

# Host phenology ~~drives~~ can drive the evolution of intermediate ~~parasite virulence~~ virulence strategies in some parasites

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## 1 Abstract

Mechanistic trade-offs resulting in a negative correlation between transmission and virulence are the foundation of nearly all current theory on the evolution of parasite virulence. ~~Empirical evidence supporting these trade-offs in natural systems remains elusive, suggesting other factors could drive virulence evolution in the absence of a mechanistic trade-off. Several ecological factors~~ Although several ecological factors have been shown to modulate the optimal virulence strategies predicted from mechanistic trade-off models ~~but~~ none have been shown to be sufficient to explain the intermediate virulence strategies observed in ~~most natural systems~~ any natural system. The timing of seasonal ~~activities~~ activity, or phenology, is a common factor that influences the types and impact of many ecological interactions but is rarely considered in virulence evolution studies. We develop a mathematical model of a disease system with seasonal host activity to study the evolutionary consequences of host phenology on parasite virulence. ~~Seasonal~~ Results from this model demonstrated that seasonal host activity is sufficient to drive the evolution of intermediate parasite virulence, in some types of natural disease systems. The optimal virulence strategy is in these systems can be determined by both the duration of the host activity period as well as the variation in the host emergence timing. Parasites with low virulence strategies are favored in environments with long host activity periods and in environments in which ~~all~~ hosts emerge synchronously. ~~These~~ The results demonstrate that host phenology ~~may be sufficient, in the absence of mechanistic trade-offs, can be sufficient~~ can be sufficient to select for intermediate optimal virulence strategies, providing an alternative mechanism to account for virulence evolution in some natural systems.

## 2 Introduction

The evolutionary causes and consequences of parasite virulence remain enigmatic despite decades of research. It was once thought that parasites continue to evolve ever lower levels of virulence to preserve their primary resource for future parasite generations.<sup>1</sup> However, the idea that parasites would limit damaging their host for the benefit of future generations violates multiple core principles of our modern understanding of evolutionary biology.<sup>2,3</sup> Natural selection, as framed in the modern evolutionary synthesis, favors traits that improve short-term evolutionary fitness even if those traits negatively impact the environment for future generations.<sup>2,3</sup> Thus, the level of virulence that maximizes parasite fitness is favored by natural selection despite its impact on the host population.<sup>4</sup> Identifying environmental conditions and mechanistic constraints that drive the evolution of the vast diversity of parasite virulence strategies observed in nature has been ~~a~~ an important research focus for decades.

Establishing that mechanistic trade-offs constrain parasite virulence strategies was ~~the~~ a key breakthrough that propels virulence evolution research to this day. In the now classic paper, Anderson and May demonstrated that within-host parasite densities increase the probability of transmission to a new host - a component of parasite fitness - but also ~~cause host damage leading to shorter infection durations and thus shorten infection duration resulting in~~ fewer opportunities for transmission to naive hosts.<sup>4</sup> That is, parasites can only produce more infectious progeny if they ~~utilize~~ cause host damage by utilizing more host resources ~~which causes host damage~~. This mechanistic trade-off ~~that results in a negative correlation~~ between virulence and transmission ~~has been~~ remains the foundational theoretical framework used to ~~explain the diversity of~~ account for the evolution of all parasite virulence strategies observed in nature.<sup>5,6</sup>

~~The ubiquity of transmission-virulence trade-offs to explain virulence evolution in theoretical research is at odds with the rarity of empirical data supporting. Many ecological factors and environmental conditions have been shown to alter the optimal virulence strategies driven by mechanistic trade-offs in natural systems <sup>7,8</sup>. This suggests that other factors might be driving the evolution of intermediate virulence. One such factor is environmental heterogeneity. It is within models. For example, it is well-established that varying environmental conditions, such as the extrinsic host death rate, often shift the optimal virulence strategy governed by a mechanistic trade-off.<sup>4,9-11</sup> Yet we don't know if variation in environmental conditions can select for intermediate virulence. However, no environmental condition, in the absence of mechanistic trade-offs, has been shown to select for intermediate virulence.~~

The timing of seasonal activity, or phenology, is an environmental condition affecting all aspects of life cycles, including reproduction, migration, and diapause, in most species.<sup>12-18</sup> The phenology of host species also impacts the timing and prevalence of transmission opportunities for parasites which could alter optimal virulence strategies.<sup>19-26</sup> For example, host phenological patterns that extend the time between infection and transmission are expected to select for lower virulence, as observed in some malaria parasites (*Plasmodium vivax*). In this system, high virulence strains persist in regions where mosquitoes are present year-round while low virulence strains are more common in regions where mosquitoes are nearly absent during the dry season.<sup>27</sup> While host phenology likely impacts virulence evolution in parasites<sup>28-31</sup> it remains unclear whether this environmental condition ~~has~~ can have a sufficiently large impact to select for an intermediate virulence phenotype in the absence of a mechanistic trade-off.

Here we investigate the impact of host phenology on the ~~evolution of parasite virulence~~ virulence evolution of an obligate-killer parasite. We demonstrate that intermediate virulence is adaptive when host activity patterns are highly seasonal in the absence of any explicit mechanistic trade-off, establishing that environmental

43 context alone ~~can~~ is sufficient to drive the evolution of intermediate virulence in disease systems that conform  
 44 to the assumptions of the model. Further, multiple features of host seasonal activity, including season length  
 45 and the synchronicity at which hosts first become active during the season, impact the optimal virulence  
 46 level of parasites. These results provide an alternative framework that can account for virulence evolution  
 47 in some natural systems.

### 48 3 Model description

49 The model describes the transmission dynamics of a free-living, obligate-killer parasite that infects a seasonally  
 50 available host (Figure 1). The host cohort,  $\hat{s}$ , enters the system at the beginning of the season over a period  
 51 given by the function  $g(t, t_1)$ . Hosts,  $s$ , have non-overlapping generations and are alive for one season. The  
 52 parasite,  $v$ , infects hosts while they are briefly susceptible early in their development (e.g. monocyclic parasites  
 53 of annual plants, baculoviruses of forest *Lepidoptera*<sup>32–36</sup> and univoltine insects parasitized by ichneumonids<sup>37–39</sup>  
 54 ). The parasite must kill the host to release new infectious progeny. The parasite completes one round of  
 55 infection per season because the incubation period of the parasite is longer than the duration of time the host  
 56 spends in the susceptible developmental stage. This transmission scenario occurs in nature if all susceptible  
 57 host stages emerge over a short period of time each season so that there are no susceptible host stages available  
 58 when the parasite eventually kills its host. Parasites may also effectively complete only one round of infection  
 59 per season if the second generation of parasites do not have enough time in the season to complete their life  
 60 cycle in the short-lived host.

