virulence and Equation (7) as a measure of lethal virulence a parasite causes to the host.

3 | EVOLUTION MODEL

To investigate the evolution of the within-host parasite net replication rate, we assume that a resident parasite strain with a net replication rate \( \alpha_1 \) is present in the host population at a locally stable endemic equilibrium and a rare mutant strain with a net replication rate \( \alpha_2 \) arises in the population. Assuming that only one strain can infect one host at the same time, the evolutionary dynamics are described by the following system of differential equations:

\[
\frac{ds_m}{dt} = \theta + \gamma (I_{m1} + I_{m2} + I_{r1} + I_{r2}) - S_m (\Lambda_1 + \Lambda_2 + d)
\]

\[
\frac{dl_{m1}}{dt} = \Lambda_1 S_m - I_{m1} [d + \gamma + \psi(\alpha_1)]
\]

\[
\frac{dl_{m2}}{dt} = \Lambda_2 S_m - I_{m2} [d + \gamma + \psi(\alpha_2)]
\]

\[
\frac{dl_{r1}}{dt} = \psi(\alpha_1) I_{m1} - I_{r1} [d + \gamma + \nu(\alpha_1)]
\]

\[
\frac{dl_{r2}}{dt} = \psi(\alpha_2) I_{m2} - I_{r2} [d + \gamma + \nu(\alpha_2)].
\]

where \( \Lambda_1 = \alpha_1 (c_m I_{m1} + c_r I_{r1}) \) and \( \Lambda_2 = \alpha_2 (c_m I_{m2} + c_r I_{r2}) \) are the force of infections associated with the resident and the mutant strains respectively. Let \( I_{m1} \) and \( I_{r1} \) denote the number of infected hosts in the moving and the resting states respectively infected with the resident strain, and \( I_{m2} \) and \( I_{r2} \) denote the number of infected hosts in the moving and the resting states respectively infected with the mutant strain.

To investigate the evolutionary dynamics, we analyse the stability of the mutant-free equilibrium (the endemic equilibrium of the system (1–3)) using the next-generation matrix approach for evolutionary invasion analysis (see, Hurford et al., 2010). We derive the expression for the invasion fitness, \( R(\alpha_2, \alpha_1) \), which is the expected lifetime infection success of a rare mutant strain, \( \alpha_2 \), in a host population where the resident strain, \( \alpha_1 \), is at endemic equilibrium, and it gives the conditions for \( \alpha_2 \) to replace \( \alpha_1 \). (see, Diekmann, 2002; Otto & Day, 2007). The stability analysis of the mutant-free equilibrium reveals that \( \alpha_2 \) replaces \( \alpha_1 \) at the endemic equilibrium if

\[
R(\alpha_2, \alpha_1) = \frac{\alpha_2 (c_m [d + \gamma + \nu(\alpha_2)] + c_r \psi(\alpha_2))}{[d + \gamma + \nu(\alpha_2)] [d + \gamma + \psi(\alpha_2)]} \times \frac{[d + \gamma + \nu(\alpha_1)] [d + \gamma + \psi(\alpha_1)]}{\alpha_1 (c_m [d + \gamma + \nu(\alpha_1)] + c_r \psi(\alpha_1))} > 1.
\]
Effect of the parasite's within-host replication rate on the epidemiological dynamics

LOW within-host replication rate, \( \alpha \)
- \( \alpha \) stable (ESS \( \alpha^* \)) can not be invaded, and as such its net replication rate is evolutionarily stable (ESS \( \alpha^* \)). The expression \( \alpha \) of supporting information. 

\[ \frac{a_2 c_m}{d + \gamma + \psi(a_2)} + \frac{a_2 c_r}{d + \gamma + \psi(a_2)} \times \frac{\psi(a_2)}{d + \gamma + \psi(a_2)} \]

then the mutant strain \( \alpha_2 \) replaces the resident strain \( \alpha_1 \). Therefore, a resident strain that maximizes

\[ R'(\alpha_1) = \frac{a_1 c_m}{d + \gamma + \psi(a_1)} + \frac{a_1 c_r}{d + \gamma + \psi(a_1)} \times \frac{\psi(a_1)}{d + \gamma + \psi(a_1)} \]

\[ R'(\alpha_1) > \frac{a_1 c_m}{d + \gamma + \psi(a_1)} + \frac{a_1 c_r}{d + \gamma + \psi(a_1)} \times \frac{\psi(a_1)}{d + \gamma + \psi(a_1)} \]

To investigate the within-host parasite net replication rate that is evolutionarily stable (ESS \( \alpha^* \)) and to determine the conditions for

the ESS \( \alpha^* \) to be convergence stable (CSS \( \alpha^* \)), we perform an evolutionary invasion analysis (Dieckmann, 2002; Otto & Day, 2007).

