Opinion

The influence of biological rhythms on host–parasite interactions

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Biological rhythms, from circadian control of cellular processes to annual cycles in life history, are a main structural element of biology. Biological rhythms are considered adaptive because they enable organisms to partition activities to cope with, and take advantage of, predictable fluctuations in environmental conditions. A flourishing area of immunology is uncovering rhythms in the immune system of animals, including humans. Given the temporal structure of immunity, and rhythms in parasite activity and disease incidence, we propose that the intersection of chronobiology, disease ecology, and evolutionary biology holds the key to understanding host–parasite interactions. Here, we review host–parasite interactions while explicitly considering biological rhythms, and propose that rhythms: influence within-host infection dynamics and transmission between hosts, might account for diel and annual periodicity in host–parasite systems, and can lead to a host–parasite arms race in the temporal domain.

Biological timekeeping

Environmental rhythms are a ubiquitous feature of our planet. Many rhythms are caused by geophysical cycles, including diel, tidal, lunar, and annual rhythms (see Glossary). These rhythms are predictable and have resulted in the evolution of biological clocks throughout the tree of life [1]. Most biological activities have rhythmic time structure, which scales from gene expression to life-history events, such as breeding and hibernation. Rhythmic time structure enables organisms to partition and prioritize life-history activities, whether molecular or behavioral, relative to predictable fluctuations in environmental conditions. For example, for cyanobacteria, which are an ancient lineage, sunlight provides both energy and risk. Cyanobacteria have adapted to this challenge by temporally partitioning photosynthesis from UV-sensitive DNA replication [2]. Likewise, throughout the year, organisms must meet survival needs, while seasonally requiring further resources for reproduction and other activities. This leads to annual cycles of life history, when animals alternate between reproductively active states and inactive states, such as dormancy, hibernation, or migration

(a retreat to wintering grounds that buffer against resource scarcity) [1].

Over evolutionary time, organisms have adapted to environmental fluctuations by an internal representation of time (endogenous biological clocks) that perpetuate biological rhythms even when environmental conditions are kept constant. These rhythms are characteristically innate, evidenced by the observation that individuals who have never experienced environmental fluctuations display rhythmicity [1]. Endogenous biological rhythms oscillate

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Glossary

Adaptive immune system: cells of the adaptive immune system include B cells and T cells. The initiation of the adaptive immune response occurs after the initiation of the innate immune response. Receptors of adaptive immune cells require genetic recombination and alteration to be generated, resulting in antigen specificity and immunological memory [51,105].
Annual cycle: cycle with a length of approximately 1 y, with phases occurring consistently at a particular time every year, during the annual cycle.
Circadian: cycle that occurs with an approximate 24-h period, used in reference to endogenous rhythms.
Circannual: cycle that occurs with a period of approximately 1 y, used in reference to endogenous rhythms.
Diel cycle: cycle with a length of approximately 1 day, with phases occurring consistently at a particular time during the day–night cycle.
Immune defense: immune defense includes(i) resistance against the establishment of infection and the reproduction of parasites; and (ii) parasite tolerance, in which the host mitigates the pathological consequences of infection, but tolerates infection.
Innate immune system: cells of the innate immune system include macrophages and neutrophils. Innate immune cells are immediate responders to infection. A fundamental distinction between innate and adaptive immune cells is that innate immune cell receptors responsible for immune recognition are encoded in the germline, whereas receptors of adaptive immune cells require genetic recombination and alteration to be generated. It was previously thought that the innate immune response is not parasite specific and lacks memory, but that characterization is now considered incorrect [105].
LD cycle: cycle in which light and darkness alternate, and each last for a given duration, for example in LD 12:12 h, light and darkness both last for 12 h.
Macroparasites: parasites that are large and typically metazoans (e.g., helminths).
Microparasites: parasites that are small and often unicellular (e.g., pathogenic viruses, bacteria, and fungi).
Macrophage: phagocytes, often referred to as 'big eaters' because they engulf invading bacteria and are responsible for clearance of dead (apoptotic) cells. Macrophages are one of the cells responsible for detection and restriction of parasite invasion.
Parasite resistance: the ability of the immune response of the host to prevent infection from establishing or to limit parasite replication. Parasite resistance has a negative impact on parasite fitness [106].
Parasite tolerance: the ability of the host to mitigate the pathological consequences of infection, rather than mitigate infection itself. Parasite tolerance does not necessarily have a negative impact on parasite fitness [106].
Seasonal: referring to one or more different phases in the annual cycle of either an organism or its environment. The timing of seasonal events is termed phenology.

with period lengths that approximate those of geophysical cycles, and are accordingly called circadian, circatidal, circalunar, and circannual. Circadian rhythms, which are most heavily studied, are driven by cell-autonomous transcription–translation feedback loops that are integrated across the organism. The evolutionary origin of internal clocks is ancient, with circadian clocks being a unifying feature of eukaryotes and cyanobacteria [3], and a new area of research in other bacterial lineages [4]. The endogenous circannual clock underlying seasonal rhythms is also thought to be evolutionarily conserved, because circannual clocks are found in organisms ranging from dinoflagellates [5] to mammals and birds [6,7].

An internal representation of time enables the anticipation of favorable environmental conditions, ensuring that activities are initiated in advance to match the opportune time. For example, to rear offspring at the time of maximal food abundance, many species activate their reproductive system and copulate far in advance, potentially under harsh conditions. If individuals initiated breeding activities when food abundance was maximal, offspring would be reared outside the optimal environmental window [6].

Endogenous biological clocks function in concert with the geophysical cycles to which they synchronize [8,9]. Synchronizing cues (also called 'zeitgebers') include diel and annual changes in light, temperature, and other factors. Jetlag, the overturning of rhythms resulting from changing time zones, and the subsequent resynchronization of the circadian clock, is familiar to many of us. Species and even populations vary in the way their clocks interact with the environment. They assume different phases, for example, of activity or reproduction, relative to the environmental cycle, and also differ in the use of synchronizing cues. To varying degrees, organisms retain the ability to adjust their rhythms to respond to current, less predictable, conditions. While the rhythms of some species show considerable phenotypic plasticity (e.g., the reproductive rhythm of great tits, *Parus major*), other species have rigid rhythms that impose fitness costs under rapid environmental change (e.g., the seasonal phenology of snowshoe hare *Lepus americanus* coat color) [8,10,11]. In addition to phenotypic plasticity, evolutionary malleability of biological rhythms is supported by directional evolution of time adjustments in multiple species, which include heritable shifts in the seasonal timing of life-history events, such as reproduction, dormancy, and migration [12,13].

Biological rhythms are observed across biological processes. In addition to substantial diel and annual fluctuations in activity, reproduction, and metabolism, there is also overwhelming evidence for temporal structuring of immunity. Importantly, such fluctuations cannot be comprehensively characterized as changes in overall immunity; rather, they are a selective reorganization of structural and functional aspects of the immune system [14–16]. Differentiated temporal structuring of immune defenses can arise from heterogeneous requirements and costs of specific defenses, investment in self-maintenance versus immunity, or the integration of immunity with other aspects of physiology [17,18]. In light of this, here we review biological rhythms pertinent to host–parasite interactions, and propose that rhythms of hosts, parasites, and the environment impose temporal structure on epidemiological and evolutionary dynamics.

Timekeeping in the host–parasite context

Interactions between hosts and parasites (i.e., microparasites and macroparasites) are embedded within environmental rhythms (Figure 1A). In addition to the environment, host immunity imposes selective pressure on parasites, while parasite-driven morbidity and mortality reduces host fitness. These multiple selective forces make optimal timing of allocation of limited resources to survival and reproduction tricky. For hosts, massive investment into parasite resistance, for instance, might only be energetically feasible during a resource pulse (i.e., opportunity) that is also favorable for reproduction, resulting in an optimization problem for resource allocation to survival versus reproduction [19]. Hosts also undoubtedly face the challenge of mitigating the deleterious effects of parasites when resources are scarce, a situation that might favor investment into parasite tolerance versus resistance. For parasites, not only does the host immune response impose risk, but additional risks can also be introduced by environmental regimes during transmission [20] or environmental life stages [21]. This has led to parasite risk avoidance strategies, such as climate-driven arrested development [22]. Therefore, for both hosts and parasites, external environmental conditions impose selective pressure by providing fluctuating opportunity for reproduction and risk of mortality. These exogenous factors need not be identical for hosts and parasites, although they co-occur in the same physical environment. For example, we need not expect that rhythms in parasite reproduction, host reproduction, and host immune investment be synchronous. An empirical case of this is the seasonal influence of temperature and humidity on development of a free-living nematode parasite (*Trichostrongylus*) of rabbits, which results in an Autumn peak in the force of infection; by contrast, the rhythm in host immunocompetence has a peak in Spring [23].

