Host immunity shapes the impact of climate changes on the dynamics of parasite infections

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Global climate change is predicted to alter the distribution and dynamics of soil-transmitted helminth infections, and yet host immunity can also influence the impact of warming on host–parasite interactions and mitigate the long-term effects. We used time-series data from two helminth species of a natural herbivore and investigated the contribution of climate change and immunity on the long-term and seasonal dynamics of infection. We provide evidence that climate warming increases the availability of infective stages of both helminth species and the proportional increase in the intensity of infection for the helminth not regulated by immunity. In contrast, there is no significant long-term positive trend in the intensity for the immune-controlled helminth, as immunity reduces the net outcome of climate on parasite dynamics. Even so, hosts experienced higher infections of this helminth at an earlier age during critical months in the warmer years. Immunity can alleviate the expected long-term effect of climate on parasite infections but can also shift the seasonal peak of infection toward the younger individuals.

long-term climate warming | seasonality | host–parasite interaction | gastrointestinal helminths | European rabbit

The marked progression of climate warming and intensification of extreme climatic events have been implicated in the increased prevalence of infections, epidemic outbreaks, and the geographical shifting of endemic foci of infections (1–3). Experimental manipulations of vectors and infective stages have shown that warming, coupled with increased variability in temperature, can influence the vital rates of the parasite and the immunophysiological characteristics of the host (4–9). Predictive models of infection dynamics have reinforced the importance of these findings by showing that the risk of infection and transmission are likely to increase with the projected temperature changes (10–15) and synchronous, unpredicted weather events (16), although exceptions have been reported (17–19). Despite these findings, the extent to which climate disruption is in fact having an effect on parasite infections in natural systems is far from clear, as nonlinear effects in the parasite–host relationship and confounding variables can be difficult to disentangle.

The way climate change modifies the development and survival of vectors and infective stages, and the consequences for the contact rate between infective and susceptible individuals, has been the central focus of many of the predictions and trials. However, this approach ignores the contribution of variability in the response of the hosts, which we expect to be critical in regulating the parasite abundance and the changes in the transmission rate. Given that immunity to infections is an important source of variation among individuals (20–23), if climate increases exposure to parasites, do we expect a proportional increase in the intensity of infection in hosts that mount an immune response against these parasites? In other words, how does variation in the immunity among individuals contribute to, or mitigate against, the impact of disease severity driven by climate changes? Empirical evidence from natural settings is lacking (but see ref. 24), and the question of whether the interactions between climate and immunity have contrasting seasonal and long-term consequences for host morbidity needs to be elucidated. This is fundamental, given that climate change can modify the biological processes driving trophic interactions with consequences for the evolution of species persistence and ecosystem functioning (25).

Here, we propose two testable scenarios for the effect of climate on immune-regulated helminth infections. In the first scenario, warming alters the seasonal dynamics of the parasite by increasing the force of infection such that the parasite intensity peaks in younger hosts but has no long-term net impact on the whole population, as the immunity maintains the interannual mean parasite load at an equilibrium. In the second scenario, warming affects both the seasonal and the long-term force of infection such that high parasite intensity in the juvenile, susceptible hosts is weakly counterbalanced by lower, regulated infections in the adults and the net outcome is an increase in the mean infection of the host population over time. The extreme of this scenario is where there is no apparent regulation and the parasites accumulate with host age as a consequence of warming.

We rationalized these scenarios by developing a deterministic mathematical framework for soil-transmitted gastrointestinal helminths with direct life cycles (no intermediate hosts or vectors) in seasonal environments exposed to climate warming (*Materials and Methods*). The framework was tested against two helminth species, *Trichostrongylus retortaeformis* and *Graphidum strigosum*, collected from a population of European rabbits (*Oryctolagus cuniculus*) sampled monthly from 1977 to 2002 in Scotland (26, 27). We selected these parasites because they inhabit different organs of the same host (the small intestine and the stomach, respectively), their free-living stages are exposed to identical climatic conditions,

Significance

To understand and mitigate the impact of climate change on host-parasite trophic interactions, we need to know how variation in immune responses among hosts can modify the effect of warming on infectious disease processes. By modeling the dynamics of infection of two parasite species in a rabbit population, we show that immunity can interact with climate. Specifically, the annual intensity of infection remains relatively constant over time, although younger hosts carry heavier infections in the summer in warming years. In contrast, in the second parasite the lack of immune control leads the intensity to increase with warming. Immunity can reduce the severity of population infection, but it can also exacerbate parasite intensity in the younger individuals exposed to climate warming.

