Received: 11 March 2021 | Revised: 14 June 2021 | Accepted: 18 June 2021

DOI: 10.1111/gcb.15761

Global Change Biology WILEY

RESEARCH REVIEW

Thermal limits in the face of infectious disease: How important are pathogens?

Tobias E. Hector[1] | Carla M. Sgrò[1] | Matthew D. Hall[1,2]

[1]School of Biological Sciences, Monash University, Melbourne, Vic., Australia

[2]Centre of Geometric Biology, Monash University, Melbourne, Vic., Australia

Correspondence and present address
Tobias E. Hector, Department of Zoology, University of Oxford, Oxford, UK.
Email: tobias.hector@zoo.ox.ac.uk

Funding information
Monash University; Australian Research Council

Abstract

The frequency and severity of both extreme thermal events and disease outbreaks are predicted to continue to shift as a consequence of global change. As a result, species persistence will likely be increasingly dependent on the interaction between thermal stress and pathogen exposure. Missing from the intersection between studies of infectious disease and thermal ecology, however, is the capacity for pathogen exposure to directly disrupt a host's ability to cope with thermal stress. Common sources of variation in host thermal performance, which are likely to interact with infection, are also often unaccounted for when assessing either the vulnerability of species or the potential for disease spread during extreme thermal events. Here, we describe how infection can directly alter host thermal limits, to a degree that exceeds the level of variation commonly seen across species large geographic distributions and that equals the detrimental impact of other ecologically relevant stressors. We then discuss various sources of heterogeneity within and between populations that are likely to be important in mediating the impact that infection has on variation in host thermal limits. In doing so we highlight how infection is a widespread and important source of variation in host thermal performance, which will have implications for both the persistence and vulnerability of species and the dynamics and transmission of disease in a more thermally extreme world.

KEYWORDS
CT_{max}, disease ecology, heat stress, infectious disease, thermal ecology, thermal limits, thermal mismatch, thermal performance, thermal tolerance

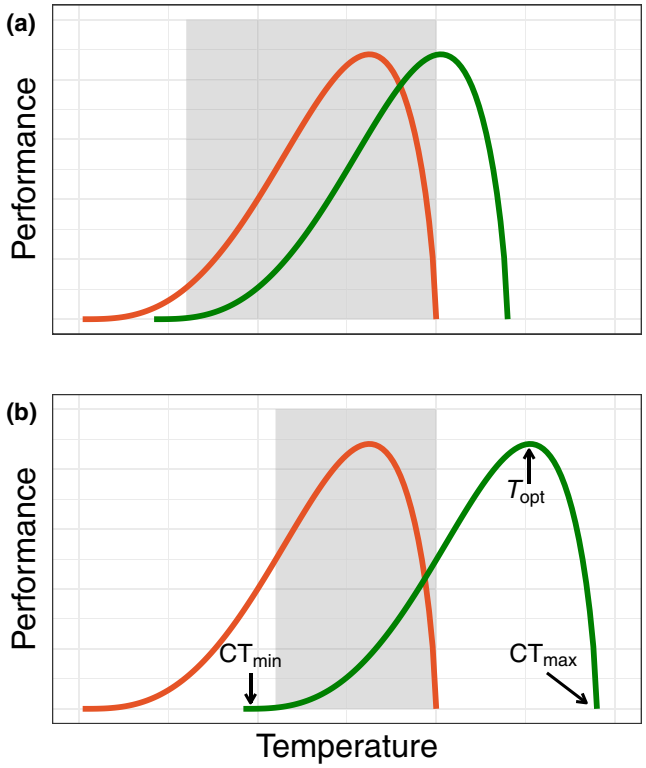
1 | INTRODUCTION

With the severity and frequency of both extreme thermal events and disease outbreaks predicted to continue to shift as a result of global change (Altizer et al., 2013; Buckley & Huey, 2016; Price et al., 2019; Rahmstorf & Coumou, 2011; Rohr et al., 2011), the interaction between hosts, pathogens and their thermal environment will be key in shaping how populations respond to further change (e.g. Claar & Wood, 2020; Cohen et al., 2019, 2020; Furlong & Zalucki, 2017; Rohr & Cohen, 2020). Recent research, particularly in the field of mosquito-borne disease, has exemplified how important temperature is for predictions of the spread and occurrence of infectious disease (discussed in Mordecai et al., 2019). In a typical study, thermal performance curves (Box 1) of host and pathogen traits are measured across multiple static temperatures and used within trait-based epidemiological models to predict how changes in temperature will shape disease transmission and distribution (e.g. Gehman et al., 2018; Shocket et al., 2020). A central insight emerging from such models is that the thermal response of pathogen transmission is tightly linked to the effects of temperature on multiple host and pathogen traits (e.g. Mordecai et al., 2017; Shocket, Ryan, et al., 2018; Tesla et al., 2018). By incorporating the thermal sensitivity of host and pathogen traits, these models are