The temporal structure of host immunity and parasite success suggests that constraints: (i) preclude hosts from maintaining high levels of parasite resistance; and (ii) prevent parasites from sustaining high reproductive output (fitness). Such constraints would result in trade-offs between investments in opportunity versus risk avoidance [19,24]. Consequently, we hypothesize that both hosts and parasites time their biological processes with reference to both the external environment and each other, and that in many cases, periodic incidence of infectious disease is a consequence of biological rhythms, (see also, e.g., [25]). Below, we first lay out empirical evidence for the role of rhythms in host–parasite interactions. To inspire quantitative study of biological rhythms in host–parasite systems, we utilize a transmission model to illustrate the epidemiological consequences of rhythms. We then formulate a conceptual evolutionary model for understanding host–parasite dynamics embedded within the rhythmic context in which they are evolving.

Biological rhythms in host and parasite traits

The incidence of many infectious diseases displays substantial seasonality [26–28]. Seasonally structured disease
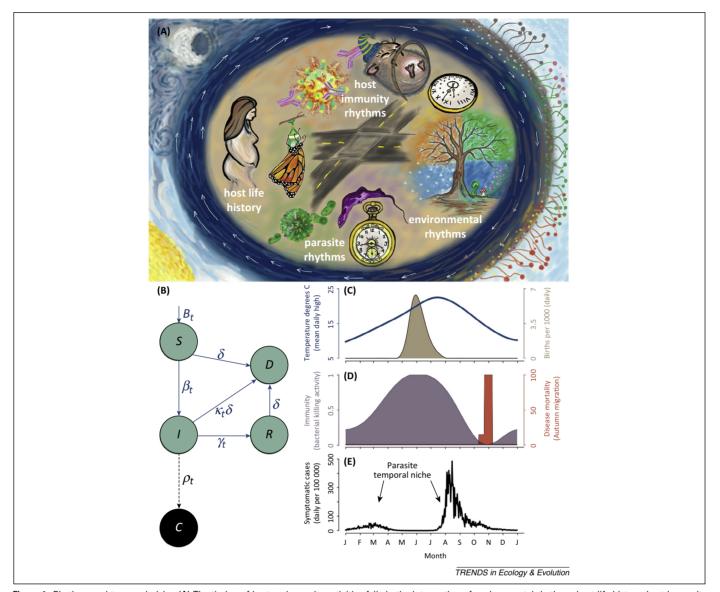
Figure 1. Rhythms and temporal niche. **(A)** The timing of host and parasite activities falls in the intersection of environmental rhythms, host life history, host immunity rhythms, and parasite rhythms. This intersection is embedded within geophysical rhythms, including diel and annual cycles. **(B)** Biological and environmental rhythms can enter into epidemiological models in multiple ways. The schematic shows a susceptible–infected–recovered model (*SIR*), with natural and disease-induced deaths, *D*. The model distinguishes between infections, *I*, and the subset of infections that are observed as symptomatic cases, *C*. The model is parameterized using the life history of Siberian stonechats. Four seasonal rhythms were entered into the model (births, temperature, immunity, and migration). Host births, B_t, are seasonal. The transmission rate, β_t, is a function of (i) an environmental rhythm (i.e., temperature) that influences parasite transmissibility; and (ii) the seasonal immune status of hosts. We assume that seasonal immunity also influences the recovery rate, γ_t, and the probability of symptoms, ρ_t. We also assume infected individuals suffer disease-induced mortality, κ_t, associated with the Autumn migration (i.e., migratory culling), which multiplies the (here constant) rate of natural mortality δ. **(C)** Annual fluctuations in ambient temperature and birth seasonality in Siberian stonechats [95]. **(D)** Annual host immunity is based on *Staphylococcus aureus* bacterial killing activity [53] and elevated mortality during Autumn migration is inferred from natural migratory timing. **(E)** Incidence of symptomatic cases assuming that temperature has a positive correlation with transmission, bacterial killing activity reduces transmission, reduces the probability of symptoms, and increases the recovery rate. The four seasonal rhythms act collectively to determine the temporal niche of the parasite, that is, the time of year when the parasite is abundant and disease outbreaks occur.

incidence can be discussed from the viewpoint of hosts or parasites. From the host perspective, parasite exposure can be influenced by host behavior, such as seasonal aggregation; a contemporary example is the epidemic seasonality of mycoplasmal conjunctivitis in house finches [29]. However, physiological factors influencing host susceptibility to infection and symptomatic disease, such as seasonal changes in immunity, can also drive disease seasonality [23,28,30]. Table 1 summarizes some known diel and annual rhythms in host immunity and parasite traits (reviewed in [16,31–34]). Although rhythms in immunity are observed across an array of taxa, including

plants [35,36] and animals, we focus on mammalian and avian hosts to enhance the link to human health. An active area of biomedical research is characterizing temporal structure in both innate and adaptive immunity and, correspondingly, in disease susceptibility [32,33]. Biomedical studies currently use model organisms, but in the future should include nonmodel species [37], which are either directly relevant for understanding natural host–parasite systems, or enable a broader understanding of within-host dynamics of infection. Longitudinal studies of wild or captive animals compare immune parameters during active versus resting phases and are typically combined with

Table 1. Diel (circadian) and annual (circannual and/or seasonal) rhythms in host immunity, parasite reproduction, and parasite release

Type	Period	Host trait or parasite description	Organism and/or species	Rhythm	Refs
Immunity	Diel	Macrophages (detection and restriction of parasite invasion)	Mice	>8% of transcripts circadian; autonomous macrophage circadian clock controls rhythm	[46]
		Natural killer cells (early defense against viruses and intracellular bacteria)	Humans	Circadian trafficking between the blood and organ compartments; inverse trafficking compared with T lymphocytes	[107]
		Toll-like receptor 9 (TLR9), evolutionarily conserved receptor that recognizes bacteria and viruses	Mice	Expression and function controlled by circadian clock	[47]
		T lymphocytes (surveillance for infected cells)	Humans	Cytokine production is circadian	[108,109]
		Leukocytes	Humans	Abundance in blood follows circadian rhythm for neutrophils, lymphocytes, monocytes, and eosinophils	[110]
		Whole blood response to LPS stimulation	Humans	Cytokine and chemokine production is circadian in environment free of time cues	[111]
		Salmonella colonization and host cytokine response to infection	Mice	Mice have a different immunological response to infection depending on whether infection challenge occurs during the day or at night; infection during the day results in more inflammation; this effect is due to clock-controlled gene expression	[49]
		Clock genes and pro-inflammatory cytokines in spleen; inflammatory response	Birds (captive)	mRNAs of cytokines and clock genes are rhythmic under LD cycles and constant conditions; inflammation is rhythmic under LD cycles	[112]
		Cellular (phytohemagglutinin) and humoral immune response	Birds (captive)	PHA response and antibody production depend on time of challenge, but their peaks are phase inversed	[17]
	Annual	Bacterial killing activity	Birds (captive), turtles (wild), and humans	Lower bactericidal activity during migration, especially in Autumn (birds); higher bactericidal activity during breeding season (turtles); higher bacterial killing by neutrophils in Summer (humans)	[53,113–115]
		Leukocytes	Birds (captive)	Annual cycles in several immune measures, no effect of coccidia on annual cycle of immune measures	[116]
		Lysis	Birds (wild)	Lower ability of plasma to lyse foreign cells during migration and Winter	[38]
		Sickness behavior in response to LPS	Birds (captive and wild) and hamsters	Repression of sickness behavior during reproduction in summer (birds); repression of sickness behavior during Winter (hamsters)	[39,117]
		Acquired Immunity	Rabbits (wild)	Resistance against nematodes is seasonal	[23]
		Spleen size (spleen is important for both innate and adaptive immunity)	Birds (wild)	Regression of spleen during migration	[118]
		Cytokine production stimulated by bacterial endotoxin	Humans, rats, and hamsters	Seasonal differences in pro- and anti-inflammatory cytokine production (humans);	[119–121]

Table 1 (*Continued*)