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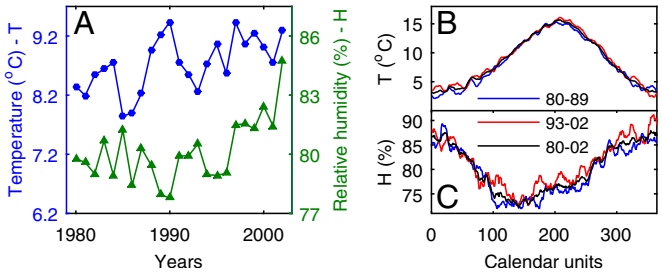

Fig. 1. Air temperature and relative humidity by years and months. Annual mean air temperature and relative humidity have increased 1 °C and 3%, respectively, during the study period 1980–2002 (*A*). Intraannually, there is a strong seasonal regime (1980–2002, black line) and significant differences between the cold (1980–1989, blue line) and the warm (1993–2002, red line) decades (*SI Appendix*, Section SI-3) both for temperature and humidity (*B* and *C*).

and yet the parasites show contrasting infection dynamics (26, 27) and a distinct response to host immunity (28, 29). Additionally, the system is under the influence of climate warming (30, 31) and a strong seasonal regime (26, 27, 32) (Fig. 1), and preliminary data indicated that the annual intensity of *G. strigosum* infection, but not *T. retortaeformis*, is positively related to temperature (33).

The accumulation of parasites within the hosts is determined by changes in exposure, susceptibility, and establishment (34). Exposure depends on the force of infection, here defined as the density of free-living parasite stages on the herbage, which in turn is determined by temperature and/or humidity and the intensity of infection in the hosts (*Materials and Methods*). Once shed in the environment, eggs readily develop into infective larvae, but their availability and uptake is the result of present and previous meteorological conditions, which are shaped by long-term climate warming and short-term seasonal fluctuations. These assumptions are consistent with laboratory and field experiments by others and ourselves (31, 35, 36). For example, we previously showed that the hatching rate of eggs exposed to diverse climatic regimes increases with thermal accumulation (31), and immunity does not appear to affect the rate of hatching (37).

Infected individuals can develop two responses: They either mount an immune response that controls the infection, albeit this is not lifelong protective, or immunity is less effective and parasites accumulate at a rate proportional to the force of infection but with the possibility of intensity-dependent constraints, where parasite competition for resources, such as space or food, increases with the parasite intensity (34). These contrasting dynamics can be captured within the rabbit–helminth system. We have shown experimentally that *T. retortaeformis* is reduced or cleared in older hosts by a strong type 1–type 2-acquired immune response, whereas *G. strigosum* persists with high abundances despite a type 2 immune reaction typical to helminths (28, 29, 38). Our model framework assumes that host susceptibility and helminth establishment are affected by immunity and/or parasite intensity dependence. Acquired immunity develops proportionally to the accumulated exposure to parasites and is determined by the host immunocompetence (i.e., the ability of an individual to produce a normal immune response), which in turn is subjective to individual attributes (32, 39) (*Materials and Methods*). Parasite intensity-dependent constraints are proportional to the parasite load.

This framework and the system selected capture a range of helminth–host interactions, including features that have been observed in soil-transmitted helminths of human and livestock, and provide a common starting point for exploring a number of climate-associated hypotheses across a wide range of settings and temporal scales.

We modeled each helminth species independently using the same host population and assuming a time-invariant rabbit density and a flat age structure (*Materials and Methods*). This is based on the findings that the helminths used in this study cause subclinical disease and although they can induce tissue pathology and morbidity, these conditions rarely lead to mortality at intensities comparable to field observations (28, 40). Rabbit mortality can occur in concurrent infections with virulent strains of myxoma virus (41) or of rabbit hemorrhagic disease virus (42). Because myxoma virus interacts disproportionately with the intensity of the two helminths (27, 43), the myxoma-infected cases were removed from our analysis. To avoid further model complexity, the role of coinfection with the second helminth was not explicitly addressed in the current study. Finally, to support our assumption that host demography is not disrupted by these parasites and to confirm that the patterns observed were indeed driven by the dynamics of the parasite, rather than the host, changes in the rabbit demographic structure and the phenology of reproduction were also investigated.