We ignore the progression of the susceptible stage, ~~to the resistant life stage~~, to later life stages as it  
 does not impact transmission dynamics. To keep track of these dynamics, we refer to the generation of  
 parasites that infect hosts in the beginning of the season as  $v_1$  and the generation of parasites released from  
 infected hosts upon parasite-induced death as  $v_2$ . The initial conditions in the beginning of the season are  
thus  $s(0) = 0, v_1(0^+) = v_2(0^-), v_2(\tau) = 0$ . The transmission dynamics in season  $n$  are given by the following  
 system of ordinary delay differential equations (all parameters are described in Table 1): ~~This simplifies the~~  
~~dynamics to-~~

$$\frac{ds}{dt} = \hat{s}g(t, t_1) - ds(t) - \alpha s(t)v_1(t), \quad (1a)$$

$$\frac{dv_1}{dt} = -\delta v_1(t), \quad (1b)$$

$$\frac{dv_2}{dt} = \alpha\beta e^{-d\tau} s(t - \tau)v_1(t - \tau) - \delta v_2(t). \quad (1c)$$

61 where  $d$  is the host death rate,  $\delta$  is the decay rate of parasites in the environment,  $\alpha$  is the ~~product of the~~  
 62 ~~contact rate between  $s$  and  $v_1$  and the probability of transmission given contact~~ transmission rate,  $\beta$  is the  
 63 number of parasites produced upon host death and  $\tau$  is the delay between host infection and host death.  
 64  $\tau$  is equivalent to virulence where low virulence parasites have long  $\tau$  and high virulence parasites have  
 65 short  $\tau$ . We make the common assumption for free-living parasites that the removal of parasites through  
 66 transmission ( $\alpha$ ) is negligible,<sup>36,40,41</sup> i.e. (1b) ignores the term  $-\alpha s(t)v_1(t)$ .  
 67 The function  $g(t, t_1)$  is a probability density function that ~~describes the~~ captures the per-capita host emergence  
 68 rate by specifying the timing and length of host emergence. We use a uniform distribution ( $U(\bullet)$ ) for analytical  
 69 tractability, but other distributions can be used.

$$g(t, t_l) = \begin{cases} \frac{1}{t_l} & 0 \leq t \leq t_l \\ 0 & t_l < t \leq T \end{cases}$$

70  $t_l$  denotes the length of the host emergence period and  $T$  denotes the season length. The season begins  
 71 ( $t_0 = 0$ ) with the emergence of the susceptible host cohort,  $\hat{s}$ . The host cohort emerges from  $0 \leq t \leq t_l$ .  $v_2$   
 72 parasites remaining in the system at  $t = T$  give rise to next season's initial parasite population ( $\hat{v} = v_1(0)$ ).  
 73 Parasites that have not killed their host by the end of the season do not release progeny. We-Background  
 74 mortality arises from predation or some other natural cause. We assume that infected hosts that die from  
 75 background mortality do not release parasites because the parasites are either consumed or the latency  
 76 period corresponds to the time necessary to develop viable progeny<sup>42,43</sup>. We ignore the impact of infection  
 77 for host demography and assume  $\hat{s}$  is constant each year (e.g. ~~crops~~, a system where host regulation by  
 78 parasites is negligible).

79 We solve equations 1a-c analytically Appendix A.

### 80 3.0.1 Parasite fitness

A parasite introduced into a naive host population persists or goes extinct depending on the length of the host emergence period and season length. The stability of the parasite-free equilibrium is determined by the production of  $v_2$  resulting from infection of  $s$  given by

$$v_2(T) = e^{-\delta(T-t_l-\tau)}(v_2(t_l+\tau)) + \alpha\beta e^{-d\tau} \hat{v}s(t_l) \int_0^{T-t_l-\tau} e^{\frac{\alpha\hat{v}(-1+e^{-\delta s})-\delta t_l-ds}{\delta} - \frac{\alpha\hat{v}e^{-\delta(s+t_l)}(-1+e^{\delta s})-\delta t_l-ds}{\delta}} ds$$

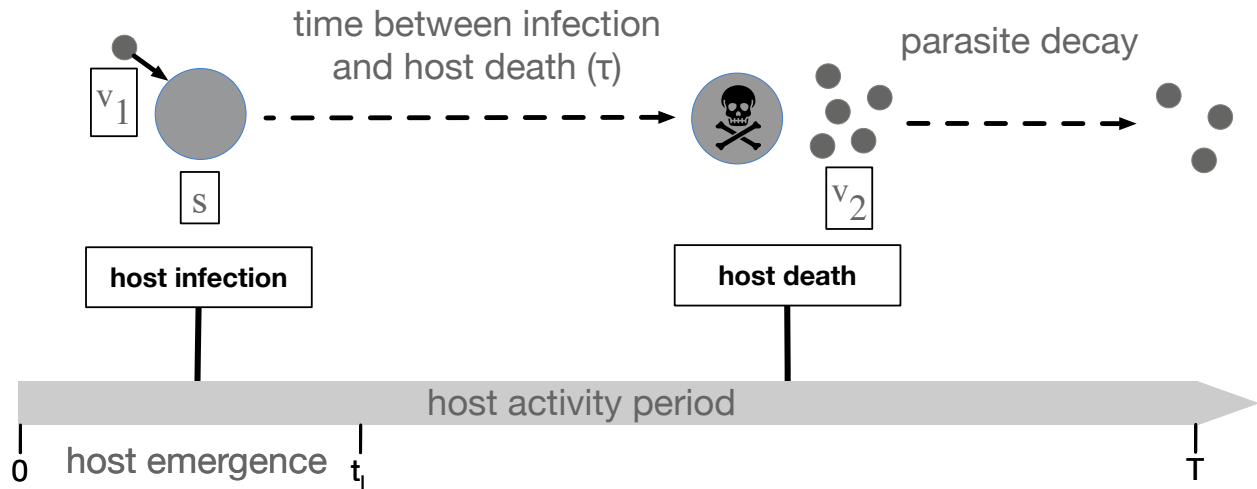


Figure 1: **Infection diagram** The host cohort,  $\hat{s}$ , emerges from time  $t = 0$  to  $t = t_l$ , all  $v_1$  parasites emerge at  $t = 0$ . Hosts do not reproduce during the season. Infections generally occur early in the season when host density is high. Parasite-induced host death occurs after time  $\tau$ , at which point new parasites,  $v_2$  are released.  $v_2$  decays in the environment from exposure. Parasites only have time to complete one round of infection per season.  $v_2$  parasites in the environment at  $t = T$  will carryover and emerge at the beginning of the next season.