Type	Period	Host trait or parasite description	Organism and/or species	Rhythm	Refs
				summertime photoperiod increases production of pro-inflammatory cytokine tumor necrosis factor α and extends (rats) or elevates (hamsters) disease symptoms	
		Vaccine response	Humans	Seasonal variation in symptoms following live influenza vaccine	[122]
		Intestinal immunity	Ground squirrels (captive)	Increase in intestinal leukocytes, pro- and anti-inflammatory cytokines during hibernation	[66]
Susceptibility	Diel	Bacterial burden, pathogenesis, and/or virulence of infection	Mice	Timing of infection can affect: (i) bacterial burden due to circadian variation in monocyte trafficking and/or gene expression at site of infection; (ii) disease severity from sepsis due to circadian TLR9 expression; and (iii) virulence	[45,47,49,123,124]
	Annual	Susceptibility to fungal growth	Bats (wild)	Hibernating bats have temperatures that match that of hibernacula, allowing explosive growth of WNS fungal pathogen *Pseudogymnoascus destructans*	[30]
Parasite reproduction	Diel	*Plasmodium* species (malaria parasite) asexual reproduction	Various mammalian hosts	Parasite cohorts of millions of individuals synchronously burst from red blood cells at a particular time in LD cycle	[75]
	Annual	Microfilariae (heartworm)	Dogs	Strong seasonal rhythm in microfilaria abundance in dogs infected in a laboratory setting	[97]
Parasite development	Annual	Nematodes (parasitic roundworms)	Domestic mammals	Parasites engage in seasonal hypobiosis (arrested development within hosts that allows for parasite persistence when environmental conditions are unfavorable for transmission between hosts)	[96]
Parasite discharge	Diel	Coccidia	Birds (wild and captive)	Oocyte release is strictly circadian; although parasites are vulnerable to sun exposure, the rhythmic pattern persists under continuous light during the Arctic Summer	[21,125]
		Echinostoma (parasitic flatworms), pinworms, *Schistosoma*	*Echinostoma* in mice, pinworms and Schistosomes in humans	The release of *Echinostoma* eggs by hosts occurs during night when mice are active. Human pinworms migrate out of anus during night to lay eggs. By contrast, *Schistosoma* eggs are discharged in urine during the day	[74,126]
	Annual	Nematodes (roundworms)	Dall's sheep (wild)	Seasonal variation in intensity of parasite larvae shed in feces	[127]
Parasite manipulation of host behavior	Diel	*Dicrocoelium* trematode	Ants (intermediate host)	In the evening, infected ants affix themselves to the top of blades of grass and enter torpor until the next morning, allowing them to be eaten by grazing mammals (definitive hosts)	[90]
		Manipulating fungus *Ophiocordyceps*	Ants	*Ophiocordyceps* manipulates host behavior and causes host death at characteristic times of day	[87]

experimental approaches. In the wild, these may include repeated immune challenges [38–40], and in captivity may involve constant conditions, shifted environmental rhythmicity, or biological clock disruption. Studies of rhythms in immunity under natural conditions (wild immunology) are important for understanding how nonmodel organisms deal with exposure to multiple co-occurring parasites [41]. Studies of wild systems enable us to test, for instance, how seasonal allocation into defense against one parasite can result in enhanced susceptibility to another [42], and whether temporal variation in immune status covaries with other physiological traits and is influenced by nutritional status and parasite exposure [18,43,44]. Laboratory studies, in turn, are necessary for distinguishing between endogenous rhythms in immunity versus variation that occurs as a result of patterns of infection or other biotic factors.

By profiling the response to infection across time, progress has been made in characterizing biological rhythms in immunity. For example, in mice, the circadian rhythmicity of a receptor that recognizes pathogens substantially influences the inflammatory response and survival prospects (Box 1). The health implications of circadian rhythms in immunity have also been demonstrated using hosts entrained to different light–dark cycles, and mice with genetically modified circadian clocks. Such recent

studies revealed that the immune system is fundamentally circadian in nature [33,45–49], which is highlighted by the local circadian clock of macrophages [46], and the feedback between immunity and molecular, cellular, and behavioral rhythms. The emerging picture is that the immune system is an active component of integrated whole-body circadian rhythms in animals [50] and plants [35,36], lending support to the idea that sophisticated mechanisms of immune defense were also present in their common ancestor [51].

Annual cycles in immunity are not as well characterized as circadian cycles because of the timescale of experimentation [16,31], but are epidemiologically relevant [28]. Longitudinal studies under controlled captive conditions have revealed substantial annual changes in immune parameters (Table 1). These included downregulation of key aspects of immunity during the time of reproductive activation, induced solely by photoperiodic simulation [14,16,34,52]. Such rhythms might have evolved from a trade-off between immune defense and demanding life-cycle stages, and can underlie annual patterns of disease incidence, as suggested, for example, by rhythms of bactericidal capacity of whole blood (Box 1; Figure 1D [53]). However, based on the existing evidence for both circadian and annual immunomodulation, temporal patterns can

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Box 1. Circadian and seasonal (circannual) modulation of host immune defense

Circadian immune cycles

For hosts to mount an immune response against an infecting pathogen, the immune system must first detect the presence of the pathogen. One way in which animals detect pathogens is by immune surveillance for pathogen-associated molecular patterns (PAMPs), which are shared across groups of pathogens. Host cells express pattern recognition receptors (PRRs) that recognize PAMPs. Toll-like receptor 9 (TLR9) is an important PRR that can recognize both viruses and bacteria, and is highly evolutionarily conserved. In 2012, Silver *et al.* [47] discovered that expression of TLR9 by macrophages and B cells follows a circadian rhythm. Importantly, the circadian rhythm of TLR9 has a significant effect on the immune response and disease severity because the rhythm of TLR9 also produces a rhythm in inflammatory cytokines. The implications were experimentally demonstrated by inducing sepsis. Sepsis can occur during bacterial infections when a severe inflammatory immune response causes damage to the host. Bacterial infection was induced in laboratory mice using a puncture that allowed commensal bacteria to enter the body cavity from the intestine. Mice were entrained to a LD 12:12 h and infection was induced either at the midpoint of the light period or of the dark period. Mice that were infected during the night, when the TLR9 inflammatory response was elevated, had higher bacterial burdens, earlier mortality, and worse disease scores, hypothermia, and tissue damage compared with mice that were infected during the day. This study demonstrated that the functional response of the immune system varies according to a circadian rhythm, and this variation is biologically relevant because it can have a significant effect on the dynamics of infection [47].

Seasonal immune cycles

Faced with stark annual fluctuations in environmental conditions and resources, many avian and mammalian species partition life-history events, such as reproduction, growth, and hibernation, into distinct times of year, and their immune system also undergoes seasonal changes. Versteegh *et al.* [53] investigated whether annual variation in immunity is due to seasonal adjustments directly driven by environmental or physiological conditions, or originates from a

genetically based circannual rhythm that allows organisms to prepare for changes in the environment. They looked at five different immune measures, including bactericidal competence of whole blood as a proxy for functional implications.

To determine whether seasonal immunity is a genetically encoded circannual rhythm, genetically distinct subgroups of a widespread songbird, the stonechat (*Saxicola torquata*), were bred and raised in a common garden experiment. The subgroups chosen for this experiment differed in their seasonal life history and traits. They included a: (i) long-distance migrant; (ii) short-distance migrant; and (iii) a nonmigrant, along with hybrids. The prediction was that, if seasonal immunity is a direct response to seasonal environmental conditions and energy demands, then by raising birds in an environment where (i) they have ample food; (ii) they are not allowed to migrate or breed and (iii) the only fluctuation to which they are exposed is changing day length, their annual rhythms in immunity would be lost.

The authors found that not only did the annual rhythm in immunity persist under these controlled conditions but also that the subgroups and hybrids of the birds showed specific patterns. The long-distance migrants displayed seasonality in four immunity parameters, which included bacterial killing ability (Figure 1D, main text). The short-distance migrants displayed seasonality in only three immunity parameters, and the nonmigrants displayed seasonality in only two parameters. Furthermore, the amplitude of the annual fluctuation was greatest in long-distance migrants. The inheritance of the rhythm in hemolysis (i.e., the ability of antibodies and their compliment system to lyse foreign cells) was also striking. Both the long- and short-distance migrants showed reduced hemolysis during the time of the natural Autumn migration. The reduction in hemolysis in long-distance migrants was more extreme than that of short-distance migrants, and intermediate in F1 hybrids. This work demonstrated that an inherited, biological clock controls seasonal immunity in stonechats, and these rhythms vary across groups that differ in their seasonal life history [53]. Related avian studies generally confirm annual cycles in immune parameters and, although species differ, there is a common tendency for greater seasonal immunomodulation with increasing migratory lifestyle.

differ between innate and adaptive immunity and among traits even within the same immune cell subset [16,33].

