Author:
Beltrame, Ludovica

Title:
Simulating the risk of liver fluke infection in the UK through mechanistic hydro-epidemiological modelling

Simulating the risk of liver fluke infection in the UK through mechanistic hydro-epidemiological modelling

Ludovica Beltrame

Department of Civil Engineering

University of Bristol

A dissertation submitted to the University of Bristol in accordance with the requirements for award of the degree of Doctor of Philosophy in the Faculty of Engineering.

July 2019

Abstract

Control of many environment-driven infectious diseases is increasingly challenged by climate change and the emergence of drug resistance, calling for new approaches such as prevention through simulation of future risk and more comprehensive strategies, rather than exclusively relying on treatment. The role environmental processes play in mediating climate impacts on disease transmission may offer opportunities to use environmental interventions for complementing treatment in reducing disease burdens. However, most current models do not represent these mechanisms explicitly, which limits their ability to assess infection risk under changing conditions and test interventions. By focusing on the parasitic liver fluke disease in the UK as a case study, this research aims at investigating how process-based knowledge of the environment and water environment can be used in support of the study and management of infectious diseases under current and potential future conditions. Firstly, we develop a new mechanistic hydro-epidemiological model that simulates disease risk in connection with key underlying environmental processes (HELF). We show that the model can reproduce observed infection patterns, but also introduce an expert-driven calibration strategy to make it more robust to data with limited reliability and in the presence of climate change. Secondly, we use HELF with sensitivity analysis to investigate disease risk drivers across the UK, and explore opportunities for risk reduction through environmental management. We demonstrate that where landscape heterogeneity plays a larger role on disease transmission, risk avoidance management strategies can provide a valuable alternative to treatment. Finally, by driving HELF with climate projection data, we assess potential climate change impacts on future infection risk patterns. We find that projected changes are not spatially nor temporally homogeneous, but that altered parasite-specific climatic characteristics result in longer transmission seasons in most UK regions. This reduces the effectiveness of current drug-based control, further highlighting the need for alternative approaches.

Acknowledgements

Thanks to Thorsten Wagener, for guiding me through my research by always aiming high, while sharing his passion for and being committed to every step of the way. Thanks for the opportunity to work on themes I care about, alongside a group of people that values collaboration across disciplinary boundaries.

Thanks to Eric Morgan, to whom I owe most of what I have learnt about liver fluke over my PhD, for having always been enthusiastic, from epidemiology 101 to intervention strategies and beyond.

Thanks to the rest of our Water and Health group for the experience and challenge of truly being at the interface between disciplines: Toby Dunne, for the valuable help with Chapter 3, as well as Hannah Rose, Josephine Walker and Peter Vickerman.

Thanks to Yoshi Wada, for the chance of experiencing how doing research at an international institute like IIASA may look like, and for the useful discussions, which have contributed to Chapter 5. Thanks also to Ting and Canada, among other friends, for making me feel at home in Vienna.

Thanks to Francesca Pianosi, from whom it all started, and without whose advice I probably would not have moved to Bristol nor embarked on this PhD adventure, and thanks to EPSRC, as this work would not exist without their support either.

Thanks to my officemates over these years, Fanny, Joost, Dongik, Charlie, Lina and Giulia, for the daily workshop on how to smash it while enjoying the ride; to the whole woodland road gang, especially Vale, Sus, Elisa, Sebastian, Barnabis, Wouter and Lina, for all the animated discussions on flights, veganism and Brexit; to the WISE friends, especially Ioanna and Olive, for being my groovy and wonderfully weird Brit-Med family, as well as Anna and Cain, for the much needed daily yoga and for trying (with little success) to make me a bit less of a grandma; and to my lifelong friends, Vivi, Sere, Civis, Garra, Ale and Co, for standing by me no matter what.

Most of all, thanks to my family for being supportive of everything I do, while reminding me of what matters most, and to Francesco, for not letting me fall to my fears and making everything feel like downwind planing.

Author’s declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED:

DATE:

19/07/2019

List of publications

Chapters 3 to 6 and Appendix A.1 to A.3 of this thesis are based on works which are either published or in preparation for submission as listed below.

Chapter 3 and Appendix A.1 are adapted from:

Beltrame, L., Dunne, T., Vineer, H. R., Walker, J. G., Morgan, E. R., Vickerman, P., McCann, C. M., Williams, D. J. L. and Wagener, T. (2018). A mechanistic hydro-epidemiological model of liver fluke risk. Journal of the Royal Society Interface, 15(145). http://doi.org/10.1098/rsif.2018.0072

Chapter 4 and Appendix A.2 are adapted from:

Beltrame, L., Vineer, H. R., Walker, J. G., Morgan, E. R., Vickerman, P. and Wagener, T. Opportunities for disease control through environmental management: the example of liver fluke in the UK. Under submission to PNAS

Chapter 5 and Appendix A.3 are adapted from:

Beltrame, L., Vineer, H. R., Walker, J. G., Morgan, E. R., Vickerman, P., Wada, Y. and Wagener, T. Future risk of liver fluke infection across the UK under climate change. In preparation

Chapter 6 (Section 6.1) is adapted from:

The abstracts of the above-mentioned works.

Table of Contents

Page

List of Figures and Tables

Page

Chapter 1. Introduction

1.1 Relevance of environment-driven infectious diseases

Infectious diseases are an important burden on public health and global economies. Despite the achievements of the United Nations Millennium Development Goals initiatives, infectious (or communicable) diseases are still a major cause of morbidity and mortality worldwide (Dye 2014). Developing countries in particular suffer a high burden of disease owing to diarrhoea and malaria, which are among the 10 leading causes of death, globally (Dye 2014; Global Burden of Disease Study 2018; Murray et al. 2012). Similar in burden to these main infections, foodborne diseases (i.e. those caused by ingestion of contaminated food) are also a significant threat to human health and obstacle to socio-economic development throughout the world (Havelaar et al. 2015). Over 2001-2013, infectious diseases represented 84% of the health hazards reported to the World Health Organisation (WHO), following the International Health Regulations (Figure 1.1). Moreover, they are among the major global threats identified by the Cambridge Global Risk Index, which assesses the economic implications of rising risk challenges, from natural disasters to financial and geopolitical crises (Cambridge Centre for Risk Studies 2018).

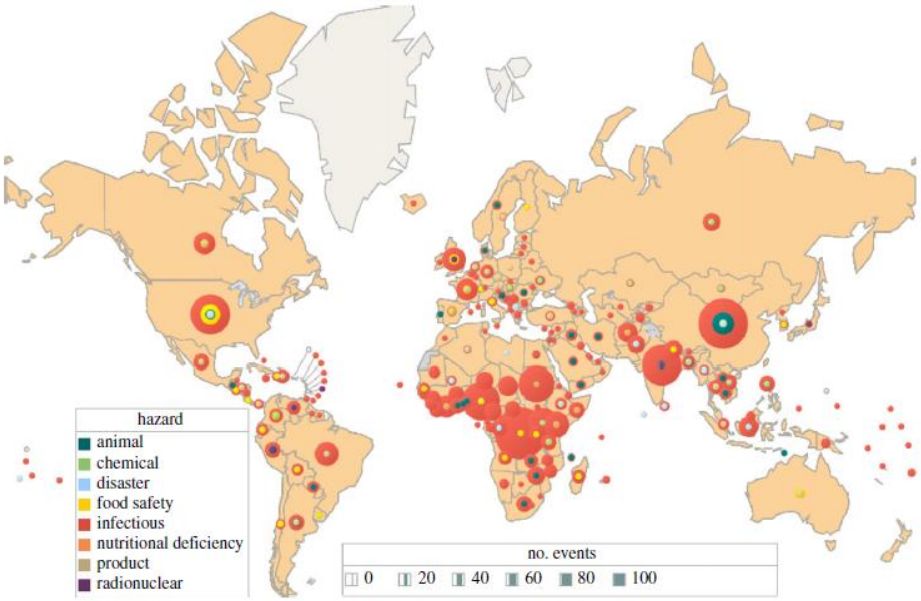

Figure 1.1 Global distribution of 2797 health hazards reported to the WHO following the International Health Regulations (January 2001 – September 2013). 84% are outbreaks of infectious diseases. Figure from Dye (2014).

Many human and animal infectious diseases have strong environmental components to their transmission. Infectious diseases are caused by a wide range of pathogenic agents (such as bacteria, viruses and parasites) that can be transmitted from host to host and/or from an environmental media to a host, either directly or indirectly via another organism (an intermediate host or vector, which carries and transmits the pathogen to the final host) (WHO 2016). Depending on the disease pathway, pathogen, host and transmission environment can all be affected by a multitude of meteorological, environmental, biological and socio-economic factors, which may act in a non-linear fashion and over different space-time scales, often leading to complex infection dynamics and patterns (Figure 1.2) (Cable et al. 2017; Lo Iacono et al. 2017; Parham et al. 2015; Semenza et al. 2016; Wu et al. 2016).

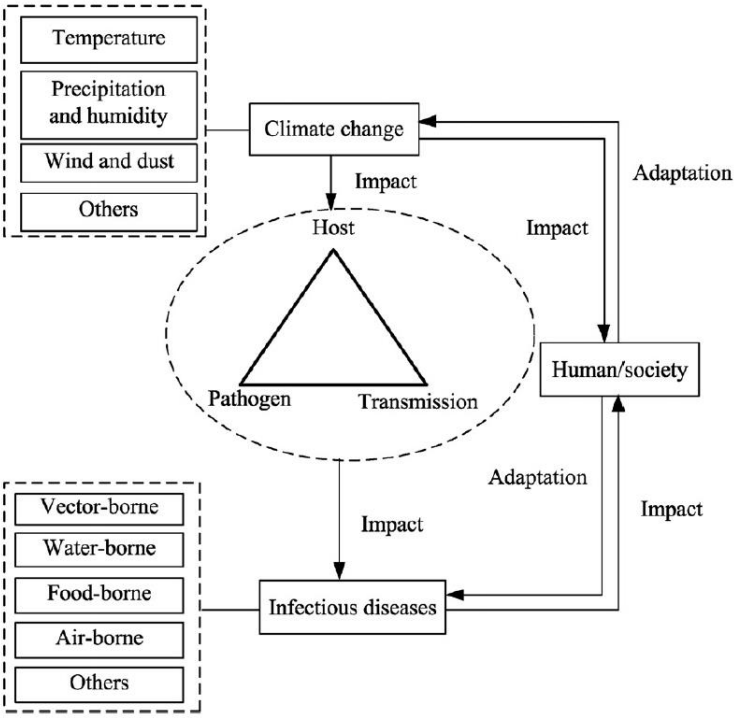

Figure 1.2 Complexity of factors involved in the transmission of infectious diseases. Figure from Wu et al. (2016).

Environmental factors, in particular, are crucial determinants of transmission for: *(i)* diseases that are directly spread from the environmental reservoir (whether that is water, soil, or food) to the final host (e.g. cholera and other diarrhoeal diseases through water); and *(ii)* diseases that are transmitted through a vector or intermediate host, that lives and develops in the environment (e.g. malaria and dengue through mosquitoes, schistosomiasis and fasciolosis through snails, and Lyme disease through ticks) (see Figure 1.3) (Eisenberg et al. 2007; Rinaldo et al. 2018). For such infections, environmental conditions often affect multiple disease components (e.g., they may define the environmental stage of the pathogen, but also affect population levels of the vector/host, as well as the rate at which pathogens

are transmitted between hosts, vectors and the environment), and have both direct and indirect effects. For example, weather characteristics can directly influence the survival and reproduction of pathogens and vectors, with implications for their physiology and demography, but can also indirectly affect these, through changes to their habitat. In the latter case, we can say environmental drivers include "distal" variables, that influence epidemiological processes through intermediate steps, and "proximal" characteristics, that more closely affect disease transmission (Eisenberg et al. 2007). For cholera, mainly transmitted through the ingestion of contaminated water, intense rainfall can lead to pathogen dilution, but also large-scale contamination, through changes in water level and flooding. For malaria, caused by parasites transmitted through mosquitoes, temperature can directly affect disease risk, through its impact on the parasite development/survival rates, and rainfall can indirectly affect it, through its impact on the availability of water pools, needed by mosquitoes for breeding. For zoonoses (i.e. animal infections that can be transmitted to people), transmission is further mediated by the ecology of animal hosts.

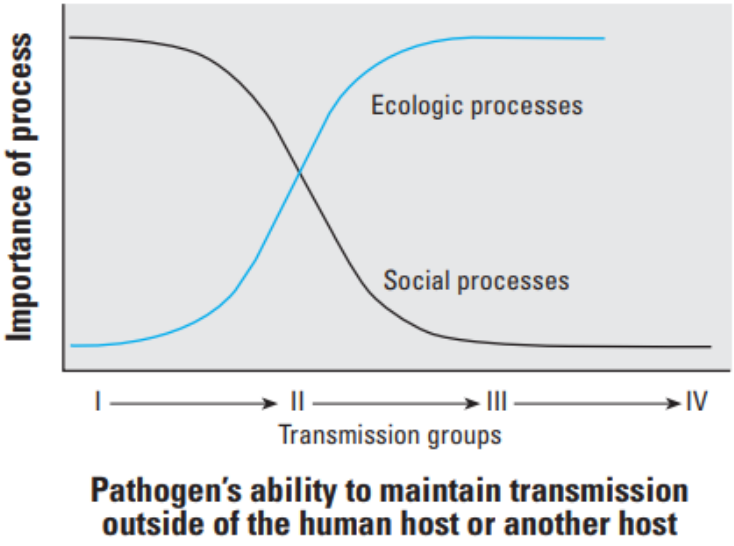

Figure 1.3 Relevance of ecologic and social processes for different disease transmission routes: I = direct host-to-host (e.g. influenza); II = vector-borne (e.g. malaria); III = environment-mediated (e.g. cholera); IV = zoonotic (e.g. fasciolosis or Lyme disease). Figure from Eisenberg et al. (2007).

As global change accelerates, changes in disease prevalence (i.e. number of infected individuals), seasonality and distribution are increasingly observed, raising concerns about implications for human and animal health in the future. The total number of infectious disease outbreaks has been rising since the 1980s, with zoonoses representing the majority of emerging infectious diseases in people, globally (Figure 1.4) (Jones et al. 2008; Smith et al. 2014). This has been referred to as the potential beginning of an age of epidemics (Hotez 2016; Weiss and McMichael 2004).

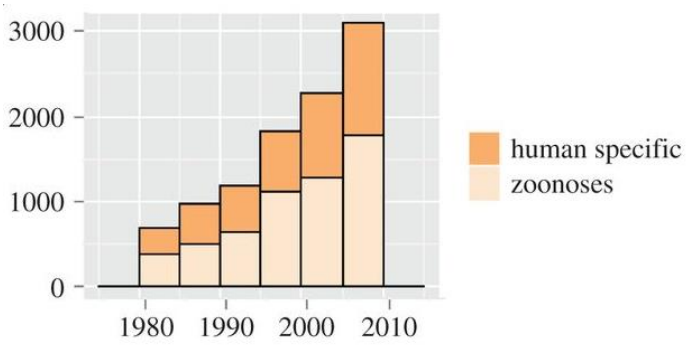

Figure 1.4 Global number of human infectious disease outbreaks 1980-2010. Figure from Smith et al. (2014).

Changes in climate have already altered transmission of infectious diseases by affecting the pathogens, vectors/hosts and/or their living environment (Altizer et al. 2013; Mas-Coma et al. 2009; Wu et al. 2016). Global warming has been playing a key role in driving the emergence or resurgence at new times or places of infectious diseases (Wu et al. 2016). For example, increased temperatures have been responsible for the expansion of malaria to higher altitudes in regions of South America and Africa (Siraj et al. 2014). Similarly, the increase in frequency and intensity of extreme weather events is altering the occurrence of floods and droughts, changing the concentration of infectious agents in the water environment and human exposure to infection (Rinaldo et al. 2018; Whitmee et al. 2015). For example, unusually intense rainfall events have been linked to the resurgence of cholera observed during the 2011 outbreak in Haiti (Righetto et al. 2013; Rinaldo et al. 2012), and changes in the patterns of drought events, followed by re-wetting, have been shown to be increasingly impacting mosquito populations responsible for the transmission of vector-borne diseases such as the West Nile virus in Europe (Brown et al. 2014).

On the other hand, we are experiencing significant landscape changes due to an expanding human footprint, which also have been shown to be important determinants of the emergence or resurgence of many diseases (Altizer et al. 2013; Whitmee et al. 2015). For example, deforestation and agricultural development have been found to affect the risk of malaria transmission across different regions, through changes in mosquito abundance, survival, and distribution (Yasuoka and Levins 2007). In Africa, changes in the prevalence of schistosomiasis have been observed due to the expansion of the intermediate snail host habitat, following the expansion of water development projects to meet demands for food and energy from increasing numbers of people (Steinmann et al. 2006). Similarly, in China, the recent resurgence of one of the major infectious agents of schistosomiasis, despite a 50-year intensive national control programme, has been linked to the construction of the Three Gorges dam and ecological

recovery of the Dongting Lake, in combination with changes in the occurrence of major flooding events (Mas-Coma et al. 2009).

At the same time, the rapid emergence of resistance to currently used drugs is making disease control challenging. Currently, drug treatment is the main control strategy for many of these diseases (e.g. see Lo et al. 2018; Webster et al. 2014). However, while interventions focused exclusively on treatment may lead to the elimination of infections transmitted directly from host-to-host, there is growing recognition of their limited effectiveness for controlling pathogens with an environmental reservoir (Garchitorena et al. 2017). Among reasons why control of such diseases is particularly challenging is that reinfection may occur rapidly after treatment, as long as environmental conditions remain suitable for transmission. In addition, the rapid and widespread development of drug resistance, accelerated by the global change-driven spatial and temporal shifts in disease transmission, is beginning to threaten the efficacy of treatment-based strategies and the long-term success of control programmes for a large range of parasitic and other infections (Garchitorena et al. 2017; Webster et al. 2014). For example, resistance is expected to evolve rapidly to existing drugs for Neglected Tropical Diseases (NTDs), as most of these are being targeted with only a single available medicine, which is often used across hundreds of millions of people (Webster et al. 2014).

1.2 Need and opportunity to support the study and management of environment-driven infections through integrated mechanistic modelling

Faced with the challenge of global change, compounded by the emergence of drug resistance, prevention through simulation of future disease risk and devising alternative control strategies have now become an urgent need. As medicine alone seems increasingly insufficient to achieve disease eradication, the conceptual difference of environmentally-transmitted diseases from host-to-host directly-transmitted ones, highlights opportunities for prevention through disease risk forecasting and for control using environmental interventions (Dye 2014; Garchitorena et al. 2017; Rinaldo et al. 2017). Simulation of future disease risk and testing of control strategies under changing conditions require:

1. Acknowledging the environment as an essential element of complex infectious disease systems, deepening our understanding of the mechanisms underlying transmission, including the causal relationships between distal variables and more proximal characteristics, which directly drive seasonality and spatial distribution of epidemiological processes (Bertuzzo et al. 2012; Eisenberg et al. 2007; Garchitorena et al. 2017; Liang et al. 2007; Parham et al. 2015; Rinaldo et al. 2017, 2018).
2. Developing mechanistic models (or process-based models, as they are based on process understanding rather than empirical correlations), which explicitly describe these mechanisms

in space and time (Rinaldo et al. 2017, 2018) in order to: *(i)* more reliably estimate the long-term impact of potential changes in climate and the environment on disease risk, overcoming the limitations of extrapolating from historic data in a non-stationary world (e.g. see Wagener et al. 2010); and *(ii)* investigate what-if (climate and management) scenarios to inform the design of robust and targeted intervention strategies to limit transmission and improve health outcomes. This includes supporting the development of comprehensive strategies to complement drug treatment with environmental interventions that may be more sustainable and cost-effective in the long term (Liang et al. 2005, 2007; Mellor et al. 2016; Wu et al. 2016).

However, most current studies investigating environmentally transmitted diseases to date are not based on the use of mechanistic models. A growing body of literature examining the link between climate and infectious disease has emerged in recent decades in response to concerns about potential global change impacts. However, while many have called for the use of process-based models to address this challenge, most currently available studies investigating this link are still based on empirical approaches (Figure 1.5) (Altizer et al. 2013; Mellor et al. 2016; Wu et al. 2016). Specifically, a number of studies found an association between the occurrence of certain weather conditions and disease incidence (i.e. number of reported cases per unit time), highlighting the potential for disease risk to change with future climates, but, in most cases, such links are correlational relationships, which may not be causally connected. This has been mentioned as a potential reason for the findings of such works to be sometimes contradictory, or very local or region-specific (Eisenberg et al. 2002; Mellor et al. 2016; Pearson et al. 2006; Rinaldo et al. 2017; Wu et al. 2016). For example, for cholera, empirical studies have found a number of correlations between rainfall and disease risk, both positive and negative (e.g. see Ruiz-Moreno et al. 2007), and for schistosomiasis, while some models predict an increased transmission potential due to global warming, others expect an overall risk reduction (e.g. see Pedersen et al. 2014; Stensgaard et al. 2013, 2016), suggesting that the mechanisms by which weather impacts transmission processes may be complex and diverse (Rinaldo et al. 2017). Despite increasing awareness that their effect on epidemiological processes may be significantly modified by other on-the-ground environmental conditions, rainfall and temperature are the most common drivers considered in current studies (Figure 1.6) (Lo Iacono et al. 2017; Mellor et al. 2016; Parham et al. 2015; Rinaldo et al. 2017). Most importantly, as climate change and direct anthropogenic activities have already pushed hydro-climatic and environmental conditions beyond historically observed variability, we cannot rely on relationships found between past data to simulate future risk and inform disease control strategies in a non-stationary world (Milly et al. 2008; Urban et al. 2016; Wagener et al. 2010).

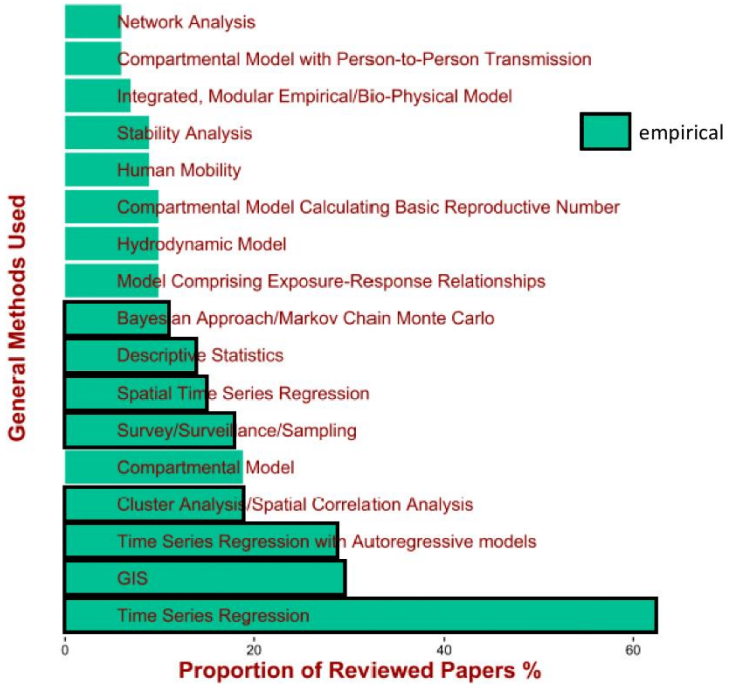

Figure 1.5 Most current studies examining climate and climate change impacts on water-related diseases to date are empirical. Figure adapted from Lo Iacono et al. (2017).

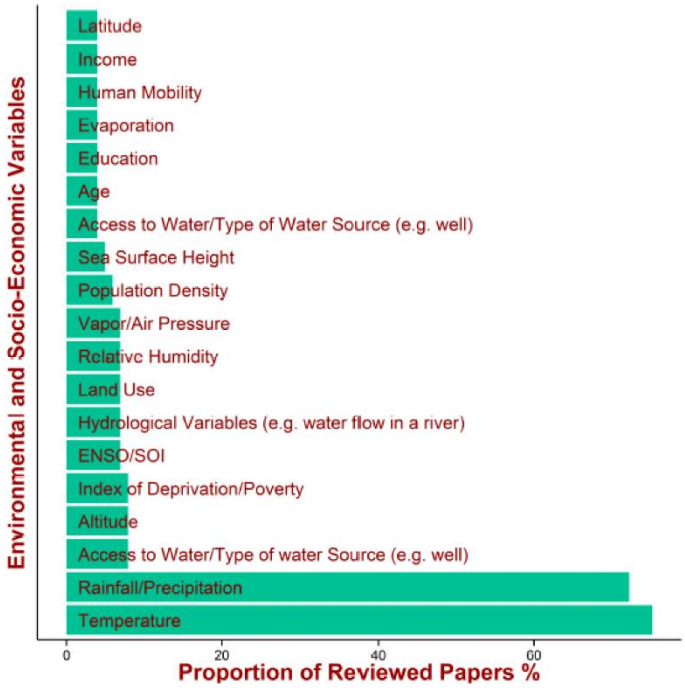

Figure 1.6 Currently assumed drivers of disease risk are mainly climatic. Figure from Lo Iacono et al. (2017).

Arguably partly compounded by the fact that most current disease risk models are empirical and do not consider on-the-ground environmental processes, environmental strategies to supplement treatment are

still poorly developed. Examples of successful cases where treatment is supplemented with interventions focusing on the environmental reservoir of the pathogen include: *(i)* mosquito control strategies for reducing risk of infection with malaria (Garchitorena et al. 2017; WHO 2019); and *(ii)* the use of environmental management, incorporated in agricultural activities, water resources development, and forestry projects, against schistosomiasis. The latter has been shown to be effective for control of the intermediate snail host and has achieved the interruption of transmission in regions of China and Japan (Liang et al. 2007; Lo et al. 2018). However, "despite showing promising results in the fight against these diseases, environmental strategies to complement medical approaches still remain under-recognised" (Garchitorena et al. 2017).

The availability of models that explicitly represent a variety of environmental processes driving disease transmission, and recent advances in mechanistic epidemiological understanding, provide opportunities to address this challenge. While only few studies have taken an integrated mechanistic approach to study the links between infectious disease and environmental processes, these have been the subject of much independent investigation (Bertuzzo and Mari 2017; Eisenberg et al. 2007; Garchitorena et al. 2017; Mellor et al. 2016). On the environment side, a large number of mechanistic models -of varying complexity and at varying scales and resolutions- are now available to represent a multitude of hydrological and environmental processes in time and space (from runoff to soil moisture, to hydrological extremes such as floods and droughts). At the same time, data to drive and calibrate these models has also grown significantly (Addor et al. 2017; Bierkens 2015; Wood et al. 2011). In recent decades, this progress has contributed to the expansion of environmental sciences, such as hydrology, into more interdisciplinary fields, with studies looking at interactions with ecological processes ("eco-hydrology" (Rinaldo et al. 2018; Rodriguez-Iturbe 2000)) and human activities ("socio-hydrology" (Sivapalan et al. 2012)), among other examples (Thompson et al. 2013; Wagener et al. 2010). On the disease side, while mechanistic models representing epidemiological processes may be available (e.g. (Macdonald 1965; Turner et al. 2016)), they often ignore underlying on-the-ground environmental drivers (Lo Iacono et al. 2017; Rinaldo et al. 2018). Only recently, spatially explicit schemes have begun to be adopted to describe disease transmission processes in connection with environmental mechanisms (beyond weather characteristics) (Lo Iacono et al. 2017; Rinaldo et al. 2018). However, this has mainly been the case for diseases directly transmitted from the environment to the host (e.g. see Bertuzzo et al. 2008, 2011, 2016; Mari et al. 2012; Rinaldo et al. 2012, for cholera), whereas, with only few exceptions (e.g. see Bomblies et al. 2008; Gurarie and Seto 2009; Perez-Saez et al. 2015), vector-borne and foodborne zoonoses including an intermediate host have so far been neglected (Lloyd-Smith et al. 2009).

Therefore, to address the challenges arising from the ecology of many infections, there is a need, and opportunity, to integrate disease transmission processes with their underlying environmental drivers

within space-time explicit frameworks, by focusing on the interactions and feedbacks between the two. This mechanistic coupling across environmental sciences (which traditionally investigate the links between distal and proximal environmental processes) and epidemiology (traditionally focused on transmission cycles and disease burdens) seems paramount to deepen our understanding of complex infectious disease systems, to yield more reliable simulations of future disease risk, and to guide control strategies, including potential environmental interventions (Bertuzzo and Mari 2017; Eisenberg et al. 2002, 2007; Lloyd-Smith et al. 2009; Rinaldo et al. 2018).

1.3 Research questions

The overall aim of this thesis is to support the study and management of environment-driven infectious diseases, under current and future potential conditions, by explicitly linking environmental and epidemiological processes through mechanistic modelling.

Fasciolosis (or liver fluke disease), a widespread zoonosis, is used as a case study. This parasitic infection is responsible for production losses in livestock of above US$ 3 billion per year, globally, and is emerging in humans, with the total number of reported cases going from less than 3000 to approximately 17 million in recent decades (Mas-Coma et al. 2009). Its transmission pathway is inextricably linked with the environment (group IV in Figure 1.3), with environmental characteristics affecting multiple disease components (i.e. the free-living stages of the parasite, as well as the intermediate host) both directly and indirectly (e.g. direct effect of temperature on the survival of the parasitic stages, and indirect effect of rainfall on the presence of intermediate hosts, through its effect on their habitat) (e.g. see Ollerenshaw and Rowlands 1959).

We focus on the UK because:

1. Liver fluke is the major economically important parasitic worm affecting livestock, together with gastrointestinal nematodes (van Dijk et al. 2010), affecting almost 80% of dairy herds in England and Wales (McCann et al. 2010a), and costing the British agriculture sector approximately £300 million per year due to lost production (Williams et al. 2014).
2. Climate-driven changes in infection patterns have already been observed across the country, which have resulted in an increased use of treatment, exacerbating the development of resistance to available antiparasitic drugs (Charlier et al. 2014).
3. Existing empirical liver fluke risk forecasting models are being used by the UK National Animal Disease Information System (NADIS) to inform farmers about potential future risk of infection across areas (NADIS 2019).

4. The historical presence and veterinary importance of the disease in the country have resulted in a good mechanistic understanding of the environmental-epidemiological system, which has been reinforced by a significant amount of information from field studies and laboratory experiments emerged as the disease attracted renewed attention following the recently observed changes (Charlier et al. 2014; van Dijk et al. 2010; McCann et al. 2010a; VIDA 2019).

Specifically, we address the following research questions:

1. *How can we advance the study of fasciolosis beyond empirical associations of infection levels with climatic characteristics?*
2. *How sensitive is the risk of infection with liver fluke to heterogeneous environmental conditions? What are potential implications for disease management and especially for environmental interventions?*
3. *How can we expect risk of liver fluke infection to change in response to climate change going forwards?*

Regarding (1), we aim to incorporate mechanistic understanding of disease transmission processes and key underlying weather–water–environment conditions into a new integrated model. In contrast to liver fluke risk forecasting models currently available, which are based on historically observed correlations between climatic and disease prevalence data, this involves explicitly describing the bio-physical processes underlying transmission of fasciolosis, including how climatic effects are mediated by on-the-ground environmental characteristics. The result would be the first mechanistic hydro-epidemiological model of liver fluke risk that could be used to simulate conditions beyond those previously observed, as well as to investigate what-if scenarios for decision support. To address this question, we also need to identify a strategy to constrain and test the new model. To this end, we aim to use not only available hydrological and epidemiological datasets, but also expert knowledge of system behaviour to make the model more robust to data with limited reliability and in the presence of climate change, as similarly proposed in previous studies (e.g. Hartmann et al. 2015; Liang et al. 2005; Pianosi et al. 2016).

With respect to (2), we aim to use the new model to investigate dominant controls of disease risk across the UK. To this end, we intend to set up the model to simulate risk of infection across the nation-wide domain and to use ANalysis Of VAriance (ANOVA) as a sensitivity analysis method, considering both climatic characteristics and landscape properties as disease risk drivers. To better understand the role of environmental heterogeneity in shaping disease risk patterns, we intend to compare our results with the dominant controls we would obtain if we simulated disease risk using an existing model that does not consider the variability of on-the-ground environmental characteristics. This analysis would then provide the basis to investigate the potential of environmental interventions (such as risk avoidance

management strategies) to reduce disease risk, by exploring where in the UK these can provide benefits and how they compare with current treatment-based control. So far, such alternative strategies have often been called for (e.g. by Morgan et al. 2013), but their potential effectiveness has not yet been assessed quantitatively.

Regarding (3), our goal is to evaluate potential climate change impacts on liver fluke risk in the UK, toward the end of the century, while considering uncertainties in climate projections. So far, the response of liver fluke risk to climate change has only been assessed by extrapolating past relationships into wider geographical regions and future climates (e.g. Caminade et al. 2015; Fox et al. 2011), and without analysing the link with underlying changes in parasite-relevant climatic characteristics, which are expected to play a key role on the disease dynamics (Easterling et al. 2000; Lo Iacono et al. 2017). Moreover, implications for disease control have not yet been assessed. Instead, here, we aim to use our new mechanistic model, together with the most recent ensemble of regional climate projections available, to better uncover the relationship between projected changes in disease risk seasonality and spread with changes in liver fluke-specific climatic thresholds. Finally, we aim to explicitly evaluate implications of these projected changes in climate and liver fluke transmission on the effectiveness of current treatment-based control strategies, to understand if and where these may become unsustainable going forward.

1.4 Thesis outline

The remaining thesis is structured as follows:

Chapter 2 introduces fasciolosis, including its link with environmental processes, recently observed changes in infection patterns, and disease control challenges. Moreover, it reviews the literature on existing liver fluke models.

Chapter 3 introduces the first mechanistic hydro-epidemiological model to simulate risk of infection with liver fluke disease, with explicit connections to key underlying environmental drivers. The model is tested in two UK case study catchments for which hydrological and epidemiological data are available. A novel strategy to constrain the model is also presented based on Monte Carlo sampling and expert-driven rules. A comparison with the most widely used current liver fluke risk forecasting (empirical) model is provided.

Chapter 4 investigates the role of environmental heterogeneity in driving liver fluke disease transmission across the UK by upscaling the previously developed model to the national level and by analysing modelled controls with ANOVA. Opportunities for environmental management as a disease control

alternative to drug administration are explored by implementing risk avoidance strategies in the model and by comparing the risk reduction they can achieve to the effectiveness of current treatment-based control.

Chapter 5 focuses on estimating how liver fluke risk might change under future potential climatic conditions in the UK towards the end of the century, accounting for uncertainty in climate projections. Potential seasonality and distributional shifts in disease risk are linked to changing climatic drivers and an evaluation of how these, in turn, might affect the effectiveness and sustainability of current control strategies is presented.

Finally, Chapter 6 summarises the findings and contributions of the thesis and proposes directions for future research.

Chapter 2. Fasciolosis (or liver fluke disease)

2.1 The importance of fasciolosis

Fasciolosis is a zoonotic disease caused by infection with two species of parasitic flatworms, or trematodes, of the genus Fasciola, which affect the liver (hence the common name liver fluke): *F. hepatica*, originally from temperate regions in Europe and America, and now expanded globally, and *F. gigantica*, which lives in tropical areas of Africa and Asia. Two hosts are required for these parasites to complete their life cycle. The primary host range is broad and includes several mammals (such as cattle, sheep, goats, equines, camelids and marsupials), including humans. Intermediate hosts are typically amphibious mud snails in the case of *F. hepatica*, and freshwater snails in the case of *F. gigantica*, both of the family Lymnaeidae (Wilson et al. 1982; Mas-Coma et al. 2005; WHO 2018).

It is the vector-borne parasitic disease with the widest distribution known in terms of latitude, longitude and altitude (Mas-Coma et al. 2005). Values of disease prevalence reported in the literature are rarely comparable across study sites and regions, as they are often based on different samples (including different hosts), sample sizes and time spans (Lo Iacono et al. 2017; Mehmood et al. 2017). However, high prevalence values have been documented across all continents, including in Europe (e.g. 79.7% across the UK (McCann et al. 2010a; Howell et al. 2015) and up to 82% in Ireland (Selemetas et al. 2014, 2015a, 2015b), in both cases based on dairy cattle herds), South America (e.g. mean prevalence of 21.6% across dairy cattle herds in Colombia (Valencia-López et al. 2012)), Africa (e.g. up to 71.45% in Ethiopia (Malone et al. 1998; Yilma and Malone 1998)), Oceania (e.g. 42.5% in cattle from Victoria, Australia (Durr et al. 2005)) and Asia (e.g. up to 85.2% in Cambodia (Tum et al. 2004, 2007)), with endemic areas ranging all the way from below sea level, along the Caspian Sea, to altitudes of up to 4000 meters in South America (Mas-Coma et al. 2005).

Severe acute infections in animals can lead to sudden death (with mortality rates up to 50% reported in sheep (Fiss et al. 2013)), but more frequent clinical signs of disease include weight loss and anaemia. On the other hand, the major economic losses to the livestock industry are linked to sub-clinical infections, which lead to lowered productivity e.g. reduced growth rates in beef cattle and lower milk yields in dairy cows (Kaplan 2001). Treatment and associated veterinary costs represent additional economic losses, on top of those resulting from condemnation of livers at the abattoir and lost production (Kaplan 2001; Bennett and Ijpelaar 2005). Because of the presence of a multitude of farm-specific

elements, the effects of infection on farm economics are difficult to quantify (van der Voort et al. 2013). However, with more than 600 million animals assumed to be infected, fasciolosis has been estimated to be responsible for production losses in livestock of above $3 billion per year, globally (Fairweather 2005; Turner et al. 2016; Beesley et al. 2018). Moreover, in addition to these direct impacts on the health and productivity of animals, recent research indicates that infection with liver fluke may also alter the susceptibility of animals to other pathogens, and compromise the diagnosis of co-infections such as Bovine Tuberculosis, with serious consequences for disease control (Claridge et al. 2012).

Finally, while originally considered to be of secondary importance for humans, fasciolosis is now estimated to infect about 17 million people worldwide, annually (Mas-Coma et al. 2005, 2018; McManus and Dalton 2006; Olsen et al. 2015) (Figure 2.1). Moreover, "different diagnostic limitations, and the fact that human fascioliasis is not a disease of obligatory declaration, suggest that the number of human cases is much greater than that published" (Mas-Coma et al. 2005).

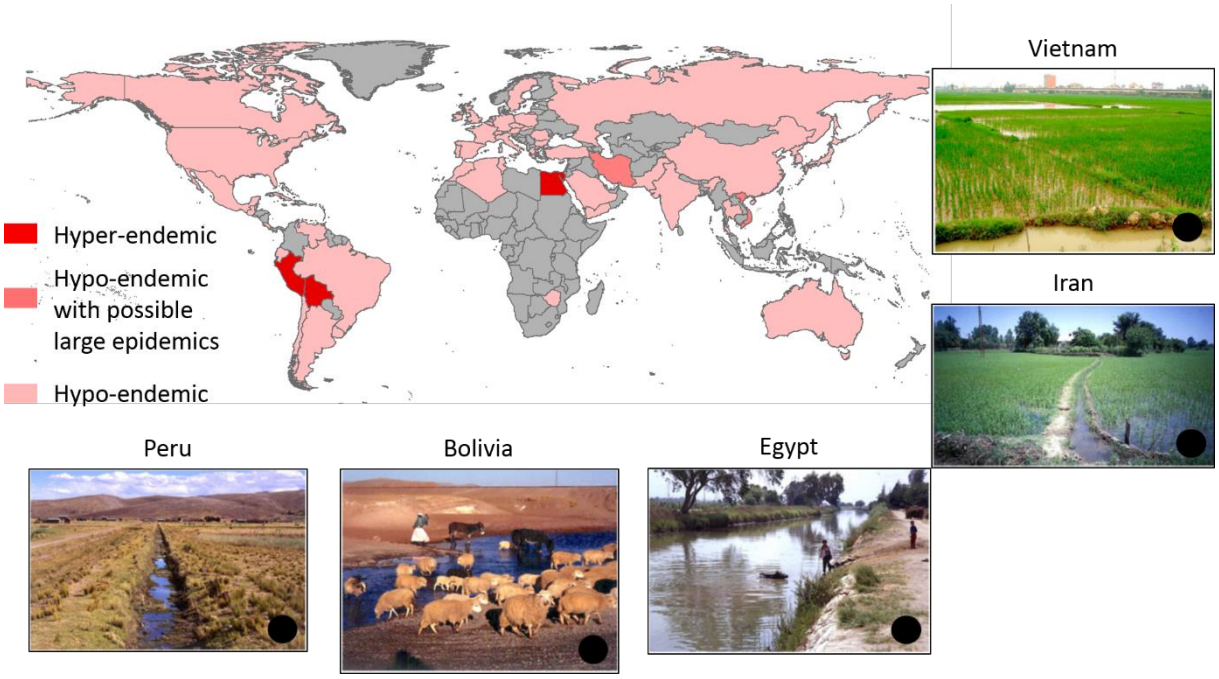

Figure 2.1 Global distribution of human fasciolosis (map based on cases reported by Esteban et al. (1998) and pictures from Mas-Coma et al. (2018)).

The WHO includes it in the list of Neglected Tropical Diseases (NTDs), among the group of foodborne trematodiases (WHO 2018), in fact people get infected through ingestion of contaminated water, watercress and other vegetables/plants for human consumption, or raw liver dishes (Mas-Coma et al. 2018). Typical symptoms of acute infection in people include fever, nausea, skin rashes and abdominal pain (WHO 2018), but extreme pathogenicity may also lead to longer-term neurological and

ophthalmological problems (Mas-Coma et al. 2018). The highest prevalence and intensity of human fasciolosis are found in high-altitude regions of Andean countries, but the disease is also encountered in the Caribbean area, northern Africa, western Europe and the Caspian region (Mas-Coma et al. 2005). In particular, in poor sheep- and cattle rearing rural communities of Bolivia, Peru, Egypt, Iran and, more recently, Vietnam, infection rates are so high that fasciolosis is a serious threat to public health, as well as a constraint on social and economic development (WHO 2018).

2.2 The link with the environment

Fasciolosis has strong environmental components to its transmission. Liver fluke, the parasite responsible for infection, has a complex life-cycle which includes stages that can persist a long time outside of the primary host (namely, eggs, miracidia, cercariae and metacercariae), as well as the obligatory passage through amphibious or aquatic snails, which serve as intermediate hosts and also live in – and are influenced by – the environment (Ollerenshaw and Rowlands 1959; Pantelouris 1963; van Dijk et al. 2010).

The dependence of the disease pathway on abiotic factors is partly related to the intermediate host specificity. In fact, as mentioned above, snails transmitting *F. hepatica* show marked amphibious traits and are more adapted to colder conditions, while those responsible for transmission of *F. gigantica* are aquatic and prefer warmer climates. In the UK, *F. hepatica* is transmitted through Galba truncatula snails (originally from Europe, then expanded to other continents, most likely with the commercial exportation of European livestock, and now considered to be the main intermediate host of *F. hepatica*, globally) (Charlier et al. 2014a). These are the least aquatic of all lymnaeid snails. Specifically, they are amphibious mud snails, which require access to the air, and typically do not survive well in standing water (Andrews 1999). Instead, their ideal habitat is along the edges of small ponds or ditches and on wet pastures, in areas with poor drainage, subject to alternate flooding and desiccation (Andrews 1999; Charlier et al. 2011; De Roeck et al. 2014). Soil type and pH may also potentially play a role in the suitability of their habitats (thus, potentially contributing to the uneven spatial distribution of fasciolosis across regions), with G. truncatula snails believed to prefer slightly acidic and loamy soils (Charlier et al. 2011; Beesley et al. 2018).

While soil moisture is key, especially for snail presence and activity, with saturated conditions favouring the presence of snails and development of the intra-molluscan parasitic stages, temperature is also critical for disease transmission. In fact, temperature affects the development rate of eggs and parasitic stages within the snail, as well as the survival of metacercariae, and lower and upper temperature

thresholds exist below/above which development and survival do not occur (Thomas 1883; Ollerenshaw and Rowlands 1959; Pantelouris 1963; Andrews 1999).

