Modelling the effects of temperature changes on Schistosoma mansoni transmission

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Abstract

Schistosomiasis is a chronic parasitic disease, estimated to affect 237 million people worldwide. It is caused by infection with *Schistosoma* helminths, which spend part of their lifecycles in aquatic snails. The mortality, development and fecundity rates of the parasites and their intermediate host snails are very sensitive to water temperature. The distribution and prevalence of schistosome parasites are therefore likely to be affected by climate change, however the potential effects of this have been largely neglected. Only two mathematical models of temperature and schistosome transmission in Africa have previously been developed, and neither explicitly simulated all temperature-dependent stages of the parasite and snail lifecycles.

The aim of this thesis is to advance understanding of the potential effects of climate change on *S. mansoni* transmission, using an agent-based modelling approach. A mathematical model of water temperature, snail population dynamics and *S. mansoni* transmission was developed. The model was parameterised using data from *Biomphalaria pfeifferi*, the most widespread intermediate host species in Africa, and the dynamics of the model were explored. Infection risk was shown to be highest (above 90% of the maximum) at a constant temperature of 15-19°C. Simulating diurnal variation in temperature and/or higher cercaria and miracidium removal rates increased the optimum temperature for transmission to 16-26°C. The effect of simulating different species of intermediate host snail was also investigated. Simulating *Bi. alexandrina* and *Bi. glabrata* increased the temperature at which infection risk was highest to 19-21°C and 20-26°C respectively.

The model was run using climate projections for eastern Africa. Comparisons of model output at baseline with empirical data showed that suitable temperatures are necessary but not sufficient for both schistosome transmission, and for high prevalences of schistosomiasis. All else being equal, infection risk may increase by up to 20% over most of the area over the next 20 and 50 years. Increases may be higher in Rwanda, Burundi, south-west Kenya and eastern Zambia, and schistosomiasis may become newly endemic in parts of these areas. The results for 20 years' time are robust to changes in simulated snail habitats. There is greater uncertainty about the effects of different habitats on changes in risk in 50 years' time.

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Statement of copyright

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Publications

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1 Background

1.1 Distribution and global burden of disease

The global distribution of schistosomiasis was first reviewed by the World Health Organization (WHO) in 1991, when 74 countries were listed as endemic (World Health Organization 1993). Two countries have since been added to the list, and a further two countries have newly formed, giving a total of 78 countries where schistosomiasis transmission has been documented during the 20th and/or 21st centuries: 42 in sub-Saharan Africa, 10 in South America and the Caribbean, 16 in the Middle East and northern Africa, nine in Asia, and Turkey (World Health Organization 2013a). Transmission may since have been interrupted in 19 countries, and the status of transmission needs to be confirmed for a further seven. This leaves 52 countries where infection is currently endemic, including all mainland sub-Saharan African countries. In Africa and the Middle East, most schistosomiasis is due to infection with *S. mansoni* or *S. haematobium*. In South America and the Caribbean, only *S. mansoni* is found. Finally, *S. japonicum* is responsible for the majority of schistosomiasis in Asia.

It is estimated that 90% of people infected with schistosomes live in sub-Saharan Africa, and that 70% live in just 10 countries (World Health Organization 2013b). This includes three eastern African countries: Kenya (5.0% of global infections), Tanzania (4.3%) and Uganda (3.7%). Based on environmental limits determined using parasitological surveys conducted in Uganda between 1998 and 2002, it is estimated that 16.7 million people in Uganda are at risk of schistosomiasis (Kabatereine, Brooker *et al.* 2004). The same surveys detected *S. mansoni* in 38 of Uganda's 56 districts, and *S. haematobium* in two (Kabatereine, Tukahebwa *et al.* 2006).

WHO estimate that at least 237 million people are infected with *Schistosoma* species (World Health Organization 2013b), and that schistosomiasis was responsible for the loss of four million disability adjusted life years (DALYs) in 2012 (World Health Organization 2014). There is some controversy over estimates of the global burden of schistosomiasis however, with many experts suggesting that the true burden may be much higher, and that schistosomiasis may be responsible for anywhere between three and 70

million lost DALYs per year (King, Dickman *et al.* 2005; King and Dangerfield-Cha 2008; Murray, Vos *et al.* 2012). The standard test for *Schistosoma* infection has a low sensitivity, and the overall number of people infected may be 40-60% higher than estimated by the WHO (King 2010). There is also much debate over the level of disability associated with schistosomiasis. Active infection with *Schistosoma* parasites causes acute morbidity due to inflammation. Chronic morbidity may persist after the parasites are cleared, as a result of cumulative, long-lasting fibrotic organ damage. It has therefore been argued that individuals with a history of *Schistosoma* infection should be considered as potentially suffering from ongoing schistosomiasis-associated morbidity, regardless of whether or not they are currently infected (King 2010). In addition to this, it has been suggested that the level of morbidity associated with active *Schistosoma* infections has been underestimated (King 2010).

1.2 Schistosome life cycle

There are six species of schistosome capable of infecting humans: *S. mansoni*, *S. haematobium*, and *S. japonicum*, which are responsible for the vast majority of infections, and *S. guineensis*, S*. intercalatum* and *S. mekongi*, which have limited distributions. Hybrids between human and ruminant schistosomes have also been reported (Webster, Diaw *et al.* 2013). All of the species reproduce sexually in humans (and, to various extents, other mammal species), and asexually in aquatic or amphibious snails. There are two free living stages which occur in fresh water and allow the parasite to pass between its two host species: cercariae between snails and mammals, and miracidia between mammals and snails.

Pairs of adult worms are found in humans in the veins of the bladder, ureters and kidneys (*S. haematobium*) or the veins of the small intestine (all other species). The worms reproduce sexually, producing around 20-3500 eggs a day (World Health Organization 1985). These eggs pass through the vein wall and tissues to the lumen of the gut or bladder, from where they are excreted in urine (*S. haematobium*) or faeces (all other species) (Sturrock 1993). Upon reaching fresh water, the eggs hatch over a period of up to five days, releasing miracidia (Upatham 1972).

To progress to the next stage of their lifecycle, miracidia must find and infect a suitable snail host before their food stores are exhausted (Sturrock 1993). Life expectancy is highest at around 15°C for *S. mansoni*, with miracidia surviving an average of 16 hours. Either side of this temperature survival is lower, with a mean life expectancy of less than five hours at 5°C and less than 10 hours at 25°C (Anderson, Mercer *et al.* 1982). Miracidia actively try to locate snails, initially swimming in straight lines, but turning more frequently when snails are nearby (Sturrock 1993). Upon locating a snail, the miracidia penetrate it and start to develop into primary sporocysts. These primary sporocysts produce secondary sporocysts, which in turn produce cercariae which are shed from the snail. The length of time between initial infection and the start of cercarial shedding varies approximately linearly with temperature, taking only 16-19 days at 32°C, and in excess of 56 days at 18°C for *S. mansoni* in *Bi. pfeifferi* (Foster 1964). The parasites are harmful to their snail hosts, increasing mortality substantially (Foster 1964) and greatly reducing or preventing snail egg production (Sturrock 1966a).

The release of cercariae from snails follows a daily pattern, with the majority of cercariae being released over a period of several hours spanning midday (Pitchford, Meyling *et al.* 1969; Prentice and Ouma 1984). Rates of cercaria shedding may be higher at higher temperatures (Pitchford, Meyling *et al.* 1969; Fried, LaTerra *et al.* 2002). Like miracidia, cercariae must find and infect a suitable host before their food reserves are depleted. Life expectancy of cercariae decreases linearly with temperature, with *S. mansoni* cercariae having a median life expectancy of only eight hours at 35°C compared with over 31 hours at 15°C (Lawson and Wilson 1980). The effects of this on infection risk may be reduced by higher probabilities of successful infection at higher temperatures (Stirewalt 1954), and lower probabilities of infection by older cercariae (Ghandour and Webbe 1973).

Upon encountering a potential host, the cercariae penetrate its skin and transform into schistosomula (Sturrock 1993). Over the course of several days, the schistosomula enter the venous system and are carried round the body. Schistosomula that are successful in reaching the liver start to feed and grow. Upon reaching sexual maturity, they form pairs and travel together to their final locations in the perivesical venous plexus of the bladder, ureters and kidneys (*S. haematobium*) or the mesenteric veins of the small intestine (all other species), where they start to produce eggs. In total, the time between infection and the first detectible excretion of eggs is around 35 days for *S. mansoni*, 70 days for *S. haematobium* and 38 days for *S. japonicum* (Sturrock 1993).

1.3 Snail ecology

1.3.1 Intermediate host species

Aquatic snails of the genera *Biomphalaria* and *Bulinus* act as intermediate hosts for *S. mansoni* and *S. haematobium* respectively. *Biomphalaria* are medium sized (usually under 20mm diameter) hermaphrodite snails. They can be found in a wide range of freshwater habitats, including streams, irrigation channels, ponds and lakes (Brown 1994). Around 12 species are found in Africa, and species of *Biomphalaria* can also be found in parts of South America, the Caribbean, and the Middle East. All African species that have been tested are capable of acting as intermediate host for *S. mansoni* (Brown 1994).

There are approximately 36 species of *Bulinus*, which are typically divided into four groups: the *Bu. forskalii* group, the *Bu. africanus* group, the *Bu. truncatus/tropicus* complex, and the *Bu. reticulatus* group (Brown 1994). The genus is widespread throughout Africa and the Middle East, and can be found in small seasonal water bodies, irrigation systems, and some lakes. Many species excel in surviving in temporary water bodies through a combination of aestivation – a form of dormancy that allows snails to survive the drying up of surface water – and a very high rate of reproduction, growth and development when conditions are more favourable.

1.3.2 Water temperature

Snails are poikilotherms – unable to regulate their internal temperature – and temperature is therefore a key determinant of both their geographical distribution, and all aspects of their lifecycles. A large number of observational studies and experiments have been conducted in field and laboratory settings, exploring the effects of different temperature regimens on the fecundity, development and mortality of *Biomphalaria* and *Bulinus* species. Experiments conducted using *Bi. pfeifferi* are summarised in chapter 2, and experiments conducted using *Bi. glabrata* or *Bi. alexandrina* are summarised in chapter 4. Similar experiments have been conducted in a range of other species, demonstrating, for

instance, that the maximum intrinsic rate of increase occurs at 25°C for *Bu. globosus* populations, and at 23-26°C in *Bu. africanus* populations (Appleton 1978).

There is circumstantial evidence from a number of studies that unfavourable temperatures limit the geographic distribution of *Biomphalaria* and *Bulinus* species. Pitchford observed that night-time temperatures that repeatedly dropped below freezing killed snails kept in outdoor aquariums in South Africa (Pitchford 1969), and *Bi. pfeifferi* and *Bu. globosus* produce few or no eggs during the winter in subtropical areas of Zimbabwe (Shiff 1964a; Shiff 1964b; Woolhouse and Chandiwana 1989). Only 0.3% of 1639 South African locations where *Bi. pfeifferi* have been reported to occur have a mean annual air temperature of below 15°C, and only 0.2% have temperatures above 25°C (De Kock, Wolmarans *et al.* 2004).

Field and experimental studies have suggested that high temperatures during snail maturation may limit *Bi. pfeifferi*'s distribution (Appleton and Eriksson 1984). In water bodies in South Africa, an association was found between the number of snails in a generation and temperatures during the previous generation's developmental period (Appleton 1977c). Snail numbers were greatly reduced when temperatures during the previous generation's developmental period exceeded a critical threshold of mean weekly levels of 120-179 degree hours above 27°C, equivalent to 17-26 degree hours above 27°C a day. The effects of high temperatures were confirmed using laboratory experiments, which demonstrated that both gonad development and egg production were impaired in snails exposed to above 39 degree hours above 27°C a day during development (Appleton and Eriksson 1984). The authors of these studies suggest that this effect was responsible for the absence of *Bi. pfeifferi* populations from shallow pans and streams, while the availability of cooler deep water allowed snail populations to survive in nearby deeper pans (Appleton 1977c). In Mali, high temperatures were thought to be responsible for the apparent absence of *Bi. pfeifferi* and *Bu. globosus* from a stream during the hottest dry season months (Coulibaly and Madsen 1990). It has also been suggested that high temperatures are responsible for *Bi. pfeifferi*'s absence from suitable habitats near the coast of East Africa (Sturrock 1966b), and in warmer regions of Madagascar (Brygoo 1967).

1.3.3 Water depth

Studies of habitat preference in *Biomphalaria* suggest that most *Biomphalaria* species have a preference for shallow water close to the edge of water bodies. In a residual pool of a river, *Bi. pfeifferi* were most abundant in locations with shallow water (<4cm), and close to the shore (within 40cm) (Utzinger and Tanner 2000). In a reservoir in Brazil, *Bi. tenagophila* populations densities were highest at the water's edge and 70cm from the edge, and lower at 1.4m from the shore (Freitas, Bedê *et al.* 1987). In Lake Albert, Uganda, *Bi. sudanica* were found exclusively in shallower sites (<1m) (Kazibwe, Makanga *et al.* 2006). *Bi. stanleyi* were found exclusively in deeper sites however (>1m and <3m), suggesting a preference for deeper water in this species. Sites deeper than 3m were not surveyed. A preference for shallower habitats has also been observed in *Bu. truncatus,* with a negative correlation being found between water depth and snail abundance (Hussein, Obuid-Allah *et al.* 2011).

Utzinger and Tanner separated out the effects of water depth and proximity to the shoreline by studying the distribution of snails in a shallow, man-made habitat with a flat, concrete bottom (Utzinger and Tanner 2000). In this water body, *Bi. pfeifferi* snails showed no preference for locations close to the shore. This suggests that apparent preferences for shoreline microhabitats are due to a preference for shallower water only.

Despite an overall preference for shallower water, *Biomphalaria* have occasionally been observed in much deeper water. Snails have been found in water at depths of 4.3 m for *Bi. smithi*, 12.2m for *Bi. choanomphala*, 4-5m for *Bi. glabrata*, and 4.5m for *Bi. pfeifferi* (Jurberg, Schall *et al.* 1987). Snails are capable of surviving for extended periods at these depths; for example, *Bi. glabrata* (Deschiens and Jadin 1954) and *Bi. pfeifferi* (Gillet, Bruaux *et al.* 1960) have been shown to survive for 24 and 31 days when submerged in boxes at depths of 10m and 15.25m respectively. Seeking deeper water may often be a response to above optimal temperatures near the surface of the water. Burrowing in a mud substratum may further decrease the maximum temperatures to which snails are exposed (Klumpp, Chu *et al.* 1985). There is also some evidence that the reverse occurs, with snails in a South African pond spending less time in deeper water in winter when water temperatures are below optimal (Shiff 1966).

1.3.4 Water chemistry

A large number of studies have conducted general chemical analyses of water from a wide range of snail habitats. These have been reviewed by Appleton (1978) and Brown (1994), who concluded that host snail species are tolerant of waters with widely differing dissolved chemical content, and that their distribution is largely independent of water chemical content within the range of chemical contents typically found in fresh water bodies.

The exception to this is calcium concentrations, the effects of which have been studied in greater detail than any other aspect of water chemistry, due to the potential importance of calcium for shell growth (Brown 1994). Schutte and Frank collected snail samples and conducted chemical analysis of water samples from 95 water bodies in south-eastern Transvaal, South Africa and Northern Swaziland (Schutte and Frank 1964). *Biomphalaria* or *Bulinus* snails were found more frequently in locations with higher concentrations of $CaCO_3$. They were found in approximately 90% of 22 locations where the water was classified as 'very hard' (mean $CaCO_3$ concentration 63ppm), 80% of 16 locations where it was classified as 'hard' (mean $CaCO_3$ concentration 41ppm), 70% of 63 locations where it was classified as 'soft' (mean $CaCO_3$ concentration 17ppm), and 50% of locations where it was classified as 'very soft' (mean $CaCO_3$ concentration 6ppm).

Williams investigated the population density of snails in a range of different types of water body in Zimbabwe (Williams 1970a). Five water bodies were classified as soft (<5ppm Ca and <20ppm $CaCo_3$), six as medium (5-40ppm Ca and 20-200ppm $CaCo_3$), and three as hard (>40ppm Ca and >200ppm $CaCo_3$). His results suggested that different species of host snails may have different tolerances and preferences for different calcium concentrations. *Bu. tropicus* snails were found in all medium water bodies, but no hard or soft water bodies. *Bu. globosus* were found in all but one water body, and had similar densities in all types of water body. *Bi. pfeifferi* were abundant in both medium and hard water bodies, but very few snails were found in soft water bodies. Williams went on to confirm his findings using laboratory experiments (Williams 1970b). The intrinsic rates of increase (r_m) of both *Bi. pfeifferi* and *Bu. globosus* were highest at moderate calcium concentrations. There was much greater variation in r_m at different calcium concentrations for *Bi. pfeifferi* however, and the variation was not significant for *Bu. globosus.*

A more recent experimental study explored the effect of different concentrations of calcium on juvenile snail growth and shell strength (Brodersen and Madsen 2003). Laboratory-bred *Bi. sudanica* were kept for 10 weeks in water with five different concentrations of Ca^{2+}, ranging from 0.8-80ppm. A linear relationship was found between log calcium concentration and mean shell diameter at 10 weeks ($p<0.001$), and between log calcium concentration and log inorganic dry weight ($p<0.001$). Crush weight (the weight of sand required to crush the shell) was also found to be correlated with log calcium concentration, controlling for inorganic weight ($p<0.001$). The shells of snails kept at the highest concentration were found to have crush weights around 10 times higher than the shells of snails kept at the lowest concentration. This suggests that snails may be more vulnerable to predation in waters with a low concentration of calcium.

Taken together, the results of experiments investigating the effects of calcium concentrations on *Biomphalaria* and *Bulinus* snails and snail populations suggest that many species may not survive well at low calcium concentrations.

Many *Biomphalaria* species have a high tolerance for water contaminated with organic matter. *Bi. pfeifferi* kept in sewage/waste water purified in stabilisation ponds were able to survive in water with chemical oxygen demands of up to 1060mg/l (Klutse and Baleux 1996). In Brazil, *Bi. tenagophila* populations were found in watercress gardens irrigated with water contaminated with domestic sewage or organic refuse from pigsties (Baptista and Jurberg 1993). Another study observed a positive association between faecal population levels and *Bi. glabrata* densities, although this may have been due in part to the presence of denser vegetation in more polluted water (Kloos, Passos *et al.* 2004). This tolerance for polluted water enables *Biomphalaria* populations to survive in water bodies contaminated with human faeces, putting them at risk of infection with *S. mansoni* and allowing onward transmission to humans.

1.3.5 Flow rate

Fast-flowing streams and rivers are thought to be unsuitable for *Biomphalaria* and *Bulinus* snail populations. Appleton measured midstream current speed in a number of locations in a South African stream (Appleton 1975). Snail surveys were conducted in the same locations. No *Bi. pfeifferi* or *Bulinus* species were found in locations with flow rates of

greater than 0.3ms^{-1}, despite the presence of other genera of snails. Appleton concluded that the reason for their absence was that *Biomphalaria* and *Bulinus* snails cannot tolerate flow rates above this speed. In a river in Tanzania, *Bi. pfeifferi* showed a preference for micro-habitats with flow rates of 0.12-0.21ms^{-1}, although some snails were also found in areas with the maximum measured flow rates of 0.27-0.31ms^{-1} (Utzinger, Mayombana *et al.* 1997).

Unfavourable flow rates may have the greatest effect on juvenile snails, however evidence is inconclusive. No significant correlation was found between shell size and micro-habitat preference in *Bi. pfeifferi* in Tanzania, although areas with flow rates above 0.31ms^{1} were not surveyed (Utzinger, Mayombana *et al.* 1997). Loreau and Baluku suggested that flow rates in excess of 0.4ms^{-1} following heavy rains were the most likely reason for high rates of juvenile mortality during the rainy seasons in a stream in the Democratic Republic of Congo (Loreau and Baluku 1987b). Unusually high flow rates in a normally slow flowing stream or river may also temporarily or permanently destroy the entire snail population in an area (Kariuki, Madsen *et al.* 2013).

1.3.6 Survival in temporary water bodies

Many species of *Bulinus* specialise in inhabiting small, temporary water bodies, which often dry out entirely during the dry season(s) (Brown 1994). Two characteristics make them successful in these types of water body: aestivation, and a very high intrinsic rate of increase. Some species of *Biomphalaria* also exploit temporary water bodies, although the genus as a whole is less well adapted to these habitats.

Aestivation is a type of dormancy entered into by the snails in the absence of surface water. Snail mortality is high during aestivation, with estimated mortality rates in *Bu. globosus* varying between 0.05-0.43 per week (reviewed in Brown (1994)). Despite high mortality rates, aestivating *Bu. globosus* have been reported to survive for periods of 5-8 months (Webbe and Msangi 1958). Survival during aestivation may be higher in humid conditions. 82% of medium sized *Bu. globosus* survived being buried in soil for a period of 90 days when the soil moisture content at a depth of 4cm was 5.0% (Cridland 1967). When the soil moisture was 1.3%, only 14-22% survived. Survival may be lower for snail populations with little history of previous desiccation. 89% and 52% of *Bi. glabrata* taken

from a temporary pool survived 10 and 36 days of desiccation respectively, compared with only 56% and 3% of *Bi. glabrata* taken from a permanent lake (Olivier 1956).

The ability to rapidly develop and reproduce is also essential in allowing *Bulinus* to exploit temporary water bodies. Pools may contain water for only a few months a year, and in that time the snail population must gain sufficient numbers to survive the high losses sustained during the dry season(s). The act of aestivating may even drive individual snails to adopt a faster, more strongly r-selected life history strategy. *Bu. rohlfsi* snails emerging from 1-2 months of aestivation ate substantially more food, had a much higher rate of egg production, and had a slightly faster growth rate than snails of a similar size that had not aestivated (Oyeyi and Ndifon 1990). Mortality rates were not recorded, however it is probable that the higher fecundity rates were achieved at the expense of a longer lifespan.

A study of population dynamics of *Bu. globosus* in two interconnected temporary ponds demonstrates how *Bulinus* populations are able to survive and thrive in seasonal water bodies (Shiff 1964a). Over a period of a year, the ponds were measured and sampled monthly, and the total number of snails and snail eggs in the ponds estimated. In May 1962, the ponds measured 448m^2, and contained an estimated 62,000 snails. This rose to a maximum of 67,000 in June, but from then onwards the ponds started to dry up. The size of the ponds and number of snails found in the water dropped dramatically, and by early August the ponds were completely dry. Some snails remained on the surface of the mud, but these were quickly eaten by predatory ants. Only snails that were buried in the mud survived. The ponds started to fill again on the 22nd of November. Only five days later, an estimated 1387 snails were found alive, and the ponds already contained an estimated 32,000 eggs. This is equivalent to an egg production rate of 4-5 eggs/snail/day. After a further 22 days, the ponds had reached their maximum size and there were an estimated 22,000 new snails, in addition to 2020 snails that had survived aestivation and 580,000 snail eggs. By mid-January there were an estimated 96,000 snails, demonstrating that snail numbers could reach their pre-dry season levels within two months of the pond starting to refill.

Infected snails can remain infected throughout periods of aestivation, however some may lose their infection. Woolhouse and Taylor compared four-week survival of uninfected and patently infected *Bu. globosus* kept in naturally drying mud (Woolhouse and Taylor 1990). *S. haematobium* infected snails had a mortality rate of 0.43/week, compared with 0.19/week for uninfected snails ($p<0.01$). Two infected snails survived the four weeks of

desiccation, and neither subsequently shed cercariae. However some *Bulinus* snails have been demonstrated to emerge from aestivation with patent infections. Two out of 23 *Bu. nasutus* found immediately after a pond in Tanzania started to refill following the dry season were found to be shedding *S. haematobium* cercariae (Webbe 1962). In addition, aestivation during the prepatent period has been found to have little effect on cercaria production by *Bi. glabrata* snails infected with *S. mansoni* (Cooper, Richards *et al.* 1992).

1.3.7 Light/shade

Observational studies have suggested that *Biomphalaria* snails prefer non-shaded habitats (Appleton 1978). Covering irrigation scheme syphon boxes reduced *Bu. truncatus* population densities in Morocco, and greatly reduced the number of egg masses found (Khallaayoune, Madsen *et al.* 1998; Laamrani, Khallaayoune *et al.* 2000).

Laboratory experiments where snail populations are maintained in darkness suggest differences between species. Many species appear to be unaffected by darkness (reviewed by Appleton (1978)), however *Bi. alexandrina* kept in darkness died within two weeks in one experiment (El-Emam and Madsen 1982). It has been hypothesised that the negative effects of shade on wild *Biomphalaria* populations are indirect, and occur as a result of a lack of food, or a lack of oxygen due to poor growth of vegetation, or as a result of cooler water temperatures in the shade.

One experiment supports the view that the negative effects of shade on snail populations are indirect, at least for *Bi. pfeifferi*. Loreau and Baluku experimentally shaded a section of a canal where *Bi. pfeifferi* were found using a dense cover of banana leaves (Loreau and Baluku 1991). Over a period of six weeks, the number of snails sampled each week fell to zero. The number in an adjacent section increased over the same time period, suggesting migration by the snails. After 14 weeks, the cover was removed, and snail numbers increased again over a period of eight weeks. The authors suggest that the slow rate of recolonisation indicated that a lack of food was responsible for the absence of snails, as the snails should have recolonised the stream within a few days if the unsuitability of the covered habitat was directly due to a lack of light.

1.3.8 Population fluctuations and seasonality

All species of *Biomphalaria* and *Bulinus* snails that have been extensively studied have been found to be iteroparous, producing multiple egg masses in repeated cycles of reproduction (Brown 1994). Despite this, distinct, seasonal generations of snails and/or populations fluctuations can be observed in many habitats, usually driven by changes in temperature and/or the seasonal drying up of water bodies. In seasonal water bodies, generations may be distinct, with no egg production occurring when the water bodies are dry. In permanent water bodies, egg production may occur throughout the year, but definite peak(s) of egg production and snail numbers may still be seen. The number and timing of generations appears to be determined more by the climate and habitat than by the species of snail. A large number of studies have tracked snail population numbers over the course of several months or years, and have investigated the climatic and/or environmental factors that may be responsible for population fluctuations. Many of these studies are summarised by Brown (1994). Some typical examples of the seasonal patterns observed are given below.

Seasonal water bodies:

- One or two generations per year coinciding with the rainy season(s)
    - *An example is given in section 1.3.6 (Shiff 1964a)*
- In larger seasonal water bodies several overlapping generations may occur each year, followed by a period of aestivation.
    - *In a section of a stream that dried out for four months of the year,* Bi. pfeifferi*,* Bu. globosus*, and* Bu. truncatus *numbers increased steadily over time, reaching a maximum density at a time between the point at which the water started to dry up, and just before the water dried up entirely (Coulibaly and Madsen 1990). Numbers of egg masses or sizes of snails were not recorded, so it is not clear how many generations of snails of each species occurred. Snails were first found again a month after water started to return. It was not known if they emerged from aestivation or originated from more permanent habitats upstream.*

Permanent water bodies where temperatures are marginal for snail survival, development and/or reproduction for part of the year:

- One or multiple generations a year, with lower rates of egg production during periods when temperatures are unfavourable.
    - *In a reservoir on the Kenyan coast, where temperatures were above optimal for* Bu. globosus *populations, egg production was observed to occur throughout most of the year (O'Keeffe 1985). There was a large peak in egg production rates in July-August when temperatures were coolest however, followed shortly after by a peak in snail numbers.*
    - Bi. pfeifferi *populations were found to have three overlapping generations a year in two very different habitats in South Africa: a stream and a pond (Appleton 1977c). In the pond in particular, the first and third generations each year consisted of far fewer snails than the second generation. The low numbers in two of the generations were attributed to above optimum temperatures during the maturation period of their parents' generation. Maximum temperatures in the stream were lower, and there was less variation in generation size over the course of the year.* Bi. pfeifferi *snails were entirely absent from a nearby pan where daily maximum temperatures during summer were higher.*
    - *In a permanent section of stream in Mali, large and stable numbers of* Bi. pfeifferi *were found throughout much of the year (Coulibaly and Madsen 1990). There was a sharp fall in snail numbers in May however, and numbers did not increase again until November. The reduction in numbers coincided with the hottest part of the dry season, when a combination of high air temperatures and a low water level greatly increased water temperatures.*

Permanent water bodies where temperatures are suitable for snail survival, development and reproduction throughout the year:

- Egg production occurring throughout the year, but with an obvious peak in snail numbers related to the timing of the main rainy season.
    - *Temperatures in the permanent Virunga stream, Democratic Republic of Congo, were suitable for* Bi. pfeifferi *all year round (Loreau and Baluku 1987b). Egg production occurred continuously throughout the year, however snail numbers varied greatly, with a single peak in May-September. The authors suggested that the most likely explanation for the seasonal variation in numbers was high flow rates during the rainy season carrying away juvenile snails.*

- A number of overlapping generations or no discernible generations. There may be large variations in snail numbers throughout the year, which may or may not be obviously attributable to any climatic or environmental factor.
    - *In a pond in Tanzania, there was large variation in* Bu. globosus *numbers over the course of a year, with a large peak in January (Marti 1986). The pond was large and permanent, and temperatures varied little over the course of a year. The authors suggested that the large variation in snail numbers could be attributable to high snail densities greatly reducing rates of egg production.*
    - Bi. sudanica *and* Bi. stanleyi *populations were surveyed monthly for a period of three years at a number of sites in Lake Albert (Kazibwe, Makanga et al. 2006). There was an overall trend over the three years towards higher numbers of* Bi. sudanica *and lower numbers of* Bi. stanleyi*, and smaller fluctuations in numbers occurred throughout the period. Snail numbers were found to be associated with a number of environmental variables with a lag of three months, including temperature, rainfall and lake level. No seasonal pattern in snail numbers could be observed however.*

Irrigation canals:

- Distinct generations and population fluctuations may occur in irrigation canals, due to a combination of artificially controlled water availability and flow rates, and natural variation in temperatures.
    - *In irrigation canals in Egypt*, *two peaks in* Bi. alexandrina *population density were observed (Yousif, Kamel et al. 1993). Drops in snail numbers occurred in January, due to the closure of the canals and a fall in water level, and from May to October, due to high temperatures.*

1.4 Focality of transmission

The prevalence of schistosomiasis in humans can vary greatly on a small geographical scale. In six zones of one district of Ghana, with an estimated population of only 144,000 and an area of 1674km^2, the prevalence of *S. mansoni* in children ranged from 0% (geometric mean egg burden 0 eggs per gram (epg)) to 54% (128 epg) (Anto, Asoala *et al.* 2014). The high levels of variation in schistosomiasis prevalence between, and even within, villages has

implications for the design and implementation of control programs, which are typically targeted at whole districts for many diseases.

Local variation in prevalence of infection can be driven by a wide range of different factors. A common explanation for variation is distance to the nearest water body, with shorter distances shown to be a strong predictor of high schistosomiasis prevalence in a number of settings (e.g. Handzel, Karanja *et al.* 2003; Kabatereine, Brooker *et al.* 2004; Kapito-Tembo, Mwapasa *et al.* 2009). Differences in the suitability of water contact sites for snail populations are also likely to be important in many areas. Monthly *Bi. pfeifferi* surveys were conducted in 14 sites in irrigation canals in the entire area surrounding a typical village in the Gezira Irrigated Area, Sudan (Babiker, Fenwick *et al.* 1985). The distribution of both snails and infected snails varied greatly between different sites, with the total proportion of all snails collected that were collected at each site ranging from 0-20%, the proportion of snails shedding cercariae ranging from 0-9%, and the proportion of all infected snails collected found at each site from 0-54%. A strong positive correlation was found between numbers of infected snails at a site and proximity to human dwellings, however the proportion of infected snails at a site did not always correspond closely to *S. mansoni* prevalence in humans using the sites.