When a parasite strain with the \( \alpha \) value that is evolutionarily stable is dominant in the host population, then no parasite strain with a different \( \alpha \) value can replace it. An evolutionarily stable within-host net replication rate (ESS \( \alpha^* \)) that is also convergence stable (CSS \( \alpha^* \)) is an evolutionary attracting equilibrium, in other words, parasites evolve towards \( \alpha^* \) by a succession of small mutations and selection (Dieckmann, 2002; Dieckmann, 2004; Eshel, 1983; Otto & Day, 2007).

To illustrate our analytical results, we use Pairwise Invasibility Plot (PIP), which is a graphical representation used for evolutionary invasion analysis, and numerical simulation (Dieckmann, 2002; Dieckmann, 2004; Geritz et al., 1998).

4 | STOCHASTIC SIMULATION

To simulate the evolution of the within-host parasite replication rate \( \alpha \), we formulated a spatially explicit and stochastic version of the system of ordinary differential Equations 1–3. We assumed that all host individuals move randomly in a two-dimensional spatial domain with periodic boundaries, except infected hosts at the resting state who do not move. The epidemiological model is described in section (2) and see Appendix S2 of supporting information for details. In the simulation model, the transition rates in Equations 1–3 are formulated as durations. We assumed that the time to host recovery, the
time to host lethargy and host death due to infection are gamma-distributed (Brauer, 2008; Bretscher et al., 2011). For the evolutionary dynamics, we set an initial within-host parasite replication rate $a_1$ as the dominant strain in the host population. Every time a new infection occurs, the transmitted strain has a slightly different $a$ value, and as such, $\psi(a)$ and $\nu(a)$ are also different due to the evolutionary trade-offs. The new strain is drawn from a normal distribution where the mean is the $a$ value of the infecting strain and the standard deviation $\sigma = 0.01$ and $\sigma = 0.01$ for small- and large-effect mutations respectively. We run the evolutionary model for 100,000 time steps, and we graphed all the strains that are present in the host population each 100 time steps.

5 | RESULTS

We derived the within-host parasite net replication rate that is evolutionarily stable, and the conditions for an ESS $a^*$ to be convergence stable. Also, we investigated the effects of some important parameter values on the ESS $a^*$ and the corresponding virulence (Equations 5 and 7).

5.1 | The evolutionarily stable within-host parasite net replication rate ($ES\alpha^*$)

At the within-host parasite net replication rate that is evolutionarily stable, the expected number of new infections generated by an infected host in the moving and the resting state is maximal (Equation 15). To determine the ESS $a^*$, we evaluate the first derivative of the invasion fitness $R(a_2, a_1)$, Equation 13 equal to zero at $a_1 = a_2 = a^*$ and we solve for $a^*$. To verify under what conditions $a^*$ is a maximum, we require the second derivative of $R(a_2, a_1)$ at $a_1 = a_2 = a^*$ to be less than zero. We find that when

$$a^* = \frac{[c_m(d + \gamma + v) + c_w][d + \gamma + v][d + \gamma + v]}{[(c_m - c_v)(d + \gamma) + c_m][d + \gamma + v][d + \gamma + v]} \quad \text{(Equation 16)}$$

Equation (15) is maximal, where $\psi'$ and $\nu'$ are the first derivatives of $\psi(a)$ and $\nu(a)$ with respect to $a_2$ evaluated at $a^*$ respectively (Equation 16 is an implicit expression). When $\psi(a)$ is a concave-up trade-off and $\nu(a)$ has a concave-up or linear form, then Equation (16) is a maximum and a biologically feasible evolutionarily stable within-host parasite net replication rate, ESS $a^*$ (see Appendix S1.3 of supporting information for details). Where PIP are presented, we model the parasite-induced host lethargy rate as $\psi(a) = a^*$ (where $\alpha > 1$), and the parasite-induced host mortality rate as $\nu(a) = b\psi(a)$ (where $b$ is the ratio of the parasite-induced mortality rate to the lethargy rate). The lower the parameter $b$, the lower the fraction of lethargic hosts that die in the resting state, and as such, decreasing $b$ may represent host adaptations (host resistance) or medical interventions that prevent disease-induced host death. Figure 3a,b illustrates the concave-up trade-offs ($\psi(a)$ and $\nu(a)$), and the non-lethal and lethal virulence (Equations 5 and 7) a parasite with a given net replication rate causes its host. Supporting details for the evolutionary invasion analysis are available in Appendices S1.3 and S1.4, and description of the simulation is provided in Appendix S2. The code used for PIP, simulation and Movie is available as electronic supplementary materials, S1–S3 Codes, and is publicly available on Figshare (https://doi.org/10.6084/m9.figshare.14658828).