Specifically, the parasite life cycle unfolds as follows. Once passed out on pasture in the faeces of infected animals, and washed out of the faeces, fluke eggs start developing at a temperature-dependent rate. Once fully developed, eggs hatch into miracidia when both temperature and soil moisture conditions are suitable (Andrews 1999; Williams et al. 2014). Miracidia require water to swim through and are short lived: either they find a snail host or die within 24 hours (Andrews 1999; Thomas 1883; Williams et al. 2014). Galba truncatula snails, which -as previously mentioned- live in poorly drained areas, are also known to hibernate with cold weather and aestivate during hot dry periods (Andrews, 1999). At these times, development of the parasitic stages within the snail may be halted (Pantelouris, 1963). Within the snail, the fluke multiplies and, after about six to eight weeks, depending on temperature, cercariae are released (a snail infected with a single miracidium can produce up to several hundred cercariae, which are released over a period of time). Cercariae then encyst on grass to form infective metacercariae, which survive on pasture and retain infectivity based on temperature, with moderate weather being most favourable (Andrews 1999; Williams et al. 2014). When grazing animals ingest infective metacercariae, the immature flukes migrate into their liver, reach the bile ducts in about 8-10 weeks, mature reaching up to about 5cm in length and 1cm in width, and start producing eggs that -again- can be detected in faeces after approximately 5 weeks (resulting into an overall prepatent period -i.e. interval between infection of an animal and first ability to detect it- of about 3 months) (Kaplan 2001; Williams et al. 2014). The larger the amount of infective metacercariae ingested, the higher the infection intensity in the animal, and, therefore, the number of eggs produced.

Traditionally, in humid temperate climates, such as in the UK, the combination of temperature and soil moisture conditions has resulted in a distinct seasonal pattern of disease (e.g. see Ollerenshaw and Rowlands 1959; Williams et al. 2014). Eggs shed onto pasture in winter and spring usually begin to develop in early April, with large numbers of miracidia hatching in late May. This is also the time when snails emerge from hibernation, as the weather warms up at the end of winter, and the parasite life cycle resumes. If soil moisture is available, cercariae therefore emerge from snails from mid-July onwards, resulting into a peak of metacercarial availability on pasture in late summer and autumn.

2.3 Observed changes in disease patterns

The strong dependence of fasciolosis on environmental factors has contributed to altered disease epidemiology as a result of recent changes in climate and the environment (Mas-Coma et al. 2009; Charlier et al. 2014b). At present, the disease is believed to be emerging or re-emerging in many areas

of South America, Africa, Asia, and Europe, both in animals and humans, at least partly as a consequence of environmental changes, including direct human interventions (Mas-Coma et al. 2005).

- At the animal level, increases in disease prevalence and shifts in its spatial distribution have been documented primarily in the UK, which have been attributed to milder winter temperatures and altered precipitation patterns. In England, prevalence of infection in dairy herds increased from 48% in 2003 to 72% in 2006 (McCann et al. 2010a). Moreover, fasciolosis has recently been reported in previously unaffected regions of the country, such as in Scotland and East Anglia (Pritchard et al. 2005; Kenyon et al. 2009). Similarly, shifts in seasonality have been observed in the UK and Ireland, which have also been linked to changing climatic conditions, and have resulted in the disease shifting towards being more of a year-round – and less of a seasonal – threat (Relf et al. 2011; Fairweather 2011). On the other hand, in South America (mainly Ecuador and Peru), outbreaks of animal fascioliasis were detected following changes in the occurrence of droughts and floods linked to the 1997-1998 El Niño-Southern Oscillation event (Mas-Coma et al. 2009).
- At the human level, the global number of reported cases of fasciolosis has increased from less than 3000, prior to 1992, up to the most recent figure of 17 million (Mas-Coma et al. 2018). While this is partly linked to factors such as the availability of better diagnostic tools, more surveys and increased awareness, rises in health risk due to fasciolosis have also been associated to recently developed water resources and irrigation projects. For example, a significant increase in human infection, following the quick colonisation of a man-made irrigation system by *F. hepatica* and lymnaeid snails, was recently observed in the Asillo zone of the Northern Altiplano, in Peru (Esteban et al. 2002; Mas-Coma et al. 2005).

This evidence of climate and environment-driven changes in the epidemiology of liver fluke and incidence of fasciolosis further suggests that climate change will have significant impacts on the future evolution of the disease. For example, in Bolivia, where G. truncatula snails thrive in waters that come from the perpetual snow of the Andes, it is believed that short-term increases in runoff due to warming-driven glacier retreats, and subsequent long-term reductions in water supply, will greatly influence the disease epidemiology going forwards; on the other hand, in the Nile Delta region in Egypt, where snail intermediate hosts inhabit irrigation canals, complications are expected as raising temperatures and more extreme droughts may increasingly impact and change human agricultural activities (Mas-Coma et al. 2009).

2.4 Disease control challenges

Effective control of fasciolosis is challenging for a number of reasons. Most importantly, despite several trials in recent years, no commercial vaccine is yet available for prevention (McManus and Dalton 2006). Therefore, current control is largely based on the use of antiparasitic drugs (mainly Triclabendazole, TBZ, for both people and animals) (Fairweather 2011; Beesley et al. 2018). However, there are many limitations to their use:

- First, hosts can be repeatedly infected (i.e. they develop partial or no immunity e.g. see Anderson et al. 2014) and there is no drug with persistent action to prevent reinfection. Therefore, farmers, for example, may have to treat their animals multiple times every year (Morgan et al. 2012).
- Moreover, current treatment options against the parasitic immature stages, which are the most damaging for animals, are limited (e.g. at the moment, TBZ is the only licensed treatment available in the UK against these) (Fairweather 2005, 2011; Statham 2015; Beesley et al. 2018).
- Furthermore, repeated drug use, partly linked to the increasing climate change-driven shifts in liver fluke seasonality and spread, has led to treatment failure being reported more and more frequently. For example, resistance to TBZ has been already observed in a number of countries, including in the UK (Brennan et al. 2007; Kamaludeen et al. 2019; Kelley et al. 2016).
- Finally, concerns about treatment residues in meat and milk have restricted the use of flukicides (i.e. drugs against liver fluke) in animals producing meat/milk for human consumption, and to an increase in withdrawal periods for many products (NOAH 2013; Statham 2015).

2.5 Liver fluke models

Three modelling directions can be found in the literature in relation to liver fluke: (*i*) climate-based empirical indices for disease risk forecasting, which started being developed in the 1950s and later expanded through the use of Geographic Information Systems; (*ii*) early attempts to model the parasite life cycle mechanistically; and (*iii*) a more recent body of work, again based on empirical approaches, mainly aimed at investigating the role of environmental and other risk factors in relation to observed infection patterns.

With respect to the first modelling direction, several climate-based liver fluke risk forecasting systems have been developed based on empirical relationships found between historic climate and disease data. However, their empirical nature makes them unsuitable for assessing disease risk and guiding interventions under changing conditions (Beesley et al. 2018).

- Ollerenshaw and Rowlands (1959) were the first to quantitatively link weather characteristics to levels of fascioliasis in grazing animals, but their index is still widely used for forecasting purposes, including by the UK National Animal Disease Information System (NADIS 2019) and the Irish Department of Agriculture and Food, to warn farmers about potential high-risk years. The model calculates seasonal risk of infection as a function of monthly number of rainy days, rainfall and potential evapotranspiration, based on a relationship found with incidence of acute fasciolosis data on the island of Anglesey, Wales (UK), over the period 1948-1957 (also see Appendix Section A.1.4).
- The Stormont wet-day Index (Ross 1970) was developed for use in Northern Ireland and is a simplified version of the previous Ollerenshaw Index, based on the accumulation of wet days only.
- The Water Budget-Based System (Malone et al., 1987) calculates a yearly index of suitability for disease transmission as a function of growing degree days (i.e. number of days above a baseline parasite-specific temperature threshold) and the Thornthwaite water budget (obtained from rainfall and min/max temperature data), based on a relationship found with the annual number of flukes transmitted on a study herd in Louisiana (US), over the period 1978-1983.

Despite being empirical in nature, both the Ollerenshaw Index and the Water Budget-Based System have been widely used (often after applying some modifications to the original calculations and, increasingly, by using Geographic Information Systems) for long-term forecasts and for mapping liver fluke risk over large areas, including in Europe (e.g. Ollerenshaw 1966; Fox et al. 2011; Caminade et al. 2015), Middle East (e.g. Halimi et al. 2015), Africa (e.g. Malone et al. 1998; Yilma and Malone 1998), America (e.g. Fuentes et al. 1999; Valencia-López et al. 2012), and Oceania (e.g. Haydock et al. 2016).

Regarding the second modelling direction, despite the key spatial aspect in the epidemiology of fasciolosis (because of its dependence on development of the free-living stages and presence of snail hosts, which in turn strongly depend on environmental conditions (Charlier et al. 2014a), none of the mechanistic models available simulates the dynamics of soil moisture and its effects, with temperature, on life-cycle progress and disease transmission. Specifically:

- Early mechanistic models for liver fluke focus on one or two stages of the parasite life cycle and describe their development as a function of temperature only (e.g. Gettinby et al. 1974; Nice and Wilson 1974).
- Similarly, a more recent model, built with the aim of investigating the effectiveness of potential components of a vaccine, describes the acquisition and development of liver fluke within the primary host, including a temperature-dependent survival of metacercariae (Turner et al. 2016).

However, the model cannot evaluate impacts on infection levels in subsequent seasons, as it does not represent the life-cycle stages evolving on pasture, nor how these are affected by environmental conditions.

- Meek and Morris (1981) provide a more comprehensive representation of the life cycle, recognising the importance of soil moisture on herbage growth and snail activity (Meek and Morris 1981). However, both rainfall and irrigation status are inputs to their model, which still neglects the effects of soil moisture dynamics in the landscape on the suitability for disease transmission.

More recently, the observed general rise in infection pressure has resulted into a renewed interest in fasciolosis and to a new body of work, again using empirical approaches, aimed at investigating disease risk factors. Specifically, most of these studies use similar climate-environment-management variables and explore their ability to explain spatial infection patterns observed at a certain moment in time, at different scales – from farm to post code areas – and in different countries, mainly UK, Ireland and Belgium (Beesley et al. 2018). Usually, this is achieved either by performing statistical tests to analyse potential differences in explanatory variables between positive and negative farms (e.g. Selemetas et al. 2014, 2015b), or by developing multi-variable regression models, including linear or logistic regressions, and regression trees (e.g. McIlroy et al. 1990; McCann et al. 2010b; Charlier et al. 2011; Howell et al. 2015; Bennema et al. 2011; Ducheyne et al. 2015; Selemetas et al. 2015a). The type of explanatory factors which are found to be important are often similar across studies (both environmental and management variables, with rainfall and temperature always resulting relevant). However, (*i*) different rainfall and temperature characteristics may result useful; (*ii*) the level at which these variables explain the observed patterns varies, and (*iii*) the sign of influence (positive or negative) is also often different from study to study. For example, poorly drained soil types have been linked to both a higher and a lower risk of infection in dairy herds in Ireland (Bennema et al. 2011; Selemetas et al. 2014, 2015b; McCann et al. 2010b), suggesting that the indirect information about infection levels that these models provide may not be sufficient for understanding the processes underlying disease transmission and for predictive purposes under changing conditions (Eisenberg et al. 2002; Mellor et al. 2016; Wu et al. 2016; Rinaldo et al. 2017).

Chapter 3. A mechanistic hydro-epidemiological model for liver fluke

3.1 Introduction

The transmission of several highly pathogenic infectious diseases is closely linked to weather and environmental conditions (Altizer et al. 2006). Waterborne diseases, like cholera, are directly affected by hydro-meteorological factors such as rainfall, through transport and dissemination of the pathogens, and water temperature, through their development and survival rates. Diseases involving a vector or intermediate host as part of their life cycle, such as schistosomiasis or fasciolosis, are also indirectly controlled by characteristics of the water environment and land surface, through their influence on the vector or host (Perez-Saez et al. 2016; Rinaldo et al. 2018).

Our environment is changing at unprecedented rates due to climate change and direct human activities (Coumou and Rahmstorf 2012; Van Loon et al. 2016), with implications for the behaviour, seasonality and distribution of many diseases and their carriers (Jones et al. 2008; Wu et al. 2016). Evidence of climate and environment-driven changes in the phenology of pathogens and incidence of diseases already exists. The increase in frequency and intensity of extreme weather events is altering the occurrence of floods and droughts, changing the concentration of infectious agents in the water environment and human exposure to infection (Righetto et al. 2013; Rinaldo et al. 2012, 2018). Similarly, changes in the prevalence of schistosomiasis have been observed due to the expansion of the snail intermediate host habitat, following the construction of dams and implementation of irrigation schemes to meet demands for food/energy from increasing numbers of people (Steinmann et al. 2006).

As climate change accelerates and other human-caused disturbances increase, it is urgent to assess impacts on disease transmission, to guide interventions that can reduce and/or mitigate risk (Bouley et al. 2014). To this end, we need to: (a) understand the mechanisms by which the environment affects epidemiological processes, addressing the system as a whole, (b) represent these processes with models that are explicit in space and time, to more reliably simulate conditions beyond historically observed variability, and (c) test these models in new ways, since simply reproducing past observations may no longer be sufficient to justify their use for decision support (Altizer et al. 2006; Fox et al. 2012; Lloyd-Smith et al. 2009; Rinaldo et al. 2018; Wagener et al. 2010; Wu et al. 2016).

However, most current models that predict changes to disease patterns in response to climate change are empirical (Lo Iacono et al. 2017; Urban et al. 2016; Wu et al. 2016). This means they do not explicitly represent mechanisms, but are based on statistical correlations between historical data, thus becoming unreliable when extrapolated to novel conditions, e.g. into different regions or future climates (Dormann et al. 2012). Moreover, empirical models do not allow for what-if analyses, i.e. they cannot be used to test the effect of interventions on disease incidence, which would be valuable for decision-making (Eisenberg et al. 2002; Lloyd-Smith et al. 2009).

In this work, we incorporate knowledge of environmental and epidemiological processes into a new integrated mechanistic model, using fasciolosis as an example. This is a globally distributed parasitic disease of livestock and zoonosis, whose most widespread agent is *Fasciola hepatica*, the common liver fluke (Mas-Coma et al. 2005). Clinical signs of disease in animals include weight loss, anaemia and sudden death, while sub-clinical infections result in lowered productivity and are estimated to cost the livestock industry $3 billion per year, globally (Kaplan 2001; Turner et al. 2016). Risk of infection with liver fluke is strongly influenced by weather and environmental conditions, especially temperature and soil moisture, as the parasite has an indirect life-cycle involving an intermediate host (in the case of *F. hepatica*, the amphibious mud snail Galba truncatula) and free-living stages, which grow and develop in the environment (van Dijk et al. 2010; Ollerenshaw and Rowlands 1959; Pantelouris 1963).

Addressing fasciolosis is urgent for many reasons. First, resistance to available antiparasitic drugs is on the rise worldwide, making disease control challenging (Charlier et al. 2014). Second, increases in disease prevalence, expansions into new areas and shifts in its seasonality have been observed in recent years and attributed to altered temperature and rainfall patterns, raising concerns about the effects of climate change in the future (Charlier et al. 2014; Relf et al. 2011). Finally, fasciolosis is emerging as a major disease in humans, with about 17 million people infected around the world, and human treatment relying on the same veterinary drug to which resistance is increasing (Mas-Coma et al. 2005). Climate-based fluke risk forecasting models have been developed since the 1950s (e.g. see Ollerenshaw and Rowlands 1959; Malone et al. 1987), the Ollerenshaw Index being the best-known example, which is still actively used to predict disease severity in Europe (Caminade et al. 2015; Fox et al. 2011; Ollerenshaw 1966; NADIS 2019). However, these models are empirical in nature and therefore of little use for assessing risk under changing conditions. On the other hand, previous attempts to model fasciolosis mechanistically neglect the role of soil moisture dynamics in driving infection and do not account for the spatial aspect of the disease (e.g. Nice and Wilson 1974; Turner et al. 2016).

Therefore, in this study, we introduce a new mechanistic coupled hydro-epidemiological model for liver fluke, which explicitly represents the parasite life cycle in time and space, linked with key environmental

conditions. We then parameterise the model for two case studies in the UK and assess whether it can replicate temporal and spatial variability of observed infection levels. To overcome limitations of available epidemiological data, we propose a calibration approach that combines observations and expert knowledge. Finally, we further evaluate the model by comparing it with the widely used empirical Ollerenshaw Index.

3.2 The Hydro-Epidemiological model for Liver Fluke

The Hydro-Epidemiological model for Liver Fluke (HELF) quantitatively captures the mechanisms underlying transmission of fasciolosis, describing the causal relationships between hydro-meteorological factors and biological processes, instead of relying on correlation. To this end, HELF integrates TOPMODEL (Beven and Kirkby 1979; Beven et al. 1995), an existing hydrological model which we use to simulate soil moisture dynamics, and a novel epidemiological model, which represents the parasite life cycle. TOPMODEL is chosen because its underlying assumptions are physically realistic for humid-temperate catchments, such as UK catchments, where the dominant mechanism of runoff generation is soil saturation (Beven and Kirkby 1979). The epidemiological model is developed based on current understanding of the life cycle of *Fasciola hepatica* and its dependence upon soil moisture and air temperature (van Dijk et al. 2010; Ollerenshaw and Rowlands 1959; Pantelouris 1963).

3.2.1 Hydrological model component

TOPMODEL is a catchment-scale rainfall-runoff model, which was developed for hydrological predictions and has been extensively used for different water resources applications (e.g. see references in Beven 1997). The model uses temperature, rainfall and Digital Elevation Model (DEM) data to estimate, at each time step, spatially distributed soil moisture over the catchment (calculated as a saturation deficit), as well as streamflow at the catchment outlet. The model we use is based on the version explained by Beven et al. (1995) and has seven parameters (Table 3.1).

#	Parameter	Description	Unit	Min	Max
1	LnTe	Log of transmissivity of soil when saturated to the surface	mm^2/day	-5	10
2	m	Soil parameter controlling decline of transmissivity as saturation deficit increases	mm	1	200
3	Srz_init	Initial saturation deficit in root zone	mm	0	300
4	Srz_max	Maximum allowable saturation deficit in root zone	mm	5	300
5	td	Time delay from unsaturated to saturated zone	day/mm	0	0.9
6	a	Shape parameter for gamma distribution used for routing	-	0.01	5
7	b	Scale parameter for gamma distribution used for routing	day	0.01	5

Table 3.1 Hydrological model parameters and initial ranges.

In TOPMODEL, hydrological processes are represented using a sequence of conceptual stores for which the model estimates and tracks water balances. An interception store, representing vegetation cover, must be filled by rainfall before infiltration into the soil can occur. When water infiltrates into the soil, it first enters the root zone, from which it evaporates as a function of potential evapotranspiration, maximum capacity of the store, and its actual water content. Water that is not evaporated or retained by the soil percolates to the saturated zone (i.e. the groundwater), which contributes to the channel network through subsurface flow.

To simulate the spatial distribution of soil water content over the catchment, this water balance accounting routine, which is lumped at the catchment scale, is integrated with spatially distributed topographic information derived from DEM data. Specifically, the effect of topography is captured, for each grid cell in the catchment, through calculation of a Topographic Index: $TI = \ln\left(\frac{a}{\tan(\beta)}\right)$, where a is the upslope contributing area and $\tan(\beta)$ the local slope. TI is used as a measure of the likelihood that a grid cell becomes saturated by downslope accumulation: high values occur over flat regions in valleys, which tend to saturate first, whereas low values are associated with areas at the top of hills, where there is little upslope area and slopes are steep (Figure 3.1). The model assumes that all points with the same index value will respond similarly, hydrologically. For computational efficiency, the distribution of TI values is then discretised into classes, so that computations are performed for each class instead of for each grid cell.

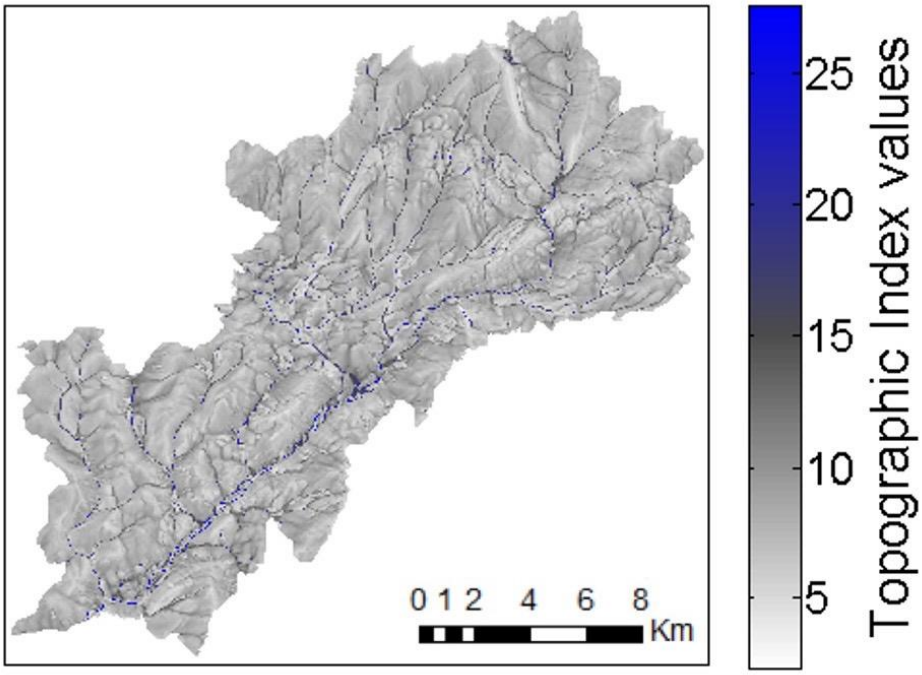

Figure 3.1 Spatial pattern of Topographic Index values for the River Tawe Catchment (UK).

Therefore, a saturation deficit for each *TI* class is calculated as a function of the catchment average saturation deficit, updated at each time step by water balance calculation, and the spatial distribution of the *TI*s. Rainfall that falls on saturated areas (i.e. where deficit is less than or equal to zero) cannot infiltrate into the soil and generates saturation-excess overland flow. Finally, total streamflow is calculated as the integrated subsurface flow and saturation-excess overland flow, and a gamma distribution is used to model the time delay in discharge generation at the catchment outlet, due to water moving through the river network of the catchment.

3.2.2 Epidemiological model component

The epidemiological component of HELF represents the stages of the liver fluke life cycle that live on pasture: eggs, miracidia, snail infections and metacercariae (Figure 3.2). Development and survival of these, as well as the presence of mud snails, require particular temperature conditions and wet soil. Therefore, the model takes as input variables temperature and soil moisture, as well as an egg scenario (i.e. number of embryonic eggs we assume are deposited on each *TI* class at each time step by infected animals), to calculate the abundance of individuals in each life-cycle stage.

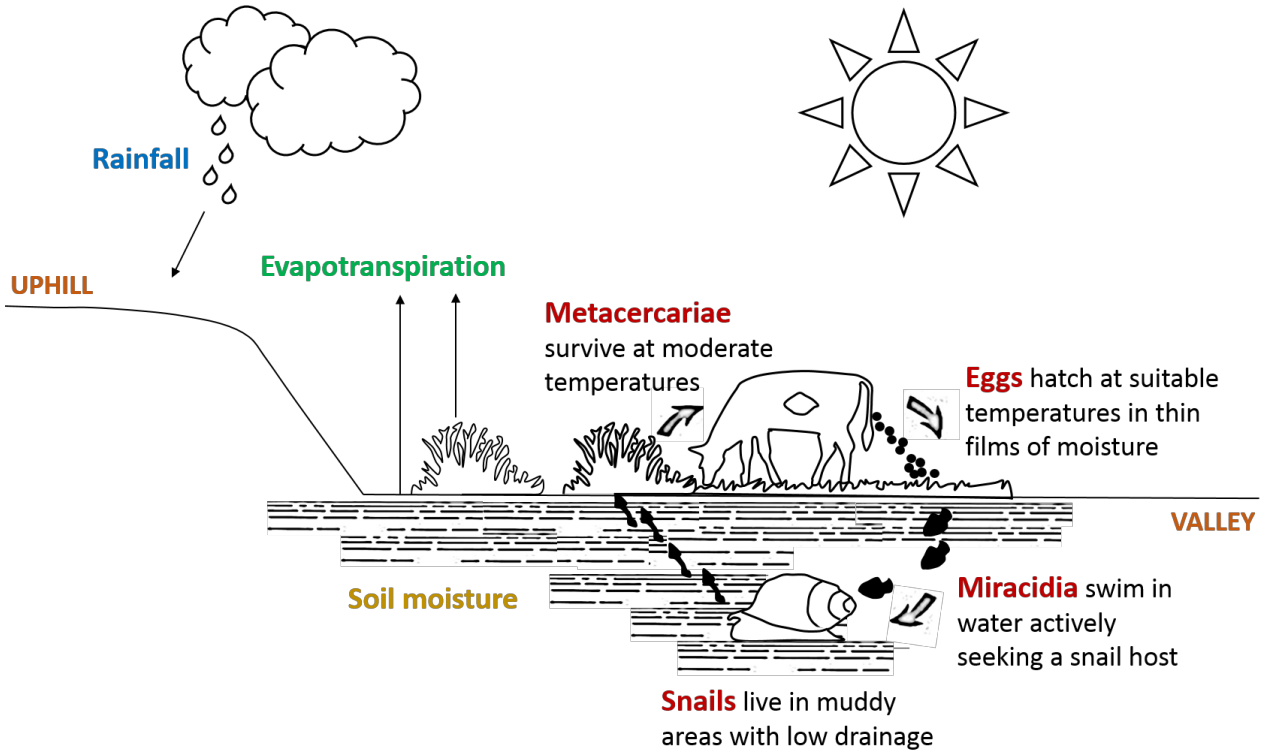

Figure 3.2 Simplified representation of the liver fluke life cycle, with an amphibious mud snail serving as intermediate host.

Once passed out on pasture in the faeces of infected animals, Eggs (E) develop at a temperature-dependent rate, and hatch into miracidia when both temperature and soil moisture conditions are suitable (Andrews 1999). Miracidia (Mi) are short lived: either they find a snail host or die within 24 hours (Andrews 1999; Thomas 1883). Therefore, progression from miracidium to the next stage is calculated as the probability of finding a snail. This is assumed to depend on soil moisture levels and temperature, as Galba truncatula snails are only found in poorly drained areas and are known to hibernate with cold weather and aestivate during hot dry periods (Andrews 1999). Snail infections (SI) also develop in the model as a function of both temperature and soil moisture, as development within the snail may be halted due to hibernation and aestivation (Pantelouris 1963), until parasites finally emerge from snails in the form of cercariae. Once attached to grass as Metacercariae (Me), these survive on pasture and retain infectivity based on temperature, with moderate weather being most favourable (Andrews 1999).

Each stage, except for miracidia that only have a lifespan of one day, is represented as a pool of developing cohorts of individuals to capture maturation progress in a more realistic way. Individuals in different cohorts are exposed to different environmental conditions, and therefore will develop at different times (Andrews 1999; Thomas 1883). We account for this by using two state variables for each cohort within each stage: number of individuals and maturation state of the cohort. The rationale is that each cohort has a certain maturation state, which increases with the number of days that have suitable environmental conditions, until the cohort eventually matures to the next life-cycle stage. Output from a stage is then the sum of cohorts per unit area which mature to the next one.

At each time step, development and/or survival rates for a stage are calculated based on the value of the relevant environmental conditions for that stage at that time step, and on the stage-specific requirements for development/survival, which are defined through model parameters (Table 3.2). The technique employed to build the functions to calculate these rates has previously been used for modelling both liver fluke and other parasites (e.g. Nice and Wilson 1974; Rose et al. 2015; Turner et al. 2016). For temperature-dependent rates, we use information in the literature from laboratory experiments or controlled micro-environment studies that examine the time to development or death at a range of constant temperatures. First, rates are calculated for each constant temperature from the reported e.g. time to development (i.e. rate = 1/time to development); then piecewise linear models are fitted to these rates, yielding a regression equation which can be used to estimate the daily rates based on a time series of observed temperature. For soil moisture, we adopt the same approach, assuming that development is fastest when the soil is fully saturated (i.e. when deficit = 0) and that there is no development above a certain maximum deficit (Andrews 1999; Ollerenshaw and Rowlands 1959). For stages with both temperature and soil moisture requirements, we allow for development to progress as a function of both (Figure 3.3).

#	Parameter	Description	Unit	Min	Max	References
1	S1MinTemp	Min temp for egg development	°C	5	15	Ollerenshaw and Rowlands 1959; Pantelouris 1963; Andrews 1999.
2	S1PeakTemp	Optimal temp for egg development	°C	15	27	Thomas 1883; Andrews 1999.
3	S1PeakRate	Egg development rate at optimal temp	day^{-1}	0.025	0.5	Thomas 1883; Andrews 1999.
4	S1MortRate	Egg mortality rate	day^{-1}	0	0.0693	Andrews 1999
5	S1MaxTemp	Max temp for egg development	°C	27	40	Andrews 1999
6	S1TrigSatDef	Max saturation deficit for egg hatching	mm	1	100	Pantelouris 1963; Andrews 1999.
7	S1TrigMinTemp	Min temp for egg hatching	°C	5	15	Pantelouris 1963
8	S2SatDef	Max saturation deficit for miracidia finding snails	mm	1	100	Thomas 1883; Ollerenshaw and Rowlands 1959; Andrews 1999.
9	S2SatSlope	Slope defining optimal saturation deficit for miracidia finding snails	mm^{-1}	0.01	0.5	
10	S2MinTemp	Min temp for miracidia finding snails	°C	5	15	Andrews 1999
11	S2PeakTemp	Optimal temp for miracidia finding snails	°C	15	27	Andrews 1999
12	S2MaxTemp	Max temp for miracidia finding snails	°C	27	40	Pantelouris 1963
13	S3SatDef	Max saturation deficit for snail infections development	mm	1	100	Thomas 1883; Ollerenshaw and Rowlands 1959; Andrews 1999.
14	S3SatSlope	Slope defining optimal saturation deficit for snail infections development	mm^{-1}	0.01	0.5	
15	S3MinTemp	Min temp for snail infections development	°C	5	15	Ollerenshaw and Rowlands 1959; Pantelouris 1963; NADIS 2019.
16	S3PeakRate	Snail infections development rate at optimal temp	day^{-1}	0.0204	0.0357	Andrews 1999
17	S3MortRate	Snail infections mortality rate	day^{-1}	0	0.0693	-
18	S4MinTemp	Min temp for metacercariae survival	°C	-20	10	Andrews 1999 and therein
19	S4PeakTemp	Optimal temp for metacercariae survival	°C	10	15	Andrews 1999 and therein
20	S4MaxTemp	Max temp for metacercariae survival	°C	15	40	Andrews 1999 and therein
21	S4PeakRate	Metacercariae survival rate at optimal temp	day^{-1}	0.0027	0.0333	Andrews 1999 and therein
22	S4MinRate	Metacercariae survival rate at min/max temp	day^{-1}	0.0333	0.5	Andrews 1999 and therein

Table 3.2 Epidemiological model parameters and initial ranges.

3.2.3 Coupled model

The coupled hydro-epidemiological model runs at a daily time step and has a total of 29 parameters. For each day, HELF updates the catchment average saturation deficit based on rainfall and temperature, and derives the saturation deficit for each of 25 *TI* classes, as a function of this and the *TI* value for the class. Then, for each class and life-cycle stage, the model calculates the relevant development and/or survival rates, based on environmental conditions.

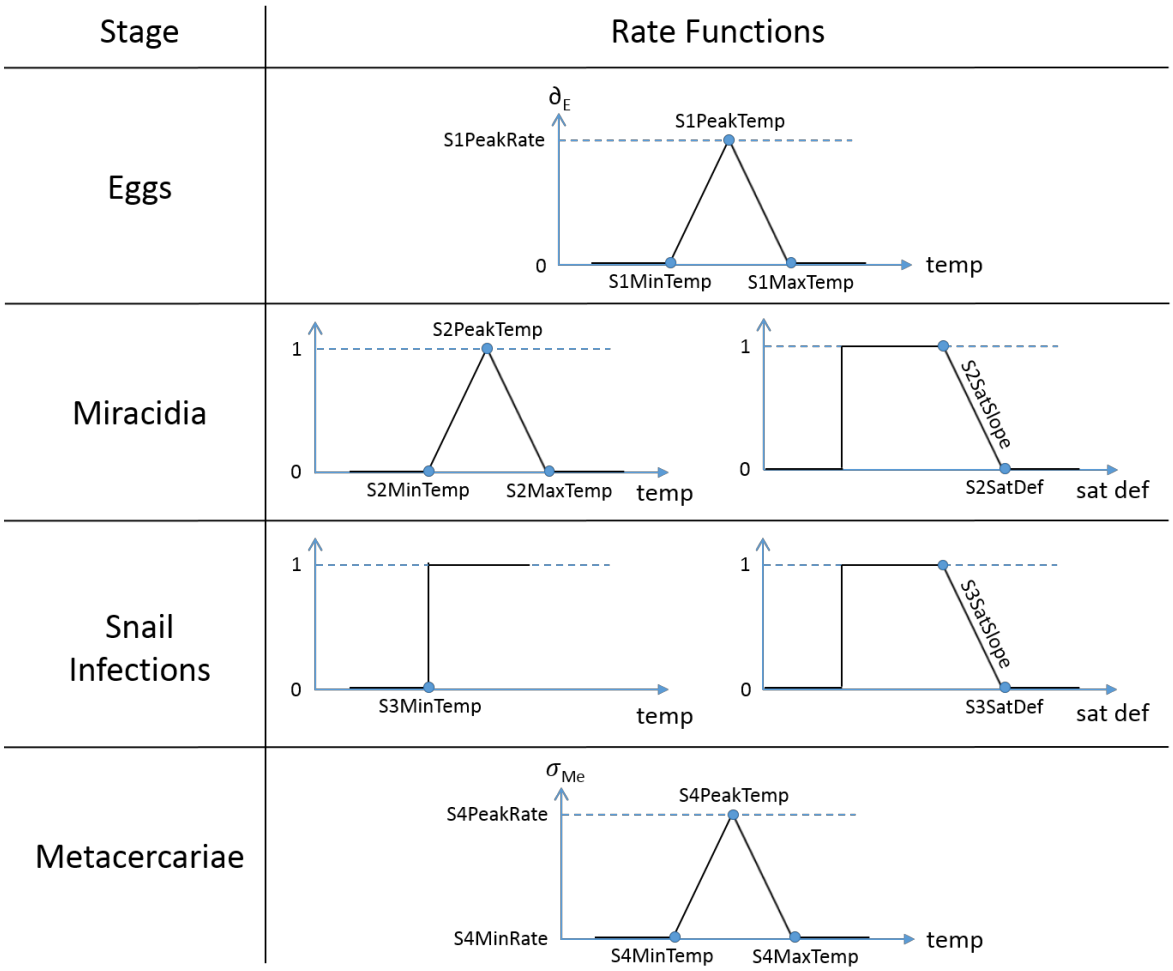

Figure 3.3 Functions used in HELF to calculate temperature and soil moisture-dependent development and survival rates.

The maturation state of each cohort is updated based on the development rate, and, given an egg scenario, the model finally computes the number of individuals in the stage as a function of the number from the previous time step, plus the sum of the cohorts developed from the previous stage, minus those that develop to the next one, minus those that die (Figure 3.4). Therefore, the model outputs are the abundances of hatched eggs, snails located and infected by miracidia, developed snail infections, and infective metacercariae surviving on pasture, which represents the environmental suitability for disease transmission to grazing livestock. These variables, calculated for each *TI* class, can then be mapped back onto each grid cell in the catchment.

Regarding the egg scenario, the current assumption is that 100 embryonic eggs are introduced on each *TI* class daily, over the whole simulation period. This means we are considering a scenario of continuous livestock grazing and no disease management over the catchment. However, this assumption can be easily changed. The fact that the egg scenario is a model input gives the model-user the possibility to

estimate how the environmental suitability for disease transmission translates into risk of infection, based on local farm management factors such as grazing season length or disease control strategy. More information about both hydrological and epidemiological model components of HELF is provided in the Appendix, Section A.1.1.

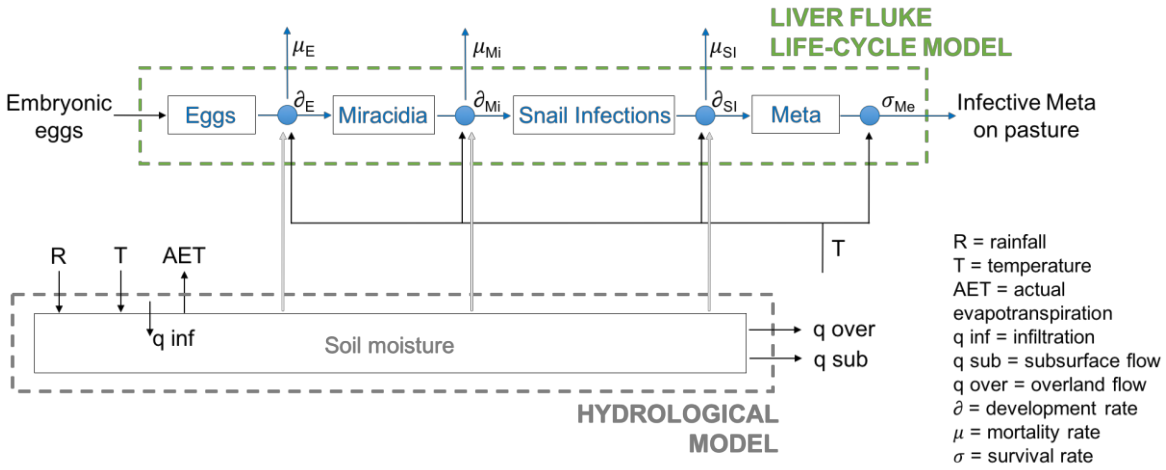

Figure 3.4 Simplified flow diagram of HELF, which integrates a hydrological and a liver fluke life-cycle component, to simulate the abundance of infective metacercariae (Meta) on pasture.

3.3 Study sites and data

We test HELF at two UK catchments, located in South Wales and North-West Midlands (England), respectively. The datasets employed include both hydro-meteorological and epidemiological data.

3.3.1 The Tawe and Severn Catchments

The River Tawe flows approximately 50 km south-westwards from its source in the Brecon Beacons to the Bristol Channel at Swansea. The catchment is about 240 km2 in size, with elevation ranging from about 10 to 800 m a.s.l., and most of the area characterised by a relatively impermeable bedrock. The River Severn rises in mid Wales and flows through Shropshire, Worcestershire and Gloucestershire, before also discharging into the Bristol Channel. The catchment, gauged at Upton-on-Severn, is about 6850 km2 in area, with elevation range and geological characteristics similar to the Tawe (NRFA 2019). Both catchments have grassland as the dominant land cover (Figure 3.5), which is extensively used for livestock farming, and are located in known liver fluke endemic areas (McCann et al. 2010a; Williams et al. 2014). Moreover, these areas are predicted to become increasingly warmer and wetter on average (Murphy et al. 2009), which suggests they will become even more favourable for liver fluke transmission in the future.

3.3.2 Hydro-meteorological and epidemiological data

The hydro-meteorological dataset includes daily observations of rainfall, temperature and discharge. Gridded time series of rainfall and temperature are obtained from CEH-GEAR (Tanguy et al. 2014) and the UK MetOffice (MetOffice 2017), respectively. For both case studies, to run HELF, we take the average over the grid cells overlapping with the catchment area. For the Tawe, we use these time series for a 12-year period (1999-2010), whereas, for the Severn, we use 2 years of data (2013-2014), in line with the available epidemiological data periods. Observed discharge, at Ynystanglws for the Tawe and Upton-on-Severn for the Severn, is derived from the National River Flow Archive (NRFA 2019). DEM data for both catchments are obtained from NextMap with spatial resolution of 5m, then aggregated to 25m (Intermap Technologies 2009).

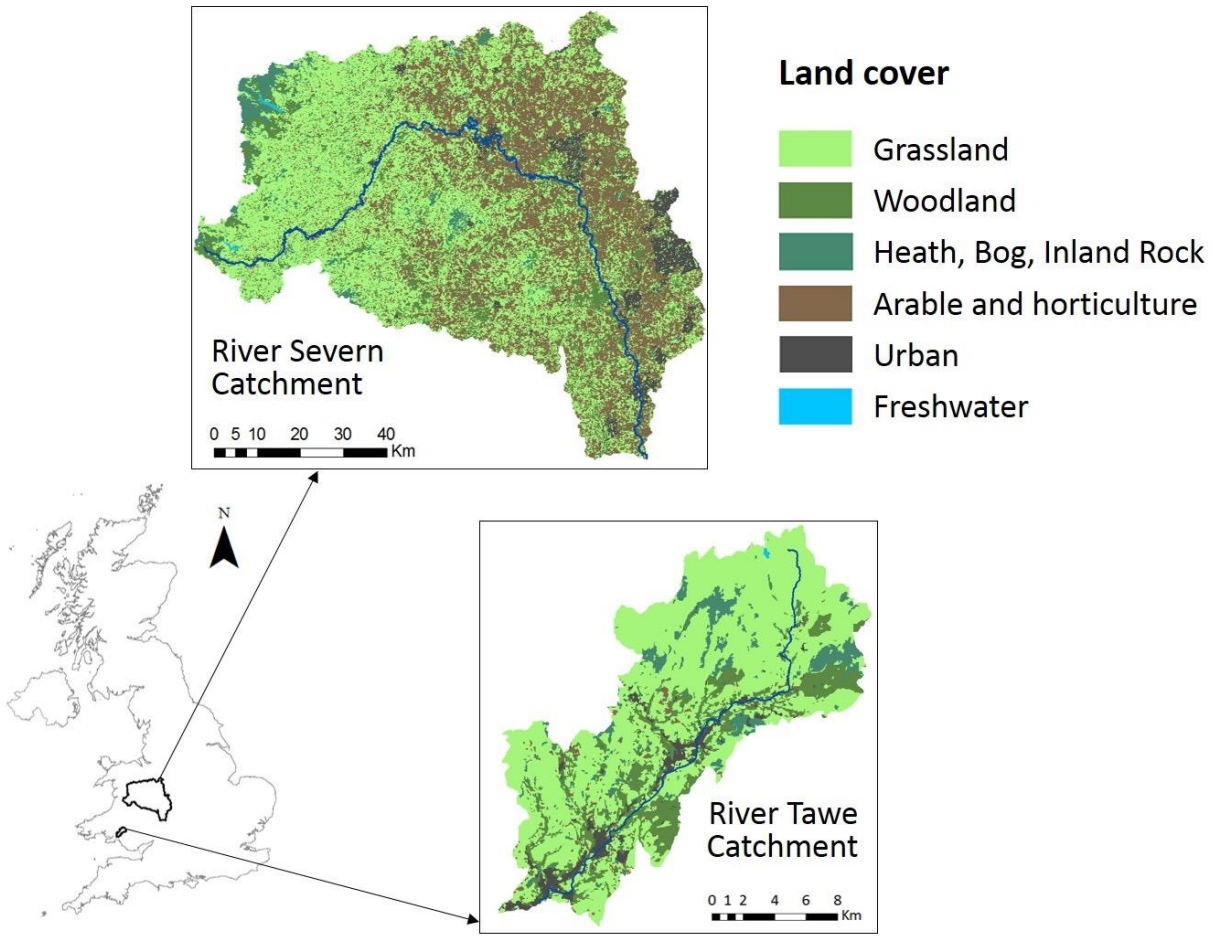

Figure 3.5 Location and Land Cover Map (LCM) for the Tawe and Severn Catchments (LCMs from Rowland et al. 2017).