Differences in human behaviour may also affect schistosomiasis prevalence on a very local scale. For instance, in a fishing community in Uganda, odds of reinfection with *S. mansoni* 12 months after treatment was significantly associated with both ethnic group (OR=0.08, p<0.0001) and sex (OR=0.32, p=0.05), with very strong evidence for an interaction between the two variables (p<0.0001) (Pinot de Moira, Fulford *et al.* 2007). After controlling for observed duration of water contact in the 12 months after treatment, the effects of sex and the interaction term were no longer significant (OR for sex=0.66; p=0.7 and p=0.07 respectively), demonstrating that human water contact behaviour can be responsible for differences in prevalence of infection. Ethnic group remained strongly associated with odds of reinfection (OR=0.14, p=0.002), however adjusting for estimated cercarial exposure greatly reduced the association (OR=0.54, p=0.06). Cercarial exposure for each individual was calculated as:

$$X = \sum_{j=1}^{n} site_j * hr_j * deg_j * dur_j$$

where X was the exposure score, n was the number of times the individual was observed in contact with the water, dur_j was the duration of the j^{th} contact, and $site_j$, hr_j and deg_j were

the site, time of day and degree of immersion weightings for the j^{th} contact. Site weightings were based on the abundance of *Biomphalaria* snails at the site. The greater reduction in the association between ethnic group and odds of reinfection when cercarial exposure was adjusted for, as opposed to when duration of water contact was adjusted for, suggests that in the study setting exact location of water contact within the village had a large effect on schistosomiasis risk (although it cannot be ruled out that the greater reduction in the odds ratio was due to differences between the ethnic groups in the degree of immersion and time of day of water contact).

1.5 Schistosomiasis control and elimination

The distribution and prevalence of *Schistosoma* infection in much of sub-Saharan Africa may be greatly altered over coming years and decades by schistosomiasis control programs. The effects of these programs will interact with the effects of climate change, impacting on future schistosome transmission patterns. For instance, changes in temperatures that increase the suitability of an area for high levels of schistosome transmission may have no effect if *Schistosoma* infections have been locally eliminated. On the other hand, elimination may be impeded in some areas by climate-driven increases in transmission.

1.5.1 Mass drug administration

The WHO recommends that all school aged children living in areas where schistosomiasis transmission occurs are treated for schistosomiasis once a year, every two years, and twice during their school years in areas where the prevalence of schistosomiasis in school aged children is ≥50%, ≥10% but <50%, and <10% respectively(World Health Organization 2006). They also recommend that certain groups of at risk adults are treated in areas where the prevalence in school aged children is ≥10%. A World Health Assembly resolution passed in 2001 set a goal of at least 75% treatment coverage of at risk school children by 2010 (World Health Assembly 2001). Despite this, only 50% of countries where preventative

chemotherapy is needed had programs in place in 2010, and it is estimated that only 13% of people at risk received treatment (World Health Organization 2012).

Treatment is with praziquantel, taken orally. A single dose of 40mg/kg is typically used against all species of schistosome. It has an initial cure rate of around 60-90%, with egg reductions of around 90-99% in individuals where egg reductions are not 100% (World Health Organization 1993). Minor adverse effects are common (including abdominal pain, headaches, nausea, vomiting, general malaise, fever, loose bowel, itching, body pain and dizziness), but no serious adverse effects have been reported in trials (Danso-Appiah, Utzinger *et al.* 2008).

There is some evidence that mass treatment programs may be reducing the incidence of *Schistosoma* infections in some areas. In Uganda, the prevalence of *S. mansoni* infection in previously untreated six year olds fell from 35% at baseline, to 23% after two years of mass drug administration (Zhang, Koukounari *et al.* 2007). The mean intensity of infection fell from 171epg to 72epg. It is unclear if annual mass drug administration will continue to reduce new infections in many areas however. In six sites in Mali, the prevalence (mean intensity) of *S. haematobium* infection in seven year olds fell from 91% (195 eggs/10ml urine) in 2004 to 47% (38 eggs/10ml urine) in 2005, before rising to 59% (26 eggs/10ml urine) in 2010 (Landouré, Dembélé *et al.* 2012). The prevalence (mean intensity) of *S. mansoni* infection fell from 20% (85epg) in 2004 to 16% (50epg) in 2005, before rising to 27% (72epg) in 2010. This is suggestive of an increase in incidence, despite mass drug administration. Howver other explanations cannot be ruled out. The seven year olds had not previously been treated at school, but should have been treated as part of the community mass drug administration program. Increases in prevalence may therefore reflect poorer treatment coverage in the community. In addition, drug administration did not occur in two years in two of the six sites tested.

1.5.2 Lack of engagement with mass drug administration programs

The impact of mass drug administration programs may be reduced by a lack of engagement in some areas. It has been argued that treatment coverage can be low among some groups with the highest need. This is particularly the case for fishermen, who often spend days or weeks fishing away from their villages (Parker, Allen *et al.* 2012). Other people may refuse

treatment. Several anthropological studies have been conducted in Uganda since the start of the mass treatment program in 2003, exploring reasons for resistance to treatment (Parker, Allen *et al.* 2008; Fleming, Fenwick *et al.* 2009; Parker and Allen 2011; Parker, Allen *et al.* 2012). A commonly reported reason for refusing treatment in one study was fear of side effects (Parker, Allen *et al.* 2008). For instance, one participant said "*When I took the tablet, 'praziquantel',* [in 2004] *it disturbed me for 2 to 3 weeks … I am a fisherman [and] I cannot afford not to fish. This is why I did not take it* [in 2005]." Other informants reported fears that treatment with praziquantel could lead to infertility and miscarriage, with one even suggesting that some people think that mass treatment with praziquantel is a Ministry of Health strategy to reduce birth rates. Accounts were also given of people dying after taking praziquantel, sometimes linked to concerns that the fact that praziquantel doses are calculated by height not weight could lead to overdoses (this is not the case). Other studies found that participants were more accepting of side effects however, and even questioned whether the drug was still working during later rounds when they experienced milder or no side effects (Fleming, Fenwick *et al.* 2009; Parker and Allen 2011).

Another major barrier to treatment reported by the studies was belief in "*awola*" (Parker, Allen *et al.* 2008; Parker, Allen *et al.* 2012) or "*esidada"* (Fleming, Fenwick *et al.* 2009), ailments with similar symptoms to schistosomiasis that are caused by witchcraft. This was reported to prevent people from seeking biomedical treatment, as they believed that it would be ineffective. In the case of *awola*, it was also reported to make people afraid to take praziquantel due to a belief that individuals inflicted with *awola* could die if they take medicine.

Finally, some respondents stated that they did not think it was appropriate to take praziquantel when they felt well (Parker, Allen *et al.* 2008; Parker and Allen 2011). For instance, one man said "*It is not in our culture to take drugs unless we are sick … the idea of taking a drug when you are well is strange to people here … people do not wish to take it, especially as it can make you sick.*" (Parker, Allen *et al.* 2008). This view will not only prevent people who are not infected from taking praziquantel, but is likely to also reduce treatment coverage among people with asymptomatic schistosomiasis, and among infected people with symptoms that they attribute to other causes.

Schistosomiasis mass treatment programs often have the additional goal of promoting treatment seeking behaviour among people with schistosomiasis. It is unclear if this goal is

feasible for *S. mansoni* infection, as few people may have the knowledge of disease symptoms that are necessary if they are to seek treatment with praziquantel. Booma village, Uganda has been the site of multiple research projects into schistosomiasis since 1996, exposing residents to far greater levels of education about schistosomiasis than is typical in the region (Dunne, Vennervald *et al.* 2006). When questioned about symptoms of schistosomiasis, 80% of people correctly identified a distended abdomen as a symptom. Only 34% of people reported the next most commonly reported symptom, diarrhoea (Pinot de Moira 2008). This is problematic as visibly distended abdomens only occur when the infection has already caused considerable morbidity (Balen, Stothard *et al.* 2006). Furthermore, it was also reported that some individuals attribute distended abdomens to 'charms', something for which they are unlikely to seek biomedical treatment. The situation was found to be similar at another long-term *S. mansoni* study site. Only half of residents in a village in Senegal were able to describe the symptoms of schistosomiasis following seven years of research projects (Sow, de Vlas *et al.* 2003). Levels of knowledge away from sites of repeated research programs are likely to be even lower.

1.5.3 Snail control and environmental modification

Mass drug administration programs are currently the principal means of schistosomiasis control employed in sub-Saharan Africa. Other methods have been used with some success in the past however, and schistosomiasis elimination is unlikely to be achieved using mass drug administration alone.

Prior to the late 1970s, snail control through the application of molluscicides was the mainstay of schistosomiasis control (Sturrock 2001). Repeated application of niclosamide successfully reduced transmission in many locations. In some areas, snail populations were eliminated entirely and schistosome transmission halted. In southern Tunisia, *Bu. truncatus* were eliminated from nearly 200 sites by the application of niclosamide (Rey, Hachicha *et al.* 1982). In conjunction with a program of chemotherapy and water resource and agricultural infrastructure development, this led to countrywide elimination of *S. haematobium* by 1982 (Rollinson, Knopp *et al.* 2013). In most areas, the repeated application of niclosamide had more temporary effects. Schistosomiasis prevalence was often greatly reduced while control programs were ongoing, however the costs of the

programs were high and snail populations and schistosomiasis prevalences rapidly increased when the programs were stopped (Brown 1994). Application of niclosamide to seasonal rainpools over a period of three years in Ghana reduced *Bu. senegalensis* numbers to around 1% of the numbers found in control pools (Goll and Wilkins 1984). The intensity of *S. haematobium* infection in a cohort of children fell by more than 50% over the three years, compared with a ten-fold increase in a similar cohort living in an untreated area. Applications of niclosamide were stopped after three years, and in the following rainy season snail numbers in the previously treated pools reached levels close to those found in the untreated pools.

Environmental control has also been employed to control or eliminate snail populations, particularly in manmade water bodies such as irrigation canals. Methods employed include the lining of irrigation ditches with cement (Minai, Hosaka *et al.* 2003; Ohmae, Iwanaga *et al.* 2003), the introduction of predator species (Van Schayck 1986), seasonal drying out of canals (Yousif, Kamel *et al.* 1993), and releasing stored water rapidly as a 'flushing wave' (Fritsch 1992). These methods can be extremely successful in controlling or eliminating snail populations, but have the potential to cause environmental damage if employed in natural watercourses (Brown 1994).

1.5.4 Elimination

In recent years, there has been an increased interest in the possibility of achieving schistosomiasis elimination in many low transmission areas. The WHO's 2012 Neglected Tropical Disease control 'Roadmap for Implementation' (World Health Organization 2012) sets a goal of regional elimination of schistosomiasis in the Eastern Mediterranean Region, Caribbean, Indonesia, and the Mekong River Basin by 2015; regional elimination in regions of the Americas and Western Pacific Region by 2020; and elimination in selected African countries by 2020. Most endemic countries in sub-Saharan Africa are not currently in a position to work towards countrywide elimination, due to a combination of high prevalences and a lack of resources. It has nevertheless been suggested that local elimination could be achieved in low prevalence areas of many countries (Rollinson, Knopp *et al.* 2013).

In most cases, elimination will not be achieved through current control efforts. WHO guidelines recommend infrequent treatment in low prevalence areas (World Health Organization 2006). These areas are also likely to be accorded a low priority by resource-limited programs focussing on morbidity reduction. A conscious decision to switch to an elimination strategy, incorporating active case finding and targeted treatment, will be needed to achieve local elimination. Snail control may also play an important part, along with water, sanitation, and education programs.

It is crucial to consider the effects of climate change when deciding when and where to switch from a control to an elimination strategy. In many areas, low prevalences may be due, at least in part, to temperatures which are marginal for transmission. In some of these areas, increasing temperatures may make elimination goals increasingly feasible, making them attractive targets for elimination programs. On the other hand, the parasite and/or intermediate snail hosts may become extinct in these areas even in the absence of increased control efforts. In contrast, in cooler areas, warming temperatures may increase transmission, and control and elimination targets may not be met without increased resource allocation. Schistosomiasis may also spread to new areas, outside the boundaries of any current control efforts, impacting on local elimination.

1.6 Climate change

The Intergovernmental Panel on Climate Change (IPCC) was established in 1988 by the United Nations Environment Programme and the World Meteorological Organization with the aim of providing "*internationally coordinated scientific assessments of the magnitude, timing and potential environmental and socio-economic impact of climate change and realistic response strategies"* (UN General Assembly 1988). The IPCC publishes regular reports every few years, detailing the state of knowledge on climate change at the time of publication. The first part of the IPCC's Fifth Assessment Report, 'The physical science basis' (Stocker, Qin *et al.* 2013), was published in 2013. Climate projections in the report are based around four representative concentration pathways (RCPs), which make different assumptions about future greenhouse gas concentrations (Van Vuuren, Edmonds *et al.* 2011). The four RCPs are:

- RCP2.6, which assumes that greenhouse gas emissions peak between 2010-2020 and decline substantially afterwards.
- RCP4.5, which assumes that emissions peak in 2040, then decline.
- RCP6, which assumes that emissions peak in around 2080, then decline.
- RCP8.5, which assumes that emissions continue to rise throughout the 21st century.

RCP2.6, RCP4.5, and RCP8.5 are considered in this thesis.

Global mean surface temperatures in 2016-2035 are likely to be 0.3-0.7°C higher than temperatures in 1986-2005 (Stocker, Qin *et al.* 2013). By 2081-2100, increases are likely to range from 0.3-1.7°C for RCP2.6, 1.1-2.6°C for RCP4.5, and 2.6-4.8°C for RCP8.5.

In eastern Africa, temperatures are projected to increase by 0.39°C (0.25-0.47°C) between 2006-2015 and 2026-2035 for RCP2.6, 0.54°C (0.43°C-0.65°C) for RCP4.5, and 0.67°C (0.59°C-0.83°C) for RCP8.5 (van Oldenborgh). By 2056-2065, temperatures are projected to increase by 0.68°C (0.45°C-0.81°C) for RCP2.6, 1.23°C (1.00°C-1.55°C) for RCP4.5, and 2.09°C (1.73°C-2.54°C) for RCP8.5. The figures given in this paragraph are the CMIP5 ensemble multi-model medians, with the ranges equal to the 25% and 75% percentiles. Figure 1.1 illustrates maps of the mean projected changes in temperatures in eastern Africa over the next 20 and 50 years. Trends over time and the projections from individual model runs are shown in Figure 1.2.

Although projected changes in temperature vary greatly between different representative concentration pathways and individual model runs, there is widespread agreement that temperatures are going to increase. The situation is much more uncertain when it comes to changes in precipitation over eastern Africa. As Figure 1.2 shows, the multi-model means indicate that overall amounts of precipitation may increase slightly. Individual model projections are consistent with either increases or decreases however, with 25% and 75% percentiles for changes in precipitation over the next 20 and 50 years being negative and positive respectively for all RCPs (van Oldenborgh).

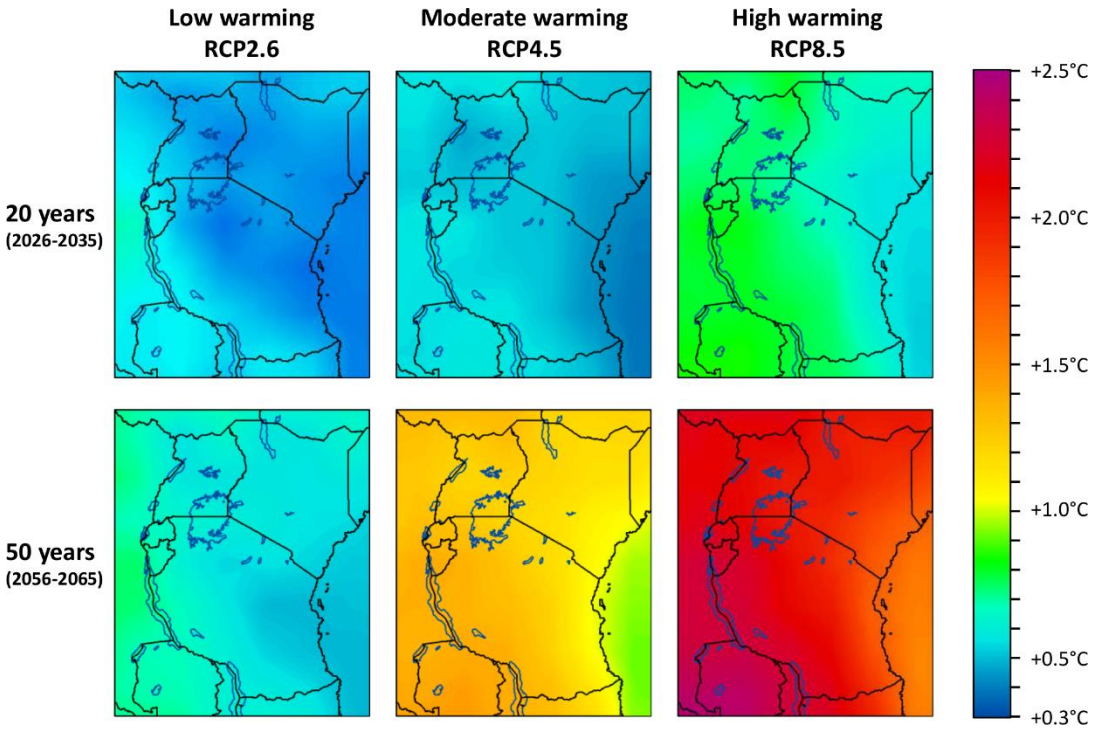

Figure 1.1. Projected changes in temperature in eastern Africa over the next 20 and 50 years. Temperatures are the mean temperatures from the full CMIP5 ensemble. Data were extracted from the KNMI Climate Explorer web application (van Oldenborgh).

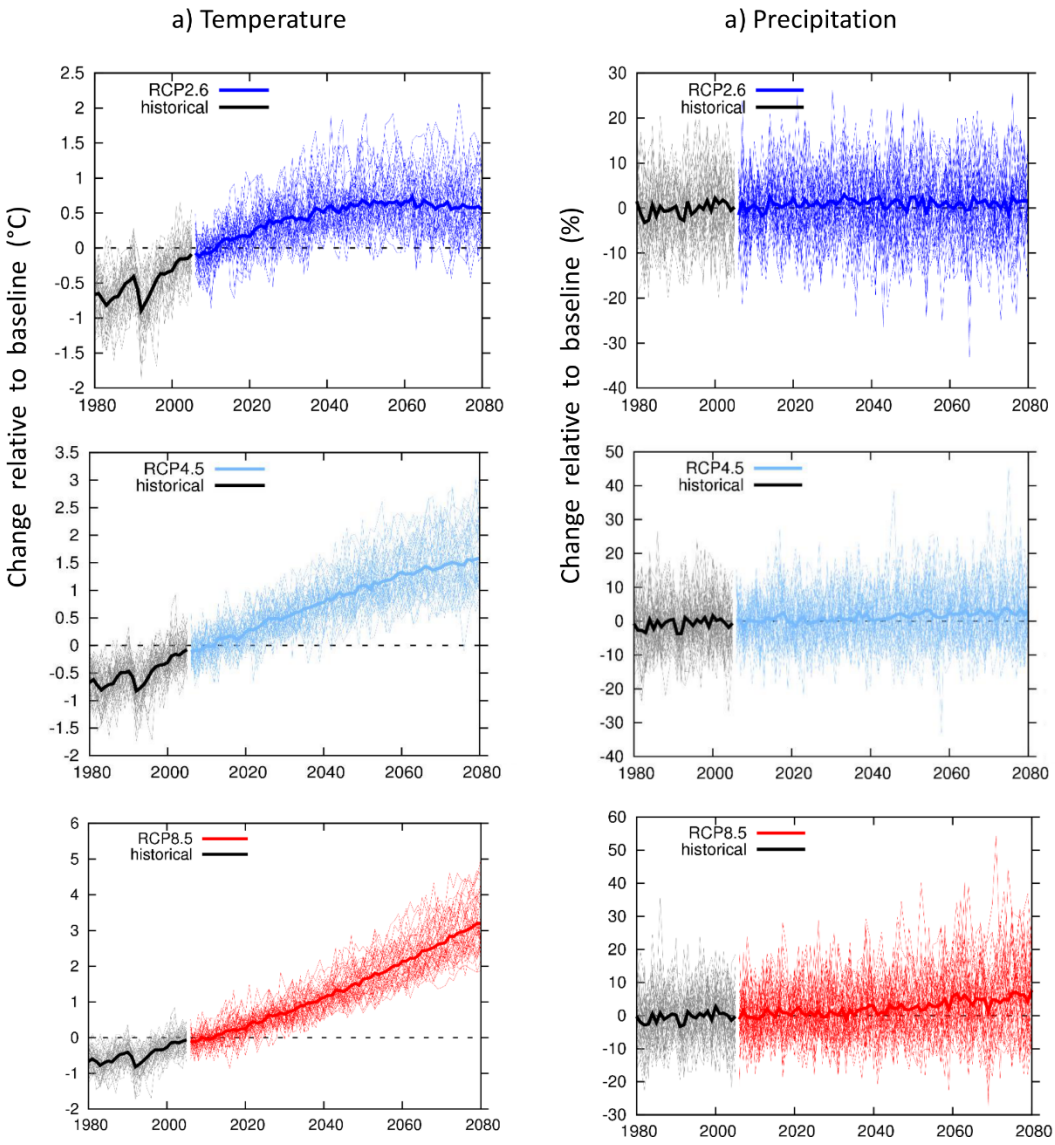

Figure 1.2. Projected changes in temperature and precipitation in East Africa.

Each line shows results from one CMIP5 ensemble model realisation. Thick lines show the multi-model mean. Changes are relative to 2006-2015. East Africa is defined as 11.3°S to 15°N, 25°E to 52°E. Plots were generated using the KNMI Climate Explorer web application (van Oldenborgh).

1.7 Mathematical modelling of schistosome transmission and intermediate host snail populations

Mathematical modelling has been used to investigate a large number of aspects of schistosome transmission. The majority of models have focused on infection in humans, however a number have also simulated snail population dynamics and snail infection in detail.

The first models of schistosome transmission were developed in the 1960s. Hairston developed static models of *S. mansoni*, *S. haematobium*, and *S. japonicum* transmission at equilibrium, estimating the net reproduction rates of the three parasites from estimates of net reproduction in the snail and mammalian hosts, and the probability of miracidia and cercariae successfully infecting a snail and mammal host respectively (Hairston 1965b). He estimated net reproduction rates of 1.85, 2.74 and 0.59 for the three schistosome species, and concluded that a lack of complete information on the parasites was responsible for the fact that estimated net reproduction rates were not equal to one, as would be expected for a system at equilibrium. In the same year, he fitted catalytic force of infection models to age-prevalence data on schistosome infections, estimating human rates of parasite acquisition and loss for the three main human schistosome species (Hairston 1965a).

A few years later, catalytic models were applied to snail populations for the first time. Catalytic models assume constant rates of infection and loss of infection, and use age-prevalence data to estimate these rates. Sturrock and Webb found that a two-stage curve gave the best fit to data from wild snail populations, and suggested that the 'rate of loss of infection' should be interpreted as the additional mortality experienced by infected snails (Sturrock and Webbe 1971). Cohen built on their work, explicitly including a higher mortality rate in infected snails in a catalytic model of snail infection, with mortality rates based on data from a laboratory study (Cohen 1973).

Jobin and Michelson considered the intermediate host snail populations in more detail, incorporating the effects of high snail densities on snail fecundity into a mathematical model of snail population dynamics (Jobin and Michelson 1967). They demonstrated the importance of simulating constraints on snail population growth, and showed that their model gave a good approximation to empirical data on temporal changes in *Bu. globosus* numbers in a pond in Zimbabwe. Nåsell incorporated a stage for snails with prepatent

infections, and allowed snail mortality rates to vary depending on the snails' infection status (Nåsell 1976).

MacDonald developed the first model of the schistosome transmission cycle, incorporating mating probabilities between the sexually reproducing adult worms (Macdonald 1965). He used the model to determine transmission 'break points': a critical threshold number of worms below which transmission is likely to die out as a result of few mixed sex infections occurring in humans. Barbour added a number of additional complexities to a simplified version of MacDonald's model, resulting in a model that gave a closer fit to data on wild snail populations (Barbour 1978). These include adding a prepatent period in snails, incorporating multiple water contact sites with different snail densities, and simulating different seasons with different proportions of infected snails. Anderson used dynamical modelling to estimate the proportion of snails that become infected after exposure to a known number of miracidia for a set length of time, and to investigate the effects of heterogeneity between snails in attractiveness or susceptibility to miracidia (Anderson 1978).

During the 1980s, the focus of modelling work in helminth infections largely shifted from understanding the dynamics of transmission to developing models that could be directly applied to answering questions of relevance to control policy (Basáñez, McCarthy *et al.* 2012). This coincided with a shift in the primary methods used to control schistosomiasis, from snail control to chemotherapy. A large number of models exploring the effects of different selective and mass drug administration programs were developed. A comprehensive review of earlier models is provided by Anderson and May (1991), who also contributed greatly to the field. A major advance came in 1995, with the development of a user-friendly program 'EpiSchisto' (Chan, Guyatt *et al.* 1995). EpiSchisto is based on a deterministic transmission model, and provides a tool that allows program managers to estimate the effects of different treatment strategies on parasite abundance. More recent models have benefited from the large amounts of empirical data on humans populations generated by studies evaluating the impact of mass drug administration programs (French, Churcher *et al.* 2010).

The majority of mathematical models of schistosomiasis have focused on *S. mansoni* or *S. haematobium*, with few considering *S. japonicum*. An exception to this is more recent modelling work focusing on understanding transmission at a specific study site in Sichuan Province, China (Liang, Maszle *et al.* 2002). Coupled hydrological and schistosome

transmission models were used to illustrate the importance of hydrological differences between villages in determining transmission, and demonstrated that small-scale, site-specific models could contribute greatly to our understanding of schistosome transmission (Remais, Liang *et al.* 2008; Remais 2010). Dynamical modelling has also been used to predict the effects of a range of possible interventions at the study site (Liang, Seto *et al.* 2007).

1.7.1 Mathematical models of schistosomiasis and temperature

Mathematical modelling has been used to demonstrate the importance of temperature in driving fluctuations in snail densities in some water bodies. Woolhouse and Chandiwana incorporated temperature-dependent recruitment and mortality rates into a model of *Bu. globosus* population dynamics (Woolhouse and Chandiwana 1990a). They found that the model was able to give a good fit to short-term (≈6 month) data on snail densities in two rivers in Zimbabwe when run using daily mean water temperatures.

With an increased interest in the potential effects of climate change on human health, a number of researchers have developed models of water temperature and snail and schistosome populations, aimed at predicting the impact of rising temperatures on schistosomiasis. Martens *et al* (Martens, Jetten *et al.* 1995; Martens, Jetten *et al.* 1997) calculated the 'epidemic potential' of schistosomiasis at different temperatures by combining a number of different temperature-dependent rates into a single equation. Their model took the form:

$$N_1 N_2 = k_2 * \frac{u_1 u_3 u_4 (u_2 + \sigma)}{\beta_1 \beta_2 \sigma}$$

where N_1 and N_2 were the human and snail densities respectively; u_1, u_2, u_3, and u_4 were the miracidium, uninfected snail, infected snail, and cercaria mortality rates respectively; β_1 and β_2 were the human and snail infection rates; and $1/\sigma$ expressed the latent period of the parasite inside the snails. k_2 represented factors that the authors assumed to be independent of temperature. These included the rate of cercaria production by snails, which has since been shown to vary greatly with temperature (Fried, LaTerra *et al.* 2002). Rates at different temperatures were estimated from empirical data on *S. mansoni* and *S. haematobium*, and a range of different snail species. Results were presented for a generic

human schistosome, and were not snail or schistosome species-specific. The authors concluded that schistosomiasis may spread into new areas, but that overall schistosome transmission may decrease.

More recently, Mangal *et al* developed a population-based dynamical transmission model for *S. mansoni* (Mangal, Paterson *et al.* 2008). The model consisted of four differential equations describing the size of the adult parasite population within humans, the density of uninfected snails, the density of latently infected snails, and the density of patently infected snails. Snail eggs and juveniles, miracidia, and cercariae were not explicitly simulated. Temperature-dependent values were used for a number of model parameters: the cercaria production and infection rates, the adult worm mortality rate, the miracidium infection and mortality rates, the within snail parasite maturation rate, the snail egg production and hatching rates, the snail development rate, juvenile and adult snail mortality rates, and the additional rate of mortality in infected snails. Cercaria mortality rates were not temperature-dependent in the model. The model was parameterised to four constant temperatures: 20°C, 25°C, 30°C and 35°C, and the majority of data used in parameterising the model were from experiments with *Bi. alexandrina*. Human disease burden (mean worms/person) was highest at 30°C, and lowest at 20°C. At 35°C, human disease burden oscillated over time. At all other temperatures, disease burden was stable. The authors conducted a sensitivity analysis, and determined that the most sensitive parameters were different at different temperatures. From this, they concluded that chemotherapy may be the most effective control method at lower temperatures, but that snail control may be increasingly effective at higher temperatures.

Finally, Zhou *et al.* used an approach which combined elements of biological and statistical modelling to predict the potential northwards spread of *S. japonicum* in China (Zhou, Yang *et al.* 2008). The biological component of the model used experimental data on snails and temperature data to determine whether temperatures were suitable for a generation of *Oncomelania hupensis* to occur each year, and for *S. japonicum* infections in snails to become patent. The statistical component assumed that snail populations were restricted to areas where the mean January temperature was above freezing, based on earlier studies of historical data (Yang, Vounatsou *et al.* 2005). The combined model suggested that the area of China that is suitable for endemic *S. japonicum* may increase by 662,373 km^2 by 2030 (relative to 2000), and by 783,883 km^2 by 2050. It is unclear what climate projections were used in estimating these increases.

1.8 Modelling the effects of climate change on vector-borne disease transmission

As shown above, with a few exceptions, the potential for using mathematical modelling to predict the effects of climate change on the distribution and intensity of schistosomiasis transmission has been largely neglected. The same is not true for all infectious diseases, and a far greater body of work exists on the effects of temperature on the transmission of two vector-borne diseases: malaria and dengue. The lifecycles of the malaria parasite and dengue virus and their vectors are fundamentally different from the lifecycles of schistosome parasites and their intermediate host snails. Nevertheless, many key developments in mosquito-borne disease modelling are also applicable to schistosomiasis modelling. Recent review articles exist for both diseases (Mandal, Sarkar *et al.* 2011; Naish, Dale *et al.* 2014), and I describe selected studies that address issues of relevance to the modelling of climate and schistosomiasis below.