In addition to immunomodulation, several other aspects of host rhythmicity can have population-scale consequences for host–parasite dynamics. Relevant host annual cycles include aggregation [29,54,55], sexual contacts (with regard to sexually transmitted diseases), habitat use, migration [56–58], and birth pulses that: (i) act to replenish the pool of susceptible individuals; (ii) can influence the critical community size required for parasite persistence; and (iii) can determine the geographic synchrony of outbreaks [59–63]. The sweeping effects of annual cycles in host physiology on disease incidence are exemplified by White-Nose Syndrome (WNS), which is drawing many North American bat species near extinction. A new longitudinal study indicated that neither birth pulses nor social behavior affect the transmission and intensity of WNS. Instead, WNS is associated with hibernation [30], which in mammals that have been studied in captivity is a programmed circannual rhythm [6]. We speculate that the link between WNS and hibernation is mediated by hibernation-associated changes in immunity. Evidence thus far suggests that there are large adjustments in immunity in hibernating mammals, including a 90% decrease in circulating white blood cells [64], downregulation of the acute-phase response to lipopolysaccharides (LPS) [65], and modifications of intestinal immunity [64,66].

Migration is another host rhythmicity receiving attention in infectious disease ecology. In monarch butterflies, the protozoan parasite *Ophryocystis elektroscirrha* displays a seasonal pattern of prevalence and a spatial gradient along the migratory flyway of monarchs. Parasite prevalence declines as monarchs migrate, which is likely due to migratory culling [57]. In migratory culling, the coupled energetic demands of migration and fighting infection result in increased mortality of infected individuals during Autumn and Spring migrations. The uninfected are most likely to survive the journey to the breeding or wintering grounds, allowing the destination to be relatively parasite free. Thus, migratory culling is a direct intersection of host seasonal rhythms and disease prevalence [56], and anthropogenically driven disruption of this rhythm results in elevated disease burden [58].

From the perspective of the parasite, rhythmic patterns in parasite dissemination can be influenced by fluctuating abiotic and biotic conditions that affect parasite survival and transmission. Clear examples of abiotic influences are: (i) the role of temperature and humidity in transmission of influenza [67], which might be responsible for latitudinal clines observed in influenza incidence [68,69]; and (ii) the UV sensitivity of sporulation in *Isospora*, which might have driven the remarkably robust diel pattern of oocyst outputs [21]. In addition to abiotic effects, biotic influences can stem from rhythms of vectors [70] and other parasites [71]. Effects of vector circadian rhythmicity have been studied in the malaria vector *Anopheles gambiae*, whose rhythmic gene expression persists under constant conditions. Rhythmically expressed genes include those implicated in the melanization immune response, which encapsulates the *Plasmodium* parasites, and can thereby affect mosquito to human transmission. Vectors can also

temporally structure parasite transmission via their diel patterns of feeding [72] and their phenology [73]. The interspecific influence of parasites on one another's rhythm, to our knowledge, has only been described for *Drosophila* parasitoids, which gain a fitness advantage by temporally segregating circadian rhythms in egg oviposition [71]. Temporal segregation was hypothesized to alleviate competition.

Perhaps then unsurprisingly, parasites, faced with rhythms in their abiotic environment, hosts, and vectors, display what seem to be biological rhythms. Documentation of parasite rhythms dates back over 100 years, long before the discovery of biological clocks. In fact, the early observation that both malaria parasites and microfilariae are abundant in the blood of hosts at night was instrumental to the discovery of mosquitoes as the malaria vector [74]. Experimental studies of parasites report diel and annual rhythms, as measured by fluctuations in parasite burden and infectivity (Table 1), but disentangling the contributions of host and parasite to these rhythms is difficult [75]. To our knowledge, the only described example of a parasite life-history event that depends on a host rhythm is reproduction in the ectoparasitic rabbit flea, a vector of myxoma virus. To reproduce, rabbit fleas must undergo maturation on a pregnant or newborn rabbit host. Flea maturation is controlled by host hormone cues associated with pregnancy and parturition, thereby synchronizing parasite and host life cycles [76–78]. There is solid evidence for adjustment of diel parasite rhythms to those of the host, for example from trematodes such as *Schistosoma mansoni* (an agent of schistosomiasis in humans), whose emergence from snail hosts occurs during periods of illumination [79,80]. These parasites display diel cycles that shift to match perturbations in the day-night cycle of their host [80,81]. Similar results were found in rodent-infecting trypanosomes. Rats infected with *Trypanosoma lewisi* and housed under a normal light–dark cycle (LD 12:12 h) experienced a peak in circulating *T. lewisi* during the early part of night and a trough during the early morning. However, when the host photoperiod was inverted, the parasite rhythm was also reversed [82]. In *Isospora*, the characteristic diel pattern of oocyst output persisted under continuous light in the high Arctic, although feeding and activity rhythmicity of their avian hosts was diminished, suggesting synchronization to subtle host rhythms or possibly self-sustained parasite rhythms [21].

Experimental studies give clear evidence that synchronization to host rhythms impacts parasite fitness. For example, murine host rhythms were experimentally mismatched to that of their malaria parasite (*Plasmodium chabaudi*). This mismatch resulted in ~50% reduction in both parasite replication and production of transmissible life stages [83]. Follow-up experiments revealed additional complexities, with the effect of mismatch manifesting differently between parasite life stages, and downstream effects on host disease severity. Mismatch can confer a substantial cost to the parasite, and this cost is experienced at the onset of infection, rather than acquired throughout infection [84,85]. This suggests there is intense selective pressure on parasites to maintain a specific phase position

relative to their host rhythms, or to vector rhythms, because the ability of parasites to infect vectors is also time-of-day dependent [72]. Fortunately, the amassing knowledge of biological clocks might help identify host cues used for entrainment of parasite rhythms. For example, the nocturnally peaking hormone melatonin is a core circadian feature of many vertebrates, and applying this knowledge produced an indication that parasites might be using melatonin to synchronize their circadian cell cycle [21,86].

While we still lack unambiguous evidence for endogenous circadian or circannual rhythms of parasites, recent research suggests the intriguing possibility that parasites actively manipulate host and vector rhythms to their advantage. For example, various parasites interrupt host diel activity at specific times of day to enhance transmission [87,88]. The diel timing and synchrony of host behavioral manipulation, along with candidate molecular mechanisms of manipulation, strongly implicate circadian clock pathways [87,89]. By integrating chronobiology with infectious disease ecology, we might be able to identify, for example, the mechanism by which the trematode *Dicrocoelium* manipulates diel host behavior, inducing suicide, and facilitating trophic transmission [90], and how the notoriously manipulative fungus (*Ophiocordyceps unilateralis s.l.*) seemingly breaks the host circadian clock to perpetuate transmission [87]. Transkingdom crossregulation of rhythms is plausible because it has already been documented for other systems (e.g., in bioluminescent squid and their light organ symbionts and in mammalian gut microbiota) [4,91].

Despite our knowledge of rhythmic host immunity and physiology, rhythms in parasite reproduction and transmission, and enticing evidence that host rhythms can impact parasite fitness and be exploited by parasites, the effects of biological rhythms on host–parasite dynamical processes remain poorly understood. We surmise that careful consideration of biological rhythms in infectious disease ecology and evolution will provide a better understanding of the diel and annual patterns of diseases, within-host parasite dynamics, and parasite transmission.

Models for investigating host–parasite contributions to rhythms in infectious disease

To determine how biological rhythms impose temporal structure on host–parasite dynamical processes, we can integrate empirical data on host and/or parasite rhythms into epidemiological and evolutionary models. Biological rhythms research has great potential for feedback between laboratory studies, field ecology, and dynamical systems modeling. First, rhythms in immunity characterized under laboratory or field conditions can be used in transmission models to make predictions about the epidemiological consequences of those rhythms in nature. Second, observations of diel and annual cycles in infection (characterized via disease incidence, parasite abundance, or host serological markers of infection history) can be used to make predictions regarding rhythms generating such patterns. A new study of the first type [92] explored the effect of annual and biannual rhythms in births (in bats) on the persistence of filoviruses (i.e., Marburgvirus and Ebolavirus). Transmission models predicted that filoviruses can persist in species with biannual birth pulses, making them potential reservoirs of infection, and this prediction was supported by serology data showing that species with biannual birth pulses are more likely to be seropositive for filoviruses. This also demonstrated that explicit consideration of host rhythms can inform targeted surveillance and control of emerging zoonotic diseases. A study of the second type is that of [23], in which long-term field data on nematode infections in European rabbits were used to discriminate among multiple potential seasonal rhythms in the host–parasite system. This led to identification of epidemiologically relevant seasonality in host immunity, the endogenous nature of which can be tested in the lab.