The epidemiological dataset consists of a time series from the Veterinary Investigation Diagnostic Analysis (VIDA) database for the Tawe (VIDA 2019), and a spatial dataset based on Faecal Egg Counts

(FECs) for the Severn (McCann et al. 2017). The VIDA database, compiled from reports from the UK Government's Animal and Plant Health Agency regional laboratories, provides diagnoses of fasciolosis made from ill or dead animals. The time series we use is the monthly number of sheep diagnosed with acute fasciolosis from the post code district areas within the Tawe Catchment over 1999-2010. This data is believed to reflect well the temporal dynamics of within–year infection levels, but may not always reflect the magnitude of infection in the field, as the rate of submission of animals to the laboratories is potentially influenced by multiple factors (van Dijk et al. 2008). In our series, no cases are reported for 2001 and values over the following years are low, which may have been affected by the 2001 foot-and-mouth outbreak, which killed over 10 million animals in the UK, affecting submissions to the veterinary laboratories. On the other hand, the spatial dataset for the Severn Catchment consists of 174 cattle herds, from farms within a 60km x 75km area in Shropshire, that have been classified into infected and non-infected based on FECs collected over the period October 2014 – April 2015. Unlike VIDA, this is active surveillance data, and thus more likely to reflect true levels of infection. However, rather than a continuous and quantitative measure of the magnitude of infection, this dataset only provides a binary classification into positive-negative farms, at one moment in time and at a limited number of points within the catchment (also see Appendix Section A.1.2 for more information about these datasets).

3.4 Model calibration and testing

HELF comprises parameters related to the environment and parameters related to the phenology of liver fluke (Tables 3.1 and 3.2). Usually, more or less well-defined ranges of values can be found in the literature for these, rather than point estimates, partly because of their associated natural variability, and partly due to uncertainty and poor understanding. Different parameter sets, selected from these ranges, can often provide equally good representations of system behaviour, with implications in terms of predictive uncertainty and limitations for the applicability of the model (Beven 1993; Dormann et al. 2012). This type of parameter uncertainty can be reduced through a calibration or constraining process.

Traditionally, models are calibrated and validated using historic records, assuming that the data available reflect the underlying system, and that conditions in the period considered are similar to those under which the model will be used. However, this may not be sufficient if data are disinformative in some respects and/or if the purpose of the model is to simulate conditions that are significantly different to those previously observed (Beven 1993; Klemeš 1986; Wagener et al. 2010).

Our calibration strategy involves multiple datasets and methods. On one hand, we have high quality continuous data for both the meteorology and the hydrology. Therefore, as a starting point, we calibrate and validate the hydrological component of HELF by adopting a standard split-sampling approach

(Klemeš 1986). On the other hand, given the epidemiological data limitations mentioned in Section 3.3.2., our approach for constraining the epidemiological model component not only uses past observations, but also expert-driven rules.

3.4.1 Calibration and testing of the hydrological model component

To estimate TOPMODEL parameter values and evaluate its prediction capabilities, we perform a split-sample test using streamflow observations (years 2000-2006 for calibration and 2007-2010 for validation, with 1999 as warm-up period) (Klemeš 1986). The Shuffled Complex Evolution (SCE-UA) global optimisation method is employed to find the parameter set which maximises the coefficient of determination (R2) between simulations and observations on our catchments (Duan et al. 1992). The algorithm samples an initial population of parameter sets from a priori defined ranges (Table 3.1) and then evolves this population of sets to find the best performing one with respect to R2.

3.4.2 Calibration and testing of the epidemiological model component

Using the best performing parameterization obtained for TOPMODEL (and therefore for now neglecting the uncertainty in representing the hydrology), first, we fit the liver fluke component of HELF to the two epidemiological datasets, and assess whether we can reproduce the observed patterns of infection, ignoring the data limitations discussed. Second, under the assumption that these data may be disinformative, and given that we ultimately want to use HELF to simulate disease risk under changing conditions, we propose an alternative calibration approach based on Monte Carlo sampling and expert knowledge. Finally, we evaluate the model by comparing results to information from previous studies and to the commonly used Ollerenshaw Index.

Single-objective approach using epidemiological data

To estimate parameters of the epidemiological model component for the Tawe Catchment, we fit HELF to the VIDA time series by using SCE-UA to maximise the Pearson coefficient of correlation (r) between simulated abundance of infective metacercariae and observed number of sheep infections. As the VIDA dataset only provides a single time series for the Tawe, we aggregate the simulated abundance of metacercariae over the catchment by taking the average across TI classes. Moreover, to account for the delay between the variable we simulate and the observations, a lag parameter is included in the optimisation process, which is allowed to vary between 0 (no delay) and +5 months (Kaplan 2001). Similarly, to estimate parameters for the Severn Catchment, we fit HELF to the FEC-based spatial dataset. First, we divide the area over which we have observations into sub-areas with a minimum of 15 data points each. Second, we use SCE-UA to find the parameter set which maximises r between the simulated percentage of grid cells at risk of infection and the observed percentage of herds infected,

over each sub-area. To this end, for each parameter set, we aggregate the simulated abundance of metacercariae over months July-December 2014, assuming that pasture contamination over this period will be responsible for the observed disease incidence (Williams et al. 2014). Then, we classify the simulated abundance of metacercariae in each grid cell into two classes (no-risk and risk) by setting a threshold based on the overall observed percentage of infection. More information about model testing using epidemiological data is provided in the Appendix, Section A.1.2.

Monte Carlo sampling-based approach using expert opinion

Given the limitations of the epidemiological datasets, we believe that simply fitting these may not be sufficient to guarantee reliability of our new model. Moreover, if HELF is to be used to assess future disease risk, its credibility should be assessed via more in-depth evaluation of the consistency with the real-world system, instead from just comparison against historical data (Beven 1993; Pianosi et al. 2016; Wagener et al. 2010). To this end, we collect information from the literature (e.g. see McCann et al. 2010b; Relf et al. 2011; NADIS 2019) and use our perceptions to characterise the seasonality of the liver fluke life-cycle stages in the UK over years 2000-2010. This currently includes shifts in seasonality experienced over this time period, compared to what has been traditionally observed, driven by altered temperature and rainfall patterns, but could be adjusted to account for further changes and shifts, going forwards. Then, we formalise this knowledge into a set of rules:

- Rule 1: Retain parameter sets that every year predict the first month of snail presence (i.e. with positive number of infected snails) to happen earlier than average, if temperature is above average over January-March.
- Rule 2: Retain parameter sets that every year produce higher mean number of developed snail infections over summer (June-August), if the number of rainy days over May-July is above average.
- Rule 3: Retain parameter sets that every year produce higher mean number of infective metacercariae over autumn (August-October), if rainfall is above average and the number of days above 20°C is below average over May-August.
- Rule 4: Retain parameter sets that every year produce higher mean number of metacercariae over winter (January-February), if the total number of days above 10°C is above average over January-February.

Finally, we randomly sample 8000 parameter sets using uniform distributions from ranges in Table 3.2, and reject all parameterisations producing model outputs that are inconsistent with these rules.

Comparison with the Ollerenshaw Index

To further evaluate HELF, we use the "behavioural" parameterisations, i.e. those retained from sequential application of the rules described above, and compare disease risk simulated using these with

the Ollerenshaw Index (Ollerenshaw and Rowlands 1959). This, calculated at the monthly scale based on rainfall and temperature characteristics as explained by Fox et al. (2011) (see Appendix Section A.1.4), is the current standard for providing liver fluke risk forecasts in the UK, where it is used by the National Animal Disease Information Service to warn farmers about potential high-risk years (NADIS 2019).

3.5 Results

3.5.1 Performance of the hydrological model

Comparison of simulated and observed daily streamflow shows that TOPMODEL is capable of reproducing the temporal dynamics of observations well, including the peaks and recession periods of the hydrograph. The model achieves an R2 = 0.87 during calibration and 0.84 in the validation phase (Figure 3.6).

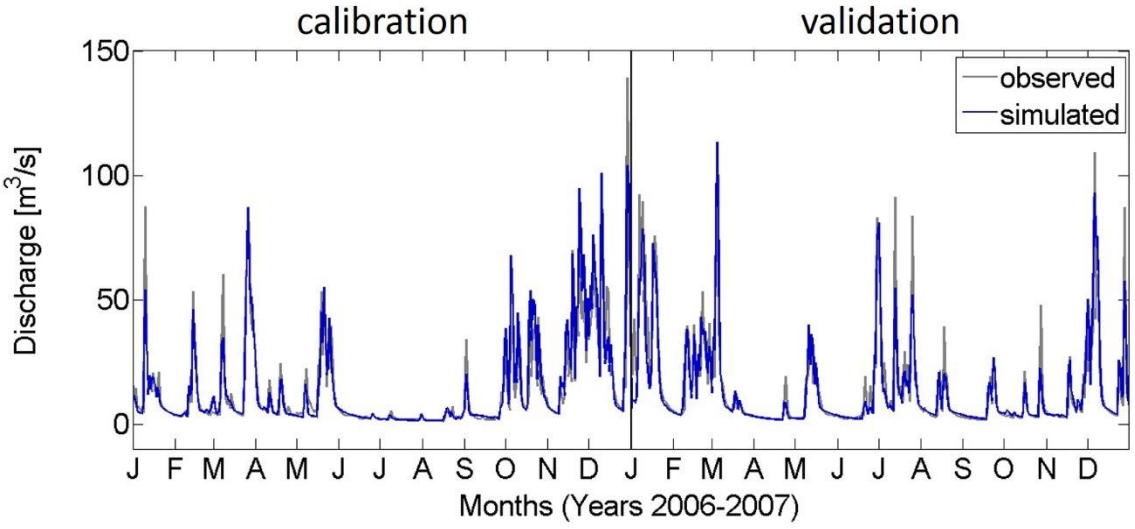

Figure 3.6 Extract of the calibration and validation periods using daily streamflow data for the River Tawe Catchment (the total period is 2000-2006 for calibration and 2007-2010 for validation).

3.5.2 Performance of the epidemiological model

Fit to epidemiological data

A delay is evident between the simulated catchment average number of metacercariae and the reported number of sheep diagnosed with fasciolosis in the Tawe Catchment (Figure 3.7). This is due to the time-lag between pasture contamination, which HELF simulates, and infection diagnosed in the animal,

which the VIDA dataset reports. Except for the year 2000, for which the model predicts risk of infection that is not reflected in the VIDA numbers over 2001, HELF seems to adequately predict the observed temporal dynamics of infection. It simulates low pasture contamination for most of the period and captures the higher peaks over winters 2008-2009 and 2009-2010, driven by the preceding exceptionally wet summers and rainy autumns. The highest correlation between the two series (r = 0.62) is found at a lag of three months, which corresponds to the prepatent period of fasciolosis reported in the literature (Kaplan 2001). If, instead of using the whole dataset for calibration, we perform a 5-fold cross-validation (see Appendix Section A.1.2), mean correlation results are 0.52 in calibration and 0.41 in validation.

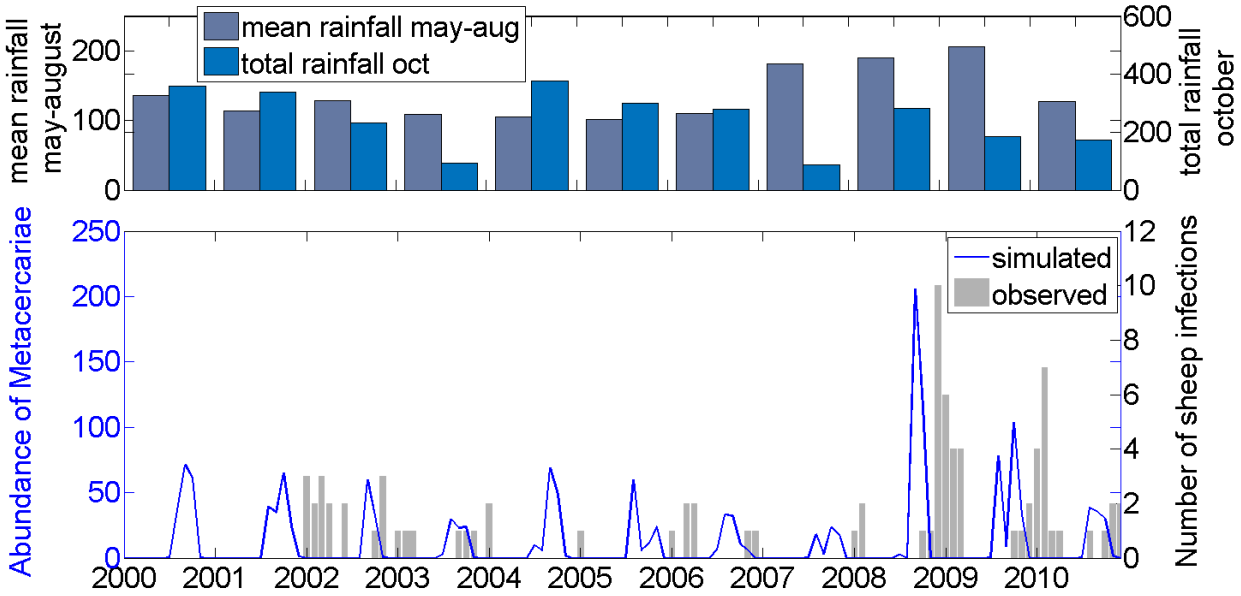

Figure 3.7 (bottom) Monthly comparison of simulated catchment average number of metacercariae and observed number of infections (VIDA data) over 2000-2010 for the Tawe Catchment. (top) Years 2008 and 2009 have the highest mean summer rainfall within the simulation period, as well as a sufficiently wet autumn, resulting in high suitability of disease transmission.

Division of the area for which we have observations within the Severn Catchment into sub-areas with at least 15 data points each, results into 9 sub-areas (Figure 3.8). When we compare the simulated percentage of grid cells at risk of infection with the observed percentage of infected herds, in each of the sub-areas, the two are in good agreement (r = 0.83), suggesting that the model can replicate the observed spatial pattern (here, performing a leave-one-out cross-validation -as explained in Appendix Section A.1.2- results in a mean absolute error of 0.1). Risk of infection seems overestimated in sub-areas A2 and A5. However, these areas were significantly drier than the others in 2014 (Figure A.1 in Appendix Section A.1.3) and have a lower percentage of area suitable for snail hosts in terms of soil pH (Figure A.2 in Appendix Section A.1.3), which are aspects that HELF currently does not account for.

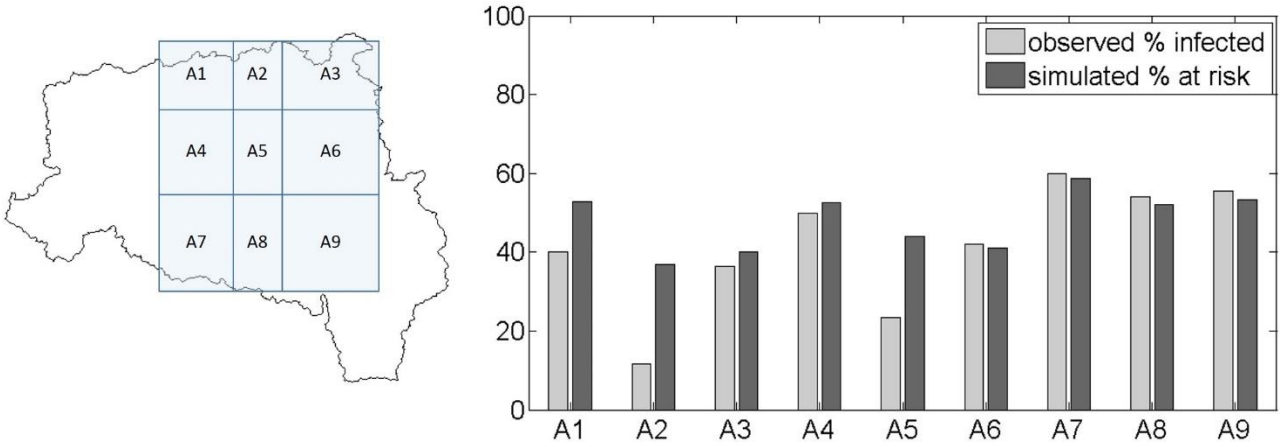

Figure 3.8 (left) Sub-areas within the Severn Catchment for which we have data points (i.e. cattle herds classified into infected and not infected). (right) Comparison of simulated percentage of grid cells at risk of infection and observed percentage of infected herds for each sub-area.

Results of the expert-driven approach

Sequential application of the expert-driven rules reduces the initial sample of 8000 parameter sets to 14 behavioural parameterisations (Figure 3.9). The resulting simulated abundance of developed eggs on pasture seems to increase in March, as the weather warms up, before decreasing gradually over the following months, as hatching into miracidia begins (Figure 3.10). Snail activity, and therefore infection of snails by miracidia, also starts in spring and carries on until November, when frosts may send snails back into hibernation. Development of intra-molluscan infections peaks around August, leading to high numbers of infective metacercariae on pasture in Autumn.

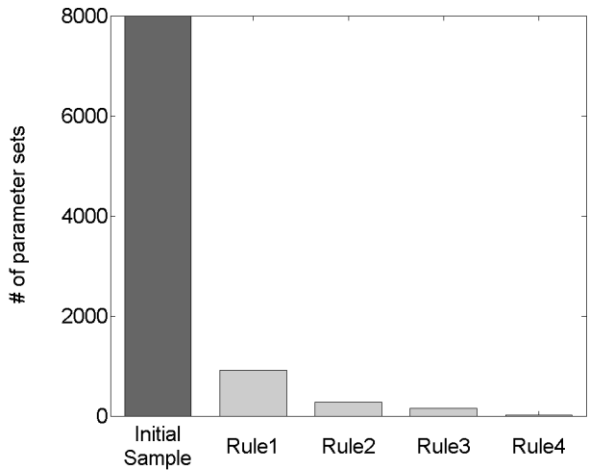

Figure 3.9 Evolution of the initial sample of parameterisations (each including the 22 epidemiological model parameters sampled from within their initial ranges) along the four confinement steps.

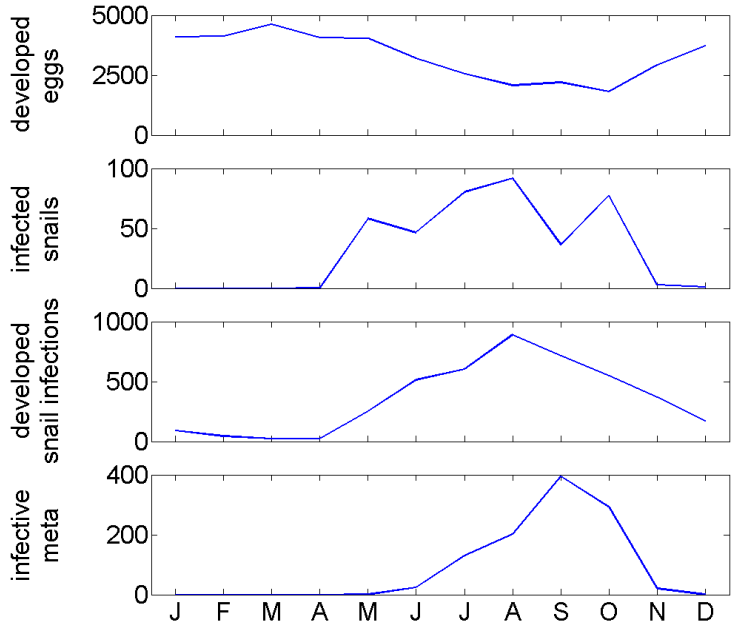

Figure 3.10 Monthly behaviour of the parasite life-cycle stages simulated with HELF for 2001, as an example (median of the behavioural simulations).

Finally, if we compare the abundance of metacercariae – this time obtained using the whole set of behavioural parameterisations - with the VIDA time series, first, we still see the expected delay between simulations and observations (Figure 3.11). Second, we note that, while uncertainty is still large in terms of magnitude of the yearly peak of infection, bounds are narrower in terms of timing and duration of the outbreaks, with the number of infective metacercariae on pasture beginning to increase in July, reaching a peak in September, before decreasing again in December, on average.

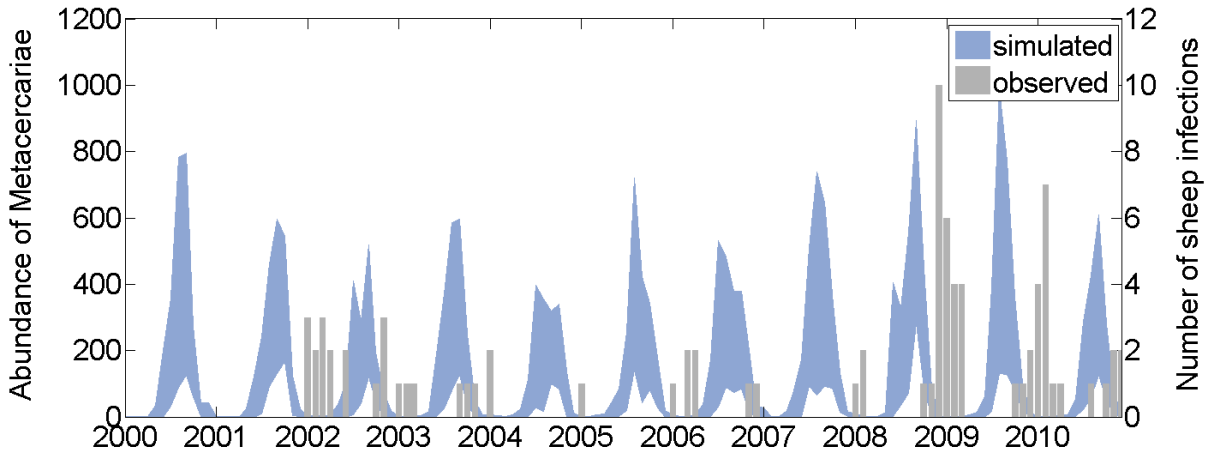

Figure 3.11 Monthly comparison of simulated catchment average number of metacercariae, obtained using the behavioural parameter sets (90% bounds), and observed number of infections (VIDA data) over 2000-2010 for the Tawe Catchment.

Comparison with the Ollerenshaw Index

Temporal comparison of the suitability for disease transmission simulated by HELF, constrained using the rules, with the Ollerenshaw Index, shows a time-lag of one month between the two series (Figures 3.12a and A.3 in Appendix Section A.1.4). This is due to the two models representing different things: a risk index based on monthly temperature and rainfall in the case of Ollerenshaw, and the abundance of metacercariae, based on soil moisture and accounting for the delays in the parasite life cycle, in the case of HELF. Moreover, we see that, while matching the empirical index on interannual variation (at lag of one month, r = 0.73), the two models' responses may differ at higher temporal resolution. For example, the Ollerenshaw Index reaches the same peak value in years 2007 and 2008, but risk of infection in 2007 seems lower than the following year according to HELF.

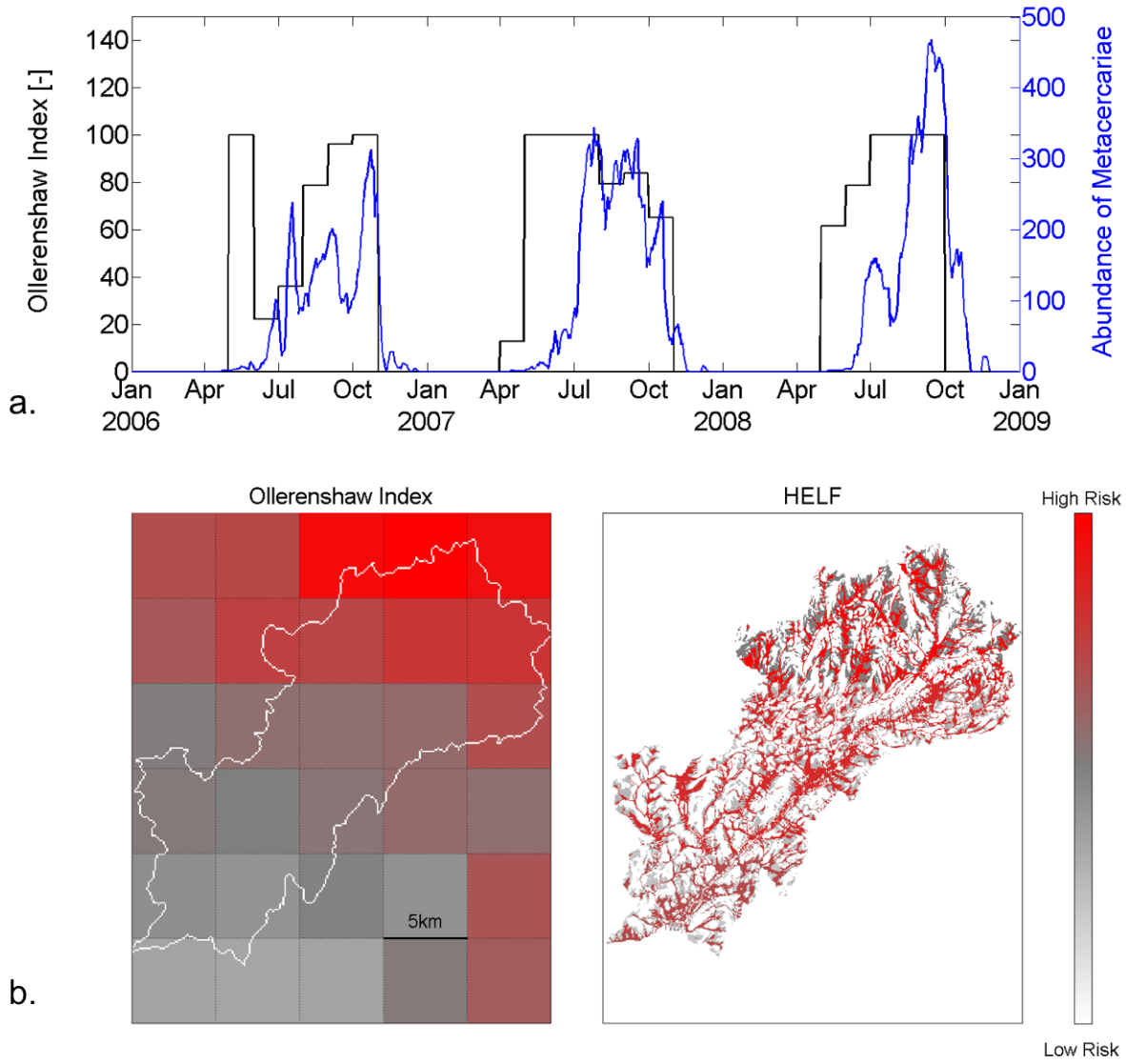

Figure 3.12 Comparison between the Ollerenshaw Index and HELF for the Tawe Catchment: (a) in time, for an extract of the simulation period (median of the behavioural parameterisations in blue); and (b) in space, for August 2006, as an example.

Comparison of the two models in space (presented in Figure 3.12b for August 2006, as an example) shows the presence of high-risk areas in the River Tawe Catchment according to both models. However, when using the Ollerenshaw Index, no proportion of the catchment seems risk-free and risk of infection is highest in the North-East where rainfall levels are highest (NRFA 2019). In contrast, for the same month, assuming an area is at risk if its number of metacercariae is positive, HELF estimates that 17.3% of the catchment is risk-free, and that there are 134 patches at risk, spread throughout the catchment, with mean size of 1.6 km2.

3.6 Discussion

In this study, we developed the first mechanistic model which explicitly simulates the risk of infection with *F. hepatica* in time and space, driven by temperature and soil moisture dynamics. The novelty of our work lies in the description of the bio-physical processes underlying transmission of fasciolosis, advancing the study of the disease beyond empirical associations of infection levels with temperature and rainfall. Despite current forecasting models calculating liver fluke risk based on these meteorological variables (Caminade et al. 2015; Fox et al. 2011; Ollerenshaw 1966; NADIS 2019), soil moisture has always been recognised as the critical driver of disease transmission for its role on development of the free-living stages and presence of the snail intermediate hosts (e.g. see Ollerenshaw and Rowlands 1959). Here we included it using an existing hydrologic model, which is based on spatially distributed topographic information, also known as an important fluke risk factor (McCann et al. 2010b). Moreover, collaboration across the physical and biological sciences was necessary to analyse the effect of both soil moisture and temperature on the multiple parasite life-cycle stages (Figure 3.3), and translate the mechanistic understanding of the system into an integrated model (Figure 3.4).

By simulating the system at 25 m resolution with a daily time step, HELF provides new insight into the space-time patterns of disease risk, which will be valuable for decision support. Compared to the Ollerenshaw Index, which considers each month independently from every other, HELF is dynamic. Therefore, high rainfall may result into high risk of infection depending on the antecedent moisture conditions of the soil and their effect on the life-cycle progress (Figure 3.12a). Moreover, by providing greater temporal resolution, HELF allows capturing the impact of shorter-term weather events, such as extremely warm days or intense concentrated rainfall, which are believed to be particularly relevant for the biological system (Dormann et al. 2012; Lo Iacono et al. 2017; Urban et al. 2016). Combined with the fact that HELF can identify hotspots of transmission potential (Figure 3.12b), this means it may be possible for farmers to control the magnitude of exposure to liver fluke in the field, e.g. by altering management practices to avoid livestock grazing in high risk areas during peak metacercarial abundance. Finally, the stages included in HELF represent the part of the life cycle which is missing in the model

of liver fluke dynamics within the primary host (i.e. livestock) developed by Turner et al. (2016). Integration of the two models would allow a mechanistic description of the whole life cycle, thus providing the opportunity to assess, for example, the impact of vaccines on infection levels.

In addition to aiding the management of fasciolosis, HELF could also benefit the study of other diseases. A similar model could be useful for rumen fluke, which is on the rise in British and Irish livestock, and has a similar life cycle to liver fluke, sharing the same intermediate host (Huson et al. 2017). On the other hand, a different hydrological model component could be employed instead of TOPMODEL, depending on the hydro-environmental drivers relevant for the disease considered (Rinaldo et al. 2018), while adopting the same integrated mechanistic modelling approach proposed here. For example, a model describing freshwater connectivity would be needed for diseases involving aquatic intermediate hosts, such as freshwater snails in the case of schistosomiasis (Perez-Saez et al., 2016).

Several assumptions are embedded in HELF. Notably, to account for seasonality and distribution of the disease, we assumed the parasite life cycle is entirely driven by environmental conditions, simplifying the mechanisms related to the intra-molluscan stage and neglecting density-dependent processes. Even with regard to environmental factors, characteristics such as soil pH and texture have been described as potentially relevant for the suitability of snail habitats (Charlier et al. 2011; McCann et al. 2010b), but have not been included in our model, yet. Similarly, surplus runoff water may have a role in the infection transmission pathway, contributing to the dispersal of snails and metacercariae down water courses (Mas-Coma et al. 2009). However, HELF could be expanded to incorporate these, as well as other spatially distributed information, including from remote sensing data.

To address common disease data limitations, we proposed an approach which includes the use of expert knowledge to constrain and evaluate our new model. Fitting observations is standard practice for calibration of hydrologic models, when there is a gauging station providing data to compare simulations against (Figure 3.6). Distributed soil moisture observations were not available for our case studies, but previous works have shown that TOPMODEL can provide good representation of the spatial pattern of saturated areas (e.g. see Güntner et al. 2004). More rarely, when data are available, calibration is performed to parameterise epidemiological models (e.g. Bertuzzo et al. 2011, 2016; Eisenberg et al. 2002; Mari et al. 2012, 2015) (Lloyd-Smith et al., 2009). Our results show that HELF is flexible enough to replicate the observed time-space patterns of infection over two case study catchments (Figures 3.7 and 3.8). We speculate that remaining mismatches, when we fit the two datasets, are not necessarily due to aspects not yet included in the model only, but may also be related to data issues. The absence of reported cases for 2001 from the Tawe Catchment is believed to have been influenced by the UK outbreak of foot-and-mouth disease in the same year. Similarly, discrepancies in some sub-areas of the

Severn Catchment may also be due to our underlying assumption of uniform distribution of farms per sub-area, which may not reflect the real-world system. Mis-reporting and low space-time resolution of data are common issues for many diseases and have often been recognised as a bottleneck to developing models providing meaningful predictions of disease risk (Eisenberg et al. 2002; Fox et al. 2012; Urban et al. 2016). Recent correlative liver fluke studies (e.g. see Byrne et al. 2016), have used geo-referenced data from abattoir liver condemnations, which, if routinely collated and made available, may benefit testing of models such as HELF across wider areas. However, even if larger, potentially more reliable epidemiological data were available, they would still reflect historical conditions, which may not necessarily be relevant for the future (Dormann et al. 2012; Wagener et al. 2010). Our calibration strategy includes the use of expert-driven rules to overcome these issues. The rules represent mechanistic knowledge of the system translated into prior information about the output variables. By using these, we can constrain aspects of the model for which no hard data are available in a process-based manner, without biasing the parameters towards external drivers not included in the model. The current formulation reflects changes in seasonality experienced over our simulation period. However, going forward, this can be adjusted to account for further changes, in order to reliably assess the impact on disease risk of conditions beyond the range of historical variability (Singh et al. 2011). Our results show there are parameterisations satisfying all four our rules (Figure 3.9), and that the behaviour of the simulated stages and the lags between them (Figure 3.10) agree with what is reported in the literature (Ollerenshaw and Rowlands 1959; Relf et al. 2011). This suggests that HELF reflects well (our current knowledge of) the real-world system. The fact that simulations are rejected from the initial sample indicate that our parameter confinement strategy is effective, which is crucial as the inability to identify behavioural parameterisations may result in significant predictive uncertainty when using the model under changing conditions (Beven 1993; Dormann et al. 2012). Moreover, using HELF in combination with Monte Carlo sampling allows explicit consideration of the uncertainty, by propagating it from the parameter ranges to the model simulations. This means we can provide decision-makers with a degree of confidence attributed to the model results. The reason why uncertainty in the simulated risk of infection still seems high in terms of magnitude (Figure 3.11) is that the rules are currently based on information about the seasonality of the disease only, driven by our aim of providing a model that is generally applicable across the UK. However, if reliable local data were available, the rules could be modified or increased in number to make the model more accurate locally (e.g. see Eisenberg et al. 2002; Liang et al. 2005). Instead, the fact that uncertainty bounds are narrow in terms of timing and duration of the disease outbreaks is particularly useful to inform farmers' decisions about e.g. when to allow grazing of animals or when to treat them.

3.7 Conclusions

We developed and tested a new mechanistic hydro-epidemiological model to simulate the risk of liver fluke infection linked to key weather-water-environmental processes (HELF). The fact that, unlike previous models, HELF explicitly describes processes, rather than relying on correlation, makes it better suited for capturing the impact of 'new' conditions on disease risk. We showed that the model is sufficiently flexible to fit observations for two UK case studies, but also introduced an expert-driven calibration strategy to make the model more robust to data with limited reliability and in the presence of climate change. Finally, comparison with a widely used empirical model of liver fluke risk showed that, while matching the existing index on interannual variation, HELF provides better insight into the time-space patterns of disease, which will be valuable for decision support. Driving the model with climate and management scenarios will enable assessment of future risk of infection and evaluation of control options to reduce and/or mitigate disease burden. This is urgent, given the widespread rapid development of drug resistance and threat of altered patterns of transmission due to climate-environmental change. Through the example of fasciolosis, we demonstrated *(i)* that sufficient mechanistic understanding of the bio-physical system may be available to develop and test a process-based model for an environment-driven disease, without having to rely only on limited and potentially disinformative data, and *(ii)* how accounting for the critical hydro-environmental controls underlying transmission can be valuable to better understand seasonality and spread of emerging or re-emerging threatening diseases.

Chapter 4. Opportunities for environmental management to control liver fluke infection risk

4.1 Introduction

Infectious diseases are a significant cause of morbidity and mortality worldwide (Dye 2014). The number of human infectious disease outbreaks has been increasing globally, especially those of zoonotic origin, and much of this increase has been linked to climate change (Jones et al. 2008; Smith et al. 2014). For example, 63% of pathogens have been estimated to be climate-sensitive in Europe (McIntyre et al. 2017), and costs associated with climate-sensitive health impacts (in humans and animals) have been estimated to be as high as 9% of Gross Domestic Product in certain countries in Africa and South Asia (Bierbaum et al. 2010).

The role the environment plays on the transmission of infectious diseases varies depending on their pathway. On one hand, transmission is mainly governed by direct host-to-host contact for pathogens that cannot survive long in the landscape (e.g. influenza). On the other hand, environmental conditions become important the longer pathogens are able to survive outside of their hosts (e.g. schistosomiasis or fasciolosis) (Eisenberg et al. 2007). Crucially, while some disease agents are mostly driven by meteorological factors, such as temperature and rainfall, transmission routes through vectors, food, soil and water are often also associated with other environmental drivers. For example, weather/climate is only one element of a complex system of controls for many infections transmitted through intermediate hosts or vectors that live and develop in the environment (Craig et al. 1999; McIntyre et al. 2017). In such cases, epidemiological processes are controlled by a wide range of interacting drivers, including landscape characteristics, which may be distributed unevenly, change rapidly over time, occur at different space-time scales (Cable et al. 2017; Parham et al. 2015), and directly and/or indirectly affect multiple disease components (Eisenberg et al. 2007).

Control of many environment-driven infections is increasingly challenged by climate change and the emergence of drug resistance. For many of these infections, no commercial vaccines are yet available for prevention, and control relies entirely on drug administration. However, as long as environmental conditions remain suitable for transmission, reinfection may occur rapidly after treatment (Garchitorena et al. 2017). Moreover, the widespread development of drug resistance – from overreliance on a single

medicine – is threatening the efficacy of control strategies for an increasing range of parasitic and other infectious diseases, globally (Garchitorena et al. 2017; Webster et al. 2014; WHO 2019). For example, resistance has been documented to all classes of drugs used against *Vibrio cholerae*, and is starting to complicate the fight against malaria, jeopardising important recent gains in disease control (WHO 2019). Similarly, the prospect of emerging drug resistance is worrisome for schistosomiasis and fasciolosis, as treatment of these diseases almost entirely relies on a single drug (Beesley et al. 2018; WHO 2016). Finally, for many infections, this is aggravated by the frequent misuse and overuse of drugs linked to altered space-time epidemiological patterns caused, at least partly, by climate change and direct human activities such as land use change (Mas-Coma et al. 2009; Siraj et al. 2014; Smith et al. 2014; Sokolow et al. 2017). In fact, the direct response to an increased disease challenge is often an increased use of treatment, which is self-defeating and accelerates development of drug resistance (Morgan et al. 2013).

As climate change accelerates and disease control becomes increasingly challenging, devising of more comprehensive strategies – rather than exclusively relying on treatment – is becoming a key concern. The role environmental conditions play in driving disease transmission may offer an opportunity to use environmental interventions as complementary -or even as alternative- strategies to drug administration to reduce disease burdens and improve health outcomes (Bierbaum et al. 2010; Garchitorena et al. 2017). To be able to explore the potential of environmental management for risk reduction, better mechanistic understanding of the link between disease transmission processes and underlying (direct and indirect) drivers is needed (Beltrame et al. 2018; Eisenberg et al. 2002; Lloyd-Smith et al. 2009; Rinaldo et al. 2018; Wu et al. 2016). Crucially, this includes on-the-ground environmental characteristics (beyond climatic variables alone), which are those decision-makers might be able to manipulate locally to contribute to sustainable and effective control (Morgan et al. 2013; Prüss-Ustün et al. 2016). Accounting for the heterogeneity of environmental drivers and studying disease risk sensitivity to them is critical for understanding where environmental management may be an option and where it may be most valuable in complementing drug treatment in the future (Liang et al. 2007; Mari et al. 2017).

However, currently considered drivers of disease risk are often only climatic, and environmental strategies to complement medical approaches still under-recognised. The importance of on-the-ground environmental processes and their spatial heterogeneity – in mediating disease risk responses to climatic factors – is increasingly acknowledged (Lo Iacono et al. 2017; Rinaldo et al. 2018). For example, accounting for hydrologic transport across human communities has advanced the understanding of the complex dynamics of cholera (Bertuzzo et al. 2008, 2012). Similarly, consideration of hydrologic characteristics, including human modifications, has proven critical for better insights into the transmission of other water-related diseases, e.g. ephemeral vs. permanent hydrological regime, as well as damming and irrigation practices, for schistosomiasis (Liang et al. 2007; Perez-Saez et al. 2016;

Steinmann et al. 2006), presence and persistence of water pools for malaria (Bomblies et al. 2008), and soil moisture and irrigation of crops for fasciolosis (Beltrame et al. 2018; Nzalawahe et al. 2014). However, the majority of current modelling studies only assume climatic drivers of disease risk, usually focussing on temperature and rainfall characteristics alone (Lo Iacono et al. 2017). Consequently, despite showing promising results in the fight against diseases such as malaria and schistosomiasis, strategies targeting the environmental stage of the pathogen to complement treatment are still poorly developed (Garchitorena et al. 2017).

Therefore, in this work, focusing on fasciolosis in the UK, we explore opportunities for environmental management as a control strategy, while considering the diversity of disease drivers across this heterogeneous domain. First, to better understand the role of landscape heterogeneity in shaping disease patterns, we simulate liver fluke risk using two different representations, one only accounting for climatic factors (the Ollerenshaw Index) and one also considering the variability of on-the-ground environmental drivers (the HELF model). Second, we assess the sensitivity of liver fluke infection risk to environmental variability by performing an ANalysis Of VAriance (ANOVA). Finally, we investigate the potential of risk avoidance management strategies by analysing where they can provide benefits in terms of risk reduction and how they compare with current treatment-based control.

4.2 Materials and methods

The data and models we use to simulate the risk of liver fluke infection across the UK are described below, together with information on how we analyse disease risk sensitivity to its underlying drivers and on how we implement treatment and environmental interventions in our mechanistic hydro-epidemiological model.

4.2.1 Data

The dataset we use includes meteorological, hydrological and Digital Elevation Model (DEM) data. Our domain consists of 935 catchments across Great Britain for which both meteorological and hydrological data are available for the recent period 2006-2015. Gridded (1km resolution) daily time series of observed rainfall and min/max temperature are obtained from CEH-CHESS (Robinson et al. 2017). For each catchment, a rainfall and a min/max temperature time series are derived from this gridded dataset by averaging grid cells that overlap with the catchment area. Streamflow data for the same 10-year period are obtained for all catchments from the National River Flow Archive (NRFA 2019). Finally, gridded DEM data for Great Britain are obtained from NextMap, with spatial resolution of 50m (Intermap Technologies 2009), and used as a basis for digital terrain analysis to derive a map of

topography for each catchment as in Coxon et al. (2019) (see DEM data and catchment masks for Great Britain in Figure 4.1, together with a land cover map (Rowland et al. 2017)).