Paaijmans *et al.* demonstrated the importance of simulating diurnal variation in temperature when estimating malaria transmission potential (Paaijmans, Read *et al.* 2009). As a result of a non-linear relationship between temperature and parasite development, diurnal variation in temperature around mean temperatures greater than 21°C slowed parasite development compared with constant temperatures, and diurnal variation in temperature around mean temperatures less than 21°C speeded up parasite development. As a consequence of this, simulating daily mean temperatures will result in malaria risk being overestimated in warmer areas and underestimated in cooler areas. Liu-Helmersson *et al.* took this work further for dengue transmission, determining the effects of diurnal variation in temperature on five different model parameters (Liu-Helmersson, Stenlund *et al.* 2014). They showed that simulating diurnal variation in temperature has no effect on the average daily vector biting rate, little effect on the duration of the extrinsic incubation period or the probability of human to vector infection per bite, an effect on the vector mortality rate only at extreme temperatures with high diurnal variation in temperature, and a large effect on the probability of vector to human transmission per bite. The overall combined effect of simulating diurnal variation in temperature was to increase epidemic potential at temperatures away from the optimum constant temperature of 29°C. At mean temperatures close to 29°C, simulating a small amount of diurnal variation in temperature increased the epidemic potential, and simulating a large amount of diurnal variation

decreased it. Similar non-linear relationships exist between temperature and snail and schistosome life history traits, and it is therefore probable that simulating daily mean temperatures will result in similar inaccuracies in mathematical models of schistosomiasis and climate change.

Most models of climate change and malaria have focused on predicting the effects of increasing temperatures. A number of models have also incorporated the effects of rainfall on mosquito populations however. For instance, Parham and Michael incorporated rainfall into their dynamical model of malaria transmission, in addition to temperature (Parham and Michael 2010). They assumed that increasing daily rainfall, up to a threshold, increases the survival of mosquito eggs, larvae and pupae. Above the threshold, it is assumed that the eggs, larvae and pupae die through being 'flushed out' of their habitat. They determined that changes in rainfall patterns strongly affect malaria endemicity, invasion, and extinction. Rainfall may be similarly important in determining schistosome transmission in some areas. It is likely, however, that the large range of different habitat types suitable for *Biomphalaria* and *Bulinus* snail populations will impede the incorporation of rainfall into any large-scale *S. mansoni* or *S. haematobium* transmission model.

Some researchers have called for caution in interpreting the results of climate change and malaria studies, arguing that the effects of changes in climate on malaria transmission may be small compared with the effects of other changes. Gething *et al.* compared the predictions of mathematical models of climate change and malaria with historic and current maps of malaria endemicity, and data on the effects of public health interventions (Gething, Smith *et al.* 2010). They concluded that predicted effects of climate change on malaria are at least one order of magnitude smaller than the changes that have occurred since 1900, and up to two orders of magnitude smaller than those that could be achieved by increased coverage of malaria control measures. Similarly, increasing coverage of mass drug administration for schistosomiasis is likely to have a large impact on the intensity of schistosome transmission.

1.9 Geostatistical modelling of schistosomiasis and climate

Mathematical modelling is one of two main methods used to determine the effects of temperature on disease transmission. The other method is statistical modelling, which

looks for statistical correlations between temperature and other variables, and the prevalence or incidence of disease. Observations used in statistical models of temperature and disease can vary in time and/or space. Due to the poor availability of temporal data, statistical models of temperature and schistosomiasis generally use spatial data.

There is a long history of using spatial data in schistosomiasis research, starting with the simple mapping of schistosomiasis prevalence data. In 1987, the 'Atlas of the Global Distribution of Schistosomiasis' was published, bringing together schistosomiasis prevalence data from a wide range of surveys conducted over preceding decades (Doumenge, Mott *et al.* 1987). More recently, two online databases have been developed, bringing together geo-referenced prevalence and infection intensity data from surveys of schistosomiasis and other helminths or neglected tropical diseases (Brooker, Hotez *et al.* 2010; Hürlimann, Schur *et al.* 2011). Efforts have also been made to map data on the distribution of *Biomphalaria* in Africa (Stensgaard, Utzinger *et al.* 2013).

The study of the spatial epidemiology of schistosomiasis has developed greatly over the past three decades with advances in geographic information systems, which aid in the analysis and display of spatial data, and remote sensing, which provides high resolution data on climatic and land-use variables (Brooker 2007). Statistical methods have also improved in recent years. Traditional regression modelling was initially used to predict the probability of an area having a prevalence of infection greater than a threshold (e.g. Brooker, Hay *et al.* 2001; Brooker, Hay *et al.* 2002). This approach did not take into account spatial correlation in infection and environmental data however, which led to the increasing use of Bayesian based methods (e.g. Raso, Matthys *et al.* 2005; Clements, Lwambo *et al.* 2006). Regardless of the methods used, most statistical studies look for correlations between explanatory variables and some measure of schistosomiasis risk, usually point prevalence, over a defined geographical area. Commonly included variables include some measure of mean, minimum and maximum temperatures, normalized difference vegetation index, distance to water bodies, elevation, and precipitation (Simoonga, Utzinger *et al.* 2009).

Geostatistical modelling has also been used to predict the effects of climate change on *S. mansoni* transmission in Africa (Stensgaard, Utzinger *et al.* 2013). Stensgaard *et al.* developed a range of statistical models, consisting of two components: models predicting the distributions of five species of *Biomphalaria*, and a model predicting the suitability of temperatures for the *S. mansoni* parasite. Variables that were considered for inclusion in

the snail models were mean diurnal temperature range, mean temperatures of the warmest and coolest quarters, annual precipitation, precipitation seasonality (coefficient of variation), precipitation of driest quarter, and six non-climatic variables. The *S. mansoni* model was an estimate of the annual number of growing degree days available for *S. mansoni* development within intermediate host snails. A range of different models were fitted using Bayesian methods, with different groups of variables considered for inclusion in each model. The snail models fitted well to the snail distribution data (area under the receiver operator characteristics curve (AUC) of 0.836-0.997). The climatic variables contributed little to model training gain, with habitat-related variables being found to be stronger predictors of the presence or absence of snails. A combined model weighting the *S. mansoni* model output according to the *Bi. pfeifferi* and *Bi. choanomphala* snail model outputs gave the closest fit to empirical prevalence data. Climate change projections were used to estimate changes in the distribution of *Biomphalaria* snails and *S. mansoni* potential transmission index between 1950-2000 and 2080. From this, it was estimated that the potential transmission area of *S. mansoni* in Africa may increase, while the snail ranges may contract and/or move into cooler areas in the south and east.

1.10 Rationale, aims and objectives

Both schistosome parasites and their intermediate host snails are very sensitive to water temperature. It is therefore probable that climate change will alter the suitability of many areas for schistosome transmission. Knowledge of where schistosome transmission may increase or decrease, and in particular knowledge of where conditions may become newly suitable for endemic schistosomiasis, will allow policy makers to anticipate and plan for these changes. Predicting the effects of climate change on schistosomiasis is an area that has been largely neglected. Few mathematical models of water temperature and schistosome transmission exist, and none explicitly simulate all temperature sensitive stages of the snail and parasite lifecycles. Statistical models are unable to accurately capture complex, non-linear relationships, and may be unreliable if applied over areas with multiple snail hosts. There is therefore a real need for the development of new mathematical models of water temperature and schistosome transmission. These models can be used to produce predictions of the effects of climate change on schistosome transmission over defined geographical areas, enabling policy makers to incorporate the

effects of climate change into control and elimination plans. The models can also be used to investigate the effects of complexities in the snail and schistosome lifecycles on the relationship between water temperature and schistosome transmission (e.g. different snail species or habitat types).

The overall aims of this thesis were to use mathematical modelling to investigate the effects of water temperature on *Biomphalaria* population dynamics and *S. mansoni* transmission, and to develop a model that can be used to inform policy makers of the potential effects of climate change on schistosome transmission. In doing so, I aim to advance the state of the art in the field, and open up new avenues for further research. Specific objectives of this thesis are:

1) To develop a new, agent-based model of water temperature, *Biomphalaria* snails, and *S. mansoni* transmission (Chapter 2).
2) To describe the parameterisation of the model to *S. mansoni* and three species of *Biomphalaria*: *Bi. pfeifferi*, *Bi. glabrata*, and *Bi. alexandrina* (Chapters 2 and 4).
3) To investigate in detail the dynamics of the model when parameterised to *S. mansoni* and *Bi. pfeifferi* (Chapter 3).
4) To determine the effect of simulating different intermediate host snail species on the relationship between water temperature and *S. mansoni* infection risk (Chapter 4).
5) To predict the effects of climate change on *S. mansoni* infection risk in eastern Africa (Chapter 5).

2 Model description and parameterisation

2.1 Background

As ectotherms, both the schistosome parasite and its intermediate snail hosts are very sensitive to water temperature. Increasing temperatures are therefore likely to alter both the distribution of schistosomiasis, and its intensity in areas where it is currently found. A large number of studies have used mathematical models to explore the relationship between temperature and malaria and/or attempt to predict the effects of climate change on malaria transmission. They have considered factors as diverse as interactions between climate change and drug resistance (Artzy-Randrup, Alonso *et al.* 2010), the effect of diurnal temperature fluctuations on malaria transmission (Paaijmans, Blanford *et al.* 2010), and the effect of simulating non-linear relationships on optimum transmission temperatures (Mordecai, Paaijmans *et al.* 2013). Models have been parameterised separately for different species of mosquito (Tonnang, Kangalawe *et al.* 2010), and have included rainfall in addition to temperature (Hoshen and Morse 2004).

In contrast with malaria, the effect of climate change on schistosomiasis has been largely neglected. In 1995, Martens *et al* developed a simple population-based model of a generic snail and human schistosome population in relation to temperature, from which he concluded that increasing temperatures would expand the range of schistosomiasis (Martens, Jetten *et al.* 1995), but reduce transmission in areas where it is currently endemic (Martens, Jetten *et al.* 1997). In 2008, Zhou *et al* considered the minimum temperature requirements of *O. hupensis* and *S. japonicum*, and used them to predict a northward shift in possible range for *S. japonicum* in China over the next few decades (Zhou, Yang *et al.* 2008). Most recently, Mangal *et al* (Mangal, Paterson *et al.* 2008) simulated *S. mansoni* transmission at 20°C, 25°C, 30°C and 35°C using a non-species-specific *Biomphalaria* snail population, and determined that the mean worm burden in humans increases between 20-30°C before falling at 35°C. The model also suggested that optimum control strategies may be different at different temperatures.

These models have a number of limitations. With the exception of the *O. hupensis* model (Zhou, Yang *et al.* 2008), the models are parameterised using data from many different species of snail of the same genus (Mangal, Paterson *et al.* 2008), or even

simulate generic snail and human schistosome populations (Martens, Jetten *et al.* 1995; Martens, Jetten *et al.* 1997). Different intermediate host snail species have very different habitat requirements and distributions however, while snail experiments show that the relationship between temperature and mortality and recruitment rates varies between snail species (Brown 1994). Wherever possible, I parameterised my model using data from a single snail species: *Bi. pfeifferi. Bi. pfeifferi* is by far the most widespread *S. mansoni* intermediate host snail species in Africa, with a distribution that extends over much of sub-Saharan Africa (Stensgaard, Utzinger *et al.* 2013). Simulating *Bi. pfeifferi* therefore maximises the generalisability of my model and the model results.

In addition to this, existing models of *S. mansoni* and/or *S. haematobium* transmission do not take into account the large variation in cercaria production by temperature (Martens, Jetten *et al.* 1995; Martens, Jetten *et al.* 1997), and none include all temperature-sensitive stages of the snail and schistosome lifecycles. The rate of cercaria production by infected snails has been shown to vary by over 1500% between 12°C and 35°C (Fried, LaTerra *et al.* 2002), and it is therefore vital to include it in any model of schistosome transmission and temperature. Explicitly simulating all temperature-dependent stages of the schistosome lifecycle is also crucial, as cercaria and miracidium mortality rates (Lawson and Wilson 1980; Anderson, Mercer *et al.* 1982), infectivity (Anderson, Mercer *et al.* 1982), and decline in infectivity over time (Ghandour and Webbe 1973; Anderson, Mercer *et al.* 1982) all vary greatly with temperature.

The aims of this chapter are to describe a new, agent-based model of water temperature, snail population dynamics, and schistosome transmission, and to describe its parameterisation to *Bi. pfeifferi* and *S. mansoni*. The model dynamics will be investigated in greater detail in subsequent chapters.

2.2 Model description and parameterisation

2.2.1 Overview

A dynamic, stochastic, agent-based model was written in Netlogo (Wilensky 1999). The model simulates the growth and mortality of a snail population, and infection by *S.*

mansoni. The model has a time step of one hour. Figure 2.1 shows a diagram of the model structure.

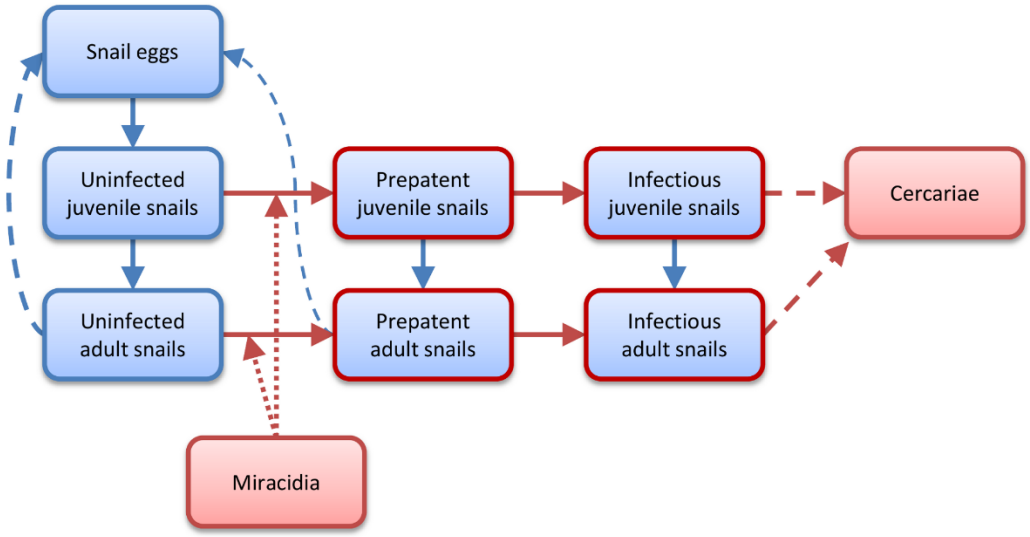

Figure 2.1. Diagram of the model structure.

Boxes indicate classes of agents. Solid arrows indicate that agents can change from one class into another. Dashed lines indicate the production of one class by another. Dotted lines indicate infection. Agents of all classes can die and be removed from the model.

All birth, development, infection and mortality rates in the model are temperature-dependent. In general, only a small number of data points were available for estimating the relationship between temperature and the rate in each case. To calculate the rates used in the model at temperatures between the data points, linear, quadratic, exponential, Weibull, Lactin (Lactin, Holliday *et al.* 1995), Gompertz or piecewise equations were fitted to the data points using a least squares method. The choice of equation to use in each case was decided by a combination of looking at plots of the data, and knowledge of which relationships were biological plausible. Details of all of the rates used in the model are given in Appendix 1 (Table 8.1 and Table 8.2).

Unless stated otherwise, all data used in the development of the model come from studies of *Bi. pfeifferi* snails and *S. mansoni*.

The main output of the model is human infection risk, a measure of the number of cercariae in the model, adjusted by their decreasing probability of successfully causing infection with increasing biological age (Ghandour and Webbe 1973). Human and adult worms are not simulated. This is because the worm stage of the parasite's lifecycle takes place inside a mammalian host, and is therefore unlikely to be affected by temperature. The link between human infection risk and snail infection risk is also unclear. It is plausible that there is an overall positive correlation between cercaria numbers and miracidium numbers, however differences in human water contact, defecation practices and migration will mean that the relationship varies greatly in different areas. Finally, the relationship between infection risk and the number of worms will depend on the overall prevalence and intensity of infection in an area (which will depend on human water contact and defecation practices as well cercaria numbers) as repeated infection leads to partial immunity (Pinot de Moira, Fulford *et al.* 2010). For these reasons, humans and schistosome worms are not explicitly modelled. Instead, miracidia are introduced into the model at a constant rate and human infection risk is indicated by a function of the number of cercariae in the model adjusted by their probability of causing infection upon contact.

2.2.2 Heat units and degree days

Many models of temperature and schistosomes or vector-borne parasite species use daily average temperatures and a 'growing degree-day' approach to parameterise models (Moore, Liang *et al.* 2012). The approach is based on the idea that the organisms in question require a certain number of heat units to complete their development. These heat units are measured in growing degree-days, and are calculated as the difference between the mean daily temperature and the development threshold temperature of the organism, which is the temperature below which the organism will not develop (Yang, Gemperli *et al.* 2006). The number of growing degree-days are taken to be zero for a day if the mean daily temperature is below the development threshold temperature. A degree-day approach can be applied to the development of both the intermediate host, and the schistosome within the intermediate host.

The model described here has a time step of one hour, and therefore does not use a degree-day approach. Instead, the number of heat units gained is calculated hourly, with

the number of heat units required to complete development set to an arbitrary value of 100. For instance, a juvenile snail living at a constant temperature of 15°C will take 32 hours to gain one heat unit, and 131 days to become sexually mature; and a juvenile snail living at 27°C will take 9 hours to gain one heat unit, and 39 days to become mature.

2.2.3 Snails

Snails in the model are represented through the three life stages: egg, juvenile (unable to produce eggs) and adult (sexually mature). Adults and juveniles can be uninfected, prepatent (infected but not yet producing cercariae) or infectious (infected and producing cercariae).

2.2.3.1 Juvenile development

Data on the number of days between hatching and the start of egg laying at known temperatures for *Bi. pfeifferi* were available from a number of different laboratory studies (Shiff and Garnett 1963; Sturrock 1966a; Nduku and Harrison 1976; Appleton 1977b; De Kock, Van Eeden *et al.* 1981; de Kock and Van Eeden 1986; Loreau and Baluku 1987a) (Figure 2.2a), and from one field study at a mean water temperature of 25.6°C (Kariuki 1994). The data were translated into heat units gained/hour, with 100 units necessary to start egg laying. Data were available from one of the laboratory studies (De Kock, Van Eeden *et al.* 1981) at temperatures of 17°C, 20°C, 23°C, 26°C, 29°C and 32°C. The data from this single study were fitted with a Lactin equation. The other laboratory studies each gave data from only one to three different water temperatures each, and showed variation between studies. All found much slower rates of development than de Kock and van Eeden did however, as did the field study. The fitted Lactin model rates were therefore reduced by a factor of 0.54, which caused them to pass through the single data point available from a field study, and this scaled Lactin model was used to simulate juvenile snail development in the model (Figure 2.2a). The fitted equation met the x-axis at 6.1°C and 33.6°C, and it was therefore assumed that no development occurred below and above these temperatures respectively.

A field study which compared the number of snails in a generation with temperatures during the development period of its parents' generation suggested that fecundity may decrease above a critical threshold of mean weekly levels of 120-179 degree hours above 27°C, equivalent to 17-26 degree hours above 27°C a day (Appleton 1977c). This was investigated further with a laboratory study where developing snails were kept in tanks at diurnally fluctuating temperatures. The study found that both gonad development and egg production were impaired in snails exposed to above 39 degree hours above 27°C a day (Appleton and Eriksson 1984), and snails kept at the highest temperature regimen of 75 degree hours above 27°C a day produced very few eggs. The author suggests that the reason for the different threshold found in the two studies is that in the field there was variation between days and weeks in the number of degree hours above 27°C a day. This suggests that short periods of very high temperatures are more damaging to snail development than longer periods of more moderate high temperatures.

In the model, during each juvenile snail's development period a record is kept of the total number degree hours spent above 27°C, above a threshold of 39 degree hours above 27°C a day. For example, if one day contains 52 degree hours above 27°C, then the snail's total number of degree hours above 27°C will be increased by 52 - 39 = 13 degree hours. The snail's total number of degree hours above 27°C will not be increased on days where there are ≤39 degree hours above 27°C. When the snail has accumulated sufficient heat units to start producing eggs, its high temperature egg production weight is calculated. If the number of degree hours above 27°C was ≤39 degree hours every day during its development, the weight is set equal to one. If the number of degree hours above 27°C was >39 degree hours on any day, then the value of the weight is determined from an exponential line fitted to the data described above (Figure 2.2b).

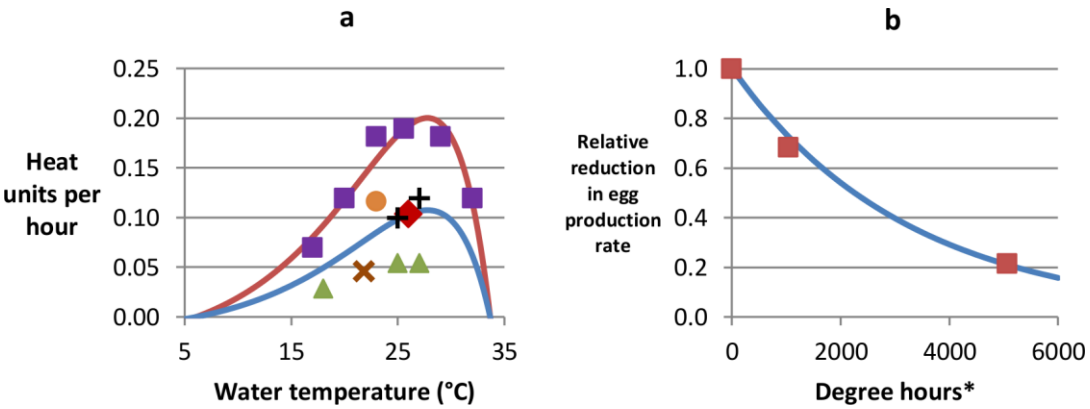

Figure 2.2. Effect of water temperature on juvenile development.

a) Rate of juvenile heat unit gain/hour by water temperature. 100 heat units are necessary to complete development and start egg laying. The green triangles (Shiff and Garnett 1963), brown cross (Loreau and Baluku 1987a), black crosses (Appleton 1977b), orange circle (de Kock and Van Eeden 1986), and purple squares (De Kock, Van Eeden *et al.* 1981) show empirical data from laboratory studies. The red diamond shows empirical data from a field study (Kariuki 1994). The red line is a Lactin model fitted to the data from De Kock, Van Eeden *et al.* (1981). The blue line is the Lactin model scaled to pass through the field data point, and the relationship used in the model. b) Effect of high temperatures during juvenile development on the adult egg production rate. Red squares show data (Appleton and Eriksson 1984) and the blue lines shows the relationship used in the model. *Cumulative number of degree hours above 27°C, above a threshold of 39 degree hours above 27°C/day.

2.2.3.2 Egg production

De Kock *et al.* recorded the mean number of eggs produced/snail every two weeks for snails kept at constant temperatures of 17°C, 20°C, 23°C, 26°C, 29°C and 32°C in a laboratory (De Kock, Van Eeden *et al.* 1981) (Figure 2.3a). These were converted into hourly rates and fitted with a Lactin model. A field study suggests that egg production rates in a more natural environment may be much lower however (Kariuki 1994). The highest rate of egg production found in the field study was only 0.22 times the rate predicted by the Lactin model for the same temperature. The simulated maximum egg production rate by water temperature was therefore taken to be equal to the value given by the Lactin model times 0.22 (Figure 2.3b). No egg production occurs in the model at temperatures below 13.8°C and above 32.1°C where the model crosses the x-axis.

In laboratory studies the vast majority of snail eggs kept in suitable conditions successfully hatch and survive the first few days after hatching (Sturrock 1966b). This is not the case in more natural conditions. At one field site, where water temperatures ranged from 17-22°C, it was estimated that only 2.7-8.5% of eggs laid hatched and survived the period immediately following hatching (Loreau and Baluku 1987b). Simulating the eggs that do not survive would have no effect on the model other than to slow it down, and therefore this initial high mortality is simulated in the model by reducing birth rates to 5.6% of the rate they would otherwise take. The number of eggs that successfully hatch is then reduced further by an additional temperature-dependent egg mortality rate, which is described in the section on egg hatching.

Adult *Bi. pfeifferi* kept at 25°C and infected with *S. mansoni* ceased to produce eggs when they were around halfway through their pre-patent period (Meuleman 1971). Simulated prepatent snails therefore stopped producing eggs after they had accumulated 50% of the heat units necessary to become infectious (see Section 2.2.2 for an explanation of heat units).

Overall egg production in the model is therefore calculated for each snail/hour as follows. Firstly, snails which have not accumulated sufficient heat units to become adults and snails which are infectious or more than halfway through their prepatent period do not produce eggs. Secondly, the maximum possible rate of egg production that hour, given the water temperature, is calculated. The rate is then adjusted for snail density, as described in Section 2.2.3.5, and for high temperatures during development, as described in Section 2.2.3.1. High mortality before and during hatching is then accounted for by multiplying the rate by 0.056. Finally, a floating point number between 0 and 1 is chosen at random for that snail. If the number is less than the final egg production rate, the snail lays an egg. This process is repeated for each snail, and repeated for all snails every hour.

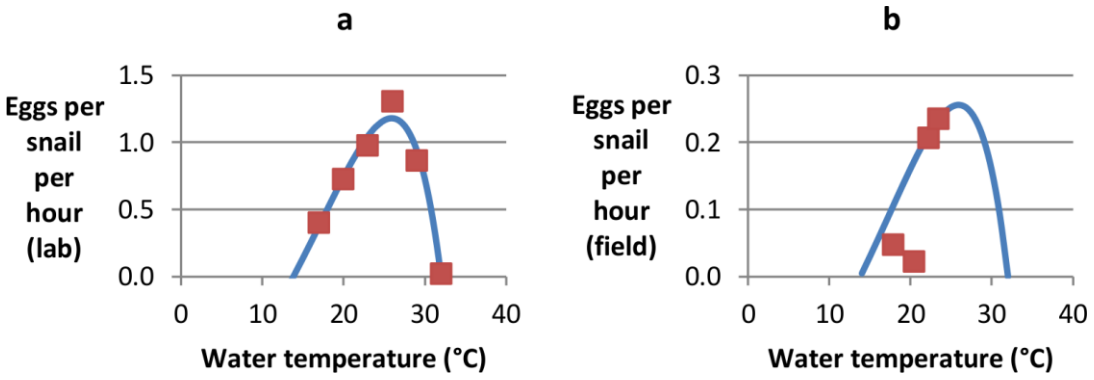

Figure 2.3. Effect of water temperature on snail egg production rates.

a) Egg production rate/snail/hour in a laboratory. The red squares give data from a laboratory study (De Kock, Van Eeden *et al.* 1981) and the blue line gives a Lactin model fitted to the data. b) Egg production rate/snail/hour in the field. The red squares give data from a field study (Kariuki 1994) and the blue line gives a scaled version of the Lactin model shown in a). This scaled Lactin model is used in the dynamical model.

2.2.3.3 Egg development

De Kock *et al* recorded the number of days until egg hatching for *Bi. pfeifferi* eggs kept at constant temperatures of 17°C, 20°C, 23°C, 26°C, 29°C and 32°C in a laboratory (De Kock, Van Eeden *et al.* 1981). Their findings were consistent with the number of days until hatching recorded for snail eggs kept in cages in two streams during two seasons in Kenya, with mean water temperatures of 19.7°C, 21.5°C, 24.6°C and 25.6°C (Kariuki 1994). The laboratory data were converted into heat unit gain/hour, with 100 heat units necessary for hatching (Figure 2.4a). A linear line was fitted through these points and was used to simulate egg development rates in the model. No egg development is assumed to occur below 5.9°C in the model, where the fitted line meets the x-axis.

In De Kock *et al*'s experiments, 91-96% of snail eggs hatched at temperatures between 17°C and 29°C, and 75% hatched at 32°C (De Kock, Van Eeden *et al.* 1981). The proportions of eggs that hatched and the number of days until hatching were converted into mortality rates/hour for each temperature (Figure 2.4b). Below 29°C, a constant mortality rate was modelled. Above 29°C, the egg mortality rate increases linearly with temperature.

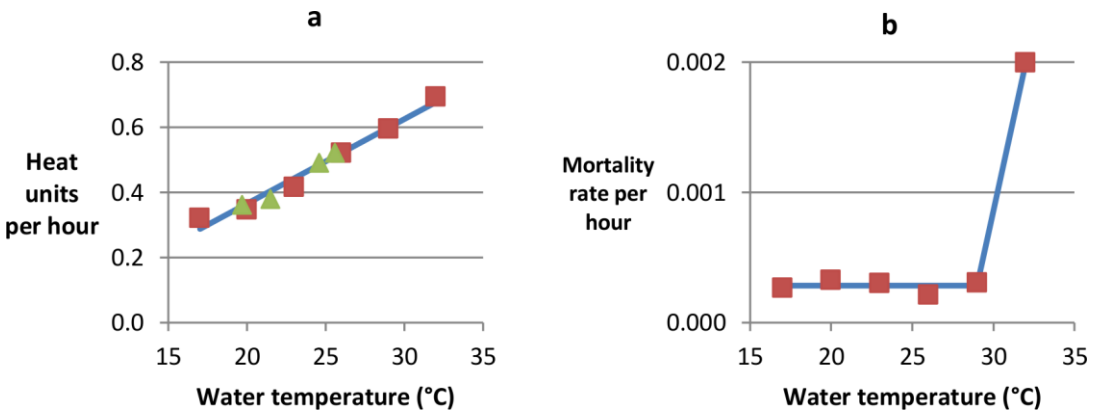

Figure 2.4. Effect of water temperature on snail egg development.

a) Rate of heat unit gain/hour. 100 heat units are needed for eggs to hatch. The red squares show experimental data (De Kock, Van Eeden *et al.* 1981), the green triangles show field data (Kariuki 1994), and the blue line shows the relationship used in the model. b) Egg mortality rate/hour. The red squares show experimental data (De Kock, Van Eeden *et al.* 1981) and the blue line shows the relationship used in the model.

2.2.3.4 Mortality

Although laboratory studies can observe sharp increases in mortality at around 10 months of age (Loreau and Baluku 1987a), snails can be found in the field with sizes corresponding to ages of around 19 months (Loreau and Baluku 1987b). A longitudinal field study at a site in the Democratic Republic of Congo where water temperatures varied between 17-22°C (mean 19°C) suggested that, after hatching, the mortality rate of *Bi. pfeifferi* was approximately constant at 0.00037/hour in 1982 and 0.00021/hour in 1984 (Loreau and Baluku 1987b). The mortality rate at 19°C in the model was therefore taken to be the average of these two values.

Data on effect of temperature on *Bi. pfeifferi* mortality rates are sparse. Woolhouse *et al.* estimated mortality rates in a field study at a range of mean weekly water temperatures between 13-25°C using a mark-recapture method (Woolhouse 1992). The best linear fit trend suggested that mortality increases slightly with increasing temperature within this range, but the standard errors of the data points were large and the results were consistent

with a range of different relationships. De Kock *et al* recorded weekly survival rates for snails kept in a laboratory at 17°C, 20°C, 23°C, 26°C, 29°C and 32°C (De Kock, Van Eeden *et al.* 1981). A linear line was fitted through median survival times and used to estimate the mortality rate at 19°C. The mortality rates at each temperature relative to the mortality rate at 19°C were then calculated. A linear line was fitted through these relative mortality rates and this, in combination with the field mortality rate at 19°C, was used to calculate the mortality rate at temperatures between 13°C (the lower end of the temperature range for which Woolhouse *et al*. estimated field mortality rates (Woolhouse 1992)) and 32°C (Figure 2.5a).

Joubert *et al* measured *Bi. pfeifferi* mortality at very low temperatures (0°C, 2°C, 4°C and 6°C) in a laboratory study (Joubert, Pretorius *et al.* 1984) (Figure 5b). Mortality rates increased sharply with decreasing temperature, with median survival rates for the snails varying between 25 hours at 0°C and 75 hours at 6°C. A quadratic equation was fitted between the four low temperature data points and the simulated mortality rate at 13°C, and this was used to calculate mortality rates at temperatures below 13°C in the model.