5.2 | Evolutionary bistability arises when hosts make contacts during lethargy

5.2.1 | Hosts make no contacts in the resting state ($c_r = 0$)

We found that if hosts make no contact in the resting state ($c_r = 0$), then the evolutionarily stable within-host net replication rate, ESS $a^*$, is also convergence stable, suggesting that parasites will evolve towards $a^*$ by a succession of small mutations and selection (see Appendix S1.4 for details). The stochastic simulation confirms that when hosts make no contacts in the resting state ($c_r = 0$), then parasites evolve towards an intermediate $a^*$ which corresponds to moderate non-lethal virulence (moderate fraction of infected hosts becoming lethargic, Equation 5) and moderate lethal virulence (moderate case fatality ratio, Equation 7). The PIP shows that a resident strain with a within-host net replication rate corresponding to $a^*$ cannot be replaced by any rare mutant strain, and the stochastic simulation shows parasite evolution towards an intermediate ESS $a^*$ (Figure 4a–c).

When $c_r = 0$, only the moving state contributes to the total number of secondary infections and an intermediate value of $a^*$ maximizes Equation (15), which is the expected secondary infections by a single infected host per susceptible host, $R^*(a^*)$ (Figure 5a). An intermediate value of $a^*$ is optimal because for low values of $a$ the probability of disease transmission given a contact is too low, and for high $a$ values, the duration of the moving state, which is the only state where parasites can be transmitted, is too short due to the concave-up trade-off, $\psi(a)$. Therefore, decreased $R^*(a^*)$ due to lethargy occurring earlier in the infection, which we term the lethargy cost, is the main factor that maintains intermediate $a^*$ and prevents evolution towards higher virulence.

5.2.2 | Hosts make contacts in the resting state ($c_r > 0$)

We found that when hosts make contacts in the resting state ($c_r > 0$), evolutionary bistability, with a lower and an upper ESS, is possible for a set of parameter values (Figure 4d). As such, the evolutionary trajectory depends on the initial value of $a$. For all initial $a$ below a critical level, parasites evolve towards the lower ESS $a^*$ by a succession of small mutations and selection. This critical level corresponds to an invisible repellor which is an invisible and non-convergent
evolutionary equilibrium (Dieckmann, 2002; Diekmann, 2004; Evans et al., 2010; Otto & Day, 2007). In contrast, for initial α values above the invisible repellor parasites evolve towards the upper ESS α* by a succession of small mutations and selection.

When hosts make contacts in the resting state (c, > 0), both moving and resting states contribute to the total number of secondary infections, and the expected secondary infections by one infected host per susceptible host (R*(α)) can have more than one maxima (i.e., local and global maxima). The parasite strain with the lower ESS α* is mostly transmitted in the moving state (Figure 5b, dashed line), whereas the parasite strain with the upper ESS α* induces lethargy very early in the infection and is mostly transmitted in the resting state (Figure 5b, dotted line). For any α, above the upper ESS the duration of the entire infectious period is too short due to the concave-up trade-off β(a), and the overall transmission of the parasite decreases. Therefore, decreased transmission due to shorter infectious period, which we term the disease-induced mortality cost, limits evolution towards much higher α and maintains the upper ESS α*. In absence of a concave-up β(a) trade-off, ever-increasing values of α will evolve.

In addition to the initial within-host parasite net replication rate α, the effect of mutations can affect the evolutionary dynamics. For example, when large-effect mutations can occur and a rare mutant strain can be very different from the resident strain, then parasites can evolve towards the upper ESS even if α is initially below the invisible repellor (Figure 4f). However, when α is less variable within the parasite population, because only small-effect mutations can occur, the evolutionary outcome depends on the initial α value (Figure 4e). The bistability suggests that a transient coexistence of two strains with different virulence is possible in the host population. As such, evolution can maintain two strains with low and high virulence in a transient coexistence, before eventually the elimination of one strain by competitive exclusion (Figure 4f). No long-term coexistence is possible because the environmental feedback in our model, which is captured by the size of susceptible hosts available to infect in the population, is one-dimensional (Lion & Metz, 2018).