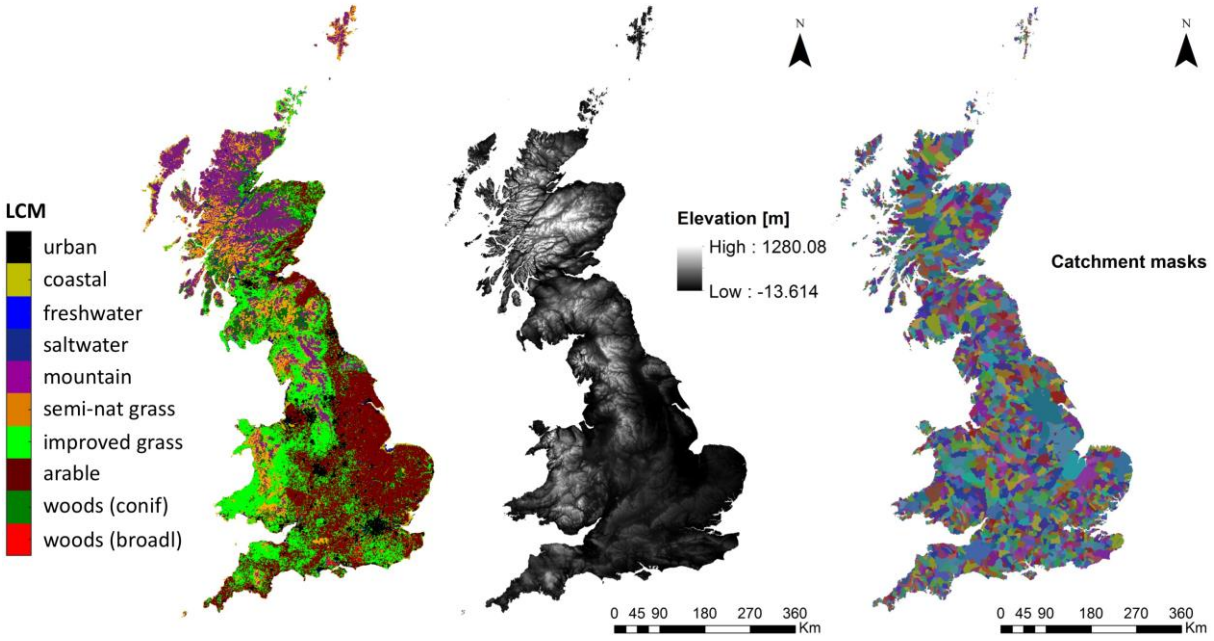

Figure 4.1 Land Cover Map (LCM), Digital Elevation Model (DEM) data, and catchment masks for Great Britain.

4.2.2 Disease risk models

We simulate disease risk using both a homogeneous and a heterogeneous representation of the landscape. We employ the widely used empirical Ollerenshaw Index model for the former (Fox et al. 2011; Ollerenshaw and Rowlands 1959) and the mechanistic Hydro-Epidemiological model for Liver Fluke (HELF) – introduced in the previous chapter – for the latter (Beltrame et al. 2018). Instead of estimating risk of infection based on weather variables only, HELF explicitly describes how the impact of rainfall on the parasite's life cycle is mediated by on-the-ground environmental characteristics through the mechanism of soil moisture, known to directly drive disease transmission, mainly due to its control on the snail host habitat (van Dijk et al. 2010; Ollerenshaw and Rowlands 1959; Pantelouris 1963). The model estimates the propensity of an area to saturate through calculation of a Topographic Index (TI), and discretises the distribution of TI values of a catchment into classes, from the highest, most prone to saturation, to the lowest, assumed least likely to saturate (see Chapter 3, Section 3.2.1). Output of HELF is the abundance of infective metacercariae on pasture, i.e. the stage of the liver fluke life cycle that, when ingested, infects grazing animals. This abundance is therefore an indicator of environmental suitability for disease transmission that we can compare to the Ollerenshaw Index.

Setting up HELF to run over the UK involves introducing a loss term in the hydrological component of the model to better represent the hydrology in case of groundwater-dominated catchments. Specifically, to account for groundwater that may not reach the river in catchments with low runoff ratio (i.e. with low ratio of runoff to rainfall), we introduce an extra parameter in the model and assume that, at each time step, storage in the saturated zone (i.e. the groundwater) not only is refilled by vertical flow from the root zone and drained by subsurface flow, but also decreases linearly with storage through this extra parameter (e.g. see Wagener et al. 2004).

With regard to model calibration, on one hand, we estimate parameters for the hydrological component of HELF by using signatures derived from streamflow observations, namely, runoff ratio and central slope of the flow duration curve, calculated as in Sawicz et al. (2011) and Yadav et al. (2007) (see Appendix Section A.2.1). On the other hand, no additional calibration of the epidemiological component of the model is performed compared to Chapter 3, since nation-wide continuous disease prevalence data is not available. Instead, we use one (mean) parameter set from the ranges obtained after application of the expert-driven rules in Chapter 3 (Section 3.4.2), assuming liver fluke life-history parameters to be relatively constant across the UK. Similar assumptions have been made in previous studies focussed on regions of similar ecology and single snail host species (e.g. see Liang et al. 2002), which are conditions consistent with our case.

4.2.3 ANOVA

ANalysis Of VAriance (ANOVA) is a mathematical technique for partitioning the observed variance in a variable of interest (the response variable) into contributions from individual drivers (the factors) and their interactions. It has been widely used for different applications including for uncertainty estimation in climate change impact studies (e.g. see Vetter et al. 2015), and for dominant control analysis, i.e. to assess the relative contribution of drivers of different processes (e.g. see Shen et al. 2013).

The response variable we focus on in our analysis is the catchment-average disease risk (for HELF this is the mean abundance of infective metacercariae, weighted based on the frequency of TI classes). Because of the known seasonality of fasciolosis in Europe, following previous liver fluke studies across the UK (e.g. Fox et al. 2011; Ollerenshaw 1966), this is averaged to obtain seasonal values. Then, the mean over 9 years of the simulation period is considered, excluding 2006 for warm-up. The factors we use for variance decomposition include climatic characteristics (i.e. temperature, potential evapotranspiration, rainfall and number of rainy days), but also topography (specifically, the mean of TI values over each catchment), for a total of 5 factors (i.e. we perform a 5-way ANOVA test, assessed at the 95% confidence level). In order to perform the test, we group each of our factors into two levels (low and high), each with a similar number of catchments and level of disease risk variability. This set

up (i.e. using disease risk variability of the 9-year means and two levels per factor) allows us to have response variable observations for all combinations of factor levels (i.e. a "fully-crossed" experiment), making it possible to estimate the contribution of two-way interactions.

In ANOVA, the total variation in the response variable, to be attributed to the different factors, is expressed though the total sum-of-squares. This is split into main effects, corresponding to individual drivers, and interaction terms, related to non-additive or non-linear effects (Vetter et al. 2015). Therefore, the contribution of each factor to disease risk variability can be calculated as the proportion of its (partial) sum-of-squares and the total sum-of-squares (multiplied by 100 to obtain a percent contribution). The higher the contribution, the more the factor plays a key role in driving disease risk. Given our ANOVA experiment is unbalanced, i.e. we have unequal number of observations of the combinations of factor levels, the sum-of-squares will depend on the order in which the sources of variation are considered. Therefore, to make sure our resulting raking of drivers is independent from such order, we perform ANOVA for each possible order of drivers and then calculate and analyse average contributions of factors.

We carry out the analysis at the regional scale to better capture the spatial distribution of dominant disease risk drivers. Specifically, we divide our domain into nine regions, as much as possible resembling the standard areas for which the National Animal Disease Information System (NADIS) currently provides forecasts of liver fluke risk based on the Ollerenshaw Index (NADIS 2019). These, in turn, are based on the districts used by the MetOffice when generating climatologies for the UK (MetOffice 2017). The regions are: South East of England (SE), East Anglia (EAng), South West of England and West Wales (SW), the rest of Wales and the Midlands (Mid), North West and North East of England (NW and NE), and, finally, West, East and North of Scotland (WScot, EScot, NScot).

4.2.4 Disease control strategies

There are not many published data on how farmers in the UK control infection with fasciolosis. Though, a recent survey throughout Great Britain and Ireland shows that almost 70% of farmers routinely treat their animals against liver fluke, Triclabendazole being the most common drug, which can reach above 90% efficacy, preventing egg shedding on pasture for up to 12 weeks (Morgan et al. 2012). However, climate-driven changes in disease patterns and the rapid emergence of drug resistance indicate that current treatment-based control is costly and might become unsustainable in the long run, while new approaches, such as risk avoidance management strategies, have often been advocated (e.g. temporarily limiting access of livestock to potential snail habitats at high-risk times) (Beesley et al. 2018; Fairweather 2011; Gordon et al. 2012; Mitchell 2002; Morgan et al. 2013; Skuce and Zadoks 2013; SRUC 2016). Therefore, using HELF, we implement disease control strategies as follows:

1. We investigate the effect of current drug-based control practice on risk of infection. Based on information in the literature and available guidelines (Fairweather and Boray 1999; Morgan et al. 2012), we assume farmers treat animals twice per year, once in January and a second time in April, with a product that has 90% efficacy and suppresses egg shedding onto pasture for 12 weeks (i.e. using Triclabendazole). This is meant to reflect the top reduction in disease risk that can currently be achieved in the field using treatment (also see Appendix Section A.2.2).
2. We simulate the effect of fencing off high-risk areas to prevent animals from grazing during high-risk periods, and investigate where in the UK this may provide benefits. Traditionally, the period at highest risk of infection in the UK is summer, when temperatures are generally more favourable for the parasite life cycle to progress. The areas at highest risk are those most prone to saturation, i.e. those particularly flat, at the bottom of valleys. Therefore, we implement this intervention by sequentially removing summer infective metacercariae from TI classes (i.e. setting them to zero), starting from that with the highest value, which will saturate first, until the whole catchment is virtually fenced off. At each step, we evaluate the benefit of using this strategy by calculating the achieved reduction in disease risk compared to the case of no intervention. We do this for each catchment and then evaluate results at the regional level using the 9 administrative areas defined above.
3. Finally, for each catchment, by using the summer risk level achieved by treating animals in winter/spring as a baseline, we estimate the percentage of area we would have to fence off if we wanted to obtain the same level or lower through environmental management.

4.3 Results

4.3.1 Simulated UK-wide disease risk

Despite the differences between the Ollerenshaw Index and HELF, with only the latter mechanistically accounting for soil moisture dynamics driving the parasite life cycle (see Chapter 3), some similarities can be found when comparing disease risk simulated using the two models across the UK (Figure 4.2). First, summer risk values are significantly higher than winter values with both representations, across all regions. Second, in winter, the only regions where weather conditions may allow for some development of the life cycle are those in the south of the country, where temperatures are milder. Third, in summer, if we look at median risk levels, risk is highest on the west coast of England and Wales (especially SW and NW, where rainfall is abundant even during the warmer months), lower in the South East of the country, which in summer may become too warm and dry for parasite survival and development, and even lower in Scotland, where, even during milder summer months, temperatures may still be unfavourable (also see maps in Figure 4.3).

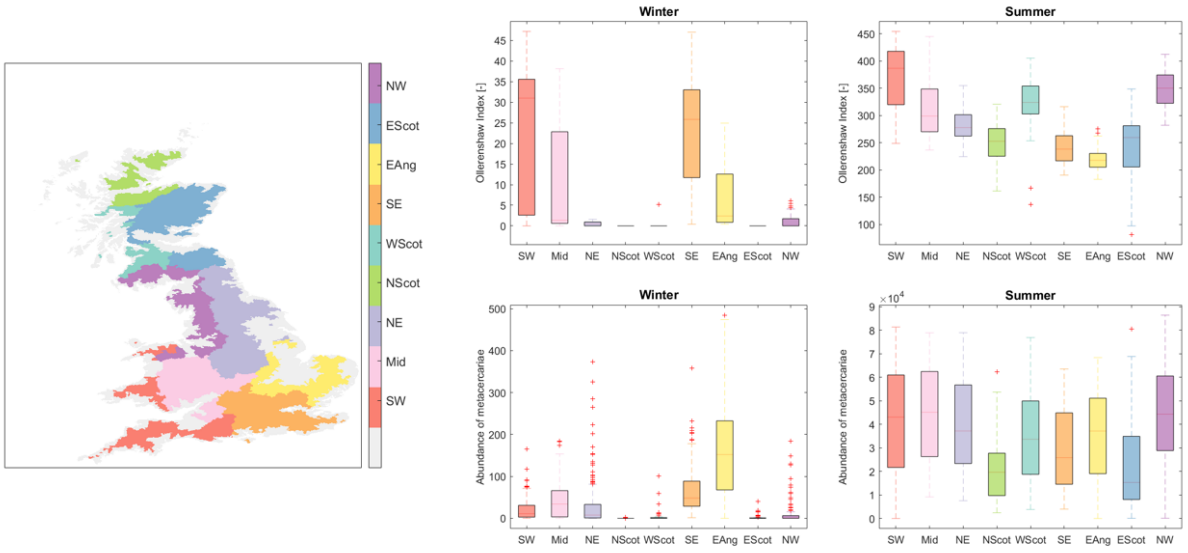

Figure 4.2 Difference in disease risk simulated with the Ollerenshaw Index (top) and HELF (bottom) for winter and summer, across 9 UK regions (in the map, ungauged catchments -i.e. with no hydrological data over the simulation period- are masked in grey). Boxplots represent variability in disease risk between catchments within regions, on average over 2007-2015.

These patterns are in agreement with current understanding and data. For example, one of the largest UK studies on liver fluke prevalence found the highest infection levels in wetter western areas of the country, which historically have been providing ideal climatic conditions for disease transmission (McCann et al. 2010a). Moreover, these results suggest that climatic factors are important controls on risk of infection with both representations.

However, the two representations of disease risk differ notably in that summer values simulated using HELF show significantly more variability compared to what we obtain using the Ollerenshaw Index, especially in SW and NW. In fact, even if, in summer, risk values are generally high, we see there still can be areas associated with low abundance of infective metacercariae. This difference between the two representations can be explained as, on one hand, with the Ollerenshaw Index, if temperatures are favourable, two areas with similar rainfall amounts will be associated with similar risk levels. On the other hand, this may not be true using HELF, depending on landscape heterogeneities (namely, topography and antecedent moisture conditions of the soil), as well as dynamic weather effects on development within the parasite life cycle. This also is in agreement with existing datasets, which show significant differences in disease prevalence between neighbouring areas within homogeneous climate regions, already suggesting that other factors may affect the prevalence of liver fluke in addition to climate (McCann et al. 2010a).

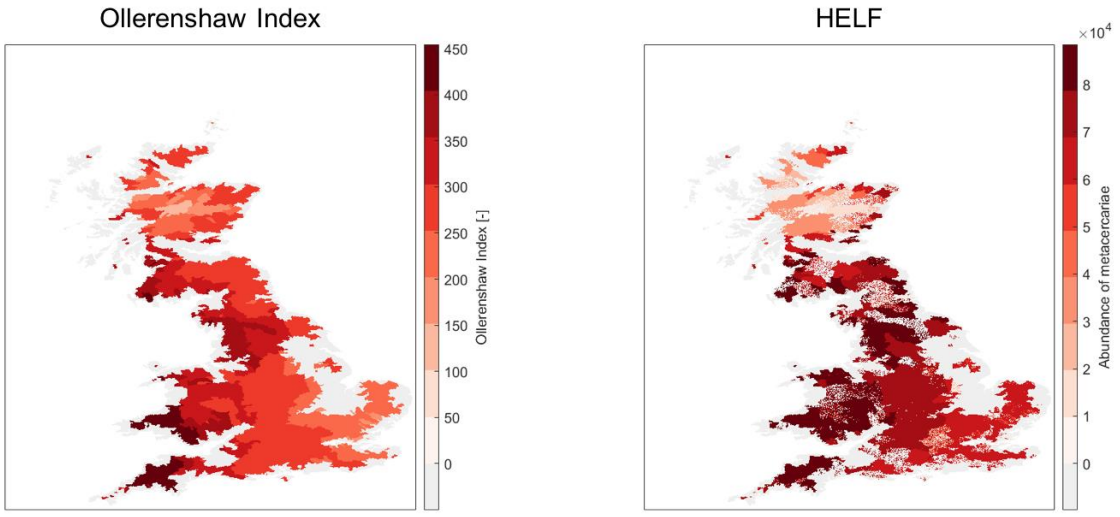

Figure 4.3 Example of summer risk maps obtained using the Ollerenshaw Index (left) and HELF (right), for 935 gauged UK catchments (ungauged catchments are masked in grey).

4.3.2 Disease risk sensitivity to environmental drivers

Performing ANOVA at the regional level enables us to investigate what drives disease risk across areas and better understand reasons for the greater variability we see in summer when using HELF. Figure 4.4, which -for each region- presents the average percent contribution of the top three drivers to summer disease risk variability, calculated with the Ollerenshaw Index and HELF, shows different sensitivities to environmental drivers between the two models. In particular, disease risk simulated with the Ollerenshaw Index is mainly limited by rainfall characteristics (rainfall, R, and rainy days, RD, in blue) in the drier and warmer south-east of the UK, and by temperature-related variables (temperature, T, and potential evapotranspiration, P, in red) over the wetter and colder North West of England and Scotland. Notable is the low share of the interaction terms (which in the figure are combined into one single term, INT, in yellow) to the total variance, when simulating disease risk using this model, with INT figuring among the top three contributing drivers only for NW and Scotland.

On the other hand, variance decomposition identifies interactions between factors to play a significant role across all regions when using HELF (with INT dominant driver in 5 out of 9 areas), suggesting that, without considering interactions, the importance of individual drivers may be overestimated. While in flat areas in the south east of the country (SE and EAng), it is the interaction between climatic drivers that explains most of disease risk variability, in the south west of the UK and north of England (e.g. SW and NW) disease risk shows higher sensitivity to interactions between climatic characteristics and topography (see Table A.2 in Appendix Section A.2.3 for sum-of-squares and p-values of individual

factors including two-way interaction terms). Notably, in the three Scottish regions, while temperature is still the dominant driver of risk of infection as with the Ollerenshaw Index model, topography (TOPO, in green) individually emerges as important, potentially because it creates differences in disease risk even in areas close to each other, highlighting opportunities for environmental management to control disease transmission.

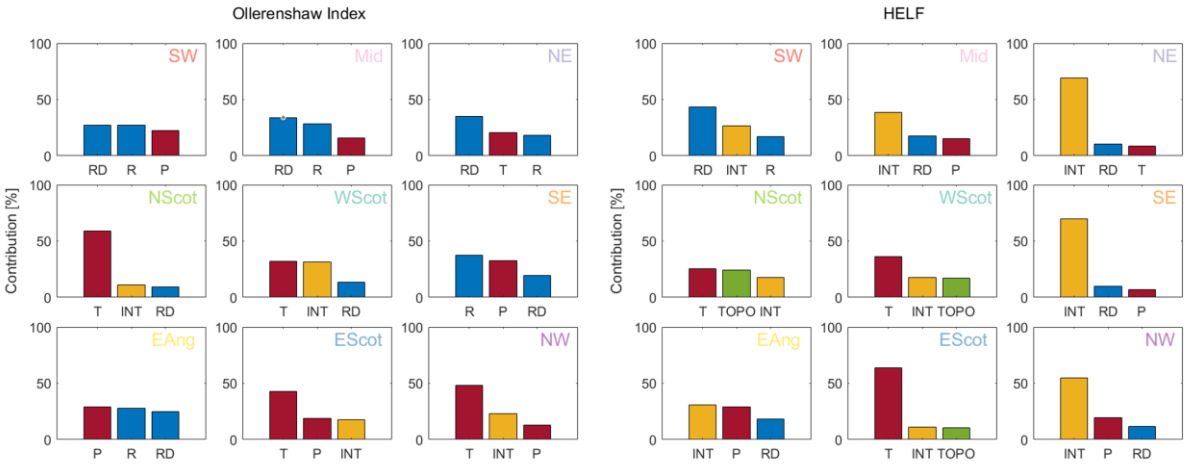

Figure 4.4 Average percent contribution of the top three environmental drivers to summer disease risk variability simulated using the Ollerenshaw Index (left) and HELF (right), per region. Rainfall-related characteristics (RD=number of rainy days and R=rainfall) are coloured in blue; temperature-related variables (P=potential evapotranspiration and T=temperature) are coloured in red; topography (TOPO) is in green; and the interaction term (INT), which combines here all two-way interactions between factors, is in yellow.

4.3.3 Effectiveness of disease control strategies

Effect of current treatment-based control

Figure 4.5 shows the effect of treating animals with antiparasitic drugs on risk of infection modelled using HELF, in space and time. On average, our results show that drug treatment over winter/spring achieves a reduction in disease risk over summer months of 65%. For most catchments, risk is reduced by more than 70%. However, due to differences in climatic-environmental conditions and their seasonality, the reduction in egg output onto pasture, obtained with treatment, can have different effects on the abundance of infective metacercariae across our domain. Specifically, the histogram of summer risk reductions shows that treatment-driven reductions in risk range between 45% and 84.9% across catchments. On the other hand, if we look at the impact of treatment on disease risk in time (on average across catchments and years), we see that the rise in metacercarial abundance on pasture is delayed by approximately one month, compared to the option of not treating. Moreover, in addition to being significantly reduced, the peak of disease risk is also shifted to later in the year (approximately from

August-September to October) as a result of drug administration. These effects of our modelled treatment-based strategy seem plausible, in fact reinforcement of the treatment in January with the spring dose is expected to reduce pasture contamination with eggs when intermediate snail hosts are most primed for summer infections and production of metacercariae in late summer / autumn.

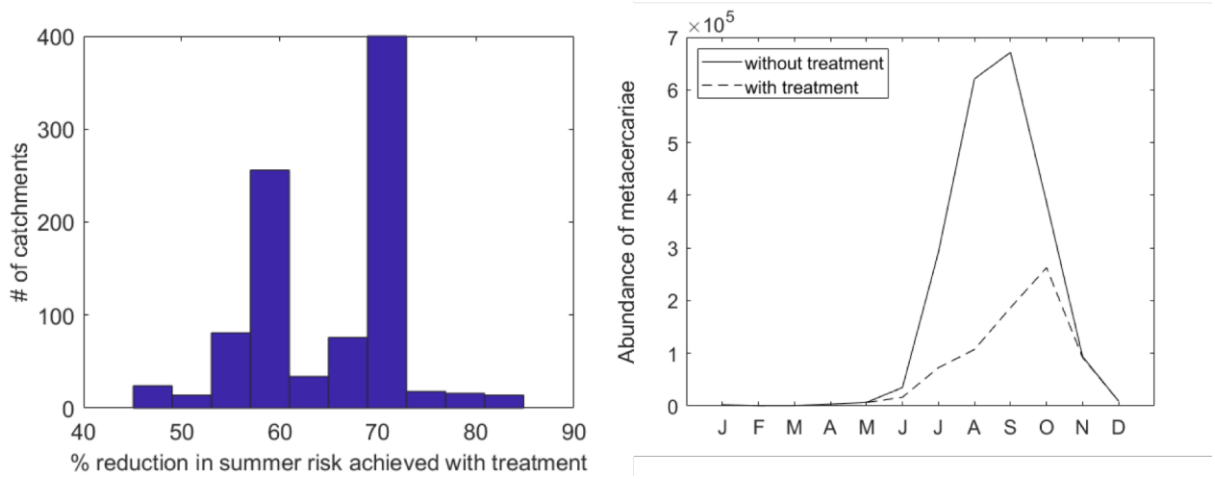

Figure 4.5 Effect of treating livestock over winter/spring with antiparasitic drugs on: (left) summer disease risk across all 935 catchments; (right) the monthly behaviour of metacercarial abundance on pasture, on average across catchments and years.

Potential benefits of temporary fencing of high-risk areas

Simulating disease risk using HELF also allows us to understand how different sensitivities to environmental drivers may translate into different effectiveness of environmental management across areas (Figure 4.6). For all 9 regions considered, represented one per box in Figure 4.6, percentages of catchment area on the x–axes are ordered by *TI* class, from the most to the least prone to saturation. From this figure we see, on one hand, that the impact of fencing off the highest *TI* classes, which represent on average 5-10% of the catchment area, is similar across regions. These are presumably areas of a catchment that are saturated for much of the year (e.g. see Güntner et al. 1999, 2004). On the other hand, the risk reductions achieved by fencing off larger portions of catchment area differ between regions. For example, to reduce risk of infection by 65%, as we currently obtain with treatment on average (as found above), we can see that grazing should be avoided on large fractions of catchment area in East Anglia (approximately 56%), but on smaller percentages in Wales/Midlands (on average about 38% for Mid), and even smaller percentages in Scotland (e.g. approximately 18% for NScot). Moreover, in Figure 4.6, the 9 years of our simulation period are colour-coded from that with the driest summer (in red) to that with the wettest summer (in blue), for each region. In terms of risk reduction achieved with environmental management, this seems to make a difference in some areas (such as SE and NScot) more than others, but not consistently between drier and wetter years. For example,

percentages of land to be fenced off seem to generally increase in Mid, NE, NScot and EScot, when moving from the year with the driest summer to that with the wettest one. However, this is not the case e.g. for SE and does not seem to hold for every year, suggesting that other factors also play a role, such as rainfall and temperature distributions over preceding months, rather than just during the season under consideration. In summary, these results show how opportunities for environmental management differ with place and weather in a particular year or season. Specifically, they indicate that fencing off high-risk areas may provide benefits especially in regions where topography plays a larger role on disease transmission, which is where snail habitats will be more localised, particularly in relatively dry years. This is in line with recommendations of recent guidelines for liver fluke control (e.g. see SRUC 2016).

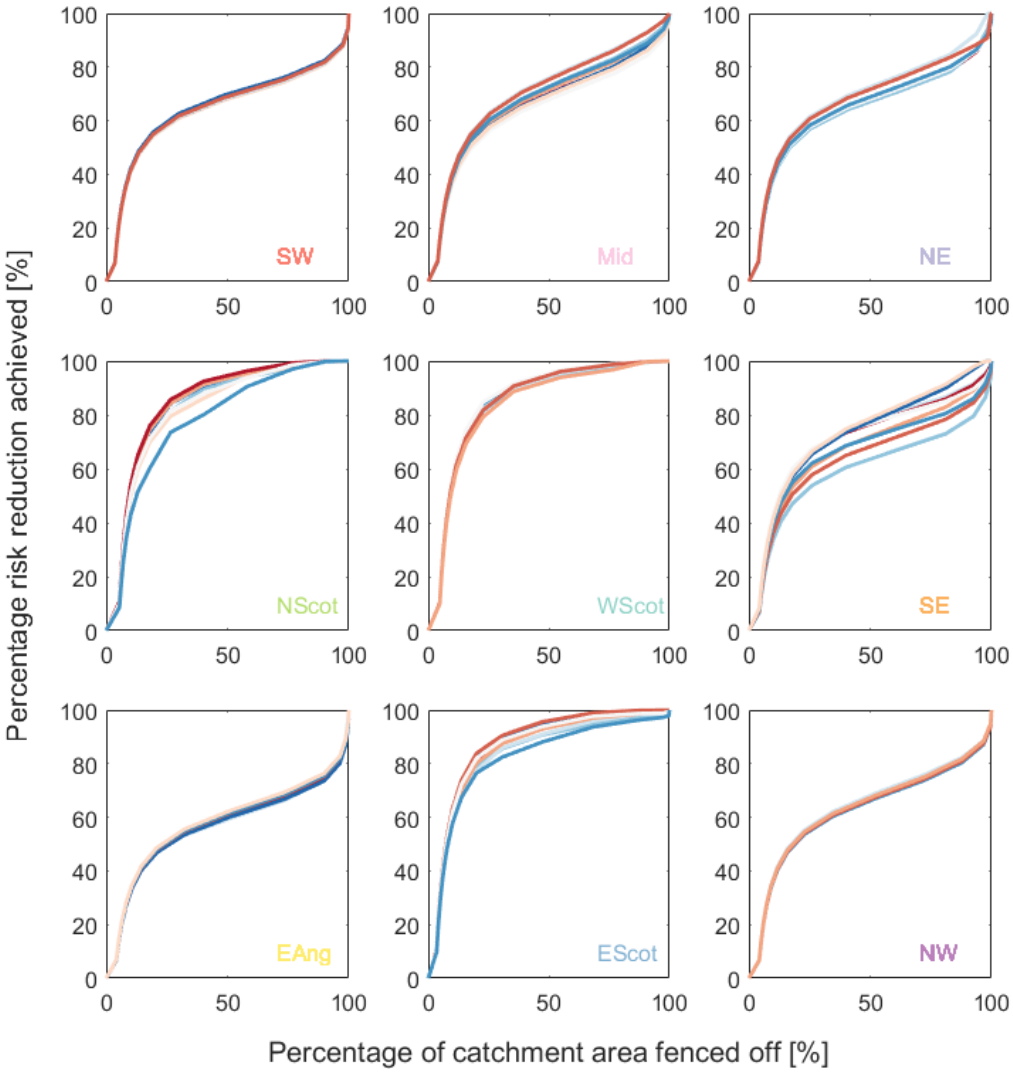

Figure 4.6 Percentage reduction achieved in summer risk of infection by fencing off portions of catchment area, starting from the most prone to saturation (mean across catchments within each region, one line for each of the 9 years in the simulation period, color-coded from that with the driest summer in red to that with the wettest summer in blue).

Comparison of environmental management vs. current drug-based practice

Figure 4.7 shows, for each of our 9 regions, the percentage of catchment area we would have to fence off – on average across catchments within the region – if we wanted to reduce summer risk by at least the same percentage achieved over the same region using treatment, comparing a relatively dry and a relatively wet year within our simulation period (i.e. 2013 vs. 2014). The map for 2013 shows that the highest percentages that require fencing off are found in the south east (specifically, East Anglia, where 42.1% of land has to be avoided, on average), despite areas in this region being the driest and warmest of the country. In comparison, portions of land to be avoided in the wetter south west of England and west Wales (SW) are more than 15% lower, confirming that temporary fencing may be particularly convenient where topographic variations are larger, rather than where the landscape is mostly flat. Overall, the lowest percentages are found in Scotland (23.8%), where topography varies the most (see Figure 4.1) and were risk of infection is generally lower due to less favourable temperatures.

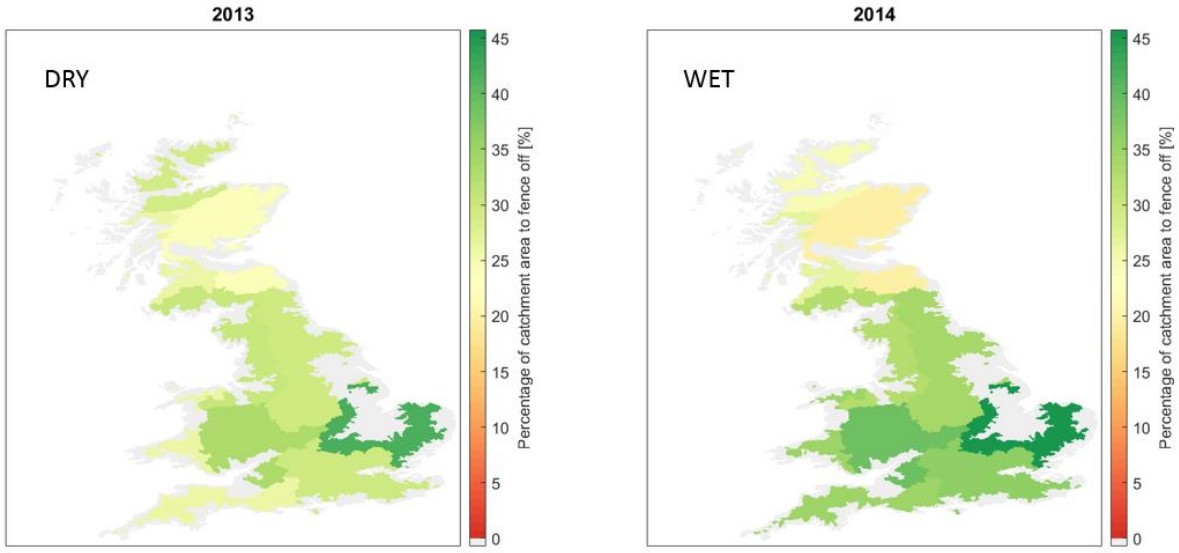

Figure 4.7 Percentage of catchment area that would need fencing off to reduce summer risk of infection by at least the same percentage achieved using treatment (on average across catchments within each region). Comparison of 2013 and 2014, which represent a relatively dry and a relatively wet year within our simulation period, respectively.

Comparison of wet 2014 with dry 2013 shows similar patterns across administrative regions but different values. In North and East Scotland, where summer temperatures decrease moving from the former to the latter year in this specific example, percentages of land to fence off are lower in 2014. In fact, a colder summer will result in less favourable conditions for development of the parasite life cycle in these areas where disease risk is significantly limited by temperature (as seen in section 4.3.2). In all other regions, the portions of land to be fenced off – to be at least as effective as treatment in each area– are

higher in 2014 (by 5.7% on average). This means that, as expected, even on the west coast of the country including in the North, where snail habitats will be more localised than on flat areas in the east, temporary fencing becomes less effective in case of particularly wet years.

4.4 Discussion

This study, for the first time, considers environmental drivers of fasciolosis, beyond just climatic characteristics, across a large heterogeneous domain and in a mechanistic (rather than empirical) manner. Specifically, instead of only focusing on temperature and rainfall-related controls, as in previous large-scale liver fluke studies (e.g. Caminade et al. 2015; Fox et al. 2011; Ollerenshaw 1966), we also account for soil moisture patterns, which vary with heterogeneous topography, and directly control habitat suitability for liver fluke intermediate host and free-living stages (van Dijk et al. 2010; Ollerenshaw and Rowlands 1959; Pantelouris 1963). This represents the first step for then investigating opportunities for environmental management as a disease control strategy across the UK. In fact, on-the-ground environmental characteristics may be modifiable or "reasonably amenable to management or change given current knowledge and resources" towards reducing risk of infection (Prüss-Ustün et al. 2016).

Our analysis of disease risk sensitivity to environmental factors shows that, while climatic drivers remain key across the country, topography emerges as important in specific areas. While environmental effects on epidemiological processes are increasingly acknowledged, the role of specific factors in modulating disease transmission is still rarely characterized quantitatively (Lo Iacono et al. 2017; Liang et al. 2007; Morgan et al. 2013). Our simulations of liver fluke risk over UK catchments suggest that climatic characteristics are important with both homogeneous and heterogeneous representations of the landscape, as well as with empirical and mechanistic modelling approaches (Figure 4.3). However, if we tease apart the effect of factors regionally, we find that accounting for environmental heterogeneity, using HELF, shows a larger role of interactions between drivers across regions and a significant contribution of topography in higher relief areas of the country (Figure 4.4 and Figure 4.1 for the UK DEM map). First, the fact that drivers other than climate may come into play when moving towards more regional levels, confirms information in previous studies on fasciolosis, as well as findings of works on other environment-driven diseases. Crucially, Fox et al. (2011) warn about using the Ollerenshaw Index at regional levels as, at these scales, many non-climatic factors become relevant in driving liver fluke survival and transmission. Similarly, Liang et al. (2007) find that, within a climatologically homogeneous region in China, land use and characteristics of the irrigation system are the main drivers of human infection with schistosomiasis. Second, the fact that landscape heterogeneity may alter risk of liver fluke infection, and its sensitivity to climate variability, suggests that future UK

disease control strategies will need to explicitly account for it, and that current simulations of disease risk based on models with no representation of landscape heterogeneities (such as those used by NADIS) may have limited utility over regions with more pronounced topographic variability going forwards.

The role of topography in controlling soil moisture patterns, and therefore snail host habitats and subsequent liver fluke transmission, in north-western regions of the UK, indicates opportunities for environmental management to reduce risk of infection, with important implications for disease control. More frequent reporting of treatment failure for an ever-increasing range of infections caused by parasites like liver fluke, but also viruses and bacteria, globally, demonstrates the urgent need to use available drugs in a more targeted way to help slow down the development of resistance and preserve their efficacy for when they are most needed (Garchitorena et al. 2017; Kamaludeen et al. 2019; Morgan et al. 2012, 2013; Webster et al. 2014; WHO 2019). With regard to fasciolosis in the UK, temporary fencing off of high-risk areas to avoid grazing over high-risk periods, which we implement here, has been often called for as an aid to current treatment-based control (e.g. see Mitchell 2002; Morgan et al. 2012, 2013). The fact that fencing off high-risk areas results to provide greatest benefits in terms of risk reduction in the north-west of the country (Figure 4.6) is of interest as these areas: *(i)* are characterised by extensive grazing (see land cover map in Figure 4.1); *(ii)* are those where treatment is most common (Morgan et al. 2012) and Triclabendazole resistance is prevalent (Kamaludeen et al. 2019); and *(iii)* are either those associated with the highest liver fluke prevalence historically (e.g. see McCann et al. 2010a and Figures 4.2 and 4.3), or where liver fluke is expanding rapidly with warmer climates (as rainfall is not the dominant limiting factor) (Kenyon et al. 2009). Therefore, they are areas where treatment is particularly expected to become unsustainable in the future.

The percentages of land to fence off, to achieve at least the same risk reduction as that obtained with treatment, are relatively high, ranging from approximately 20% of catchment area up to almost 50% on the flattest regions, on average (Figure 4.7). This may make environmental management seem difficult to implement in practice. However, first, these values depend on the treatment option implemented, and our current treatment assumption aims to reflect the maximum reduction in risk obtainable with available drugs (Figure 4.5). In reality, farmers may treat at different times, with different (and often a combination of) products, that have different efficacy and impact on infections and egg shedding based on time of year, fluke age, drug resistance, etcetera (Morgan et al. 2012). Therefore, different treatment strategies should be tested using our same approach and compared with environmental management according to specific interests (e.g. see Meek and Morris 1981). Second, the percentages we calculate here represent the proportion of land to fence off if we wanted to match or outperform treatment by using environmental management only, while -in reality- temporary fencing would most likely be implemented in combination with (targeted) treatment rather than individually, still contributing to

reduce reliance on drugs and delaying development of resistance. Third, our study investigates the importance of landscape heterogeneity on risk of infection through the analysis of topographic variability to start with, based on current knowledge that topography is the strongest landscape control on habitat distribution for both liver fluke intermediate snail host and free-living stages (van Dijk et al. 2010; Ollerenshaw and Rowlands 1959; Pantelouris 1963). However, there are other spatially heterogeneous on-the-ground environmental properties, that may have an influence on liver fluke risk in the UK and may be possible to manipulate to reduce disease transmission, which we are currently neglecting, e.g. soil type and pH or land cover/pasture type (Bennema et al. 2011; Charlier et al. 2011; McCann et al. 2010b). This means the catchment fractions to fence off that we obtain represent – once again – upper limits, and suggests that they could be smaller if soil pH and other environmental variables further limited habitat suitability.

Finally, environmental management could also take other forms than fencing off high-risk areas. For example, permanent eradication of snail habitats through drainage of pastures, which is currently considered prohibitively expensive, may become a competitive option for risk reduction in the long-run, faced by changing climatic conditions, even if in the UK is increasingly discouraged for environmental reasons (Fairweather 2011; Howell et al. 2015; Mitchell 2002; SAC 2003; SRUC 2016). Most importantly, several factors underlie farmers' decisions about which parasite control programmes to put into practice, as maximal and sustainable disease control may be mutually exclusive aims, and multiple other trade-offs may be involved, e.g. the need to reduce liver fluke transmission while preserving wetlands (see Pritchard et al. 2005). Ultimately, the optimal strategy will be farm-specific and depend on agricultural policy and on the long-term costs and benefits of less intensive disease control strategies (Morgan et al. 2013; van der Voort et al. 2013).

4.5 Conclusions

We investigated the role of heterogeneous environmental drivers on risk of infection with liver fluke across 935 UK catchments using a new mechanistic hydro-epidemiological model. Crucially, in contrast to existing studies, our analysis included not only climatic factors but also on-the-ground environmental characteristics, which may be possible to modify locally to reduce and/or mitigate disease burdens. We showed that, while rainfall and temperature-related characteristics are key determinants of risk across the country, topographic variability plays a role through interactions with these and emerges as important in higher relief areas of the UK. This *(i)* suggests that future simulation of disease risk will need to explicitly account for it to be able to provide decision support over areas with larger topographic variability, and *(ii)* highlights opportunities for environmental management to reduce disease transmission. Specifically, having recognized the importance of landscape heterogeneity in driving risk

of infection, we demonstrated how, in these areas, tackling disease transmission through isolating specific areas at high risk over periods of high metecarcarial abundance can be particularly effective, especially in relatively dry years. This will be paramount to maintain or regain control over fasciolosis in the UK, as current treatment-based control becomes costly and unsustainable. The same approach as that adopted here can be valuable to assess potential benefits of using environmental management – as an alternative or complementary strategy to treatment – in the fight against other environmentally-transmitted diseases, as global change increasingly alters their seasonality and spread, and drug resistance increases rapidly.

This page was intentionally left blank

Chapter 5. Future risk of liver fluke infection across the UK under climate change

5.1 Introduction

The WHO estimates that one-quarter of the global disease burden, mostly felt in less developed countries, is linked to environmental change associated with human activity (Prüss-Ustün et al. 2016; Whitmee et al. 2015). In fact, a multitude of anthropogenic stressors are already having measurable effects on disease transmission processes, globally (Cable et al. 2017; Hotez 2016; Parham et al. 2015). In response to increasing temperatures (IPCC 2014), several species have started invading higher elevations or latitudes, towards cooler climates (Altizer et al. 2013; Fischlin et al. 2007; Harvell et al. 2002; WHO 2003), with implications for the distribution of many vector-borne diseases. For example, a shift in the distribution of malaria towards higher altitudes has been documented in areas of South America, Africa and Oceania (Park et al. 2016; Siraj et al. 2014). Observed increases in the frequency of floods and droughts, linked to more frequent extreme weather events as well as to direct human interventions (Coumou and Rahmstorf 2012; Dai 2013; Hirabayashi et al. 2013; Van Loon et al. 2016; Milly et al. 2002; Sheffield and Wood 2008), has resulted in large-scale contamination with waterborne infections and affected disease transmission patterns through habitat alteration (Cann et al. 2013; Harvell et al. 2002; WHO 2003). For example, a resurgence of cholera occurred in Haiti in 2011, following unusually intense rainfall events (Righetto et al. 2013), while drought conditions have been documented to trigger outbreaks of horse sickness in Africa (Baylis et al. 1999). Habitat change, with its implications for epidemiological processes, is also on the rise due to direct human activities (Allan et al. 2003; Altizer et al. 2013; Cable et al. 2017; Fischlin et al. 2007; Keesing et al. 2010; LoGiudice et al. 2003; Patz et al. 2008). For example, changes in the prevalence of schistosomiasis and foodborne trematodiases have been observed in Africa and Asia, due to the expansion of snail intermediate host habitats following the construction of dams and the implementation of irrigation schemes to meet demands for water/food/energy from a growing population (Hotez 2016; Steinmann et al. 2006). On the other hand, in Europe, many regions have been experiencing an increase in snail-borne parasites following the restoration of wetlands (in combination with grazing of marshy areas by new potential reservoir hosts and a milder climate), with implications for animal health and productivity of the livestock industry (van Dijk et al. 2008; Pritchard et al. 2005). Finally, land use change is also documented and predicted to

have direct effects on human and animal health. Over the last 50 years, unprecedented changes in land use, driven by demands for higher yields (Balmford et al. 2005; FAO 2015), have resulted in a growing number of large-scale farming practices relying on concentrating and containing animals, which increases exposure to parasites and facilitates disease transmission (Cable et al. 2017). Going forwards, higher vulnerability to diseases like dengue (most prevalent in high human density cities due to the presence of man-made habitats for the transmitting mosquito) is expected (Cable et al. 2017), as 68% of the world population is projected to live in urban areas by 2050 (United Nations 2014).

Implications of future climatic-environmental changes for disease transmission processes will be complex, especially for vector- and snail-borne diseases. Climate change is not homogeneous in time nor space and could make previously unaffected regions suitable for transmission and vice versa, potentially leading to the emergence or re-emergence of threatening diseases (e.g. Mas-Coma et al. 2009). Moreover, climate projections are subject to large uncertainties due to the unknown state of the climate system and the simplified model representation of complex physical mechanisms (e.g. see Dalelane et al. 2018; Meinshausen et al. 2011). Furthermore, while climate change processes occur on timescales of years to centuries, knowledge of ecological and physiological processes provides evidence that shorter-duration episodes of extreme weather, and changes in the frequency of conditions exceeding species-specific temperature/rainfall thresholds, are often responsible for the major impacts on health, other than long-term changes in climate averages (Easterling et al. 2000; Parham et al. 2015). Finally, the fact that parasites often need to undergo several developmental stages to complete their life cycle, each with its own space-time scale, makes predictions especially complicated for many vector- or snail-borne diseases (as opposed to infections transmitted directly from an environmental media to the host). In fact, multiple stressors might act simultaneously on multiple life-history traits and their combined impacts may be synergistic, but also antagonistic, potentially leaving the total rate of parasite transmission unaltered (Cable et al. 2017; van Dijk et al. 2010; Molnar et al. 2013; Rohr et al. 2011).