A second study investigated *Bi. pfeifferi* mortality in a laboratory at high temperatures (34°C, 36°C, 38°C and 40°C) (Joubert, Pretorius *et al.* 1986) (Figure 2.5b). Median survival at these temperatures ranged from around three hours at 40°C to eight days at 34°C. An exponential equation was fitted between the four high temperature data points and the simulated mortality rate at 32°C and this was used to calculate mortality rates above 32°C in the model.

Foster compared mortality rates in shedding and non-shedding *Bi. pfeifferi* kept at four temperatures between 23-28°C (Figure 2.5c) (Foster 1964). Mortality rates were found to be 2.1-6.6 times higher in shedding snails, with the ratio increasing with increasing temperature. It was assumed that the ratio was equal to one below 11.2°C, the estimated temperature below which snails do not produce cercariae. The best fit exponential trend line was fitted between the five points, and this was used to model increased mortality in infectious snails compared with uninfected snails at temperatures above 11.2°C. Below 11.2°C, the modelled ratio was equal to one.

Prepatent *Bi. glabrata* show no increase in mortality compared with uninfected controls, although the mortality rate increases greatly once the infections become patent (Minchella

and Loverde 1981). No increase in mortality rates was therefore simulated for prepatent snails.

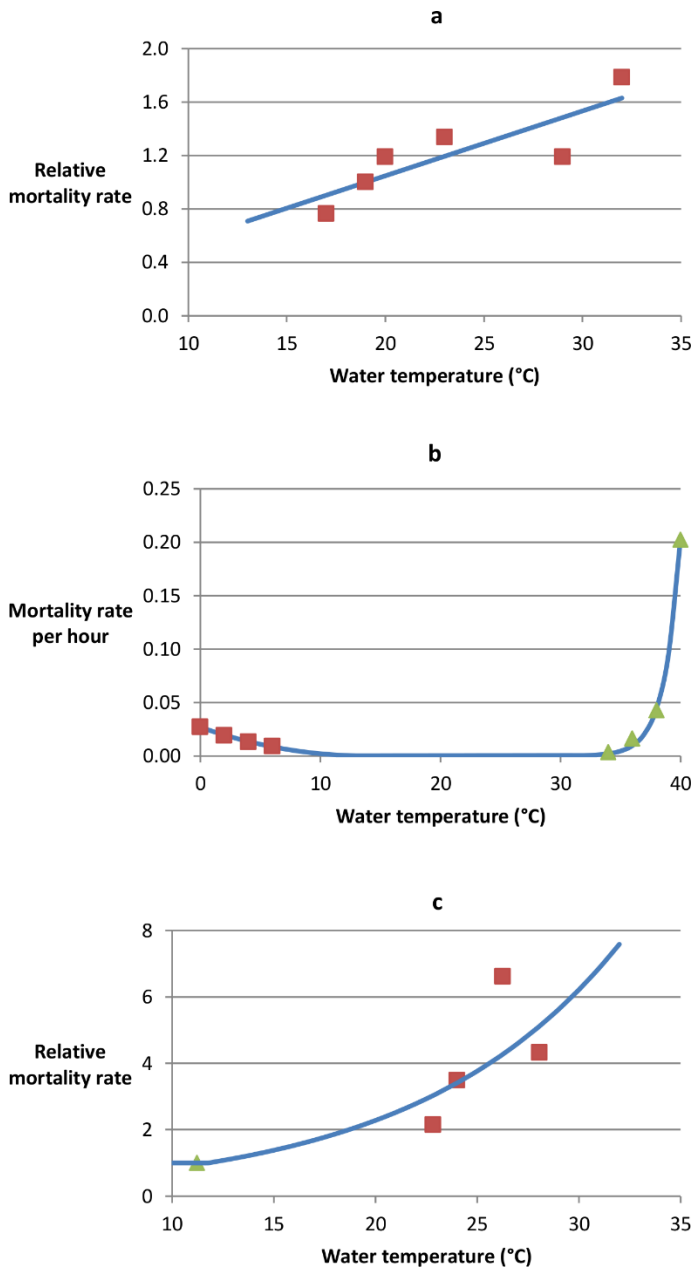

Figure 2.5. Effect of water temperature on snail mortality rates.

a) Mortality rates relative to the mortality rate at 19°C. Red squares show data from De Kock, Van Eeden *et al.* (1981). The blue line shows the relationship used in the model. b) Snail mortality rates/hour at extreme temperatures. The red squares (Joubert, Pretorius *et al.* 1984) and green triangles (Joubert, Pretorius *et al.* 1986) show experimental data. The blue line shows the relationship used in the model. c) Mortality rates in infectious snails relative to mortality rates in uninfected snails. The red squares show experimental data (Foster 1964). The green triangle shows the estimated temperature below which snails do not produce cercariae. The blue line shows the relationship used in the model.

2.2.3.5 Snail density dependence.

In laboratory conditions, a high density of snails did not affect the time to first or maximum egg laying, or snail mortality rates (Loreau and Baluku 1987a). It did however reduce the number of fertile eggs laid by each snail each week. Field studies support the idea that unfavourable conditions have a greater effect on egg production rates than on snail survival. A longitudinal study of a snail population in a stream, where water temperatures were favourable for snails all year round, found a 12 fold variation in estimated egg production rates/snail over the course of the study, but little variation in life expectancy after hatching (Loreau and Baluku 1987b).

In the model, it is assumed that the environment can support 300 snails with no negative effect on egg production. Above this number, the rate of egg production drops following a Gompertz distribution (Figure 2.6a). At population numbers of more than 600 snails, snail mortality rates also increase, increasing linearly with temperature (Figure 2.6b). Thresholds of 300 and 600 snails were chosen for practical reasons, with models with higher numbers taking longer to run, and models with smaller numbers requiring more runs in total to reduce stochasticity. These numbers can be scaled up or down with no effect on mean model results, provided that all parameters that are functions of snail population size, and the rate of miracidium introduction, are scaled accordingly.

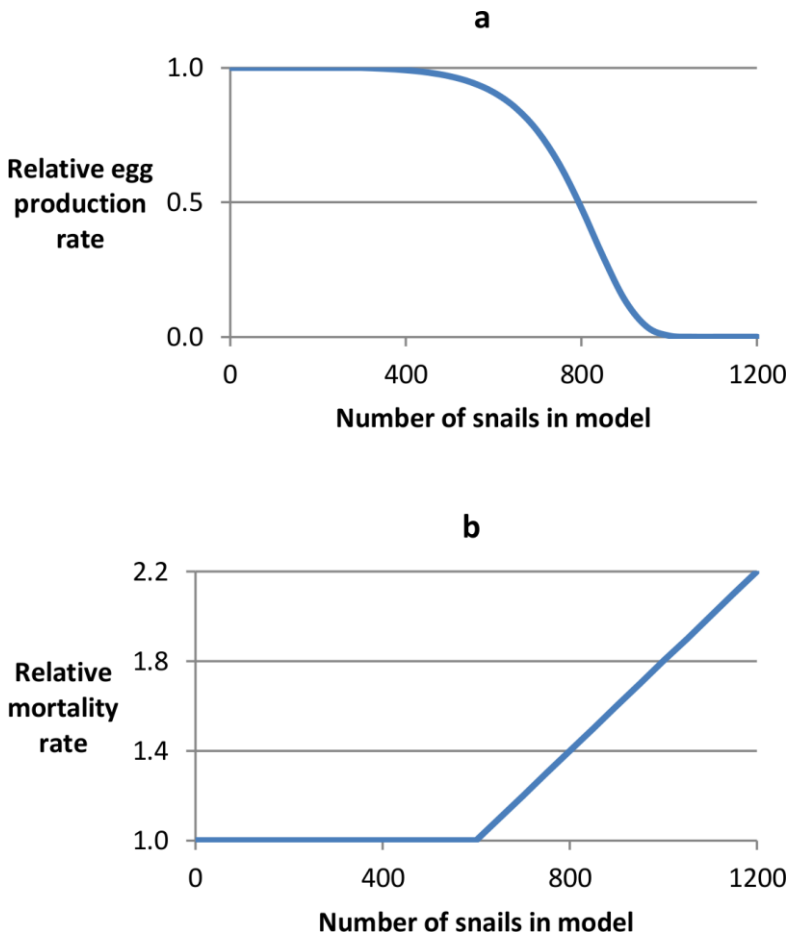

Figure 2.6. Effect of high snail population densities on simulated egg production and mortality rates.

a) Simulated drop in egg production rates at high snail numbers. b) Simulated increase in snail mortality rates at high snail numbers.

2.2.4 Parasite

2.2.4.1 Parasite development within the snail

Once a snail becomes infected in the model, it starts to accumulate heat units at a temperature-dependent rate. This represents parasite development within the snail. When a sufficient number of heat units have been accumulated the snail becomes infectious.

Foster measured the mean time between infection and the start of shedding for *S. mansoni* in *Bi. pfeifferi* kept at eight temperatures between 18°C and 32°C (Foster 1964) (Figure 2.7). Parasite development took only 17.5 days at 32°C, compared with 57 days at 18°C, and the data showed a clear linear trend. This was converted into a heat unit accumulation rate, with 100 heat units needed for the snail to become infectious, and was used to simulate parasite development with the temperature range 17-32°C.

Pflüger measured prepatency times at different fluctuating temperature regimens for *S. mansoni* in *Bi. glabrata* (Pfluger 1981). He found that the assumption of a linear relationship between temperature and development rate does not hold for temperature regimens incorporating temperatures outside the range of approximately 16-32°C. Outside this range, development periods were shorter and longer than would be expected at low temperatures and high temperatures respectively. A non-linear relationship was therefore modelled for temperatures less than 17°C and greater than 32°C.

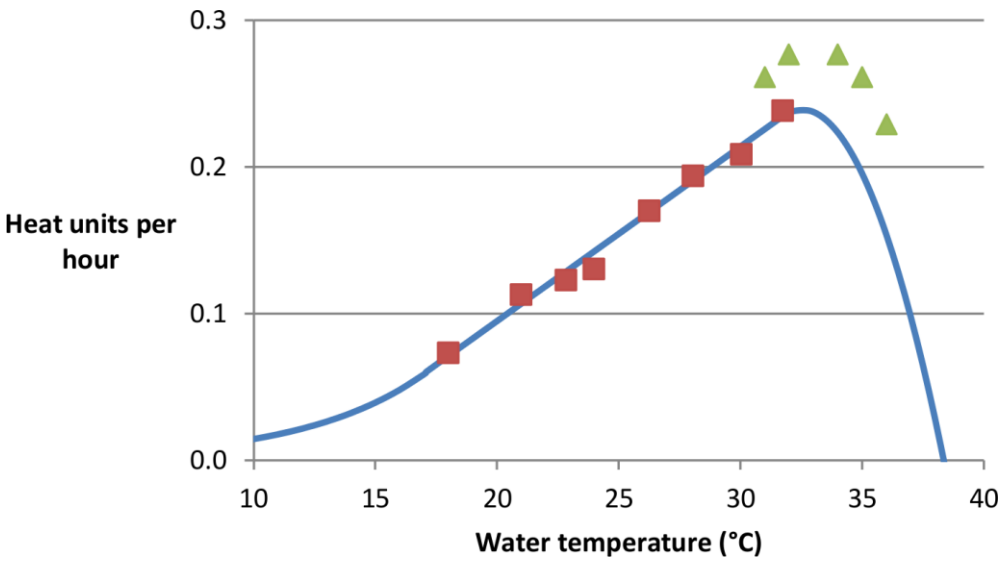

Figure 2.7. Effect of water temperature on the rate of parasite development with the snail.
Rate of heat unit gain/hour, with 100 heat units needed for the snail to become infectious. The blue line shows the relationship used in the model. The red squares represent data from Foster (1964). Green squares show data for *Bi. glabrata* (Pfluger 1980).

2.2.4.2 Miracidia

Miracidia are born into the model at a constant rate of 10/hour. No diurnal variation in the rate of introduction is simulated as schistosome eggs in stool hatch gradually over a period of many hours or days, as the stool breaks down in water (Upatham 1972). This will have the effect of 'smoothing out' any diurnal variation in the rate of stool entering water bodies.

In the real world, miracidia are born with an energy reserve which depletes over time (Morley 2012). As their energy reserves get lower, their mortality increases and the probability of them successfully infecting a snail decreases (Anderson, Mercer *et al.* 1982). The rate at which their energy reserves are depleted is temperature-dependent (Morley 2012).

Anderson *et al.* measured the survival over time of *S. mansoni* miracidia kept at eight constant temperatures between 5°C and 40°C (Anderson, Mercer *et al.* 1982). Median life expectancy was highest at 15°C. Gompertz functions were fitted to the survival curves at each temperature ≥15°C. Below a constant temperature of 10-15°C, miracidium mortality rates do not increase with age, suggesting that the miracidia may be inactive below this temperature. In the model, when the water temperature is ≥15°C biological age is used instead of chronological age to determine mortality rates by age. This allows the rate of aging to be calculated for snails living in fluctuating temperature regimens. Biological age gain each hour at water temperatures ≥15°C was calculated as a function of current age and water temperature, with biological age gain equal to chronological age gain at 25°C (Figure 2.8a). Mortality rates each hour at each biological age were taken to be equal to the mortality rates at 25°C at the same chronological age, adjusted for the amount of biological age the miracidium had gained over the preceding hour (Figure 2.8b). Above a biological age of 10.6 hours all miracidia die. Below 15°C, biological age does not increase with time, and a temperature-dependent, age-independent mortality rate is modelled (Figure 2.8c). An additional, constant mortality rate each hour can also be modelled, representing non-natural causes of mortality or removal, such as the washing away of miracidia in moving water, or mortality due to predation.

Anderson *et al.* also measured the rates of infection of a *Bi. glabrata* snail by miracidia of different ages kept at five temperatures between 15°C and 35°C (Anderson, Mercer *et al.*

1982). The rate of infection at age zero was highest at 25°C, and lower at higher and lower temperatures. The rate of infection decreased with miracidium age at all temperatures, but decreased more rapidly at higher temperatures. In the model, the decline in infection rate with biological age was taken to be equal to the decline in infection rate with chronological age at 25°C, which was estimated using a Weibull model fitted to the empirical infection rates (Figure 2.8d). No infection occurs in the model at water temperatures <15°C.

Each hour, every miracidium in the model has the chance to infect a snail. The probability of infection is dependent on the biological age of the miracidium, the water temperature, and the number of snails in the model. The effect of biological age on infection probability is described above. Exponential lines were fitted to the rates of infection for a miracidium of age zero at 15°C, 20°C and 25°C, and at 25°C, 30°C and 35°C and these relationships were used to model the relative probabilities of infection at different water temperatures (Figure 2.8e). The probability of infection increases with the number of snails in the model according to a cumulative distribution function, however the relationship between the number of snails in the model and infection probability is approximately linear within the range of the number of snails typically found in the model at any time (Figure 2.8f).

When it is determined that a miracidium should infect a snail, the snail is chosen at random from all snails in the model. If the snail is uninfected, the snail becomes prepatent and the miracidium dies. If the snail is already prepatent or infectious then the miracidium dies, but there is no change to the snail.

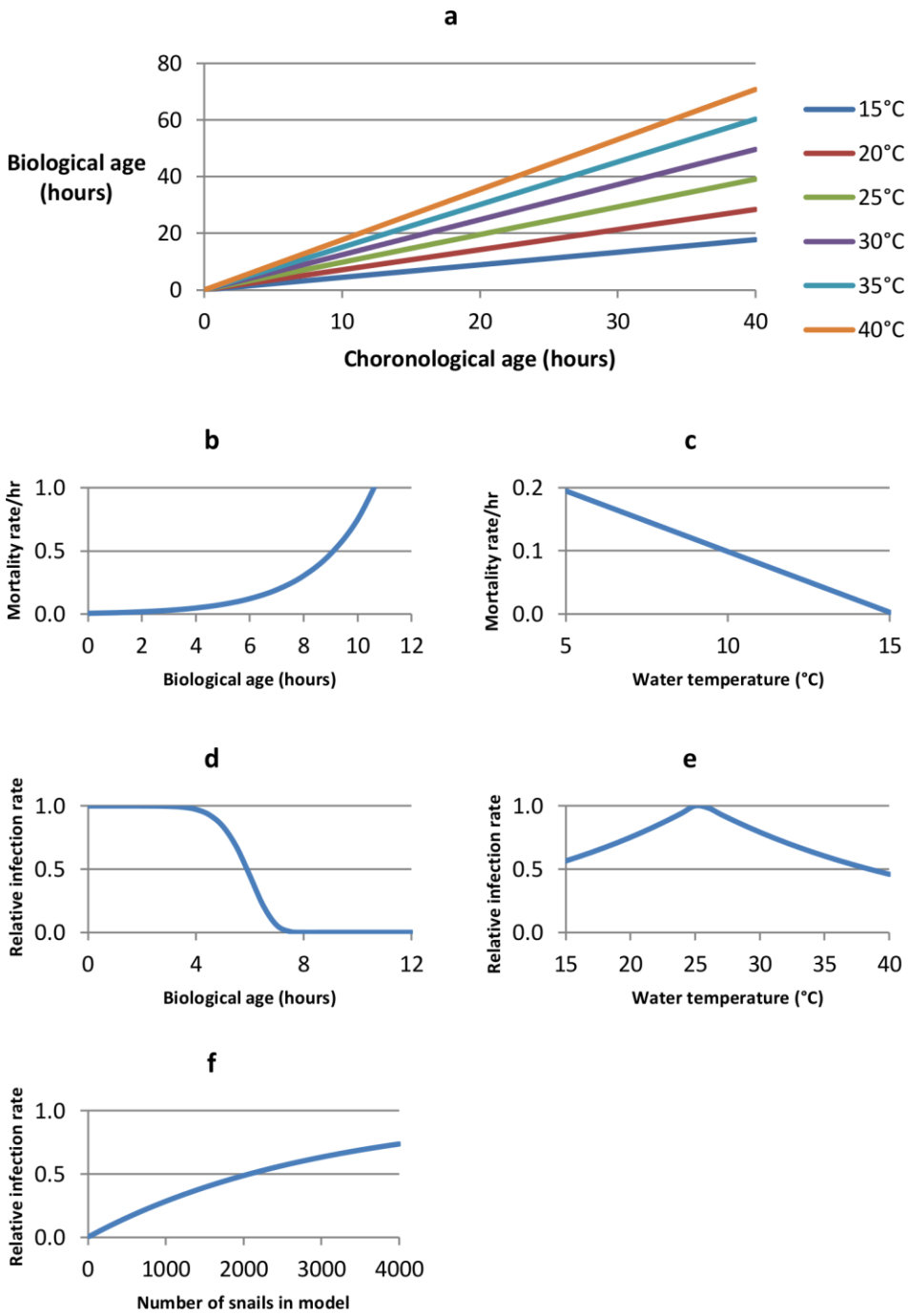

Figure 2.8. Effect of water temperature on miracidium aging, mortality and infection rates.

a) The simulated increase in biological age with chronological age at different water temperatures. b) The simulated relationship between biological age and the miracidium mortality rate/hour, for water temperatures ≥15°C. c) The simulated relationship between water temperature and the miracidium mortality rate/hour, for water temperatures <15°C. d) The simulated relationship between biological age and the relative miracidium infection rate. e) The simulated relationship between water temperature and the relative miracidium infection rate. f) The simulated relationship between the number of snails in the model and the relative miracidium infection rate.

2.2.4.3 Cercariae

In the model, cercariae are produced by infected snails at a rate which is dependent on temperature and the time of day.

Kazibwe *et al.* counted the number of cercariae emerging from *Bi. stanleyi* snails hourly between 9.00h and 17.00h (Kazibwe, Makanga *et al.* 2010). The snails were shed under natural light. Cercaria emergence was highest at 13.00, and dropped sharply either side of 12.00h-14.00h. Cercaria production rates relative to the peak production rate at 13.00h were calculated. A quadratic equation was fitted through these relative rates and this was used to determine the time of day dependence of the number of cercariae produced/infected snail each hour in the model (Figure 2.9a). No cercaria production occurs in the model between 17.00h and 9.00h.

Fried *et al* (Fried, LaTerra *et al.* 2002) counted the number of cercariae emerging each hour from shedding *Bi. glabrata* kept at 12°C, 25°C and 35°C. Cercaria emergence rates increased greatly with increasing temperature, from an average of 21 cercariae/snail at 12°C to 350 cercariae/snail at 35°C. A linear equation was fitted through the points and, after adjusting for time of day, used to calculate the number of cercariae produced/ infectious snail/hour in the model (Figure 2.9b). No cercaria production occurs in the model at temperatures below 11.2°C where the line meets the x-axis.

Lawson and Wilson measured the survival by age of cercariae kept at six constant temperatures between 15-40°C (Lawson and Wilson 1980). Gompertz functions were fitted to the survival curves at each temperature. Median survival was 31 hours at 15°C and decreased with increasing temperature to only three hours at 40°C. Aging and mortality rates of cercariae were simulated in the model in a similar way to the aging and mortality rates of miracidia. Biological age gain was equal to chronological age gain at 25°C (Figure 2.9c), and mortality rates each hour at each biological age were equal to the mortality rates at 25°C at the same chronological age, adjusted for the amount of biological age the cercaria had gained over the preceding hour (Figure 2.9d). As for the miracidia, an additional, constant mortality rate can be included in the model, representing temperature-independent, non-natural causes of mortality.

Two indicators of human infection risk can be outputted by the model. The first is simply the number of cercariae alive in the model at any point in time. A proportion of cercariae

that successfully penetrate a potential host's skin will die without developing into an adult worm however. Ghandour *et al* measured the proportion of cercariae that died during the penetration of mouse skin for 2, 4, 6, 8, 10, 18 and 24 hour old cercariae, kept at 25-27°C (Ghandour and Webbe 1973). The proportion of cercariae that were *not* found dead in the mice's skin declined exponentially over time from 71% at two hours to 16% at 24 hours. The second measure of human infection risk outputted by the model is therefore calculated as the number of cercariae in the model, adjusted by the biological age-dependent probability that they would die during skin penetration (Figure 2.9e).

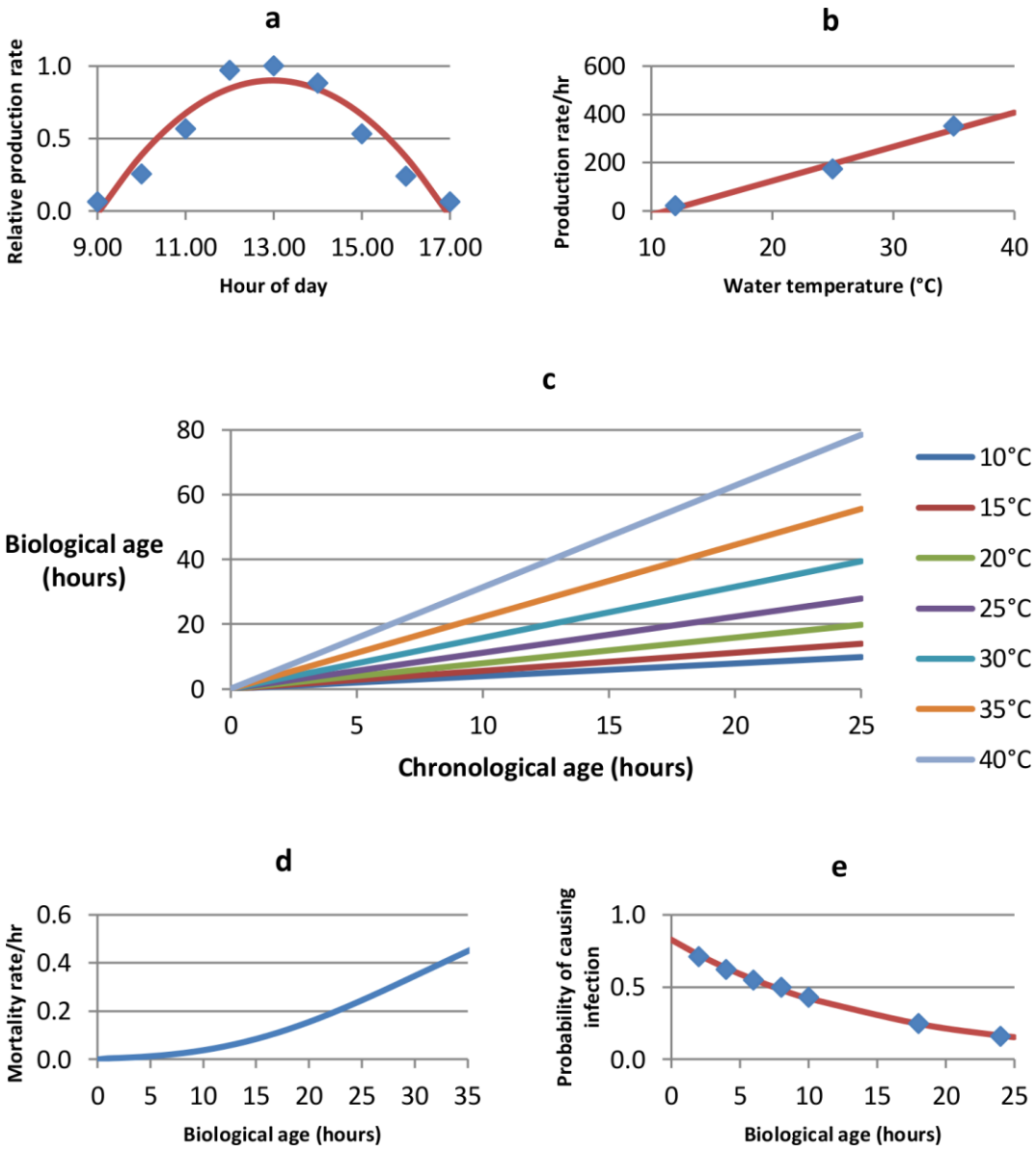

Figure 2.9. Effect of water temperature on cercaria production, aging, mortality and infection rates.

a) The relative production rate of cercariae by time of day. The blue squares show experimental data (Kazibwe, Makanga *et al.* 2010) and the red line shows the modelled relationship b) Cercaria production by water temperature. The blue squares show experimental data (Fried, LaTerra *et al.* 2002) and the red line shows the modelled relationship. c) The simulated increase in biological age with chronological age at different water temperatures. d) The simulated relationship between biological age and the cercaria mortality rate/hour. e) The simulated relationship between cercaria biological age and infection probability. The blue squares show experimental data (Ghandour and Webbe 1973) and the red line shows the modelled relationship.

2.3 Discussion

A recent review article described 'models for assessing the impact of climate change' as one of four major research gaps in helminth modelling (Basáñez, McCarthy *et al.* 2012). Few models of schistosome transmission and water temperature currently exist, and none incorporate all temperature sensitive stages of the snail and parasite lifecycles. In explicitly simulating all temperature-dependent stages, the model described in this chapter potentially fills a major research gap of public health importance, and may greatly advance the field of helminth modelling.

The model is also the first agent-based model of schistosomiasis and water temperature. Using an agent-based approach allows the age and/or development of each juvenile snail, prepatent snail, miracidium and cercaria to be individually tracked. This is particularly important when fluctuating temperatures are simulated, when each individual agent will be exposed to a unique history of temperatures. An agent-based approach also allows the local extinction of the snails, and their stochastic re-emergence. This is crucial when considering the effects of climate change on the geographical extent of schistosome transmission.

The model has a time-step of one hour only, in contrast to many models of temperature and schistosomes or vector-borne parasite species, which use daily average temperatures and a 'growing degree-day' approach (see Section 2.2.2 for details) (Moore, Liang *et al.* 2012). For the growing degree-day method to be valid, after adjustment for time spent below the development threshold temperature, the decrease in development rate when the temperature is below average must be exactly balanced by the increase in rate when the temperature is above average. This assumption is valid only if, above the development threshold temperature, there is a linear relationship between temperature and rate of development. Experimental work suggests that the relationship is linear for *S. mansoni* development when temperatures do not fluctuate outside of 16-35°C , but non-linear outside this range (Pfluger 1981). Models that assume a linear relationship over a greater range will either over-estimate or under-estimate the rate of schistosome development, and current degree-day models of schistosomiasis distribution and climate change could greatly underestimate the potential for schistosomiasis to spread to areas currently too cold for transmission (Yang, Gemperli *et al.* 2006; Zhou, Yang *et al.* 2008). Using daily

minimum and maximum temperatures to estimate hourly temperatures, as done in this model, greatly minimises this potential source of model error.

There is a second advantage to using hourly temperatures and a time step of an hour in the model. While the snails can live for many weeks, the schistosome miracidia and cercariae have life spans of the order of hours (Lawson and Wilson 1980; Anderson, Mercer *et al.* 1982). With longer time steps, the free living stages cannot be accurately simulated, and the effect of varying temperatures on the stages cannot be accurately incorporated into the model. This is particularly important for the cercariae, which are released only during daylight hours (with peak emergence occurring around midday (Kazibwe, Makanga *et al.* 2010)), and rapidly start to become less infectious and die (Ghandour and Webbe 1973; Lawson and Wilson 1980). Daily average temperatures therefore do not accurately reflect the temperatures to which cercariae are exposed.

There are a number of limitations of the data used to parameterise the model. For the majority of temperature-dependent rates contained in the model, data from *S. mansoni* and *Bi. pfeifferi* were available to inform parameterisation. There were four exceptions to this however:

1. No data were available on the effect of prepatent infections on *Bi. pfeifferi* mortality. Based on experimental data from *Bi. glabrata* (Minchella and Loverde 1981), it was assumed that prepatent *S. mansoni* infections do not increase *Bi. pfeifferi* mortality rates.
2. Experimental data from *Bi. pfeifferi* infected with *S. mansoni* suggested that the relationship between water temperature and schistosome development within the snail is constant between 18-32°C (Foster 1964). Experimental data from infected *Bi. glabrata* kept at higher and lower temperatures suggested a non-linear relationship at temperatures outside 18-32°C however (Pfluger 1981), and this was simulated in the model.
3. Data from *Bi. glabrata* were used to simulate the relationship between water temperature and the rate of infection by miracidia (Anderson, Mercer *et al.* 1982).
4. Data used to inform the relationships between time of day and water temperature and cercaria emergence were taken from experiments with *Bi. stanleyi* (Kazibwe, Makanga *et al.* 2010) and *Bi. glabrata* (Fried, LaTerra *et al.* 2002) respectively.

With the exception of the effect of prepatent infection on snail mortality, the four simulated rates all control stages of the parasite lifecycle. There is therefore no reason to believe that the species of snail will have a large effect on the overall shape of the relationship between water temperature and the rate, although it may have an effect on the absolute values of the rates. The lack of data on the effect of prepatent infection on *Bi. pfeifferi* mortality rates is more problematic, as it is plausible that the effect of prepatent infection could vary by snail species. *Bi. pfeifferi* is a common and widespread intermediate host species however (Stensgaard, Utzinger *et al.* 2013), with a much longer history of co-evolution with *S. mansoni* than the New World species *Bi. glabrata* (Morgan, Dejong *et al.* 2005). Evolutionary pressures on both the snail and the parasite are therefore likely to have resulted in prepatent infections being minimally damaging to *Bi. pfeifferi*.

Many of the data used to parameterise the model were taken from experiments conducted in the 1960s-1980s. This is problematic for two reasons. The first is that the snails used in the experiments will have been identified using morphological methods only, and molecular analysis suggests that morphological identification is not always accurate (Plam, Jørgensen *et al.* 2008; Standley, Wade *et al.* 2011). Ideally, these experiments should be repeated using snails from populations identified using molecular methods. The second is that the data were often presented in graphical form only, and slight inaccuracies will have arisen when data points were read from the graphs. The effects of this will be very minor however, and well within the confidence intervals of the experimental data.