BOX 1 Understanding thermal performance curves and disease

Thermal performance curves describe how metrics of an individual's performance respond as a function of temperature (Angilletta, 2009). Such curves are defined by having a minimum, optimum and maximum temperature, and are almost universally unimodal (Box Figure 1); with a slow increase in trait values with increasing temperature up to the optimum, above which trait values quickly decline (Chown et al., 2010; Kingsolver & Buckley, 2017). Measures of the upper and lower temperatures at which an individual is able to remain physiologically active (Hoffmann et al., 2012; Kingsolver & Buckley, 2017), known as the thermal limits, are obtained either through dynamic ramping assays where critical temperatures (CT_{max} and CT_{min}) are assessed by gradual increases or decreases in temperature towards lethal levels, or by measuring knockdown times after individuals are placed at a static lethal temperature (Hoffmann et al., 2003; Jørgensen et al., 2019; Rezende et al., 2010; Terblanche et al., 2011). Thermal optima, in contrast, require traits to be measured in a series of static temperatures. If the range of static temperatures is broad enough, then extrapolation of a thermal performance curve can also give some insight into where the upper and lower thermal limits are.

Disease-related traits such as host survival, pathogen reproduction and infection probability commonly follow a characteristic unimodal thermal performance curve, albeit with different thermal optima and limits, and are increasingly being used in a number of ways to understand the impact of global change on infectious disease. First, the thermal performance curves of many host and pathogen traits are incorporated into mechanistic trait-based models to predict the thermal sensitivity of disease transmission and the potential distributions of vectors and pathogens under different warming scenarios (see Cator et al., 2020; Mordecai et al., 2019). Second, the degree of mismatch between the thermal performance curves of hosts and pathogens has also been used to explain the susceptibility of hosts to infection under shifting average temperatures (Cohen, McMahon, et al., 2019; Cohen et al., 2017, 2020; Furlong & Zalucki, 2017; Nowakowski et al., 2016). When host–pathogen thermal tolerances overlap, a host has limited access to thermal niche space that is unsuitable for a pathogen to invade and proliferate (Box Figure 1a). In contrast, when there are large differences between a host and a pathogen's thermal ecology, a host can inhabit a greater range of operative temperatures that can inhibit pathogen performance (Box Figure 1b).



BOX FIGURE 1 Schematic representation of a thermal performance curve of a hypothetical host (green) and pathogen (orange) with lower thermal limits (CT_{min}), thermal optima (T_{opt}) and upper thermal limits (CT_{max}) of the thermal performance curve shown. Relative infection risks, or other symptoms of infectious disease, can depend on the degree of thermal niche overlap and thermal opportunity for coexistence (grey shading). (a) A large overlap in thermal tolerances between host and pathogen is predicted to facilitate coexistence and an increased risk of infection. (b) As the overlap in tolerances is reduced, so too is the thermal niche space in which coexistence can occur, limiting a host's risk of encountering a pathogen and becoming infected

used to predict disease spread under projected changing average temperatures.

Yet missing from the intersection between infectious disease and thermal ecology is the capacity for pathogens themselves to disrupt a host's ability to cope with thermal stress. Thermal limits (Box 1), which are measures of the upper and lower temperature at which an individual can remain active, have recently emerged as being highly sensitive to the damage a pathogen causes to its host (Greenspan et al., 2017; Hector et al., 2019; Laidlaw et al., 2020). In the broader thermal ecology literature, understanding processes that drive variation in upper and lower thermal limits has proven essential for describing the current and future distributions of species (Bush et al., 2016; Furlong & Zalucki, 2017; Kellermann et al., 2012; Sunday et al., 2019), and identifying the vulnerability of species to the risk of extinction due to global change (Diamond et al., 2011; Kingsolver et al., 2013; Pinsky et al., 2019; Tewksbury et al., 2008). Studies, for example, have shown how more tropical populations tend to have a higher thermal tolerance (Hoffmann et al., 2002; Sgrò et al., 2010) and how prior thermal experience can have considerable impacts on individual performance under thermal stress (Gunderson & Stillman, 2015; Rohr et al., 2018; van Heerwaarden & Kellermann, 2020). However, this perspective, which embraces an understanding of within and between population heterogeneity in thermal limits, has yet to be fully integrated into the study of global change and infectious disease.

In this review, we outline how an understanding of the way pathogens might shape the thermal performance of hosts in the face of thermal stress will benefit from integrating the approaches common to the study of thermal ecology (Chown et al., 2009; Hoffmann et al., 2012; Jørgensen et al., 2019; Kingsolver & Buckley, 2017; Rezende et al., 2010). We begin by quantifying the extent to which infection typically changes upper and lower thermal limits, before benchmarking these effects against the impact of a variety of other ecologically relevant stressors. We then discuss how there are many intrinsic sources of heterogeneity, both within and between populations, that have the potential to contribute to substantial variation in the thermal performance of host–pathogen systems and yet are currently often left unaccounted for in models of species persistence and disease spread.