Building upon the examples above, as well as other transmission models that incorporate reproductive rhythms [59–61,93,94], here we provide a susceptible–infected–recovered (SIR) model of a directly transmitted hypothetical bacterial infection in the Siberian stonechat to illustrate the numerous entry points for biological rhythms into epidemiological processes (Figure 1B). We narrate our model with seasonal rhythms in mind; however, this can be extended to circadian rhythms. The model incorporates ambient temperature as a covariate influencing parasite transmission, as well as empirical data on host circannual cycles in reproduction, immunity, and migration (Figure 1C,D; *cf*. Box 1) [53,95]. The model assumes a temporary increase in disease mortality during Autumn migration, when host bacterial killing activity is lowest (i.e., migratory culling [53]). Importantly, we propose that circannual cycles in host immunity can influence the transmission rate, the recovery rate, and the pathological consequences of infection, which manifest as symptomatology and enter the model as the report rate. The multiple rhythms (temperature, births, bacterial killing activity, and migratory culling) act collectively to shape the observed incidence of disease, which is the model output shown in Figure 1E. We define the resulting seasonal window of elevated disease incidence as the temporal niche of the parasite. The seasonal incidence that arises from this model matches the expectations from the underlying data. However, in contrast to most models of seasonal infectious diseases, which only place sinusoidal seasonality in the transmission rate, our model contains multiple axes of seasonal forcing. Thus, we provide this model to encourage the inclusion of empirically characterized rhythms into models as covariates. Such models can be used to explore the epidemiological consequences of host and parasite rhythms, although for simplicity the parasite is not explicitly modeled here. Host–parasite systems where modeling parasite rhythms is particularly compelling include nematodes with seasonal arrested development [22,96], microfilariae that display both circadian and seasonal cycles [97], and *Plasmodium* within-host circadian cycles [75]. Major challenges of incorporating biological rhythms into epidemiological or within-host models will be recognizing which host and/or parasite rhythms are epidemiologically relevant, and identifying the functional relations between rhythms and epidemiological parameters, including transmission, recovery, and symptomatology.

In addition to the epidemiological consequences of rhythms, we can benefit from understanding the feedback

between host and parasite rhythms and the multiple axes that shape their temporal structure. Thus, we provide a conceptual evolutionary model for understanding how hosts and parasites time their biological processes with reference to each other while being embedded in environments with temporally structured risk and opportunity. We pose this model in evolutionary terms, but depending on the varying degrees of phenotypic plasticity of biological rhythms, individuals may also adjust their rhythms during their life.

Our evolutionary model illustrates three idealized scenarios of how host immune defense varies seasonally, relative to fluctuating environmental conditions (Figure 2A–C). These scenarios are motivated by life-history theory and by empirical observations of seasonal immunity in mammals and birds (Table 1). The scenarios assume that immune defense, specifically, parasite resistance, either parallels the availability of resources (Figure 2A, 'resource driven'), or is reduced when resources are used for reproduction (Figure 2B, 'traded off'). The third is an extension of the 'resource-driven' scenario with modulation related to life-history events that can lead to complicated, but potentially important, annual patterns. In our example of migration (Figure 2C), we assume downregulation of immune defense during migration (Figure 1D; this could also occur during other vulnerable times, such as molting or hibernation [65]), and a shallow trough under favorable conditions in the wintering grounds. We then (Figure 2D) switch to the perspective of the parasite and illustrate, for
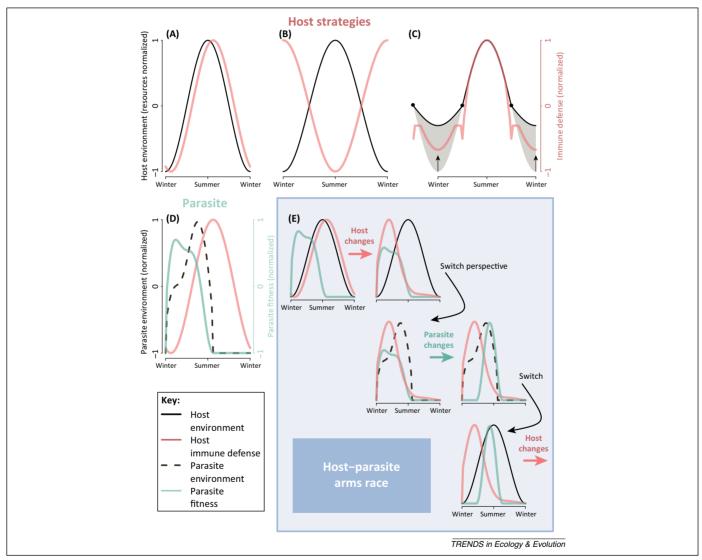

Figure 2. Conceptual model for investigating host–parasite contributions to rhythms in infectious disease. **(A)** Host immune defense is resource driven and tracks the environmental conditions of the host (i.e., host resource availability). **(B)** Host immune defense has an inverse relation with environmental conditions; this could occur due to a trade-off against investment into reproduction during high resource availability. **(C)** Resource-driven immune defense in a migrating species that has reduced immune defense during migration. Migrations (black points) result in shallower environmental troughs because individuals migrate to regions with higher resource availability. For all scenarios, we consider immune defense to be resistance to the parasite in question, although we acknowledge that this simplifies the complexity of the immune system (e.g., independent immunomodulation of innate or adaptive immune parameters). For the resource-driven host immune defense strategy, in **(D)** we show seasonal parasite fitness shaped by both environmental conditions and seasonal host immune defense. Although host and parasite co-occur in the same physical environment, the environmental rhythms pertinent to the parasite need not be identical to the environmental rhythms pertinent to the host, which is why we distinguish host versus parasite environmental rhythms. **(E)** Arms race between host and parasite. For illustrative purposes, the arms race is initiated with resource-driven host immune defense and parasite seasonality. The host changes the seasonal timing of peak immune defense to coincide with peak parasite fitness. We then switch to the parasite perspective to consider the environment of the parasite. In response to the new host seasonality, the parasite changes its timing of peak reproductive output. These cycles can continue, with both host and parasite seasonality shifting within the bounds of their respective environmental constraints.

the resource-driven scenario (A), how parasites are subject to two axes of seasonal fluctuations: (i) seasonal environmental conditions outside the host; and (ii) seasonal immune defense of the host. We propose that together the two seasonal axes shape parasite transmission (i.e., parasite fitness; which is captured by the basic reproductive number).

The last and crucial component of our model is the evolutionary feedback between host and parasite rhythms. We propose that, due to parasite-induced host morbidity and mortality, selection can drive changes in host seasonal immune defense. Subsequently, because host immune defense is one of the seasonal axes influencing parasites, selection will favor changes in the parasite rhythm. This interplay can continue, driving hosts and parasites to sequentially alter their seasonal rhythms while working within the constraints of environmental conditions. Figure 2E shows these steps.

We suggest that, under certain conditions, this can escalate into an evolutionary arms race. In this framework, the prerequisite for an arms race is that parasite fitness is sufficiently impacted by the temporal structure of the host immune response, and that the host immune response is predictably rhythmic. To be clear, when considering the temporal structure of immune defense, reference to 'low' host immune defense pertains to the parasite in question. However, it must be appreciated that a time of diminished resistance to one parasite (e.g., a helminth) can be a time of high investment into fighting another (e.g., a virus). Furthermore, infection with one parasite can seasonally elevate host susceptibility to another, as exemplified by concomitant infections of myxoma virus and nematodes [98] and increased susceptibility to bovine TB resulting from helminth coinfection [18]. The arms race itself has two requirements. First, hosts must be able to shift their immune defense to counter exploitation by parasites (host changes in Figure 2E). Changes in host rhythms then translate into a new landscape of time-structured risk and opportunity for parasites. Upon experiencing a new temporal landscape, a dynamic host–parasite arms race can arise only if the second requirement is met: parasites shift their rhythm by changing reproduction within hosts, or release from hosts (parasite changes in Figure 2E). As with other host–parasite arms races, an arms race in the temporal domain is subject to trade-offs for both the host and the parasite that might constrain the extent to which their rhythms can be altered. Host trade-offs can include an immunity–reproduction trade-off [99]; whereas trade-offs for the parasite can include a transmission–virulence or transmission–recovery trade-off [99–101]. Also, due to the rapid generation time of parasites, relative to hosts, evolution of host rhythm shifts might be slow relative to the evolution of parasite rhythms, but this would not preclude an arms race from occurring.

