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The evolutionary ecology of circadian rhythms in infection

Mary L. Westwood[1*], Aidan J. O'Donnell[1], Charissa de Bekker[2], Curtis M. Lively[3], Marlene Zuk[4] and Sarah E. Reece[1]

Biological rhythms coordinate organisms' activities with daily rhythms in the environment. For parasites, this includes rhythms in both the external abiotic environment and the within-host biotic environment. Hosts exhibit rhythms in behaviours and physiologies, including immune responses, and parasites exhibit rhythms in traits underpinning virulence and transmission. Yet, the evolutionary and ecological drivers of rhythms in traits underpinning host defence and parasite offence are largely unknown. Here, we explore how hosts use rhythms to defend against infection, why parasites have rhythms and whether parasites can manipulate host clocks to their own ends. Harnessing host rhythms or disrupting parasite rhythms could be exploited for clinical benefit; we propose an interdisciplinary effort to drive this emerging field forward.

Circadian rhythms have long been taken for granted by science. Indeed, the first observation of a clock-controlled behaviour (leaf opening and closing in *Mimosa pudica*) was not recorded until the 18th century[1]. Following the fundamental observation that organisms can adaptively anticipate daily rhythms in their environment, the field of 'chronobiology' took off in the mid-20th century, with a focus on evolutionary and ecological questions. However, the advent of genetic tools a few decades later shifted the remit to the determination of the molecular and genetic workings of circadian clocks. Yet, despite the major impact on fitness that they are assumed to have, circadian rhythms remain overlooked in evolutionary ecology[2–4]. Here, we propose that the integration of chronobiology and evolutionary ecology should be returned to its roots to tackle a topic of growing and applied interest: the role of rhythms in host–parasite interactions. Note that we use the term parasite to collectively refer to all agents of infection (for example, single-celled and multicellular eukaryotes, bacteria and viruses).

One of the most fundamental ecological interactions is that between hosts and parasites. Research from diverse taxa (plants, mammals and insects) reveals that host clocks drive daily rhythms in immune defences, disease severity and spread[5,6]. Parasites display daily rhythms in traits underpinning within-host survival and between-host transmission[7,8]. Rhythms in parasite activities and in host responses to infection could provide an advantage to parasites, hosts, both or neither. To what extent parasites and hosts are in control of their own and/or each other's rhythms is also poorly understood.

Understanding the evolution (and possibly, coevolution) of rhythms may enable development of vaccines and drugs that take advantage of rhythmic vulnerabilities in parasites or harness host rhythms to improve efficacy and reduce drug toxicity. To make such interventions resistant to parasite evolution, an understanding of how host–parasite interactions shape rhythms in hosts and parasites is necessary[7]. Key questions include how rhythms in diverse host traits contribute to defence, how parasites cope with exposure to their hosts' rhythms and whether hosts and parasites can each manipulate the other's rhythms for their own advantage. We discuss these three scenarios, identify systems to explore them and offer ways in which this knowledge can be exploited to improve health. An evolutionary ecologist's introduction to chronobiology is provided in Boxes 1 and 2.

Rhythms in host defence

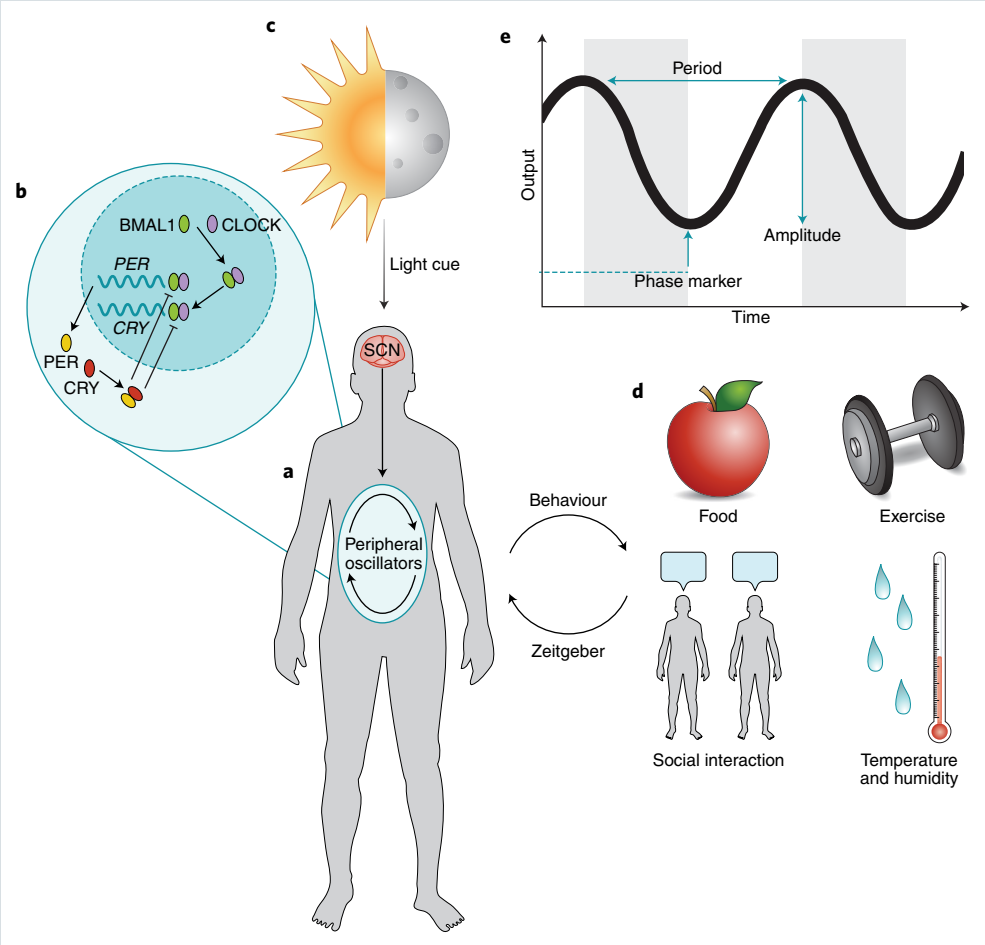
The most patent defence against infection is the immune response, and a wealth of evidence has revealed that circadian clocks play a role in orchestrating immune defences[5]. Circadian clock genes are expressed in many types of immune cells, and the immune and circadian systems are connected in multiple ways[9,10]. For instance, the clock gene *ARNTL* (also known as *BMAL1*) mediates the balance between pro- and anti-inflammatory responses[11]. Rhythmic production of the pro-inflammatory cytokines tumour-necrosis factor (TNF)-α and interleukin (IL)-6 by macrophages is clock controlled[12], and mobilization of inflammatory monocytes is also regulated by the clock[10]. This phenomenon, termed 'anticipatory inflammation', appears to be uncoupled to metabolic rhythms and may defend against incoming parasites[13]. Similarly, in humans, pro-inflammatory cytokines peak in circulation during the day (active phase)[14], whereas haematopoietic stem and progenitor cells, and most mature leukocytes, peak at night[14,15]. In nocturnal mammals, an inverse rhythm is often observed, with innate defences peaking at night (active phase) and repair mechanisms peaking during the day (resting phase)[9].