5.3 | The effects of model parameters on the evolutionary dynamics

To gain a better understanding of how the parameter values affect the evolutionary dynamics, we graph the case fatality ratio (Equation 7) corresponding to the different evolutionary equilibria as a function of the host contact rate during lethargy (c*) and the constant b (the ratio of disease-induced host mortality rate to disease-induced host lethargy rate). We found that reduced c* selects for parasite strains that induce lower virulence (Figure 6a, see also Movie in Figure S2 in Appendix S3 of supporting information). One way that c* could be reduced is through interventions to reduce infectious contacts (e.g., isolation of infectious people), and our results suggest that these interventions would select for parasite strains that induce lower virulence. In contrast, medical interventions that treat the symptoms of lethargy, but do not prevent parasite transmission (e.g. painkillers), might increase c* and select for parasite strains that induce higher virulence.

Similarly, as b decreases parasite strains that induce higher virulence are selected. One way that b might decrease is through medical interventions that reduce disease-induced host death rate, and our results suggest that these interventions are more likely to induce higher virulence (Figure 6b, see also Movie in Figure S3 in Appendix S3 of supporting information). Examples of these medical interventions are imperfect vaccines that decrease the probability that the host dies due to infection, but do not prevent the transmission of infectious stages (Gandon et al., 2001, 2003; Read et al., 2015). Moreover, when c* as well as b increases, then virulence increases slowly except for a range of c* and b values where a backward bifurcation occurs with an evolutionary bistable equilibrium (Figure 6a,b). As such, a small increase in c* or a small decrease in b within this range of parameter values can result in a large increase in the evolutionary equilibrium and the corresponding virulence. When all other parameters are kept fixed, a 0.01 increase in c* can select for a strain that is ≈12-fold more virulent and a 0.01 decrease in b can select for a strain that is ≈15-fold more virulent.

5.4 | Evolutionary dynamics when parasite infection is non-lethal

We investigated the evolution of the within-host parasite net replication rate (α) when no infected host dies from the disease (b = 0), and we derived the corresponding non-lethal virulence (the fraction of infected hosts that become lethargic, Equation 5). Many human parasites such as rhinoviruses are in this category because they do cause lethargy and negligible or no-host mortality (Walther & Ewald, 2004). Also, for many human parasites, a large proportion of infected individuals eventually recover from the disease after they receive appropriate medical treatment, and only a small proportion die from the disease. When no infected host dies from the disease, then the cost of lethargy is the main factor that governs the evolutionary dynamics, and this cost is higher when c* is smaller. Evolution converges towards a parasite strain that is mainly transmitted in the moving state because severe lethargy is not beneficial for parasite transmission and a high fraction of hosts do not become lethargic (Figure 7a, and details of the model and the evolutionary dynamics are provided in Appendix S1.5 of supporting information). In contrast, when the transmission rate in the resting state increases due to increased c*, the incentive to avoid lethargy is lessened and without a disease-induced mortality cost (b = 0), the parasite can evolve ever-increasing α with all infected hosts experiencing lethargy (Figure 7b). When there is no disease-induced mortality, the evolutionary bifurcation diagram as a function of host contact rate in the resting state (c*) is similar to Figure 6a but without the upper ESS.

Throughout this paper, we assumed that the probability of disease transmission given an infectious contact, which is proportional to the within-host parasite net replication rate (α), is the same in the
moving and the resting states, but the probability of disease transmission given an infectious contact may be higher in the resting state because of a higher parasite load. We investigated the case where the probability of disease transmission given an infectious contact (proportional to $\alpha$) is higher in the resting state than the moving state ($\alpha_m > \alpha_r$, where $\alpha_m$ and $\alpha_r$ are the within-host parasite net replication rates in the moving and the resting states respectively). We found that the results are qualitatively similar to the case where the probability of disease transmission given an infectious contact is the same in the moving and the resting states (see Movie in Figure S4 in Appendix S3 of supporting information).

6 | DISCUSSION

Disease-induced mortality as an unavoidable consequence of increasing parasite transmission is the most frequently evoked explanation for the evolution and the maintenance of virulence. Virulence, however, is not limited to host mortality, as reduced-host movement (lethargy) is common in many host–parasite systems and can result in a behavioural shift in host movement from a moving to a resting state (Eames et al., 2010; Perkins et al., 2016). As such, our epidemiological model considers discrete movement states, moving and resting, with a transition rate between the states, to understand how non-lethal in combination with lethal parasite-induced harm influences the evolution of the parasite net replication rate and the corresponding virulence.