The dynamics of the model described in this chapter will be explored in Chapter 3.

3 Model dynamics

3.1 Background

In this chapter, I explore the dynamics of the model system described in Chapter 2, and investigate the effects of different temperatures on the simulated *Bi. pfeifferi* snail population and on human *S. mansoni* infection risk. The aims of this chapter are to:

i) Determine the effects of different constant and diurnally varying temperatures on simulated *Bi. pfeifferi* population size and human *S. mansoni* infection risk.

ii) Investigate the effects of different water body types on the relationship between water temperature and simulated snail population size and human infection risk.

iii) Conduct sensitivity analyses, exploring the effects of assumptions made in the rate of miracidium introduction and the choice of model density dependence functions.

The aims are achieved using four experiments:

Experiment 1. The first experiment combines two elements. In both, the model is run at a wide range of mean temperatures. The first element investigates the effects of different amounts of diurnal variation in temperature on snail numbers and human infection risk (aim i). The second element investigates the effect of simulating different temperature-independent cercaria and miracidium mortality rates. These rates include any mortality or removal of cercariae and miracidia that is not due to the natural depletion of their glycogen stores. A major cause of this additional mortality/removal in some habitats may be the 'washing away' of the free living stages in flowing water. For this reason, the two scenarios simulated are referred to as 'lake' (no additional temperature-independent mortality) and 'river' (half of all cercariae and miracidia removed each hour). In Experiment 1, in addition to looking at the effects of water temperature and the different scenarios on the snail population and overall human infection risk, I also investigate their effect on infection risk by time of day.

Experiment 2. Current models of schistosome transmission and water temperature do not allow for the fact that intermediate host snails are not confined to the shallows of deeper

ponds and lakes. In some bodies of water, surface water temperatures are considerably higher than water temperatures at greater depths (Shiff 1966; Hecky, Bugenyi *et al.* 1994). Snails may exploit these temperature gradients to increase their own survival and fecundity, and *Bi. pfeifferi* have been found in natural water bodies at depths of 4.5m (Jurberg, Schall *et al.* 1987). Snails are capable of surviving for extended periods at these depths. For example, *Bi. pfeifferi* have been shown to survive for 31 days when submerged in boxes at depths of 15.25m (Gillet, Bruaux *et al.* 1960). For snails in deep bodies of water, spending time at depths of several meters could therefore be a way of avoiding above-optimum temperatures. I investigate the effects of this by simulating one potential water temperature gradient, with deeper water temperatures 4°C cooler than the surface water temperature (aim ii).

Experiment 3. Miracidia are introduced into the model at a constant rate of 10/hour. I do not simulate a link between the output infection risk and the rate of miracidium introduction, as there is no single correct linking function. Instead, the correct linking function will vary from transmission site to transmission site, depending on many factors, including human sanitation and water contact behaviour. In Experiment 3, I determine the effects of a range of different plausible exponential linking functions on the relationship between water temperature and infection risk (aim iii). I also determine the effects of simulating a range of higher and lower constant rates of miracidium introduction. The lower rates can be viewed as the potential effects of an intervention to reduce environmental contamination, for instance by increasing latrine use. The higher rates can be viewed as the effect of increased environmental contamination, for instance following local population growth or reduced sanitation following a natural disaster.

Experiment 4. In the model, it is assumed that the environment can support 300 snails with no negative effects on egg production. Above this number, the rate of egg production drops following a Gompertz distribution (Figure 2.6). At population numbers of more than 600 snails, snail mortality rates also increase, increasing linearly with temperature. This is the 'best guess' approximation of the effect of high snail densities on snail reproduction and mortality rates, based on the laboratory and field data available. To explore the effects of different assumptions about density dependence, four additional scenarios with different density dependence functions were simulated, making five scenarios in total (aim iii).

3.2 Methods

3.2.1 Model and parameterisation

The model used in this chapter is described in Chapter 2.

3.2.2 Experiments

3.2.2.1 Experiment 1: Effect of water temperature in lakes and rivers on snail population dynamics and human infection risk

Daily water temperatures were modelled as a sine wave, with the maximum temperature reached at 3-4pm (Paaijmans, Jacobs *et al.* 2008). Three sets of scenarios with different levels of diurnal variation in temperature were modelled: one with constant temperatures, one where maximum and minimum temperatures varied from the mean temperature by ±2°C, and one where they varied by ±5°C. For each of the three sets of scenarios, two scenarios were modelled. In one, the 'lake' scenarios, cercariae and miracidia had temperature-dependent mortality rates only, estimated from mortality rates in laboratory experiments. In the other, the 'river' scenarios, an additional temperature-independent mortality rate of 0.5 per cercaria and miracidium per hour was simulated. The first scenario ('lake') approximates conditions in still water such as lakes and ponds and the second ('river') conditions in flowing water such as streams and rivers, where many miracidia and cercariae are likely to be quickly washed away. The scenarios are summarised in Table 3.1. The lake and river scenarios can be thought of as extremes, with conditions in many water bodies falling somewhere between the two. In all scenarios miracidia were introduced into the model at a constant rate of 10/hour.

Each scenario was run for temperatures between 13.5°C and 32.0°C, the temperature extremes at which the simulated snail populations can no longer survive indefinitely (snail populations may survive short periods outside these temperatures, but eventually die out), with temperature increasing in 0.5°C increments.

The number of snails in the model was calculated as the total number of uninfected, prepatent and infectious juvenile and adult snails.

Outputs were averaged over a minimum of one year and 200 runs. Each model run was run for a minimum of one year before any output was recorded, to ensure that the output was independent of the initial conditions.

Scenario 1: Lake ±0°C	**Scenario 2: Lake ±2°C**	**Scenario 3: Lake ±5°C**
- No additional temperature-independent cercaria and miracidium mortality rate. - No diurnal variation in water temperature. -Baseline scenario used in all experiments throughout the thesis, unless stated otherwise.	- No additional temperature-independent cercaria and miracidium mortality rate. - Daily minimum and maximum water temperatures 2°C lower and higher than the mean water temperature.	- No additional temperature-independent cercaria and miracidium mortality rate. - Daily minimum and maximum water temperatures 5°C lower and higher than the mean water temperature.
Scenario 4: River ±0°C	**Scenario 5: River ±2°C**	**Scenario 6: River ±5°C**
- An additional temperature-independent cercaria and miracidium mortality rate of 0.5 per cercaria or miracidium per hour was simulated. - No diurnal variation in water temperature.	- An additional temperature-independent cercaria and miracidium mortality rate of 0.5 per cercaria or miracidium per hour was simulated. - Daily minimum and maximum water temperatures 2°C lower and higher than the mean water temperature.	- An additional temperature-independent cercaria and miracidium mortality rate of 0.5 per cercaria or miracidium per hour was simulated. - Daily minimum and maximum water temperatures 5°C lower and higher than the mean water temperature.

Table 3.1. Summary of the simulated scenarios in experiment 1.

3.2.2.2 Experiment 2: Effect of water depth on the relationship between water temperature and snail population dynamics and human infection risk

The effect of deep, cooler water was simulated by changing the water temperature which each agent experiences (and which therefore determines their mortality, development, etc. rates). For each surface water temperature, T_w, it was assumed that temperature in the water body varied from T_w at the surface to $T_w - 4$ in the deepest water.

It was assumed that each class of snail agent (except eggs) was capable of identifying and moving to the depth which would give them the greatest overall reproductive fitness, based on the water temperature at that depth. It was assumed that all eggs would be laid at the depth which would give them the highest probability of hatching, based on the water temperature. For each agent, all rates were therefore calculated using the water temperature (between $T_w - 4$ and T_w) that would optimise their fitness, as described below.

Eggs: The temperature where the probability of hatching is greatest was chosen. This was calculated from the rate of heat unit accumulation and the egg mortality rate.

Uninfected, juvenile snails: The temperature where the probability of becoming an adult is greatest was chosen. This was calculated from the rate of heat unit accumulation and the uninfected mortality rate.

Uninfected, adult snails: The temperature where the median lifetime egg production is highest was chosen. This was calculated from the rate of egg production and the uninfected mortality rate.

Prepatent juvenile snails: The temperature was chosen which minimises the mean number of parasite heat units the parasite has accumulated by the time the juvenile snail becomes an adult. This was calculated using the juvenile snail and parasite heat unit accumulation rates and the prepatent mortality rate. When calculating the mean, the value for snails that die or accumulate more than 50 parasite heat units before they reach adulthood was set to 50 (prepatent snails stop producing snail eggs when their parasite has accumulated 50 heat units).

Prepatent adult snails: The temperature where the median lifetime egg production is highest was chosen. This was calculated from the rate of egg production, the prepatent mortality rate, and the parasite heat unit accumulation rate.

Infectious juvenile and adult snails: Infectious snails do not produce snail eggs, and therefore, once the infection becomes patent, water temperature has no further effect on their evolutionary fitness. For that reason, it was assumed in the model that juvenile and adult infectious snails favour the same temperatures as prepatent juvenile and adult infectious snails respectively.

Miracidia: *S. mansoni* miracidia need to locate and infect a snail to continue with their lifecycle, and there is evidence that they are attracted to substances secreted by snails (Etges and Decker 1963; Roberts, Ward *et al.* 1979). Miracidia are also negatively phototactic at high temperatures, but move towards light and warmer temperatures as overall temperatures decrease (Shiff 1974). Due to the high mortality rates experienced by snails, a large proportion of the snails in the model at any one time are juveniles. The temperature chosen for miracidia in the model was therefore taken to be the same as the temperature chosen for uninfected juvenile snails.

Cercariae:

S. mansoni cercariae alternate periods of active, vertical swimming with periods of passive sinking (Brachs and Haas 2008), but tend to accumulate at intermediate depths (Haas, Beran *et al.* 2008). The simulated cercariae were therefore assumed to experience temperatures 2°C cooler than the surface temperature, the temperature found at intermediate depths in the simulated water body.

3.2.2.3 Experiment 3: Effect of variation in the rate of miracidium introduction on human infection risk

In the baseline model, miracidia are introduced at a constant rate of 10/hour. In this experiment, I explored the effect on the relationship between water temperature and infection risk of simulating 12 different constant and exponential functions linking infection risk and the rate of miracidium introduction. Ten of the relationships used are shown in Figure 3.1. The other two relationships were a constant rate of miracidium introduction of 50/hour, and a constant rate of 100/hour.

Each scenario was run for constant temperatures between 14°C and 32°C, with temperatures increasing in 1°C increments. Outputs were averaged over two years and 100 runs.

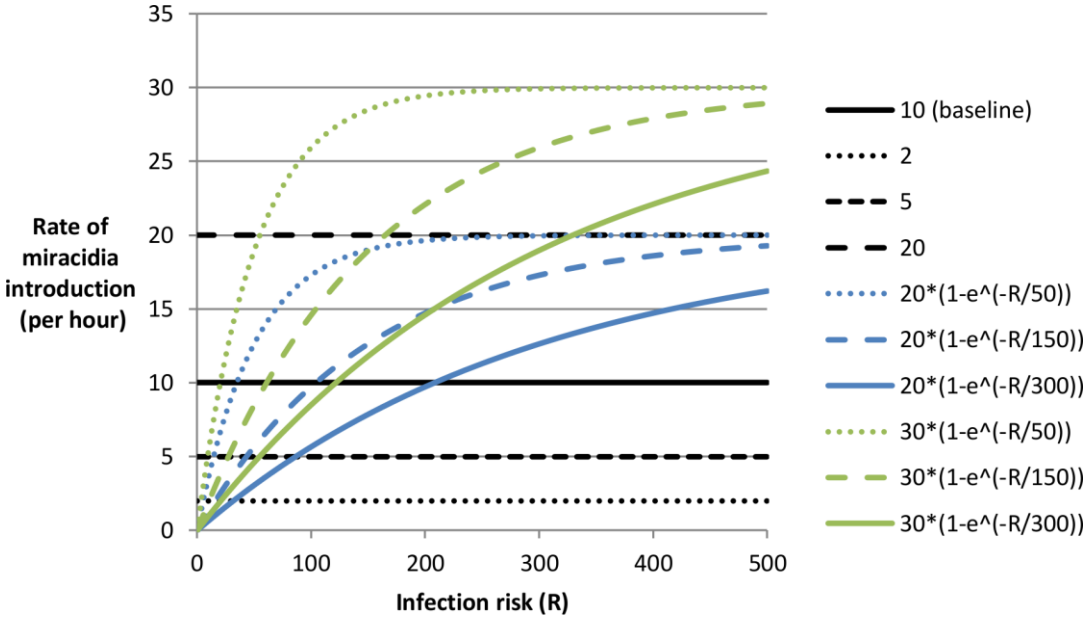

Figure 3.1. Simulated relationships between human infection risk and the rate of miracidium introduction.

R=infection risk. Constant introduction rates of 50 and 100/hour not shown.

3.2.2.4 Experiment 4: Investigating the sensitivity of model results to the choice of density dependence functions

Five scenarios were simulated, with different relationships between snail population size and snail egg production and mortality rates:

1. The baseline scenario. Density dependent reductions in egg production (with more than 300 snails in the model) and increases in mortality (with more than 600 snails in the model).
2. Density dependent reductions in egg production only (with more than 300 snails in the model).

3. Density dependent increases in mortality only (with more than 600 snails in the model).
4. Density dependent reductions in egg production (with more than 300 snails in the model) and increases in mortality (with more than 300 snails in the model).
5. Density dependent reductions in egg production (with more than 300 snails in the model) and increases in mortality (with more than 600 snails in the model), with each adult snail counting as one snail and each juvenile snail counting as half a snail.

The exact relationships used in each scenario are shown in Figure 3.2. Each scenario was run for temperatures between 13.5°C and 32.0°C, the temperature extremes at which the simulated snail populations can no longer survive indefinitely, with temperature increasing in 0.5°C increments.

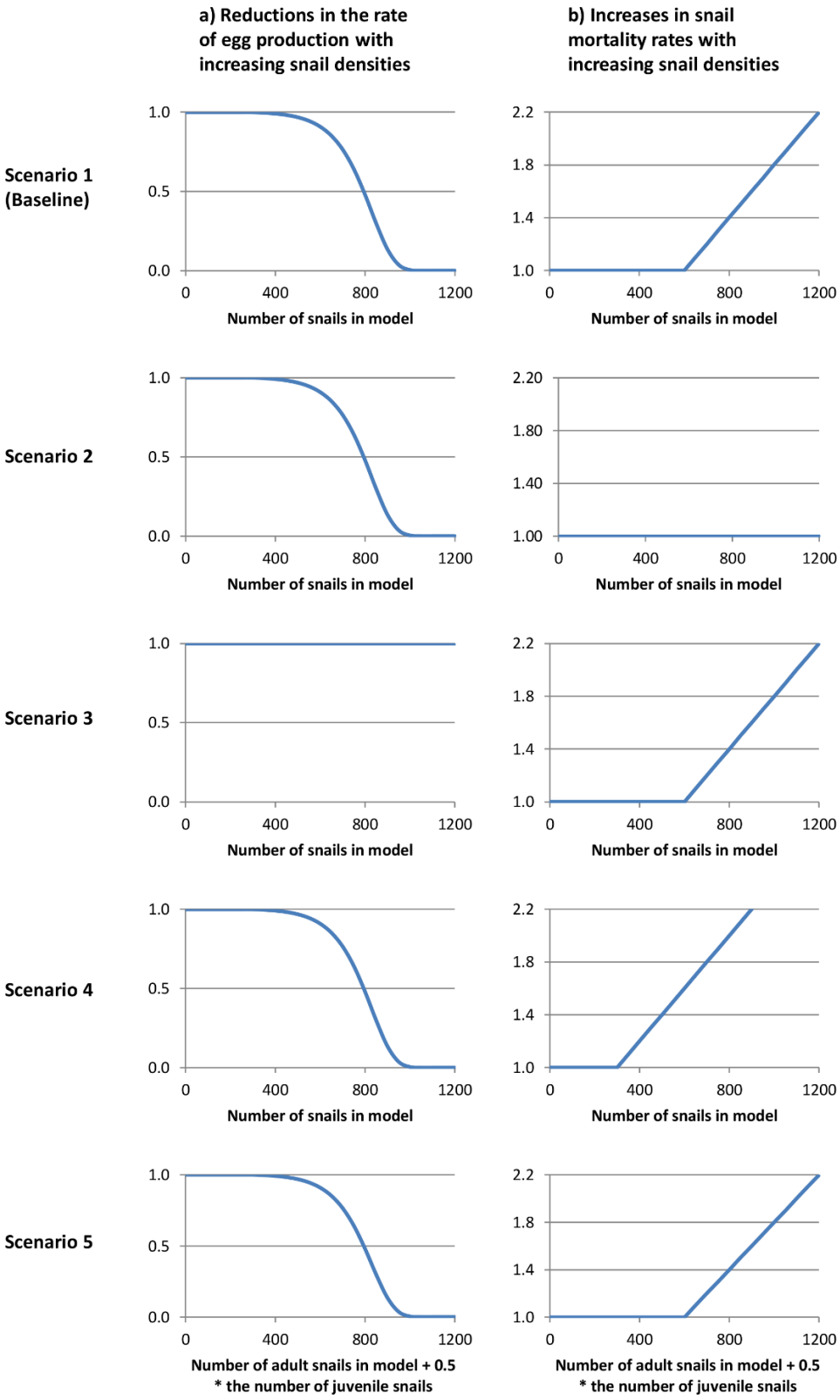

Figure 3.2. Simulated density dependence functions.

a) Simulated relationships between snail population size and reductions in egg production rates. b) Simulated relationships between snail population size and increases in snail mortality rates.

3.3 Results

3.3.1 Experiment 1: Effect of water temperature in lakes and rivers on snail population dynamics and human infection risk

3.3.1.1 Snail population dynamics

The total number of snails in the model was approximately constant between 14.5-31.0°C when there was no or little (±2°C) diurnal variation in temperature, and between 15.5-29.0°C with a diurnal temperature range of ±5°C (Figure 3.3). Either side of these temperatures, snail numbers dropped sharply, and the snail population was unable to survive indefinitely outside the range 14.0-31.5°C at constant temperatures. Simulating a diurnal variation of ±2°C greatly increased snail population numbers at 14.0°C and decreased the highest temperature at which the snail population could survive indefinitely by 0.5°C. Simulating a diurnal variation of ±5°C reduced the range of mean temperatures within which the population could survive indefinitely to 15.0-29.5°C. There was no difference in snail numbers between the lake and river scenarios.

Mean generation time, the time between an egg being laid and it developing into an adult snail and first producing eggs, decreased with increasing constant temperature from 176 days at 14.0°C to a minimum of 46 days at 26.0°C, before increasing slightly to 74 days at 32.0°C (Figure 3.4). The length of time between a snail first being infected and becoming infectious also decreased with increasing temperature, from 130 days at 14.0°C to 18 days at 32.0°C. Finally, the proportion of snails that were infectious decreased with increasing temperatures above 15.0-18.0°C in the lake scenario and 15.0-20.0°C in the river scenario, with the temperature at which the proportion of infectious snails peaked being highest with higher levels of diurnal variation in temperature (Figure 3.5).

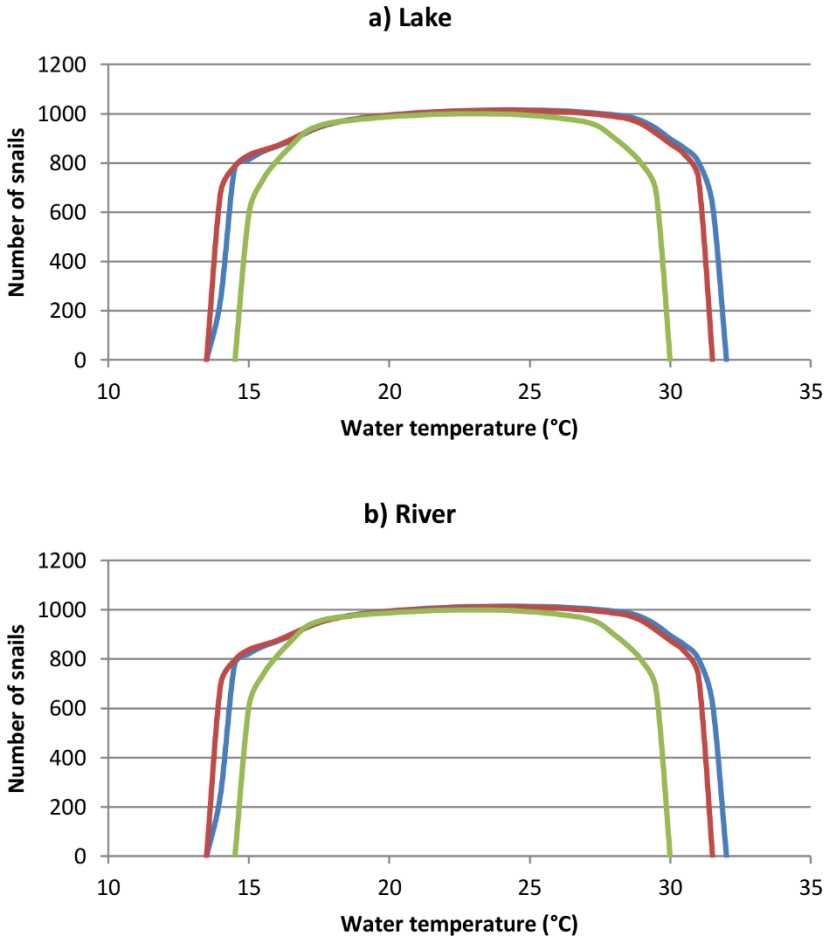

Figure 3.3. Effect of water temperature on snail population size.

a) Lake scenario. b) River scenario. The blue line shows the total number of snails in the model with no diurnal variation in temperature, the red with ±2°C variation in temperature, and the green with ±5°C variation.

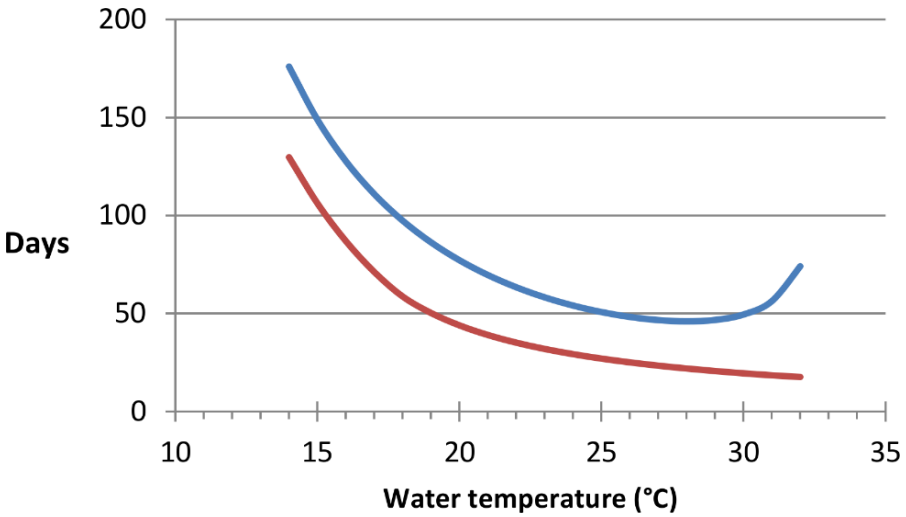

Figure 3.4. Effect of water temperature on snail generation time and prepatent period.

The blue line shows the number of days between an egg being laid, and the snail that hatched from the egg first producing eggs. The red line shows the number of days between a snail being infected and it first producing cercariae.

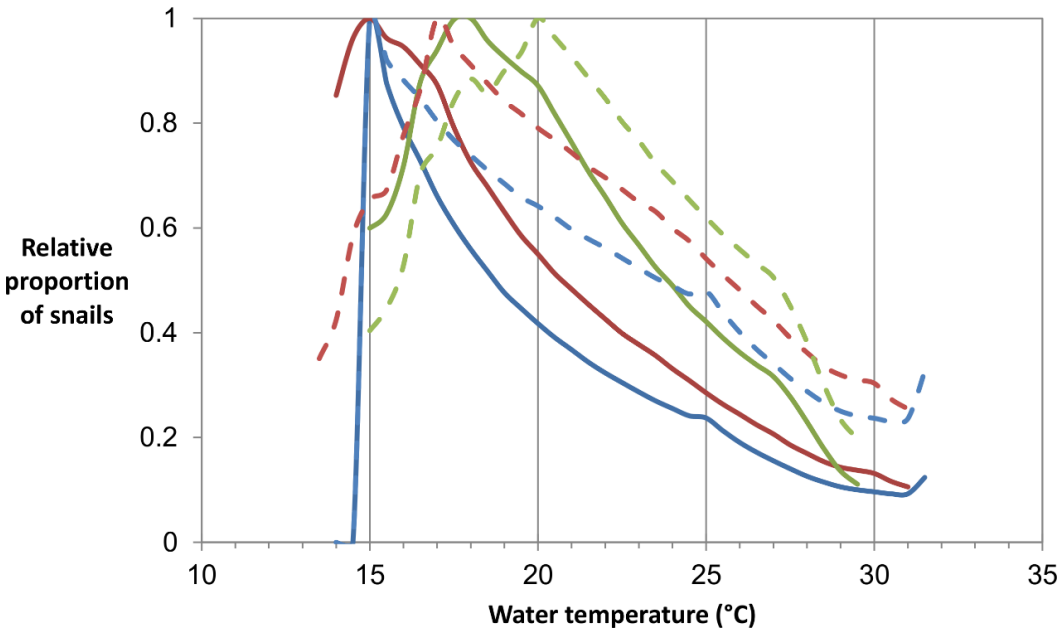

Figure 3.5. Effect of water temperature on the proportion of snails that are infectious, relative to the maximum proportion in the same scenario.

The blues lines show risk with no diurnal variation in temperature, the red lines with ±2°C variation, and the green lines with ±5°C variation. The solid lines show the results of the lake scenarios and the dashed lines the results of the river scenario.

3.3.1.2 Human infection risk

In the lake scenario, human infection risk was highest at 16.5-18.0°C (Figure 3.6). Compared with the lake scenario, infection risk in the river scenario was highest at higher temperatures, reaching its maximum at 20.5-25.0°C. In both the lake and river scenarios, with ±2°C and ±5°C diurnal variation in temperature there was a risk of infection at all temperatures at which snail populations could survive indefinitely. With no diurnal variation in temperature, snail populations could survive at 14.0°C but there was no infection risk at temperatures below 15.0°C. In all lake scenarios, infection risk increased sharply as temperature increased above the minimum temperature at which transmission could occur. The increase in risk was more gradual in the river scenarios.

Both cercaria numbers and human infection risk were highest between 3pm and 5pm in the lake scenario and between 1pm and 3pm in the river scenario (Figure 3.7). In the lake scenario, infection risk remained high for longer at cooler temperatures. At 15.0°C, cercaria numbers were above 75% of their maximum numbers between 12pm and 2am and infection risk was above 75% of its maximum between 1pm and 9-10pm. At 29.5°C, cercaria numbers were above 75% of their maximum numbers between 1-2pm and 8-9pm and infection risk was above 75% of its maximum between 1pm and 5-6pm. Times are given to the nearest hour as the model has a time-step of one hour. Compared with the lake scenario, in the river scenario both cercaria numbers and infection risk were high for shorter periods of time. Temperature had little effect on the relationship between time of day and cercaria numbers and infection risk in the river scenario, and both cercaria numbers and infection risk were above 75% of their maximum between 12pm and 4pm at all temperatures at which infection could occur. The amount of diurnal variation in temperature had little effect on the relationship between time of day and cercaria numbers and infection risk in all scenarios.

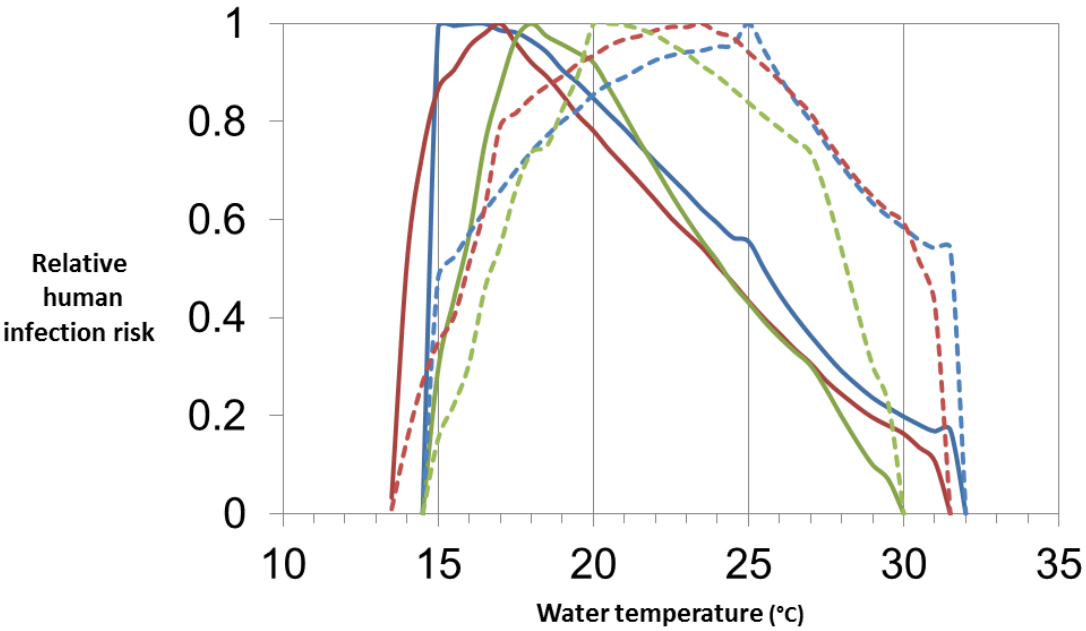

Figure 3.6. Effect of water temperature on human infection risk, relative to maximum infection risk in the same scenario.

The blues lines show risk with no diurnal variation in temperature, the red lines with ±2°C variation, and the greens lines with ±5°C variation. The solid lines show the results of the lake scenarios and the dashed lines the results of the river scenario. All risks are relative to maximum risk for the same scenario.