Parameter	Description	Value
$s$	<u>susceptible hosts</u>	<u>state variable</u>
$v_1$	<u>parasites that infect hosts in current season</u>	<u>state variable</u>
$v_2$	<u>parasites released in current season</u>	<u>state variable</u>
$t_l$	length of host emergence period	<del>varies</del> <u>time (varies)</u>
$T$	season length	<del>varies</del> <u>time (varies)</u>
$\hat{s}$	<del>host population</del> <u>emerging host cohort</u> size	$10^8$ <u>hosts</u>
$\alpha$	transmission rate	$10^{-8}$ <u>/((parasite <math>\times</math> time)</u>
$\beta$	number of parasites produced upon host death	<del>varies</del> <u>parasites (varies)</u>
$\delta$	parasite decay rate in the environment	$2$ <u>parasites/parasite/time</u>
$d$	host death rate	$0.5$ <u>hosts/host/time</u>
$\tau$	time between host infection and host death ( <u>1/virulence</u> )	<del>varies</del> <u>time (evolves)</u>

Table 1: Model parameters and their respective values.

81 The parasite-free equilibrium is unstable and a single parasite introduced into the system at the beginning  
82 of the season will persist if the density of  $v_2$  produced by time  $T$  is greater than or equal to  $\hat{v} = v_1(0) = 1$   
83 (*i.e.*  $v_2(T) \geq 1$ , modulus is greater than unity). This expression is a measure of a parasite's fitness when rare  
84 given different host phenological patterns. See Appendix A for details of the analytical solution.

### 85 3.0.2 Parasite evolution

86 To study how parasite traits adapt given different seasonal host activity patterns, we use evolutionary invasion  
87 analysis.<sup>44,45</sup> We first extend system (1) to follow the invasion dynamics a rare mutant parasite

$$\frac{ds}{dt} = \hat{s}g(t, t_l) - ds(t) - \alpha\underline{\gamma}s(t)v_1(t) - \alpha_m\underline{\gamma}_m s(t)v_{1m}(t), \quad (2a)$$

$$\frac{dv_1}{dt} = -\delta v_1(t), \quad (2b)$$

$$\frac{dv_{1m}}{dt} = -\delta_m v_{1m}(t), \quad (2c)$$

$$\frac{dv_2}{dt} = \alpha\beta\underline{\gamma}s(t - \tau)v_1(t - \tau) - \delta v_2(t), \quad (2d)$$

$$\frac{dv_{2m}}{dt} = \alpha_m\beta_m\underline{\gamma}_m s(t - \tau_m)v_{1m}(t - \tau_m) - \delta_m v_{2m}(t). \quad (2e)$$

88 where  $m$  subscripts refer to the invading mutant parasite and its corresponding traits. See Appendix B for  
89 details of the time-dependent solutions for equations (2a-2e).

90  
91 The invasion fitness of a rare mutant parasite depends on the density of  $v_{2m}$  produced by the end of the  
92 season ( $v_{2m}(T)$ ) in the environment set by the resident parasite at equilibrium density  $\hat{v}^*$ . The mutant  
93 parasite invades in a given host phenological scenario if the density of  $v_{2m}$  produced by time  $T$  is greater  
94 than or equal to the initial  $v_{1m}(0) = 1$  introduced at the start of the season ( $v_{2m}(T) \geq 1$ ).

$$v_{2m}(T) = e^{-\delta_m(T-t_l-\tau_m)}(v_{2m}(t_l+\tau_m) + \alpha_m\beta_m e^{-d\tau_m}v_{1m}(0)s_1(t_l))$$

$$\int_0^{T-t_l-\tau_m} e^{\frac{\alpha_m v_{1m}(0)e^{-\delta_m(s+t_l)}(-1+e^{-\delta_m s})}{\delta_m} + \frac{\alpha \hat{v}^* e^{-\delta(s+t_l)}(-1+e^{-\delta s})}{\delta} - \delta_m t_l - ds} \frac{\alpha_m v_{1m}(0)e^{-\delta_m(s+t_l)}(-1+e^{-\delta_m s})}{\delta_m} - \frac{\alpha \hat{v}^* e^{-\delta(s+t_l)}(-1+e^{-\delta s})}{\delta} ds$$
(3)

95 To study the evolution of virulence traits, we first assume all other resident and mutant traits are identical  
 96 (e.g.  $\alpha = \alpha_m$ ). Note that when there is no trade-off between  $\beta$  and  $\tau$ , the parasite growth rate in the host is  
 97 essentially the trait under selection. That is,  $\beta$  is constant regardless of  $\tau$  thus the time between infection and  
 98 when the parasite kills the host and releases new parasites is the rate that  $\beta$  new parasites are assembled.  
 99 To find optimal virulence for a given host phenological scenario, we find the uninvadable trait value that  
 100 maximizes (3). That is, the virulence trait,  $\tau^*$ , that satisfies

$$\frac{\partial v_{2m}(T)}{\partial \tau_m} \Big|_{\tau_m=\tau_r} = 0 \quad (4a)$$

$$\frac{\partial^2 v_{2m}(T)}{\partial \tau_m^2} \Big|_{\tau_m=\tau_r} < 0 \quad (4b)$$

101 Note that the measure in equation (3) incorporates the effect of the resident on the population state (number  
 102 of susceptibles over one season), which means that it is not a measure of  $R_0$  (which by definition assumes  
 103 a non-disease environment). Thus, we can use  $v_{2m}(T)$  as defined in (3) as a maximand in evolutionary  
 104 dynamics<sup>46</sup>.