Observations of immune rhythms have given rise to the notion that organisms invest in defence during the active phase, when a parasite encounter is assumed to be most likely to occur, and repair during the resting phase[16]. Mounting a continual immune response is likely to be energetically inefficient as well as to result in collateral damage (immunopathology[17]); these problems are minimised by temporal segregation. Also, energetic demands imposed by activity and metabolism may trade-off against immune defense[18]. Intuitively, 'defence only during the active phase' suggests that the host achieves the most 'bang for the buck' by ensuring that activities that are energetically costly or that are likely to cause collateral damage are only performed when most useful. However, this concept

[1]Institute of Evolutionary Biology and Institute of Immunology and Infection Research, School of Biological Sciences, University of Edinburgh, Edinburgh, UK. [2]Department of Biology, University of Central Florida, Orlando, FL, USA. [3]Department of Biology, Indiana University, Bloomington, IL, USA. [4]Department of Ecology, Evolution and Behavior, University of Minnesota, St. Paul, MN, USA. *e-mail: mary.westwood@ed.ac.uk

Box 1 | What are circadian rhythms?

Biological rhythms are deemed to be controlled by circadian clocks if they meet several criteria[90]. First, their duration (period) must be approximately 24 h. Second, they must persist (free-run) in conditions without time-of-day cues, which is usually assessed by observation in constant light or dark. Third, the phase of the oscillator or outputs is set (entrained) by a zeitgeber, which is usually light. Fourth, unlike the rate of many chemical reactions, there is little variation in the speed of a circadian clock over a biologically realistic range of environmental temperatures (temperature compensation). Together, these criteria allow organisms to fulfil a key feature of circadian rhythms: anticipatory, rather than reactionary, behaviour. For instance, plants ready photosynthetic machinery in anticipation of sunlight[91,92], and animals exhibit food-anticipatory activity (for example, increases in core temperature, activity, serum corticosterone and duodenal disaccharides) before foraging[93]. The workings of circadian clocks are sufficiently flexible to allow organisms to cope with gradual changes in photoperiod across seasons, but are not flexible enough to instantly cope with changes in time zones (which is why travellers experience jet lag).



a, The mammalian circadian system is composed of the 'central' clock in the brain (SCN) and 'peripheral clocks' in other organs and tissues. **b**, Clocks in nucleated cells are run by transcription–translation feedback loops (TTFLs). For example, in animals, the proteins CLOCK and BMAL1 act as activators, and members of the period (PER) and cryptochrome (CRY) families are repressors[94]. **c**, Retinal photoreceptors receive light cues, which are carried through the hypothalamic optic tract and transmitted to the SCN, resulting in its synchronization/entrainment. **d**, Clocks in organs and tissues (peripheral clocks) can be entrained by feeding rhythms, and in taxa other than mammals, exercise, social cues and abiotic rhythms in temperature and humidity may entrain clocks. **e**, Rhythms are often characterized by their period, amplitude and markers for phase (grey bars illustrate night time for a rhythmic trait measured over 48 h). They are described in relation to the time since the zeitgeber (ZT) occurred (for example, ZT6 refers to 6 h after dawn), which usually differs from the actual time of day (circadian time; CT).

may be naive. First, it ignores the potential for constraints imposed by the need to temporally couple (or de-couple) certain immune rhythms with other internal rhythms[7]. This includes separation of the timing of metabolism from defensive actions within immune cells themselves[5,16]. Second, it assumes that a parasite encounter is rhythmic and predictably occurs in the active phase. This is clearly the case for food-borne parasites, but ingestion is not the only route into a host. Rather, the immune system functions within a broad set of energetic demands, in which parasite defence is just one of many requirements. For example, bacterial pathogens often use rhythmic opening of stomata for gas exchange during the day as a route into plants[19]; consequently, *Arabidopsis* is better able to detect and defend against parasites in the morning than evening[20,21]. Given the wealth and diversity of data (shown in Table 1), meta-analyses are

Box 2 | Why have circadian rhythms evolved?

Circadian clocks appear to be so advantageous that nearly all eukaryotes have a circadian system in most of their cells[95]. Circadian clocks may confer two kinds of fitness benefit: coordinating behaviours with rhythms in the external environment (extrinsic adaptive value) and temporally compartmentalising incompatible processes (intrinsic adaptive value)[2]. For instance, intrinsic benefits are conferred when cell division in yeast is temporally constrained to the reductive phase of metabolism, minimising rates of genetic mutation[96]. However, most studies of the fitness consequences of circadian rhythms have focussed on the benefits of synchronizing activities with rhythms in the abiotic environment: matching the period of day–night rhythms enables cyanobacteria to outcompete strains whose clocks run faster or slower[97] and enhances the survival of *Arabidopsis*[92]. Rhythms in the biotic environment[2] matter too. For example, the sea urchin *Centrostephanus coronatus* avoids predatory sheepshead wrasse (*Pimelometopon pulchrum*) by foraging at night and retreating to shelter before the onset of wrasse activity[98].

Despite the diversity of extrinsic rhythms that could select for the scheduling of diverse processes, there are surprisingly few demonstrations that circadian clocks actually affect fitness. For example, fitness is greater in wild-type mice than mutant mice with shortened periods[71], flies with clock mutations die more rapidly than wild types after infection with bacteria[72,73] and circadian-knockout plants flower later and are less viable than wild-type plants[3]. However, depending on ecological context, rigidly scheduling activities according to day and night is not always the best strategy. For example, nocturnal mice boost energy efficiency by switching to diurnality when challenged with cold and hunger[74]. Nursing honeybees that remain in the hive are arrhythmic because round-the-clock care is necessary for larvae; if needed, diurnal foraging bees can revert to arrhythmic nursing behavior[75]. Shorebirds also display considerable plasticity in activity rhythms during breeding, likely explained by predator avoidance strategies[76].

The above examples illustrate the gains to be made from integrating chronobiology with evolutionary ecology in general[4]. We propose that such an approach offers a novel advance to the study of host–parasite interactions and coevolution. Coupling the well-developed conceptual frameworks for unravelling how circadian oscillators operate, and probing the costs and benefits of phenotypically plastic traits that are relevant to infection, will explain why rhythms in immune defences and parasite traits occur.

needed to test whether the timing (phase) of rhythms in immune effectors relates to nocturnal versus diurnal lifestyles and whether they function in front-line or secondary defences or in healing.

For a diverse group of hosts (flies, pants and mammals), infection in the active versus resting phase dramatically affects disease severity and mortality rates (Table 1), suggesting that the phase of immune rhythms upon infection matters. Most studies performed in plants (Table 1) point toward infection during the active phase, resulting in greater resistance to infection and less damage to the plant. But the degree to which immune rhythms result in time-of-day differences in parasite control can be counter-intuitive. For example, when challenged in their rest phase, mice mount higher clock-controlled proinflammatory responses against *Salmonella enterica* serovar Typhimurium, but bacterial load is also higher and the hosts have worse symptoms[22]. Furthermore, *Leishmania* parasites infect host neutrophils and macrophages, and the clock-controlled secretion of chemoattractants by these immune cells facilitates their infection, making parasite invasion more successful at night when immune activity is highest[23]. Thus, whether immune rhythms are sufficient to entirely explain divergent outcomes of time-of-day of infection is unclear (Table 1). Studies that separate the effects of immune rhythms on preventing infection from their role in dealing with on-going infection will reveal the extent to which immune rhythms are beneficial and when they should be overruled to deal with a major threat. Additionally, most time-of-day immune challenges have been with either bacteria or chemicals, raising the question of whether a more diverse array of challenges is needed to establish general patterns.