Concluding remarks

There is enticing evidence that biological rhythms are structuring elements of host–parasite interactions, both in within-host processes and in epidemiological dynamics. Host circadian rhythms in the immune system influence the progression of infection and parasite burden, and

annual rhythms might have similar effects [23,30]. The existing evidence leads us to conclude that the effects of biological rhythms on the perpetuation of parasites, and on host reactions during infection, can generate population-level rhythms in infectious disease incidence [25], which we here define as the temporal niche of the parasite. To formalize temporal niches across parasite taxa and life-history strategies, we will need novel integration of epidemiological, immunological, and life-history data of both hosts and parasites.

Importantly, circadian rhythms in immunity have direct implications for transmission, and practical application for (i) timing of antibiotic, antiviral, and anthelmintic treatment; and (ii) managing immunopathology, such as cytokine storms. The rhythms of parasites themselves can drive patterns of exposure and illness, as evident in malaria and filarial infections. Similarly, rhythms in parasitemia and parasite release from hosts can impose temporal structure on transmission, which can be leveraged for interventions such as deworming campaigns.

We believe that a multidisciplinary approach at the intersection of chronobiology, disease ecology, and evolutionary biology holds the key to understanding how biological rhythms influence host–parasite interactions. We have outlined open questions that will bring us closer to understanding the underlying biological interactions in the temporal domain (Box 2). We hope that this Opinion will generate discussion on how to take advantage of rhythms for translational medicine, for instance to counter the evolution of resistance; we also hope that our insights will inspire new avenues for interrogating transmission models with host–parasite data from the laboratory and the field, ultimately to better understand the forces structuring disease incidence and the immunology of nonmodel organisms.

Finally, although it is beyond the scope of this Opinion, the importance of accounting for biological rhythms is accentuated by the accumulating data on anthropogenically driven disruptions and mismatches of biological rhythms that are occurring across taxa. Circadian disruption due to light-at-night [102] and altered environmental seasonality due to climate change [13,58] are challenging the plasticity of rhythms and modifying the fitness advantages of their endogenous basis. For example, the adverse effects of circadian disruption have already been seen in human health and gut microbiota [91]. Given the pervasiveness of rhythms in host immunity, vectors, and parasites, we might soon be faced with palpable effects of rhythm disruptions on infectious diseases [74,103,104].

Box 2. Outstanding questions

- Are rhythms in the immune system adaptive for fighting infection?
- Are parasite rhythms adaptive for dealing with host rhythms or environmental conditions?
- Are observed parasite rhythms truly endogenous?
- If parasite rhythms are endogenous, are they entrained by host rhythms?
- Are host circannual rhythms in immunity an adaptive response to: (i) seasonal parasite exposure; or (ii) resource limitations and life-history trade-offs?

References

1 Foster, R.G. and Kreitzman, L. (2004) *Rhythms of Life: The Biological Clocks that Control the Daily Lives of Every Living Thing*, Profile Books

2 Hut, R. and Beersma, D. (2011) Evolution of time-keeping mechanisms: early emergence and adaptation to photoperiod. *Philos. Trans. R. Soc. Lond. B: Biol. Sci.* 366, 2141–2154

3 Dvornyk, V. *et al.* (2003) Origin and evolution of circadian clock genes in prokaryotes. *Proc. Natl. Acad. Sci. U.S.A.* 100, 2495–2500

4 Heath-Heckman, E.A.C. *et al.* (2013) Bacterial bioluminescence regulates expression of a host cryptochrome gene in the squid–*Vibrio* symbiosis. *mBio* 4, 1–10

5 Anderson, D. and Keafer, B. (1987) An endogenous annual clock in the toxic marine dinoflagellate *Gonyaulax tamarensis*. *Nature* 325, 616–617

6 Gwinner, E. (1986) *Circannual Rhythms: Endogenous Annual Clocks in the Organization of Seasonal Processes*, Springer-Verlag

7 Helm, B. *et al.* (2013) Annual rhythms that underlie phenology: biological time-keeping meets environmental change. *Proc. R. Soc. Lond. B: Biol. Sci.* 280, 20130016

8 Visser, M.E. *et al.* (2010) Phenology, seasonal timing and circannual rhythms: towards a unified framework. *Philos. Trans. R. Soc. Lond. B: Biol. Sci.* 365, 3113–3127

9 Dunlap, J.C. *et al.*, eds (2004) *Chronobiology: Biological Timekeeping*, Sinauer Associates

10 Charmantier, A. *et al.* (2008) Adaptive phenotypic plasticity in response to climate change in a wild bird population. *Science* 320, 800–803

11 Zimova, M. *et al.* (2014) Snowshoe hares display limited phenotypic plasticity to mismatch in seasonal camouflage. *Proc. R. Soc. Lond. B: Biol. Sci.* 281, 20140029

12 Tauber, E. *et al.* (2007) Natural selection favors a newly derived timeless allele in *Drosophila melanogaster*. *Science* 316, 1895–18988

13 Bradshaw, W.E. and Holzapfel, C.M. (2006) Evolutionary response to rapid climate change. *Science* 312, 1477–1478

14 Lee, K.A. (2006) Linking immune defenses and life history at the levels of the individual and the species. *Integr. Comp. Biol.* 46, 1000–1015

15 Lee, K.A. and Klasing, K.C. (2004) A role for immunology in invasion biology. *Trends Ecol. Evol.* 19, 523–529

16 Stevenson, T.J. and Prendergast, B.J. (2014) Photoperiodic time measurement and seasonal immunological plasticity. *Front. Neuroendocrinol.* Published online October 27, 2014. http://dx.doi.org/10.1016/j.yfrne.2014.10.002

17 Siopes, T. and Underwood, H. (2008) Diurnal variation in the cellular and humoral immune responses of japanese quail: role of melatonin. *Gen. Comp. Endocrinol.* 158, 245–249

18 Ezenwa, V.O. and Jolles, A.E. (2011) From host immunity to pathogen invasion: the effects of helminth coinfection on the dynamics of microparasites. *Integr. Comp. Biol.* 51, 540–551

19 Sheldon, B. and Verhulst, S. (1996) Ecological Immunology: costly parasite defences and trade-offs in evolutionary ecology. *Trends Ecol. Evol.* 11, 317–321

20 Grassly, N.C. and Fraser, C. (2006) Seasonal infectious disease epidemiology. *Proc. R. Soc. B: Biol. Sci.* 273, 2541–2550

21 Dolnik, O.V. *et al.* (2011) Keeping the clock set under the midnight sun: diurnal periodicity and synchrony of avian *Isospora* parasites cycle in the high Arctic. *Parasitology* 138, 1077–1081

22 Van Kuren, A.T. *et al.* (2013) Variability in the intensity of nematode larvae from gastrointestinal tissues of a natural herbivore. *Parasitology* 140, 632–640

23 Cornell, S.J. *et al.* (2008) Seasonality, cohort-dependence and the development of immunity in a natural host–nematode system. *Proc. R. Soc. Lond. B: Biol. Sci.* 275, 511–518

24 Tschirren, B. and Richner, H. (2006) Parasites shape the optimal investment in immunity. *Proc. R. Soc. Lond. B: Biol. Sci.* 273, 1773–1777

25 Dowell, S.F. (2012) Seasonality – still confusing. *Epidemiol. Infect.* 140, 87–90

26 Altizer, S. *et al.* (2006) Seasonality and the dynamics of infectious diseases. *Ecol. Lett.* 9, 467–484

27 Fisman, D.N. (2007) Seasonality of infectious diseases. *Annu. Rev. Public Health* 28, 127–143

28 Dowell, S.F. (2001) Seasonal variation in host susceptibility and cycles of certain infectious diseases. *Emerg. Infect. Dis.* 7, 369–374

29 Hosseini, P.R. *et al.* (2004) Seasonality and wildlife disease: how seasonal birth, aggregation and variation in immunity affect the dynamics of *Mycoplasma gallisepticum* in house finches. *Proc. R. Soc. Lond. B: Biol. Sci.* 271, 2569–2577

30 Langwig, K.E. *et al.* (2015) Host and pathogen ecology drive the seasonal dynamics of a fungal disease, white-nose syndrome. *Proc. R. Soc. Lond. B: Biol. Sci.* 282, 20142335

31 Martin, L.B. *et al.* (2008) Seasonal changes in vertebrate immune activity: mediation by physiological trade-offs. *Philos. Trans. R. Soc. Lond. B: Biol. Sci.* 363, 321–339