105 To study the impact of mechanistic trade-offs between transmission and virulence on virulence evolution, we  
 106 assume that the number of parasites produced at host death is a function of the time between infection and  
 107 host death ( $\beta(\tau)$ )

$$v_{2m}(T) = e^{-\delta_m(T-t_l-\tau_m)}(v_{2m}(t_l+\tau_m) + \alpha_m\beta(\tau_m)e^{-d\tau_m}v_{1m}(0)s_1(t_l))$$

$$\int_0^{T-t_l-\tau_m} e^{\frac{\alpha_m v_{1m}(0)e^{-\delta_m(s+t_l)}(-1+e^{-\delta_m s})}{\delta_m} + \frac{\alpha \hat{v}^* e^{-\delta(s+t_l)}(-1+e^{-\delta s})}{\delta} - \delta_m t_l - ds} \frac{\alpha_m v_{1m}(0)e^{-\delta_m(s+t_l)}(-1+e^{-\delta_m s})}{\delta_m} - \frac{\alpha \hat{v}^* e^{-\delta(s+t_l)}(-1+e^{-\delta s})}{\delta} ds$$
(5)

108 We then find  $\tau^*$  that satisfies (4a) and (4b) using equation (5).

## 4 Results

Host phenology, in the absence of a mechanistic trade-off, is sufficient to drive the evolution of intermediate virulence in systems that conform to the assumptions of the model. Host phenology is composed of the duration of the activity period and the distribution of initial emergence times, both of which impact the optimal parasite virulence level. ~~The duration of host activity~~ Temporally constrained host activity periods within each season can select against both ~~the extremely virulent and avirulent traits~~ extremely high and extremely low virulence levels resulting in an intermediate optimal level of virulence. ~~The avirulent trait~~ Low virulence is selected against as parasites that do not kill the infected host prior to the end of the host activity period fail to produce progeny and thus have no evolutionary fitness. By contrast, highly-virulent parasites kill their hosts quickly and the released progeny decay in the environment for the remainder of the activity period. Thus, progeny released early in the host activity period are more likely to die in the environment prior to contacting a naive host in the following season. An intermediate virulence level that allows parasites to kill their host prior to the end of the activity period, but not so quickly that the progeny produced are likely to decay in the environment, result in the greatest evolutionary fitness.

The optimal virulence level increases linearly with decreases in the duration of host activity (Figure 2). Virulent parasites in environments where host activity periods are ~~of short duration~~ short minimize the cost of not producing progeny from infected hosts and do not incur the costs of progeny decaying in the environment. By contrast, environments where host activity periods are long favor parasites with a long incubation period to limit the cost of progeny decay due to environmental exposure while still killing hosts prior to the end of the season. The optimal level of virulence in all environmental scenarios results in parasite-induced host death just prior to the end of the seasonal activity period. The linear increase in optimal virulence as season length decreases suggests that parasite fitness is optimized when host death occurs at a fixed time before the end of the season.

Variation in the time at which each host first becomes active during the activity period also impacts the virulence levels that maximize parasite fitness (Figure 3). Synchronous host emergence results in a rapid and early spike in infection incidence due to the simultaneous availability of susceptible hosts and the abundance of free parasites. The long duration between host infection and the end of the activity period favors low virulence parasites that kill their host near the end of the season (Figure 3A, i). Variability in the time at which each susceptible host initially becomes active decreases the average time between infection and the end of the season, thus favoring more virulent parasites (Figure 3A, ii). That is, the large proportion of infections that occur later in the season require higher virulence to be able to release progeny before the activity period ends. This higher virulence level comes at the cost of progeny from hosts infected early in the season decaying in the environment. Thus, the number of progeny that survive to the next season decreases with increasing variation in host emergence times (Figure 3B).

High variability in host emergence timing results in an optimal virulence strategy that is much greater than in environments with synchronous host emergence, but lower than in environments with a moderate distribution (Figure 3). That is, increasing variation in host emergence timing favors parasites with higher virulence, but only when variation in host emergence timing is high. In environments where the variation in host emergence timing is high, increasing variation in host emergence timing favors parasites with slightly lower virulence (Figure 3A, iii). Lower virulence is favored in high emergence variability environments because the number of new infections occurring late in the season, where high virulence would be advantageous, are relatively rare due to small parasite population sizes at the beginning of the season and parasite decay

151 during the season. Initial parasite population sizes are smaller in environments with broadly distributed  
152 host emergence timing as fewer total hosts are infected because infection probability is density dependent,  
153 and thus fewer progeny are produced. Most parasites that find a susceptible host do so early in the season  
154 resulting in additional decreases to the already small parasite population size. The optimal virulence strategy  
155 allows parasites that infect hosts around the peak of new infections - occurring mid-season when susceptible  
156 host densities are greatest and parasite populations have not decayed substantially - to release progeny while  
157 limiting decay of these progeny. Parasites in environments where the distribution in host emergence times is  
158 very broad suffer the costs of both decay of the progeny released by early-infected hosts and the cost of late  
159 infected hosts not releasing progeny, collectively causing these environments to maintain low densities of  
160 moderately virulent pathogens (Figure 33B, *iii*).

161 Mechanistic virulence-transmission trade-offs can modify the optimal virulence strategy in seasonal  
162 environments but are not necessary for natural selection to favor intermediate virulence phenotypes. The  
163 optimal virulence strategy is slightly lower in models that include a trade-off where duration of infection is  
164 positively correlated with progeny production than in models with the same phenological parameters that do  
165 not include the trade-off (Figure 4). Including this trade-off increases the fitness benefit of longer-duration  
166 infections to a greater extent than the costs associated with infected host mortality not caused by the parasite.  
167 By contrast, the optimal virulence strategy is greater in models that include a trade-off where duration of  
168 infection is negatively correlated with progeny production than in similar models without the trade-off  
169 (Figure 4). Including this trade-off increases the fitness benefit of shorter-duration infections despite the  
170 added costs of greater parasite decay due to environmental exposure. Including mechanistic trade-offs  
171 modifies the selection pressures on virulence strategies but are not essential for an intermediate virulence  
172 strategy to be optimal in seasonal environments.