The notion that host circadian clocks impact on infection via traits other than immune responses has been largely overlooked. Rhythmicity in host activity may determine when hosts provide the best resources to their parasites and offer the most opportunities for onwards transmission[24–26]. For example, a recent study of the intestinal helminth *Trichuris muris* demonstrates the role of host rhythms in foraging. Mice infected in the morning (resting phase) expel worms sooner and have a stronger T-helper 2 cell response than mice infected at dusk (active phase), and, when mice are fed only in the day, this effect is reversed in an immune-independent manner[27]. Host feeding rhythms are relevant to gut microbiota, and a two-way feedback between host and microbe rhythms has been proposed[28]. Daily rhythms in host reproductive behaviours may make hosts vulnerable to infection. For example, the crepuscular and nocturnal singing activity of the cricket *Teleogryllus oceanicus* allows the acoustically orienting parasitoid fly *Ormia ochracea* to locate hosts, but the flies are best able to hunt when darkness is incomplete[29]. A rhythmically expressed reproductive behaviour (singing) got the host into this mess, and it appears that natural selection has found two solutions (Box 3).

In addition to immune responses, infected hosts often exhibit adaptive sickness behaviours consisting of endocrine, autonomic and behavioural changes that perturb circadian rhythms[30,31]. For example, wild red colobus monkeys (*Procolobus rufomitratus tephrosceles*) decrease energetically costly activities and rest frequently while shedding whipworm eggs[32]. Fever, another common sickness behaviour, is sufficient to offset the 10–12.5% increase in metabolic rate required for each increase of 1 °C in temperature[33] and has been conserved throughout more than 600 million years of vertebrate evolution[34]. Fever enhances an organism's chance of survival by creating a hostile environment for parasites and a more active immune response[34–37]. Under normal circumstances, the so-called central clock (the suprachiasmatic nucleus (SCN)) controls body temperature rhythms, but how the SCN and inflammation interact to control temperature is unknown. Though many behaviours altered during infection are controlled by the clock when an organism is healthy, the extent to which organisms become too sick to maintain normal behaviour or adaptively disrupt their rhythms is unclear. Additionally, clock-control could facilitate recovery of rhythms during the return to health.

Viewing the host as a collection of traits connected by the circadian system has the potential to uncover novel strategies to resist infection and reveal the circumstance in which immune rhythms reflect constraints or adaptations. Indeed, rhythmic metabolism of xenobiotic substances (for example, drugs and vaccines) influences efficacy and toxicity in a time-of-day-dependent manner[38]. For example, halothane (a commonly used anaesthetic) administered to mice in the daytime results in low mortality (5%), but mortality increases (76%) if it is administered at night[39], and, in the United States, half of the best-selling drugs for humans target the products of genes that are rhythmically expressed (in mice)[40]. A better understanding of host rhythms could be harnessed to make drugs and vaccines more effective, as well as to mitigate the negative effects of modern lifestyles that involve shift work and jet lag. However, for such interventions to be sustainable in the face of parasite evolution,

Table 1 | Impact of immune challenge during the rest and active phases of hosts

Host spp.	Challenge	ToD	Outcome in rest versus active phase
Mus musculus, house mouse (nocturnal)	*Salmonella typhmurium*	ZT4/16	Greater inflammation and bacterial load when infected in the rest phase[22]
	Leishmania major	Subjective day/night	Lower parasite burden and lower severity when infected in the rest phase[23]
	Lipopolysaccharide (LPS) endotoxin	Subjective day/night	Lower concentrations of cytokines when infected in the rest phase[77]
		ZT11/19	Higher mortality when challenged in the rest phase[78]
		Subjective day/night	Greater inflammatory responses and lower bacterial burden when challenged/infected in the rest phase[79]
	Streptococcus pneumoniae	ZT0/12	Greater inflammatory responses and lower bacterial burden when challenged/infected in the rest phase[79]
	Murid herpesvirus 4	ZT0/10	Greater viral replication when infected in the rest phase[60]
	Helicobacter pylori	ZT1/7/13	Lower lymphocyte numbers when infected in the rest phase[80]
	Vesicular stomatitis virus	ZT0/12	Higher mortality when infected in the rest phase[81]
Drosophila melanogaster, fruit fly (diurnal)	*Pseudomonas aeruginosa*	ZT1/5/9/13/17/21/1	Lowest mortality when infected in the rest phase (especially ZT21)[73]
		Subjective day/night	Lowest bacterial burden when infected in the rest phase[73]
	Streptococcus pneumoniae	ZT7/19	Slowest rate of mortality when infected in the rest phase[72]
	Escherichia coli	ZT0/6/12/18	Infection at all ZT induces sleep the morning after infection and sleep was more prolonged after infection in the rest phase[82]
Anopheles stephensi, Asian malaria mosquito (nocturnal)	*Escherichia coli*	Morning/evening	Lower bacterial growth and lower mortality when infected in the rest phase[83]
Arabidopsis thaliana, thale cress (diurnal)	*Pseudomonas syringae*	ZT0/4/10/16	Immune defences are highest when inoculation occurs early in the active phase[84] Note photoperiod is 9-h light,15-h dark
	Botrytis cinerea	Dawn/dusk	Larger lesions when inoculated in the rest phase[49]
		ZT0/3/6/9/12/15/18/21/24	Greater susceptibility when inoculated in the rest phase[21]
	Pseudomonas syringae	Subjective day/night	Lower infiltration of bacteria when infected in the rest phase[85]
		Subjective morning/evening	Greater suppression of bacterial growth at the start of the rest phase when spray-inoculated and greater suppression of bacterial growth at the start of the active phase when syringe-infiltrated[20]
	Hyaloperonospora arabidopsidis	Dawn/dusk	Highest percentage of leaves with sporangiophores when infected in the start of the rest phase[86]
Danio rerio, zebrafish (diurnal)	*Salmonella typhimurium*	ZT4/16	Lower survival when infected in the rest phase[87]
Oreochromis niloticus, Nile tilapia (mostly diurnal)	LPS	ZT3/15	Greater humoral immune response when infected in the rest phase[88]
Phodopus sungorus, Siberian hamster (nocturnal)	LPS	ZT1/16	Shorter febrile response and more persistent locomotor activity when infected in the rest phase[89] Note photoperiod is 16-h light, 8-h dark

A selection of studies identified as time-of-day immune challenges from PubMed searches for 'time of day' plus 'immune and infection' and 'circadian rhythm' plus 'immune and infection'. Articles were included if the study involved a time-of-day immune challenge; those without a time-of-day immune challenge were not included in the table. Time-of-day (ToD) is given as hours since lights on (ZT) for organisms in entrainment conditions and as subjective day/night for those in constant light or dark conditions (that is, corresponding to the light or dark portion of the cycle before experiencing constant conditions). Unless otherwise stated, entrainment conditions are 12-h light, 12-h dark. Outcomes of challenge in the rest phase (daytime for nocturnal organisms, nighttime for diurnal organisms) are compared with challenge in the active phase in terms of virulence metrics and immune effectors measured.

Box 3 | Case studies illustrating the role of circadian rhythms in parasite offence, host defence and host manipulation

***Teleogryllus oceanicus* (Pacific field cricket)–*Ormia ochracea* (parasitoid fly).**

What we know. O. ochracea deposit larvae, which burrow into the host and emerge 7–10 days later, resulting in host death. A flatwing morph that is physically incapable of calling has evolved to evade the risk of parasitism by acting as a silent, satellite male[24].