We found that when infected hosts make no contacts in the resting state, $c_r = 0$, or when the ratio of the disease-induced mortality rate to the lethargy rate ($\beta$) is high, then a parasite strain that is mainly transmitted in the moving state and induces moderate virulence (non-lethal and lethal virulence) will evolve (Figures 4a and 7a). In contrast, when $c_r > 0$ and the ratio $\beta$ are low, then high virulence can evolve, and a bistable evolutionary equilibrium is possible for a range of parameters values (Figures 4d–f and 7b). As such, either a parasite strain that is mainly transmitted in the moving state and induces moderate virulence (lower ESS) or a parasite strain that is mainly transmitted in the resting state and induces high virulence (upper ESS) can evolve, depending on the initial virulence and the magnitude of the effect of mutation (Figure 4d–f). Furthermore, we show that medical interventions to treat the symptoms of lethargy (increased $c_r$) or reduce disease-induced host death (decreased $\beta$) can select for high virulence, and a small change in $c_r$ and $\beta$ can result in a large shift in the evolutionary dynamics due to the evolutionary bistability (Figure 6a,b).

Classic models of virulence evolution which ignore disease-induced lethargy and restrict virulence to parasite-induced host death suggest that the disease-induced mortality cost is the main factor that maintains intermediate virulence (Anderson & May, 1982; Frank, 1996). However, our results suggest that lethargy cost can also maintain an intermediate virulence whether parasite infection is lethal or non-lethal (see also Day, 2001). As such, defining virulence as disease-induced lethargy or non-lethal measures of virulence in general may facilitate experimental validation of the trade-off hypothesis for virulence evolution as this measure of virulence could
be applied to many host–parasite systems. (Alizon et al., 2009; Alizon & Michalakis, 2015; Cressler et al., 2016).

Previous studies have demonstrated that evolutionary bistable virulence can emerge from a variety of ecological factors. Gandon et al. (2003) showed that imperfect vaccines that do not prevent infection, but limit parasite growth in infected hosts, can select for either low or highly virulent strains depending on the initial parasite virulence for intermediate vaccination coverage. Bistability occurs because intermediate vaccination coverage creates an heterogeneous host population, with vaccinated and unvaccinated hosts, and the anti-growth component of the vaccine can maintain high virulence whereas the anti-infection component can maintain low virulence.

Similar conclusions are reached in the case where the vaccine increases the efficacy of host immunity, and the functional relationship between virulence and transmission emerges from within-host dynamics (André & Gandon, 2006). Boots et al. (2004) found that for infectious diseases that confer long-lived immunity, when some of the infections occur globally, whereas others occurs locally, then either an avirulent or a highly virulent strain can evolve depending on the initial parasite virulence, and several other examples of evolutionary bistability are given in van Baalen (1998), Boldin and Kisdi (2012) and Fleming-Davies et al. (2015). In our work, evolutionary bistability arises due to the two movement states with distinct epidemiological characteristics that create temporal heterogeneity in disease manifestation at individual host level. As such, disease transmission in the moving state maintains parasite strains with moderate virulence, whereas disease transmission in the resting state maintains parasite strains that induce high virulence.

We note that our compartment model (Equations 1–3) is structurally similar to an SEIR model, where exposed is analogous to our moving state and infectious is analogous to our resting state. All the results in our manuscript would apply to the evolution of the parasite-induced rate of transitioning from exposed to infected, if it was appropriate to assume that exposed hosts (E) are more infectious than infected hosts (I). The simplicity of our compartmental model facilitated the mathematical analyses of the epidemiological and evolutionary dynamics. The analyses were analytical tractable, which enabled us to clearly understand and explain why bistability

**FIGURE 4** Pairwise invasibility plots (PIP) and stochastic simulations illustrating the evolutionary dynamics when hosts make no contacts in the resting state (top row) and when hosts make contacts in the resting state (bottom row). Panels (a) and (d) are PIPs, and the colours represent the fate of a rare mutant strain in a host population where the resident strain is at endemic equilibrium for different combinations of mutant-resident $a$ values ($a_1$ on the x-axis and $a_2$ on the y-axis). For a given combination ($a_1$, $a_2$), white indicates that the rare mutant goes extinct (Equation 13 is negative), and black indicates that the rare mutant replaces the resident (Equation 13 is positive). The transitions between black and white occur where Equation 13 equals zero, and the intersections are evolutionary equilibria. In (a) the unique intersection ($a^*_1 \approx 0.25$) is an ESS because it cannot be invaded by any rare mutant strain, and in (b) and (c) evolution converges towards one ESS $a$ (example with initial $a = 0.29$ and 0.82, and small and large effects mutation respectively). In (d) from low to high $a$, the first intersection ($a^*_2 \approx 0.33$) is an ESS (termed the lower ESS), the second ($a \approx 0.7$) is an invisible repellor, which is an invisible and non-convergent evolutionary equilibrium, and the third ($a^*_3 = 2$) is an ESS (termed the upper ESS). In (e) only small-effect mutations occur, and evolution converges towards either the lower ESS for all initial $a$ below invisible repellor or the higher ESS for all initial $a$ above the invisible repellor (example with initial $a = 0.4$). In (f) large-effect mutations can occur and 2 equilibria are possible. For the PIPs, we model the concave-up trade-offs using a power function $\psi(a) = a^2$ and $\nu(a) = 0.01a^2$, and we set $c_m = 0.8$, $d = 0.0001$, $r = 0.065$, and $c_r = 0.08$, except the top row figures where $c_r = 0$. For the stochastic simulations, see Appendix S2 for details.
can evolve. Interestingly, the simulation results of the stochastic and spatially explicit version of our compartmental model (Equations 1–3) confirmed our analytical results.