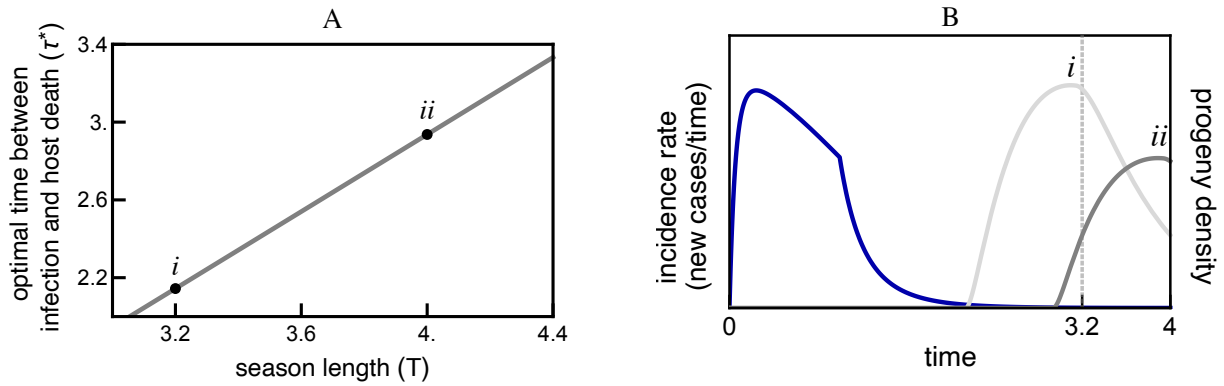


Figure 2: **Host seasonality is sufficient to select an intermediate virulence strategy.** **A.** The temporal duration between infection and host death ( $\tau^*$ ) always evolves to a value that is greater than 0 (extreme virulence) and less than ~~infinity~~ ~~the season length~~ (avirulence ~~extremely low virulence~~); the intermediate virulence strategy maximizes parasite fitness in environments where host activity is seasonal. The optimal parasite-induced host death rate results in host death and progeny release shortly before the end of the season ( $t = T$ ). The release of progeny just prior to the end of the season limits the decay of progeny due to environmental exposure while avoiding progeny dying within their host at the end of the season. *i* and *ii* are representative examples of optimal virulence strategies in environments with shorter ( $T = 3.2$ ) or longer ( $T = 4$ ) host activity periods, respectively.  $\tau^*$  is found using equation (4a) when there is no trade-off between transmission and virulence. **B.** Higher parasite virulence is favored in environments with limited host activity periods. Parasites with greater virulence produce more progeny that survive to the end of the season when seasons are short. That is, the density of the more virulent progeny (*i*) at  $T = 3.2$  is greater than the density of the less virulent progeny (*ii*). The more virulent parasites kill their hosts quickly such that few infected hosts survive to the end of the season and the progeny released spend little time in the environment. By contrast, less virulent parasites (*ii*) often fail to kill their hosts and release progeny prior to the end of short activity periods ( $T = 3.2$ ). Longer seasons ( $T = 4$ ) favor less virulent parasites (*ii*) as they kill their hosts closer to the end of the season such that fewer of their released progeny decay in the environment (*ii*) than the progeny of the more virulent parasites that are released earlier in the season (*i*). The blue line represents the incidence rate of new infections;  $t_l = 1$ ; all other parameters found in Table 1.

## 5 Discussion

The overwhelming majority of Nearly all theory developed to predict explain parasite virulence evolution has focused on utilized mechanistic trade-offs between virulence and other traits important to parasite fitness.<sup>5,6</sup> The results of this study show that seasonal host activity, in the absence of a mechanistic trade-off, can account for the diversity of virulence strategies observed in nature why intermediate virulence is adaptive in some specific situations. Both aspects of phenology, the duration of the host activity period and host emergence synchronicity, impact the virulence strategy that maximizes the evolutionary fitness of parasites. Although mechanistic trade-offs between transmission and virulence virulence and transmission can shift the optimal virulence level as predicted by prior theory, these trade-offs are not the major force driving adaptation. Given how common it is for species to alter their activity levels seasonally, this phenomena could occur more broadly than the specific system we investigate here. Further, the essential for intermediate virulence to evolve in this system. The current demonstration that an ecological context alone selects is sufficient to select for intermediate virulence broadens the scope of factors that can explain the diversity of parasite virulence strategies. Thus, the evolution of parasite virulence in systems where empirical data do not support the existence of a mechanistic trade-off may instead be governed intermediate virulence in natural systems may be governed a mechanistic trade-off or by ecological factors such as phenology alone.

Seasonal host activity selects can select for intermediate virulence by generating conflicting costs for

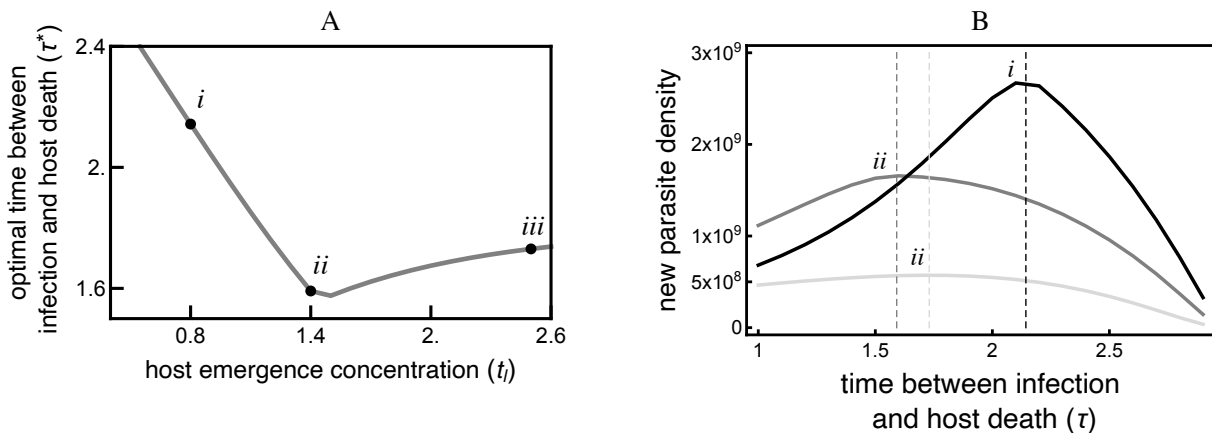


Figure 3: **The variation in host emergence timing impacts the optimal virulence strategy.** **A.** Parasites with lower virulence are favored in environments where nearly all hosts emerge simultaneously (*i*). Progeny from the low virulence parasites are released nearly simultaneously just prior to the end of the season. High virulence parasites are favored in environments where host emergence period length is moderate (*ii*). Moderate variation in host emergence decreases the average time between infection and the end of the season and favors parasites with a high virulence strategy such that few infected hosts survive to the end of the season. Parasites in environments where host emergence variation is very high maximize the number of progeny that survive to the next season by using a moderate virulence strategy (*iii*). Parasites in these environments suffer the costs of hosts that are infected later in the season not releasing progeny as well as progeny decay in the environment when released from early-infected hosts. A moderate virulence strategy allows hosts infected around the mid-season peak in incidence to release progeny while limiting the decay of these progeny.  $\tau^*$  is found using equation (4a) when there is no trade-off between transmission and virulence. **B.** Equilibrium density of parasites with the optimal virulence strategy for their environment decreases with increasing variation in host emergence timing. Optimal virulence results in peak equilibrium in new parasites density, indicated by the vertical lines.  $T = 3$ ; other parameters found in Table 1.