Is this a more nuanced form of parasite evasion? In addition to the flatwing morph, natural selection may have found another solution. Some males condense singing activity to the darkest part of the night[29], which may hamper the fly's ability to use visual cues to home in on hosts. Parasite evasion (via a flatwing phenotype or phase-shifted calling) trades off with attraction of females, potentially constraining selection on these strategies. Moreover, multiple activities need to be coordinated for successful reproduction (for example, locomotion, foraging and spermatophore production). Given that many of these traits are clock-controlled, could altering the timing outputs of the clock be a streamlined way of phase-shifting all related activities and minimising the costs of parasite evasion?

Credit: Norman Lee

Carpenter ants (*Camponotus* spp.)–*Ophiocordyceps unilateralis s.l.* (fungi).

What we know. The fungus *O. unilateralis s.l.* induces carpenter ant workers, ordinarily active during nighttime, to wander out of the ant nest during daytime. Hosts then scale vegetation and adopt a mandibular death-grip in an elevated location. This manipulated behaviour is highly time-of-day-dependent and species-specific and occurs within a 3-h window at dawn or in the mid-late morning, depending on the species[68,99]. Clinging to vegetation, the ant dies whilst the fungus completes its life cycle by growing a spore-producing stalk out of the dorsal region of the ant's thorax[99].

A case for coevolution and ecosystem specificity? The jigsaw puzzle of how the fungus controls the ant is still being pieced together. Clocks may play a central role because infection alters the expression of host clock homologs *per* and *cycle*[68]. Host manipulation also appears to involve altering host chemosensory abilities, potentially via rhythmic secretion of enterotoxins[100], all achieved from the fungus's primary location in muscle tissues[101].

Credit: Miles Zhang

Mammals–*Plasmodium* spp. (malaria parasites).

What we know. Malaria parasites synchronously burst from the host's blood cells every 24, 48 or 72 h depending on the parasite species[102]. When out of synch with the host's circadian rhythms, parasites incur an approximately 50% reduction in the densities of both asexual stages (necessary for in-host survival) and sexual stages (responsible for transmission)[103] before they become rescheduled to be in synch with host feeding rhythms[44,45].

Three worlds collide in a complex system of interactions? Why aligning the phase of parasite rhythms with the host's rhythms is important remains mysterious, but recent work suggests that parasites are also selected to coordinate with the time-of-day their mosquito vectors are active[54,55] (see Rund et al.[104] for information on *Anopheles* circadian rhythms). If differently phased rhythms for asexual replication are required to provide the best matches to host and vector rhythms, parasites face a trade-off between maximising in-host survival and between-host transmission. Such a tension could be exploited by novel drug treatments to coerce parasites into a loss of fitness. Further, mosquito nets have induced a shift in *Anopheles gambiae* biting activity, ultimately resulting in a change in host-parasite timing[8,52,53]. The epidemiological consequences of this are unknown.

Credit: Sinclair Stammers

an understanding of the ecology of rhythms from the perspective of parasites is also required.

Rhythms in parasite offence

Scheduling activities to take advantage of daily rhythms in transmission opportunities could be a general explanation for rhythms in parasites. The most well-known example concerns the transmission forms (microfilariae) of different species of filarial worms. They move from the host's organs to the capillaries during the day or night, depending on whether they are transmitted by insect vectors that bite during the day or the night[41]. In addition to the activity patterns of vectors, rhythmic interactions with hosts also matter. For example, the larval stage of the blood fluke *Schistosoma japonicum* emerges from the invertebrate host to seek a mammalian host at different times of day: flukes emerge in the afternoon when the preferred host is nocturnal, or in the morning if they are seeking a diurnal host[42]. Parasites that have free-living stages are also subject to rhythms in the abiotic environments. The coccidian parasite *Isospora* sheds from its host in the late afternoon to minimise ultraviolet exposure and desiccation risk whilst undergoing a developmental transition that is necessary for infection of new hosts[43]. However, key questions remain about the adaptive nature of these rhythms. For example, why aren't microfilariae located in the peripheral capillaries all day long? Is a cost associated with this location, which is only worth paying at times of day when vectors are active?

In contrast to the role of parasite rhythms in transmission, their role in within-host survival has received less attention. Many host rhythms (in addition to immune rhythms) present opportunities and constraints for parasites. *Trypanosoma brucei* (which causes sleeping sickness) displays circadian clock-driven rhythms in the expression of metabolic genes[8]. These rhythms correlate with time-of-day sensitivity to oxidative damage, thereby suggesting the need to cope with redox challenges caused by rhythmic digestion of food by hosts. In contrast, rhythms in the development of asexually replicating malaria parasites capitalise on daily variation in the nutritional content of blood caused by host immune responses and feeding patterns[44,45]. It is unknown whether malaria parasites cannot complete their developmental cycle until the host makes nutrients available and/or use nutrients rhythms as a time-of-day cue to set the pace of their development[46] (Box 3).

Clocks in parasites or hosts could have fitness consequences for one or both parties, or for neither. The existence of fitness consequences for both hosts and parasites suggests that clocks could coevolve. Clock coevolution is suspected for the plant–pollinator system *Petunia axillaris* and *Manduca sexta*[47], in which nocturnal scent emission by *P. axillaris* coincides with foraging activity in the hawk moth *M. sexta*. Both traits are clock-controlled and appear to be so well synchronized that, even in the absence of floral scent emission, *M. sexta* exhibits a burst in foraging activity at the same time that floral scent emission is expected to be greatest. However, foraging behaviour also remains sensitive to the environment, as evidenced by absence of activity when the moth is subjected to light at night. If rhythms in different organisms do coevolve, then they should use the same time-of-day cue (zeitgeber), but how robust should their timing systems be to fluctuations in the environment? If the rhythm of one party is more readily disrupted (masked) by environmental change, or is faster at following or determining ('tracking') seasonal changes in photoperiod, then the relationship may be disrupted to the gain of the host or the parasite. Exploring the degree and consequences of plasticity in rhythms is pertinent because climate change is interfering with the ability of interacting species to synchronise[48].

The situation is further complicated when interactions between both host and parasite clocks shape disease trajectories. For example, in a plant–fungus system (*Arabidopsis thaliana* and *Botrytis cinerea*, respectively), when both parties are in the same photoperiod schedule, primary plant defences peak in the morning, and the fungus produces the biggest lesions when inoculated at dusk[49]. The authors were able to separate the contributions to pathogenicity by host and parasite clocks using reverse lighting schedules for fungus and plant: fungus at dusk produced more severe infections than fungus at dawn regardless of time-of-day for recipient plant[49]. Furthermore, this suggests that *B. cinerea* anticipates and exploits weaknesses in plant defence at dusk rather than attempting to overwhelm dawn defences (see 'Rhythms in host defence'). Separately assigning the contributions of rhythms in hosts/vectors and parasites to virulence and transmission is necessary to understand whose genes control which rhythms and hence how these rhythms can be shaped by selection.