2 | INFECTION WILL ALTER A POPULATION'S THERMAL SAFETY MARGIN

A central concept that defines the importance of a species' thermal ecology under global change is that of the thermal safety margin. The thermal safety margin is defined as the difference between the upper thermal limit of an individual, population or species and the maximum environmental temperature (Deutsch et al., 2008; Huey et al., 2009; Sunday et al., 2014; see Box 1 for an introduction to upper and lower thermal limits). Quantifying thermal safety margins provides an approximation of the level of warming that a population would be able to cope with before experiencing temperatures that cause mortality and local extinction. A key insight from studies exploring thermal safety margins, especially interspecific analyses of upper thermal limits across large geographic ranges, is that some populations and species have far narrower thermal safety margins than others (Diamond et al., 2011; Hoffmann, 2010; Kingsolver et al., 2013). Indeed, it is becoming apparent that tropical and subtropical species may be far more impacted by global temperature changes than temperate species, despite lower levels of predicted warming and thermal variation in tropical habitats, because these species already have relatively narrow thermal safety margins (Deutsch et al., 2008; Hoffmann et al., 2012; Huey et al., 2009; Pinsky et al., 2019; Rohr et al., 2018).

Emerging research has shown that a pathogen will typically decrease the thermal safety margin of a population by reducing the thermal limits of infected hosts, with CT_{max} or knockdown times (see Box 1) of infected animals proving to be particularly susceptible. In the water flea *Daphnia magna*, for example, infection with a bacterial pathogen led to reductions in knockdown times of up to 35 min lower during static heat shock (representing a 78% reduction in knockdown times relative to healthy individuals) and CT_{max} reductions of up to 2°C (Hector et al., 2019). A survey of the broader literature across five studies (see Supporting Information for methodological details) reveals that reductions in CT_{max} due to infection of approximately 2°C (relative to uninfected animals) are quite typical (median −1.4°C, max −3.9°C; see Figure 1). Evidence for infection-induced changes in lower thermal limits is less common. However, reductions in both chill coma recovery times (10 min; Linderman et al., 2012) or CT_{min} (2.5°C; Gehman et al., 2018) have been documented, indicating that infection is likely to shape the environmental tolerance of its host by shrinking of both lower and upper thermal limits. This narrowing of a population's thermal safety margins means that even small deviations in temperature can have disproportionately large effects on individual performance.

3 | THE REDUCTION IN UPPER THERMAL LIMITS DUE TO INFECTION IS ECOLOGICALLY RELEVANT

The above studies beg the question about whether the scale of the reduction in thermal limits that we see as a result of infection will be ecologically important. A change in thermal limits of only a matter of degrees Celsius may seem trivial, but changes of this magnitude have been linked to the potential ability of species, such as *Drosophila*, to reduce range losses under scenarios of global change (Bush et al., 2016). What then is a useful benchmark for a large or small effect? To assess whether the observed reductions in thermal limits as a result of infection will be generally important for the persistence of a population or species, we compared these effects to both the scale of geographic variation commonly observed between populations of a given species and the effects of other ecologically relevant stressors, such as starvation or pollution, on upper thermal limits (see Supporting Information for methodological details).

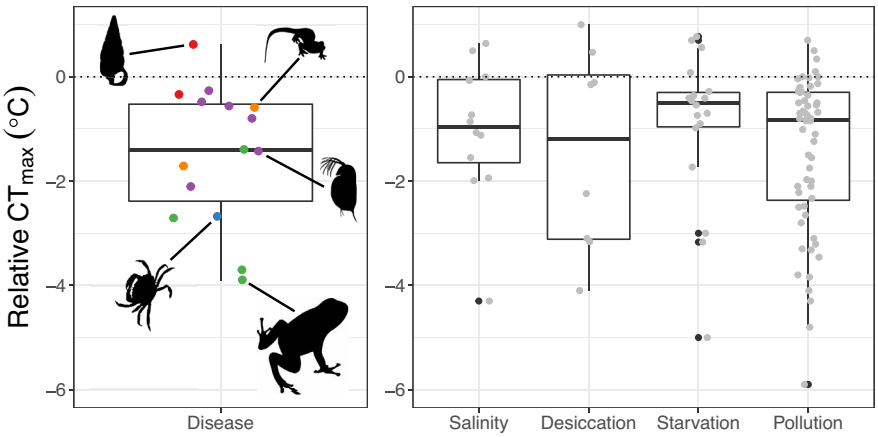


FIGURE 1 Relative difference in CT_{max} between controls and individuals exposed to disease (five studies), or the stressors salinity (10 studies), desiccation (three studies), starvation (10 studies) or environmental pollution (16 studies). Some studies contribute multiple points because they measured multiple traits, stressors, species or populations/genotypes. The dotted line at zero signifies where there would be no difference between control and stressed treatment groups. Each colour on the disease panel represents an individual study. Methodological details are reported in the Supporting Information and data are available via an online repository