190 releasing progeny too early or too late in the season. ~~Avirulence is maladaptive as parasites that~~ Low virulence  
 191 is maladaptive for parasites in this system as they do not kill their host before the end of the season and  
 192 no progeny ~~and result in no evolutionary fitness~~. High virulence is also maladaptive as progeny released early  
 193 are more likely to die due to environmental exposure. The conflicting costs of not releasing progeny before  
 194 the end of the season and releasing progeny too early in the season selects for intermediate virulence levels.  
 195 Optimal virulence results in parasite-induced host death and the release of progeny slightly before the end  
 196 of the host activity period. These results suggest that seasonal host absence can increase the evolutionary  
 197 benefit of remaining within hosts in order to reduce deaths in the free-living stage caused by environmental  
 198 exposure.

199 Variation in ~~the time at which hosts first emerge~~ host emergence synchronicity impacts the optimal  
 200 virulence strategy of parasites in this system. High parasite virulence is favored at low host emergence  
 201 synchronicity. Low emergence synchronicity slows incidence by decreasing both the rate hosts emerge and  
 202 parasite equilibrium density. When more infections occur later in the season, parasites have less time to

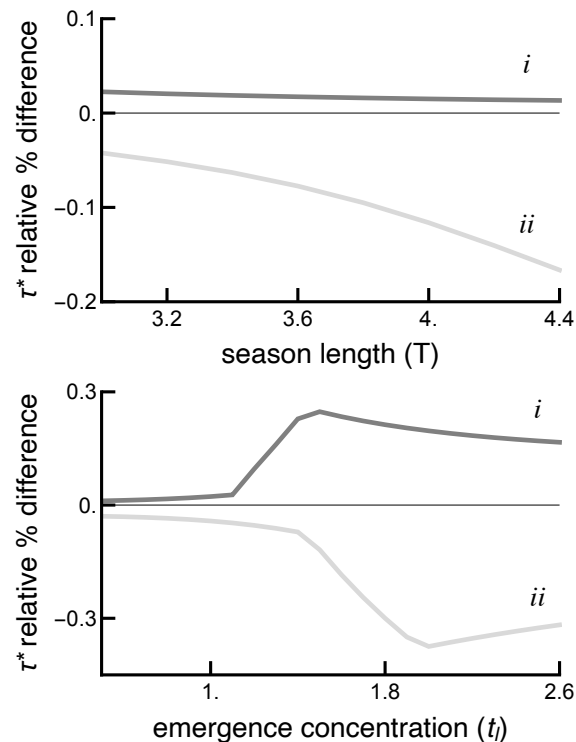


Figure 4: **Mechanistic transmission-virulence trade-offs shift the optimal virulence strategy but are not necessary to favor intermediate virulence in environments with seasonal host activity.** The optimal virulence level for parasites in which longer durations of infection result in *more* progeny is slightly lower than for parasites that are not constrained with this mechanistic trade-off in the same environment (*i*). This mechanistic trade-off elevates the fitness benefit of longer duration infections by compensating for the cost of infected hosts dying without releasing progeny. The optimal virulence level for parasites in which longer infection durations result in *fewer* progeny is greater than for parasites without this trade-off in the same seasonal environments (*ii*). This mechanistic trade-off elevates the fitness benefit of shorter duration infections despite the cost of greater progeny decay in the environment.  $\tau^*$  was found using equation (4a) when there is no trade-off between transmission and virulence and then compared to  $\tau^*$  constrained by a trade-off with transmission. Trade-off for *i* :  $\beta(\tau) = 99(\tau + 0.5)$ , trade-off for *ii* :  $\beta(\tau) = 99(-\tau + 4)$ . All other parameters found in Table 1.

203 release new parasites before the end of the season. High parasite virulence is adaptive because hosts have  
204 a low expected life span at the time of infection. This result is analogous to the prediction that high host  
205 mortality drives the evolution of high virulence.<sup>4,9-11</sup> The timing of host activity can thus lead to the evolution  
206 of high virulence in a similar manner ~~that to how~~ host demography impacts virulence.

207 The seasonal activity patterns of species with non-overlapping generations may have large impacts on  
208 the virulence strategies of the parasites they host. For example, parasites ~~of annual plants and parasitoids of~~  
209 ~~univoltine insects~~ that complete one round of infection per host generation (~~monocyclic parasites~~) may  
210 maximize their fitness by releasing progeny just prior to the end of the season<sup>47,32-39</sup>. The theoretical  
211 expectations presented here can be tested empirically by measuring the virulence strategies of parasites  
212 across the natural diversity of phenological patterns observed over the geographical range of many ~~plant~~  
213 ~~insect~~ species. Similarly, ~~common garden~~ experiments could rigorously assess the impact of both season  
214 length and host emergence variability on the fitness of parasites with different levels of virulence.

215 The prediction that shorter host activity periods can drive greater virulence is comparable to how the  
216 virulence of different *Theileria parva* strains varies between regions. High within-host densities ~~permits permit~~  
217 a virulent *T. parva* strain to be reliably transmitted to feeding nymphal tick vectors shortly after being infected  
218 by the adult stage in regions where the activity patterns of the two ~~tick~~ life stages overlap.<sup>48-50</sup> In contrast, the  
219 virulent strain is absent in regions where nymphal and adult activity is asynchronous while a less virulent  
220 strain that persists in hosts longer is maintained.<sup>48,49</sup> Thus, the prediction that the length of the host activity  
221 period is inversely correlated with virulence coincides with empirical observations of the distribution of *T.*  
222 *parva* strains.

223 Several features of the current model can be altered to investigate more complex impacts of phenology  
224 on virulence evolution. For example, relaxing the assumption of a constant host population size may result  
225 in a feedback between parasite fitness and host demography with consequences for population dynamics.  
226 Additionally, parasite virulence evolution may select for alternative host phenological patterns that in turn  
227 select for parasite traits with lower impacts on host fitness. We will extend the current model to address  
228 these questions in future studies.