If parasite rhythms are adaptive, then disrupting them could reduce disease severity as well as transmission. However, understanding the timing mechanisms of parasite rhythms is necessary to disrupt them[7]. Unravelling how parasite rhythms are controlled is a considerable challenge. Parasites might allow the host to inadvertently schedule their activities for them, in which case the genes encoding parasite timing mechanisms belong to hosts. Alternatively, parasites might keep time using a circadian clock (with the properties described in Box 1), as demonstrated for *T. brucei* and *B. cinerea*. Given the diversity in clock genes across taxa, searching genomes for known clock genes often yields 'absence of evidence', not 'evidence of absence'. Instead, round-the-clock transcriptomics or proteomics, paired with bioinformatics approaches to mine for known core clock-related functional domains and sequence patterns, may uncover candidates. However, simpler time-keeping strategies exist, though they do not necessarily have the advantages of temperature compensation or anticipation. For example, cell division cycles are often controlled by hourglass mechanisms that rely upon threshold concentrations of substances, independently of periodic phenomena[50]. Alternatively, organisms can react directly (via tracking) to temporal changes in the environment. This differs from masking, a chronobiological phenomenon in which the expression of a clock-controlled rhythm is suppressed by a change in the environment without having a direct effect on the period or phase of the underlying rhythm[51]. A response that directly tracks time-of-day cues may suit parasites with multihost lifecycles if each host type provides a different time cue.

Given that rhythms in *T. brucei* metabolism as well as plasticity in development during the asexual cycle of *Plasmodium* spp. enable these parasites to tolerate drugs, there is an urgent need for proximate and ultimate explanations of their rhythms. The *T. brucei* clock is entrained by temperature cycles, but if other parasites use easily perturbed zeitgebers to set their clocks or respond directly to time-of-day cues, it should be possible to reduce parasite fitness by interfering with their rhythms. Further, reports of changes to the biting time of mosquito populations that transmit malaria suggest that insecticide-treated bed nets are imposing selection on vector rhythms[52,53]. Given that rhythms of parasites and mosquitoes each affect malaria transmission in lab experiments[54,55], what are the likely epidemiological consequences? Recent work suggests that mosquitoes are more susceptible to infection when they feed in the daytime and parasites are more infectious at night[54]. Thus, day-biting could increase the prevalence, but not burden, of malaria in mosquitoes. However, in the longer term, if parasites evolve to invert their rhythm but mosquitoes do not, both prevalence and burden may increase.

Parasite manipulation of host rhythms

Rhythms in host processes offer opportunities that parasites could exploit. Could parasite fitness be increased through coercion of hosts to alter their rhythms? Although many striking examples of parasite manipulation of host phenotypes (that is, changes to host

traits that benefit parasites) are known[56], the notion of 'parasite manipulation of host clocks' is largely unexplored[57]. A pre-requisite for parasite manipulation is that a phenotypically plastic host trait is targeted, and circadian clocks are flexible. Because clocks control much of the host's behaviour and physiology[58] and clocks throughout a given host involve the same players in the canonical clock (the transcription–translation feedback loops), manipulation of the host's time-keeping may be an efficient way to simultaneously alter many aspects of the within-host environment. Alternatively, parasite interests may be served by bolstering circadian rhythms of their hosts during sickness to ensure that they forage and interact with conspecifics, as usual.

As outlined in the section 'Rhythms in host defence', separation of the effects of being sick per se from host defence and parasite manipulation is challenging. Recently, a combination of culture and comparison of infection models has revealed that *T. brucei* alters expression rhythms of clock genes in host mice[59]. Specifically, infected hosts are more active in the resting phase because the clock runs faster. The effects of infection at organismal, cellular and molecular levels suggest that the behaviour is not just a result of sickness[59]. However, it is not clear how *T. brucei* achieves this and whether the parasite benefits from altering host rhythms. One target of circadian disruption by viral parasites is the gene *Bmal1*, a core clock gene. Herpes and influenza A virus replication and dissemination within the host is enhanced in infections where *Bmal1* is knocked out[60]. However, it remains unclear if virus replication is maximised by simply disturbing rhythmicity in host cell cycles or if this is a case of immune manipulation since *Bmal1* appears involved in innate host defense[60]. As changes to host clocks have now been observed, the proceeding step is to decipher the ecological context behind these effects.

The above examples lend proof-of-principle to the idea that parasites can manipulate host clocks, and they could be a general explanation for examples of host manipulation. Hairworms (Nematomorpha) provide a well-known case of temporally linked behavioural manipulation. They infect various arthropods, notably crickets, and cause the host to wander in an erratic manner until a body of water is encountered. The host commits suicide by jumping into the water, and then the adult hairworm emerges. Infected hosts are found wandering only in the early part of the night[61], and uninfected hosts are rarely motivated to jump into water. Infected crickets differentially express an array of proteins, some of which are linked to visual processes and circadian clocks[62]. Culturing isolated host cells with parasite products and quantifying the expression of clock genes (following Rijo-Ferreira et al.[59]) could illuminate this case of parasite manipulation. For systems without relevant insect cell lines or for cases where manipulation is likely to be tissue/cell-type specific, a transcriptomics approach may be useful[63]. Round-the-clock expression data can be mined for putative core clock genes, and clock phase, amplitude and period may be assessed in control and manipulated hosts. This, however, is likely to be extremely challenging for host species whose timekeeping does not rely on a canonical circadian clock.

Another putative case for clock manipulation concerns the New Zealand freshwater snail (*Potamopyrgus antipodarum*), which can be infected by *Microphallus* trematodes[64] (Trematoda: Microphallidae). Uninfected adult snails forage primarily at night on the upper surfaces of rocks in the shallow-water margins of lakes. These snails retreat under rocks at sunrise, which likely reduces their risk of predation by waterfowl, the definitive host for *Microphallus*. Infected snails, however, show delayed retreating, potentially making them more likely to be consumed[25]. Crucially, the apparent manipulation only occurs when the parasite is mature. Snails infected with immature (non-transmissible) stages exhibit the same risk-averse retreating behaviour as uninfected snails[25]. In addition, snails infected with other species of sterilizing trematodes, which are not trophically transmitted, do not exhibit the same risky behaviour as those infected with *Microphallus*[65], thereby eliminating the possibility that the *Microphallus*-induced behavioural change is a simple artefact of parasitic castration. Finally, *Microphallus*-infected snails spent more time foraging on the top of rocks, even when food was removed, whereas uninfected snails retreated to shelter[65]. Taken together, the data suggest that *Microphallus* induces a change in snail behaviour that increases trophic transmission of the trematode, potentially via manipulation of clock-controlled activity rhythms.

There are many ways that parasites could interfere with clock-controlled host behaviours. One such method is alteration of perception/detection of the zeitgeber that sets the time of the host's clock, which is usually light. For example, *Microphallus* could interfere with photoreception to reduce the sensitivity of snails to dawn, causing their clocks to phase delay and forage at higher light intensities than un-manipulated snails. Alternatively, parasites could induce the host to ignore its clock (mask) or alter clock regulation of hormones that relay time-of-day information around the host. For example, baculoviruses appear to perturb the circadian rhythms of their caterpillar hosts, the European gypsy moth *Lymantria dispar dispar*, by disrupting hormones that control climbing behaviour. The baculovirus (*Lymantria dispar* nucleopolyhedrovirus) alters a single gene to inactivate 20-hydroxyecdysone[66] (a host hormone regulated by a circadian oscillator), motivating the caterpillar to climb high atop their host plants. Here, they liquefy and disseminate the virus to caterpillars below as well as infect birds who consume the caterpillar corpses[67]. Similar to the manipulation of caterpillar hosts, many species of parasitic fungi (*Ophiocordyceps* spp. and *Pandora* spp.) alter the daily behavioural rhythm of a variety of ant species[68,69] (Box 3).