32 Scheiermann, C. *et al.* (2013) Circadian control of the immune system. *Nat. Rev. Immunol.* 3, 190–198

33 Arjona, A. *et al.* (2012) Immunity's fourth dimension: approaching the circadian–immune connection. *Trends Immunol.* 33, 607–612

34 Nelson, R.J. *et al.* (2002) *Seasonal Patterns of Stress, Immune Function, and Disease*, Cambridge University Press

35 Wang, W. *et al.* (2011) Timing of plant immune responses by a central circadian regulator. *Nature* 470, 110–114

36 Hua, J. (2013) Modulation of plant immunity by light, circadian rhythm, and temperature. *Curr. Opin. Plant Biol.* 16, 406–413

37 Bolker, J. (2012) There's more to life than rats and flies. *Nature* 491, 31–33

38 Hegemann, A. *et al.* (2012) Immune function in a free-living bird varies over the annual cycle, but seasonal patterns differ between years. *Oecologia* 170, 605–618

39 Owen–Ashley, N.T. and Wingfield, J.C. (2007) Acute phase responses of passerine birds: characterization and seasonal variation. *J. Ornithol.* 148, S583–S591

40 Buehler, D.M. *et al.* (2008) Captive and free-living red knots *Calidris canutus* exhibit differences in non-induced immunity that suggest different immune strategies in different environments. *J. Avian Biol.* 39, 560–566

41 Pedersen, A.B. and Babayan, S.A. (2011) Wild immunology. *Mol. Ecol.* 20, 872–880

42 Cizauskas, C.A. *et al.* (2014) Gastrointestinal helminths affect host susceptibility to anthrax through seasonal immune trade-offs. *BMC Ecol.* 14, 1–15

43 Cizauskas C.A. *et al.* Seasonal patterns of hormones, macroparasites, and microparasites in wild African ungulates: the interplay between stress, reproduction, and disease. *PLoS ONE* (in press)

44 Sepp, T. *et al.* (2010) Hematological condition indexes in greenfinches: effects of captivity and diurnal variation. *Physiol. Biochem. Zool.* 83, 276–282

45 Nguyen, K.D. *et al.* (2013) Circadian gene Bmal1 regulates diurnal oscillations of Ly6Chi inflammatory monocytes. *Science* 341, 1483–1488

46 Keller, M. *et al.* (2009) A circadian clock in macrophages controls inflammatory immune responses. *Proc. Natl. Acad. Sci. U.S.A.* 106, 21407–21412

47 Silver, A.C. *et al.* (2012) The circadian clock controls Toll-like receptor 9-mediated innate and adaptive immunity. *Immunity* 36, 251–261

48 Casanova-Acebes, M. *et al.* (2013) Rhythmic modulation of the hematopoietic niche through neutrophil clearance. *Cell* 153, 1025–1035

49 Bellet, M.M. *et al.* (2013) Circadian clock regulates the host response to *Salmonella*. *Proc. Natl. Acad. Sci. U.S.A.* 110, 9897–9902

50 Cermakian, N. *et al.* (2013) Crosstalk between the circadian clock circuitry and the immune system. *Chronobiol. Int.* 30, 870–888

51 Janeway, C. *et al.* (2001) *Immunobiology: The Immune System in Health and Disease*. (5th edn), Garland Science

52 Nelson, R. and Demas, G.E. (1996) Seasonal changes in immune function. *Q. Rev. Biol.* 71, 511–548

53 Versteegh, M. *et al.* (2014) Genetic and phenotypically flexible components of seasonal variation in immune function. *J. Exp. Biol.* 217, 1510–1518

54 Ferrari, M.J. *et al.* (2008) The dynamics of measles in sub-Saharan Africa. *Nature* 451, 679–684

55 Fine, P.E. and Clarkson, J.A. (1986) Seasonal influences on Pertussis. *Int. J. Epidemiol.* 15, 237–247

56 Altizer, S. *et al.* (2011) Animal migration and infectious disease risk. *Science* 331, 296–302

57 Bartel, R.A. *et al.* (2011) Monarch butterfly migration and parasite transmission in eastern North America. *Ecology* 92, 342–351

58 Satterfield, D.A. *et al.* (2015) Loss of migratory behaviour increases infection risk for a butterfly host. *Proc. R. Soc. Lond. B: Biol. Sci.* 282, 20141734

59 Begon, M. *et al.* (2009) Seasonal host dynamics drive the timing of recurrent epidemics in a wildlife population. *Proc. R. Soc.* 276, 1603–1610

60 Martinez–Bakker, M. *et al.* (2014) Human birth seasonality: latitudinal gradient and interplay with childhood disease dynamics. *Proc. R. Soc. Lond. B: Biol. Sci.* 281

61 Peel, A.J. *et al.* (2014) The effect of seasonal birth pulses on pathogen persistence in wild mammal populations. *Proc. R. Soc. Lond. B: Biol. Sci.* 281, 20132962

62 Duke-Sylvester, S.M. *et al.* (2011) Strong seasonality produces spatial asynchrony in the outbreak of infectious diseases. *J. R. Soc. Interface* 8, 817–825

63 Dorélien, A. *et al.* (2013) Impact of birth seasonality on dynamics of acute immunizing infections in sub-Saharan Africa. *PLoS ONE* 8, e75806

64 Bouma, H.R. *et al.* (2010) Hibernation: the immune system at rest? *J. Leukoc. Biol.* 88, 619–624

65 Prendergast, B.J. *et al.* (2002) Periodic arousal from hibernation is necessary for initiation of immune responses in ground squirrels. *Am. J. Physiol. Regul. Int. Comp. Physiol.* 282, R1054–R1062

66 Kurtz, C.C. and Carey, H.V. (2007) Seasonal changes in the intestinal immune system of hibernating ground squirrels. *Dev. Comp. Immunol.* 31, 415–428

67 Shaman, J. *et al.* (2010) Absolute humidity and the seasonal onset of influenza in the continental United States. *PLoS Biol.* 8, e1000316

68 Yu, H. *et al.* (2013) Characterization of regional influenza seasonality patterns in China and implications for vaccination strategies: spatiotemporal modeling of surveillance data. *PLoS Med.* 10, e1001552

69 Prendergast, B.J. (2011) Can photoperiod predict mortality in the 1918–1920 influenza pandemic? *J. Biol. Rhythms* 26, 345–352

70 Meireles–Filho, A.C.A. and Kyriacou, C.P. (2013) Circadian Rhythms in insect disease vectors. *Memórias do Instituto Oswaldo Cruz* 108 (Suppl), 48–58

71 Fleury, F. *et al.* (2000) Adaptive significance of a circadian clock: temporal segregation of activities reduces intrinsic competative inferiority in *Drosophila* parasitoids. *Proc. R. Soc. Lond. B: Biol. Sci.* 267, 1005–1010

72 Rund, S.S.C. *et al.* (2011) Genome-wide profiling of diel and circadian gene expression in the malaria vector *Anopheles gambiae*. *Proc. Natl. Acad. Sci. U.S.A.* 108, E421–E430

73 Levi, T. *et al.* (2015) Accelerated phenology of blacklegged ticks under climate warming. *Philos. Trans. R. Soc. Lond. B: Biol. Sci.* 370, 20130556

74 Hawking, F. (1975) Circadian and other rhythms of parasites. *Adv. Parasitol.* 13, 123–182

75 Mideo, N. *et al.* (2013) The cinderella syndrome: why do malaria-infected cells burst at midnight? *Trends Parasitol.* 29, 10–16

76 Rothschild, M. and Ford, B. (1964) Breeding of the rabbit flea (*Spilopsyllus cuniculi* (Dale)) controlled by the reproductive hormones of the host. *Nature* 201, 103–104

77 Mead–Briggs, A. and Rudge, A. (1960) Breeding of the rabbit flea, *Spilopsyllus cuniculi* (Dale): requirement of a 'factor' from a pregnant rabbit for ovarian maturation. *Nature* 187, 1136–1137

78 Rothschild, M. and Ford, B. (1966) Hormones of the vertebrate host controlling ovarian regression and copulation of the rabbit flea. *Nature* 211, 261–266

79 Glaudel, R. and Etges, F. (1973) The effect of photoperiod inversion upon *Schistosoma mansoni* cercarial emergence from *Biomphalaria glabrata*. *Int. J. Parasitol.* 3, 619–622

80 Asch, H. (1972) Rhythmic emergence of *Schistosoma mansoni* cercariae from *Biomphalaria glabrata*: control by illumination. *Exp. Parasitol.* 31, 350–355

81 Toledo, R. *et al.* (1999) Production and chronobiology of emergence of the cercariae of *Euparyphium albuferensis* (Trematoda: Echinostomatidae). *J. Parasitol.* 85, 263–267