To support sustainable disease control in the long run, we need regional assessments of vulnerability to health risks, based on the use of models that mechanistically account for complexities and multi-scale interactions. Identifying the most vulnerable regions to climate change represents the first step to assist in targeting monitoring efforts and disease management (e.g. Patz 2005). This needs to be based on the use of mechanistic models, which can explicitly simulate the impact of climatic-environmental-hydrological processes on disease risk, coupling their time-space scales in biologically relevant ways and without relying on the assumption of stationarity. Specifically:

- Consideration of the link between climate/environment and each stage of the pathogen transmission pathway is needed to estimate the net effect of changes on disease risk (Cable et al. 2017);

- While incorporating a long-term timescale, simulation of climate change impacts must still be performed at ecologically-relevant (space-time) resolutions, so that changes in disease risk can be better linked to changes in specific drivers, beyond alterations in mean seasonal climate (Easterling et al. 2000; Lo Iacono et al. 2017; Parham et al. 2015);
- Mechanisms need to be represented explicitly, as past (empirically-derived) relationships may not hold anymore going forwards (Beltrame et al. 2018; Lloyd-Smith et al. 2009; Mellor et al., 2016; Milly et al. 2008; Wagener et al. 2010; Wu et al. 2016).

Finally, looking at the future success and sustainability of drug administration and other interventions, implications of estimated changes in epidemiological processes for disease control need to be assessed explicitly, and ensemble modelling approaches should be used to estimate projection uncertainties to support robust decision-making at various organizational levels (e.g. see Cable et al. 2017; Parham et al. 2015).

However, questions such as on which regions climate change will have the greatest impact in terms of disease transmission, have only begun to be addressed, mainly by extrapolating past relationships into wider regions and future climates (Lo Iacono et al. 2017; Parham et al. 2015; Rohr et al. 2011; Wu et al. 2016). The majority of existing models used for assessing future potential climate change effects on health are based on statistical relationships found between historic climate and disease prevalence data (e.g. Wu et al. 2016), and large-scale studies are often limited to one or few ensemble members (e.g. see Fox et al. 2011; Stensgaard et al. 2016). Moreover, most current works relate average climate to mean disease trends, with little analysis of the role of shorter term species-specific climatic characteristics on infection levels (Easterling et al. 2000; Lo Iacono et al. 2017). Finally, the implications of climate change for the long-term efficacy of current control strategies are rarely addressed and not well understood (Cable et al. 2017).

In the UK, changes in climate have already been observed with significant implications for the transmission of fasciolosis, a widespread parasitic zoonosis, raising concerns about potential future impacts on animal health and productivity of the livestock industry.

- A shift towards warmer wetter winters and hotter drier summers has been documented in recent decades, with evidence that some of these changes are at least partly linked to human influences (IPCC 2014; Kendon et al. 2014). In turn, changes in the time-space distribution and prevalence of fasciolosis (or liver fluke disease), attributed to altered rainfall and temperature patterns, have increasingly been reported (Charlier et al. 2014; Kenyon et al. 2009; McCann et al., 2010a; Pritchard et al. 2005; Relf et al. 2011).
- Projected mean climatic changes suggest that the trend towards warmer wetter winters and hotter drier summers will continue throughout the century (IPCC 2014; Murphy et al. 2018).

According to the IPCC report (2014), it is virtually certain that there will be fewer cold and more frequent hot temperature extremes (with heat waves occurring more often and lasting longer) over most areas, as global mean temperature rises. Moreover, increases in the precipitation intensity on wet days are expected in winter across the UK, as well as decreases in summer across central and southern areas of the country (Kendon et al. 2014; Murphy et al. 2018). Finally, with regard to changes in terms of soil moisture, recent research anticipates an intensification of droughts in Europe due to anthropogenic warming, and shows a decrease in soil water content in all seasons for the UK (Samaniego et al. 2018). Given the climate sensitivity of liver fluke, these changes are expected to have major implications for the transmission of fasciolosis across the country in the future. For example, northern areas (where disease risk is currently limited by temperature) may become suitable with a warmer climate, while south-eastern regions (where disease risk is limited by rainfall) may become unsuitable as periods of drought become more frequent. However, as development of both the free-living stages of liver fluke and its intermediate snail host depends (in different ways) on both temperature and soil moisture conditions, projecting net outcomes is not straightforward. How climate change may affect future liver fluke risk has been previously addressed at the national and European scale (Caminade et al. 2015; Fox et al. 2011). However, this has been achieved in both cases using the empirical Ollerenshaw Index model (Ollerenshaw and Rowlands 1959), and the implications of epidemiological changes for disease control have not yet been assessed.

Therefore, in this study, to overcome limitations of previous works, we use bias-corrected climate projection data to investigate potential future impacts on risk of infection with fasciolosis across the UK, using the recently developed mechanistic Hydro-Epidemiological model for Liver Fluke (HELF) (Beltrame et al. 2018). Specifically:

1. We assess late twenty-first century changes in mean climate and liver fluke-relevant climatic characteristics in comparison with historical conditions, based on the most recent high-resolution regional climate projections made available by the UK MetOffice. We consider twelve different realisations to estimate projection uncertainties.
2. We force HELF with these projections to determine potential impacts of such changes on future liver fluke risk, analysing changes in disease seasonality, in addition to alterations in terms of magnitude, and estimating how these may vary across the country in relation to varying climatic drivers.
3. We investigate implications for disease control regionally, by assessing projected changes in the effectiveness of current treatment-based strategies.

5.2 Materials and methods

This section presents the climate projections we use to drive HELF and assess potential future disease risk, as well as the correction methods we employ to adjust for temperature and rainfall biases. Some summary information about the domain of this study and the metrics of disease risk we calculate is also provided below.

5.2.1 Climate data

Climate data are obtained from the UKCP18 dataset (Lowe et al. 2018; Murphy et al. 2018). This is a new set of climate projections obtained from the latest generation of MetOffice Global and Regional Climate Models (GCM and RCM).

Among UKCP18 products available, we use regional projections. These are an ensemble of twelve high-resolution (12km) future climates for the UK, downscaled from global projections using the Hadley Centre most recent RCM (HadREM-GARA11M). More specifically, they are derived by forcing this RCM with the outputs from twelve variants of the latest MetOffice GCM (HadGEM3-GC3.05), produced by generating a perturbed parameter ensemble to account for process uncertainties, while providing a wide range of potential climate changes for the 21st century. Reasons for choosing this product for our analysis include the enhanced spatial detail, suitable in connection with our highly resolved hydrologic model, and the improved simulation of weather extremes at daily timescales. Global (rather than regional) projections are run at much coarser resolution. Moreover, the fact they provide data with full spatial and temporal coherence is important to investigate climate-driven changes in disease risk at multiple locations across the UK simultaneously.

These data are available for the period 1980-2080 at daily time steps and under one emission scenario (Representative Concentration Pathway RCP8.5). 8.5 is the most extreme RCP among those introduced within the Fifth IPCC Assessment Report (2013), representing a world in which global greenhouse gas emissions continue to rise, as countries choose not to shift towards a low-carbon future (IPCC 2013).

For our study, we use precipitation and near-surface minimum and maximum air temperature data for two 20-year periods (1981-2000, or "1990s", and 2061-2080, or "2070s") to evaluate changes in the future, relative to the recent past. 1981-2000 is chosen to represent present-day conditions as by Murphy et al. (2018), because the RCP emission scenario used in the projections starts from 2006, hence simulations include an element of predictive information starting from the following decade.

5.2.2 Bias correction of climate data

UKCP18 projections, common to all climate projections, contain considerable biases, i.e. there may be systematic differences between climate model results and observations (due to factors such as imperfect conceptualisation, discretisation and averaging within grid cells). Therefore, we need to adjust climate data before using them within our study by carrying out bias correction (Murphy et al. 2018).

The underlying idea of bias correction is to identify potential biases between simulated and observed climatic variables, and to use this as a basis for adjusting both past and future runs. To this end, several approaches have been developed, from simple scaling to more sophisticated methods (see Teutschbein and Seibert (2012) for a review).

Here, we use observed daily time series of rainfall and temperature for the period 1981-2000 from CEH-CHESS (Robinson et al. 2017) to correct UKCP18 simulations (for each of the 12 ensemble members) by using local intensity scaling for precipitation and variance scaling for temperature, as described by Teutschbein and Seibert (2012). Briefly, local intensity scaling of precipitation allows us to adjust both the mean and the wet-day frequencies and intensities of rainfall time series (see Appendix Section A.3.1), whereas variance scaling allows us to correct temperature by *(i)* adjusting the means of the RCM-simulated time series by linear scaling (i.e. using an additive term based on the difference of long-term monthly mean observed and simulated data), and *(ii)* scaling their standard deviations (based on the ratio of observed and simulated standard deviation).

5.2.3 Model, domain, climatic characteristics and disease risk metrics

We use the recently developed Hydro-Epidemiological model for Liver Fluke (HELF) to simulate future disease risk, as, unlike previous liver fluke risk models, it explicitly describes processes, rather than relying on correlation. Therefore, it is better suited to represent out of sample conditions (Beltrame et al. 2018). The model output we consider here, as a baseline for our analyses, is the mean metacercarial abundance over a catchment (which provides an index of environmental suitability for disease transmission), for each day over the past and future simulation periods. Our domain consists of the 935 UK catchments for which the hydrological component of HELF was calibrated by using signatures derived from streamflow observations, as described in Chapter 4 (Section 4.2). The DEM data employed to derive Topographic Index values for all catchments are described in the same section.

With regard to climatic characteristics, for each catchment, changes in seasonal mean temperature and total rainfall (averaged over the two 20-year periods, and calculated for all 12 ensemble members) are assessed first, separating winter (Nov-Apr) and summer (May-Oct), as in previous liver fluke studies (e.g. see Fox et al. 2011; Ollerenshaw 1966). Secondly, the assessment of temperature over winter is

extended to consider the number of days above 10°C, which is the minimum temperature developmental threshold for liver fluke in the UK, and the assessment of temperature over summer is extended to consider the number of days above 20°C, which is assumed to be critical for the survival and infectivity of metacercariae on pasture. Similarly, for rainfall, we investigate the fraction of rainy days (here defined as those with accumulated rainfall exceeding 1 mm) over both winter and summer, which influences whether an area is moist enough for the parasite life cycle to progress.

To investigate potential climate-driven changes in disease risk, first, we focus on the seasonal scale, estimating changes in terms of mean metacercarial abundance, number of days at risk of infection (defined as those with positive metacercarial abundance on pasture), as well as number of days at high risk (defined as those with metacercarial abundance above the 70th percentile). Second, to better capture changes in the seasonality of disease transmission, we analyse the magnitude and timing of the annual peak of infection (the latter defined as month of maximum metacercarial abundance in a year), and assess potential alterations in terms of duration of the risk period at the monthly scale. Then, to understand where disease risk may increase or decrease in the future compared to the past, projected changes are assessed for the nine administrative regions presented in Chapter 4 (see last paragraph of Section 4.2.3).

Finally, to examine how the effectiveness of current measures may change going forwards due to a changing climate, we implement the treatment-based control strategy introduced in Chapter 4 (Section 4.2.4) for both past and potential future conditions, assuming farmers treat twice per year (in January and April), with a 90% efficacy product, which suppresses egg shedding on pasture for 12 weeks.

5.3 Results and discussion

5.3.1 Changes in climate

Temperature

Figure 5.1 shows the seasonal spatial patterns of warming projected for 2061-2080 relative to 1981-2000 for the UK, on average across ensemble members. With regard to winter surface air temperature, estimated changes range from +2.2°C to more than +3.3°C across Great Britain, with the largest increases occurring over the south-east of England and the Scottish Highlands (average change across all catchments is +3°C). The changes projected for summer are larger in magnitude than those for winter, with values ranging from approximately +3°C in Northern Scotland to about +5°C across the south-east, by the 2070s. These results are consistent with changes estimated by Guillod et al. (2018), as well as with previous UK climate projections (Murphy et al. 2009).

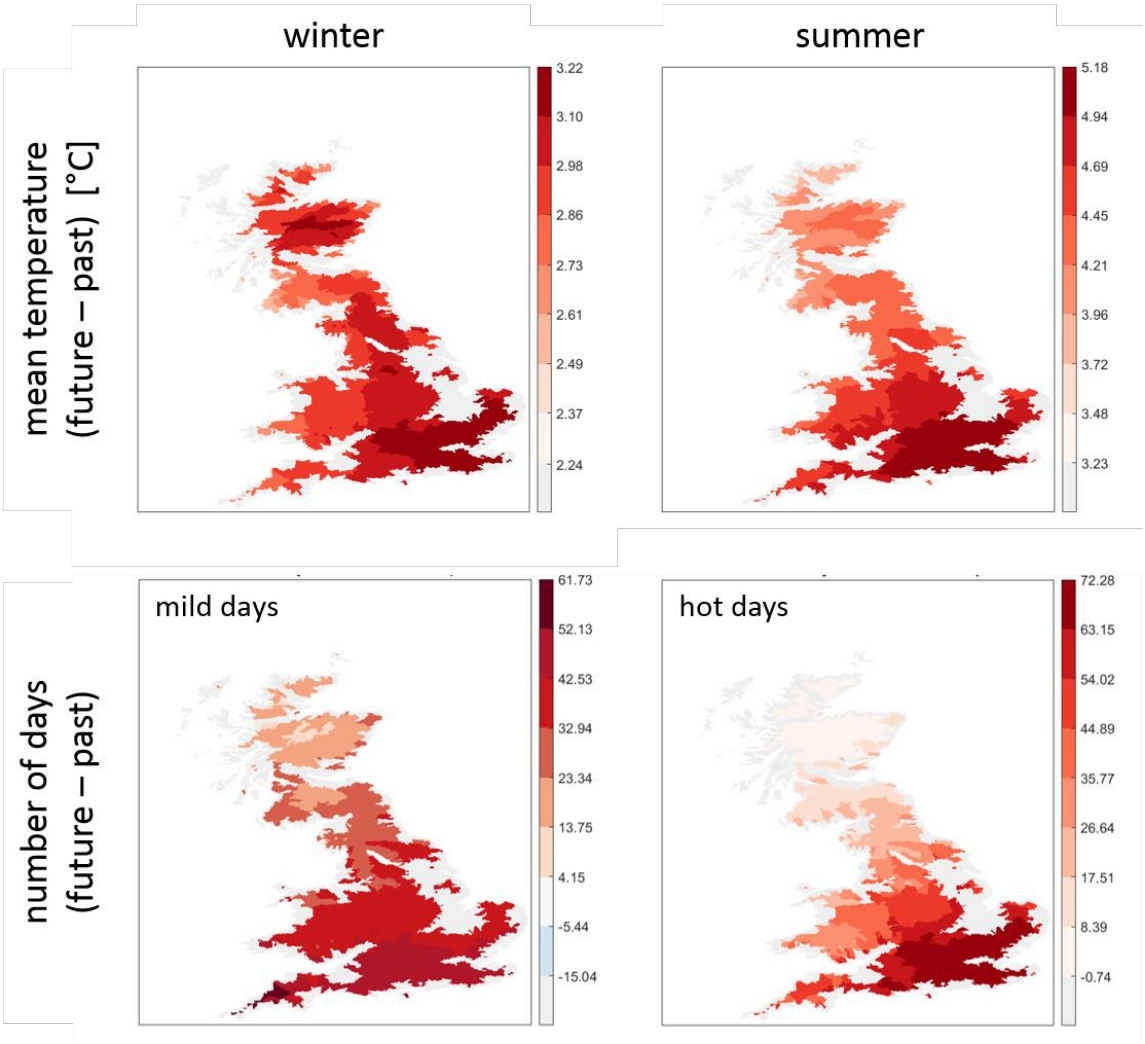

Figure 5.1 Ensemble mean difference in near-surface air temperature (top) and number of mild days and hot days (bottom) between future (2061-2080) and baseline (1981-2000), for winter (left) and summer (right). Ungauged catchments are masked in grey.

While potential future changes in mean temperature are relevant, changes in the number of days above 10°C (or "mild days") over winter are particularly interesting because of the close relationship with liver fluke epidemiology (10°C being the assumed minimum developmental threshold for the parasite life-cycle stages). Figure 5.1 shows an overall increase in the number of mild days over winter, in agreement with IPCC projections (IPCC 2014). In Scotland, the expected range is between 4 and 23 additional mild days compared to the past. Then, values get progressively larger towards the south of the country, with the number of mild days projected to increase by up to 2 months in some catchments in Cornwall. Similarly, if we look at changes in the number of days above 20°C (or "hot days") over summer, assumed to play a role on the survival and infectivity of metacercariae, we see a strong north-west to south-east gradient, from no change up to more than 70 additional hot days in East Anglia and the South East.

Rainfall

Projected changes in seasonal total rainfall between the 2070s and the 1990s are shown in Figure 5.2. For winter, increases of different magnitude are estimated across all regions. Most of the UK (78% of the analysed catchments) shows relatively modest increases, up to 90 mm. However, for 3% of the catchments, located along the west-facing coastal regions of the country, larger increases (above 220 mm) are expected. On the other hand, changes in summer precipitation reveal a substantial drying response in most areas, with strong reductions potentially exceeding 300 mm in South Wales and Cornwall by the late 21st century. The only exceptions are some coastal areas in the north-west of Scotland, where potential increases can be seen, up to approximately 120 mm. These findings are in agreement with previous projections for the UK, which also show relatively small rainfall increases in winter and large decreases in summer, on average, resulting into a general drying (Guillod et al. 2018; Murphy et al. 2009).

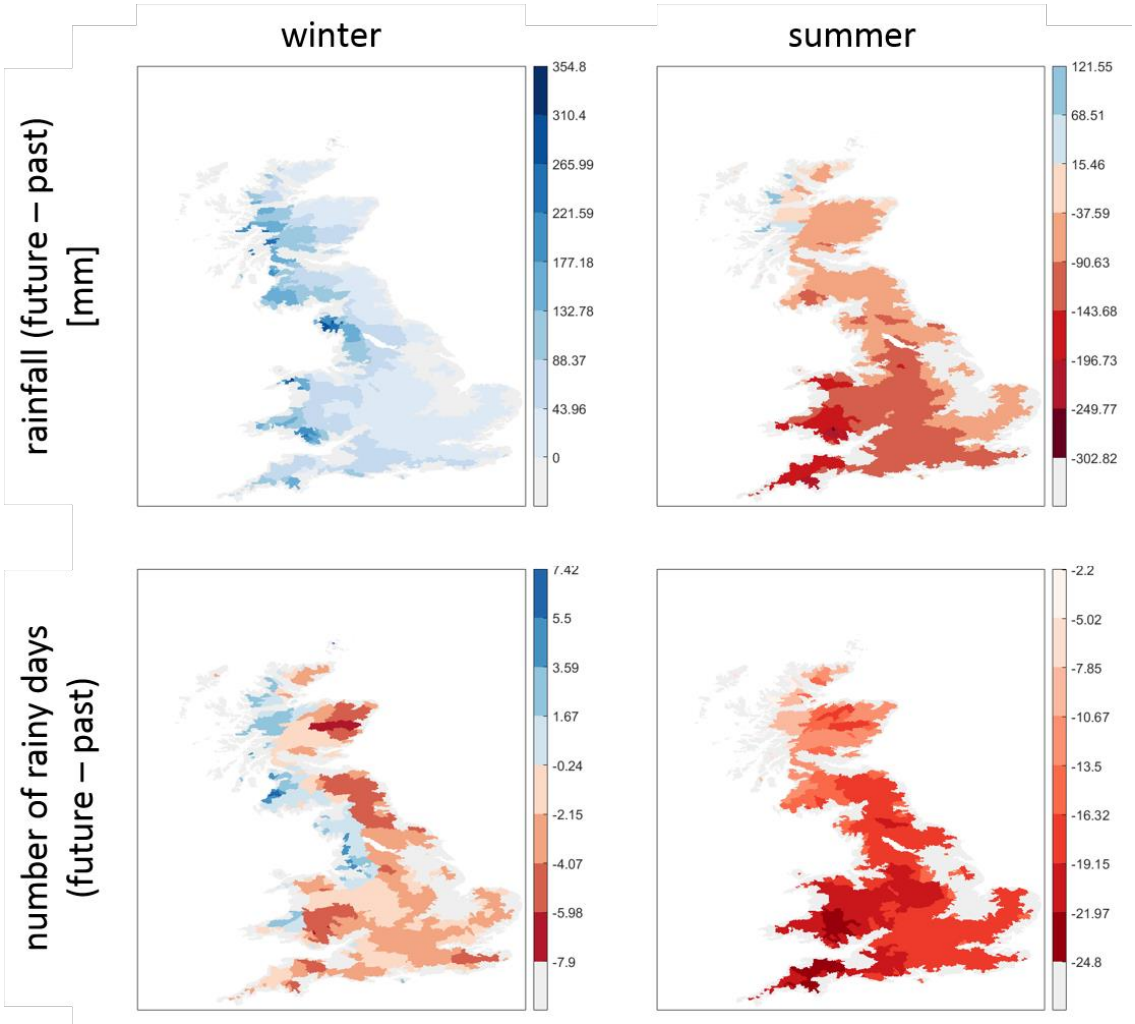

Figure 5.2 Ensemble mean difference in rainfall (top) and number of rainy days (bottom) between future (2061-2080) and baseline (1981-2000), for winter (left) and summer (right).

Figure 5.2 also shows the average response across the 12 ensemble members for changes in the number of rainy days (above 1 mm) for winter and summer. In winter, while total rainfall is projected to increase over all catchments, we see that, except for parts of Wales and the west coast of north England and Scotland, rainy days are expected to become less frequent (the relatively narrow range for these changes is ±7 rainy days, with the largest reductions occurring in the north-east of the country). This suggests that, over most areas, the projected increases in winter total rainfall discussed above mainly arise from increases in the average rainy-day intensity, which is in agreement with previous results obtained from a range of RCMs, including EUROCORDEX simulations (Kendon et al. 2014; Rajczak and Schär 2017). In contrast to the relatively modest future change in the occurrence of rainy days in winter, a strong signal for reductions in the fraction of rainy days can be seen in summer for all the catchments analysed (ensemble average decrease of 21.8%). These changes vary approximately in the range [-2 -24] rainy days across regions of the UK, with the largest reductions occurring in the south-west of England and in Wales. Drawing conclusions from here about changes in terms of heavy rainfall seems less straightforward. The decreases seen in both total rainfall and number of rainy days suggest decreases also in terms of precipitation intensity on rainy days, at least for central and southern areas of the country. However, a recent study using a sub-daily finer-scale model (1.5km) showed significant increases in heavy rainfall intensities also in summer (linked to convective enhancement of rain within large scale storms), which do not seem to be simulated by current RCMs (Kendon et al. 2014).

5.3.2 Changes in disease risk

In comparison to historic conditions, an overall increase in risk of infection with liver fluke is projected for the future across the UK (Figure 5.3). In fact, our results show that, on average across ensemble members, 84.6% of the analysed catchments are projected to experience an increase in mean annual abundance of infective metacercariae of 28.9% by the 2070s (standard deviation is 25.8%).

Seasonal projected changes in disease risk and climatic drivers, for 2061-2080 relative to 1981-2000, are shown in Figure 5.4. From here we see that, in winter, as mean temperatures approach the minimum developmental threshold of 10°C in the future, with up to a 3-fold increase in the number of mild days compared to historic conditions, risk of infection increases according to all three examined characteristics. Specifically, we see potential 10-fold increases in mean metacercarial abundance, as well as a doubling of (consecutive) days at risk of infection, compared to the past. While the increase in average wet-day rainfall intensity emerged from Figure 5.2 may be assumed to play a role, our results confirm that temperature represents the parasite life-cycle limiting factor in winter, and, therefore, that changes in temperature-related characteristics are more important drivers of projected changes over this season.

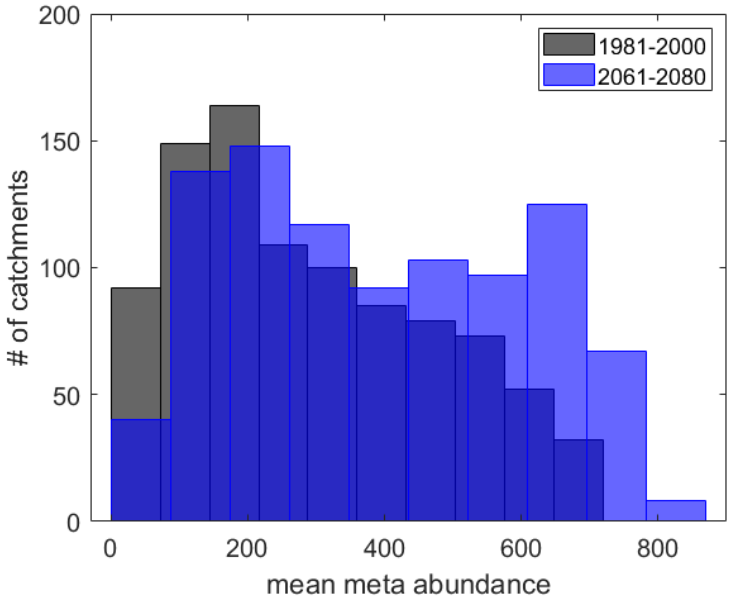

Figure 5.3 Annual mean metacercarial (meta) abundance across all analysed catchments for past (black) and future (blue), on average across ensemble members.

Also for summer, when -on average across the country- temperatures are favourable for transmission in the future as they were the past, our results show an overall increase in mean metacercarial abundance. However, while the number of days at risk is projected to increase (with approximately two additional weeks at risk over the season compared to the past), the number of days at high risk may decrease. This seems to be linked to the 21.8% reduction in the number of rainy days, which limits parasite development and survival, as well as snail intermediate host habitats, through decreasing soil water content (Samaniego et al. 2018), and is potentially exacerbated by the overall increase in the number of hot days seen in Figure 5.1. In summer, average temperatures across the country are already above the development threshold of 10°C, and therefore the main control of disease risk changes is a change in rainfall patterns. Thus, the increases in summer heavy rainfall intensities predicted by Kendon et al. (2014) may have significant implications for disease transmission. For example, extreme rainfall could limit transmission, as metacercariae may be washed away by large amounts of rain, but could also favour it, by facilitating dispersal of snails into new habitats (Fox et al. 2011; Skuce et al. 2014). However, even higher resolution models may be needed to better understand potential changes in the intensity of future rainfall events (Kendon et al. 2014), and, in turn, in liver fluke epidemiology, over summer months.

As these changes presented for winter and summer may mask changes occurring at shorter time scales, we further investigate climate-driven impacts on future disease risk seasonality focusing on the monthly scale.

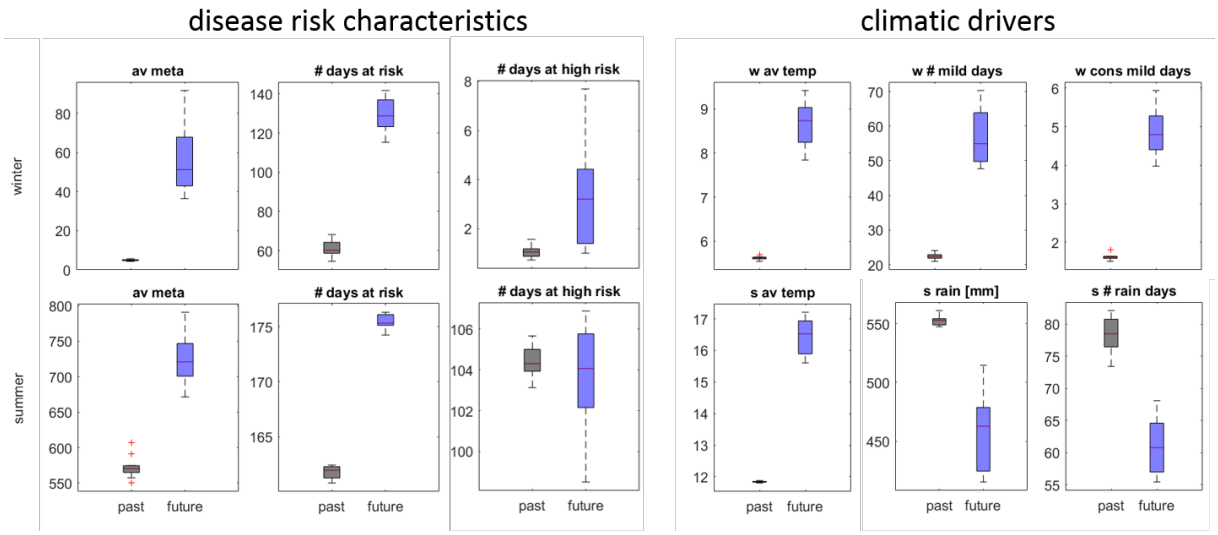

Figure 5.4 Projected seasonal changes in disease risk (left) and climate characteristics (right) for the future (2061-2080), compared to the baseline (1981-2000). Boxplots represent variability across ensemble members.

Figure 5.5 shows how the timing of greatest parasite challenge in a year is expected to change in the future compared to historic conditions (using the mode across ensemble members). From here we see, on one hand, that, historically, infection peaks in late summer across the whole of the UK (earlier, in August, in the warmer south, and later, in September, along the comparatively colder west coast and in the north), which reflects current understanding and farmers' experience (e.g. see Williams et al. 2014).

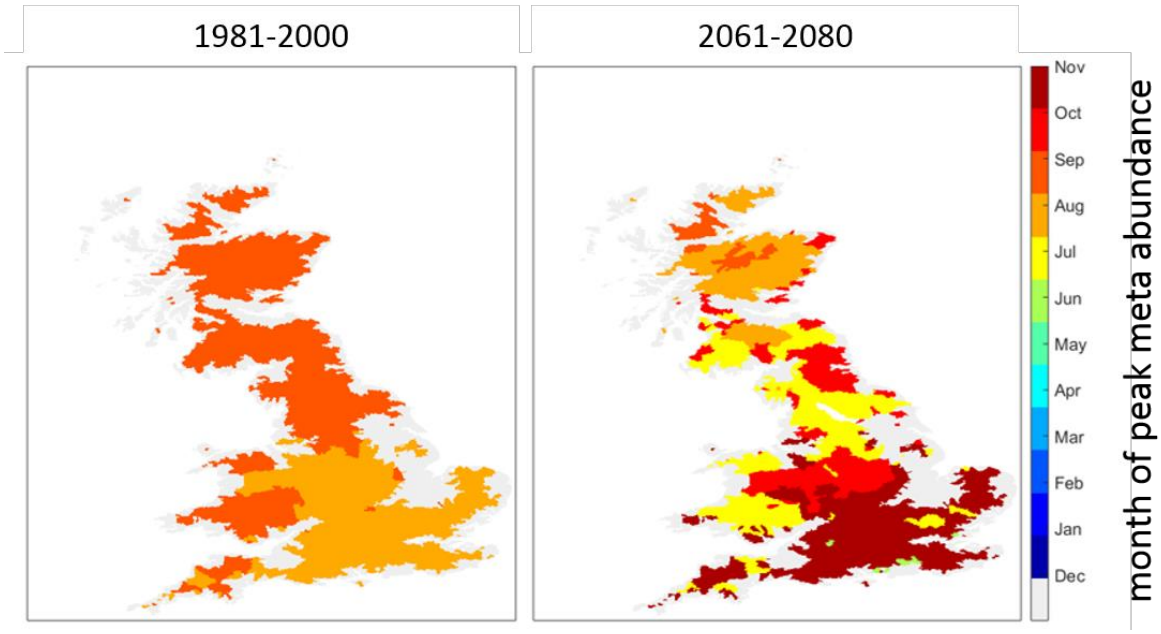

Figure 5.5 Timing of greatest parasite challenge in the past (left) vs. future (right), mode across ensemble members. Ungauged catchments are masked in grey.

On the other hand, in the future, except for Scotland, where the annual abundance of metacercariae still reaches a peak in late summer (August-September-October), disease risk is estimated to peak either earlier (in July) or later in the year (in October or November), which is expected to have important implications for disease control both at the farm level, e.g. for drug administration, and within national adaptation plans, e.g. to decide when and where to focus active disease surveillance (Beesley et al. 2018; NADIS 2019).

Future duration of the risk period also presents substantial changes compared to the past. Figure 5.6 shows that, under historic conditions, the period of positive metacercarial abundance on pasture lasts approximately from July to October (on average across all catchments). Therefore, in the past, risk of infection is confined to four months (with only two associated with particularly high risk within this period, in late summer-early autumn, as seen above), which accurately reflects the present seasonality of liver fluke in Great Britain. On the other hand, simulations of the future period using the RCP8.5 climate change scenario show an earlier emergence of infective metacercariae on pasture in spring and a later recession of disease risk in autumn, resulting into an average increase in the duration of the transmission period of 3 months. This appears to be linked to the change in the monthly number of days above the liver fluke minimum temperature development threshold compared to historic conditions. In fact, while, in the past, it was only from mid-April to mid-October that at least 10 mild days would occur per month, this is projected to extend to the period from mid-March onwards in the future.

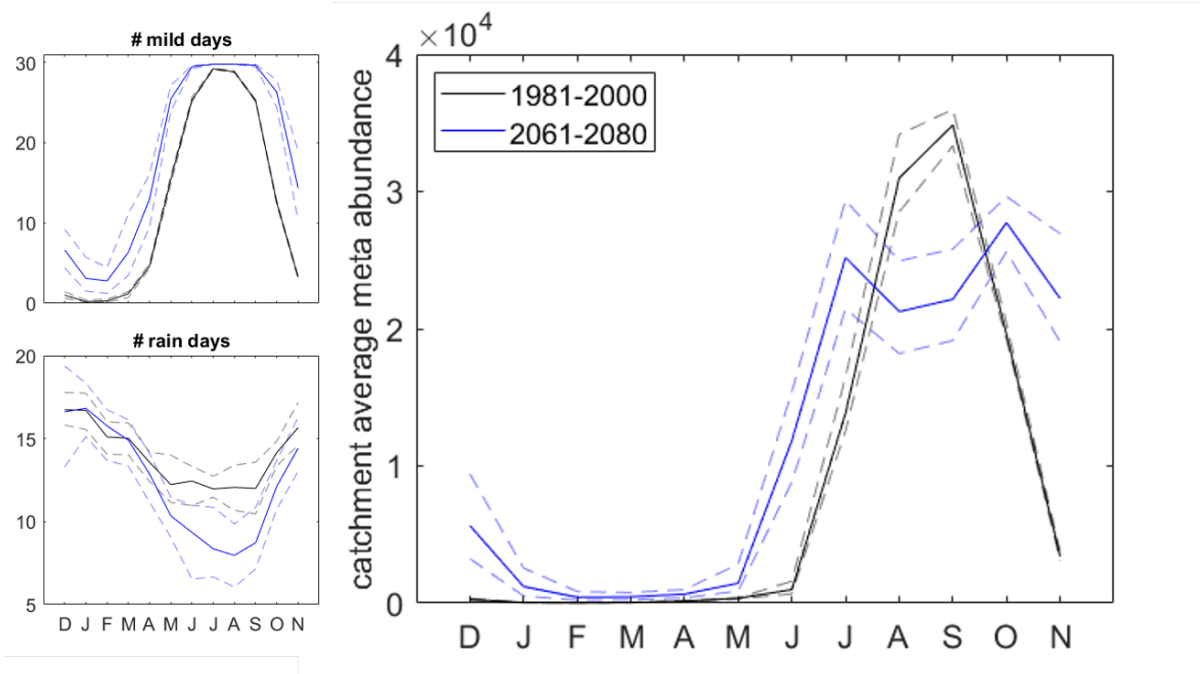

Figure 5.6 Projected monthly changes in catchment average metacercarial (meta) abundance (right) and climate characteristics (left) for the future vs. past. Dashed lines represent variability across ensemble members.

Other than an extension of the yearly risk period, a change in the number of peaks of infection is also clear from Figure 5.6. In the future, in fact, two distinct periods of high risk are expected (one earlier and one later in the season compared to historic conditions), separated by a period of lower risk over August-September. Specifically, our results show that, while 95.7% of catchments used to peak only once in the past (and 3.5% twice), the percentages of catchments with one peak and two peaks are similar for the future (approximately 48.7%). This may be explained by the trade-off emerging between increased development rates, with more frequent mild days throughout the year, and reduced snail presence and halted development within snails, when considerable reductions in the fraction of rainy days decreasing soil moisture availability (Samaniego et al. 2018) are expected. The projected shift towards a longer transmission season, with the disease becoming more of a year-round rather than a seasonal threat, and the emergence of a bimodal pattern in the yearly cycle of infection, agree with previous speculations (e.g. Fairweather 2011) and seem consistent with larger-scale and coarser projections previously developed for liver fluke, as well as for other parasites, under various climate change scenarios (e.g. see Caminade et al. 2015 for liver fluke, and Rose et al. 2015 for gastrointestinal nematodes, as well as Molnar et al. 2013 and Rose and Wall 2011). However, while existing (correlation-based) projections of climate suitability for liver fluke suggest an emergence of two peaks for the whole of northern Europe (Caminade et al. 2015), simulating risk over the UK using HELF shows that this does not necessarily hold across all regions. Specifically, in the north-east of Scotland, where summer changes in the number of hot days and rainy days are limited (see Figures 5.1 and 5.2) and where soil moisture may not become as restrictive compared to other areas, the projected increase in infection pressure appears to be linked to an increase in magnitude of the summer peak, rather than to a temporal expansion of the transmission season (see Figure A.7 in Appendix Section A.3.2).

In fact, in addition to temporal variability, changes in the spatial distribution of infection risk are also expected across the UK. Figure 5.7 shows that, in the future, risk of infection (in terms of seasonal mean metacercarial abundance) is projected to be highest in southern regions over winter (SW, SE and EAng), and along the west coast of the country over summer (especially NW, Mid and NScot, based on the median across ensemble members). This is qualitatively consistent with previous projections for the UK based on the Ollerenshaw Index (Fox et al. 2011) and gives an indication of where active disease surveillance may have to be focussed. However, when evaluating regional changes in comparison with historic conditions, our results show differences from findings of the previous UK-wide assessment of future liver fluke risk. In fact, while projections based on the Ollerenshaw Index show increases in mean disease risk in all regions over both seasons, our results show potential decreases in the south-east of the country over summer. Specifically, on the one hand, we find the largest increases in risk to occur in summer in the north of Great Britain (i.e. Scotland, followed by the North West of England), where average temperatures are expected to increase by approximately +3°C and potential increases in rainfall

are projected, with the smallest reductions in the number of rainy days across the country (see Figures 5.1 and 5.2). On the other hand, we find reductions in summer risk in East Anglia and the South East of England, where declines in the number of rainy days are large (Figure 5.2), potentially limiting soil moisture (Samaniego et al. 2018) and therefore the presence of snails and the survival of free-living stages on pasture, and where increases in the number of hot days are the largest across the UK (Figure 5.1), potentially leading to increased temperature-dependent mortality of metacercariae.

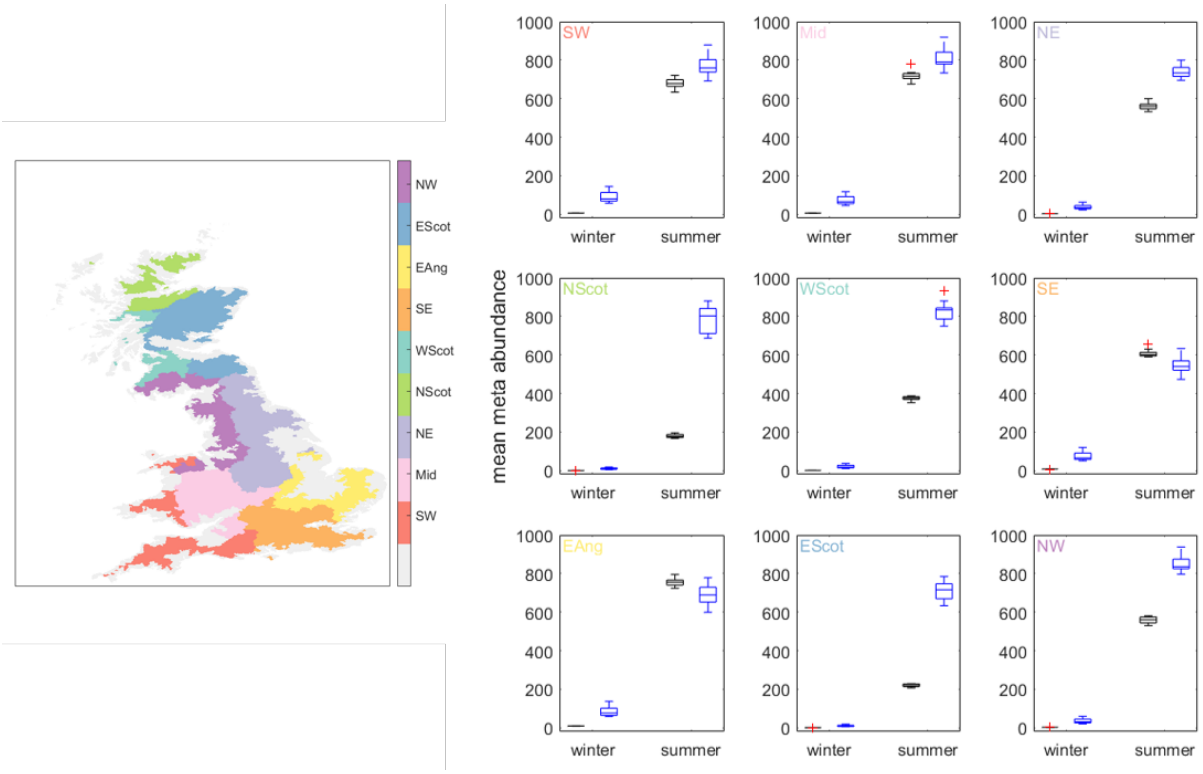

Figure 5.7 Projected changes in mean seasonal metacercarial (meta) abundance across 9 administrative regions. Boxplots represent variability across ensemble members.

Comparison with the study by Fox et al. (2011) can only be qualitative, due to differences from this work in a number of factors (e.g. use of previous and coarser UKCP09 climate projection data with a medium emission scenario). However, the fact that we see similar changes over winter and potential differences over summer seems sensible, as it is in summer that disease risk is more limited by rainfall than temperature and that how rainfall impacts on the parasite life cycle are mediated through soil moisture will matter most.

5.3.3 Implications for disease control

By altering the epidemiology of liver fluke across the UK, the projected patterns of climate change could also affect the future effectiveness of current control strategies. Specifically, our results show that

treating animals over winter/spring, as farmers have been doing historically to reduce the peak of infection in late summer, is projected to become on average 41% less effective compared to the past, across UK regions (Figure 5.8). This may require farmers to adapt by increasing the frequency of parasite treatments. For example, our results also show that treating one extra time per year (assuming to use the most effective product currently available -as in our previously implemented strategy- also in July, in addition to January and April) could achieve up to 90% risk reductions in late summer, on average across regions and ensemble members. However, this may equally become a threat to the economic sustainability of livestock farming, as increasing the frequency of drug administration involves extra costs for farmers (van der Voort et al. 2013) and carries the risk of worsening the issue of drug resistance (Fairweather 2011), further highlighting the need for a shift towards environmental management (with interventions such as those tested in Chapter 4) as a complementary or alternative disease control strategy for the future.