Parsing out whether temporal disruption is a host response or clock manipulation is nearly, if not entirely, impossible without uncovering the mechanism of manipulation. The lack of insight into the mechanisms that parasites use to interfere with their hosts has stalled progress in the field of 'host manipulation by parasites'[70]. This gap could be filled by harnessing the tools and conceptual framework developed in chronobiology. Many of the examples above have employed an ecological approach, yet a chronobiological approach can help elucidate both proximate and ultimate explanations.

Conclusion

Over the past few decades, the focus of chronobiology has been to elucidate the mechanistic underpinnings of biological rhythms. We propose that now is the time to integrate this knowledge into parasitology, evolutionary ecology and immunology (Box 2). Indeed, the role of biological rhythms in infectious disease is a growing topic that holds promise for improving human and animal health. History clearly illustrates that attempts to control parasites are usually met with counter-evolution (in the form of drug resistance, vaccine escape and host shifts). A comprehensive understanding of how rhythms affect parasite invasion and exploitation of a host (or vector) offers novel ways to disrupt the chain of transmission and treat disease. Further, clock coevolution may occur in host–parasite–vector interactions, resulting in complex arms races best understood through the lens of chronobiology coupled with evolutionary ecology. Chronobiology supplies a myriad of tools to help elucidate rhythmic phenotypes and reveal to what extent host and parasite genes are responsible for rhythms in disease phenotypes. Adding an evolutionary ecology framework will ensure this information is generalizable and used to make interventions as evolution-proof as possible.