The impact of climate change on the dynamics of infection was examined at different temporal scales to identify differences in the intensity of infection among years, during the early "cold" (1980–1989) and the late "warm" (1993–2002) decades of sampling and among months. The decadal grouping was based on our previous finding that the monthly hatching rate of eggs from both helminths was higher during the warm than the cold period (31), supporting the hypothesis that decadal changes in the seasonal force of infection could also lead to decadal variations in the seasonal parasite burden.

Results and Discussion

Model selection confirmed that the dynamics of *T. retortaeformis* infection are primarily regulated by acquired immunity and individual immunocompetence, which in turn depends on the date of birth (i.e., the rabbit monthly cohort) and the general, seasonal-related conditions of the host at time of birth (referred to as "seasonal conditions" throughout the article) (*SI Appendix*, Section SI-4 and Tables S4 and S5). The climatic setting that best describes the dynamics of the free-living stages is a linear impact of temperature on the force of infection. At the interannual scale, the reconstructed force of infection undergoes multiannual fluctuations with a positive, though nonsignificant, long-term trend (Fig. 2*A* and *SI Appendix*, Section SI-4). Immunity controls the parasite accumulation in the rabbit population, and the mean intensity of infection remains relatively constant over time (Fig. 3*C* and *SI Appendix*, Sections SI-4 and SI-5). In other words, predictions show that the annual increase of *T. retortaeformis* infection is small and does not change significantly during the 20-y study; this reflects what was seen in the historical data (Fig. 3*A* and *SI Appendix*, Section SI-5) and in the more detailed monthly–annual time series (*SI Appendix*, Section SI-4).

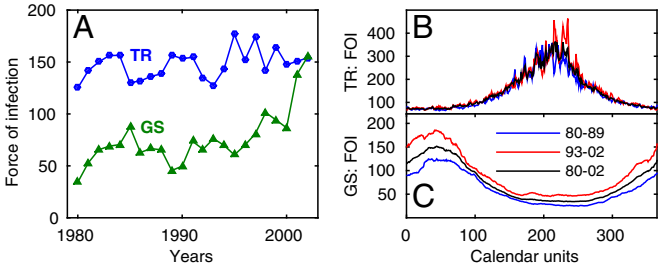

Fig. 2. Predictions of the force of infection. The annual force of infection (FOI, *A*) significantly increases over the years for *G. strigosum* [FOI vs. years, Mann–Kendall $P < 0.001$, Theil–Sen's slope = 2.16 parasites/(unit of grass * year)] but not for *T. retortaeformis* [FOI vs. years, P = n.s., Theil–Sen's slope = 0.26 parasites/(unit of grass * year)]. These trends are consistent when using the more detailed daily data (*SI Appendix*, Section SI-4). The intraannual force of infection exhibits a peak around August and a minimum in the winter–autumn months for *T. retortaeformis* (TR), (*B*) whereas the peak occurs in February and the minimum in July–August for *G. strigosum* (GS) (*C*).

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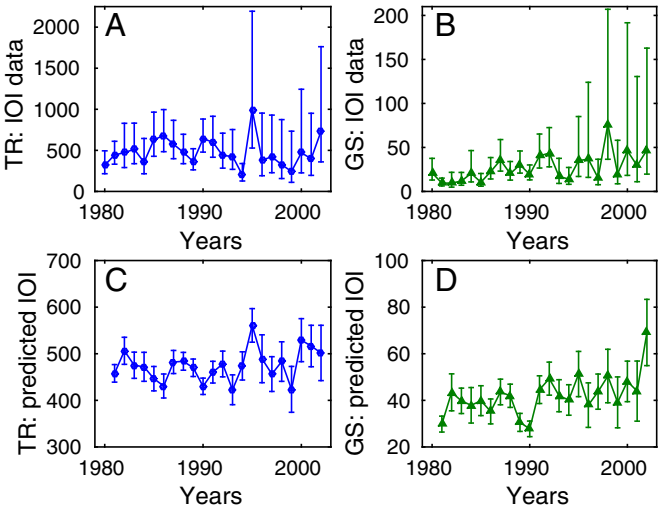