229 The ~~model presented applies to obligate-killer parasites that complete one round of infection per season~~  
230 ~~(monocyclic) in hosts that have non-overlapping generations. Currently, there is no evidence that disease~~  
231 ~~systems that do not conform to these assumptions will not require a mechanistic trade-off to select for~~  
232 ~~intermediate virulence. Nevertheless, several prior models that included both host seasonality and mechanistic~~  
233 ~~trade-offs found qualitatively similar results as those presented here despite relaxing one or more of the strict~~  
234 ~~assumptions in this model<sup>28-30</sup>, suggesting that phenology can have a large impact on virulence outcomes.~~  
235 ~~For example, longer seasons or longer periods between seasons have been shown to select for lower virulence~~  
236 ~~in polycyclic parasites in seasonal environments<sup>29,30</sup>, similar to the results presented here. Similarly, explicitly~~  
237 ~~modeling parasite growth rates within hosts, which underlie the correlation between virulence and instantaneous~~  
238 ~~transmission rates, selects for intermediate virulence levels that maximize transmission rates during host~~  
239 ~~activity periods<sup>28</sup>. By contrast, assuming that virulence levels are mechanistically associated with host~~  
240 ~~density results in selection for higher virulence in seasonal environments<sup>31</sup>. Future studies incorporating~~  
241 ~~one or more of these competing forces with environmental decay of progeny could be sufficient to select for~~  
242 ~~intermediate virulence in the absence of an explicit mechanistic trade-off.~~

243 ~~Some of the strict model assumptions can likely be relaxed without altering the result that phenology~~  
244 ~~can be sufficient to select for intermediate virulence strategies. Relaxing the obligate-killer assumption may~~  
245 ~~result in the same qualitative result that intermediate virulence is adaptive in some cases. For example,~~

246 longer latency periods that result in progeny release near the end of the season would still be adaptive for  
247 parasites that reduce host fecundity or increase host death rate, even if there is no correlation between the  
248 virulence level and instantaneous or life-time transmission. Longer latency periods are equivalent to lower  
249 virulence in this type of system as infected hosts have more time to reproduce and thus higher fitness. This  
250 extension is not expected to qualitatively alter the results if the parasite transmission period is short relative  
251 to the season length. Many parasite-host systems conform to the assumptions of this model extension such  
252 as soil-borne plant pathogens, demicyclic rusts, post-harvest diseases, and many diseases systems infecting  
253 univoltine insects<sup>51–54</sup>.

254 The importance of parasite virulence to both host-parasite interactions and public health policy has  
255 resulted in a concentrated research effort on virulence evolution. ~~The majority of theoretical research has~~  
256 ~~focused on mechanistic trade-offs~~ Nearly all theoretical research to date has incorporated a mechanistic  
257 trade-off between virulence and transmission rates or infection duration ~~although empirical support for these~~  
258 ~~models is rare.~~ Ecological, a hypothesis which is still essential to explain the evolution of intermediate  
259 virulence in most disease systems. However, ecological factors such as seasonal host activity or spatial  
260 structuring provide alternative theoretical frameworks that may account for virulence strategies in ~~many~~  
261 some natural systems.<sup>55,56</sup> Future work that identifies and empirically validates ecological factors that  
262 influence virulence evolution would be useful for predicting outbreaks of highly virulent parasites.

## 263 6 Code and data availability

264 Code is available on the Github repository: [https://github.com/hanneloremac/Host-phenology-drives-the-](https://github.com/hanneloremac/Host-phenology-drives-the-evolution-of-intermediate-parasite-virulence)  
265 [evolution-of-intermediate-parasite-virulence](https://github.com/hanneloremac/Host-phenology-drives-the-evolution-of-intermediate-parasite-virulence)

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## Appendix A

In Appendix A we find analytical solutions for equations 1a-c from the main text to study parasite fitness given different host phenological patterns.

$$\frac{ds}{dt} = \hat{s}g(t, t_l) - ds(t) - \alpha s(t)v_1(t), \quad (\text{A.1a})$$

$$\frac{dv_1}{dt} = -\delta v_1(t), \quad (\text{A.1b})$$

$$\frac{dv_2}{dt} = \alpha\beta e^{-d\tau} s(t-\tau)v_1(t-\tau) - \delta v_2(t). \quad (\text{A.1c})$$

with initial conditions:  $s(0) = 0, v_1(0^+) = v_2(0^-), v_2(\tau) = 0$ .

(A.1a-c) is solved analytically by describing host emergence using a uniform distribution

$$g(t, t_l) = \begin{cases} \frac{1}{t_l} & 0 \leq t \leq t_l \\ 0 & t_l < t \end{cases}$$

To solve the dynamics during the host's activity period, we first find the analytical solution for  $v_1(t)$ :

$$v_1(t) = \hat{v}e^{-\delta t}$$

We then use  $v_1(t)$  to find the time-dependent solutions for both  $s(t)$  and  $v_2(t)$ :

$$s(t) = \begin{cases} \frac{\hat{s}}{t_l} e^{(-dt + \frac{\alpha\hat{v}e^{-\delta t}}{\delta})} \int_0^t e^{(ds - \frac{\alpha\hat{v}e^{-\delta s}}{\delta})} ds & 0 < t < t_l \\ s(t_l) e^{(-d(t-t_l) - \frac{\alpha\hat{v}e^{-\delta t}(1-e^{\delta(t-t_l)})}{\delta})} & t_l \leq t < T \end{cases}$$

$$v_2(t) = \begin{cases} \frac{\alpha\beta e^{-d\tau} \hat{v} \hat{s}}{t_l} e^{-\delta t} \int_0^t e^{(-ds + \frac{\alpha\hat{v}e^{-\delta s}}{\delta})} \int_0^s e^{(dx - \frac{\alpha\hat{v}e^{-\delta x}}{\delta})} dx ds & \tau < t < t_l \\ e^{-\delta(t-t_l-\tau)} (v_2(t_l+\tau) + \alpha\beta e^{-d\tau} \hat{v} s(t_l) \int_0^{t-t_l-\tau} e^{-\frac{\alpha\hat{v}e^{-\delta(s+t_l)(-1+e^{\delta s})}{\delta} - \delta t_l - ds} ds) & t_l \leq t < T \end{cases}$$

where  $s(t_l)$  is the density and  $v_2(t_l)$  are the densities of  $s$  when their emergence period ends and  $v_2(t_l+\tau)$  is the density of and  $v_2$  when the emergence period of  $s$  ends.

A parasite introduced into a naive host population persists or goes extinct depending on the host emergence period length and season length. The stability of the parasite-free equilibrium is determined by the production of  $v_2$  resulting from infection of  $s$  given by

$$v_2(T) = e^{-\delta(T-t_l-\tau)} (v_2(t_l+\tau) + \alpha\beta e^{-d\tau} \hat{v} s(t_l) \int_0^{T-t_l-\tau} e^{\frac{\alpha\hat{v}(-1+e^{-\delta s})}{\delta} - \delta t_l + -ds - \frac{\alpha\hat{v}e^{-\delta(s+t_l)(-1+e^{\delta s})}{\delta} - \delta t_l - ds} ds)$$

The parasite-free equilibrium is unstable and the parasite will persist in the system if the density of  $v_2$  produced by time  $T$  is greater than or equal to  $\hat{v} = v_1(0) = 1$  introduced at the beginning of the activity period of  $s$  (i.e.  $v_2(T) \geq 1$ , modulus is greater than unity). This expression is a measure of a parasite's fitness when rare given different host phenological patterns.