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References

1. de Mairan, J. Observation botanique. *Hist. l'Academie R. des Sci. Paris* (1729).
2. Sharma, V. K. Adaptive significance of circadian clocks. *Chronobiol. Int.* **20**, 901–919 (2003).
3. Green, R. M., Tingay, S., Wang, Z.-Y. & Tobin, E. M. Circadian rhythms confer a higher level of fitness to *Arabidopsis* plants. *Plant Physiol.* **129**, 576–584 (2002).
4. Helm, B. et al. Two sides of a coin: ecological and chronobiological perspectives of timing in the wild. *Philos. Trans. R. Soc. B Biol. Sci.* **372**, 20160246 (2017).
5. Scheiermann, C., Gibbs, J., Ince, L. & Loudon, A. Clocking in to immunity. *Nat. Rev. Immunol.* **18**, 423–437 (2018).
6. Martinez-Bakker, M. & Helm, B. The influence of biological rhythms on host–parasite interactions. *Trends Ecol. Evol.* **30**, 314–326 (2015).
7. Reece, S. E., Prior, K. F. & Mideo, N. The life and times of parasites: rhythms in strategies for within-host survival and between-host transmission. *J. Biol. Rhythms* **32**, 516–533 (2017).
8. Rijo-Ferreira, F., Pinto-Neves, D., Barbosa-Morais, N. L., Takahashi, J. S. & Figueiredo, L. M. *Trypanosoma brucei* metabolism is under circadian control. *Nat. Microbiol.* **2**, 17032 (2017).
9. Scheiermann, C., Kunisaki, Y. & Frenette, P. S. Circadian control of the immune system. *Nat. Rev. Immunol.* **13**, 190–198 (2013).
10. Curtis, A. M., Bellet, M. M., Sassone-Corsi, P. & O'Neill, L. A. J. Circadian clock proteins and immunity. *Immunity* **40**, 178–186 (2014).
11. Zasłona, Z. et al. The circadian protein BMAL1 in myeloid cells is a negative regulator of allergic asthma. *Am. J. Physiol. Lung Cell Mol. Physiol.* **312**, L855–L860 (2017).
12. Keller, M. et al. A circadian clock in macrophages controls inflammatory immune responses. *Proc. Natl Acad. Sci.* **106**, 21407–21412 (2009).
13. Nguyen, K. D. et al. Circadian gene *Bmal1* regulates diurnal oscillations of Ly6Chi inflammatory monocytes. *Science* **341**, 1483–1488 (2013).
14. Haus, E. & Smolensky, M. H. Biologic rhythms in the immune system. *Chronobiol. Int.* **16**, 581–622 (1999).
15. Haus, E., Lakatua, D. J., Swoyer, J. & Sackett-Lundeen, L. Chronobiology in hematology and immunology. *Am. J. Anat.* **168**, 467–517 (1983).
16. Labrecque, N. & Cermakian, N. Circadian clocks in the immune system. *J. Biol. Rhythms* **30**, 277–290 (2015).
17. Graham, A. L., Allen, J. E. & Read, A. F. Evolutionary causes and consequences of immunopathology. *Annu. Rev. Ecol. Evol. Syst.* **36**, 373–397 (2005).
18. Kerr, A. M., Gershman, S. N. & Sakaluk, S. K. Experimentally induced spermatophore production and immune responses reveal a trade-off in crickets. *Behav. Ecol.* **21**, 647–654 (2010).
19. Roden, L. C. & Ingle, R. A. Lights, rhythms, infection: the role of light and the circadian clock in determining the outcome of plant–pathogen interactions. *Plant Cell* **21**, 2546–2552 (2009).
20. Bhardwaj, V., Meier, S., Petersen, L. N., Ingle, R. A. & Roden, L. C. Defence responses of *Arabidopsis* thaliana to infection by Pseudomonas syringae are regulated by the circadian clock. *PLoS One* **6**, e26968 (2011).
21. Ingle, R. A. et al. Jasmonate signalling drives time-of-day differences in susceptibility of *Arabidopsis* to the fungal pathogen *Botrytis cinerea*. *Plant J.* **84**, 937–948 (2015).
22. Bellet, M. M. et al. Circadian clock regulates the host response to *Salmonella*. *Proc. Natl Acad. Sci.* **110**, 9897–9902 (2013).
23. Kiessling, S. et al. The circadian clock in immune cells controls the magnitude of *Leishmania* parasite infection. *Sci. Rep.* **7**, 10892 (2017).
24. Zuk, M., Rotenberry, J. T. & Tinghitella, R. M. Silent night: adaptive disappearance of a sexual signal in a parasitized population of field crickets. *Biol. Lett.* **2**, 521–524 (2006).
25. Levri, E. P. & Lively, C. M. The effects of size, reproductive condition, and parasitism on foraging behaviour in a freshwater snail, *Potamopyrgus antipodarum*. *Anim. Behav.* **51**, 891–901 (1996).
26. Ponton, F. et al. Water-seeking behavior in worm-infected crickets and reversibility of parasitic manipulation. *Behav. Ecol.* **22**, 392–400 (2011).
27. Hopwood, T. W. et al. The circadian regulator BMAL1 programmes responses to parasitic worm infection via a dendritic cell clock. *Sci. Rep.* **8**, 3782 (2018).
28. Johnson, C. H., Zhao, C., Xu, Y. & Mori, T. Timing the day: what makes bacterial clocks tick? *Nat. Rev. Microbiol.* **15**, 232–242 (2017).
29. Zuk, M., Simmons, L. & Cupp, L. Calling characteristics of parasitized and unparasitized populations of the field cricket *Teleogryllus oceanicus*. *Behav. Ecol. Sociobiol.* **33**, 339–343 (1993).
30. Clark, I. A., Budd, A. C. & Alleva, L. M. Sickness behaviour pushed too far—the basis of the syndrome seen in severe protozoal, bacterial and viral diseases and post-trauma. *Malar. J.* **7**, 208 (2008).
31. Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W. & Kelley, K. W. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat. Rev. Neurosci.* **9**, 46–56 (2008).
32. Ghai, R. R., Fugère, V., Chapman, C. A., Goldberg, T. L. & Davies, T. J. Sickness behaviour associated with non-lethal infections in wild primates. *Proc. Biol. Sci.* **282**, 20151436 (2015).
33. Kluger, M. J. Phylogeny of fever. *Fed. Proc.* **38**, 30–34 (1979).
34. Evans, S. S., Repasky, E. A. & Fisher, D. T. Fever and the thermal regulation of immunity: the immune system feels the heat. *Nat. Rev. Immunol.* **15**, 335–349 (2015).
35. Kluger, M. J., Ringler, D. H. & Anver, M. R. Fever and survival. *Science* **188**, 166–168 (1975).
36. Schulman, C. I. et al. The effect of antipyretic therapy upon outcomes in critically ill patients: a randomized, prospective study. *Surg. Infect. (Larchmt.)* **6**, 369–375 (2005).
37. Earn, D. J. D., Andrews, P. W. & Bolker, B. M. Population-level effects of suppressing fever. *Proc. Biol. Sci.* **281**, 20132570 (2014).
38. Levi, F. & Schibler, U. Circadian rhythms: mechanisms and therapeutic implications. *Annu. Rev. Pharmacol. Toxicol.* **47**, 593–628 (2007).
39. Matthews, J. H., Marte, E. & Halberg, F. A circadian susceptibility–resistance cycle to fluothane in male B 1 mice. *Can. Anaesth. Soc. J.* **11**, 280–290 (1964).
40. Zhang, R., Lahens, N. F., Ballance, H. I., Hughes, M. E. & Hogenesch, J. B. A circadian gene expression atlas in mammals: implications for biology and medicine. *Proc. Natl Acad. Sci. USA* **111**, 16219–16224 (2014).
41. Hawking, F. The 24-hour periodicity of microfilariae: biological mechanisms responsible for its production and control. *Proc. R. Soc. Lond. B Biol. Sci.* **169**, 59–76 (1967).
42. Mouahid, G. et al. A new chronotype of *Schistosoma mansoni*: adaptive significance. *Trop. Med. Int. Health* **17**, 727–732 (2012).
43. Martinaud, G., Billaudelle, M. & Moreau, J. Circadian variation in shedding of the oocysts of *Isospora turdi* (Apicomplexa) in blackbirds (*Turdusmerula*): an adaptative trait against desiccation and ultraviolet radiation. *Int. J. Parasitol.* **39**, 735–739 (2009).
44. Prior, K. F. et al. Timing of host feeding drives rhythms in parasite replication. *PLoS Pathog.* **14**, e1006900 (2018).
45. Hirako, I. C. et al. Daily rhythms of TNFα expression and food intake regulate synchrony of *Plasmodium* stages with the host circadian cycle. *Cell Host Microbe* **23**, 796–808.e6 (2018).
46. Reece, S. E. & Prior, K. F. Malaria makes the most of mealtimes. *Cell Host Microbe* **23**, 695–697 (2018).
47. Fenske, M. P., Nguyen, L. P., Horn, E. K., Riffell, J. A. & Imaizumi, T. Circadian clocks of both plants and pollinators influence flower seeking behavior of the pollinator hawkmoth *Manduca sexta*. *Sci. Rep.* **8**, 2842 (2018).
48. Kharouba, H. M. et al. Global shifts in the phenological synchrony of species interactions over recent decades. *Proc. Natl Acad. Sci. USA* **115**, 5211–5216 (2018).
49. Hevia, M. A., Canessa, P., Müller-Esparza, H. & Larrondo, L. F. A circadian oscillator in the fungus *Botrytis cinerea* regulates virulence when infecting *Arabidopsis thaliana*. *Proc. Natl Acad. Sci. USA* **112**, 8744–8749 (2015).
50. Rensing, L., Meyer-Grahle, U. & Ruoff, P. Biological timing and the clock metaphor: oscillatory and hourglass mechanisms. *Chronobiol. Int.* **18**, 329–369 (2001).
51. Mrosovsky, N. Masking: history, definitions, and measurement. *Chronobiol. Int.* **16**, 415–429 (1999).
52. Sougoufara, S. et al. Biting by *Anopheles funestus* in broad daylight after use of long-lasting insecticidal nets: a new challenge to malaria elimination. *Malar. J.* **13**, 125 (2014).
53. Rund, S. S. C., O'Donnell, A. J., Gentile, J. E. & Reece, S. E. Daily rhythms in mosquitoes and their consequences for malaria transmission. *Insects* **7**, 14 (2016).
54. Schneider, P. et al. Adaptive periodicity in the infectivity of malaria gametocytes to mosquitoes. *Proc. Biol. Sci.* **285**, 294942 (2018).
55. Pigeault, R., Caudron, Q., Nicot, A., Rivero, A. & Gandon, S. Timing malaria transmission with mosquito fluctuations. *Evol. Lett.* **2**, 378–389 (2018).
56. Thomas, F., Rigaud, T. & Brodeur, J. in *Encyclopedia of Animal Behavior* (eds. Breed, M. & Moore, J.) 661–669 (Elsevier, 2010).
57. de Bekker, C., Merrow, M. & Hughes, D. P. 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 (2014).
58. Ko, C. H. & Takahashi, J. S. Molecular components of the mammalian circadian clock. *Hum. Mol. Genet.* **15**, R271–R277 (2006).
59. Rijo-Ferreira, F. et al. Sleeping sickness is a circadian disorder. *Nat. Commun.* **9**, 62 (2018).
60. Edgar, R. S. et al. Cell autonomous regulation of herpes and influenza virus infection by the circadian clock. *Proc. Natl Acad. Sci. USA* **113**, 10085–10090 (2016).
61. Thomas, F. et al. Do hairworms (*Nematomorpha*) manipulate the water seeking behaviour of their terrestrial hosts? *J. Evol. Biol.* **15**, 356–361 (2002).
62. Biron, D. G. et al. 'Suicide' of crickets harbouring hairworms: a proteomics investigation. *Insect Mol. Biol.* **15**, 731–742 (2006).