Fig. 3. Predictions based on historical data of the interannual dynamics of infection. The predicted annual mean intensity of infection (IOI) significantly increases over the years for *G. strigosum* [IOI vs. years, Mann–Kendall $P < 0.05$, Theil–Sen's slope = 0.32 parasites/(rabbit * year), *D*] but not for *T. retortaeformis* [IOI vs. years, P = n.s., Theil–Sen's slope = 1.39 parasites/(rabbit * year), *C*]. Accordingly, the original data show a positive long-term trend for *G. strigosum* [IOI vs. years, Mann–Kendall test $P < 0.01$, Thail–Sen's slope = 1.34 parasites/(rabbit * year), *B*] but not for *T. retortaeformis* [IOI vs. years, P = n.s., Theil–Sen's slope = 4.58, *A*]. These results are also supported by analyses using detailed monthly–annual time series (*SI Appendix*, Section SI-4). For the predictions (*C* and *D*), the annual means from the expected values and the confidence intervals, as the uncertainty in the calculation of the mean, are reported. For the original data (*A* and *B*), the annual means and confidence intervals have been calculated by fitting a negative binomial distribution to the original parasite data from the whole host population every year.

The dynamics of *G. strigosum* provides a contrasting scenario. Model selection indicates that the intensity-dependent constraints acting on the establishment of incoming larvae and the linear impact of relative humidity on the survival of free-living stages are the major drivers in the dynamics of this parasite (*SI Appendix*, Section SI-4 and Tables S4 and S5). As the annual force of infection significantly intensifies with more humid and warmer conditions (Fig. 2*A* and *SI Appendix*, Section SI-4), parasites also accumulate significantly in the host population (Fig. 3*D* and *SI Appendix*, Sections SI-4 and SI-5) and the number of eggs shed onto the herbage increases proportionately. Numerical simulations confirm that *G. strigosum* is under the positive, strong effect of climate warming, although intensity-dependent restrains and mortality of free-living stages prevent the parasite population from growing exponentially. These interannual trends are further confirmed using the exhaustive monthly–annual predictions (*SI Appendix*, Section SI-4) and, together, describe well the historical data (Fig. 3*B* and *SI Appendix*, Section SI-5).

The selection of different climatic variables within each of the two parsimonious models warrants some considerations. A large body of work has consistently shown that temperature and relative humidity do limit the development and survival of helminth free-living stages (44, 45). The higher susceptibility of *G. strigosum* to humidity is probably associated with their larger egg size (~1/5 larger than *T. retortaeformis*) (46) and the need for moister conditions for developing/hatching, when exposed to similar temperature settings as *T. retortaeformis*. A number of *Trichostrongylus* species of sheep have shown substantial dissimilarities in the survival of infective larvae under the same temperature but different relative humidity (47). Studies on *T. retortaeformis* have shown that increasing air temperature up to 35 °C did accelerate egg hatching but reduced larval survival (48, 49), whereas *G. strigosum* larvae appeared to be negatively affected by desiccation (50) or high temperature (figure 5 in ref. 31). It is then possible that under the same relative humidity, *G. strigosum*-infective stages survive longer than *T. retortaeformis*, and as humidity increases, both the parasite intensity and the force of infection also increase. This reasoning can also explain the similar fitting performance of the humidity and the temperature models for *G. strigosum* (*SI Appendix*, Table S4*B* and Section SI-4).

The impact of climate may well be limited to a specific period of the year, especially in the seasonal regimes, and it is during these critical periods that we might expect higher transmission and morbidity, which may not be captured by the interannual long-term trends. We examined the seasonal dynamics using model predictions from the whole study period (1980–2002) and then divided them into two periods, the cold (1980–1989) and the most recent warm decade (1993–2002). Predictions from the whole period confirm the negative relationship between the *T. retortaeformis* peak of infection and host age at the peak and the highest intensities experienced by the juvenile rabbits from the summer cohorts (Fig. 4*C* and *SI Appendix*, Section SI-6). This "peak shift," wherein a high force of infection leads to high infections at earlier host age and a lower force causes lower intensities peaking in older hosts, is a pattern expected when there is parasite regulation by host immunity (26, 32, 51). Here, we show that this phenomenon can be generated by temperature-driven changes in the seasonal force of infection coupled with the acquired immune response and an effective immunocompetence. These patterns match the profiles from the original data (Fig. 4*A*) and our previous work (26, 32).