## 402 Appendix B

403 In Appendix B we find analytical solutions for equations 2a-e from the main text to study the evolution of  
 404 parasite virulence given different host phenological patterns.

$$\frac{ds}{dt} = \hat{s}g(t, t_l) - ds(t) - \alpha\underline{\gamma}s(t)v_1(t) - \alpha_m\underline{\gamma}_m s(t)v_{1m}(t), \quad (\text{B.1.a})$$

$$\frac{dv_1}{dt} = -\delta v_1(t), \quad \frac{dv_{1m}}{dt} = -\delta_m v_{1m}(t), \quad (\text{B.1.b})$$

$$\frac{dv_2}{dt} \frac{dv_{2m}}{dt} = \alpha_m \beta \underline{\gamma}_m s(t - \tau_m) v_{1m}(t - \tau_m) - \delta_m v_{2m}(t). \quad (\text{B.1.c})$$

$$\frac{dv_1}{dt} = -\delta v_1(t), \quad (\text{B.1.d})$$

$$\frac{dv_{2m}}{dt} \frac{dv_2}{dt} = \alpha_m \beta_m \underline{\gamma}_m s(t - \tau_m) v_{1m}(t - \tau_m) - \delta_m v_{2m}(t). \quad (\text{B.1.e})$$

405 Where with initial conditions:  $s(0) = 0, v_{1m}(0^+) = v_{2m}(0^-), v_{2m}(\tau) = 0, v_1(0^+) = v_2(0^-), v_2(\tau) = 0$ .  $m$  subscripts  
 406 refer to the invading mutant parasite and its corresponding traits.

407

(B.1.a-e) has the following time-dependent solution:

$$\begin{aligned} v_{1m}(t) &= v_{1m}(0)e^{-\delta_m t} & 0 < t < T \\ s_1(t) &= \begin{cases} \frac{\hat{s}_1}{t_l} e^{(-dt + \frac{\alpha \hat{v}^* e^{-\delta t} + \alpha_m v_{1m}(0)e^{-\delta_m t}}{\delta_m})} \int_0^t e^{(ds - \frac{\alpha \hat{v}^* e^{-\delta s} + \alpha_m v_{1m}(0)e^{-\delta_m s}}{\delta_m})} ds & 0 < t < t_l \\ s(t_l) e^{(-d(t-t_l) - (\frac{\alpha \hat{v}^* e^{-\delta(t-t_l)}(1-e^{\delta t}) + \frac{\alpha_m v_{1m}(0)e^{-\delta_m(t-t_l)}(1-e^{\delta_m t})}{\delta_m})} t_l \leq t < T \end{cases} \\ v_{2m}(t) &= \begin{cases} \frac{\alpha_m \beta_m e^{-d\tau_m} v_{1m}(0) \hat{s}}{t_l} e^{-\delta_m t} \int_0^t e^{(-ds + \frac{\alpha \hat{v}^* e^{-\delta s} + \alpha_m v_{1m}(0)e^{-\delta_m s}}{\delta_m})} \int_0^s e^{(dx + \frac{\alpha \hat{v}^* e^{-\delta x} + \alpha_m v_{1m}(0)e^{-\delta_m x}}{\delta_m})} dx ds & \tau_m < t < t_l \\ e^{-\delta_m(t-t_l-\tau_m)} (v_2(t_l) + \alpha_m \beta_m e^{-d\tau_m} v_{1m}(0) s_1(t_l) & \\ \int_0^{t-t_l-\tau_m} e^{-\frac{\alpha_m v_{1m}(0)e^{-\delta_m(s+t_l)}(-1+e^{-\delta_m s})}{\delta_m} - \frac{\alpha \hat{v}^* e^{-\delta(s+t_l)}(-1+e^{-\delta s})}{\delta} - \delta_m t_l - ds} ds) & t_l \leq t \leq T \end{cases} \end{aligned}$$

408 The invasion fitness of a rare mutant parasite is given by the density of  $v_{2m}$  produced by the end of the season.  
 409 The mutant parasite invades in a given host phenological scenario if the density of  $v_{2m}$  produced by time  $T$   
 410 is greater than or equal to the initial  $v_{1m}(0) = 1$  introduced at the start of the season ( $v_{2m}(T) \geq 1$ ).

$$\begin{aligned} v_{2m}(T) &= e^{-\delta_m(T-t_l-\tau_m)} (v_2(t_l + \tau_m) + \alpha_m \beta_m e^{-d\tau_m} v_{1m}(0) s_1(t_l) \\ &\quad \int_0^{T-t_l-\tau_m} e^{\frac{\alpha_m v_{1m}(0)e^{-\delta_m(s+t_l)}(-1+e^{-\delta_m s})}{\delta_m} + \frac{\alpha \hat{v}^* e^{-\delta(s+t_l)}(-1+e^{-\delta s})}{\delta} - \delta_m t_l - ds} \frac{\alpha_m v_{1m}(0)e^{-\delta_m(s+t_l)}(-1+e^{-\delta_m s})}{\delta_m} - \frac{\alpha \hat{v}^* e^{-\delta(s+t_l)}(-1+e^{-\delta s})}{\delta} ds \end{aligned}$$

411 We use  $v_{2m}(T)$  to find optimal virulence for a given host phenological scenario by finding the trait value that  
 412 maximizes  $v_{2m}(T)$ . That is, the virulence trait,  $\tau^*$ , that satisfies

$$\left. \frac{dv_{2m}(T)}{d\tau_m} \right|_{\tau_m=\tau_r} = 0 \quad (\text{B.2})$$

$$\left. \frac{d^2v_{2m}(T)}{d\tau_m^2} \right|_{\tau_m=\tau_r} < 0 \quad (\text{B.3})$$

413 We use (B.2) to find  $\tau^*$  in Figures 1A, 2A, 3A and 3B in the main text. For all phenological patterns,  $\tau^*$  is  
 414 uninvadable *i.e.* condition (B.3) is satisfied.

415 To study the impact of mechanistic trade-offs between transmission and virulence on virulence evolution,  
 416 we assume that the number of parasites produced at host death is a function of the time between infection  
 417 and host death ( $\beta(\tau)$ ). This is done in Figures 3A and 3B where a mechanistic trade-off is assumed to exist  
 418 between  $\tau$  and  $\beta$  in (B.2).