63. Hughes, M. E. et al. Guidelines for genome-scale analysis of biological rhythms. *J. Biol. Rhythms* **32**, 380–393 (2017).
64. Lively, C. M. Evidence from a New Zealand snail for the maintenance of sex by parasitism. *Nature* **328**, 519 (1987).
65. Levri, E. P. Parasite-induced change in host behavior of a freshwater snail: parasitic manipulation or byproduct of infection? *Behav. Ecol.* **10**, 234–241 (1999).
66. Hoover, K. et al. A gene for an extended phenotype. *Science* **333**, 1401 (2011).
67. Goulson, D. Wipfelkrankheit: modification of host behaviour during baculoviral infection. *Oecologia* **109**, 219–228 (1997).
68. de Bekker, C. et al. Gene expression during zombie ant biting behavior reflects the complexity underlying fungal parasitic behavioral manipulation. *BMC Genomics* **16**, 620 (2015).
69. de Bekker, C., Will, I., Das, B. & Adams, R. M. M. The ants (Hymenoptera: Formicidae) and their parasites: effects of parasitic manipulations and host responses on ant behavioral ecology. *Myrmecol. News* **28**, 1–24 (2018).
70. Herbison, R., Lagrue, C. & Poulin, R. The missing link in parasite manipulation of host behaviour. *Parasit. Vectors* **11**, 222 (2018).
71. Spoelstra, K., Wikelski, M., Daan, S., Loudon, A. S. I. & Hau, M. Natural selection against a circadian clock gene mutation in mice. *Proc. Natl Acad. Sci. USA* **113**, 686–691 (2016).
72. Stone, E. F. et al. The circadian clock protein timeless regulates phagocytosis of bacteria in *Drosophila*. *PLoS Pathog.* **8**, e1002445 (2012).
73. Lee, J.-E. & Edery, I. Circadian regulation in the ability of *Drosophila* to combat pathogenic infections. *Curr. Biol.* **18**, 195–199 (2008).
74. van der Vinne, V. et al. Cold and hunger induce diurnality in a nocturnal mammal. *Proc. Natl Acad. Sci. USA* **111**, 15256–15260 (2014).
75. Bloch, G. & Robinson, G. E. Chronobiology. Reversal of honeybee behavioural rhythms. *Nature* **410**, 1048 (2001).
76. Bulla, M. et al. Unexpected diversity in socially synchronized rhythms of shorebirds. *Nature* **540**, 109–113 (2016).
77. Gibbs, J. E. et al. The nuclear receptor REV-ERBα mediates circadian regulation of innate immunity through selective regulation of inflammatory cytokines. *Proc. Natl Acad. Sci. USA* **109**, 582–587 (2012).
78. Marpegan, L. et al. Diurnal variation in endotoxin-induced mortality in mice: correlation with proinflammatory factors. *Chronobiol. Int.* **26**, 1430–1442 (2009).
79. Gibbs, J. et al. An epithelial circadian clock controls pulmonary inflammation and glucocorticoid action. *Nat. Med.* **20**, 919–926 (2014).
80. Druzd, D. et al. Lymphocyte circadian clocks control lymph node trafficking and adaptive immune responses. *Immunity* **46**, 120–132 (2017).
81. Gagnidze, K. et al. Nuclear receptor REV-ERBα mediates circadian sensitivity to mortality in murine vesicular stomatitis virus-induced encephalitis. *Proc. Natl Acad. Sci. USA* **113**, 5730–5735 (2016).
82. Kuo, T.-H., Pike, D. H., Beizaeipour, Z. & Williams, J. A. Sleep triggered by an immune response in *Drosophila* is regulated by the circadian clock and requires the NFκβ relish. *BMC Neurosci.* **11**, 17 (2010).
83. Murdock, C. C., Moller-Jacobs, L. L. & Thomas, M. B. Complex environmental drivers of immunity and resistance in malaria mosquitoes. *Proc. Biol. Sci.* **280**, 20132030 (2013).
84. Griebel, T. & Zeier, J. Light regulation and daytime dependency of inducible plant defenses in *Arabidopsis*: phytochrome signaling controls systemic acquired resistance rather than local defense. *Plant Physiol.* **147**, 790–801 (2008).
85. Korneli, C., Danisman, S. & Staiger, D. Differential control of pre-invasive and post-invasive antibacterial defense by the *Arabidopsis* circadian clock. *Plant Cell Physiol.* **55**, 1613–1622 (2014).
86. Wang, W. et al. Timing of plant immune responses by a central circadian regulator. *Nature* **470**, 110–114 (2011).
87. Du, L. Y. et al. The innate immune cell response to bacterial infection in larval zebrafish is light-regulated. *Sci. Rep.* **7**, 12657 (2017).
88. Lazado, C. C., Skov, P. V. & Pedersen, P. B. Innate immune defenses exhibit circadian rhythmicity and differential temporal sensitivity to a bacterial endotoxin in Nile tilapia (*Oreochromis niloticus*). *Fish Shellfish Immunol.* **55**, 613–622 (2016).
89. Prendergast, B. J. et al. Circadian disruption alters the effects of lipopolysaccharide treatment on circadian and ultradian locomotor activity and body temperature rhythms of female Siberian hamsters. *J. Biol. Rhythms* **30**, 543–556 (2015).
90. Johnson, C. H., Elliott, J., Foster, R., Honma, K. & Kronauer, R. *Chronobiology: Biological Timekeeping* (Sinauer Associates, 2004).
91. Michael, T. P. et al. Enhanced fitness conferred by naturally occurring variation in the circadian clock. *Science* **302**, 1049–1053 (2003).
92. Dodd, A. N. et al. Plant circadian clocks increase photosynthesis, growth, survival, and competitive advantage. *Science* **309**, 630–633 (2005).
93. Stephan, F. K. The "other" circadian system: food as a zeitgeber. *J. Biol. Rhythms* **17**, 284–292 (2002).
94. Young, M. W. & Kay, S. A. Time zones: a comparative genetics of circadian clocks. *Nat. Rev. Genet.* **2**, 702–715 (2001).
95. Dunlap, J. C. Molecular bases for circadian clocks. *Cell* **96**, 271–290 (1999).
96. Chen, Z., Odstrcil, E. A., Tu, B. P. & McKnight, S. L. Restriction of DNA replication to the reductive phase of the metabolic cycle protects genome integrity. *Science* **316**, 1916–1919 (2007).
97. Ouyang, Y., Andersson, C. R., Kondo, T., Golden, S. S. & Johnson, C. H. Resonating circadian clocks enhance fitness in cyanobacteria. *Proc. Natl Acad. Sci. USA* **95**, 8660–8664 (1998).
98. Nelson, B. V. & Vance, R. R. Diel foraging patterns of the sea urchin *Centrostephanus coronatus* as a predator avoidance strategy. *Mar. Biol.* **51**, 251–258 (1979).
99. Hughes, D. P. et al. Behavioral mechanisms and morphological symptoms of zombie ants dying from fungal infection. *BMC Ecol.* **11**, 13 (2011).
100. de Bekker, C., Ohm, R. A., Evans, H. C., Brachmann, A. & Hughes, D. P. Ant-infecting *Ophiocordyceps* genomes reveal a high diversity of potential behavioral manipulation genes and a possible major role for enterotoxins. *Sci. Rep.* **7**, 12508 (2017).
101. Fredericksen, M. A. et al. Three-dimensional visualization and a deep-learning model reveal complex fungal parasite networks in behaviorally manipulated ants. *Proc. Natl Acad. Sci. USA* **114**, 12590–12595 (2017).
102. Garcia, C. R. S., Markus, R. P. & Madeira, L. Tertian and quartan fevers: temporal regulation in malarial infection. *J. Biol. Rhythms* **16**, 436–443 (2001).
103. O'Donnell, A. J., Schneider, P., McWatters, H. G. & Reece, S. E. Fitness costs of disrupting circadian rhythms in malaria parasites. *Proc. Biol. Sci.* **278**, 2429–2436 (2011).
104. Rund, S. S. C., Hou, T. Y., Ward, S. M., Collins, F. H. & Duffield, G. E. Genome-wide profiling of diel and circadian gene expression in the malaria vector. *Proc. Natl Acad. Sci. USA* **108**, E421–E430 (2011).

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Author contributions

S.E.R. conceived the study, M.L.W. and S.E.R. drafted the manuscript, and all authors provided substantial input into ideas and the writing of subsequent drafts.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence should be addressed to M.L.W.