In the formulation of our model, we made several assumptions that require further discussion. We assumed that the parasite affects host movement via a trade-off between the parasite net replication and host contact rate during lethargy.

**Figure 5** Expected secondary infections by a single infected host per susceptible host (Equation 15) in the moving state (dashed black line), the resting states (dotted black line) and during the entire infectious period (solid black lines) as a function of within-host net replication rate $\alpha$. In (a) we set $c_r = 0$; thus, infection is possible only in the moving state. Equation (15) is maximized at $\alpha^* = 0.25$, and maximizing the number of secondary infections per susceptible hosts in the moving state also maximizes this quantity for the entire infectious period. In (b) we set $c_r = 0.08$, thus both moving and lethargic hosts contribute to the total infections and Equation (15) has two local maxima: $\alpha^* \approx 0.33$ and $\alpha^* \approx 2$, corresponding to the lower and the upper ESS respectively. A parasite strain at the lower ESS is mainly transmitted in the moving state, whereas a parasite strain at the upper ESS is mainly transmitted in the resting state. For all graphs we model the concave-up trade-offs using a power function $\psi(\alpha) = \alpha^2$, $\nu(\alpha) = 0.01\psi(\alpha)$, and we set $d = 0.0001$ and $\gamma = 0.065$.

**Figure 6** Increasing contact rate in the resting state ($c_r$) and increasing the ratio of host mortality to lethargy rates ($b$) induce a backward bifurcation in the evolutionary dynamics. In (a), we set $c_r = 0.8$, $b = 0.016$, $d = 0.0001$, $\gamma = 0.065$ and we graph the case fatality ratio (Equation 7) corresponding to evolutionary equilibria for $c_r$ values from 0 to 0.2. For $c_r$ values between $\approx 0.07$ and 0.1, there are two ESS (black open circles) separated by an invisible repellor (red filled circles), but outside this range, there is only one ESS which is also a CSS (black filled circles). In (b), we set $c_r = 0.8$, $c_r = 0.08$, $d = 0.0001$, $\gamma = 0.065$ and we graph the case fatality ratio corresponding to the evolutionary equilibria for $b$ values from 0 to 0.04. For $b$ values between $\approx 0.006$ and 0.016, there are two ESS separated by an invisible repellor, but outside this range, there is only one ESS which is also a CSS. We choose to plot only the corresponding lethal virulence (Equation 7) in function $c_r$ and $b$, but the result is the same for non-lethal virulence (Equation 5). For all graphs, we model the concave-up trade-offs using a power function $\psi(\alpha) = \alpha^2$ and $\nu(\alpha) = b\psi(\alpha)$.
replication rate and the parasite-induced host lethargy rate \(\psi(\alpha)\). Finnerty et al. (2018) demonstrate this relationship, and a number of studies have reported that human and non-human parasites frequently induce lethargy in their hosts (Ghai et al., 2015; Hart, 1988; Holmstad et al., 2006). This trade-off could be assessed experimentally by measuring the relationship between parasite load or within-host parasite growth rate and the fraction of infected hosts that become lethargic using a scoring system based on the activity level of infected hosts (Reuman et al., 1989; Zitzow et al., 2002). We assumed that infected hosts shift from a moving to a resting state, where the host–host contact rate decreases and an infected host can die from the disease. The clinical manifestation of many infectious diseases that induce lethargy prior to host death can justify this assumption, and public health initiatives such as encouraging sick people to stay home from workplace and social distancing policies can also result in two infective classes with distinct epidemiological characteristics and a behavioural shift from moving to resting state (Fenichel et al., 2011; Ghai et al., 2015; Halloran et al., 2008; Hart, 1988). We focus on parasite-induced reduced movement rates, while there are other examples of parasites (e.g. the so-called furious strain of rabies virus) that can cause increased movement in infected hosts (Bacon, 1985; Hemachudha et al., 2002; Susilawathi et al., 2012). Evolutionary bistability may not arise in the case where the parasite increases host movement \(c_r > c_m\) because the lethargy cost is no more present, and the higher the disease-induced mortality cost the lower the ESS \(\alpha^*\) that is favoured by natural selection. Our model formulation is not specific to parasites that cause lethargy, but is applicable to any host-parasite system with two infective classes with distinct epidemiological characteristics like asymptomatic and symptomatic disease transmission states.