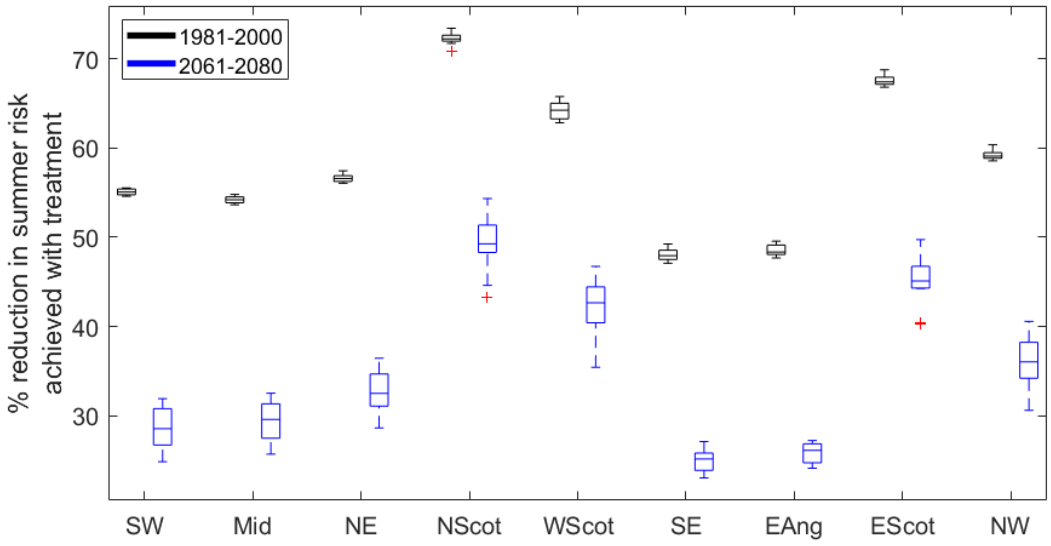

Figure 5.8 Comparison of future vs. past percent reduction in late summer risk, achieved using current treatment-based control. Boxplots represent variability across ensemble members.

While potentially requiring more frequent treatments, the impact of changing climatic conditions on disease transmission may also be complicated by the development of parasite adaptive responses to climate change (Cable et al. 2017) and by changes in a number of confounding non-climatic factors (Parham et al. 2015) that have so far been neglected. For example, changes in land use and stocking rates (i.e. number of livestock per unit area), linked to varying socio-economic, policy, as well as bioclimatic controls, may potentially exacerbate but also outweigh the contribution of climate-

environment aspects to disease risk, in the latter case potentially providing an opportunity to mitigate negative effects of a changing climate (Morgan and Wall 2009; Rose et al. 2015).

5.4 Conclusions

Assuming a stationary climate is no longer possible given anthropogenic climate change. Therefore, we assess the impact of future potential changes on liver fluke risk in the UK using, for the first time, a mechanistic hydro-epidemiological model, driven by the most recent ensemble of climate projections available to estimate related uncertainties. Maps of seasonal changes in temperature and rainfall show significant alterations for the late 21st century compared to historic conditions, including in liver fluke-relevant climatic characteristics, such as an increase in the number of mild days over winter (progressively larger towards the south of the UK, up to 2 additional months) and a strong decline in the number of rainy days across the country in summer (-21.8% on average). An overall rise in infection pressure is estimated for liver fluke in the UK under such projected changes in climate. However, this is not expected to be uniform in time nor space. Regarding changes in time, in comparison to historic conditions, RCP8.5 simulations show a temporal expansion of the yearly transmission period by approximately 3 months and the emergence of a bimodal seasonal risk pattern, linked to more frequent days above the parasite minimum temperature developmental threshold throughout the year and to a declining number of rainy days, coupled with more extremely warm days, reducing risk over summer. As a consequence, while, in the past, the greatest parasite challenge used to be confined to the months of August-September across whole of the UK, risk of infection is expected to peak all the way from June to November in the future, depending on the area. With respect to changes in space, regionally, projected increases in disease risk are found to be largest in Scotland over summer, where, while temperatures will be warmer, rainfall is not expected to become restrictive. Instead, decreases in summer risk are projected in the south-east of the UK, where reductions in rainy days are expected to be large and warming levels are the highest of the country. Finally, we demonstrate that, as climate change lengthens disease transmission seasons, more frequent treatments are required, further highlighting the need for a shift to more cost effective and sustainable disease control strategies in the future.

This page was intentionally left blank

Chapter 6. Summary and Outlook

6.1 Summary

In this potentially fast-developing and at least partially global change-driven "age of epidemics" (Hotez 2016; Weiss and McMichael 2004), the overall aim of this thesis was to better understand how we can use knowledge of the environment and water environment in support of the study and management of infectious diseases.

Using the widespread parasitic disease of fasciolosis in the UK as a case study (introduced in Chapter 2), we developed and tested a mechanistic coupled hydro-epidemiological model for disease risk (Chapter 3), which we then applied to explore opportunities for risk reduction through environmental management (Chapter 4), and to assess potential climate change impacts on future infection risk patterns (Chapter 5).

More specifically, this thesis makes three main contributions: (1) it introduces the first mechanistic hydro-epidemiological model that simulates risk of liver fluke infection in explicit connection with underlying environmental drivers (HELF), (2) it assesses the sensitivity of disease risk to environmental controls across the UK and demonstrates potential benefits of using environmental interventions for risk reduction, and (3) it evaluates late 21st century potential changes in the seasonality and spread of disease transmission, highlighting potential shortcomings of current treatment-based control strategies.

6.1.1 HELF

The majority of existing models for predicting disease risk in response to climate change are empirical. These models exploit correlations between historical data, rather than explicitly describing relationships between cause and response variables. Therefore, they are unsuitable for capturing impacts beyond historically observed variability and have limited ability to guide interventions.

In this study, we integrate environmental and epidemiological processes into a new mechanistic model of liver fluke risk. The model simulates environmental suitability for disease transmission at a daily time step and 25 m resolution, explicitly linking the parasite life cycle to key weather–water–environment conditions. Using epidemiological data, we show that the model can reproduce observed infection levels in time and space for two case studies in the UK. To overcome data limitations, we propose a calibration

approach combining Monte Carlo sampling and expert opinion, which allows constraint of the model in a process-based way, including a quantification of uncertainty. The simulated disease dynamics agree with information from the literature, and comparison with a widely used empirical risk index shows that the new model provides better insight into the time–space patterns of infection, which will be valuable for decision support.

6.1.2 Disease control strategies

Control of many environment-driven infections is increasingly challenged by climate change and the emergence of drug resistance, calling for more comprehensive strategies, rather than exclusively relying on treatment. The role on-the-ground environmental factors play, within disease transmission pathways, may offer an opportunity to use environmental interventions as complementary or alternative options to drug administration to reduce disease burdens. However, as currently considered drivers of disease risk are often only climatic, environmental strategies to complement treatment are still poorly developed and under-recognised.

In this study, we explore opportunities for environmental management to control fasciolosis in the UK, while considering the diversity of disease drivers across this heterogeneous domain. By using ANOVA, we show that, while rainfall and temperature-related characteristics are key determinants of risk across the country, topographic variability is important in higher relief areas, suggesting that future disease risk simulations will need to explicitly account for it to be able to provide plausible disease transmission patterns as well as decision support. Having recognized the importance of landscape heterogeneity in driving risk of infection, we then demonstrate how, in these regions, tackling disease transmission through risk avoidance management strategies can be particularly effective, especially in relatively dry years. This will be paramount to maintain/regain control over fasciolosis in the UK, as current treatment-based control may become costly and unsustainable.

6.1.3 Climate change impacts

Climate change is already having measurable effects on the transmission of infectious diseases, globally. However, questions such as which areas will be most impacted going forwards, have only begun to be addressed, mainly by extrapolating past relationships into wider regions and future climates, and investigating changes in climate averages, rather than pathogen-relevant characteristics. Moreover, implications for disease control strategies are rarely assessed.

In this study, we evaluate the impact of future potential changes on liver fluke risk in the UK using HELF. The most recent ensemble of regional climate projections, made available by the UK MetOffice, is employed to estimate related uncertainties. Late 21st century temperature and rainfall under the most

severe scenario (RCP8.5) suggest significant changes compared to historic climatic conditions, including an increase in the number of mild days over winter of up to 2 months and an average 21.8% decline in the number of rainy days across the country during summer. These changes result in a temporal expansion of the yearly parasite transmission period of up to 3 months, with the emergence of a bimodal seasonal risk pattern. Despite an overall increase in infection pressure, decreases in summer risk are expected in the south-eastern areas of the UK, where reductions in rainy days are large and warming levels are the highest of the country. Finally, projected changes are found to reduce the effectiveness of current treatment-based control strategies by 41% on average, affecting their sustainability and further highlighting the need for a shift towards alternative approaches.

6.2 Outlook

In this thesis, we focused on animal fasciolosis in the UK, but infectious disease systems, especially where infections are also transmitted to people, can often be more complex. Liver fluke infection in the UK provided a good case study because, due to its long-time veterinary importance, related to the substantial economic losses it causes in livestock, we now have a good mechanistic understanding of fasciolosis at the animal level, which is primarily linked to underlying environmental processes (Figure 6.1). Moreover, following the recent rise in infection pressure in the UK, a significant amount of data has been collected from field studies and laboratory experiments, and a new body of literature has been providing additional knowledge on different aspects of the disease and its environmental drivers. However, especially when it comes to human infections, higher complexity is often involved associated with human behaviour, which adds onto the sensitivity of health conditions to several environmental stressors (for example, a number of factors related to living standards and dietary habits may become key in case of foodborne diseases, in addition to environmental controls, e.g. see Figure 6.2). Therefore, for diseases affecting multiple regions around the world, not only the environmental setting may change from place to place, but also the social and other human-related drivers may vary, giving rise to significantly different disease transmission pathways. For example, in addition to its veterinary importance, in the UK and globally, fascioliasis has also recently become a serious human health problem in some regions, especially in poor rural areas in South America and in the Middle East (Mas-Coma et al. 2018). In Bolivia, where the highest prevalence levels and intensities have been reported, despite intermediate snail hosts being the same as in the UK, ecological conditions are different, with G. truncatula snails adapted to living at altitudes above 4000 m a.s.l., and in permanent water bodies rather than on the ground (Mas-Coma et al. 1999). Here, fasciolosis can be transmitted year-round - mainly through the ingestion of infected wild plants and vegetables- and children, who spend many hours in the fields involved in the tending of animals, are most at risk. On the other hand, in Iran, where

also large epidemics have occurred, the setting is very different: infection rates are highest in the lowland areas along the Caspian Sea; transmission is bi-seasonal, linked to both climate conditions and rice field irrigation practices; dietary habits associated with religion play a role; and adults get infected more often than children, as they participate in agricultural and cooking activities while children are at school (Mas-Coma et al. 2018).

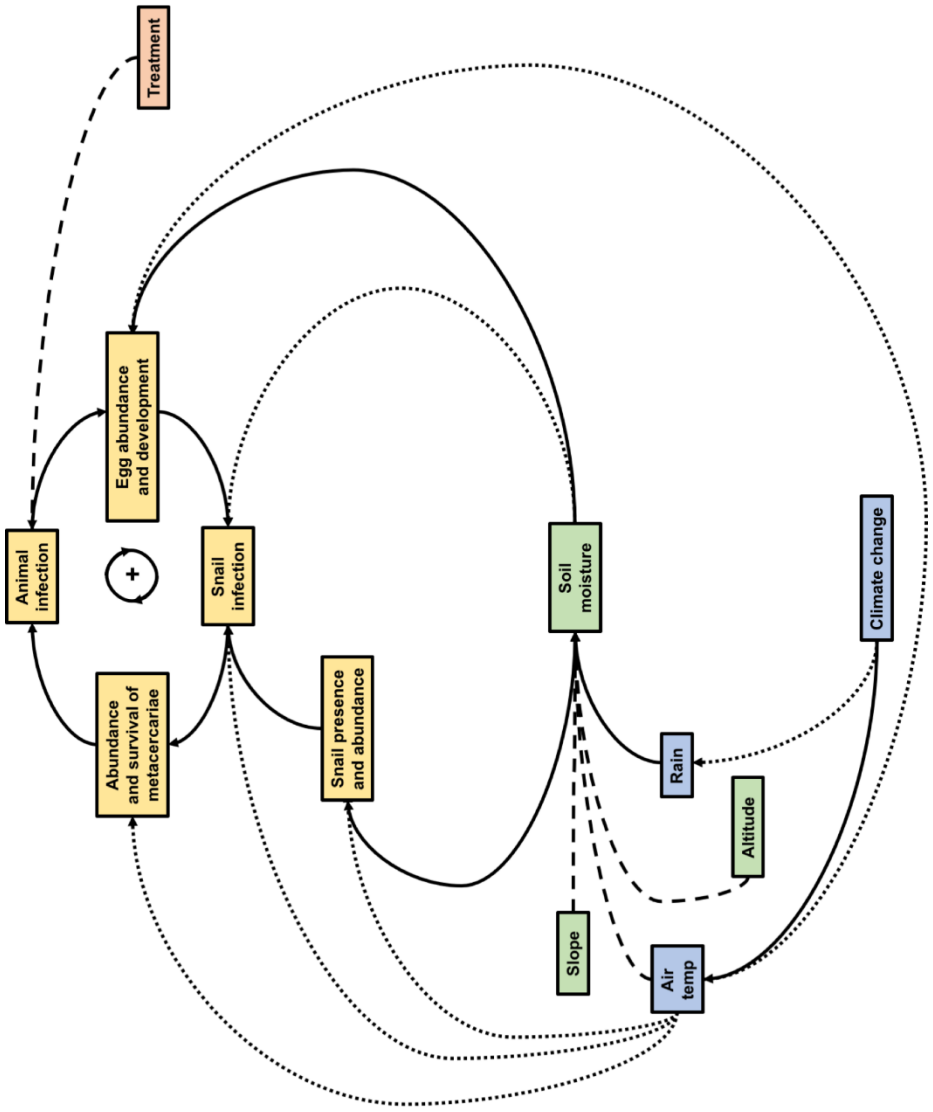

Figure 6.1 Simplified representation of the environmental-epidemiological system addressed in this thesis: animal fasciolosis in the UK.

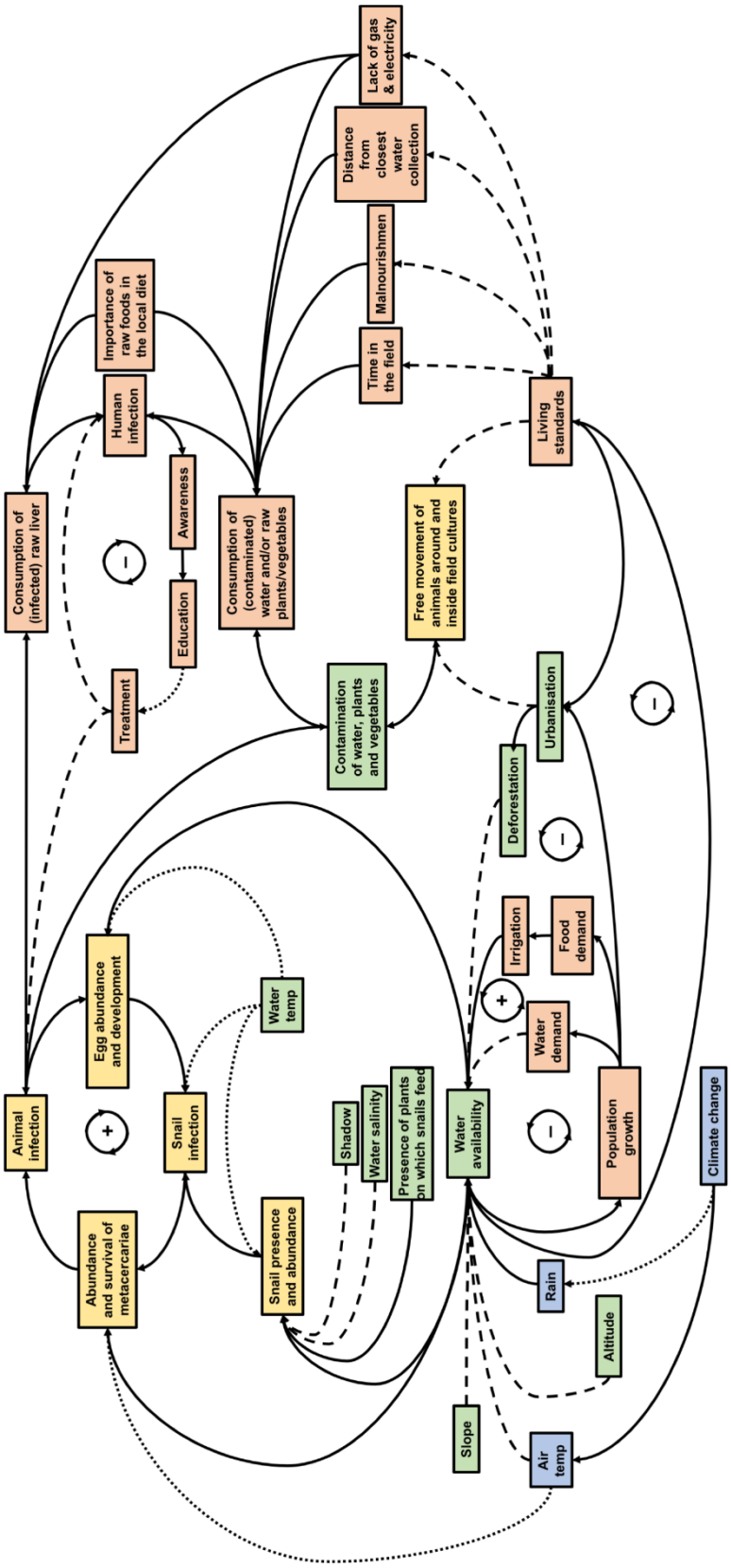

Figure 6.2 Simplified representation of the wider system of disease transmission characterising human fasciolosis hyper-endemic areas in South America.

It seems clear that progress in the study and control of such complex diseases requires to broaden the view of the system, addressing a wider set of risk factors and integrating across even more disciplines and data. To better understand the causes of disease, which is key for designing effective control strategies and interventions to reduce/mitigate risk, we need a means to incorporating knowledge about elements and mechanisms beyond environmental and epidemiological processes (e.g. Eisenberg et al. 2002). In this context, "the study of multi-layered non-linear systems, in which infections evolve and where key events can be governed by unpredictable human behaviour, represents a significant conceptual challenge. On the other hand, more practical challenges range from establishing appropriate data collection to managing increasingly large volumes of information, combining and leveraging data from different sources" (Heesterbeek et al. 2015). In fact, relevant data are often diverse (e.g. climatic, environmental, epidemiological, clinical and demographic data, plus information on social connectivity and behaviour such as travel patterns), as well as variable, uncertain, and at different spatial and temporal scales (Eisenberg et al. 2002, 2007; Heesterbeek et al. 2015).

However, the fact that available data is often limited, potentially leads to oversimplifying infectious disease systems in our studies, which may hide disease control opportunities. Even for relatively limited and well-studied systems, underreporting is a critical challenge and data can often be patchy and incomplete (Eisenberg et al. 2002; Parham et al. 2015; Urban et al. 2016), especially in developing countries (which are often also those that suffer from the greatest disease burdens e.g. see Jones et al. 2008), and in case of endemic transmission (as this is poorly measured by existing surveillance systems, in comparison with outbreak conditions (Eisenberg et al. 2002)). This is exacerbated for diseases involving a wider set of risk factors including social and other human aspects, as these require collecting and synthesizing more data, that often introduce further considerable uncertainties in the understanding of infection patterns (e.g. associated with human behaviour, including non-linear and interactive links with natural systems) (Heesterbeek et al. 2015; Mellor et al. 2016). Such knowledge and data limitations may result in oversimplifications of the infectious disease systems we address in our studies. However, by omitting parts of the system due to uncertainties or lack of quantitative data, we may overlook potential mitigation or risk reduction opportunities (Mellor et al. 2016; Ostrom 2009).

Therefore, a mechanistic systems-based approach may provide a valuable way forward and direction for future research. Rather than focusing on one mechanism, a systems-based approach can serve as a way to define important elements of an infectious disease system, integrating information from a variety of disciplines, and to explicitly represent the coupling of different components (Eisenberg et al. 2007). This can enhance understanding by providing a framework to *(i)* examine relationships between factors and address questions of causality, to explain how infection pathways may vary across different climatic-environmental-social settings, and *(ii)* identify points in the transmission pathway where disease control

strategies may be most effective (Eisenberg et al. 2002, 2007; Lloyd-Smith et al. 2009). Moreover, by providing a way to summarise what is known and unknown about the system, this approach can help assess data availability for each mechanism and highlight potential data gaps (Eisenberg et al. 2007; Lloyd-Smith et al. 2009; Mellor et al. 2016). Finally, such framework could also provide the basis for building initial mechanistic models of more complex infectious disease systems. In fact, even with limited data, these models can be used, in combination with sensitivity analysis techniques, for hypothesis testing (by evaluating the potential influence of unknown information) and to translate the identified data gaps into priorities for data collection, in order to improve understanding of the relevant processes across areas (Eisenberg et al. 2002; Lloyd-Smith et al. 2009; Mellor et al. 2016; Urban et al. 2016; Wu et al. 2016). For example, sensitivity analysis can be employed to identify factors that drive uncertainty in disease risk, or that are crucial to discriminate between disease control options, and therefore require better definition (Eisenberg et al. 2002). Once the sensitivity of infection risk to the different factors has been estimated, data collection funding resources can be allocated to refine the identified most sensitive factors (Eisenberg et al. 2002; Heesterbeek et al. 2015; Mellor et al. 2016; Urban et al. 2016; Wu et al. 2016).

In conclusion, (1) through the example of fasciolosis in the UK, we demonstrated how mechanistic knowledge of the environment can be incorporated in the study of disease transmission processes to assess risk of infection and guide interventions under current and future potential conditions; (2) we believe that, by integrating it into a wider system-based framework, which allows considering a broader set of risk factors in addition to environmental and epidemiological processes, the same mechanistic approach can also support the study and management of other (potentially more complex and less understood) infectious diseases, which is urgent as this age of epidemics potentially unfolds.

This page was intentionally left blank

Appendix

A.1 Supplements to Chapter 3

A.1.1 Additional information on HELF

HELF was implemented in the MATLAB environment (software and programming language: Matlab). The model code is available on github (https://github.com/ludobeltrame/helf). Below we provide a description of HELF that follows the protocol proposed by Grimm et al. (2006).

1. Overview

Purpose: HELF was developed as a mechanistic model to investigate the impact of weather-water-environment processes on time-space patterns of risk of infection with liver fluke under changing conditions.

State variables: The model comprises 2 levels: the parasite life cycle and the hydrologic environment. The former describes the 4 liver fluke life-cycle stages that live on pasture: eggs, miracidia, snail infections and metacercariae. Each stage (except for miracidia, that have a lifespan comparable to the temporal resolution of the model) is represented as a pool of developing cohorts of individuals. Each cohort is characterised by 2 state variables: number of individuals and maturation state, where the latter is a dimensionless quantity that depends upon stage-specific development rates. With regard to the water environment, the state variable in the model is soil moisture, expressed as a saturation deficit [mm].

Scales: HELF is a dynamic (daily temporal resolution) and spatially explicit grid-based model, in which space is represented in the form of discrete grid cells. Specifically, one cell represents a 25m x 25m area. The extent of the whole spatial domain is given by the area (i.e. number of grid cells) of the hydrological catchment under consideration.

Process overview and scheduling:

- First, spatially distributed topographic information is derived from Digital Elevation Model (DEM) data in the form of a Topographic Index (*TI*), calculated for each grid cell comprising the given catchment.

- This is followed by discretisation of the distribution of TI values into classes, so that following computations are performed for each class instead of for each grid cell.
- The model proceeds in discrete (daily) time steps.
- At every step, first, soil moisture in each TI class is calculated as a function of the TI value of the class and the catchment average saturation deficit, which is derived based on a number of processes:
    - Interception of rainfall by vegetation cover
    - Infiltration of water into the upper part of the soil (i.e. the root zone)
    - Actual evapotranspiration from the root zone, based on potential evapotranspiration, maximum capacity of the zone and its actual water content
    - Percolation of water from the root zone to the lower part of the soil (i.e. the groundwater)
    - Generation of subsurface flow and saturation-excess overland flow
- Then, soil moisture for each TI class becomes an input to the parasite life-cycle model component of HELF, where it is used, together with temperature, to calculate the relevant stage-specific development and survival rates.
- The maturation state of cohorts in each stage is updated, based on the stage-specific development rates, to derive how many individuals progress to the next stage ("matured").
- The number of individuals in each stage is then derived as a function of: the number from the previous time step, the number of individuals that die, the number of matured, and the number of those that develop from the previous stage.
- Finally, the number of individuals for each stage can be mapped back from TI classes to grid cells.

2. Design concepts

HELF is not individual-based, therefore the "Design Concepts" block as defined by Grimm et al. (2006) does not apply here. However, two key concepts underlying the development of our model are:

- Soil moisture dynamics is simulated within HELF using TOPMODEL. This model was built with the specific characteristics of UK hydrology in mind i.e. humid-temperate catchments, where the dominant mechanism of runoff generation is surface saturation, and where surface saturation is strongly related to landscape topography (Beven and Kirkby 1979). TOPMODEL is therefore a sensible choice for a hydrological model in the context of HELF, as long as this assumption is valid.
- In the liver fluke component of HELF, each life-cycle stage is represented as a pool of developing cohorts of individuals to better capture maturation progress within each stage. The

underlying idea is that different cohorts are exposed to different environmental conditions and, therefore, will develop at different times (Andrews 1999).

3. Details

- Initialization: All state variables are arbitrarily initialised to zero. However, the initial saturation deficit in the root zone is a model parameter and, as such, is calibrated, as the other parameters within the hydrological component of HELF, using streamflow observations. Moreover, the initial number of embryonic eggs on each TI class is defined (as for the rest of the simulation period) by the egg scenario considered. The model is run for one year before all analyses are started, in order to limit initialisation effects (i.e. we use 1 year of warm-up).
- Inputs: DEM data for the catchment under study; catchment average rainfall time series; catchment average minimum and maximum temperature time series; egg scenario (i.e. one time series per TI class, which can be defined based on local farm management factors).
- Sub-models:
- Hydrological model component:
    - TOPMODEL concepts and equations are explained in detail e.g. in Beven et al. (1995).
    - Topographic Index values are calculated using the Multiple Flow Direction algorithm based on Quinn et al. (1991).
    - Potential evapotranspiration is calculated using Hargreaves equation following Allen et al. (1998) and Droogers and Allen (2002).
    - A gamma distribution is employed to model the time delay in discharge generation at the catchment outlet, due to water moving through the river network (as used, for example, by Clark et al. (2008)).
    - Parameters and their initial ranges can be found in Table 3.1 (Chapter 3).
- Liver fluke model component:
    - Given the purpose of HELF, the parasite life cycle is driven in the model by temperature and soil moisture, which are known as the main environmental drivers of infection risk.
    - Eggs (E) develop on pasture at a temperature-dependent rate, and hatch into Miracidia (Mi) when both temperature and soil moisture conditions are suitable.
    - Progression from miracidia to the next life-cycle stage depends upon the probability of miracidia finding a snail host. This is assumed to be a function of soil moisture and temperature, as Galba truncatula snails are only found in poorly drained areas and are known to hibernate with cold weather and aestivate during hot dry periods. The number of snails is not explicitly modelled. Instead, increased environmental suitability is assumed to instantaneously increase snail availability, which in turn increases the

probability of miracidia finding and infecting snails (we assume infection success rate of 1).

- Snail infections (SI) develop also as a function of both soil moisture and temperature, as it is known that development within the snail may be halted due to hibernation and aestivation.
- Despite, within snails, parasites are known to pass through several developmental stages, we do not explicitly model them in HELF and simplify the process by only representing one "snail infection" stage.
- When snail infections emerge from snails (in the form of Cercariae), they instantaneously encyst on grass forming Metacercariae (Me).
- Metacercariae survive on pasture and retain infectivity as a function of temperature.
- Functions to calculate development rates for all stages and survival rates for metacercariae are derived using data and information in the literature by piecewise linear regression (Table 3.2 and Figure 3.3 in Chapter 3). For stages with both temperature and soil moisture requirements, we allow for development to progress as a function of both. The mortality rate for miracidia is set to one minus the probability of finding a snail, as miracidia either find a snail or die within 24 hours. The mortality rates for eggs and snail infections are currently assumed to be constant, as no information could be found on their dependence on environmental conditions.
- A Weibull function is used to simulate the distribution of development times, as we assume that even individuals from the same cohort, which are exposed to same environmental conditions, will not all develop at the same time (Andrews 1999).
- Parameters and their initial ranges can be found in Table 3.2 (Chapter 3), together with references.

A.1.2 Additional information on epidemiological data and model testing

The two epidemiological datasets we use are very different and come from different sources. With respect to the VIDA dataset, yearly reports containing monthly number of diagnoses of fasciolosis from the 15 UK Government's Animal and Plant Health Agency regional laboratories are freely available from www.gov.uk/apha (VIDA 2019). Extracts of diagnoses associated with specific post code districts of interest are also freely available upon request, which is how it was possible to obtain a time series specific for the River Tawe Catchment. Regarding the spatial dataset based on Faecal Egg Counts (FECs), this was derived based on a recent study aimed at assessing liver fluke infection levels and risk factors at the farm scale (McCann et al. 2017). Within the study, FECs are calculated as number of eggs found per gram of faeces. Forty cattle were sampled and four 10 x 10g composite counts were performed

per farm. Farms were subsequently classified either as positive, if at least one of the counts was positive, or negative, otherwise. Based on this, 41.9% of the farms sampled were positive (this is the overall observed percentage of infection which we use to calibrate the epidemiological component of HELF for the River Severn Catchment - see Section 3.4.2 in Chapter 3).

With regard to model performance metrics, while the coefficient of determination, $R2$, calculated as: $R2 = \frac{(\sum_{i=1}^{N}(obs_i-\overline{obs})(sim_i-\overline{sim}))^2}{\sum_{i=1}^{n}(obs_i-\overline{obs})^2 \sum_{i=1}^{n}(sim_i-\overline{sim})^2}$ is employed as a standard measure to evaluate how the hydrological component of HELF reproduces the dynamics of observed streamflow (with an emphasis on the peaks), for evaluating the epidemiological component of the model we use the Pearson correlation coefficient. In fact, as the variable we simulate (i.e. abundance of infective metacercariae on pasture) is different from the available observations, we are more generally interested in the agreement between the two.

Finally, cross-validation for the epidemiological component of HELF was performed as follows. For the Tawe Catchment, we randomly divided the VIDA time series into 5 sub-sets and repeated calibration and validation 5 times, using every time (5-1) sub-sets for calibration and the remaining one for validation. For the Severn Catchment, given the limited number of data points that could be used (in accordance with a confidentiality agreement), we performed a leave-one-out cross-validation, which consists in sequentially removing one data point only, re-fitting the model to the rest of the data, and predicting the value of the previously ignored observation. The residuals from this process were used to evaluate the predictive ability of the model based on the mean absolute cross-validation error.

A.1.3 Potential reasons for the mismatches between simulations and observations found for the Severn Catchment

When fitting the epidemiological model component of HELF to the FEC-based spatial dataset over the Severn Catchment, risk of infection seems overestimated in sub-areas A2 and A5 (Figure 3.8, Chapter 3). A first potential reason for this mismatch is that these two sub-areas were significantly drier compared to the others in 2014 (Figure A.1), but this is currently not accounted for in our model. In fact, we are currently neglecting the spatial variability of rainfall over the catchment, by driving HELF with one rainfall time series only (average of the time series from the grid cells overlapping with the catchment area). A second potential reason for this mismatch is related to how suitable these areas are in terms of soil pH for development progress of the parasite life cycle. In fact, Galba truncatula snails (the intermediate host for *F. hepatica* in the UK) are known to prefer slightly acidic soils, i.e. soil pH between 5.5 and 6.5 (Ollerenshaw 1971). Figure A.2 shows that only 25.5% of the area of A2 has slightly acidic soil (NSRI LandIS 2017) and that the value is higher for A5 (40.4%), but still lower than the

average across the 9 sub-areas (43.7%). However, risk of infection in HELF is currently calculated based on temperature and soil moisture only, neglecting potential effects of soil pH on snail presence.

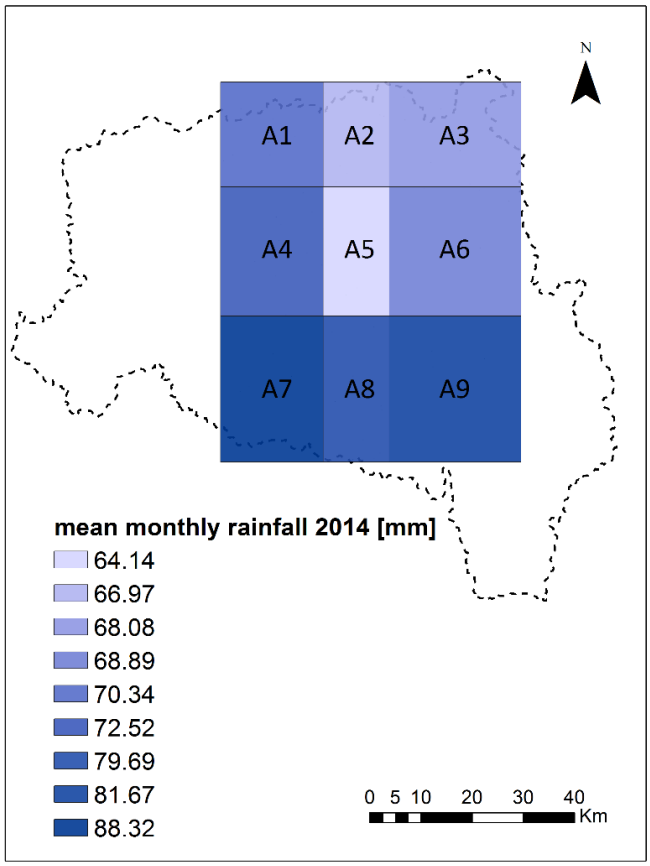

Figure A.1 2014 rainfall levels for the 9 sub-areas within the Severn Catchment, which we use when fitting the epidemiological model component of HELF to the spatial FEC-based dataset.

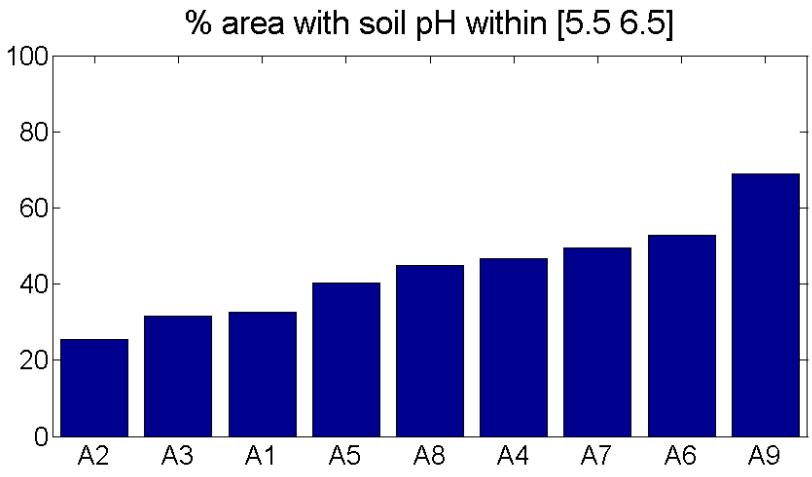

Figure A.2 Percentage area with slightly acidic soil (and thus presumably suitable for G. truncatula snails) for our 9 sub-areas within the Severn Catchment (from lowest to highest).

Finally, we are currently driving HELF with a scenario which assumes continuous livestock grazing and absence of disease management over the catchment. This could also result in mismatches depending on the real farm management strategies in use, e.g. housing of cattle or administration of treatment may result in lower observed risk than what simulated using our model.

A.1.4 Additional information on the Ollerenshaw Index

The Ollerenshaw Index (M_t), originally proposed by Ollerenshaw and Rowlands (1959), and subsequently modified for values in mm rather than inches (e.g. see Fox et al. (2011)), is calculated as follows: $M_t = n\left(\frac{R}{25.4} - \frac{P}{25.4} + 5\right)$. Where:

- M_t is a monthly index of risk of infection with fasciolosis;
- n is the monthly number of rainy days (above 1mm);
- R is the monthly rainfall [mm];
- P is the monthly potential evapotranspiration [mm], calculated using the Hargreaves equation as in HELF (Allen et al. 1998; Droogers and Allen 2002).

Figure A.3 shows a comparison in time between the Ollerenshaw risk index and the abundance of infective metacercariae on pasture simulated using HELF (measure of environmental suitability for disease transmission) for the River Tawe Catchment.

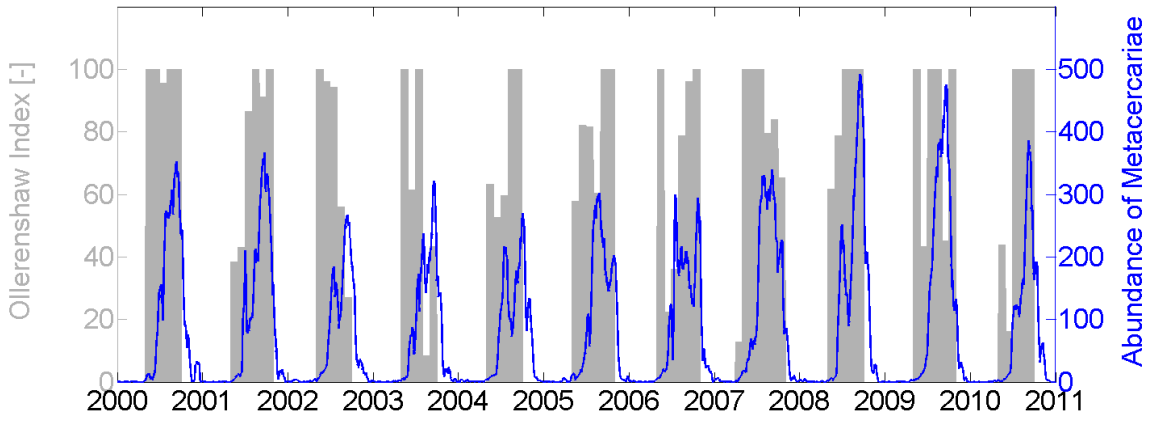

Figure A.3 Temporal comparison of the risk pattern obtained using the Ollerenshaw Index (in grey) with pasture contamination simulated using HELF (in blue), over our whole simulation period (2000-2010) for the Tawe Catchment.

A.2 Supplements to Chapter 4

A.2.1 Additional information on the parameterisation of the hydrological component of HELF across UK catchments

For simulating the risk of liver fluke infection across UK catchments, we estimate parameters for the hydrological model component of HELF by using signatures derived from streamflow observations (from the National River Flow Archive, NRFA). Different hydrological signatures can be used to constrain different aspects of the model (Sawicz et al. 2011; Yadav et al. 2007). Here, based on findings by Yadav et al. (2007), and given that we are mainly interested in constraining the water balance to verify our representation of soil moisture, we use the runoff ratio, combined with the slope of the Flow Duration Curve (FDC) as an index of flow variability (Figure A.4). We calculate both following Sawicz et al. (2011) and Yadav et al. (2007). Specifically,

- The runoff ratio is the (dimensionless) ratio between long-term average streamflow, Q, and long-term average rainfall, R. "It represents the long-term water balance separation between water being released from the catchment as streamflow and as evapotranspiration (assuming no net change in storage)" (Sawicz et al. 2011). Catchments with high ratio have large amounts of water leaving the catchment as streamflow, whereas those with low ratio are evapotranspiration-dominated, with more water leaving as evapotranspiration.

$$runoff\ ratio = \frac{Q}{R}$$

- The Flow Duration Curve (also dimensionless) is the distribution of probabilities of streamflow being equal to or greater than a certain magnitude (see Figure A.5). Here, we derive it for each (gauged) UK catchment using daily streamflow data and we focus on the part between the 33rd and the 66th streamflow percentiles as in Sawicz et al. (2011) and Yadav et al. (2007). Catchments with a high slope have a variable flow regime, while those with lower value have more damped responses (either because of widespread and year-round rainfall and/or because they are groundwater-dominated).

$$slope\ of\ FDC = \frac{\ln(Q_{33\%}) - \ln(Q_{66\%})}{(0.66 - 0.33)}$$

In order to estimate parameters, for each catchment:

- First, we sample a large number of parameter sets from a priori ranges (Table 3.1, Chapter 3);
- Second, we run the model with each set, obtaining an ensemble of model realisations;
- Third, we identify a pareto front (i.e. trade-off when maximising the match with both observed runoff ratio and observed central slope of FDC);
- Finally, we pick the corner solution as the "best" parameter set.

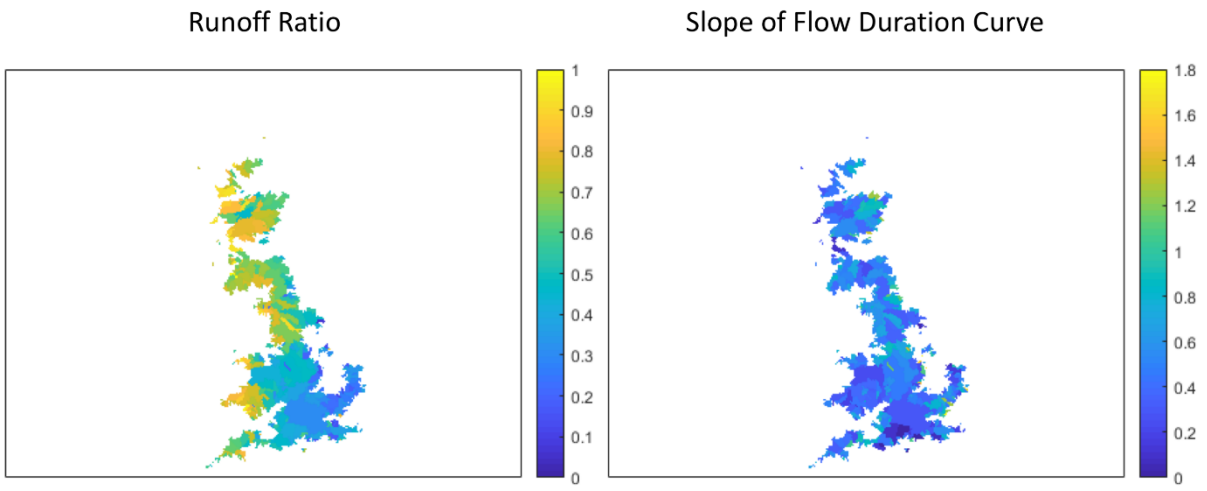

Figure A.4 Observed values for the two hydrological signatures employed in our analysis (gauged UK catchments).

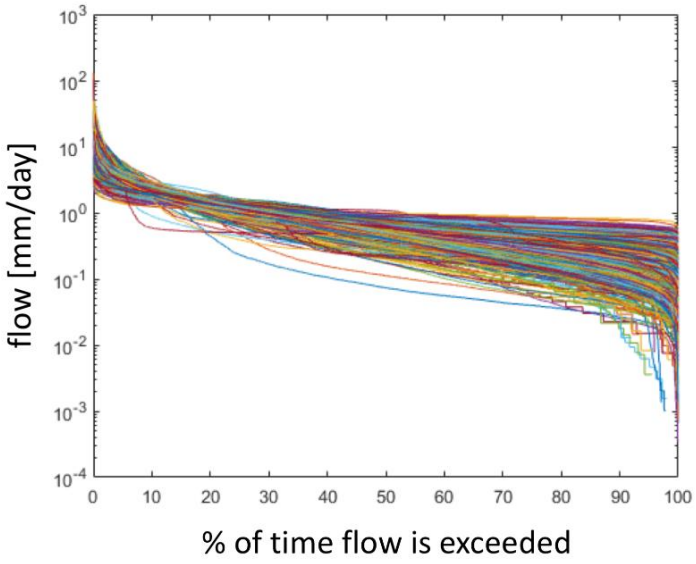

Figure A.5 Flow Duration Curves for the (gauged) UK catchments in our analysis (normalized by mean flows to facilitate comparison).