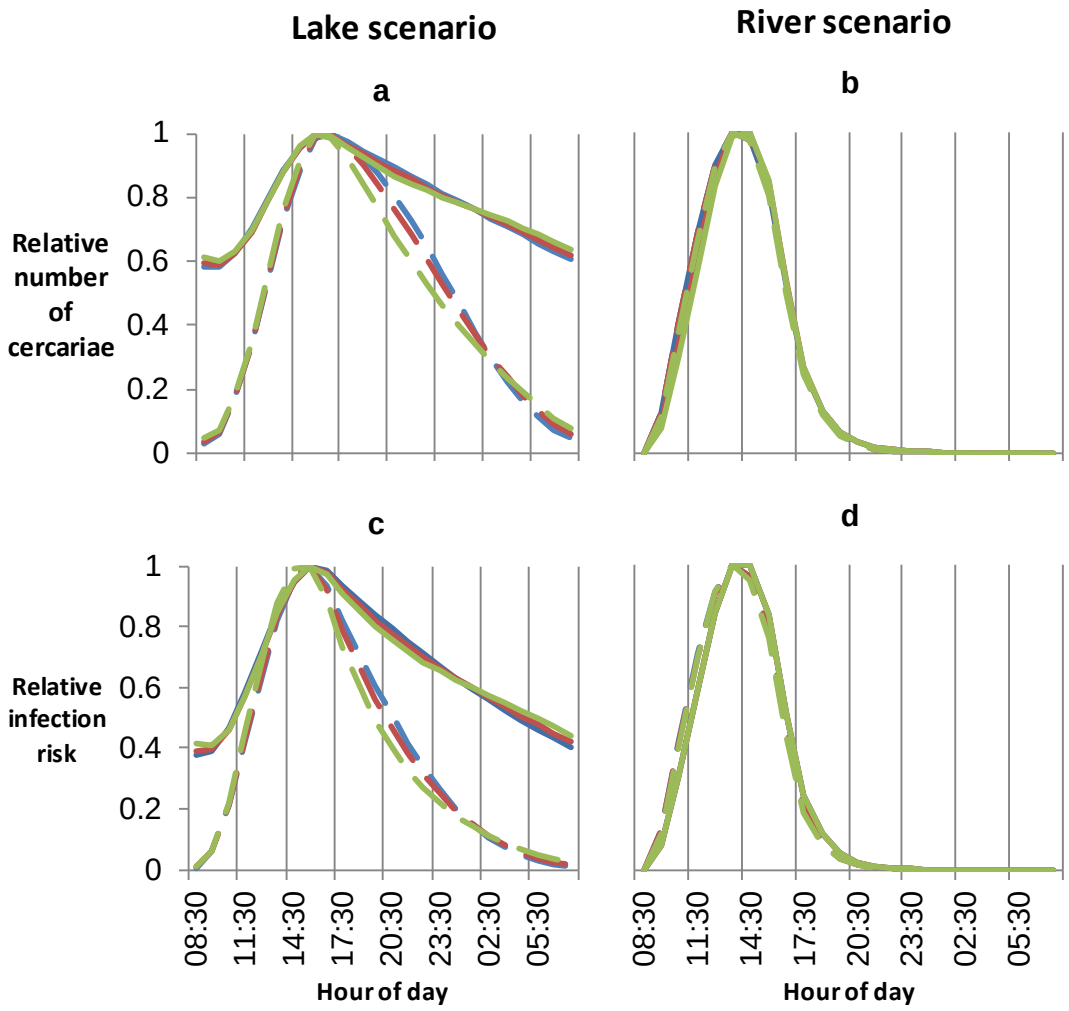

Figure 3.7. Cercaria numbers and infection risk by time of day in the lake and river scenarios. The blues lines illustrate variation in risk with no diurnal variation in temperature, the red lines with ±2°C variation, and the green lines with ±5°C variation. The solid lines show results at 15.0°C and the dashed lines at 29.5°C. Where the three colours cannot be seen the results were very similar regardless of levels of diurnal variation in temperature. Results for temperatures between 15.0°C and 29.5°C fell between the results for 15.0°C and 29.5°C, and are not shown.

3.3.2 Experiment 2: Effect of water depth on the relationship between water temperature and snail population dynamics and human infection risk

Simulating 4°C difference in water temperature between the deepest water and the water surface increased the maximum (surface) temperature at which snail populations could

survive indefinitely from 31.5°C to 35.5°C (Figure 3.8a), and increased the mean total number of snails in the model at all temperatures above 29.5°C. It had no real effect on the snail population size at temperatures below this.

Simulating 4°C difference in water temperature between shallow and deep water had no effect on the minimum temperature at which infection could occur (15.0°C), but reduced both the relative (relative to maximum risk in the same scenario) and absolute human infection risks at all temperatures between 15.5°C and 22.0°C (Figure 3.8b and Figure 3.8c). At temperatures above 22.0°C, it increased both the relative and absolute risks, and it increased the maximum temperature at which there was a risk of infection from 31.5°C to 35.5°C.

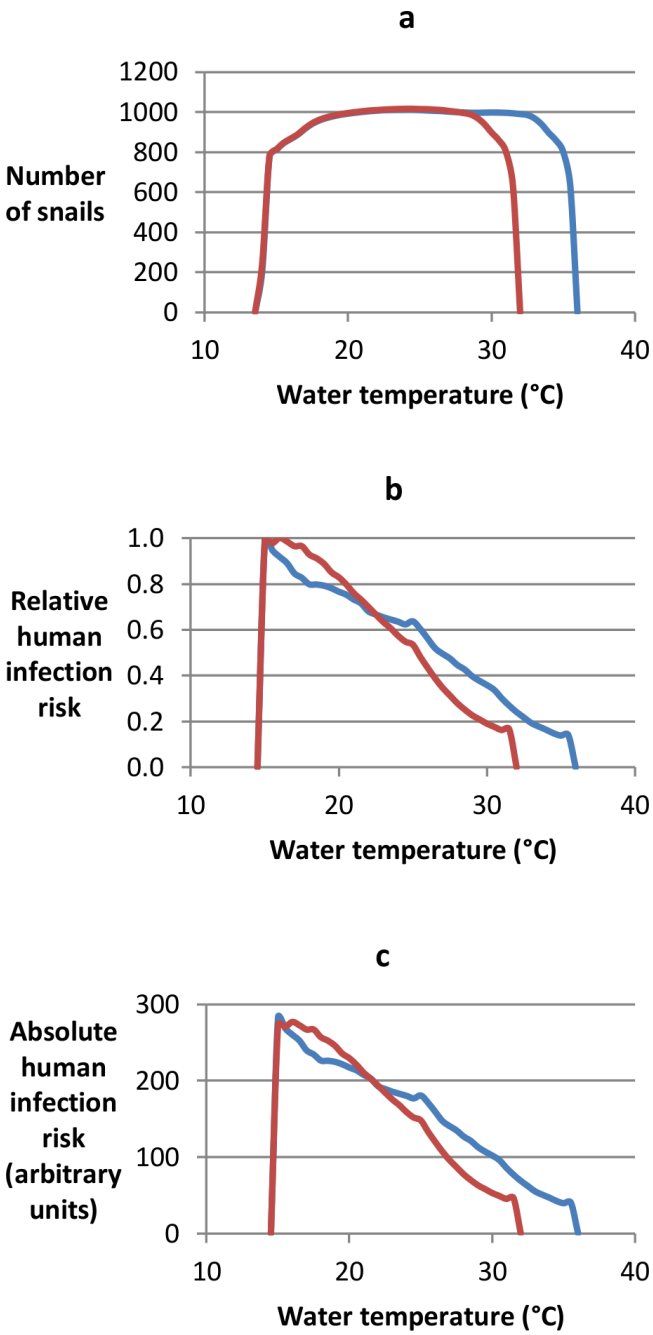

Figure 3.8. The effect of simulating water depth on the relationship between water temperature and snail population size and human infection risk.

a) The mean total number of snails in the model. b) Relative infection risk (relative to maximum risk with the same density dependence function). c) Absolute infection risk (arbitrary units). The red lines show results with no water depth simulated and the blue lines show results with temperature in the deepest water 4°C cooler than water temperature at the surface.

3.3.3 Experiment 3: Effect of variation in the rate of miracidium introduction on human infection risk

3.3.3.1 Constant rates of miracidium introduction

Figure 3.9 shows how simulating different constant rates of miracidium introduction affected the relationship between water temperature and snail population size (Figure 3.9a) and human infection risk (Figure 3.9b). Simulating rates of miracidium introduction of between 2-20/hour had no effect on the overall mean snail population size at any temperature. With rates of miracidium introduction of 50 and 100 per hour, mean snail population size fell at lower temperatures. This was particularly pronounced at 15°C with a rate of miracidium introduction of 100/hour, when the snail population died out entirely. Simulating different rates of miracidium introduction had little effect on the overall relationship between water temperature and infection risk, with the exception of an introduction rate of 100/hour. At this rate, there was no risk of infection at 15°C, due to the extinction of the snail population.

Snails in the model can produce eggs if they are adult snails and if they are either uninfected, or are prepatent and have accumulated fewer than half the heat units necessary to become infectious (see Section 2.2.3.2). The proportion of snails in the model that could produce eggs decreased as the rate of miracidium introduction increased at all temperatures (Figure 3.10). With a miracidium introduction rate of two/hour, 34%, 42%, 50% and 49% of snails could produce eggs at 15°C, 20°C, 25°C and 30°C respectively. This fell to 14%, 28%, 38% and 42% of snails when miracidia were introduced at a rate of 50/hour.

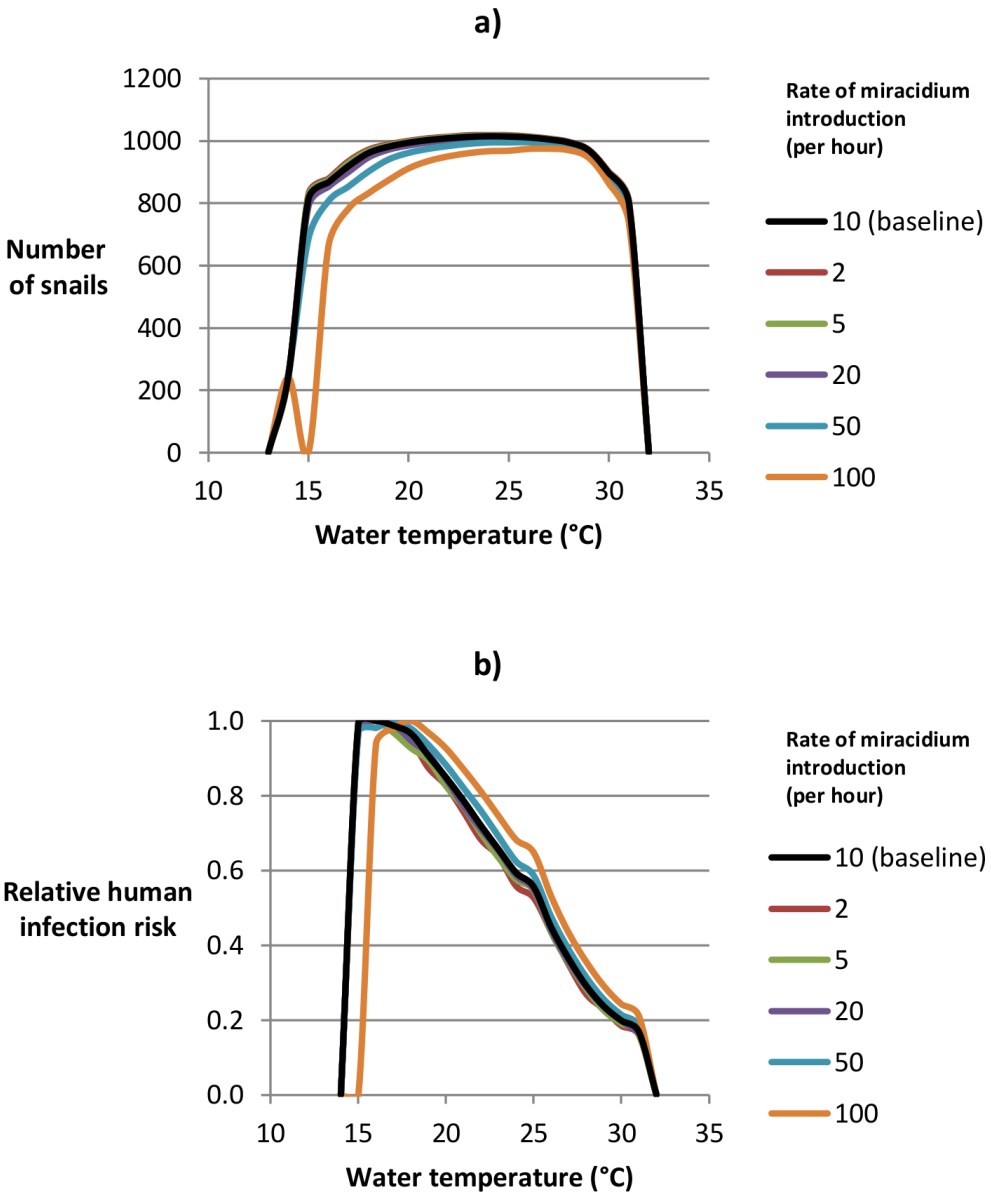

Figure 3.9. Effect of different constant rates of miracidium introduction on the relationship between water temperature and snail population size and human infection risk.

a) Mean total snail population size. b) Infection risk, relative to maximum infection risk at the same rate of miracidium introduction.

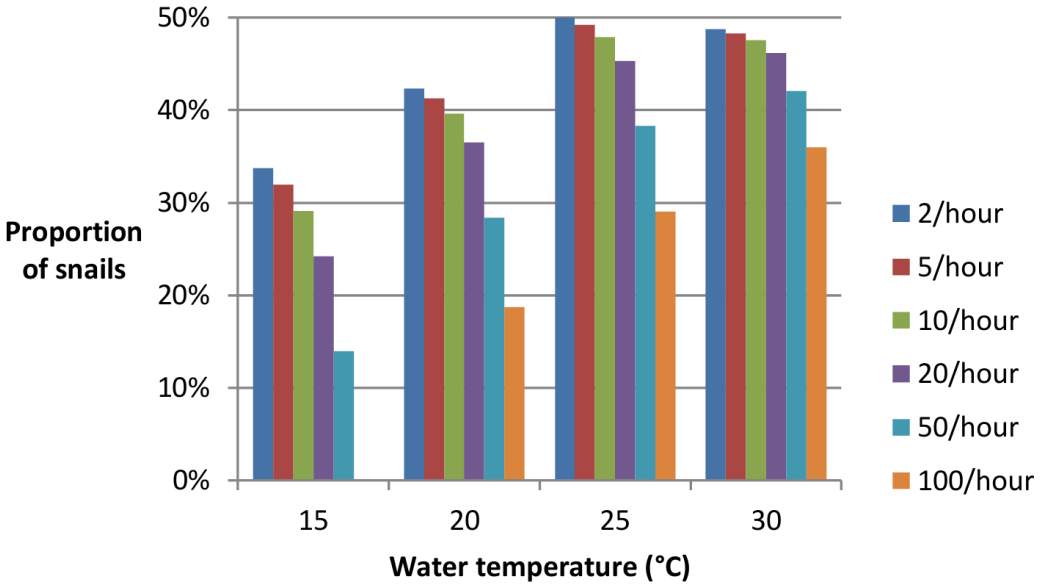

Figure 3.10. **Mean proportion of snails capable of egg production at different rates of miracidium introduction.**

Snails in the model can produce eggs if they are adult snails and if they are either uninfected or are prepatent and have accumulated fewer than half the heat units necessary to become infectious.

3.3.3.2 Exponential relationships between human infection risk and the rate of miracidium introduction

Figure 3.11 shows how simulating different exponential relationships between human infection risk and the rate of miracidium introduction (Figure 3.1) affected the relationship between water temperature and snail population size (Figure 3.11a) and human infection risk (Figure 3.11b). Simulating different exponential functions had little effect on snail numbers. Simulating exponential linking functions did however alter the relationship between water temperature and infection risk, reducing the relative risk of infection at higher temperatures, and reducing the maximum temperature at which there was a risk of infection. Both reducing the maximum rate of miracidium introduction and reducing the rate of increase in miracidium introduction with increasing human infection risk increased the rate of decline in infection risk with increasing temperature. The proportion of snails in

the model that could produce eggs decreased with decreasing temperatures below 25°C for all simulated relationships (Figure 3.12).

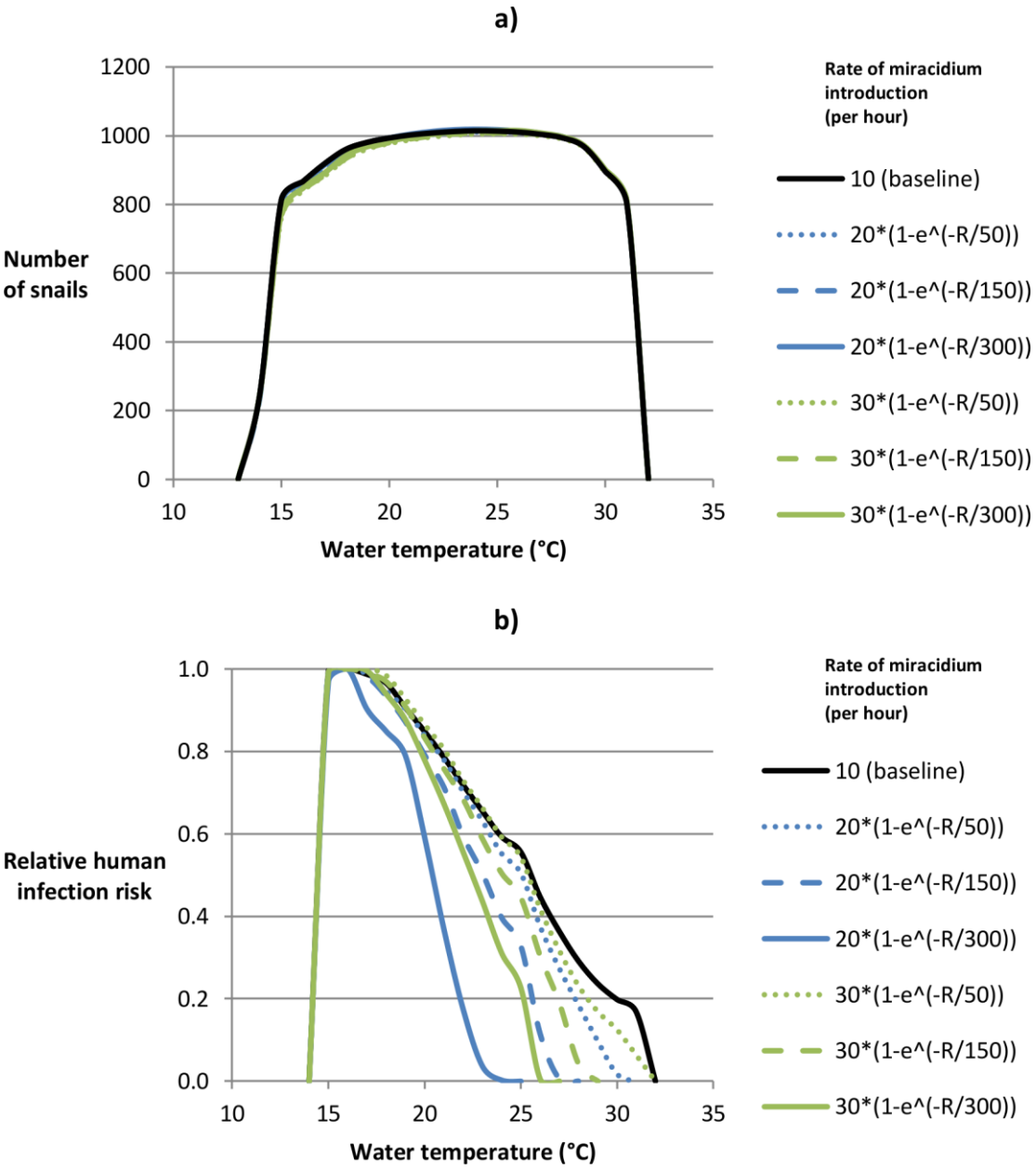

Figure 3.11. Effect of simulating different exponential relationships between human infection risk and the rate of miracidium introduction on the relationship between water temperature and snail population size and human infection risk.

a) Mean total snail population size. b) Infection risk, relative to maximum infection risk in the same scenario. R=infection risk. Lines which cannot be seen are overlapped by the black baseline scenario line.

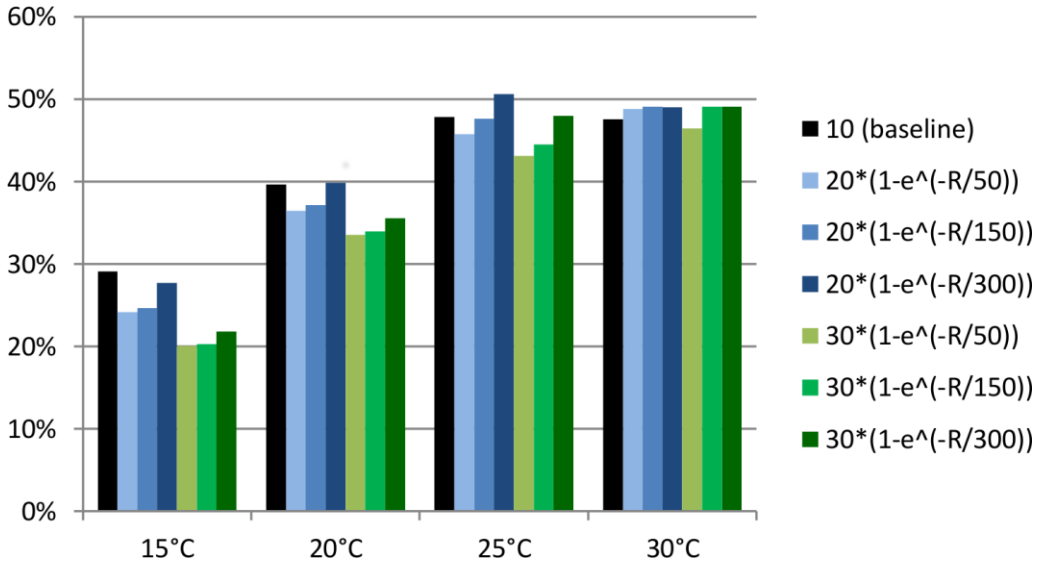

Figure 3.12. Mean proportion of snails capable of egg production with different simulated relationships between infection risk and the rate of miracidium introduction.

Snails in the model can produce eggs if they are adult snails and if they are either uninfected, or are prepatent and have accumulated fewer than half the heat units necessary to become infectious.

3.3.4 Experiment 4: Investigating the sensitivity of the model results to the choice of density dependence functions

There was little difference in the mean total snail population size between scenarios 1, 2 and 4 (Figure 3.13a) (Scenarios shown in Figure 3.2). Counting juvenile snails as half a snail (scenario 3) increased the population size by 31-49% compared with scenario 1, and simulating density dependent effects on mortality rates only increased the population size by 8-218%.

The mean total number of adult snails in the model was 6-53% higher in scenario 2 (density dependent reductions in fecundity only) compared with scenario 1, and 31-50% higher in scenario 5 (juvenile snails count as half a snail) (Figure 3.13b). Simulating both density dependent reductions in fecundity and increases in mortality rates from 300 snails (scenario 4), instead of from 300 and 600 snails respectively (scenario 1), reduced the mean number of adult snails by 20-44%. Finally, simulating density dependent reductions in

fecundity only (scenario 2) increased the mean number of adult snails at extreme temperatures by up to 12%, and reduced the mean number of adult snails at moderate temperatures by up to 39%.

There was very little difference between scenarios 1, 2, 4 and 5 in the relationship between water temperature and human infection risk, relative to the highest infection risk in the same scenario (Figure 3.13c). Simulating density dependent increases in mortality only (scenario 3) resulted in a steeper decrease in relative infection risk with increasing temperature at temperatures below 29.0°C, followed by a slight increase in infection risk as temperatures increased up to 32.0°C.

Simulating density dependent reductions in fecundity only (scenario 2) had little effect on absolute infection risk, compared with scenario 1, although it increased the temperature at which infection risk was highest from 16.5°C to 18.0°C (Figure 3.13d). Counting juvenile snails as half a snail (scenario 5) reduced absolute infection risk by 27-37%. Simulating both density dependent reductions in fecundity and increases in mortality rates from 300 snails (scenario 4), instead of from 300 and 600 snails respectively (scenario 1), reduced absolute infection risk by 66-72%. Finally, simulating density dependent increases in mortality only reduced absolute infection risk by 52-87%.

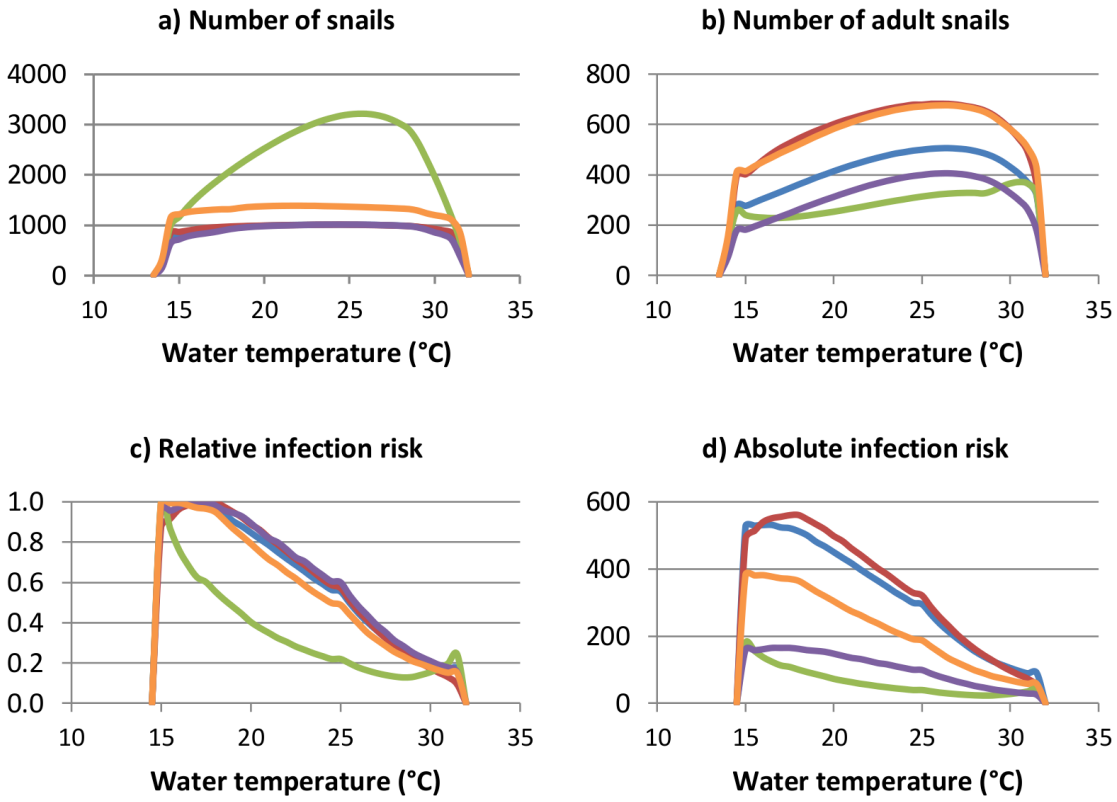

Figure 3.13. The effect of simulating different snail density dependence functions on the relationship between water temperature and snail population size and human infection risk. a) The mean total number of snails in the model. b) The mean total number of adult snails in the model. c) Relative infection risk (relative to maximum risk with the same density dependence function). d) Absolute infection risk (arbitrary units). Blue lines show the model with both density dependent reductions in egg production (with more than 300 snails in the model) and increases in mortality (with more than 600 snails in the model) (scenario 1); red lines the model with density dependent reductions in egg production only (with more than 300 snails in the model) (scenario 2); green lines with density dependent increases in mortality only (with more than 600 snails in the model) (scenario 3); purple with both density dependent reductions in egg production (with more than 300 snails in the model) and increases in mortality (with more than 300 snails in the model) (scenario 4); and orange with both density dependent reductions in egg production (with more than 300 snails in the model) and increases in mortality (with more than 600 snails in the model), with each adult snail counting as one snail and each juvenile snail counting as half a snail (scenario 5).

3.4 Discussion

In this chapter, I demonstrate the relationship between water temperature and snail population dynamics and human infection risk in the model. I show that both the degree of diurnal variation in temperature, and the type of water body, can be important modifiers of the relationships. Finally, I evaluate the sensitivity of the model results to assumptions made about the rate of miracidium introduction and snail density dependence functions.

The simulated *Bi. pfeifferi* snail population could survive indefinitely at temperatures between 14.0°C and 31.5°C when there was no diurnal variation in temperature. Simulating a small amount of diurnal variation in temperature decreased both the minimum and maximum temperatures at which the snail population could survive indefinitely, and simulating a greater amount of diurnal variation increased the minimum temperature and decreased the maximum temperature. Infection risk was highest at 16.5°C to 18.0°C in the 'lake' scenarios, and at 20.5°C to 25.0°C in the 'river' scenarios. When there was no diurnal variation in temperature, simulated snail populations could survive indefinitely at temperatures as low as 14.0°C, but there was no risk of infection below 15.0°C.

Results are presented for two scenarios with different levels of cercaria and miracidium mortality: 'lake' and 'river'. The scenario lake is designed to represent conditions where the majority of cercaria and miracidium mortality occurs as a result of the depletion of their glycogen stores. The scenario river represents conditions where the rate of cercaria and miracidium mortality or local depletion is high. In general, conditions in still water bodies will be best approximated by the lake scenario, and conditions in flowing water by the river scenario, but there will be many exceptions. For example, in lakes where predation of cercariae and miracidia is high the river scenario may be more appropriate, and in pockets of calm water at the edge of rivers, local conditions may be better approximated by the lake scenario. Furthermore, the conditions in many water bodies may fall somewhere between the two scenarios.

Simulating a temperature gradient, such as that found in deeper water bodies, increased the maximum temperature at which the snails could survive, reduced absolute and relative infection risk at low temperatures, and increased absolute and relative infection risk at high temperatures. This suggests that the limit of the snails' range and schistosomiasis infection risk is likely to depend on the type of water bodies found in an area. In areas with high

temperatures, snail populations may be found in larger water bodies, but not in streams, irrigation systems, and small ponds.

In the model, it is assumed that all snails are capable of identifying, moving to and remaining in the depth of water that optimises their reproductive fitness (based on the water temperature). In addition, it is assumed that eggs will be laid at the depth and temperature at which their probability of hatching is greatest. In reality, snails' movements will also be influenced by other factors such as food availability, crowding, and predator evasion. The choice of water depth at which to lay eggs will be influenced by the availability of suitable surfaces on which to place egg masses. The results of the experiment can therefore be viewed as an upper limit of the effects of a 4°C water gradient on snail numbers and infection risk, and the 'true' effects in different deeper water bodies are likely to fall somewhere between this upper limit and the results where no temperature gradient was simulated.

The model does not simulate the link between cercaria numbers and miracidium numbers. While this means that the model does not make assumptions about the relationship between the two, which will be different in different populations and is unlikely to be simply linear, it also means that there is no feedback between cercaria numbers and miracidium numbers. The effects of this were explored in Experiment 3, which simulated a range of different constant and exponential relationships between human infection risk and the rate of miracidium introduction. Simulating higher and lower constant rates of miracidium introduction had little effect on the relationship between water temperature and snail population size or human infection risk. The exception to this was when very high rates of miracidium introduction were simulated, when snail population numbers were greatly reduced at low temperatures, leading to much lower infection risks. The reason for these reductions is that at low temperatures and high rates of miracidium introduction a high proportion of snails were infectious or had advanced prepatent infections, and were therefore unable to produce eggs (Figure 3.10).

Simulating any link between human infection risk and the rate of miracidium introduction resulted in a sharper decline in infection risk as temperatures increased above the optimum temperature for transmission. This is an inevitable result of introducing a feedback mechanism into the model. The findings show that not simulating a link between infection risk and miracidium introduction may result in the model over-estimating the

range of schistosome transmission in hotter areas, and under-estimating the reduction in transmission that may occur with increasing temperatures in hotter areas.