In the result section, we show that for a range of parameter values a bistable evolutionary equilibrium is possible, and as such, transient coexistence of low and high virulence is possible. The coexistence of two strains with different levels of virulence is not uncommon in nature, and we provide one example where host movement can explain the coexistence of a low and a high virulent strains, and rapid emergence of high virulence.

6.1 | Example: The emergence of highly pathogenic avian influenza (HPAI) viruses

Avian influenza is caused by a type A influenza virus which infects domestic poultry (e.g. chickens and turkeys), free-living and wild bird populations (e.g. ducks, gulls and terns) (Causey & Edwards, 2008; Stallknecht, 2003; Yoon et al., 2014). Our model assumptions are valid for the avian influenza virus because it is mainly transmitted through direct contact with infected hosts or their secretions and infection does not confer long-lasting immunity (Alexander, 2000, 2007; Stallknecht et al., 1990). The avian influenza virus induces signs such as lethargy, depression and anorexia prior to death in infected hosts, and the different virus strains are often classified as low-pathogenic (LPAI) and highly pathogenic (HPAI) strains based on the severity of lethargy and the case fatality rate/ratio they cause in birds (Belser et al., 2013; Bertran et al., 2011; Mutinelli et al., 2003; Perkins & Swayne, 2001; Wu et al., 2017). Infected chickens may have more contacts before lethargy because they are more active in the chicken pen or more likely to be transported between locations. As signs of lethargy appear, infected chickens may experience a decrease in their contact rate because they are
less active in the chicken pen or less likely to enter the global poultry market.

Our results suggest an alternative to the current best explanations for the emergence of HPAI in domestic poultry: 1) that HPAI strains result from infection spillover from strains endemic to wild bird populations and 2) that HPAI can arise in poultry as a consequence of genetic mechanisms such as mutation, insertion, substitution and reassortment from an already circulating LPAI strain (Alexander, 2000; Banks et al., 2000, 2001; Nao et al., 2017; Perdue et al., 1997; Qi et al., 2018; Sims et al., 2005; Taubenberger & Kash, 2010). We show that when lethargic infected chickens can transmit the disease ($c_i>0$), then a HPAI strain can emerge rapidly even when a LPAI strain reached a local ESS. In addition, our results suggest that a HPAI strain will not evolve if chickens make no contacts during lethargy ($c_i = 0$) or if a high fraction of lethargic chickens die ($b$ is high). Therefore, our results suggest a dual benefit of quarantining or culling lethargic chickens, in that not only is infection transmission prevented, but also the evolution of highly pathogenic strains becomes less likely.

Previous studies showed that evolutionary bistability can arise due to host population heterogeneity (Gandon et al., 2003) and transmission mode heterogeneity (Boldin & Kisdi, 2012). In this paper, we considered an epidemic model with two movement states and parasite-induced shift from moving to resting state. We find that evolutionary bistability can arise due to heterogeneity at the individual host level rather than at the host population level or beyond.

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DATA AVAILABILITY STATEMENT

The code used for PIP, simulation and Movie in this paper is available as electronic supplementary materials, S1-S3 Codes, and is publicly available on Figshare (https://doi.org/10.6084/m9.figshare.14658828).