A.2.2 Additional information on implementation of the drug-based control strategy

As current treatment-based approaches usually employ whole-herd treatments, rather than having specific high-risk targets (Morgan et al. 2013), we implement our assumed treatment-based disease control strategy for all catchments by, every year, *(i)* setting egg counts to zero over January-May and *(ii)* allowing eggs to linearly increase back to the constant value of 100 eggs/day over June (as the rate of reinfection by May is expected to be rather low), over the whole catchment. This is implemented by accordingly modifying the egg scenario, which is an input to HELF (see Chapter 3, Section 3.2.3).

A.2.3 Additional information on ANOVA

To investigate the relative contribution of environmental drivers and their interactions to disease risk variability across the UK, we perform a 5-way ANOVA experiment for each of our 9 regions. This means that, for every region, we consider 5 potential sources of variation (factors) and one response variable. The 5 factors we use are: number of rainy days (RD), rainfall (R), temperature (T), potential evapotranspiration (P) and topography (TOPO). The response variable we are interested in is disease risk, as modelled using either the Ollerenshaw Index or HELF. In order to perform ANOVA, each factor needs to be classified into a number of levels. In our case, each of the 5 factors has 2 levels, which means we have a 2^5 experiment, i.e. 32 combinations of factor levels, each associated to an observation of the response variable. The fact all these combinations are present in our dataset makes our experiment "fully-crossed", which allows us to study the effect of interactions between factors on disease risk. However, the number of observations we have for each combination may differ, which often makes our ANOVA test "unbalanced". As, when applying ANOVA to unbalanced data, the resulting sum-of-squares will depend on the order in which the sources of variation are considered, instead of performing one test per region only, we perform one test for each possible order of our 5 factors, and then evaluate the resulting ranking of drivers on average across these. Tables A.1 and A.2 summarise regional ANOVA results obtained with one specific order of drivers, as an example, for the Ollerenshaw Index and HELF, respectively. They include sum-of-squares and p-values associated with individual drivers and interaction terms, as well as relative proportions of the variance that remain unaccounted for (i.e. the error terms). Results are statistically significant (i.e. factors are important drivers of disease risk) if their p-value is ≤ 0.05 (highlighted in green in both tables). In looking at differences between the two models in this example, it is interesting to note that, when disease risk is modelled using the Ollerenshaw Index (Table A.1), topography only results significant once, and the majority of significant interaction terms are interactions between climatic factors only (e.g. see RD x P for NScot, and RD x P, R x P, T x P for WScot). On the other hand, when disease risk is modelled using HELF (Table A.2), topography matters significantly in all three Scottish regions, and significant interaction terms are not always necessarily interactions between climatic factors. For example, while in flat areas in the south east of the country (SE and EAng), it is the interaction between climatic drivers that explains most of disease risk variability (e.g. see RD x T for SE, and of RD x T and R x P for EAng), along the west coast of England and Wales disease risk shows higher sensitivity to interactions between climatic characteristics and topography (e.g. see P x TOPO for SW and RD x TOPO for NW). Finally, we remark that, in this example, percent contributions do not always sum to 100 and error terms are large. The former is due to the fact that partitioned variances do not always sum up to 1 when ANOVA tests are unbalanced. The latter may partly be affected by this, but also potentially indicates that the complex dynamics of disease risk cannot be explained by simple linear models of the explanatory variables.

	SW		Mid		NE		NScot		WScot		SE		EAng		EScot		NW	
Source	**Sum Sq**	**p-val**	**Sum Sq**	**p-val**	**Sum Sq**	**p-val**	**Sum Sq**	**p-val**	**Sum Sq**	**p-val**	**Sum Sq**	**p-val**	**Sum Sq**	**p-val**	**Sum Sq**	**p-val**	**Sum Sq**	**p-val**
RD	$4.9x10^4$	0	$1.4x10^5$	0	$5x10^4$	0	94.5	0.76	$1x10^4$	$1x10^{-3}$	$2.4x10^3$	$2x10^{-4}$	$2.5x10^3$	0	$3.1x10^4$	0	475.3	0.44
R	$4.5x10^4$	0	$8.5x10^3$	$4x10^{-3}$	$4.6x10^3$	$5x10^{-3}$	291	0.59	$4.1x10^3$	0.04	$7.9x10^4$	0	$1x10^4$	0	$7.9x10^3$	0.01	279.6	0.55
T	48.8	0.86	82.1	0.77	$1.4x10^3$	0.11	$1x10^4$	$4x10^{-3}$	$3.8x10^4$	0	199.9	0.26	146.4	0.22	$1x10^5$	0	$2x10^4$	0
P	$4.1x10^4$	0	$3.5x10^3$	0.06	270.8	0.49	$7.3x10^3$	0.01	469.1	0.48	$1.3x10^4$	0	$1.4x10^4$	0	$1.6x10^4$	$3x10^{-4}$	$2.5x10^3$	0.08
TOPO	402.4	0.62	$1.6x10^3$	0.20	$3x10^3$	0.02	806.2	0.37	995	0.30	68	0.51	30.9	0.57	$2.9x10^3$	0.11	$1.8x10^3$	0.13
RD x R	$1.1x10^3$	0.42	84.3	0.77	23.7	0.84	41.5	0.84	192.6	0.65	863.8	0.02	363.9	0.05	$1.1x10^3$	0.33	31.1	0.84
RD x T	$3.2x10^3$	0.16	322	0.56	$2.1x10^3$	0.05	0.1	0.99	158.3	0.68	11.1	0.79	106.4	0.29	$1.1x10^3$	0.33	9.5	0.91
RD x P	376	0.63	$1.9x10^3$	0.16	72.3	0.72	$5x10^3$	0.03	$1.5x10^4$	$2x10^{-3}$	70.3	0.51	182.2	0.17	$1.9x10^3$	0.20	18.8	0.88
RD x TOPO	93	0.81	612	0.43	$2.9x10^3$	0.02	4.8	0.94	54.4	0.81	309.8	0.16	9.6	0.75	$6.8x10^3$	0.02	91.2	0.73
R x T	0	0.99	270.2	0.60	69.3	0.72	475.1	0.49	$1.2x10^3$	0.26	0.9	0.94	0.7	0.93	$1.2x10^3$	0.29	382.4	0.49
R x P	19.6	0.91	0	0.99	77.3	0.71	538.5	0.46	$1.1x10^4$	$1x10^{-3}$	491.2	0.08	321	0.07	483.6	0.51	13.3	0.90
R x TOPO	185.5	0.74	0.8	0.98	145.7	0.61	650.2	0.42	0	0.99	$1.7x10^3$	$1x10^{-3}$	0.2	0.96	654.9	0.45	316.7	0.53
T x P	$1.1x10^4$	0.01	6.9	0.93	730.6	0.25	187.7	0.66	$1x10^4$	$2x10^{-3}$	$1.8x10^3$	$1x10^{-3}$	21.8	0.63	$9.4x10^3$	$5x10^{-3}$	$1.5x10^3$	0.17
T x TOPO	446.8	0.60	62.3	0.80	372.8	0.42	$1.5x10^3$	0.22	$1.7x10^3$	0.17	49.7	0.58	0.4	0.95	7	0.94	1.9	0.96
P x TOPO	0.3	0.99	106.7	0.74	59	0.75	0.9	0.97	0	0.99	51.3	0.57	30.9	0.57	238.4	0.65	$2.1x10^3$	0.11
Error	$1x10^5$		$7x10^4$		$7x10^4$		$1x10^4$		$3x10^4$		$2x10^4$		$9.4x10^3$		$7x10^4$		$6x10^4$	
Total	$2.8x10^5$		$2.4x10^5$		$1.4x10^5$		$4.2x10^4$		$1.3x10^5$		$1.2x10^5$		$3.7x10^4$		$2.6x10^5$		$1x10^5$	

Table A.1 Example of regional 5-way ANOVA of Rainy Days (RD), Rain (R), Temperature (T), Potential evapotranspiration (P) and Topography (TOPO) on disease risk modelled using the Ollerenshaw Index. Significant p-values (≤ 0.05) are highlighted in green.

	SW		Mid		NE		NScot		WScot		SE		EAng		EScot		NW	
Source	**Sum Sq**	**p-val**	**Sum Sq**	**p-val**	**Sum Sq**	**p-val**	**Sum Sq**	**p-val**	**Sum Sq**	**p-val**	**Sum Sq**	**p-val**	**Sum Sq**	**p-val**	**Sum Sq**	**p-val**	**Sum Sq**	**p-val**
RD	$2.9x10^{9}$	0.008	$6.4x10^{9}$	0	$9.1x10^{8}$	0.12	$4.1x10^{7}$	0.62	$9.3x10^{7}$	0.58	$1.5x10^{9}$	0.02	$5.4x10^{6}$	0.89	$4.8x10^{8}$	0.20	$8.3x10^{7}$	0.65
R	$3x10^{9}$	0.007	$1.4x10^{8}$	0.52	$1.3x10^{9}$	0.07	$7.9x10^{8}$	0.04	$2.2x10^{7}$	0.79	$8x10^{8}$	0.09	$5.9x10^{7}$	0.66	$3.1x10^{8}$	0.31	$6.4x10^{7}$	0.69
T	$7.6x10^{7}$	0.67	$5x10^{7}$	0.70	$3.3x10^{8}$	0.349	$1.2x10^{9}$	0.01	$6.5x10^{8}$	0.15	$1.7x10^{8}$	0.42	$4.9x10^{7}$	0.69	$4.6x10^{9}$	$2x10^{-4}$	$3.2x10^{7}$	0.78
P	$7.2x10^{8}$	0.19	$7x10^{8}$	0.16	$6x10^{6}$	0.90	$9.2x10^{8}$	0.03	$3.7x10^{8}$	0.28	$6.6x10^{7}$	0.62	$1.1x10^{9}$	0.05	$2.8x10^{8}$	0.33	$2.1x10^{8}$	0.47
TOPO	$1x10^{9}$	0.11	$8.1x10^{8}$	0.13	$5.1x10^{7}$	0.71	$1.3x10^{9}$	$9x10^{-3}$	$1.5x10^{9}$	0.03	$2.7x10^{8}$	0.31	$4x10^{7}$	0.72	$2x10^{9}$	0.01	$1.7x10^{7}$	0.84
RD x R	$4.5x10^{7}$	0.74	$5.2x10^{7}$	0.70	$6.7x10^{5}$	0.97	$1.2x10^{5}$	0.98	0	0.99	$3.1x10^{7}$	0.73	$9.6x10^{7}$	0.57	$1.6x10^{7}$	0.81	$1.8x10^{8}$	0.51
RD x T	$1.4x10^{9}$	0.06	$7.6x10^{8}$	0.14	$7.4x10^{8}$	0.16	$1.2x10^{8}$	0.4	$5.6x10^{7}$	0.67	$1.6x10^{9}$	0.01	$2.9x10^{9}$	$2x10^{-3}$	$1.1x10^{8}$	0.55	$1.6x10^{8}$	0.53
RD x P	$1.9x10^{8}$	0.49	$8.9x10^{7}$	0.61	$2.3x10^{9}$	0.01	0	0.99	$1.9x10^{9}$	0.02	$8.3x10^{8}$	0.08	$3.3x10^{8}$	0.30	$6.4x10^{8}$	0.14	$4.3x10^{7}$	0.74
RD x TOPO	$8.3x10^{8}$	0.16	$1.6x10^{8}$	0.50	$3.3x10^{8}$	0.35	$7.6x10^{5}$	0.95	$4.3x10^{7}$	0.71	$2.5x10^{8}$	0.34	$7.5x10^{8}$	0.12	$3.2x10^{3}$	0.99	$2.6x10^{9}$	0.01
R x T	$7.1x10^{7}$	0.68	0	0.99	$4.3x10^{7}$	0.73	$7.1x10^{4}$	0.98	$5x10^{8}$	0.21	434.8	0.99	$3x10^{8}$	0.32	$2.1x10^{6}$	0.93	$1.8x10^{8}$	0.50
R x P	$7.4x10^{8}$	0.18	$2.5x10^{8}$	0.39	$7x10^{7}$	0.67	0	0.99	$1.2x10^{8}$	0.53	$3.8x10^{8}$	0.24	$1.2x10^{9}$	0.05	$1.2x10^{9}$	0.04	$7.5x10^{8}$	0.17
R x TOPO	$3.2x10^{8}$	0.38	$7x10^{7}$	0.65	$1.3x10^{9}$	0.06	$5.7x10^{6}$	0.85	$6.6x10^{5}$	0.96	$1x10^{9}$	0.06	$4x10^{8}$	0.25	$2.3x10^{8}$	0.38	$1.5x10^{6}$	0.95
T x P	$7x10^{7}$	0.68	0	0.99	$9.5x10^{8}$	0.11	$1.5x10^{8}$	0.34	$2.8x10^{8}$	0.34	$1.9x10^{8}$	0.40	$1x10^{9}$	0.07	$2.6x10^{8}$	0.35	$3.6x10^{7}$	0.76
T x TOPO	$5.6x10^{7}$	0.71	$1.2x10^{9}$	0.07	$3x10^{8}$	0.37	0	0.99	$4x10^{8}$	0.26	$2.7x10^{8}$	0.32	$3.6x10^{8}$	0.28	$6.7x10^{7}$	0.63	$1.9x10^{7}$	0.83
P x TOPO	$2.3x10^{9}$	0.02	$8.4x10^{5}$	0.96	$2.7x10^{8}$	0.40	$3.3x10^{8}$	0.17	$2x10^{8}$	0.42	$5.1x10^{8}$	0.17	$1.9x10^{7}$	0.80	$7.2x10^{8}$	0.12	$3.6x10^{8}$	0.35
Error	$4.4x10^{10}$		$2.6x10^{10}$		$5.2x10^{10}$		$3.5x10^{9}$		$8.8x10^{9}$		$3x10^{10}$		$3x10^{10}$		$1.8x10^{10}$		$3x10^{10}$	
Total	$5.8x10^{10}$		$3.7x10^{10}$		$6.1x10^{10}$		$8.5x10^{9}$		$1.5x10^{10}$		$4.5x10^{10}$		$4.1x10^{10}$		$2.9x10^{10}$		$3.6x10^{10}$	

Table A.2 Example of regional 5-way ANOVA of Rainy Days (RD), Rain (R), Temperature (T), Potential evapotranspiration (P) and Topography (TOPO) on disease risk modelled using HELF. Significant p-values (≤ 0.05) are highlighted in green.

A.3 Supplements to Chapter 5

A.3.1 Additional information on bias correction of precipitation data

Among the bias correction methods reviewed by Teutschbein and Seibert (2012), we choose to use the local intensity scaling approach for precipitation in order to adjust not only for potential biases in the mean, but also for errors in the wet-day frequency and intensity of our rainfall time series. In fact, overestimating the number of wet days is a common error in climate models (Murphy et al. 2018; Rajczak and Schär 2017) and the number of wet days is a particularly critical climate characteristic with respect to the life cycle of liver fluke. The local intensity scaling method consists of two main steps. First, we calibrate an ensemble member-specific precipitation threshold, so that the number of simulated days above this threshold corresponds to the number of observed days with positive rainfall (i.e. above 0 mm). Then, the number of wet days for both historical and future simulations is adjusted by using the threshold, so that all days below the threshold are set back to being days with 0 mm of rainfall. Second, both historical and future simulations are adjusted using an intensity scaling factor calculated based on simulated and observed long-term monthly mean wet-day intensities (Teutschbein and Seibert 2012). Figure A.6 shows that, in our application, the calibrated ensemble member-specific precipitation threshold varies between 0.2 and 1 mm, and (if we look at the mean across ensemble members) seems higher during spring - early summer, which indicates excessive days with low rainfall in the climate simulations especially from February to July.

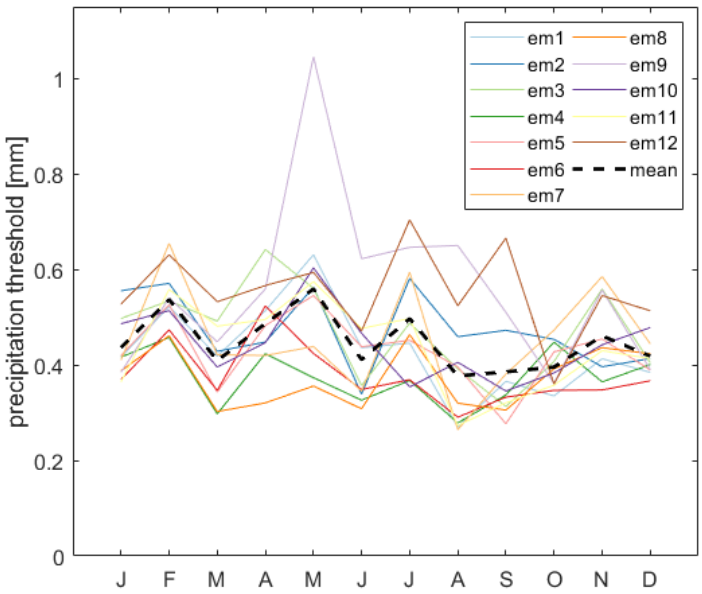

Figure A.6 Monthly adjusted precipitation thresholds used within the local intensity scaling bias correction approach. Each line is the average across catchments for an ensemble member.

A.3.2 Additional information on regional projected changes in the seasonality of liver fluke infection

Figure A.7 shows projected changes in the seasonality of liver fluke infection across UK regions (future, 2061-2080, vs. past, 1981-2000). From here we see that, in most areas, the yearly peak of infection is reduced in the future compared to the past (especially in the south regions EAng, SE, SW and Mid), and that the transmission period lengthens, with the emergence of two separate periods at higher risk rather than one. On the other hand, this does not seem to be the case for the north of the country. In fact, in north, west and east Scotland, where summer declines in the number of rainy days and increases in the number of hot days are not as extreme as in the south, the projected overall increase in infection pressure seems to be linked more to an increase in magnitude of the summer peak of infection, rather than only to an extension of the transmission season.

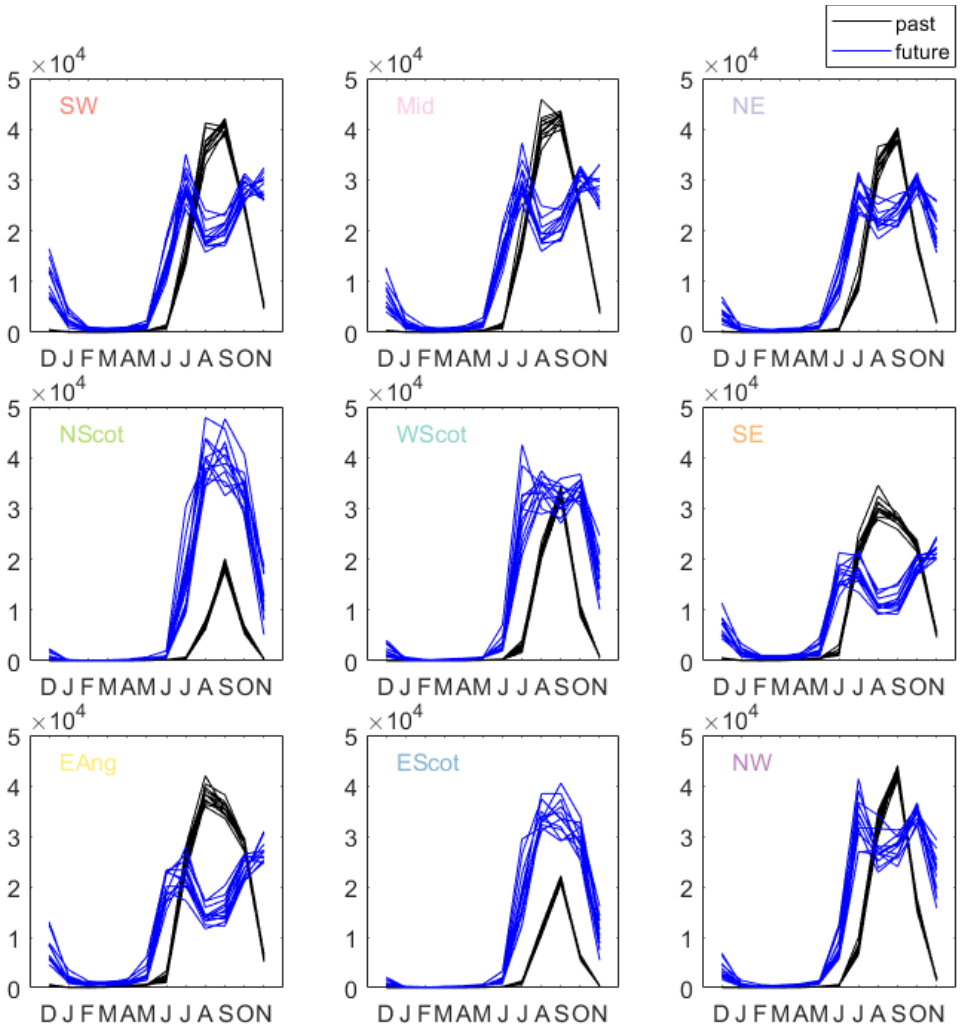

Figure A.7 Monthly changes in the seasonality of liver fluke infection projected for the future (2061-2080) compared to the past (1981-2000) across 9 UK regions.

A.4 Curriculum Vitae

Ludovica Beltrame

(ludovica.beltrame@bristol.ac.uk)

EDUCATION

07/2015- 07/2019	**PhD in Water and Environmental Engineering** University of Bristol, Bristol, UK Dissertation title: "Simulating the risk of liver fluke infection in the UK through mechanistic hydro-epidemiological modelling" Supervisors: Professor Thorsten Wagener and Professor Eric Morgan
04/2018- 07/2018	**Research visit** International Institute for Applied Systems Analysis (IIASA), Vienna, Austria Developed knowledge of large-scale climate change impact assessments using climate projection data. Supervisor: Dr. Yoshihide Wada
09/2014- 06/2015	**Water Informatics: Science and Engineering Centre for Doctoral Training postgraduate school** Modules included: Hydroinformatics Tools, Systems Analysis, Software Programming, Computational Hydrology, Environmental and Computational Hydraulics.
09/2011- 12/2013	**M.Sc. in Environmental Engineering** Politecnico di Milano, Milan, Italy Dissertation title: "ENSO teleconnection patterns on large scale water resources systems". Final mark: 110/110, *cum laude*.
09/2008- 09/2011	**B.Sc. in Environmental Engineering** Politecnico di Milano, Milan, Italy Dissertation title: "Medium-to-long term streamflow prediction for water resources systems management". Final mark: 96/110.

WORK EXPERIENCE

Autumn 2015, 2016 and 2017	**Graduate Teaching Assistant for the M.Sc. module "Matlab and Numerical Methods" at the University of Bristol, Bristol, UK** In charge of one-to-one marking of students' coursework, which involved planning with other teaching assistants, answering questions and explaining unclear points.
05/2014-08/2014	**Risk and Compliance Intern at Protiviti, Milan, Italy** Assisted senior consultants and managers in identifying business and compliance risks for client companies and contributed to developing models of enterprise risk management, tailored to the specific industries.

SCHOLARSHIPS AND AWARDS

05/2016	Best oral presentation at British Hydrological Society Peter Wolf Symposium 2016, Bristol, UK.
09/2014-09/2018	Engineering and Physical Sciences Research Council (EPSRC) Doctoral Award.
08/2013-12/2013	Scholarship "Tesi all'estero" for working at my M.Sc. thesis at the Singapore University of Technology and Design (SUTD), Singapore.
09/2010-02/2011	Erasmus scholarship to be an exchange student at the Universidad Politecnica de Madrid, Madrid, Spain.

PUBLICATIONS

Beltrame, L., Vineer, H. R., Walker, J. G., Morgan, E. R., Vickerman, P., Wada, Y. and Wagener, T. *Future risk of liver fluke infection across the UK under climate change*. In preparation.

Beltrame, L., Vineer, H. R., Walker, J. G., Morgan, E. R., Vickerman, P. and Wagener, T. *Opportunities for disease control through environmental management: the example of liver fluke in the UK*. Under submission to PNAS.

Beltrame, L., Dunne, T., Vineer, H. R., Walker, J. G., Morgan, E. R., Vickerman, P., McCann, C. M., Williams, D. J. L. and Wagener, T. (2018). *A mechanistic hydro-epidemiological model of liver fluke risk*. Journal of the Royal Society Interface, 15(145). http://doi.org/10.1098/rsif.2018.0072

Beltrame, L., Carbonin, D., Galelli, S., Castelletti, A. and Giuliani, M. (2014). *Quantifying ENSO impacts at the basin scale using the Iterative Input variable Selection algorithm*, Proceedings of the 7th International Congress on Environmental Modeling and Software (iEMSs 2014), June 15–19, edited by D. P. Ames, N. W. T. Quinn, and A. E. Rizzoli, San Diego, California.

CONFERENCE PRESENTATIONS

Talks:

How can mechanistic hydro-epidemiological models support disease management under environmental change? The example of fasciolosis. Royal Society for Public Health Conference "What is the future of water and public health?", 2018, Sheffield, UK.

How do Changes in Hydro-Climate Conditions Alter the Risk of Infection With Fasciolosis? American Geophysical Union Fall Meeting, 2017, New Orleans, USA.

Simulating the risk of Liver Fluke infection using a mechanistic hydro-epidemiological model. British Association for Veterinary Parasitology meeting, 2016, Bristol, UK.

Posters:

Understanding the variability of controls on risk of infection with liver fluke to target disease control strategies under changing climate. European Geosciences Union General Assembly, 2017, Vienna, Austria.

Assessing the impact of climate change on risk of infection with Fasciolosis using a new mechanistic hydro-epidemiological model. Epidemics6, 2017, Barcelona, Spain.

Simulating the risk of Liver Fluke infection through mechanistic hydro-epidemiological modelling. Impact of Environmental Changes on Infectious Diseases, 2017, Trieste, Italy.

Assessing the Role of Climate Variability on Liver Fluke Risk in the UK Through Mechanistic Hydro-Epidemiological Modelling. American Geophysical Union Fall Meeting, 2016, San Francisco, USA.

OTHER SKILLS AND INTERESTS

- Languages: Italian (mother tongue), English (Certificate in Advanced English), Spanish (Certificación de Español Aplicado a la Ciencia y a la Tecnología).
- IT Skills: Matlab, ArcGIS, LaTex.
- Management skills: organised project meetings in an inter-disciplinary setting as part of my PhD; co-organised the Natural Systems and Processes Poster Session 2017, a University of Bristol event for postgraduate students, aimed at promoting inter-disciplinary collaboration across departments; co-supervised a B.Sc. thesis in Global Health (University of Bristol, 2019).
- Communication skills: presented to different audiences within my PhD, including at group seminars and international conferences; contributed to public engagement projects such as "Meet the expert on World Water Day" (@Bristol, Bristol, 03/2016), engaging on water-related issues with school children and their teachers.
- Interests: I have been playing the piano since I was little, I practice yoga daily and love sailing and travelling.

This page was intentionally left blank

Bibliography

Addor, N., Newman, A. J., Mizukami, N., & Clark, M. P. (2017). The CAMELS data set: Catchment attributes and meteorology for large-sample studies. *Hydrology and Earth System Sciences*, 21, 5293–5313. http://doi.org/10.5194/hess-21-5293-2017

Allan, B. F., Keesing, F., & Ostfeld, R. S. (2003). Effect of Forest Fragmentation on Lyme Disease Risk. *Conservation Biology*, *17*(1), 267–272. http://doi.org/10.1046/j.1523-1739.2003.01260.x

Allen, R. G., Pereira, L. S., Raes, D., Smith, M., & Ab, W. (1998). Crop evapotranspiration - Guidelines for computing crop water requirements.

Altizer, S., Ostfeld, R. S., Johnson, P. T. J., Kutz, S., & Harvell, C. D. (2013). Climate Change and Infectious Diseases: From Evidence to a Predictive Framework. *Science*, *341*(6145), 514–519. http://doi.org/10.1126/science.1239401

Altizer, S., Dobson, A., Hosseini, P., Hudson, P., Pascual, M., & Rohani, P. (2006). Seasonality and the dynamics of infectious diseases. *Ecology Letters*, *9*(4), 467–484. http://doi.org/10.1111/j.1461-0248.2005.00879.x

Anderson, R., Truscott, J., & Hollingsworth, T. (2014). The coverage and frequency of mass drug administration. *Phil. Trans. R. Soc. B*, *369*(20130435). http://doi.org/http://dx.doi.org/10.1098/rstb.2013.0435

Andrews, S. J. (1999). *The Life Cycle of Fasciola hepatica*.

Balmford, A., Green, R. E., & Scharlemann, J. P. W. (2005). Sparing land for nature: Exploring the potential impact of changes in agricultural yield on the area needed for crop production. *Global Change Biology*, *11*(10), 1594–1605. http://doi.org/10.1111/j.1365-2486.2005.001035.x

Baylis, M., Mellor, P. S., & Meiswinkel, R. (1999). Horse sickness and ENSO in South Africa. *Nature*, *397*.

Beesley, N. J., Caminade, C., Charlier, J., Flynn, R. J., Hodgkinson, J. E., Martinez-moreno, A., … Williams, D. J. L. (2018). Fasciola and fasciolosis in ruminants in Europe: Identifying research needs. *Transboundary and Emerging Diseases*, *65*, 199–216. http://doi.org/10.1111/tbed.12682

Beltrame, L., Dunne, T., Vineer, H. R., Walker, J. G., Morgan, E. R., Vickerman, P., … Wagener, T. (2018). A mechanistic hydro-epidemiological model of liver fluke risk. *Journal of the Royal Society Interface*, *15*(145). http://doi.org/10.1098/rsif.2018.0072

Bennema, S. C., Ducheyne, E., Vercruysse, J., Claerebout, E., Hendrickx, G., & Charlier, J. (2011). Relative importance of management, meteorological and environmental factors in the spatial distribution of Fasciola hepatica in dairy cattle in a temperate climate zone. *International Journal for Parasitology*, *41*(2), 225–233. http://doi.org/10.1016/j.ijpara.2010.09.003

Bennett, R., & Ijpelaar, J. (2005). Updated estimates of the costs associated with thirty four endemic livestock diseases in Great Britain: A note. *Journal of Agricultural Economics*, *56*(1), 135–144. http://doi.org/10.1111/j.1477-9552.2005.tb00126.x

Bertuzzo, E., Azaele, S., Maritan, A., Gatto, M., Rodriguez-Iturbe, I., & Rinaldo, A. (2008). On the space-time evolution of a cholera epidemic. *Water Resources Research*, *44*(1), 1–8. http://doi.org/10.1029/2007WR006211

Bertuzzo, E., Mari, L., Righetto, L., Gatto, M., Casagrandi, R., Blokesch, M., … Rinaldo, A. (2011). Prediction of the spatial evolution and effects of control measures for the unfolding Haiti cholera outbreak. *Geophysical Research Letters*, 38, L06403. http://doi.org/10.1029/2011GL046823

Bertuzzo, E., Mari, L., Righetto, L., Gatto, M., Casagrandi, R., Rodriguez-Iturbe, I., & Rinaldo, A. (2012). Hydroclimatology of dual-peak annual cholera incidence: Insights from a spatially explicit model. *Geophysical Research Letters*, 39, L05403. http://doi.org/10.1029/2011GL050723

Bertuzzo, E., & Mari, L. (2017). Hydrology, water resources and the epidemiology of water-related diseases. *Advances in Water Resources*, *108*, 329–331. http://doi.org/10.1016/j.advwatres.2017.09.011

Bertuzzo, E., Finger, F., Mari, L., Gatto, M., & Rinaldo, A. (2016). On the probability of extinction of the Haiti cholera epidemic. *Stochastic Environmental Research and Risk Assessment*, *30*(8), 2043–2055. http://doi.org/10.1007/s00477-014-0906-3

Beven, K. (1993). Prophecy, reality and uncertainty in distributed hydrological modelling. *Advances in Water Resources*, 16, 41–51. http://doi.org/10.1016/0309-1708(93)90028-E

Beven, K., Lamb, R., Quinn, P., Romanowicz, R., & Freer, J. (1995). *TOPMODEL*. In: Sing V. P. (ed) *Computer models of watershed hydrology*, Water Resource Publications, Colorado. pp. 627–668.

Beven, K. (1997). TOPMODEL: a critique. *Hydrological Processes*, *11*(9), 1069–1085. http://doi.org/10.1002/(SICI)1099-1085(199707)11:9<1069::AID-HYP545>3.0.CO;2-O

Beven, K. J., & Kirkby, M. J. (1979). A physically based, variable contributing area model of basin hydrology. *Hydrological Sciences Bulletin*, *24*(1), 43–69. http://doi.org/10.1080/02626667909491834

Bierbaum, R. M., Fay, M., & Ross-Larson, B. (2010). *World Development Report 2010. Development and Climate Change*. Retrieved from http://documents.worldbank.org/curated/en/2010014681599136 57/World-development-report-2010-development-and-climate-change

Bierkens, M. (2015). Global hydrology 2015: State, trends, and directions. *Water Resources Research*, *51*(7), 4923–4947. http://doi.org/10.1002/2015WR017173

Bomblies, A., Duchemin, J. B., & Eltahir, E. A. B. (2008). Hydrology of malaria: Model development and application to a Sahelian village. *Water Resources Research*, *44*(12), 1–26. http://doi.org/10.1029/2008WR006917

Bouley, T., Gilbert, M., Whung, P.-Y., Gall, F. Le, & Plante, C. (2014). *Reducing Climate-Sensitive Disease Risks*. Retrieved from

http://documents.worldbank.org/curated/en/486511468167944431/Reducing-climate-sensitive-disease-risks

Brennan, G. P., Fairweather, I., Trudgett, A., Hoey, E., McCoy, McConville, M., … Brophy, P. M. (2007). Understanding triclabendazole resistance. *Experimental and Molecular Pathology*, *82*(2), 104–109. http://doi.org/10.1016/j.yexmp.2007.01.009

Brown, L., Medlock, J., & Murray, V. (2014). Impact of drought on vector-borne diseases - how does one manage the risk? *Public Health*, *128*(1), 29–37. http://doi.org/10.1016/j.puhe.2013.09.006

Byrne, A. W., Mcbride, S., Lahuerta-marin, A., Guelbenzu, M., Mcnair, J., Skuce, R. A., & Mcdowell, S. W. J. (2016). Liver fluke (Fasciola hepatica) infection in cattle in Northern Ireland : a large-scale epidemiological investigation utilising surveillance data. *Parasites & Vectors*, *9*(209), 1–14. http://doi.org/10.1186/s13071-016-1489-2

Cable, J., Barber, I., Boag, B., Ellison, A. R., Morgan, E. R., Murray, K., … Cable, J. (2017). Global change, parasite transmission and disease control: lessons from ecology. *Phil. Trans. R. Soc. B*, *372*(1719). http://doi.org/10.1098/rstb.2016.0088

Cambridge Centre for Risk Studies. (2018). *Global Risk Index 2019 Executive Summary*. *Cambridge Centre for Risk Studies, University of Cambridge*.

Caminade, C., van Dijk, J., Baylis, M., & Williams, D. (2015). Modelling recent and future climatic suitability for fasciolosis in Europe. *Geospatial Health*, *9*(2), 301–308. http://doi.org/10.4081/gh.2015.352

Cann, K. F., Thomas, D. R., Salmon, R. L., Wyn-Jones, A. P., & Kay, D. (2013). Extreme water-related weather events and waterborne disease. *Epidemiology and Infection*, *141*(4), 671–686. http://doi.org/10.1017/S0950268812001653

Charlier, J., Bennema, S. C., Caron, Y., Counotte, M., Ducheyne, E., Hendrickx, G., & Vercruysse, J. (2011). Towards assessing fine-scale indicators for the spatial transmission risk of Fasciola hepatica in cattle. *Geospatial Health*, *5*(2), 239–245. http://doi.org/10.4081/gh.2011.176

Charlier, J., Soenen, K., De Roeck, E., Hantson, W., Ducheyne, E., Van Coillie, F., … Vercruysse, J. (2014a). Longitudinal study on the temporal and micro-spatial distribution of Galba truncatula in four farms in Belgium as a base for small-scale risk mapping of Fasciola hepatica. *Parasites & Vectors*, *7*(528). http://doi.org/10.1186/s13071-014-0528-0

Charlier, J., Vercruysse, J., Morgan, E., van Dijk, J., & Williams, D. J. L. (2014b). Recent advances in the diagnosis, impact on production and prediction of Fasciola hepatica in cattle. *Parasitology*, *141*(3), 326–35. http://doi.org/10.1017/S0031182013001662

Claridge, J., Diggle, P., McCann, C. M., Mulcahy, G., Flynn, R., McNair, J., … Williams, D. J. L. (2012). Fasciola hepatica is associated with the failure to detect bovine tuberculosis in dairy cattle. *Nature Communications*, *3*(853). http://doi.org/10.1038/ncomms1840

Clark, M. P., Slater, A. G., Rupp, D. E., Woods, R. a., Vrugt, J. a., Gupta, H. V., … Hay, L. E. (2008). Framework for Understanding Structural Errors (FUSE): A modular framework to diagnose differences between hydrological models. *Water Resources Research*, 44, 1–14. http://doi.org/10.1029/2007WR006735

Coumou, D., & Rahmstorf, S. (2012). A decade of weather extremes. *Nature Climate Change*, *2*(7), 491–496. http://doi.org/10.1038/nclimate1452

Coxon, G., Freer, J., Lane, R., Dunne, T., Howden, N. J. K., Quinn, N., … Woods, R. (2019). DECIPHeR v1: Dynamic fluxEs and ConnectIvity for Predictions of HydRology. *Geoscientific Model Development*, *12*(2285–2306). http://doi.org/10.5194/gmd-2018-205

Craig, M., Le Sueur, D., & Snow, B. (1999). A climate-based distribution model of malaria transmission in sub-Saharan Africa. *Parasitology Today*, *15*(3), 105–111. http://doi.org/10.1016/S0169-4758(99)01396-4

Dai, A. G. (2013). Increasing drought under global warming in observations and models. *Nature Climate Change*, *3*(1), 52–58. http://doi.org/10.1038/nclimate1633

Dalelane, C., Früh, B., Steger, C., & Walter, A. (2018). A pragmatic approach to build a reduced regional climate projection ensemble for Germany using the EURO-CORDEX 8.5 ensemble. *Journal of Applied Meteorology and Climatology*, 57(3), 477–491. http://doi.org/10.1175/JAMC-D-17-0141.1

De Roeck, E., Van Coillie, F., De Wulf, R., Soenen, K., Charlier, J., Vercruysse, J., … Hendrickx, G. (2014). Fine-scale mapping of vector habitats using very high resolution satellite imagery: A liver fluke case-study. *Geospatial Health*, *8*(3), S671–S683. http://doi.org/10.4081/gh.2014.296

Dormann, C. F., Schymanski, S. J., Cabral, J., Chuine, I., Graham, C., Hartig, F., … Singer, A. (2012). Correlation and process in species distribution models: Bridging a dichotomy. *Journal of Biogeography*, *39*(12), 2119–2131. http://doi.org/10.1111/j.1365-2699.2011.02659.x

Droogers, P., & Allen, R. G. (2002). Estimating reference evapotranspiration under inaccurate data conditions. *Irrigation and Drainage Systems*, 16(1), 33–45. http://doi.org/10.1023/A:1015508322413

Duan, Q., Sorooshian, S., Gupta, H. V., & Gupta, V. (1992). Effective and efficient global optimization for conceptual rainfall-runoff models. *Water Resources Research*, *28*(4), 1015–1031. http://doi.org/10.1029/91WR02985

Ducheyne, E., Charlier, J., Vercruysse, J., Rinaldi, L., Biggeri, A., Demeler, J., … Hendrickx, G. (2015). Modelling the spatial distribution of fasciola hepatica in dairy cattle in Europe. *Geospatial Health*, *9*(2), 261–270. http://doi.org/10.4081/gh.2015.348

Durr, P. A., Tait, N., & Lawson, A. B. (2005). Bayesian hierarchical modelling to enhance the epidemiological value of abattoir surveys for bovine fasciolosis. *Preventive Veterinary Medicine*, *71*, 157–172. http://doi.org/10.1016/j.prevetmed.2005.07.013

Dye, C. (2014). After 2015: infectious diseases in a new era of health and development. *Phil. Trans. R. Soc. B*, *369*(20130426). http://doi.org/10.1098/rstb.2013.0426

Easterling, D. R., Meehl, G. A., Parmesan, C., Changnon, S. A., Karl, T. R., & Mearns, L. O. (2000). Climate Extremes: Observations, Modeling, and Impacts. *Science*, *289*(5487), 2068–2074. http://doi.org/10.1126/science.289.5487.2068

Eisenberg, J. N. S., Brookhart, M. A., Rice, G., Brown, M., & Colford, J. M. (2002). Disease transmission models for public health decision making: Analysis of epidemic and endemic conditions caused by waterborne pathogens. *Environmental Health Perspectives*, *110*(8), 783–790. http://doi.org/10.1289/ehp.02110783

Eisenberg, J. N. S., Desai, M. A., Levy, K., Bates, S. J., Liang, S., Naumoff, K., & Scott, J. C. (2007). Environmental determinants of infectious disease: A framework for tracking causal links and guiding public health research. *Environmental Health Perspectives*, *115*(8), 1216–1223. http://doi.org/10.1289/ehp.9806

Esteban, J. G., Bargues, M. D., & Mas-Coma, S. (1998). Geographical distribution, diagnosis and treatment of human fascioliasis: a review. *Research and Reviews in Parasitology*, *58*(1), 13–42.

Esteban, J. G., González, C., Bargues, M. D., Angles, R., Sánchez, C., Náquira, C., & Mas-Coma, S. (2002). High fascioliasis infection in children linked to a man-made irrigation zone in Peru. *Tropical Medicine and International Health*, *7*(4), 339–348. http://doi.org/10.1046/j.1365-3156.2002.00870.x

Fairweather, I. (2011). Reducing the future threat from (liver) fluke: Realistic prospect or quixotic fantasy? *Veterinary Parasitology*, *180*(1–2), 133–143. http://doi.org/10.1016/j.vetpar.2011.05.034

Fairweather, I. (2005). Triclabendazole: new skills to unravel an old(ish) enigma. *Journal of Helminthology*, *79*(3), 227–234. http://doi.org/10.1079/JOH2005298

Fairweather, I., & Boray, J. C. (1999). Fasciolicides: Efficacy, Actions, Resistance and its Management. *The Veterinary Journal*, *158*, 81–112.

FAO. (2015). *Climate Change and Global Food Systems: global assessments and implications for food security and trade*.

Fischlin, A., Midgley, G. F., Price, J. T., Leemans, R., Gopal, B., Turley, C., … Velichko, A. a. (2007). Ecosystems, their properties, goods and services. In *Climate Change 2007: Impacts, Adaptation and Vulnerability. Contribution of Working Group II to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change*. Retrieved from http://www.treesearch.fs.fed.us/pubs/33102

Fiss, L., Adrien, M. D. L., Marcolongo-pereira, C., Assis-brasil, N. D., Ruas, J. L., & Schild, A. L. (2013). Subacute and acute fasciolosis in sheep in southern Brazil. *Parasitology Research*, *112*, 883–887. http://doi.org/10.1007/s00436-012-3096-2

Fox, N. J., Marion, G., Davidson, R. S., White, P. C. L., & Hutchings, M. R. (2012). Livestock helminths in a changing climate: Approaches and restrictions to meaningful predic. *Animals*, *2*(1), 93–107. http://doi.org/10.3390/ani2010093

Fox, N. J., White, P. C. L., McClean, C. J., Marion, G., Evans, A., & Hutchings, M. R. (2011). Predicting impacts of climate change on fasciola hepatica risk. *PLoS ONE*, *6*(1), e16126. http://doi.org/10.1371/journal.pone.0016126

Fuentes, M. V, Valero, M. A., Bargues, M. D., Esteban, J. G., Angles, R., & Mas-Coma, S. (1999). Analysis of climatic data and forecast indices for human fascioliasis at very high altitude. *Annals of Tropical Medicine & Parasitology*, *93*(8), 835–850.