In the model, population numbers of more than 300 snails reduce snail egg production rates, and population numbers of more than 600 snails increase snail mortality rates. These density dependent effects were chosen as there is some evidence that high snail densities have a greater effect on snail fecundity than on snail mortality (see Section 2.2.3.5). To explore the effect of the choice of density dependence functions on the relationship between water temperature and snail numbers and human infection risk, four alternative scenarios were simulated with different relationships between snail population numbers and both fecundity and mortality rates. The results show very little difference between the scenarios in the relationship between water temperature and infection risk (Figure 3.13c), with the exception of the scenario with density dependent effects on mortality only (scenario 3). In this scenario, risk is highest at a lower temperature and the reduction in risk as temperatures increase is steeper. This scenario represents an absolute limit however, with high snail densities having no effect on fecundity. Even if the baseline scenario underestimates the effect of high snail densities on mortality rates (relative to the effect of high snail densities on egg production rates), the true relationship between water temperature and infection risk is likely to lie closer to that suggested by the baseline scenario than to that suggested by scenario 3. Furthermore, although the overall relationship between water temperature and infection risk depends on the density dependence functions chosen, the overall implications of this study to policy and control programs will not.

My results suggest that in many lakes, ponds, reservoirs and dams where *Bi. pfeifferi* is an intermediate host for *S. mansoni*, infection risk may decrease. In rivers and streams during seasons where mean temperatures are currently below around 20°C infection risk may increase. During seasons where mean temperatures are currently above around 25°C infection risk may decrease. In some areas currently at the limits of *Bi. pfeifferi*'s range snail populations may die out entirely. This is likely to occur at lower temperatures in areas where snails are found in streams and shallow water bodies than in areas where snails are found in deeper water bodies.

Infection risk is highest between late morning and mid-afternoon in flowing water, and this does not vary with mean temperature. In still water bodies, infection risk remains high throughout the afternoon at high temperatures and into the evening at lower

temperatures. Behaviour change interventions aimed at reducing infection by encouraging people to avoid transmission sites at high risk times of day may therefore be less feasible and effective at still water transmission sites, particularly where temperatures are low.

Snail generation times will decrease as temperatures increase, as eggs take less time to hatch at higher temperatures, and juvenile snails take less time to start producing eggs. This means that snail populations will recover faster from seasonal reductions in their numbers. Snail populations will also take less time to regain their original numbers following any snail control efforts, meaning that intervals between molluscicide applications and other control methods may need to be reduced to have the same effect. In addition, the length of time between a snail being infected and it first producing cercariae decreases with increasing temperature (Figure 3.4), meaning that infection risk will also take less time to regain its pre-control levels.

The model results show that the proportion of snails that are infectious at a transmission site cannot be used as a reliable measure of relative infection risk without water temperature being taken into consideration. At sites with lower temperatures, all else being equal, a higher proportion of snails will be infectious, but this does not necessarily translate into a higher risk of infection, particularly in flowing water. This is largely due to the fact that cercaria production by each infected snail increases greatly with increasing temperature (Figure 2.9). The number of cercariae also does not correspond directly with infection risk, as cercariae become less infectious with age.

In the model, there is a small range of temperatures and conditions at which *Bi. pfeifferi* populations can survive but at which little or no sustained transmission of *S. mansoni* can occur. This is in line with empirical data, with studies reporting the existence of *Bi. pfeifferi* or other *Biomphalaria* populations at low temperatures with no or only seasonal schistosome transmission occurring (Chu and Dawood 1970; Shiff, Evans *et al.* 1975; Kloos, Lo *et al.* 1988). This band of temperatures is relatively narrow however, and it is therefore probable that the majority of cooler areas where *Bi. pfeifferi* snails are currently found will become suitable for schistosomiasis transmission over coming decades.

The model brings some important new insights that greatly improve understanding of the complexities of the relationship between water temperature and schistosomiasis risk. I consider the effect of still and flowing water on cercaria and miracidium mortality rates, and show that water body type may be an important modifier of the relationship between

water temperature and schistosomiasis risk. I also show that the relationship between time of day and infection risk can vary with temperature and the type of water body. This will have an impact on the design and effectiveness of interventions aiming to reduce water contact at high risk times of day.

The results suggest that increasing temperatures may increase schistosomiasis risk in flowing water in cooler areas and decrease it in warmer areas and in still water bodies. They also suggest that areas where *Bi. pfeifferi* snails are currently found, but where little or no transmission occurs, will become suitable for transmission of schistosomiasis over coming years and decades. Furthermore, infection risk increases sharply once the minimum temperature necessary for transmission is reached, particularly in still water bodies, meaning that once the parasite is introduced into these areas epidemics of schistosomiasis could occur.

4 The effect of simulating three different species of *Biomphalaria* on the relationship between water temperature and *S. mansoni* infection risk

4.1 Background

Snails of the genera *Biomphalaria* and *Bulinus* act as intermediate hosts for *S. mansoni* and *S. haematobium* respectively. Within each genus, there are several species of snail capable of acting as an intermediate host, and multiple species of snail host can be found at any one site (Kazibwe 2003). There are around 12 species of *Biomphalaria* in Africa, and all species tested have been found to be capable of acting as intermediate host (Brown 1994). Elsewhere, *Biomphalaria* species and *S. mansoni* are found in parts of South America, the Caribbean, and the Middle East. Each species of snail has slightly different requirements for development, such as a preference in habitat for shallow or deep water (Kazibwe, Makanga *et al.* 2006). Temperature needs vary as well; one experimental study found that *Bi. alexandrina* eggs required temperatures between 15°C and 30°C to hatch, whereas *Bu. truncatus* eggs hatched at temperatures as low as 13°C and as high as 35°C (El-Hassan 1974).

A recent geostatistical modelling study clearly demonstrates the need to consider multiple snail species in any modelling exercise (Stensgaard, Utzinger *et al.* 2013). A statistical model was fitted separately to data on the distribution of five African species of *Biomphalaria*, and highlighted diverse potential ranges. For instance, *Bi. alexandrina* is limited to small areas of north and west Africa, whereas *Bi. pfeifferi* is found in much of sub-Saharan Africa. Models will therefore be unreliable if the varied requirements of snail species are not taken into consideration. Evidence of this is found by examining a statistical model of environmental data and *S. haematobium* risk fitted using data from one area of coastal Tanzania. The model performed well in other coastal areas of Tanzania, but not elsewhere in the country (Brooker, Hay *et al.* 2001). This was thought to be because the snails that inhabit the coastal area of Tanzania are distinct from those found elsewhere. Each species will respond differently to a specific environmental factor, resulting in the poor fit of statistical models that are not fitted separately for multiple snail species.

Current dynamical models of schistosomiasis and temperature largely neglect the issue of different intermediate host snail species having different temperature requirements. One model of *S. japonicum* transmission in China was parameterised using data from *O. hupensis* only (Zhou, Yang *et al.* 2008), but models of *S. mansoni* and/or *S. haematobium* transmission have been parameterised using data from multiple species of host snail (Martens, Jetten *et al.* 1995; Martens, Jetten *et al.* 1997; Mangal, Paterson *et al.* 2008). Models such as this allow some reflection on the relationship between temperature and transmission, but cannot reliably estimate schistosomiasis transmission potential in any one location. They will also not be able to reliably predict any expansion in the geographic distribution of schistosomiasis due to climate change. Many areas could become suitable for the survival of one or more snail species, but snail populations are unlikely to become established unless the areas become suitable for species of snails already found nearby.

Chapters 2 and 3 describe an agent-based model of snail population dynamics and schistosomiasis transmission that is parameterised to a single species of snail, *Bi. pfeifferi*. This chapter describes the fitting of the model to two additional *Biomphalaria* species: *Bi. glabrata* and *Bi. alexandrina*. These species were chosen as many of the data needed to accurately parameterise the model were available from empirical experiments. *Bi. pfeifferi* is the most widespread intermediate host of *S. mansoni* in Africa (Stensgaard, Utzinger *et al.* 2013), and can be found in a range of different types of water body including streams (Thomas and Tait 1984), lakes (Appleton 1977a), reservoirs (Dupouy and Mimpfoundi 1986), irrigated areas (Wibaux-Charlois, Yelnik *et al.* 1982; Gryseels 1985; Madsen, Daffalla *et al.* 1988), and rice-paddies (Dennis, Vorkpor *et al.* 1983). *Bi. alexandrina* is found in North Africa only, in Egypt, Sudan, and north-west Libya (Doumenge, Mott *et al.* 1987; Stensgaard, Utzinger *et al.* 2013). It is very common in the water supply and drainage networks of the Nile Delta (Dazo, Hairston *et al.* 1966; Doumenge, Mott *et al.* 1987), and can also be found in springs, streams and the edges of swamps (Doumenge, Mott *et al.* 1987). *Bi. glabrata* has a widespread distribution in South America and the Caribbean (Paraense 2001), and can be found in pools, marshes, and streams (Sturrock 1973).

This chapter explores the effect of simulating the three different *S. mansoni* intermediate host species on the relationship between water temperature and snail population dynamics and human infection risk. In doing this, it demonstrates the importance of

parameterising models to individual species of snail, and of considering the species of intermediate host snail found in an area when making predictions. In addition, it also explores the effect of diurnal variation in temperature and increased mortality rates on the relationships.

4.2 Methods

4.2.1 Model

The model used in this chapter is described in Chapter 2.

4.2.2 Model parameterisation

The model was parameterised using data from two additional species of intermediate host snail: *Bi. glabrata* and *Bi. alexandrina.* The data used, and parameter values chosen, are described below. Tables 9.1 - 9.4 in Appendix 1 give details of all of the rates used in the model for all three species of snail.

4.2.2.1 Juvenile development

Bi. glabrata

Data on the number of days between hatching and the start of egg laying at 20°C, 25°C and 30°C were available from one laboratory study (Sturrock and Sturrock 1972). They were converted into heat units gained/hour, with 100 heat units needed for the juvenile snails to become adults. It was assumed that no juvenile development occurs above and below the maximum and minimum temperatures for *Bi. pfeifferi* juvenile development estimated in Section 2.2.3.1. These were 6.1°C and 33.6°C respectively. A Lactin curve was fitted through the three empirical data points, subject to the constraint that the values the curve took at 6.1°C and 33.6°C were less than or equal to zero, and this curve was used to simulate

juvenile *Bi. glabrata* development in the model (Figure 4.1a). It was assumed that no development occurs at temperatures below and above 6.5°C and 33.6°C respectively, the temperatures at which the curve meets the x-axis.

Bi. alexandrina

Data on the number of days between hatching and the start of egg laying were available from one laboratory study at 20°C, 25°C, 28°C and 30°C (El-Hassan 1974), and from a second laboratory study at 18°C, 26°C and 28°C (El-Emam and Madsen 1982). They were converted into heat units gained/hour and a Lactin equation fitted through the seven points was used to simulate juvenile *Bi. alexandrina* development in the model (Figure 4.1b). It was assumed that no development occurs below and above 5.2°C and 31.1°C respectively, the temperatures at which the curve meets the x-axis.

Bi. glabrata and *Bi. alexandrina*

Field (Appleton 1977c) and laboratory (Appleton and Eriksson 1984) studies in *Bi. pfeifferi* demonstrated that high temperatures during a juvenile snail's development period could result in a permanent reduction in egg production rates as an adult. To my knowledge, no similar studies have been conducted with *Bi. glabrata* or *Bi. alexandrina*. The same relationship between high temperatures in development and reduced adult egg production was therefore simulated for *Bi. glabrata* and for *Bi. alexandrina* as for *Bi. pfeifferi*.

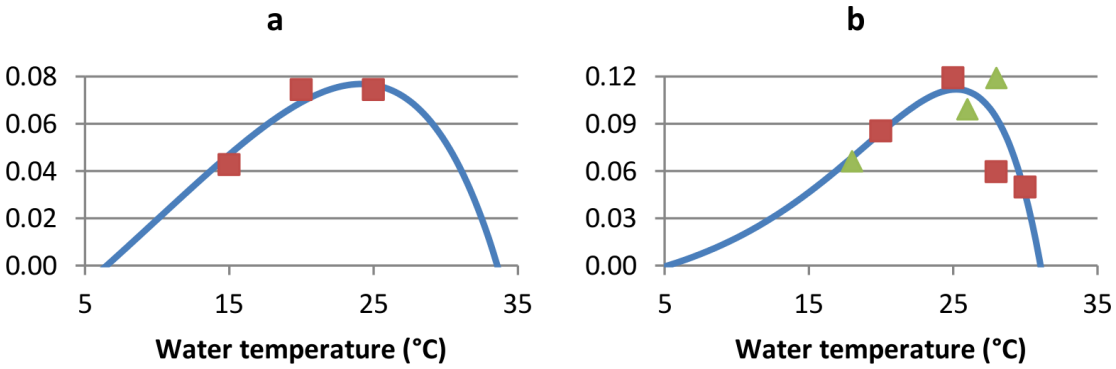

Figure 4.1. **Effect of water temperature on the rate of juvenile snail development.**
Rate of juvenile heat unit gain/hour by water temperature. 100 heat units are necessary to complete development and start egg laying. a) *Bi. glabrata*. Red squares show data from a laboratory study (Sturrock and Sturrock 1972). The blue line shows a Lactin model fitted through the data, and is used to determine juvenile development rates in the model. b) *Bi. alexandrina*. Red squares (El-Hassan 1974) and green triangles (El-Emam and Madsen 1982) show data from laboratory studies. The blue line shows a Lactin model fitted through the data, and is used to determine juvenile development rates in the model.

4.2.2.2 Egg production

Bi. glabrata

A laboratory study recorded the mean number of eggs produced/snail/day by adult *Bi. glabrata* kept at 17.5°C, 20.0°C, 22.5°C, 25.0°C and 27.5°C (Pimentel-Souza, Barbosa *et al.* 1990). This was converted into eggs/snail/hour and a Lactin equation was fitted through the five data points (Figure 4.2a). This equation gave an estimated egg production rate at 23°C of 19 eggs/snail/day. This is much higher than the estimated 6 eggs/snail/day laid by snails in a pond with an average temperature of 23°C (Jobin 1970), and therefore the equation was scaled by 6/19 at all temperatures. No egg production occurred in the model at temperatures below 11.7°C or above 30.4°C, the temperatures at which the Lactin equation meets the x-axis.

As for *Bi. pfeifferi* (Section 2.2.3.2), egg production in the model was reduced by a further 90% to simulate temperature-independent egg mortality before and during hatching.

Experimental data suggest that there is little or no difference in egg production rates between uninfected and prepatent *Bi. glabrata* kept at 25°C at seven or 14 days post-exposure (Crews and Yoshino 1989). Egg production in prepatent snails compared with uninfected snails dropped sharply from 21 days post-exposure however. Patency was reached at around 28 days. In another study, prepatent snails ceased producing eggs entirely five weeks post-exposure (Pan 1963). In the model, prepatent snails stop producing eggs after they have accumulated 50% of the heat units necessary to become infectious.

Bi. alexandrina

Experimental data were available on the number of eggs produced/snail/day by adult *Bi. alexandrina* kept at six temperatures between 12.5°C and 30°C (El-Hassan 1974). The same study found that no egg production occurred at 10°C or 35°C. A Lactin equation was fitted through the six points, subject to the constraint that values at 10°C and 35°C were less than or equal to zero. This fitted equation was used to determine egg production rates in the model (Figure 4.2b). No egg production occurred in the model at temperatures below 10.0°C or above 30.1°C, the temperatures at which the Lactin equation meets the x-axis.

For both *Bi. pfeifferi* and *Bi. glabrata*, simulated egg production rates were set 90% lower than estimated egg production rates to incorporate temperature-independent egg mortality before and during hatching. The egg production rates estimated for *Bi. alexandrina* from the experimental data described above were 8-22 times lower than the *Bi. alexandrina* egg production rates found in another study however (Mangal 2009). The maximum rate was also 8.6 and 9.5 times lower than the maximum rates estimated for *Bi. pfeifferi* and *Bi. glabrata* respectively. Furthermore, the simulated *Bi. alexandrina* population very quickly dies out at all temperatures if simulated egg production rates are reduced by 90%. For these reasons, egg production rates were set equal to the rates estimated using the Lactin equation described above, and were not reduced.

No data were available on egg production by prepatent or patently infected *Bi. alexandrina*. Both *Bi. pfeifferi* and *Bi. glabrata* cease to produce eggs roughly halfway through their prepatent periods however, and therefore simulated prepatent *Bi. alexandrina* stop producing eggs after they had accumulated 50% of the heat units necessary to become infectious.

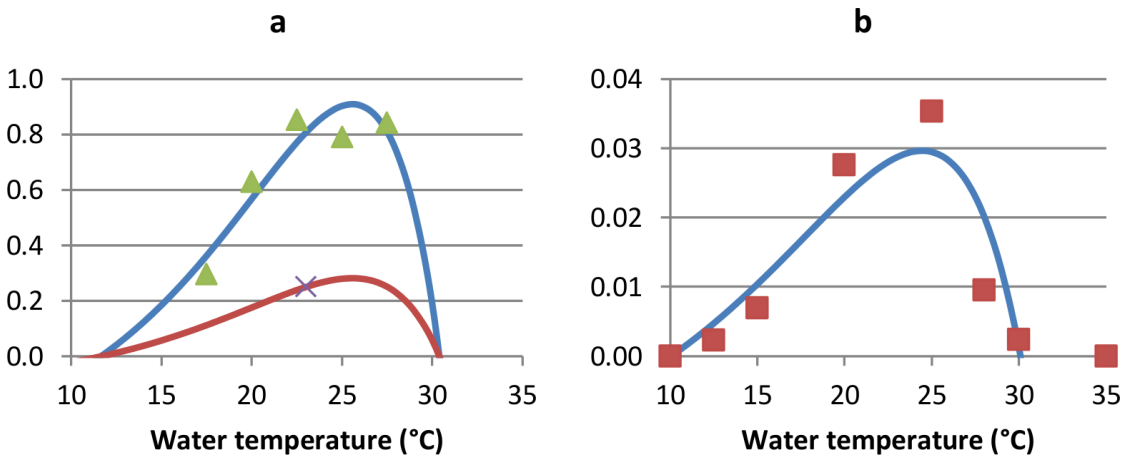

Figure 4.2. Effect of water temperature on snail egg production rates.

Eggs/snail/hour. a) *Bi. glabrata.* The green triangles show empirical data from a laboratory study (Pimentel-Souza, Barbosa *et al.* 1990). The purple cross shows empirical data from a field study (Jobin 1970). The blue line is a Lactin model fitted to the laboratory data. The red line is the Lactin model scaled to pass through the field data point, and the relationship used in the model before adjustment for temperature-independent egg mortality. b) *Bi. alexandrina*. Red squares show data from a laboratory study (El-Hassan 1974). The blue line shows a Lactin model fitted through the data, and is used to determine egg production rates in the model.

4.2.2.3 Egg development

Bi. glabrata

A laboratory study recorded the number of days until hatching, and the proportion of eggs that hatched, for eggs from pigmented and unpigmented *Bi. glabrata* kept at 11 temperatures between 14°C and 34°C (Joubert and Pretorius 1985). There was very little difference between pigmented and unpigmented snails in either development or mortality rates, and, as the data were presented as a graph only, the data from the pigmented snails were therefore used.

Days until hatching were converted into heat unit gain/hour (with 100 heat units needed for hatching) and a Lactin equation was fitted through the points (Figure 4.3a). This equation was used to simulate egg development rates in the model. No egg development

was assumed to occur below 13.8°C and above 40.0°C in the model, where the fitted line meets the x-axis.

Data on the proportion of eggs that hatched and the number of days to hatching were used to calculate the mortality rate/hour at each temperature. Mortality rates were less than 0.0021/hour at all temperatures except 34°C. A quadratic equation was fitted through these points and used to calculate egg mortality rates in the model at all temperatures ≤32°C (Figure 4.3c). The mortality rate was much higher at 34°C (0.017/hour). A linear equation was fitted between the empirical mortality rates at 32°C and 34°C and this was used to calculate mortality rates in the model at all temperatures >32°C.

Bi. alexandrina

Data were available from a laboratory study on the number of days until hatching and the proportion of eggs that hatched for *Bi. alexandrina* eggs kept at 12.5°C, 15°C, 20°C, 25°C, 30°C and 35°C (El-Hassan 1974). No eggs hatched at 12.5°C or 35°C. The number of days until hatching was converted into heat units gained/hour and a quadratic equation was fitted through the points (Figure 4.3c). This was used to determine egg heat unit gain in the model. No egg development occurs in the model below 10.1°C, where the line meets the x-axis. Data on the proportion of eggs that hatched and the number of days to hatching were used to calculate the mortality rate/hour at each temperature between 15°C and 30°C. A quadratic equation was fitted through these points and used to simulate egg mortality rates in the model (Figure 4.3d).

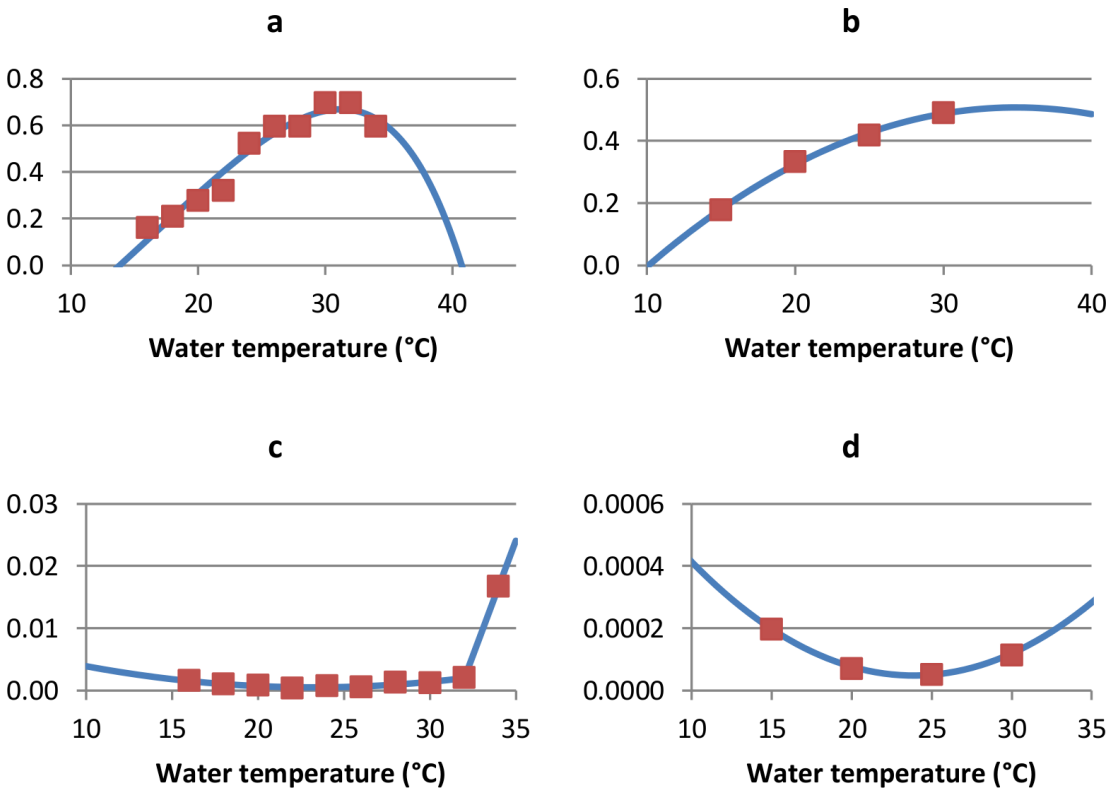

Figure 4.3. Effect of water temperature on snail egg development and mortality.

a) *Bi. glabrata* egg heat unit gain/hour. 100 heat units are needed for hatching. Red squares show data from a laboratory study (Joubert and Pretorius 1985). The blue line shows a Lactin model fitted through the data, and is used to determine egg development rates in the model. b) *Bi. alexandrina* egg heat unit gain/hour. 100 heat units are needed for hatching. Red squares show data from a laboratory study (El-Hassan 1974). The blue line shows a quadratic equation fitted through the data, and is used to determine egg development rates in the model. c) *Bi. glabrata* egg mortality rates/hour. Red squares show data from a laboratory study (Joubert and Pretorius 1985). The blue line shows a piecewise quadratic and linear equation fitted through the data, and is used to determine egg mortality rates in the model. d) *Bi. alexandrina* egg mortality rates/hour. Red squares show data from a laboratory study (El-Hassan 1974). The blue line shows a quadratic equation fitted through the data, and is used to determine egg mortality rates in the model.

4.2.2.4 Mortality

Bi. glabrata

No suitable data were available on the mortality rates of uninfected *Bi. glabrata* at different water temperatures. Experimental data were available on the mortality rates of *Bi. glabrata* with prepatent *S. mansoni* infections at 14 temperatures between 16°C and 36°C however (Pfluger 1980), and studies suggest that there is little or no difference between mortality rates in uninfected and prepatent *Bi. glabrata* (Pan 1963; Minchella and Loverde 1981). These mortality rates were therefore used to estimate mortality rates for prepatent and uninfected snails.

The data suggested that water temperature has little or no effect on mortality rates at moderate temperatures of between 16°C-33°C (Pfluger 1980). The mean mortality rate between these temperatures was therefore calculated (Figure 4.4a). Laboratory data were available on *Bi. glabrata* mortality rates at higher temperatures: at 34°C (Pfluger 1980), 35°C (Pfluger 1980), and 40°C (Joubert and Pretorius 1985). An exponential line was fitted through these three points and the moderate temperature mortality rate at 33°C (Figure 4.4b). For lower temperatures, data were available at 0°C only (Joubert and Pretorius 1985). An exponential line was fitted through this point and the moderate temperature mortality rate at 16°C.

No suitable data were available on the mortality rates of infectious *Bi. glabrata* compared with the mortality rates of uninfected *Bi. glabrata* at different water temperatures. The same relative increase in mortality rates at different temperatures following the start of cercarial shedding was therefore simulated for *Bi. glabrata* as was simulated for *Bi. pfeifferi* (see Section 2.2.3.4).

Bi. alexandrina

El-Hassan recorded the proportions dead after two weeks for uninfected juvenile and adult *Bi. alexandrina* kept at seven temperatures between 10°C and 37°C (El-Hassan 1974). There was very little difference between the mortality of juvenile and adult snails, and therefore the mean proportion dead at each temperature was calculated. All snails died within two weeks at 37°C. Mortality rates were calculated for the other six temperatures, and a

quadratic equation fitted through them. This was used to calculate the mortality rates for uninfected snails at all temperatures in the model (Figure 4.4c).

No suitable data were available on mortality rates in prepatent *Bi. alexandrina*. Prepatent *Bi. glabrata* show no increase in mortality compared with uninfected controls however (Minchella and Loverde 1981), and therefore no increase in mortality in prepatent *Bi. alexandrina* was simulated.

No suitable data were available on the mortality rates of infectious *Bi. alexandrina* compared with the mortality rates of uninfected *Bi. alexandrina* at different water temperatures. The same relative increase in mortality rates at different temperatures following the start of cercarial shedding was therefore simulated for *Bi. alexandrina* as was simulated for *Bi. pfeifferi* and *Bi. glabrata* (see Section 2.2.3.4).

Bi. glabrata and *Bi. alexandrina*

When simulating *Bi. pfeifferi*, mortality rates from laboratory data were multiplied by 1.35 (estimated from field data (Loreau and Baluku 1987b)) to account for increased mortality rates in a natural setting (see Section 2.2.3.4 for details). Data from field studies of *Bi. glabrata* populations suggest that *Bi. glabrata* mortality rates may be between 2.08 (Jobin 1970) and 2.17 (Sturrock 1973) times higher in a natural setting than in a laboratory. Data from a field study of *Bi. alexandrina* suggest that *Bi. alexandrina* field mortality rates in one setting may be 10.05 times greater than laboratory mortality rates (Dazo, Hairston *et al.* 1966). Field mortality rates are estimated using indirect methods however, and will vary greatly between different locations and seasons due to differences in factors such as predation, interspecific competition, and water quality. To enable more direct comparisons between model outputs for the different snail species, it is therefore assumed in the models for all three species that field mortality rates are 1.35 times higher than rates estimated from laboratory data.

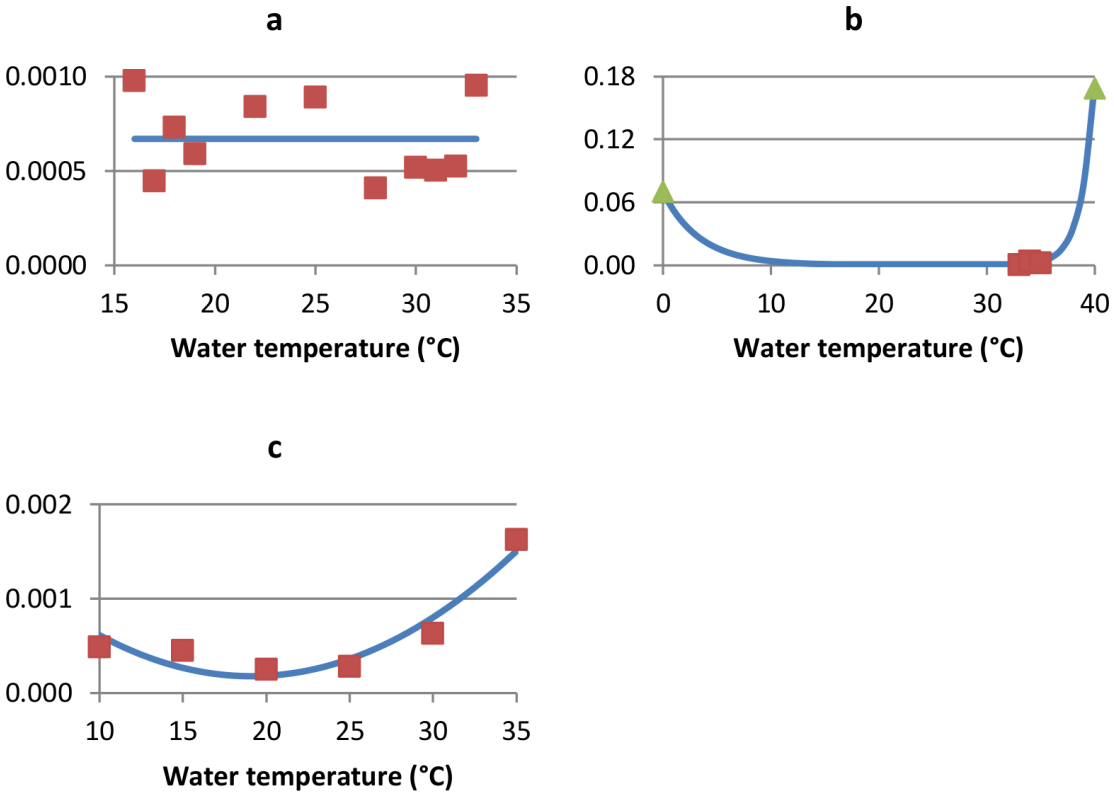

Figure 4.4. Effect of water temperature on snail mortality rates.

Mortality rate/hour. a) *Bi. glabrata* 16°C to 33°C. The red squares show data from a laboratory study (Pfluger 1980) and the blue line shows the mean mortality rate between 16°C and 33°C. b) *Bi. glabrata* all temperatures. The red squares (Pfluger 1980) and green triangles (Joubert and Pretorius 1985) show data from laboratory studies and the blue line shows a piecewise equation fitted through the points. A scaled version of the equation shown by the blue line was used to determine uninfected snail mortality rates in the model. c) *Bi. alexandrina*. The red squares show data from a laboratory study (El-Hassan 1974) and the blue line shows a quadratic line fitted through the points. A scaled version of the equation shown by the blue line was used to determine uninfected snail mortality rates in the model.

4.2.2.5 Snail density dependence

As for *Bi. pfeifferi*, experimental data suggest that high snail densities have a greater effect on egg production rates than on mortality rates in both *Bi. glabrata* (Thomas and Benjamin 1974) and *Bi. alexandrina* (Mangal, Paterson *et al.* 2010). The same relationships between

snail numbers and egg production and mortality rates were therefore used for all three snail species (see Section 2.2.3.5 for details).