Given these seasonal dynamics and the scenarios initially proposed, we should expect climate warming to alter the age–intensity relationship by both increasing and moving the peak of infection to a younger host age, within the same rabbit cohort. Model predictions examined in the cold and warm decades confirm the significant peak shift for the June and July cohort, such that younger hosts carry higher infections in the warmer, recent years than hosts of the same age cohort from the colder period (Fig. 5 *A* and *C*). The significant climatic differences in these two summer cohorts are sufficient to modify the age–intensity relationship at the peak of infection among cohorts (*SI Appendix*, Section SI-6), supporting the

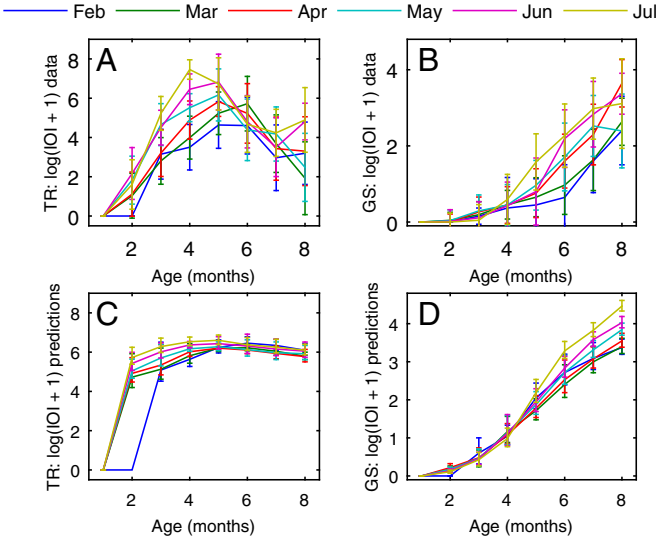

Fig. 4. Predictions based on historical data of the intraannual dynamics of infection. Host age–parasite intensity profiles from cohorts of rabbits born in the months of February to July for *T. retortaeformis* (*A* and *C*) and *G. strigosum* (*B* and *D*). The predicted age-cohort mean intensities of infection (*C* and *D*) are based on infections estimated from the individuals matching the hosts effectively sampled and presented in *A* and *B*. Mean intensities of infection and confidence intervals have been calculated as reported in Fig. 3 but for every age-cohort level.

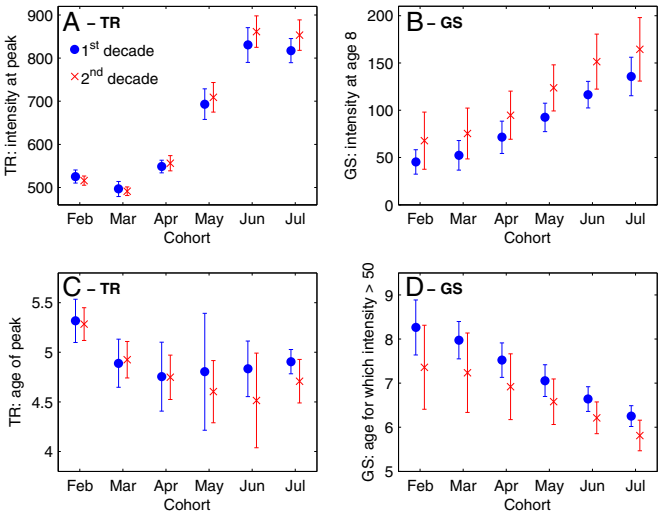

Fig. 5. Relationships between predicted peak intensity of infection, or host age, by monthly cohorts and in the cold (first) and the warm (second) decade. *T. retortaeformis* shows decadal differences in both the peak parasite intensity and the host age at the peak for the June and the July cohort (for both *t* tests, $P < 0.05$) (*A* and *C*). *G. strigosum* exhibits decadal differences in the peak intensity of infection (8/8+mo-old hosts) and minimum host age with an intensity > 50 parasites/rabbit across all of the cohorts (ANCOVA with cohort as a covariate for decadal differences in peak intensity, $P < 0.001$, and host age with >50 parasites/rabbit, $P < 0.0001$) (*B* and *D*). Means and SD of predictions are reported.

impact of long-term climate warming on seasonal changes in infection and transmission for *T. retortaeformis*. The lack of a peak shift between decades in the winter–spring cohorts appears to be caused by a relatively low variation in the force of infection (Fig. 2*B*) and thus a weaker impact of the parasite at this time of the year. Overall, although immunity prevents any significant long-term net accumulation of *T. retortaeformis* in the rabbit population, its seasonal effect is to increase heterogeneity in infection and transmission between individuals by worsening the parasite burden in the juveniles exposed to climate warming.