PEER REVIEW

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REFERENCES

Abbate, J., Kada, S., & Lion, S. (2015). Beyond mortality: Sterility as a neglected component of parasite virulence. PloS Pathogens, 11, e1005229.
Acevedo, M., Dillemuth, F., Flick, A., Faldyn, M., & Elderb, B. (2019). Virulence-driven trade-offs in disease transmission: A meta-analysis. Evolution, 73, 636–647.
Alexander, D. (2000). A review of avian influenza in different bird species. Veterinary Microbiology, 74, 3–13.
Alexander, D. (2007). An overview of the epidemiology of avian influenza. Vaccine, 25, 5637–5644.
Alizon, S., Hurford, A., Mideo, N., & van Baalen, M. (2009). Virulence evolution and the trade-off hypothesis: History, current state of affairs and the future. Journal of Evolutionary Biology, 22, 245–259.
Alizon, S., & Michalakis, Y. (2015). Adaptive virulence evolution: The good old fitness-based approach. Trends in Ecology & Evolution, 30, 248–254.
Alizon, S., & van Baalen, M. (2005). Emergence of a convex trade-off between transmission and virulence. The American Naturalist, 165, E155–E167.
Anderson, R., & May, R. (1982). Coevolution of hosts and parasites. Parasitology, 85, 411–426.
André, J., & Gandon, S. (2006). Vaccination, within-host dynamics, and virulence evolution. Evolution, 60, 13–23.
Antía, R., Levin, B., & May, R. (1994). Within-host population dynamics and the evolution and maintenance of microparasite virulence. The American Naturalist, 144, 457–472.
Bacon, P. (1985). Population dynamics of rabies in wildlife. Academic Press Inc. (London) Ltd.
Banks, J., Speidel, E., McCauley, J., & Alexander, D. (2000). Phylogenetic analysis of h7 haemagglutinin subtype influenza a viruses. Archives of Virology, 145, 1047–1058.
Banks, J., Speidel, E., Moore, E., Plowright, L., Piccirillo, A., Capua, I., Cordioli, P., Fioretti, A., & Alexander, D. (2001). Changes in the haemagglutinin and the neuraminidase genes prior to the emergence of highly pathogenic H7N1 avian influenza viruses in Italy. Archives of Virology, 146, 963–973.
Bell, A., de Roode, J., Sim, D., & Read, A. (2006). Within-host competition in genetically diverse malaria infections: Parasite virulence and competitive success. Evolution, 60, 1358–1371.
Belsur, J., Gustin, K., Pearce, M., Maines, T., Zeng, H., Pappas, C., Sun, X., Carney, P., Villanueva, J., & Stevens, J. (2013). Pathogenesis and transmission of avian influenza a (H7N9) virus in ferrets and mice. Nature, 501, 556–559.
Berngruber, T., Lion, S., & Gandon, S. (2015). Spatial structure, transmission modes and the evolution of viral exploitation strategies. PloS Pathogens, 11, e1004810.
Bertran, K., Pérez-Ramirez, E., Busquets, N., Dolz, R., Ramis, A., Darj, A., Abad, F., Valle, R., Chaves, A., Vergara-Alert, J., Barral, M., Höfle, U., & Majó, N. (2011). Pathogenesis and transmissibility of highly (H7N1) and low (H7N9) pathogenic avian influenza virus infection in red-legged partridge (Alectoris rufa). Veterinary Research, 42, 24.
Best, A., White, A., & Boots, M. (2017). The evolution of host defence when parasites impact reproduction. Evolutionary Ecology Research, 18, 393–409.
Binning, S., Shaw, A., & Roche, D. (2017). Parasites and host performance: Incorporating infection into our understanding of animal movement. Integrative and Comparative Biology, 57, 267–280.
Blanquart, F., Grabowski, M., Herbeck, J., Nalugoda, F., Serwadda, D., Eller, M., Robb, M., Gray, R., Kigozi, G., Laeyendecker, O., Lythgoe, K., Nakigozi, G., Quinn, T., Reynolds, S., Wawer, M., & Fraser, C. (2016). A transmission-virulence evolutionary trade-off explains attenuation of HIV-1 in Uganda. eLife, 5, e20492.
Boldin, B., & Kisdi, É. (2012). On the evolutionary dynamics of pathogens with direct and environmental transmission. Evolution, 66, 2514–2527.
Bonds, M. (2006). Host life-history strategy explains pathogen-induced sterility. The American Naturalist, 168, 281–293.
Boots, M., Hudson, P., & Sasaki, A. (2004). Large shifts in pathogen virulence relate to host population structure. Science, 303, 842–844.
Brauer, F. (2008). Compartmental models in epidemiology. In Mathematical epidemiology (chap. 2, pp. 19–79). Springer.
Williams, P., Dobson, A., Dhondt, K., Hawley, D., & Dhondt, A. (2014). Evidence of trade-offs shaping virulence evolution in an emerging wildlife pathogen. *Journal of Evolutionary Biology, 27*, 1271-1278.

Wu, Z., Zhang, Y., Zhao, N., Yu, Z., Pan, H., Chan, T., Zhang, Z., & Liu, S. (2017). Comparative epidemiology of human fatal infections with novel, high (H5N6 and H5N1) and low (H7N9 and H9N2) pathogenicity avian influenza a viruses. *International Journal of Environmental Research and Public Health, 14*, 263.

Yoon, S., Webby, R., & Webster, R. (2014). Evolution and ecology of influenza a viruses. In *Influenza pathogenesis and control-volume I* (pp. 359–375). Springer.

Zitzow, L., Rowe, T., Morken, T., Shieh, W., Zaki, S., & Katz, J. (2002). Pathogenesis of avian influenza a (H5N1) viruses in ferrets. *Journal of Virology, 76*, 4420–4429.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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