From a search of the current literature regarding thermal tolerances along latitudinal clines, we found that infection has the capacity to detrimentally alter thermal limits of a host to a degree that is at best equal and likely far greater than the variation we see within species across substantial geographic gradients. Over the 13 studies considered, we found average difference in CT_{max} along latitudinal clines to be just over 1°C (IQR: 0.87, 1.32), while average difference in knockdown time during static heat shock was around 8 min (IQR: 2.81, 12.59). In Australian populations of *Drosophila melanogaster*, for example, thermal tolerances along a latitudinal cline from tropical to temperate zones varied by up to 8 min for knockdown times and over 1°C for CT_{max} (Hector et al., 2020; Hoffmann et al., 2002; Lasne et al., 2018; Sgrò et al., 2010), with comparable differences observed in the water flea *D. magna* (Geerts et al., 2014; Yampolsky et al., 2014), the springtail *Orchesella cincta* (Jensen et al., 2019), the dung fly *Scathophaga sercoraria* (Bauerfeind et al., 2018) and other *Drosophila* species (Arthur et al., 2008; Castañeda et al., 2015; Ranga et al., 2016). As outlined above (and in Figure 1), the magnitude of changes in thermal limits due to infection often exceeds this level of variability.

We also quantified the impact of other co-occurring stressors on thermal limits from a broad search of the available literature (see Supporting Information). Much like the damage a pathogen causes a host, any co-occurring stressor may detrimentally impact thermal tolerance if they impose a physiological cost that subsequently hinders an individual's capacity to cope with thermal stress (Hofmann & Todgham, 2010; Kaunisto et al., 2016). From these data we were able to quantify, in addition to disease, the average change in CT_{max} values associated with exposure to increasing salinity, desiccation, starvation and environmental pollution. Overall, we found a broad range of effects; for example, for CT_{max}, co-occurring stress could reduce thermal limits by up to 6°C and in limited cases improve thermal limits by up to 1°C (Figure 1). On average, however, the effects appeared to be mostly negative, with between 1 and 2°C reductions in CT_{max} as a result of pre-exposure to a co-occurring stress. These data suggest that disease will impact thermal stress resistance at an equivalent magnitude to a wide variety of ecologically relevant stressors, confirming the importance of infectious disease in shaping the extremes of host thermal performance.

4 | ANY REDUCTION IN THERMAL LIMITS WILL DEPEND ON THE TYPE OF THERMAL CHANGE

Studies examining the link between infectious disease and host thermal performance generally focus on constant temperature treatments (e.g. Gehman et al., 2018; Mordecai et al., 2017, 2019; Shocket, Strauss, et al., 2018; Shocket et al., 2020; Tesla et al., 2018). Most commonly animals are raised under a range of constant sublethal temperatures in order to measure the thermal performance curves of traits related to host and pathogen fitness (infection rates, survival, pathogen load etc. Box 1). In natural populations, however, there will be substantial variation in the rate at which thermal change is experienced across time and space (Buckley & Huey, 2016; Geerts, 2003; Paaijmans et al., 2008). As a result, dynamic ramping assays, whereby critical temperatures (CT_{max} and CT_{min}) are assessed as temperatures are gradually increased or decreased, are recommended as a more ecologically relevant assay (Box 1; Chown et al., 2009; Overgaard et al., 2012; Terblanche et al., 2007, 2011, although see Jørgensen et al., 2019; Rezende et al., 2010, 2014). While a mainstay of thermal ecology, dynamic ramping assays have rarely been adapted to the study of infection-mediated thermal limits (see Bates et al., 2011; Greenspan et al., 2017; Sherman, 2008, and Hector et al., 2019 discussed below).

Depending on how ramping rates and the impact of infection interact, a number of outcomes are possible for how the rate that temperature changes during dynamic ramping assays is likely to modify the effects of infection on host thermal limits. When unexposed to a pathogen, slower ramps, in general, lead to reduced thermal limits due to the accumulation of physical damage as a result of the confounding interaction between temperature and exposure time (Jørgensen et al., 2019; Kingsolver & Umbanhowar, 2018; Rezende et al., 2010; Terblanche et al., 2007). But in some species, slower ramps may instead allow for plastic acclimation responses that could help buffer individuals against further damage, resulting in improved thermal limits (Rohr et al., 2018). The impact of infection on thermal limits, therefore, may be smaller or larger than expected from static temperature assays, depending on whether the damage caused by a pathogen during infection acts additively, synergistically or antagonistically with either the accumulation of physiological damage (as depicted in Figure 2), the potential for temperature acclimation to occur during a slower temperature ramp (Rohr et al., 2018) or some balance between these two competing processes.