As expected for *G. strigosum*, numerical simulations lack evidence of immune-driven changes in the age–intensity relationship among monthly cohorts. Based on the whole study period, parasites accumulate with host age and adults carry most of the burden; moreover, infection builds up faster in the summer than in the late winter–spring cohorts (Fig. 4*D* and *SI Appendix*, Section SI-6). These trends are consistent with the original dataset (Fig. 4*B*). As with *T. retortaeformis*, the evidence that long-term warming affects the seasonal dynamics of *G. strigosum* is substantiated by showing that in the warmer and more humid decade the consistently higher force of infection (Fig. 2*C*) is associated with hosts that become infected at a faster rate (Fig. 5 *B* and *D* and *SI Appendix*, Section SI-6). Together, these findings provide evidence that climate warming enhances *G. strigosum* transmission and infection both within and between years, with adults maintaining most of the parasite load.

To reinforce our conclusions and to gain a better understanding of how model outcomes relate to model framework and parameters, we examined the contribution of key model parameters on the force and the intensity of infection of both helminths. We show that *T. retortaeformis* is highly sensitive to age-independent immunity, β_0, and less responsive to temperature-driven mortality of free-living stages, α_{1T}, although sensitivity to temperature can increase only if immunity decreases (Fig. 6 *A* and *B*). This implies that the immune control has to diminish to allow the accumulation of parasites both in the host and on the pasture with climate warming. This also shows that individuals with low immunity, such as kittens and juveniles, are at higher risk of infection as temperature increases.

For *G. strigosum*, both the force and the intensity of infection were similarly affected by changes in intensity-dependent parasite establishment, δ, and humidity-driven free-living parasite mortality, α_{1H} (Fig. 6 *C* and *D*). The population of *G. strigosum* can grow quickly under high relative humidity and a low intensity-dependent constraint, but these extremes are never met in our system. Interestingly, high intensity dependence does not fully control the parasite, and a high relative humidity can have some impact on the dynamics of infection. Overall, we provide support that, for the parameter range investigated, intensity dependence in establishment is less effective in buffering the climate impact on *G. strigosum* than is the intensity dependence generated through host immunity for *T. retortaeformis*.

Although our primary focus has been on the influence of climate warming on helminth dynamics, we cannot rule out the confounding, direct effect of climate change on rabbit demography. Evidence from animal and plant species indicates that geographical ranges and timing of reproduction have been adjusted (52–55) or disrupted (55) as a consequence of warming or variability in the interannual weather. A modification of the host dynamics can influence "who" are at a greater risk of infection and "when" they are at a greater risk of infection and thus their contribution to transmission. We looked for changes in the age structure of the rabbit population and found no significant long-term trends in the fraction of kittens, juveniles, and adults sampled over the years (*SI Appendix*, Section SI-7). We also found no changes in the annual breeding phenology. The reconstructed monthly breeding success (kittens/total juvenile and adult females) peaked in the summer months and showed no evidence of monthly shift or expansion of the breeding period over the years (*SI Appendix*, Section SI-8). Analysis repeated by a cold and warm decade confirmed this general pattern. These findings suggest that climate warming has had no evident impact on the demography of this rabbit population, and the dynamics of infection observed are indeed a consequence of the interaction between climate and host immunity.

The long-term and seasonal dynamics described for *T. retortaeformis* and *G. strigosum* can be considered a representation of the extreme ends of a range of patterns we should expect under climate changes for soil-transmitted helminths from wildlife, livestock, and human systems. We show that positive trends of ∼1 °C mean air temperature and ∼3% mean relative humidity over 20 y have increased the exposure and risk of infection of a natural population of rabbits to two of its common parasite species. However, we also show that a host immune response that lacks life-long protection can still control the parasite intensity, attenuate the overall impact of climate on the host population, and contribute to individual variation in infection and age-related patterns in transmission. Our results indicate that immunity prevents the climate-driven, long-term net accumulation of *T. retortaeformis* in the population of rabbits but can also shift the peak of infection toward the younger hosts that do not have adequate immunity and are under the seasonal influence of climate warming.