82 Cornford, E. *et al.* (1976) Physiological relationships and circadian periodicities in rodent trypanosomes. *Trans. R. Soc. Trop. Med. Hyg.* 70, 238–243

83 O'Donnell, A.J. *et al.* (2011) Fitness costs of disrupting circadian rhythms in malaria parasites. *Proc. R. Soc. Lond. B: Biol. Sci.* 278, 2429–2436

84 O'Donnell, A.J. *et al.* (2013) Disrupting rhythms in *Plasmodium chabaudi*: costs accrue quickly and independently of how infections are initiated. *Malar. J.* 12, 372

85 O'Donnell, A.J. *et al.* (2014) Correction: disrupting rhythms in *Plasmodium chabaudi*: costs accrue quickly and independently of how infections are initiated. *Malar. J.* 13, 503

86 Hotta, C.T. *et al.* (2000) Calcium-dependent modulation by melatonin of the circadian rhythm in malarial parasites. *Nat. Cell Biol.* 2, 466–468

87 De Bekker, C. *et al.* (2014) From behavior to mechanisms: an integrative approach to the manipulation by a parasitic fungus (*Ophiocordyceps unilateralis s.l.*) of its host ants (*Camponotus* spp.). *Integr. Comp. Biol.* 54, 166–176

88 Adamo, S.A. (2013) Parasites: evolution's neurobiologists. *J. Exp. Biol.* 216, 3–10

89 Van Houte, S. *et al.* (2013) Walking with insects: molecular mechanisms behind parasitic manipulation of host behaviour. *Mol. Ecol.* 22, 3458–3475

90 Smith Trail, D. (1980) Behavioral interactions between parasites and hosts: host suicide and the evolution of complex life cycles. *Am. Nat.* 116, 77–91

91 Thaiss, C.A. *et al.* (2014) Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. *Cell* 159, 1–16

92 Hayman, D.T.S. (2015) Biannual birth pulses allow filoviruses to persist in bat populations. *Proc. R. Soc. Lond. B: Biol. Sci.* 282, 20142591

93 Ireland, J.M. *et al.* (2004) The effect of seasonal host birth rates on population dynamics: the importance of resonance. *J. Theor. Biol.* 231, 229–238

94 Ireland, J.M. *et al.* (2007) The effect of seasonal host birth rates on disease persistence. *Math. Biosci.* 206, 31–45

95 Helm, B. (2009) Geographically distinct reproductive schedules in a changing world: costly implications in captive stonechats. *Integr. Comp. Biol.* 49, 563–579

96 Gibbs, H.C. (1973) Hypobiosis in parasitic nematodes: an update. *Adv. Parasitol.* 25, 129–174

97 Hawking, F. (1967) The 24-hour periodicity of microfilariae: biological mechanisms responsible for its production and control. *Proc. R. Soc. Lond. B: Biol. Sci.* 169, 59–76

98 Cattadori, I.M. *et al.* (2007) Variation in host susceptibility and infectiousness generated by co-infection: the myxoma–*Trichostrongylus retortaeformis* case in wild rabbits. *J. R. Soc. Interface* 4, 831–840

99 Best, A. *et al.* (2009) The Implications of coevolutionary dynamics to host–parasite interactions. *Am. Nat.* 173, 779–791

100 Bull, J.J. and Lauring, A.S. (2014) Theory and empiricism in virulence evolution. *PLoS Pathog.* 10, e1004387

101 Alizon, S. *et al.* (2009) Virulence evolution and the trade-off hypothesis: history, current state of affairs and the future. *J. Evol. Biol.* 22, 245–259

102 Navara, K.J. and Nelson, R.J. (2007) The dark side of light at night: physiological, epidemiological, and ecological consequences. *J. Pineal Res.* 43, 215–224

103 Garamszegi, L.Z. (2011) Climate change increases the risk of malaria in Birds. *Global Change Biol.* 17, 1751–1759

104 Paull, S.H. and Johnson, P.T.J. (2014) Experimental warming drives a seasonal shift in the timing of host–parasite dynamics with consequences for disease risk. *Ecol. Lett.* 17, 445–453

105 Lanier, L.L. (2013) Shades of grey – the blurring view of innate and adaptive immunity. *Nat. Rev. Immunol.* 13, 73–74

106 Raberg, L. (2014) How to live with the enemy: understanding tolerance to parasites. *PLoS Biol.* 12, e1001989

107 Trifonova, S.T. *et al.* (2013) Diurnal redistribution of human lymphocytes and their temporal associations with salivary cortisol. *Chronobiol. Int.* 30, 669–681

108 Kirsch, S. *et al.* (2012) T-cell numbers and antigen-specific T-cell function follow different circadian rhythms. *J. Clin. Immunol.* 32, 1381–1389

109 Bollinger, T. *et al.* (2010) The influence of regulatory T cells and diurnal hormone rhythms on T helper cell activity. *Immunology* 131, 488–500

110 Haus, E. and Smolensky, M.H. (1999) Biological rhythms in the immune system. *Chronobiol. Int.* 16, 581–622

111 Rahman, S.A. *et al.* (2014) Endogenous circadian regulation of pro-inflammatory cytokines and chemokines in the presence of bacterial lipopolysaccharide in humans. *Brain Behav. Immun.* http://dx.doi.org/10.1016/j.bbi.2014.11.003

112 Naidu, K.S. *et al.* (2010) Inflammation in the avian spleen: timing is everything. *BMC Mol. Biol.* 11, 1–13

113 Zimmerman, L.M. *et al.* (2010) Variation in the seasonal patterns of innate and adaptive immunity in the red-eared slider (*Trachemys scripta*). *J. Exp. Biol.* 213, 1477–1483

114 Klink, M. *et al.* (2012) Seasonal changes in activities of human neutrophils in vitro. *Inflamm. Res.* 61, 11–16

115 Buehler, D.M. *et al.* (2008) Seasonal redistribution of immune function in a migrant shorebird: annual-cycle effects override adjustments to thermal regime. *Am. Nat.* 172, 783–796

116 Pap, P.L. *et al.* (2014) No evidence for parasitism-linked changes in immune function or oxidative physiology over the annual cycle of an avian species. *Physiol. Biochem. Zool.* 87, 729–739

117 Baillie, S.R. and Prendergast, B.J. (2008) Photoperiodic regulation of behavioral responses to bacterial and viral mimetics: a test of the winter immunoenhancement hypothesis. *J. Biol. Rhythms* 23, 81–90

118 Deerenberg, C. *et al.* (2002) Spleen size variation during long-distance migration in the garden warbler *Sylvia borin*. *Avian Sci.* 2, 217–226

119 Myrianthefs, P. *et al.* (2003) Seasonal variation in whole blood cytokine production after LPS stimulation in normal individuals. *Cytokine* 24, 286–292

120 Prendergast, B.J. *et al.* (2007) Winter day lengths enhance T lymphocyte phenotypes, inhibit cytokine responses, and attenuate behavioral symptoms of infection in laboratory rats. *Brain Behav. Immun.* 21, 1096–1108

121 Pyter, L.M. *et al.* (2005) Photoperiod alters hypothalamic cytokine gene expression and sickness responses following immune challenge in female Siberian hamsters (*Phodopus sungorus*). *Neuroscience* 131, 779–784

122 Paynter, S. *et al.* (2015) Seasonal immune modulation in humans: observed patterns and potential environmental drivers. *J. Infect.* 70, 1–10

123 Feigin, R.D. *et al.* (1969) Daily periodicity of susceptibility of mice to pneumococcal infection. *Nature* 224, 379–380

124 Shackelford, P.G. and Feigin, R.D. (1973) Periodicity of susceptibility to pneumococcal infection: influence of light and adrenocortical secretions. *Science* 182, 285–287

125 Martinaud, G. *et al.* (2009) Circadian variation in shedding of the oocysts of *Isospora turdi* (Apicomplexa) in blackbirds (*Turdus merula*): an adaptive trait against desiccation and ultraviolet radiation. *Int. J. Parasitol.* 39, 735–739

126 Platt, T.R. *et al.* (2013) Circadian egg production by *Echinostoma caproni* (Digenea: Echinostomatidae) in ICR mice. *J. Parasitol.* 99, 179–182

127 Jenkins, E. *et al.* (2006) Climate change and the epidemiology of protostrongylid nematodes in northern ecosystems: *Parelaphostrongylus odocoilei* and *Protostrongylus stilesi* in Dall's sheep (*Ovis d. dalli*). *Parasitology* 132, 387–401