One study that has assessed the impact of infection on thermal limits of hosts across a variety of ramping rates and compared this to static measures is that of Hector et al. (2019), again using the water flea *D. magna*. As is often found in uninfected invertebrates (e.g. Terblanche et al., 2007), extending the length of time spent at sublethal temperatures by slowing ramping rates (from 0.06 to 0.02°C min^{-1}) led to a reduction in CT_{max} values of nearly 3°C. At all ramping rates, infection decreased a host's upper thermal limits, but with a trend towards a lessened impact of infection at the very slowest ramping rates (antagonistic scenario Figure 2b; Hector et al., 2019). In this case, either thermal acclimation in infected individuals, and only infected animals, counteracted some of the damage caused by the pathogen and extended thermal stress, or uninfected animals simply have a greater capacity to suffer from the accumulation of damage. Regardless of the underlying mechanism, this example shows how infection can impair host thermal limits across a range of ecologically relevant ramping rates, not just under the extremes of thermal heat shock. It also suggests, at least in this study species, that the impact of infection on thermal limits is likely to be greatest when hosts are exposed to extreme temperature events or rapidly changing thermal conditions.

5 | NOT ALL INDIVIDUALS WITHIN A POPULATION WILL SUFFER A REDUCTION IN THERMAL LIMITS EQUALLY

Natural populations inevitably consist of individuals that vary in some phenotypic characteristic, be it their age, sex, genetic background or prior thermal exposure. Integrating sources of host or pathogen heterogeneity into the combined study of infectious disease and thermal performance, however, has proven challenging. Owing in part to a lack of data, a single estimate of critical thermal limits and thermal optima is often used to represent the thermal ecology of an entire host–pathogen system or even multiple closely related species (see Mordecai et al., 2019, and references and discussion therein). While benchmarking against field data ensures that model predictions based on an 'average' thermal biology are robust (Gehman et al., 2018; Mordecai et al., 2017, 2019; Shocket, Ryan, et al., 2018; Shocket, Strauss, et al., 2018; Tesla et al., 2018), an

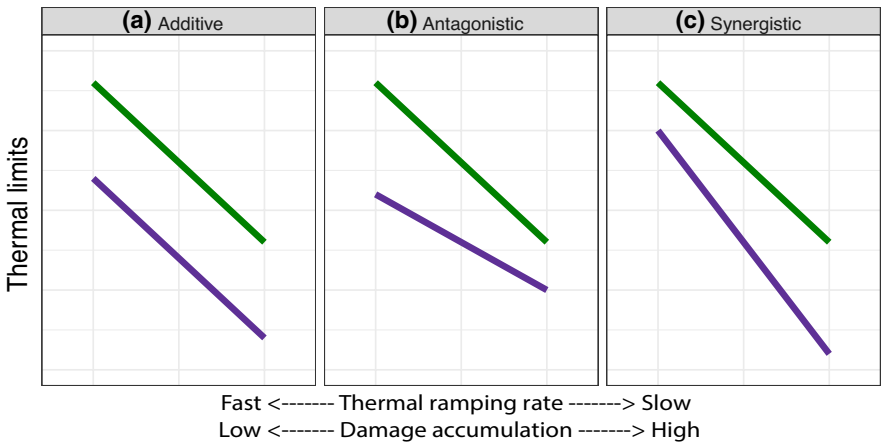


FIGURE 2 Three scenarios for how infection could reduce thermal limits under varying rates of temperature change (ramping rates), based on concepts of how stressors interact (Hall et al., 2012; Marcogliese & Pietrock, 2011) and the common observation that slower ramping rates lead to greater times spent at stressful temperatures and generally lower thermal limits due to the accumulation of physical damage (Chown et al., 2009; Terblanche et al., 2007; but see Rohr et al., 2018). Green lines represent healthy individuals and purple lines represent infected individuals. (a) Additive: infection and thermal ramping act independently. Infection lowers thermal limits by a constant amount across all ramping rates. (b) Antagonistic: thermal ramping and infection oppose each other, and the combined effect is less than predicted. Infection lowers thermal limits, but the relative reduction is smallest under slower ramping rates. (c) Synergistic: the combined effect of thermal ramping and infection is greater than predicted. Infected individuals suffer the greatest reduction in thermal limits as ramping rates slow

BOX 2 The question of host sex

A common source of heterogeneity in natural populations arises due to differences between males and females. One sex is often more susceptible to infection and will develop higher parasite loads than the other (Gipson & Hall, 2018; Zuk, 2009), although the identity of the 'sicker sex' varies by species (Cousineau & Alizon, 2014; Poulin, 1996; Sheridan et al., 2000). Similar pattern of sexual dimorphism is evident in critical thermal limits (Lasne et al., 2018; Lyons et al., 2012; Sasaki et al., 2019). Across 11 species of *Drosophila*, for example, the more heat-resistant sex was females in five species, males in two species, with no obvious sex differences observed in the rest (Mitchell & Hoffmann, 2009). This sexual dimorphism in both thermal limits and the resistance to infection poses a challenge when modelling the impact of global change, as both sexes do not always contribute equally to population growth. In this way, heterogeneity due to sex differences is a unique source of variability within and between populations.