Age-related shifts in the peak of infection by helminths have been reported for human populations (51, 56) and also predicted for malaria under different levels of bednet coverage (57). This feature should also be common in farm and wild animals where host immunity plays an important role in parasite dynamics. Given that seasonality (both temperature and rainfall) influences the large majority of human and livestock populations and considering that long-term predictions are for a warmer climate, we should expect younger, susceptible individuals to be exposed and carry higher parasite burdens at critical times of the year, and more attention should be focused on mitigating the infection of this particular group. Counter to this, different approaches might be required for parasite species that elicit a weak immune response and cause heavier infections in older individuals.

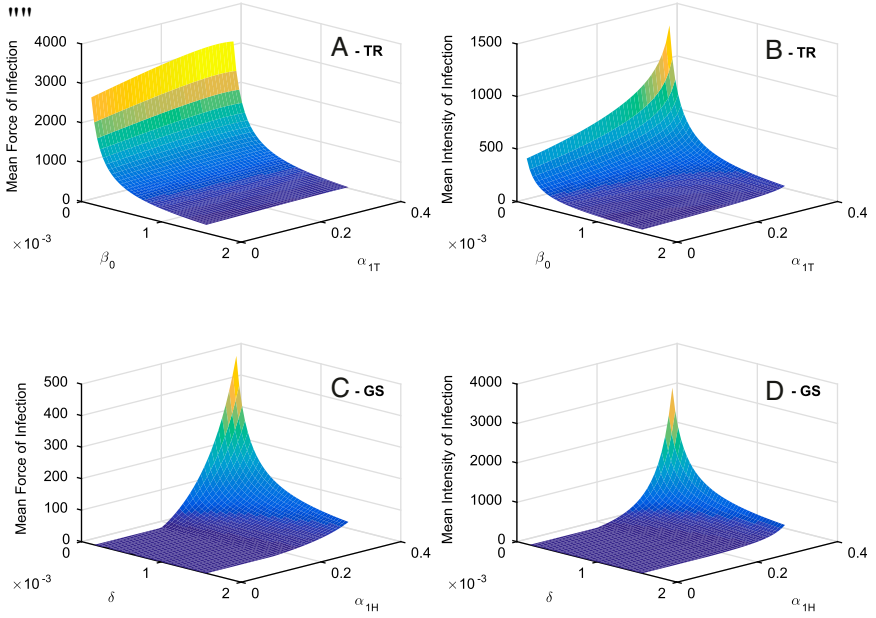

Fig. 6. Relationship between key model parameters and force (FOI) or intensity (IOI) of infection. For *T. retortaeformis*, changes in the FOI and the IOI are strongly affected by age-independent immunity, β_0, whereas temperature-driven free-living parasite mortality, α_{1T}, impacts parasite dynamics only when immunity is low (*A* and *B*). For *G. strigosum*, intensity-dependent parasite establishment, δ, and humidity-driven free-living parasite mortality, α_{1H}, have similar impacts on the FOI and the IOI; intensity dependence has to be consistently low and humidity consistently high to allow the rapid accumulation of parasites in the host and in the environment (*C* and *D*).

Materials and Methods

Data Collection. Rabbits were sampled monthly from 1977 to 2002 according to UK regulations for control of pest species. All the animal procedures were approved by the Institutional Animal Care and Use Committee of The Pennsylvania State University and carried out in accordance with the approved guidelines (IACUC #263883 and #34489). Helminths were collected from the gastrointestinal tract of each rabbit and abundance estimated by aliquots using standardized parasitological techniques (26, 27). Host age and date of birth were determined as described previously (26, 27).

Fundamental Model and Assumptions. The mathematical framework was based on an age-structured immunoepidemiological model for helminth infections in a seasonal environment, which we developed by expanding a parasite–host model proposed formerly (32). Specifically, the intensity of infection $P(a,t)$ changes with host age, a, and time, t, as:

$$\frac{\partial P(a,t)}{\partial t}+\frac{\partial P(a,t)}{\partial a}=\Phi(a)F(t)\exp[-I(a,t)-\delta P(a,t)]-\mu P(a,t), \quad [1]$$