Garchitorena, A., Sokolow, S. H., Roche, B., Ngonghala, C. N., Jocque, M., Lund, A., … De Leo, G. A. (2017). Disease ecology, health and the environment: a framework to account for ecological and socio- economic drivers in the... *Phil. Trans. R. Soc. B*, *372*(20160128). http://doi.org/10.1098/rstb.2016.0128

Gettinby, G., Hope-Cawdery, M. J., & Graingen, J. N. (1974). Forecasting the incidence of fascioliasis from climatic data. *International Journal of Biometeorology*, *18*(4), 319–323. http://doi.org/10.1007/BF01463722

Global Burden of Disease Study. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990 – 2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*, *392*(10159), 1798–858. http://doi.org/10.1016/S0140-6736(18)32279-7

Gordon, D. K., Zadoks, R. N., Stevenson, H., Sargison, N. D., & Skuce, P. J. (2012). On farm evaluation of the coproantigen ELISA and coproantigen reduction test in Scottish sheep naturally infected with Fasciola hepatica. *Veterinary Parasitology*, *187*(3–4), 436–444. http://doi.org/10.1016/j.vetpar.2012.02.009

Grimm, V., Berger, U., Bastiansen, F., Eliassen, S., Ginot, V., Giske, J., … DeAngelis, D. L. (2006). A standard protocol for describing individual-based and agent-based models. *Ecological Modelling*, 198(1–2), 115–126. http://doi.org/10.1016/j.ecolmodel.2006.04.023

Guillod, B. P., Jones, R. G., Dadson, S. J., Coxon, G., Bussi, G., Freer, J., … Hall, J. W. (2018). A large set of potential past, present and future hydro-meteorological time series for the UK. *Hydrology and Earth System Sciences*, *22*(1), 611–634. http://doi.org/10.5194/hess-22-611-2018

Güntner, A., Uhlenbrook, S., Seibert, J., & Leibundgut, C. (1999). Multi-criterial validation of TOPMODEL in a mountainous catchment. *Hydrological Processes*, *13*(11), 1603–1620. http://doi.org/10.1002/(SICI)1099-1085(19990815)13:11<1603::AID-HYP830>3.0.CO;2-K

Güntner, A., Seibert, J., & Uhlenbrook, S. (2004). Modeling spatial patterns of saturated areas: An evaluation of different terrain indices. *Water Resources Research*, *40*(5), W05114. http://doi.org/10.1029/2003WR002864

Gurarie, D., & Seto, E. Y. W. (2008). Connectivity sustains disease transmission in environments with low potential for endemicity: modelling schistosomiasis with hydrologic and social connectivities. *Journal of the Royal Society Interface*, *6*(35), 495–508. http://doi.org/10.1098/rsif.2008.0265

Halimi, M., Farajzadeh, M., Delavari, M., & Arbabi, M. (2015). Developing a climate-based risk map of fascioliasis outbreaks in Iran. *Journal of Infection and Public Health*, 8, 481–486. http://doi.org/10.1016/j.jiph.2015.04.024

Hartmann, A., Gleeson, T., Rosolem, R., Pianosi, F., Wada, Y., & Wagener, T. (2015). A large-scale simulation model to assess karstic groundwater recharge over Europe and the Mediterranean. *Geoscientific Model Development*, *8*(6), 1729–1746. http://doi.org/10.5194/gmd-8-1729-2015

Harvell, C. D., Mitchell, C. E., Ward, J. R., Altizer, S., Dobson, A. P., Ostfeld, R. S., & Samuel, M. D. (2002). Climate Warming and Disease Risks for Terrestrial and Marine Biota. *Science*, *296*(5576), 2158–2162. http://doi.org/10.1126/science.1063699

Havelaar, A. H., Kirk, M. D., Torgerson, P. R., Gibb, H. J., Hald, T., Lake, R. J., … Silva, N. R. De. (2015). World Health Organization Global Estimates and Regional Comparisons of the Burden of Foodborne Disease in 2010. *PLoS Medicine*, *12*(12), e1001923. http://doi.org/10.1371/journal.pmed.1001923

Haydock, L. A. J., Pomroy, W. E., Stevenson, M. A., & Lawrence, K. E. (2016). A growing degree-day model for determination of Fasciola hepatica infection risk in New Zealand with future predictions using climate change models. *Veterinary Parasitology*, *228*, 52–59. http://doi.org/10.1016/j.vetpar.2016.05.033

Heesterbeek, H., Anderson, R. M., Andreasen, V., Bansal, S., De Angelis, D., Dye, C., … Viboud, C. (2015). Modeling infectious disease dynamics in the complex landscape of global health. *Science*, *347*(6227), aaa4339. http://doi.org/10.1126/science.aaa4339

Hirabayashi, Y., Mahendran, R., Koirala, S., Konoshima, L., Yamazaki, D., Watanabe, S., … Kanae, S. (2013). Global flood risk under climate change. *Nature Climate Change*, *3*(9), 816–821. http://doi.org/10.1038/nclimate1911

Hotez, P. J. (2016). Neglected Tropical Diseases in the Anthropocene: The Cases of Zika, Ebola, and Other Infections. *PLOS Neglected Tropical Diseases*, *10*(4), e0004648. http://doi.org/10.1371/journal.pntd.0004648

Howell, A., Baylis, M., Smith, R., Pinchbeck, G., & Williams, D. (2015). Epidemiology and impact of Fasciola hepatica exposure in high-yielding dairy herds. *Preventive Veterinary Medicine*, *121*(1–2), 41–48. http://doi.org/10.1016/j.prevetmed.2015.05.013

Huson, K. M., Oliver, N. A. M., & Robinson, M. W. (2017). Paramphistomosis of Ruminants: An Emerging Parasitic Disease in Europe. *Trends in Parasitology*, *33*(11), 836–844. http://doi.org/10.1016/j.pt.2017.07.002

Intermap Technologies. (2009). NEXTMap British Digital Terrain 50m resolution (DTM10) Model Data by Intermap, NERC Earth Observation Data Centre, available at: http://catalogue.ceda.ac.uk/uuid/f5d41db1170f41819497d15dd8052ad2

IPCC. (2013). *Climate Change 2013. The Physical Science Basis. Summary for Policymakers*. *Climate Change 2013: The Physical Science Basis. Contribution of Working Group I to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change*.

IPCC. (2014). Climate Change 2014. Synthesis Report. Summary for Policymakers. *IPCC*, 151. http://doi.org/10.1017/CBO9781107415324

Jones, K. K. E., Patel, N. G. N., Levy, M. A., Storeygard, A., Balk, D., Gittleman, J. L., & Daszak, P. (2008). Global trends in emerging infectious diseases. *Nature*, *451*(7181), 990–3. http://doi.org/10.1038/nature06536

Kamaludeen, J., Graham-Brown, J., Stephens, N., Miller, J., Howell, A., Beesley, N. J., … Williams, D. (2019). Lack of efficacy of triclabendazole against Fasciola hepatica is present on sheep farms in three regions of England, and Wales. *Veterinary Record*, 184(16), 502–502. http://doi.org/10.1136/vr.105209

Kaplan, R. M. (2001). Fasciola hepatica: a review of the economic impact in cattle and considerations for control. *Veterinary Therapeutics: Research in Applied Veterinary Medicine*, *2*(1), 40–50.

Keesing, F., Belden, L. K., Daszak, P., Dobson, A., Harvell, C. D., Holt, R. D., … Ostfeld, R. S. (2010). Impacts of biodiversity on the emergence and transmission of infectious diseases. *Nature*, *468*(7324), 647–652. http://doi.org/10.1038/nature09575

Kelley, J. M., Elliott, T. P., Beddoe, T., Anderson, G., Skuce, P., & Spithill, T. W. (2016). Current Threat of Triclabendazole Resistance in Fasciola hepatica. *Trends in Parasitology*, 32(6), 458–469. http://doi.org/10.1016/j.pt.2016.03.002

Kendon, E. J., Roberts, N. M., Fowler, H. J., Roberts, M. J., Chan, S. C., & Senior, C. A. (2014). Heavier summer downpours with climate change revealed by weather forecast resolution model. *Nature Climate Change*, *4*(7), 570–576. http://doi.org/10.1038/nclimate2258

Kenyon, F., Sargison, N. D., Skuce, P. J., & Jackson, F. (2009). Sheep helminth parasitic disease in south eastern Scotland arising as a possible consequence of climate change. *Veterinary Parasitology*, *163*(4), 293–297. http://doi.org/10.1016/j.vetpar.2009.03.027

Klemeš, V. (1986). Operational testing of hydrological simulation models. *Hydrological Sciences Journal*, *31*(1), 13–24. http://doi.org/10.1080/02626668609491024

Liang, S., Maszle, D., & Spear, R. C. (2002). A quantitative framework for a multi-group model of Schistosomiasis japonicum transmission dynamics and control in Sichuan, China. *Acta Tropica*, *82*(2), 263–277. http://doi.org/10.1016/S0001-706X(02)00018-9

Liang, S., Seto, E. Y. W., Remais, J. V, Zhong, B., Yang, C., Hubbard, A., … Spear, R. C. (2007). Environmental effects on parasitic disease transmission exemplified by schistosomiasis in western China. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(17), 7110–5. http://doi.org/10.1073/pnas.0701878104

Liang, S., Spear, R. C., Seto, E., Hubbard, A., & Qiu, D. (2005). A multi-group model of Schistosoma japonicum transmission dynamics and control: Model calibration and control prediction. *Tropical Medicine and International Health*, *10*(3), 263–278. http://doi.org/10.1111/j.1365-3156.2005.01386.x

Lloyd-Smith, J. O., George, D., Pepin, K. M., Pitzer, V. E., Pulliam, J. R. C., Dobson, A. P., … Grenfell, B. T. (2009). Epidemic Dynamics at the Human-Animal Interface. *Science*, *326*(5958), 1362–1367. http://doi.org/10.1126/science.1177345

Lo Iacono, G., Armstrong, B., Fleming, L. E., Elson, R., Kovats, S., Vardoulakis, S., & Nichols, G. L. (2017). Challenges in developing methods for quantifying the effects of weather and climate on water-associated diseases: A systematic review. *PLoS Negl Trop Dis*, *11*(6), e0005659. http://doi.org/10.1371/journal.pntd.0005659

Lo, N. C., Gurarie, D., Yoon, N., Coulibaly, J. T., Bendavid, E., Andrews, J. R., & King, C. H. (2018). Impact and cost-effectiveness of snail control to achieve disease control targets for schistosomiasis. *Proceedings of the National Academy of Sciences*, *115*(4), E584–E591. http://doi.org/10.1073/pnas.1708729114

LoGiudice, K., Ostfeld, R., Schmidt, K. A., & Keesing, F. (2003). The ecology of infectious disease: Effects of host diversity and community composition on Lyme disease risk. *Proceedings of the National Academy of Sciences*, *100*(2), 567–571. http://doi.org/10.1073/pnas.0233733100

Lowe, J. A., Bernie, D., Bett, P., Bricheno, L., Brown, S., Calvert, D., … Belcher, S. (2018). *UKCP18 Science Overview Report* (Vol. 2). Retrieved from https://www.metoffice.gov.uk/pub/data/weather/uk/ukcp18/science-reports/UKCP18-Overview-report.pdf

Macdonald, G. (1965). The dynamics of helminth infections, with special reference to schistosomes. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 59(5), 489–506. http://doi.org/10.1016/0035-9203(65)90152-5

Malone, J. B., Gommes, R., Hansen, J., Yilma, J. M., Slingenberg, J., Snijders, F., … Ataman, E. (1998). A geographic information system on the potential distribution and abundance of Fasciola hepatica and F. gigantica in east Africa based on food and agriculture organization databases. *Veterinary Parasitology*, *78*(2), 87–101. http://doi.org/10.1016/S0304-4017(98)00137-X

Mari, L., Bertuzzo, E., Righetto, L., Casagrandi, R., Gatto, M., Rodriguez-Iturbe, I., & Rinaldo, A. (2012). Modelling cholera epidemics: The role of waterways, human mobility and sanitation. *Journal of the Royal Society Interface*, 9, 376–388. http://doi.org/10.1098/rsif.2011.0304

Mari, L., Bertuzzo, E., Finger, F., Casagrandi, R., Gatto, M., & Rinaldo, A. (2015). On the predictive ability of mechanistic models for the Haitian cholera epidemic. *Journal of the Royal Society Interface*, 12, 20140840. http://doi.org/10.1098/rsif.2014.0840

Mari, L., Ciddio, M., Casagrandi, R., Perez-Saez, J., Bertuzzo, E., Rinaldo, A., … Gatto, M. (2017). Heterogeneity in schistosomiasis transmission dynamics. *Journal of Theoretical Biology*, *432*, 87–99. http://doi.org/10.1016/j.jtbi.2017.08.015

Mas-Coma, S., Bargues, M. D., & Valero, M. A. (2005). Fascioliasis and other plant-borne trematode zoonoses. *International Journal for Parasitology*, *35*(11–12), 1255–1278. http://doi.org/10.1016/j.ijpara.2005.07.010

Mas-Coma, S., Bargues, M. D., & Valero, M. A. (2018). Human fascioliasis infection sources, their diversity, incidence factors, analytical methods and prevention measures. *Parasitology*, 1–35. http://doi.org/10.1017/ S0031182018000914

Mas-Coma, S., Valero, M. A., & Bargues, M. D. (2009). Climate change effects on trematodiases, with emphasis on zoonotic fascioliasis and schistosomiasis. *Veterinary Parasitology*, *163*(4), 264–280. http://doi.org/10.1016/j.vetpar.2009.03.024

Mas-Coma, S., Anglés, R., Esteban, J. G., Bargues, M. D., Buchon, P., Franken, M., & Strauss, W. (1999). The Northern Bolivian Altiplano: A region highly endemic for human fascioliasis. *Tropical Medicine and International Health*, *4*(6), 454–467. http://doi.org/10.1046/j.1365-3156.1999.00418.x

McCann, C. M., Baylis, M., & Williams, D. J. L. (2010a). Seroprevalence and spatial distribution of Fasciola hepatica-infected dairy herds in England and Wales. *Veterinary Record*, *166*(20), 612–617. http://doi.org/10.1136/vr.b4836

McCann, C. M., Baylis, M., & Williams, D. J. L. (2010b). The development of linear regression models using environmental variables to explain the spatial distribution of Fasciola hepatica infection in dairy herds in England and Wales. *International Journal for Parasitology*, *40*(9), 1021–1028. http://doi.org/10.1016/j.ijpara.2010.02.009

McCann, C. M., Williams, D. J. L., Baylis, M., & Graham-Brown, J. (2017). Farm Liver Fluke study 2014-2015. http://dx.doi.org/10.17638/datacat.liverpool.ac.uk/406

McIlroy, S. G., Goodall, E. A., Stewart, D. A., Taylor, S. M., & McCracken, R. M. (1990). A computerised system for the accurate forecasting of the annual prevalence of fasciolosis. *Preventive Veterinary Medicine*, *9*(1), 27–35. http://doi.org/10.1016/0167-5877(90)90039-K

McIntyre, K. M., Setzkorn, C., Hepworth, P. J., Morand, S., Morse, A. P., & Baylis, M. (2017). Systematic Assessment of the Climate Sensitivity of Important Human and Domestic Animals Pathogens in Europe. *Scientific Reports*, *7*(1), 1–10. http://doi.org/10.1038/s41598-017-06948-9

McManus, D. P., & Dalton, J. P. (2006). Vaccines against the zoonotic trematodes Schistosoma japonicum, Fasciola hepatica and Fasciola gigantica. *Parasitology*, *133*(Suppl. S2), S43–S61. http://doi.org/10.1017/S0031182006001806

Malone, J. B., Williams, T. E., Muller, R. A., Geaghan, J. P., & Loyacano, A. F. (1987). Fascioliasis in cattle in Louisiana: development of a system to predict disease risk by climate, using the Thornthwaite water budget. *Am. J. Vet. Res.* 48, 1167– 1170.

Meek, A. H., & Morris, R. S. (1981). A computer simulation model of ovine fascioliasis. *Agricultural Systems*, *7*(1), 49–77. http://doi.org/10.1016/0308-521X(81)90028-7

Mehmood, K., Zhang, H., Jawad, A., Zahid, R., Ijaz, M., Zameer, A., … Li, J. (2017). A review on epidemiology, global prevalence and economical losses of fasciolosis in ruminants. *Microbial Pathogenesis*, *109*, 253–262. http://doi.org/10.1016/j.micpath.2017.06.006

Meinshausen, M., Smith, S. J., Calvin, K., Daniel, J. S., Kainuma, M. L. T., Lamarque, J., … van Vuuren, D. P. P. (2011). The RCP greenhouse gas concentrations and their extensions from 1765 to 2300. *Climatic Change*, 109(1), 213–241. http://doi.org/10.1007/s10584-011-0156-z

Mellor, J. E., Levy, K., Zimmerman, J., Elliott, M., Bartram, J., Carlton, E., … Nelson, K. (2016). Planning for climate change: The need for mechanistic systems-based approaches to study climate change impacts on diarrheal diseases. *Science of the Total Environment*, *548–549*, 82–90. http://doi.org/10.1016/j.scitotenv.2015.12.087

MetOffice. (2017). https://www.metoffice.gov.uk/research/climate/maps-and-data

Milly, P. C. D., Betancourt, J., Falkenmark, M., Hirsch, R. M., Kundzewicz, Z. W., Lettenmaier, D. P., & Stouffer, R. J. (2008). Climate change. Stationarity is dead: whither water management? *Science*, *319*(5863), 573–574. http://doi.org/10.1126/science.1151915

Milly, P. C. D., Wetherald, R. T., Dunne, K. a, & Delworth, T. L. (2002). Increasing risk of great floods in a changing climate. *Nature*, *415*, 514–517. http://doi.org/10.1038/415514a

Mitchell, G. (2002). Update on Fasciolosis in cattle and sheep. *In Practice*, *24*(7), 378–385.

Molnar, P. K., Kutz, S. J., Hoar, B. M., & Dobson, A. P. (2013). Metabolic approaches to understanding climate change impacts on seasonal host-macroparasite dynamics. *Ecology Letters*, *16*(1), 9–21. http://doi.org/10.1111/ele.12022

Morgan, E. R., Charlier, J., Hendrickx, G., Biggeri, A., Catalan, D., von Samson-Himmelstjerna, G., … Vercruysse, J. (2013). Global Change and Helminth Infections in Grazing Ruminants in Europe: Impacts, Trends and Sustainable Solutions. *Agriculture*, *3*(3), 484–502. http://doi.org/10.3390/agriculture3030484

Morgan, E. R., Hosking, B. C., Burston, S., Carder, K. M., Hyslop, A. C., Pritchard, L. J., … Coles, G. C. (2012). A survey of helminth control practices on sheep farms in Great Britain and Ireland. *Veterinary Journal*, *192*(3), 390–397. http://doi.org/10.1016/j.tvjl.2011.08.004

Morgan, E. R., & Wall, R. (2009). Climate change and parasitic disease: farmer mitigation? *Trends in Parasitology*, *25*(7), 308–313. http://doi.org/10.1016/j.pt.2009.03.012

Murphy, J. M., Harris, G. R., Sexton, D. M. H., Kendon, E. J., Bett, P. E., Clark, R. T., … Yamazaki, K. (2018). *UKCP18 Land Projections: Science Report November 2018*.

Murphy, J., Sexton, D., Jenkins, G., Boorman, P., Booth, B., Brown, K., … Kendon, L. (2009). *UK Climate Projections Science Report: Climate change projections*. *Climate Change and Agriculture*. http://doi.org/10.1787/9789264086876-5-en

Murray, C. J. L., Rosenfeld, L. C., Lim, S. S., Andrews, K. G., Foreman, K. J., Haring, D., … Lopez, A. D. (2012). Global malaria mortality between 1980 and 2010: a systematic analysis. *The Lancet*, *379*(9814), 413–431. http://doi.org/10.1016/S0140-6736(12)60034-8

National Animal Disease Information System (NADIS). (2019). https://www.nadis.org.uk/parasite-forecast.aspx

National River Flow Archive (NRFA). (2019). NERC CEH, Wallingford. https://nrfa.ceh.ac.uk/

National Soil Resources Institute Land Information System (NSRI LandIS). (2017). Cranfield University, UK. http://www.landis.org.uk.

Nice, N. G., & Wilson, R. A. (1974). A study of the effect of temperature on the growth of Fasciola hepatica in Lymnaea truncatula. *Parasitology*, *68*(1), 47–56. http://doi.org/10.1017/S0031182000045364

NOAH. (2013). Joint statement from the National Office of Animal Health (NOAH) and the Veterinary Medicines Directorate (VMD) on the use of flukicides in dairy cattle, (June). http://www.noahcompendium.co.uk

Nzalawahe, J., Kassuku, A. A., Stothard, J. R., Coles, G. C., & Eisler, M. C. (2014). Trematode infections in cattle in Arumeru District, Tanzania are associated with irrigation. *Parasites and Vectors*, 7(107). http://doi.org/10.1186/1756-3305-7-107

Ollerenshaw, C. B. (1966). The approach to forecasting the incidence of fascioliasis over England and Wales 1958–1962. *Agricultural Meteorology*, *3*(1–2), 35–53. http://doi.org/10.1016/0002-1571(66)90004-5

Ollerenshaw, C. B. (1971). Some observations on the epidemiology of fascioliasis in relation to the timing of molluscicide applications in the control of the disease. *Veterinary Record,* 88, 152-64. http://dx.doi.org/10.1136/vr.88.6.152.

Ollerenshaw, C. B., & Rowlands, W. T. (1959). A method of forecasting the incidence of fascioliasis in Anglesey. *The Veterinary Record*, *71*(29), 591–598.

Olsen, A., Frankena, K., Bødker, R., Toft, N., Thamsborg, S. M., Enemark, H. L., & Halasa, T. (2015). Prevalence, risk factors and spatial analysis of liver fluke infections in Danish cattle herds. *Parasites & Vectors*, *8*(1), 160. http://doi.org/10.1186/s13071-015-0773-x

Ostrom, E. (2009). A General Framework for Analyzing Sustainability of Social-Ecological Systems. *Science*, *325*(5939), 419–422. http://doi.org/10.1126/science.1172133

Pantelouris, E. M. (1963). Environmental influences on the life-cycle of the liver-fluke, Fasciola hepatica L. *The Irish Naturalists' Journal*, *14*(5), 94–97.

Parham, P. E., Waldock, J., Christophides, G. K., Hemming, D., Agusto, F., Evans, K. J., … Michael, E. (2015). Climate, environmental and socio-economic change: weighing up the balance in vector-borne disease transmission. *Phil. Trans. R. Soc. B*, *370*(1665). http://doi.org/10.1098/rstb.2013.0551

Park, J.-W., Cheong, H.-K., Honda, Y., Ha, M., Kim, H., Kolam, J., … Mueller, I. (2016). Time trend of malaria in relation to climate variability in Papua New Guinea. *Environmental Health and Toxicology*, *31*, e2016003. http://doi.org/10.5620/eht.e2016003

Patz, J. A. (2005). Impact of regional climate change on human health. *Nature*, *438*, 310–7. http://doi.org/10.1038/nature04188

Patz, J. A., Olson, S. H., Uejio, C. K., & Gibbs, H. K. (2008). Disease Emergence from Global Climate and Land Use Change. *Medical Clinics of North America*, *92*(6), 1473–1491. http://doi.org/10.1016/j.mcna.2008.07.007

Pearson, R. G., Thuiller, W., Arau, M. B., McClean, C. & Miles, L. (2006). Model-based uncertainty in species range prediction. *J. Biogeography.*, 33, 1704-1711. http://doi.org/10.1111/j.1365-2699.2006.01460.x

Pedersen, U. B., Birgitte, J., Kristensen, T. K., Midzi, N., Mduluza, T., & Soko, W. (2014). Modelling spatial distribution of snails transmitting parasitic worms with importance to human and animal health and analysis of distributional changes in relation to climate. *Geospatial Health*, *8(2)*, 335-343. http://doi.org/10.4081/gh.2014.23

Perez-Saez, J., Mande, T., Ceperley, N., Bertuzzo, E., Mari, L., Gatto, M., & Rinaldo, A. (2016). Hydrology and density feedbacks control the ecology of intermediate hosts of schistosomiasis across habitats in seasonal climates. *Proceedings of the National Academy of Sciences*, *113*(23), 6427–6432. http://doi.org/10.1073/pnas.1602251113

Perez-Saez, J., Sokolow, H., Leo, G. A. De, Mande, T., & Ceperley, N. (2015). A Theoretical Analysis of the Geography of Schistosomiasis in Burkina Faso Highlights the Roles of Human Mobility and Water Resources Development in Disease Transmission. *PLoS Negl Trop Dis*, *9*(10), e0004127. http://doi.org/10.1371/journal.pntd.0004127

Pianosi, F., Beven, K., Freer, J., Hall, J. W., Rougier, J., Stephenson, D. B., & Wagener, T. (2016). Sensitivity analysis of environmental models: A systematic review with practical work flow. *Environmental Modelling and Software*, *79*, 214–232. http://doi.org/10.1016/j.envsoft.2016.02.008

Pritchard, G. C., Forbes, A. B., Williams, D. J. L., Salimi-Bejestani, M. R., & Daniel, R. G. (2005). Emergence of fasciolosis in cattle in East Anglia. *Veterinary Record*, *157*, 578–582. http://doi.org/10.1136/vr.157.19.578

Prüss-Ustün, A., Wolf, J., Corvalan, C., Bos, R., & Neira, M. (2016). *Preventing disease through healthy environments: A global assessment of the burden of disease from environmental risks. World Health Organisation.*

Quinn, P., Beven, K., Chevallier, P., & Planchon, O. (1991). The prediction of hillslope flow paths for distributed hydrological modelling using digital terrain models. *Hydrological Processes*, 5, 59–79. http://doi.org/10.1002/hyp.3360050106

Rajczak, J., & Schär, C. (2017). Projections of Future Precipitation Extremes Over Europe: A Multimodel Assessment of Climate Simulations. *Journal of Geophysical Research: Atmospheres*, 122(20), 10,773-10,800. http://doi.org/10.1002/2017JD027176

Relf, V., Good, B., Hanrahan, J. P., McCarthy, E., Forbes, A. B., & DeWaal, T. (2011). Temporal studies on Fasciola hepatica in Galba truncatula in the west of Ireland. *Veterinary Parasitology*, *175*(3–4), 287–292. http://doi.org/10.1016/j.vetpar.2010.10.010

Righetto, L., Bertuzzo, E., Mari, L., Schild, E., Casagrandi, R., Gatto, M., … Rinaldo, A. (2013). Rainfall mediations in the spreading of epidemic cholera. *Advances in Water Resources*, *60*, 34–46. http://doi.org/10.1016/j.advwatres.2013.07.006

Rinaldo, A., Bertuzzo, E., Mari, L., Righetto, L., Blokesch, M., Gatto, M., … Rodriguez-Iturbe, I. (2012). Reassessment of the 2010-2011 Haiti cholera outbreak and rainfall-driven multiseason projections. *Proceedings of the National Academy of Sciences*, *109*(17), 6602–6607. http://doi.org/10.1073/pnas.1203333109

Rinaldo, A., Bertuzzo, E., Blokesch, M., Mari, L., & Gatto, M. (2017). Modeling Key Drivers of Cholera Transmission Dynamics Provides New Perspectives for Parasitology. *Trends in Parasitology*, *33*(8), 587–599. http://doi.org/10.1016/j.pt.2017.04.002

Rinaldo, A., Gatto, M., & Rodriguez-Iturbe, I. (2018). River networks as ecological corridors: A coherent ecohydrological perspective. *Advances in Water Resources*, *112*, 27–58. http://doi.org/10.1016/j.advwatres.2017.10.005

Robinson, E. L., Blyth, E. M., Clark, D. B., Finch, J., & Rudd, A. C. (2017). Trends in atmospheric evaporative demand in Great Britain using high-resolution meteorological data. *Hydrology and Earth System Sciences*, *21*(2), 1189–1224. http://doi.org/10.5194/hess-21-1189-2017

Rodriguez-Iturbe, I. (2000). Ecohydrology: A hydrologic perspective of climate-soil-vegetation dynamics. *Water Resources Research*, *36*(1), 3–9. http://doi.org/10.1029/1999WR900210

Rohr, J. R., Dobson, A. P., Johnson, P. T. J., Kilpatrick, A. M., Paull, S. H., Raffel, T. R., … Thomas, M. B. (2011). Frontiers in climate change-disease research. *Trends in Ecology and Evolution*, *26*(6), 270–277. http://doi.org/10.1016/j.tree.2011.03.002

Rose, H., Caminade, C., Bolajoko, M. B., Phelan, P., van Dijk, J., Baylis, M., … Morgan, E. R. (2015). Climate-driven changes to the spatio-temporal distribution of the parasitic nematode, Haemonchus contortus, in sheep in Europe. *Global Change Biology*, *22*, 1271–1285. http://doi.org/10.1111/gcb.13132

Rose, H., & Wall, R. (2011). Modelling the impact of climate change on spatial patterns of disease risk: Sheep blowfly strike by Lucilia sericata in Great Britain. *International Journal for Parasitology*, *41*(7), 739–746. http://doi.org/10.1016/j.ijpara.2011.01.012

Rose, H., Wang, T., van Dijk, J., & Morgan, E. R. (2015). GLOWORM-FL: A simulation model of the effects of climate and climate change on the free-living stages of gastro-intestinal nematode parasites of ruminants. *Ecological Modelling*, *297*, 232–245. http://doi.org/10.1016/j.ecolmodel.2014.11.033

Ross, J. G. (1970). The Stormont "wet day" forecasting system for fascioliasis. *The British Veterinary Journal*, *126*(8), 401–408. http://doi.org/10.1016/S0007-1935(17)48248-0

Rowland, C. S., Morton, R. D., Carrasco, L., McShane, G., O'Neil, A. W. & Wood, C. M. (2017) Land Cover Map 2015 (vector, GB). *NERC Environmental Information Data Centre*. https://doi.org/10.5285/6c6c9203-7333-4d96-88ab-78925e7a4e73

Ruiz-Moreno, D., Pascual, M., Bouma, M., Dobson, A., & Cash, B. (2007). Cholera seasonality in Madras (1901-1940): Dual role for rainfall in endemic and epidemic regions. *EcoHealth*, 4, 52–62. http://doi.org/10.1007/s10393-006-0079-8

SAC. (2003). *TN557: Treatment and Control of liver fluke in Sheep and Cattle*. *SAC Technical note*.

Samaniego, L., Thober, S., Kumar, R., Wanders, N., Rakovec, O., Pan, M., … Marx, A. (2018). Anthropogenic warming exacerbates European soil moisture droughts. *Nature Climate Change*, *8*, 421–426. http://doi.org/10.1038/s41558-018-0138-5

Sawicz, K., Wagener, T., Sivapalan, M., Troch, P. A., & Carrillo, G. (2011). Catchment classification: Empirical analysis of hydrologic similarity based on catchment function in the eastern USA. *Hydrology and Earth System Sciences*, *15*, 2895–2911. http://doi.org/10.5194/hess-15-2895-2011

Selemetas, N., Ducheyne, E., Phelan, P., O'Kiely, P., Hendrickx, G., & de Waal, T. (2015a). Spatial analysis and risk mapping of fasciola hepatica infection in dairy herds in Ireland. *Geospatial Health*, *9*(2), 281–291. http://doi.org/10.4081/gh.2015.350

Selemetas, N., Phelan, P., O'Kiely, P., & de Waal, T. (2015b). The effects of farm management practices on liver fluke prevalence and the current internal parasite control measures employed on Irish dairy farms. *Veterinary Parasitology*, *207*(3–4), 228–240. http://doi.org/10.1016/j.vetpar.2014.12.010

Selemetas, N., Phelan, P., O'Kiely, P., & de Waal, T. (2014). Weather and soil type affect incidence of fasciolosis in dairy cow herds. *The Veterinary Record*, *175*(15), 371. http://doi.org/10.1136/vr.102437

Semenza, J. C., Lindgren, E., Balkanyi, L., Espinosa, L., & Almqvist, M. S. (2016). Determinants and Drivers of Infectious Disease Threat Events in Europe. *Emerging Infectious Diseases*, *22*(4), 581–589. http://doi.org/10.3201/eid2204

Sheffield, J., & Wood, E. F. (2008). Projected changes in drought occurrence under future global warming from multi-model, multi-scenario, IPCC AR4 simulations. *Climate Dynamics*, *31*(1), 79–105. http://doi.org/10.1007/s00382-007-0340-z

Shen, C., Niu, J., & Phanikumar, M. S. (2013). Evaluating controls on coupled hydrologic and vegetation dynamics in a humid continental climate watershed using a subsurface-land surface processes model. *Water Resources Research*, *49*(5), 2552–2572. http://doi.org/10.1002/wrcr.20189

Singh, R., Wagener, T., Van Werkhoven, K., Mann, M. E., & Crane, R. (2011). A trading-space-for-time approach to probabilistic continuous streamflow predictions in a changing climate-accounting for changing watershed behavior. *Hydrology and Earth System Sciences*, *15*, 3591–3603. http://doi.org/10.5194/hess-15-3591-2011

Siraj, A. S., Santos-Vega, M., Bouma, M. J., Yadeta, D., Ruiz Carrascal, D., & Pascual, M. (2014). Altitudinal Changes in Malaria Incidence in Highlands of Ethiopia and Colombia. *Science*, *343*(6175), 1154–1159. http://doi.org/10.1126/science.1244325

Sivapalan, M., Savenije, H. H. G., & Blöschl, G. (2012). Socio-hydrology: A new science of people and water. *Hydrological Processes*, *26*(8), 1270–1276. http://doi.org/10.1002/hyp.8426

Skuce, P. J., & Zadoks, R. N. (2013). Liver fluke A growing threat to UK livestock production. *Cattle Practice*, *21*(2), 138–149.

Skuce, P., Dijk, J. Van, Smith, D., & Morgan, E. (2014). Implications of extreme weather events for risk of fluke infection. *The Veterinary Record*, *175*, 198–200. http://doi.org/10.1136/vr.g5377

Smith, K. F., Goldberg, M., Rosenthal, S., Carlson, L., Chen, J., Chen, C., & Ramachandran, S. (2014). Global rise in human infectious disease outbreaks. *Journal of the Royal Society Interface*, *11*(101), 20140950. http://doi.org/10.1098/rsif.2014.0950

Sokolow, S. H., Jones, I. J., Jocque, M., La, D., Cords, O., Knight, A., … De Leo, G. A. (2017). Nearly 400 million people are at higher risk of schistosomiasis because dams block the migration of snail-eating river prawns. *Phil. Trans. R. Soc. B*, *372*(1722), 20160127. http://doi.org/10.1098/rstb.2016.0127

SRUC. (2016). *TN677: Treatment and Control of Liver Fluke*.

Statham, J. M. E. (2015). Control of liver fluke: an emerging issue in terms of veterinary residues. *The Veterinary Record*, *177*, 519–522. http://doi.org/10.1136/vr.h6287

Steinmann, P., Keiser, J., Bos, R., Tanner, M., & Utzinger, J. (2006). Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. *Lancet Infect Dis*, *6*(7), 411–425. http://doi.org/10.1016/S1473-3099(06)70521-7

Stensgaard, A., Utzinger, J., Vounatsou, P., Hurlimann, E., Schur, N., Saarnak, C. F. L., Simoonga, C., Mubita, P., Kabatereine, N. B., Tchuente, L. A. T., Rahbek, C. & Kristensen, T. K. (2013). Large-

scale determinants of intestinal schistosomiasis and intermediate host snail distribution across Africa: does climate matter? *Acta Tropica,* 128, 378-90. http://doi.org/10.1016/j.actatropica.2011.11.010

Stensgaard, A., Booth, M., Nikulin, G. & McCreesh, N. (2016). Combining process-based and correlative models improves predictions of climate change effects on schistosoma mansoni transmission in eastern Africa. *Geospatial Health*, 11(s1), 406. http://doi.org/10.4081/gh.2016.406

Tanguy, M., Dixon, H., Prosdocimi, I., Morris, D. G. & Keller, V. D. J. (2014). Gridded estimates of daily and monthly areal rainfall for the United Kingdom (1890-2012) [CEH-GEAR]. *NERC Environmental Information Data Centre*. https://doi.org/10.5285/5dc179dc-f692-49ba-9326-a6893a503f6e

Teutschbein, C., & Seibert, J. (2012). Bias correction of regional climate model simulations for hydrological climate-change impact studies: Review and evaluation of different methods. *Journal of Hydrology*, *456–457*, 12–29. http://doi.org/10.1016/j.jhydrol.2012.05.052

Thomas, A. (1883). The Life History of the Liver-Fluke (Fasciola hepatica). *Quarterly Journal of Microscopical Science*, *23*, 99–133. Retrieved from http://jcs.biologists.org/content/s2-23/89/99.full.pdf

Thompson, S. E., Sivapalan, M., Harman, C. J., Srinivasan, V., Hipsey, M. R., Reed, P., … Bloschl, G. (2013). Developing predictive insight into changing water systems: use-inspired hydrologic science for the Anthropocene. *Hydrol. Earth Syst. Sci.*, *17*, 5013–5039. http://doi.org/10.5194/hess-17-5013-2013

Tum, S., Puotinen, M. L., & Copeman, D. B. (2004). A geographic information systems model for mapping risk of fasciolosis in cattle and buffaloes in Cambodia. *Veterinary Parasitology*, *122*(2), 141–149. http://doi.org/10.1016/j.vetpar.2004.03.016

Tum, S., Puotinen, M. L., Skerratt, L. F., Chan, B., & Sothoeun, S. (2007). Validation of a geographic information system model for mapping the risk of fasciolosis in cattle and buffaloes in Cambodia. *Veterinary Parasitology*, *143*(3–4), 364–367. http://doi.org/10.1016/j.vetpar.2006.08.033

Turner, J., Howell, A., McCann, C., Caminade, C., Bowers, R. G., Williams, D., & Baylis, M. (2016). A model to assess the efficacy of vaccines for control of liver fluke infection. *Scientific Reports*, *6*, 23345. http://doi.org/10.1038/srep23345

United Nations. (2014). *World Urbanization Prospects: The 2014 Revision*. *United Nations, Department of Economic and Social Affairs, Population Division*.

Urban, M. C., Bocedi, G., Hendry, A. P., Mihoub, J.-B., Pe'er, G., Singer, A., … Travis, J. M. J. (2016). Improving the forecast for biodiversity under climate change. *Science*, *353*(6304). http://doi.org/10.1126/science.aad8466

Valencia-López, N., Malone, J. B., Carmona, C. G., & Velásquez, L. E. (2012). Climate-based risk models for Fasciola hepatica in Colombia. *Geospatial Health*, *6*(3), S75–S85. http://doi.org/10.4081/gh.2012.125

van der Voort, M., Charlier, J., Lauwers, L., Vercruysse, J., Van Huylenbroeck, G., & Van Meensel, J. (2013). Conceptual framework for analysing farm-specific economic effects of helminth infections

in ruminants and control strategies. *Preventive Veterinary Medicine*, *109*(3–4), 228–235. http://doi.org/10.1016/j.prevetmed.2012.10.017

van Dijk, J., David, G. P., Baird, G., & Morgan, E. R. (2008). Back to the future: Developing hypotheses on the effects of climate change on ovine parasitic gastroenteritis from historical data. *Veterinary Parasitology*, *158*(1–2), 73–84. http://doi.org/10.1016/j.vetpar.2008.08.006

van Dijk, J., Sargison, N. D., Kenyon, F., & Skuce, P. J. (2010). Climate change and infectious disease: helminthological challenges to farmed ruminants in temperate regions. *Animal*, *4*(3), 377–392. http://doi.org/10.1017/s1751731109990991

Van Loon, A. F., Gleeson, T., Clark, J., Van Dijk, A. I. J. M., Stahl, K., Hannaford, J., … Van Lanen, H. A. J. (2016). Drought in the Anthropocene. *Nature Geoscience*, *9*(2), 89–91. http://doi.org/10.1038/ngeo2646

Vetter, T., Huang, S., Aich, V., Yang, T., Wang, X., Krysanova, V., & Hattermann, F. (2015). Multi-model climate impact assessment and intercomparison for three large-scale river basins on three continents. *Earth System Dynamics*, *6*(1), 17–43. http://doi.org/10.5194/esd-6-17-2015

VIDA. (2019). http://apha.defra.gov.uk/vet-gateway/surveillance/scanning/vida.htm.

Wagener, T., Wheater, H. S. & Gupta, H. V. (2004). *Rainfall-Runoff Modelling in Gauged and Ungauged Catchments*. https://doi.org/10.1142/p335

Wagener, T., Sivapalan, M., Troch, P. A., McGlynn, B. L., Harman, C. J., Gupta, H. V., … Wilson, J. S. (2010). The future of hydrology: An evolving science for a changing world. *Water Resources Research*, *46*, W05301. http://doi.org/10.1029/2009WR008906

Webster, J. P., Molyneux, D. H., Hotez, P. J., & Fenwick, A. (2014). The contribution of mass drug administration to global health: Past, present and future. *Phil. Trans. R. Soc. B*, *369*(1645), 20130434. http://doi.org/10.1098/rstb.2013.0434

Weiss, R. A., & McMichael, A. J. (2004). Social and environmental risk factors in the emergence of infectious diseases. *Nature Medicine*, *10*, S70–S76. http://doi.org/10.1038/nm1150

Whitmee, S., Haines, A., Beyrer, C., Boltz, F., Capon, A. G., De Souza Dias, B. F., … Yach, D. (2015). Safeguarding human health in the Anthropocene epoch: Report of the Rockefeller Foundation-Lancet Commission on planetary health. *The Lancet*, *386*(10007), 1973–2028. http://doi.org/10.1016/S0140-6736(15)60901-1

WHO. (2003). *Climate change and human health: risks and responses*. Retrieved from http://www.who.int/globalchange/environment/en/ccSCREEN.pdf?ua=1%5Cnhttp://www.jstor.org/stable/2137486?origin=crossref

WHO. (2016). https://www.who.int/topics/infectious_diseases/en/.

WHO. (2018). https://www.who.int/foodborne_trematode_infections/en/.

WHO. (2019). https://www.who.int/malaria/areas/vector_control/core_methods/en/.

Williams, D. J. L., Howell, A., Graham-Brown, J., Kamaludeen, J., & Smith, D. (2014). *Liver fluke - An overview for practitioners*. *Cattle Practice* (Vol. 22).

Wilson, R. A., Smith, G., & Thomas, M. R. (1982). *Fascioliasis*. In: Anderson R. M. (eds) *The population Dynamics of Infectious Diseases: Theory and Applications*. Population and Community Biology. Springer, Boston, MA. https://doi.org/10.1007/978-1-4899-2901-3_9

Wood, E. F., Roundy, J. K., Troy, T. J., van Beek, L. P. H., Bierkens, M. F. P., Blyth, E., … Whitehead, P. (2011). Hyperresolution global land surface modeling: Meeting a grand challenge for monitoring Earth's terrestrial water. *Water Resources Research*, 47, W05301. http://doi.org/10.1029/2010WR010090

Wu, X., Lu, Y., Zhou, S., Chen, L., & Xu, B. (2016). Impact of climate change on human infectious diseases: Empirical evidence and human adaptation. *Environment International*, *86*, 14–23. http://doi.org/10.1016/j.envint.2015.09.007

Yadav, M., Wagener, T., & Gupta, H. (2007). Regionalization of constraints on expected watershed response behavior for improved predictions in ungauged basins. *Advances in Water Resources*, *30*(8), 1756–1774. http://doi.org/10.1016/j.advwatres.2007.01.005

Yasuoka, J., & Levins, R. (2007). Impact of Deforestation and Agricultural Development on Anopheline Ecology and Malaria Epidemiology. *The American Journal of Tropical Medicine and Hygiene*, *76*(3), 450–460. http://doi.org/10.4269/ajtmh.2007.76.450

Yilma, J. M., & Malone, J. B. (1998). A geographic information system forecast model for strategic control of fasciolosis in Ethiopia. *Veterinary Parasitology*, *78*(2), 103–127. http://doi.org/10.1016/S0304-4017(98)00136-8