For many species, females make the largest contributions to population growth (i.e. female demographic dominance) owing to their greater investment in reproduction and parental care, and the fact that female fecundity is somewhat independent of male abundance, while the same is not true for males (Crowley, 2000; Harts et al., 2014). For these species, female thermal performance should predominately determine how well a population performs under scenarios of global change, especially if transmission of a pathogen is also limited to the same sex (e.g. mosquito- and vector-borne diseases). In other species, both sexes contribute more equally to population growth and so predictions should be tailored to the joint thermal ecology of the two sexes instead. To date, however, few studies have considered how sex and infection jointly shape thermal limits, but recent evidence suggests the potential for strong sex-biased effects (see Laidlaw et al., 2020 and discussions therein).

understanding of when and where any concordance may breakdown is also important (see also discussion in Cator et al., 2020). Below we focus on three widespread factors that will shape variation in the critical thermal limits of both hosts and pathogens, namely, prior thermal exposure, genotypic differences and in Box 2, sex differences amongst hosts.

Prior thermal exposure is known to modulate thermal limits through plastic effects such as thermal acclimation or hardening (Hoffmann et al., 2012; Rohr et al., 2018; Sgrò et al., 2016; Sinclair et al., 2016; van Heerwaarden & Kellermann, 2020). Both processes buffer populations against further thermal change, with individuals able to produce a stronger plastic response potentially better able to survive thermal extremes in the short term (Hoffmann & Sgrò, 2011; Kellermann et al., 2017, but see Gunderson & Stillman, 2015; Sørensen et al., 2016; van Heerwaarden et al., 2016). Opportunities for prior thermal exposure to shape the thermal performance of host and pathogens are therefore substantial (Claar & Wood, 2020; Ferguson & Sinclair, 2020; Raffel et al., 2013; Rohr et al., 2011; Thomas & Blanford, 2003). For a host, thermal acclimation can improve both host thermal limits and resistance to infection (Allen & Little, 2011; Garbutt et al., 2014), although correlated increases in pathogen virulence can negate these beneficial changes (Greenspan et al., 2017). Likewise, pathogens reared under warmer temperatures have been shown to be more infectious to their subsequent host (Altman et al., 2016; Shocket, Vergara, et al., 2018), although hot temperatures prior to contacting a host can lead to a decrease in infectiousness (Shocket et al., 2019). How prior thermal experience affects host thermal limits during infection will therefore depend on the interaction between both host and pathogen thermal plasticity; something which models of disease dynamics parameterized from constant temperature experiments will not be able to account for (see also Raffel et al., 2013).

Finally, whenever hosts and pathogens encounter each other, the genotypes of both, and their interactions, are likely to shape any changes in thermal limits or optima. Genotype-by-genotype interactions are commonly observed for many characteristics of disease (Carius et al., 2001; Clerc et al., 2015; Hall et al., 2017; Hall & Ebert, 2012; Lambrechts et al., 2005, 2006; Lazzaro & Little, 2009; Wolinska & King, 2009), including host and pathogen traits that are known to be sensitive to thermal change (Blanford et al., 2003; Bryner & Rigling, 2011; Fels & Kaltz, 2006; Laine, 2007; Mitchell et al., 2005; Thomas & Blanford, 2003; Vale & Little, 2009; Vale et al., 2008). Upper thermal limits have also been shown to vary across host genotypes, adding to the evidence that there is genetic variation, albeit limited in some species, for thermal tolerance (Geerts et al., 2014; Williams et al., 2012; Yampolsky et al., 2014). Thermal limits of infected hosts, however, are not simply dependent on their own genotype, with emerging evidence suggesting that the magnitude of any reduction in thermal limits will depend on both the host genotype and pathogen genotype involved (Hector et al., 2019; Laidlaw et al., 2020). Adding to the complexity of predicting disease spread and host persistence under global change, therefore, is the fact that host thermal limits will not only depend on the frequency of host genotypes in any population but also on the frequency of pathogen genotypes and how these genotypes interact.