where $\Phi(a)$ is the age-dependent host feeding rate, calculated as an allometric function; $F(t)$ is the force of infection; $I(a,t)$ is the host acquired immune response; $\delta P(a,t)$ is the intensity-dependent effect on parasite establishment; and μ is the natural mortality of established parasites. $F(t)$ describes the density of free-living infective parasite stages per unit of herbage at time t, and the dynamics are driven by the mean intensity of infection in the host, $\overline{P}(t)$, and the effect of mean air temperature $T(t)$ and/or relative humidity $H(t)$ on the mortality, μ_F, of free-living stages as:

$$\frac{dF(t)}{dt}=\alpha_p\overline{P}(t)-\mu_F(T(t),H(t))F(t). \quad [2]$$

The quantity of parasites on the pasture is not explicitly dependent on host density, which we consider time constant and included in the parameter α_p. Helminth establishment in the host is affected by acquired immunity and parasite intensity-dependent constraints. Immunity develops proportionally to the accumulated exposure, $E(a,t)=\Phi(a)F(t)$, and is affected by the host immunocompetence, $\beta(a,t)$. $\beta(a,t)$ is dependent on three main host components: the age, the general conditions that are seasonal-related, and the breeding cohort. Cohort and seasonal condition effects are modeled as sinusoidal forcings. Parasite intensity dependence builds proportionally to the accumulated intensity of infection. There is no time delay or arrestment from the ingestion of larvae to the mature adult stages. The model provides an estimate of the expected value of the intensity of infection by time and host age. Numerical integration was performed using a fixed time step of 0.01 d and the Escalator Boxcar Train method (58). Additional details are available in *SI Appendix*, Sections SI-1 and SI-2.

Parameter Calibration and Model Selection. Starting from the fundamental framework, we developed a hierarchy of competing models by (*i*) removing some components and/or (*ii*) defining different functional forms for acquired immunity and/or the weather-dependent mortality of free-living stages. We then fit each model to the time series by calibrating model parameters for each helminth species independently. Additional details are available in *SI Appendix*, Section SI-2. We based the parameter calibration on maximum likelihood by assuming that the intensity of infection in the host population is distributed as a negative binomial (27) with an age- and time-dependent mean, $P(a,t)$, and a fixed dispersion parameter, k. For every model, calibration was performed in two different steps. First, we used the "genetic" algorithm available in the MATLAB GA toolbox (59). At each iteration of the calibration loop (i.e., generation), the algorithm tests several different sets of parameters (i.e., individuals) and selects the best individuals that will serve to generate the individuals of the following generation. The set of individuals tested at each generation is called "population." For our calibrations, we used a population of 100 individuals and a maximum of 500 generations. Second, to improve parameter calibration, all of the individuals from the last generation of the genetic algorithm were used as a starting point for a nonlinear least squares curve fitting (60). The parameter set that maximized the likelihood was finally selected. The model that best described the dynamics of each parasite species was chosen as the most parsimonious among those that scored a ΔAIC < 4 relative to the model with the lowest AIC (61, 62). Finally, we examined how model outputs were sensitive to climatic and within host parameter values. Starting from the best model for each parasite species, the values of the chosen parameters were changed in the surrounding of their optimal values and then related to two model outcomes: (*i*) the predicted mean force of infection and (*ii*) the predicted mean intensity of infection; the annual averages from the estimates of the entire study period were used in the sensitivity plots.

Climatic Variables. Daily temperature and humidity records were kindly provided by The James Hutton Institute (Scotland, United Kingdom), located a few miles from the study site (31). Model integrations were based on daily mean air temperature, from maximum and minimum values, and daily relative air humidity, based on dry and wet bulb temperatures and an atmospheric pressure at sea level of 101.3 kPa. During the 1980–2002 study, annual mean air temperature increased 1 °C (Mann–Kendall $P < 0.01$, Theil–Sen's slope = 0.042 °C/y), a trend that remained consistent at least until 2009 (31), whereas annual mean relative humidity increased 3% (Mann–Kendall $P < 0.05$, Theil–Sen's slope = 0.12%/y). Seasonally, July is the hottest month, and December and January are the coldest and the most humid. Additional details are available in *SI Appendix*, Sections SI-1 and SI-3.

Historical Data Analysis. Host demography and dynamics of infection were also analyzed using standard analytical approaches on the original data. Detailed analyses on changes in the age structure of the rabbit population and host phenology are reported in *SI Appendix*, Sections SI-7 and SI-8, and the long-term dynamics of infection by host age classes are highlighted in *SI Appendix*, Section SI-5.

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