6 | FEVER IN RESPONSE TO INFECTION MAY INCREASE THE RISK OF REDUCED THERMAL LIMITS

Some host species are known to respond to infection by increasing their average body temperatures above its normal range to induce a fever. This results either from a physiological response within the host that modifies its body temperature upon recognizing a pathogen, or through behavioural changes whereby an infected host moves to a warmer location (Thomas & Blanford, 2003). In both

cases inducing fever is predicted to assist a host in reducing pathogen burden, by either increasing the efficiency of their immune system or by directly harming temperature-sensitive pathogens as their body temperature rises beyond a pathogen's optima (Elliot et al., 2002; Sauer et al., 2019; Thomas & Blanford, 2003; increasing thermal mismatch Box 2). However, not all host–pathogen interactions lead to or involve host fever responses (e.g. Sauer et al., 2018), and so there is variation across host and pathogen systems in the level to which behavioural or physiological fever will occur. For pathogens that do induce a fever, by increasing their host's body temperatures, they may push a host closer to their upper thermal limits. When this coincides with a reduction in upper thermal limits due to infection, then fever-inducing pathogens may be particularly problematic for hosts that concurrently face thermal stress, although the interplay between host fever and thermal limits, as of now, remains untested.

7 | LOCAL ADAPTATION WILL SHAPE THE INTERPLAY BETWEEN INFECTIOUS DISEASE AND GLOBAL CHANGE

Local adaptation in thermal performance, especially upper and lower thermal limits, is common across ectotherms (Kelly et al., 2012; Yampolsky et al., 2014). Along large latitudinal clines, more tropical populations tend to have greater upper thermal limits than populations from higher latitudes (e.g. Hoffmann et al., 2002; Lasne et al., 2018; Sgrò et al., 2010). When populations differ in their response to temperature across space, predictions of species-level responses may therefore have to be tailored to account for this context dependence (e.g. Bush et al., 2016). To date, however, most models of species distribution, adaptation and disease transmission assume common global thermal limits across large geographic areas, and sometimes across species (discussed in Bush et al., 2016; Cator et al., 2020; Mordecai et al., 2019; Peterson et al., 2019; Sternberg & Thomas, 2014). Incorporating local adaptation of thermal performance across populations could help account for variation that is currently unexplained in predictions of host vulnerability and disease spread (see Sternberg & Thomas, 2014). Even subtle effects of local adaption on individual host and pathogen traits would add up to substantial changes in predictions once all traits have been integrated into a model.

Whether the observed signals of adaptation to local thermal environments are robust to infection will also matter. If all populations are equally affected by infection, then predictions for population persistence, such as those made for tropical or temperature populations (e.g. Diamond et al., 2011), need only account for the reduction in thermal safety margins that typically result from infection (see Figure 1). Alternatively, if populations presumed to be locally adapted have inconsistent or unpredictable responses to infection, then some populations may be much more susceptible to the dangers of global change than others. Yet evidence for whether patterns of local adaptation to temperature will be maintained, or rather disrupted, by exposure to a pathogen remains rare. However, a recent study has indicated that immune activation in response to infection is sufficient to erase clinal signals of local adaptation in thermal tolerance in *D. melanogaster* (Hector et al., 2020), suggesting that it may be necessary to explicitly consider population specific responses to both infection and thermal stress.

8 | THERMAL OPTIMA AND THERMAL LIMITS ARE LIKELY SENSITIVE TO HUMAN INTERVENTIONS

We have so far considered how pathogens themselves are able to shape the thermal performance of the host and discussed how an understanding of the thermal ecology of individual host and pathogens, and even populations distributed across geographic regions, may be required to accurately predict, and control, the spread of infectious disease (see also Cator et al., 2020; Sternberg & Thomas, 2014). A recent study by Nguyen et al. (2021), however, provides the first evidence that measures implemented to control the spread of pathogens can themselves shape the thermal optima and thermal limits of host and pathogen populations. By simulating the consequences of controlling the vector, a freshwater snail, of the human pathogen underlying schistosomiasis, they show how removal of snails from a population could potentially shift the thermal optimum for disease transmission upwards by nearly 2°C (Nguyen et al., 2021). This occurs because the additional vector mortality induced by artificial snail removal reduces the relative contribution of natural temperature-driven mortality, and so allows for an increase in the temperature at which transmission risk will likely peak.

Interventions that increase the thermal optima for disease transmission could thus facilitate disease outbreaks during warmer periods of the year, and when exposed hosts are more likely to experience thermal stress and temperatures close to their upper thermal limits (discussed in Nguyen et al., 2021). Where infection also reduces a host's thermal limits (as is likely, see Figure 1), this may substantially reduce the thermal safety margins of an individual or population, placing a host at greater risk of mortality and local extinction. However, a host's upper and lower thermal limits themselves may also be an inadvertent target of interventions. Most measures of thermal tolerance are sensitive to changes in general host physiology and condition (e.g. immune activity, nutritional intake; Andersen et al., 2010; Hector et al., 2020; Hoffmann et al., 2012), and as a result, potentially influenced by many drug, supplement or sanitation-based control measures. Understanding the conditions in which the attempted control of infectious disease might lead to host or pathogen thermal optima or thermal limits to increase (as in Nguyen et al., 2021), or even decrease, will shed new light on the management of infectious disease under global change.

9 | CONCLUDING REMARKS

In this review, we have shown that infection can shape variation in thermal limits as much, if not more, than the variation we see in both

the thermal limits of species across large geographic gradients and the effects of other ecologically relevant stressors. This result alone highlights that the general absence of pathogen exposure from studies of the thermal ecology of species has missed one of the most powerful and potentially widespread drivers of variation in thermal limits that exists in natural populations. We also show that there is substantial variation in the thermal ecology of hosts and pathogens within populations that is currently unaccounted for in models of disease transmission (see also Cator et al., 2020). Finally, we identify that it is currently unclear how infection will mediate host thermal limits across locally adapted populations. This potential for the variation in thermal limits, as shaped by local adaptation, to be altered or even disrupted by infection may complicate our ability to generalize how species will respond to the simultaneous impacts of infection and thermal stress.

Our focus throughout has been solely on the short-term ecological implications for the impact of infection on host thermal performance. We have argued, and provided evidence, that individuals and populations that are exposed to a pathogen are likely to be far more susceptible to the stress caused by thermal extremes. Considering the abundance of pathogens in natural populations, this suggests many species or populations may be at greater risk to the danger of global change than is currently acknowledged. However, exposure to pathogens also has the capacity to shape the longer term evolutionary responses of host populations to changes in temperature. Both the capacity of populations to adapt and the rate of evolution to thermal extremes depend on the degree of genetic variation for thermal limits within a population (Hangartner & Hoffmann, 2016; Hoffmann & Sgrò, 2011). If infection changes the expression of genetic variation of thermal limits within populations, or if there are trade-offs between resistance to thermal stress and infection (Hector et al., 2019), we could see the evolutionary capacity of populations to adapt to further environmental change being altered or even constrained (Sgrò & Hoffmann, 2004).

Throughout this review, we have also focussed our discussion of the impacts of infection on the thermal limits of animals, as the methodologies and traits discussed throughout (i.e. the measurement of knockdown times and CT_{max}) are mostly relevant to animals. However, there is no doubt that there is the potential for infection to impact the thermal performance of other organisms which play a key role in ecosystems and community structures, including plants. Both infection and thermal stress are likely to shape the response of plants to environmental change, with the potential for antagonistic or correlated responses to the two stressors (Desaint et al., 2021; González et al., 2020; Márquez et al., 2007; Pandey et al., 2015; Porras et al., 2020). For example, heat stress can lead to either greater susceptibility or resistance to disease in multiple plant systems depending on the species in question (Pandey et al., 2015), suggesting that infection may in turn have a variable impact on the performance of host plants exposed to extreme temperatures. Heat stress and pathogen exposure are also known to influence similar underlying genetic responses in plants, meaning that a response to infection could mediate any response to subsequent thermal stress (Aparicio et al., 2005; Atkinson & Urwin, 2012; González et al., 2020; Prasch & Sonnewald, 2013). So, while the metrics used to measure thermal limits and performance are not the same across these disparate groups of organisms, nonetheless all the principles discussed above may still apply. Greater effort must be made to investigate the potential impacts of infection on plant performance under thermal extremes, and also in connecting research on the stress responses of plants and animals in order to direct future hypothesis testing.

In conclusion, the recent growth of interest in incorporating host and pathogen thermal performance into predictions of disease spread is greatly progressing our understanding of host and pathogen population dynamics in nature (Cohen et al., 2020; Mordecai et al., 2019). However, sources of heterogeneity in thermal limits are likely to have substantial impacts on both the capacity of populations to cope with thermal stress and the spread of disease (see also Cator et al., 2020; Sternberg & Thomas, 2014). Here, we have highlighted how infection itself can be a significant and important source of variation in a host's thermal limits. To improve predictions for the impact of global change on population persistence and adaptation, as well as the dynamics of infectious disease, it will therefore be necessary to explicitly account for the capacity for infection to directly interfere with host thermal performance under thermal extremes.

ACKNOWLEDGEMENTS

This work was supported by funding from Monash University and the Australian Research Council.

DATA AVAILABILITY STATEMENT

All data presented are available via an online repository at https://doi.org/10.26180/14199839.

ORCID

Tobias E. Hector https://orcid.org/0000-0003-0615-6578
Matthew D. Hall https://orcid.org/0000-0002-4738-203X

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How to cite this article: Hector, T. E., Sgrò, C. M., & Hall, M. D. (2021). Thermal limits in the face of infectious disease: How important are pathogens? *Global Change Biology*, 00, 1–12. https://doi.org/10.1111/gcb.15761