4.2.2.6 Parasite development within the snail

Bi. glabrata

Pflüger measured the time to patency in *S. mansoni* infected *Bi. glabrata* kept at 14 constant temperatures between 16°C and 36°C (Pfluger 1980). These times were converted into heat units gained/hour. Between 16°C and 32°C, there was a positive linear relationship between water temperature and heat unit gain, and a linear equation fitted through the points was used to determine parasite development rates in *Bi. glabrata* in the model (Figure 4.5). Above 32°C, development rates start to decrease with increasing temperature. This was simulated in the model using a quadratic equation fitted to the data points.

Pflüger also measured prepatency times at different fluctuating temperature regimens for *S. mansoni* in *Bi. glabrata* (Pfluger 1981). He found that the assumption of a linear relationship between temperature and development rate does not hold for temperature regimens incorporating temperatures below approximately 16°C, with development periods being shorter than would be expected at low temperatures. A non-linear relationship was therefore also modelled for temperatures less than 17°C.

Bi. alexandrina

Very few data were available on the length of prepatency of *S. mansoni* in *Bi. alexandrina* at different water temperatures. One study recorded a prepatency period in susceptible snails kept at 25°C of 27 days (Shoukry, el-Assal *et al.* 1997). Another recorded a prepatency period of 22-28 days at 26-28°C, depending on the strain of *S. mansoni* used (Cridland 1968). These studies suggest that the duration of prepatency in *Bi. alexandrina* is closer to the duration of prepatency in *Bi. pfeifferi* than the duration in *Bi. glabrata*. The same relationship between temperature and parasite heat unit gain was therefore used for *Bi. alexandrina* as for *Bi. pfeifferi* (see Section 2.2.4.1).

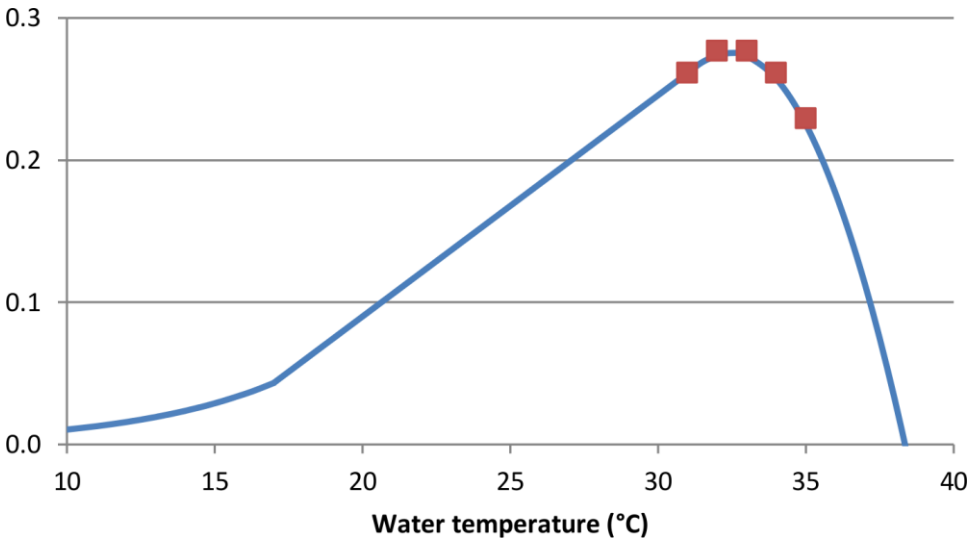

Figure 4.5. Effect of water temperature on the rate of parasite development within *Bi. glabrata*. Rate of heat unit gain/hour, with 100 heat units needed for the snail to become infectious. The blue line shows the relationship used in the model. The red squares represent laboratory data (Pfluger 1980). Laboratory data for temperatures between 16°C and 32°C are not shown as they were given as a fitted equation in the original paper (Pfluger 1980).

4.2.2.7 Miracidium and cercaria aging and mortality

As miracidia and cercariae are free living stages, it is assumed that the species of snail involved in maintaining the lifecycle has no effect on their mortality rates or decrease in infectiousness with age. The same rates were therefore used for *Bi. glabrata* and *Bi. alexandrina* as for *Bi. pfeifferi* (Sections 2.2.4.2 and 2.2.4.3).

4.2.2.8 Susceptibility to infection and cercaria production

The rate of infection of snails by miracidia in the model is a function of the miracidia's biological ages, water temperature, and the number of snails in the model (see Section 2.2.4.2 for details). It does not depend on the species of snail. This is because the susceptibility of *Biomphalaria* snails to *S. mansoni* infection varies as greatly within species

as it does between snail species, and depends on the source of the snails and parasite (Files 1951; Cridland 1968; Cridland 1970; Richards 1975).

Data on the relationship between water temperature and cercaria production were only available from *Bi. glabrata* (Fried, LaTerra *et al.* 2002), and therefore these data were used to simulate cercaria production at different temperatures for *Bi. glabrata*, *Bi. alexandrina* and *Bi. pfeifferi*. Similarly, suitable data on the relationship between time of day and cercaria release were only available from experiments with *Bi. stanleyi* (Kazibwe, Makanga *et al.* 2010), and therefore these data were used to simulate variation in cercaria production by time in all three snail species. Data on absolute numbers of cercariae produced per day by infectious snails show a large amount of variation within the same snail species (McClelland 1965; Frandsen 1979; Cooper, Ramani *et al.* 1992), and for that reason differences between snail species in the absolute numbers of cercariae produced per day were not incorporated into the model.

4.2.2.9 Comparison between parameter values for the three species of Biomphalaria

Figure 4.6 shows a comparison of the parameters used in the model for each snail species, for each rate which varies by species. Full details of the rates for all three species are given in Appendix 1.

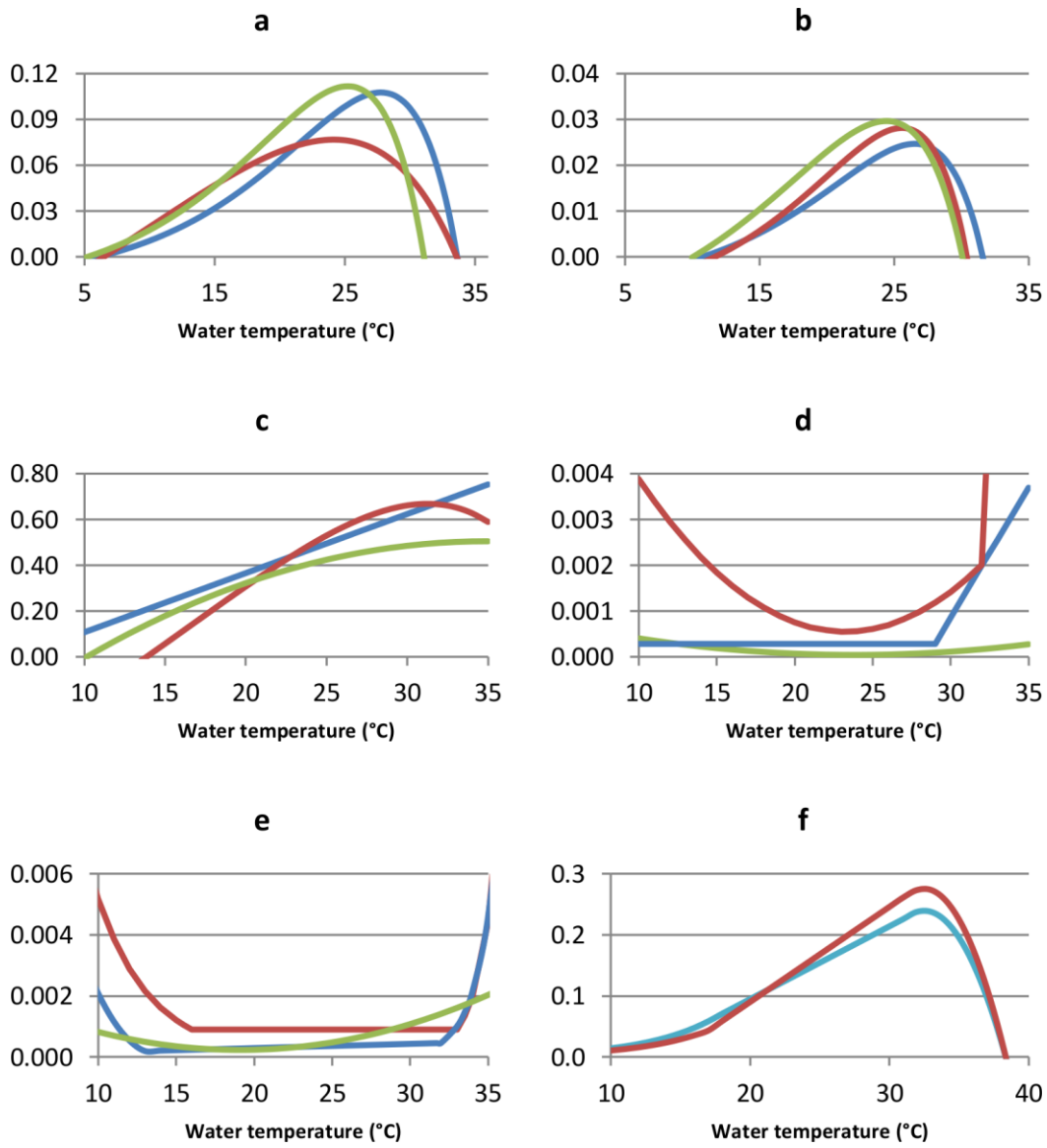

Figure 4.6. Comparison of parameters used in models of *Bi. pfeifferi*, *Bi. glabrata* and *Bi. alexandrina*.

Blue lines show parameters for *Bi. pfeifferi*, red for *Bi. glabrata*, green for *Bi. alexandrina*, and turquoise for both *Bi. pfeifferi* and *Bi. alexandrina*. a) Juvenile development. Heat units gained/hour. Snails start producing eggs once they have gained 100 heat units. b) Egg production. Eggs/snail/hour. c) Egg development. Heat units gained/hour. Egg hatch once they have gained 100 heat units. d) Egg mortality rate/hour. e) Uninfected and prepatent snail mortality rate/hour. f) Parasite development within the snail. Heat units gained/hour. Snails become infectious once they have gained 100 heat units.

4.2.3 Experiments

4.2.3.1 Experiment 1: Effect of water temperature on snail population dynamics and human infection risk

The model was run separately for *Bi. pfeifferi*, *Bi. glabrata* and *Bi. alexandrina* at all temperatures at which the simulated snail populations could survive indefinitely, with temperature increasing in 0.5°C increments. Outputs were averaged over a minimum of one year and 200 runs. The number of snails in the model was calculated as the total number of uninfected, prepatent and infectious juvenile and adult snails.

A number of intermediate results were also calculated by temperature for each snail species. These results were calculated from the equations used in the model only, and were designed to help improve understanding of the overall model results. They were:

1) The mean proportion of eggs that hatch, calculated from egg development rates and egg mortality rates.
2) The mean proportion of juvenile snails that survive to become adults, calculated from juvenile development rates and the uninfected/prepatent mortality rates.
3) The mean proportion of infected snails that survive to become infectious, calculated from parasite development rates and the prepatent mortality rates.
4) The median lifetime cercaria production of infectious snails, calculated from the cercaria production rates and the infectious snail mortality rates.

As these intermediate results were calculated from the input parameters only, and not from model output, 2) to 4) assume that there is no density dependent increase in mortality rates. 2) also assumes that no juvenile snails develop patent infections before becoming adults (which would increase their mortality rate).

4.2.3.2 *Experiment 2: Effect of diurnal variation in water temperature on* Bi. glabrata *and* Bi. alexandrina *numbers and human infection risk*

Water temperatures were modelled as a sine wave with the maximum temperature reached at 3-4pm (Paaijmans, Jacobs *et al.* 2008). Two sets of scenarios with different levels of diurnal variation in temperature were modelled: one where maximum and minimum temperatures varied from the mean temperature by ±2°C, and one where they varied by ±5°C.

Each scenario was run separately for *Bi. glabrata* and *Bi. alexandrina* at all temperatures at which the simulated snail populations could survive indefinitely, with temperature increasing in 0.5°C increments. Outputs were averaged over a minimum of one year and 200 runs.

4.2.3.3 *Experiment 3: Effect of increased mortality rates on snail population dynamics and human infection risk*

In the models for all three snail species, mortality rates estimated from laboratory data were multiplied by 1.35 to account for increased mortality in natural conditions. However, estimates of mortality rates in wild snail populations suggest that mortality rates can be much higher than this. The effect of this was explored by further doubling mortality rates for all snails (juvenile and adult; uninfected, prepatent and infectious).

This high mortality scenario was run separately for *Bi. pfeifferi*, *Bi. glabrata* and *Bi. alexandrina* at all temperatures at which the simulated snail populations could survive indefinitely, with temperature increasing in 0.5°C increments. Outputs were averaged over a minimum of one year and 200 runs.

4.3 Results

4.3.1 Experiment 1: Effect of water temperature on snail population dynamics and human infection risk

4.3.1.1 Proportions of eggs hatching, juveniles surviving to adulthood and snails surviving prepatency; and cercaria production by infected snails

Figure 4.7a shows the proportion of eggs in the model that hatch into juvenile snails. Proportions are greater than 80% for all snail species at all temperatures between 21°C and 30°C, and are lowest for *Bi. glabrata* at all temperatures.

Figure 4.7b shows the proportion of juvenile snails that survive to adulthood in the model, assuming that there is no density dependent increase in mortality rates. Proportions surviving are lowest for *Bi. glabrata* at all temperatures below 30°C, with a maximum of only 16% of juveniles surviving to adulthood (at 24°C). Proportions surviving are high for *Bi. pfeifferi* at all temperatures, with between 40% and 69% surviving to adulthood at all temperatures between 13°C to 32°C inclusive. *Bi. alexandrina* show more variation in proportions surviving to adulthood with temperature, with 77% surviving at 20-21°C, falling to less than 40% at temperatures outside 15°C to 28°C.

Figure 4.7c shows the proportion of infected snails that survive to patency in the model, again assuming that there is no density dependent increase in mortality rates. Proportions are highest for *Bi. pfeifferi* at all temperatures. For both *Bi. pfeifferi* and *Bi. glabrata*, proportions increase with temperature between 10°C and 32°C. For *Bi. alexandrina*, proportions increase up to 21°C before falling as temperatures increase further.

Figure 4.7d shows the median number of cercariae produced by each infectious snail during its lifetime, assuming no density dependent mortality. The median number per infectious snail peaks at 26,300 at 18.0°C for *Bi. pfeifferi* and at 31,300 at 19.5°C for *Bi. alexandrina*. It remains above 80% of its maximum between 14.5°C and 23.5°C for *Bi. pfeifferi* and 17.5°C and 22.0°C for B. alexandrina. Median numbers are much lower for *Bi. glabrata*, and vary less with temperature, peaking at 8,400 at 21.0°C, and remaining above 80% of their maximum between 16.0°C and 29.0°C.

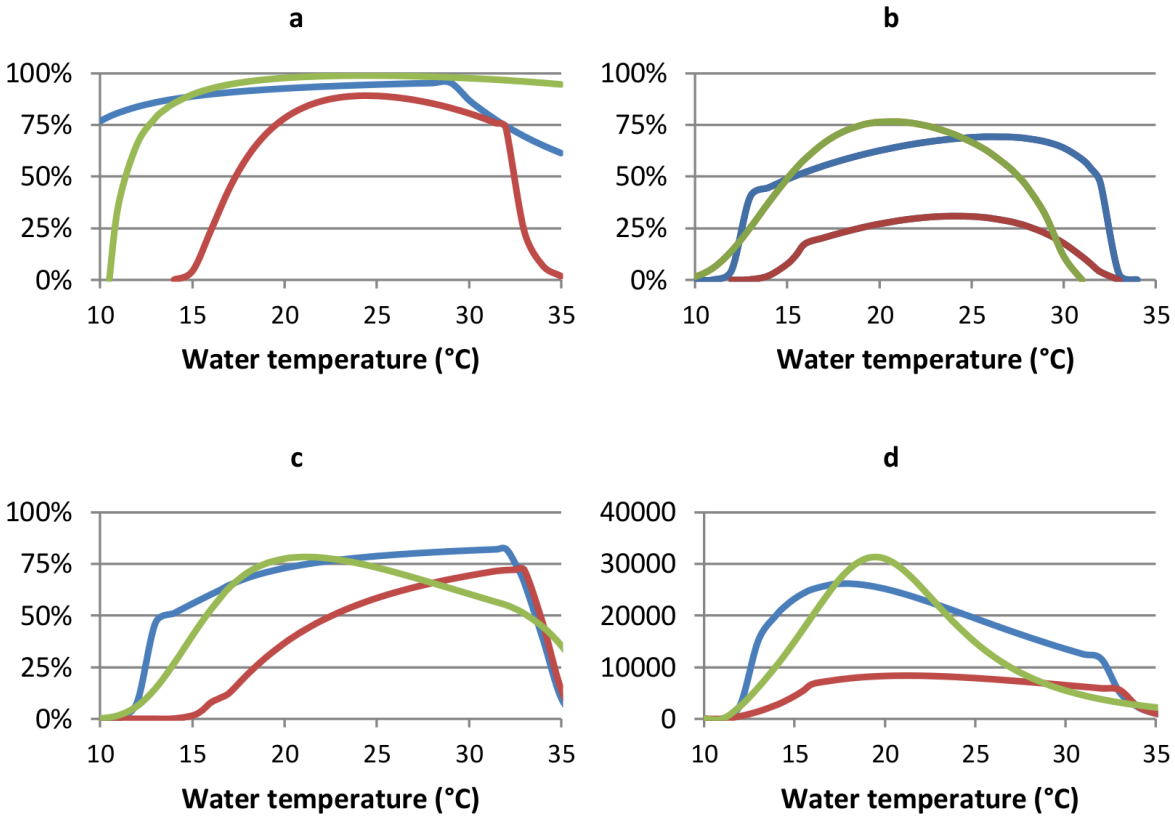

Figure 4.7. Effect of water temperature on the proportions of eggs hatching, juveniles surviving to adulthood and snails surviving prepatency, and cercaria production by infected snails.
Blue lines show *Bi. pfeifferi*, red lines show *Bi. glabrata* and green lines show *Bi. alexandrina.* a) Proportion of eggs laid that hatch. b) Proportion of juvenile snails that survive to adulthood (assuming no additional density dependent mortality). c) Proportion of infected snails that survive to patency (assuming no additional density dependent mortality or increased mortality rates due to late pre-patent or patent infections). d) Median lifetime cercaria production by an infectious snail (assuming no additional density dependent mortality). Results are shown for the low mortality scenario.

4.3.1.2 Model results

4.3.1.2.1 Snail numbers

The mean total number of *Bi. glabrata* in the model was lower than that of *Bi. pfeifferi* at all water temperatures, with a maximum mean total number of *Bi. glabrata* of 850 (at

23.5°C), compared with 1015 *Bi. pfeifferi* (at 24.5°C) (Figure 4.8a). The difference in the mean total number of adult snails was greater still, with a maximum mean total number of adult *Bi. glabrata* of 145 (at 24.0°C), compared with 506 adult *Bi. pfeifferi* (at 26.5°C) (Figure 4.8b). *Bi. alexandrina* mean total population size was higher than *Bi. pfeifferi* population size at all temperatures below 27.0°C. Above this temperature, *Bi. alexandrina* population sizes were lower.

The range of temperatures between which simulated snail populations could survive indefinitely was smallest for *Bi. glabrata*, with snail populations unable to survive at temperatures outside 17.0°C to 29.5°C, compared with 14.0°C to 31.5°C for *Bi. pfeifferi*. Simulated *Bi. alexandrina* populations survived at lower temperatures than either *Bi. glabrata* or *Bi. pfeifferi*, with a minimum temperature for survival of 12.5°C, but did not survive as well as *Bi. pfeifferi* at high temperatures, dying out at temperatures above 29.5°C.

4.3.1.2.2 Human infection risk

Human infection risk was highest at 16.5°C when *Bi. pfeifferi* was the intermediate host snail species, at 19.0°C when *Bi. alexandrina* was the host, and at 25.0°C when *Bi. glabrata* was the host (Figure 4.8c). Either side of these temperatures, infection risk fell for all snail species, however infection risk remained high over a wide range of temperatures when *Bi. glabrata* was the intermediate host snail species. Infection risk remained above 80% of its maximum value at all temperatures between 18°C and 26.5°C in the *Bi. glabrata* model, between 15°C and 20.5°C in the *Bi. pfeifferi* model, and between 18°C and 21°C in the *Bi. alexandrina* model.

There was a non-zero human infection risk at all temperatures at which simulated *Bi. glabrata* populations could survive indefinitely. There was no infection risk below 15.0°C in any model however, while simulated *Bi. pfeifferi* and *Bi. alexandrina* populations could survive indefinitely at temperatures as low as 14.0°C and 12.5°C respectively.

Absolute infection risk was highest when *Bi. pfeifferi* were simulated at all temperatures except between 18.5°C and 22.0°C, when absolute infection risk was highest when *Bi. alexandrina* were simulated (Figure 4.8d). Absolute infection risk was lowest when *Bi. glabrata* were simulated at all temperatures below 28.5°C. Above this temperature,

absolute infection risk was lowest when *Bi. alexandrina* were simulated. Compared with when *Bi. pfeifferi* populations were simulated, maximum absolute infection risk was 0.6% higher when *Bi. alexandrina* were simulated and 83% lower when *Bi. glabrata* were simulated.

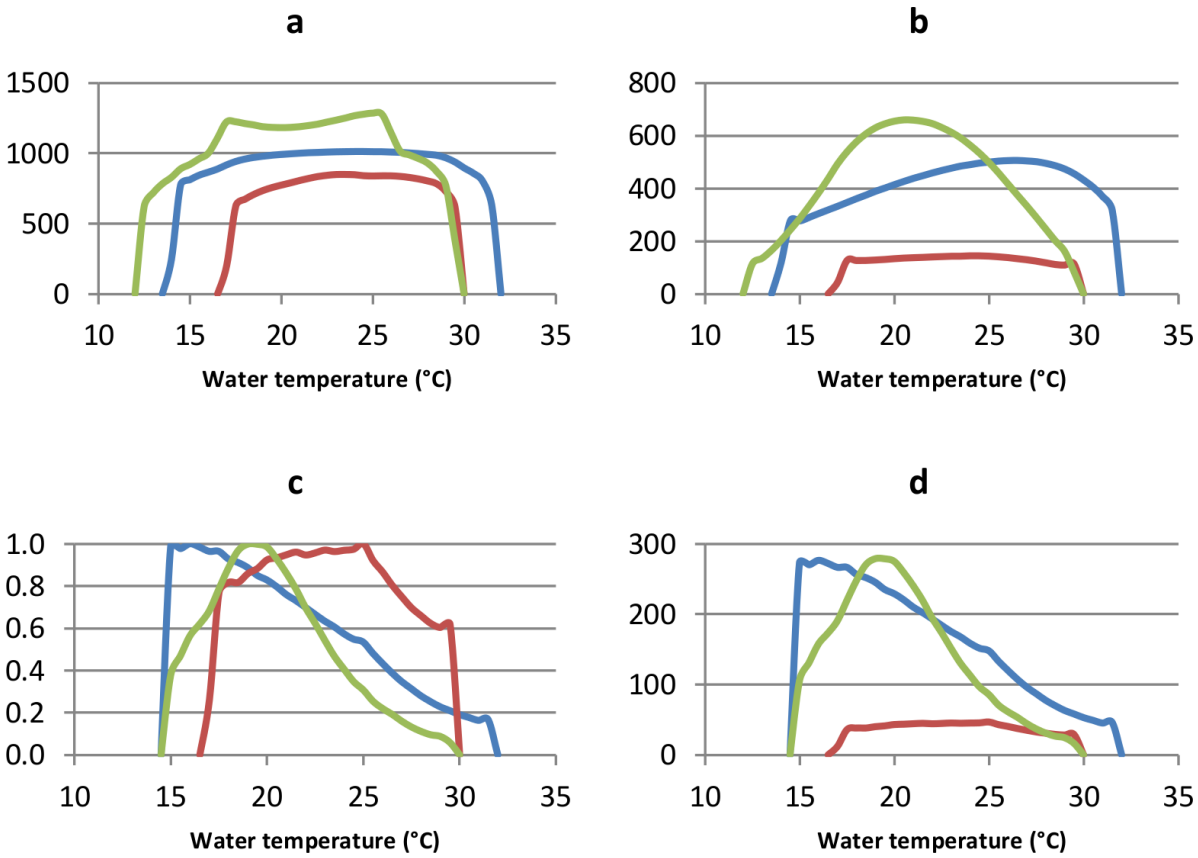

Figure 4.8. Effect of water temperature on the number of snails and adult snails, and relative and absolute infection risk, for different simulated snail species.

a) Mean total number of snails in the model. b) Mean total number of adult snails in the model. c) Infection risk, relative to the maximum risk for the same snail species. d) Absolute infection risk (arbitrary units). Blue lines show *Bi. pfeifferi*, red lines show *Bi. glabrata*, and green lines show *Bi. alexandrina.*

4.3.2 Experiment 2: Effect of diurnal variation in water temperature on *Bi. glabrata* and *Bi. alexandrina* numbers and human infection risk.

4.3.2.1 Snail numbers

Simulating ±2°C diurnal variation in temperature had little effect on either the mean total number of snails in the model (Figure 4.9a) or the mean number of adult snails in the model (Figure 4.9b) for both *Bi. glabrata* and *Bi. alexandrina*. It did, however, increase the minimum temperature at which simulated *Bi. glabrata* populations could survive indefinitely by 0.5°C, and reduced the maximum temperature at which simulated *Bi. alexandrina* populations could survive indefinitely by 0.5°C.

Simulating ±5°C diurnal variation in temperature reduced *Bi. alexandrina* mean total snail population size by up to 24% at temperatures above 23.0°C, and reduced the maximum temperature at which simulated snail populations could survive indefinitely by 0.5°C. It reduced the mean number of adult snails in the model at all temperatures by 12-45%. Simulating ±5°C diurnal variation in temperature reduced *Bi. glabrata* mean total snail population size and the number of adult snails in the model at all temperatures by 3-18% and 7-25% respectively, and increased the minimum and reduced the maximum temperatures at which simulated snail populations could survive indefinitely by 1.5°C.

4.3.2.2 Human infection risk

When *Bi. alexandrina* were modelled, simulating ±2°C and ±5°C diurnal variation in temperature reduced the minimum temperature at which there was a risk of infection in humans by 2.0°C and 2.5°C respectively (Figure 4.9c). Simulating diurnal variation in water temperature had little effect on the relationship between water temperature and infection risk (relative to maximum infection risk in the same scenario) at higher temperatures. Simulating ±2 variation in temperature increased absolute infection risk by up to 22% at temperatures below 22.5°C, and simulating ±5°C variation in temperature reduced absolute infection risk by up to 32% at all temperatures above 16°C (Figure 4.8d).

When *Bi. glabrata* were modelled, simulating ±2°C diurnal variation in temperature had little effect on the relationship between water temperature and infection risk (relative to maximum infection risk in the same scenario). Simulating ±5°C diurnal variation reduced the temperature at which infection risk was highest from 25.0°C to 21.0°C, and caused infection risk to fall more sharply with increasing temperatures. Simulating ±2°C and ±5°C diurnal variation in temperature increased absolute infection risk by up to 31% and 36% respectively at all temperatures at which snail populations could survive, except at 25.0°C where absolute infection risk fell by 1% and 3% respectively. Increases in infection risk were higher at lower temperatures.

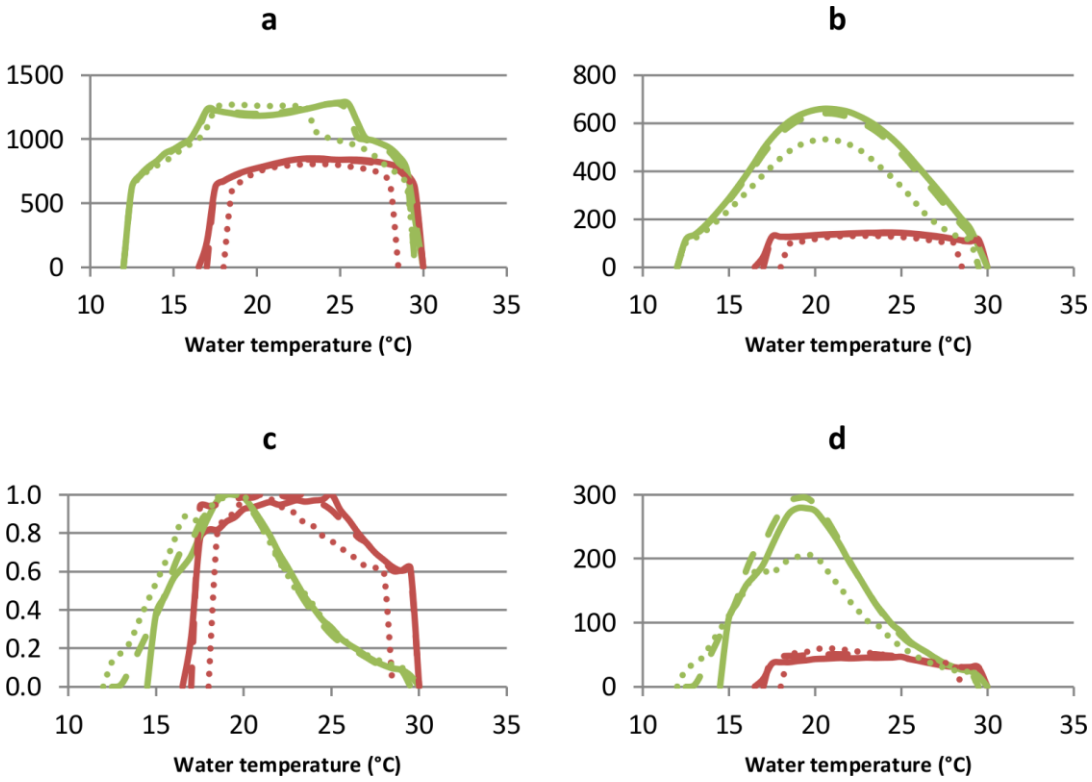

Figure 4.9. Effect of diurnal variation in temperature on the relationship between water temperature and snail population size and human infection risk.

a) Mean total number of snails in the model. b) Mean total number of adult snails in the model. c) Infection risk, relative to the maximum risk for the same snail species with the same amount of diurnal variation in temperature. d) Absolute infection risk (arbitrary units). Red lines show results for *Bi. glabrata* and green lines for *Bi. alexandrina*. Solid lines show results with no diurnal variation in temperature, dashed lines with ±2°C variation, and dotted lines with ±5°C variation.

4.3.3 Experiment 3: Effect of increased mortality rates on snail population dynamics and human infection risk

4.3.3.1 Snail numbers

Doubling snail mortality rates slightly reduced the range of temperatures at which simulated *Bi. pfeifferi* and *Bi. alexandrina* populations could survive indefinitely from 14.0°C-31.5°C to 15.0°C-31.0°C and from 12.5°C-29.5°C to 14°C-28.5°C respectively (Figure 4.10a). Doubling mortality rates had a much greater effect on simulated *Bi. glabrata* populations, reducing the range of temperatures at which they could survive indefinitely from 17.0°C-30.0°C to only 23.0-26.5°C. Doubling mortality rates reduced the maximum mean snail population size by 5% for *Bi. pfeifferi*, 6% for *Bi. alexandrina*, and 29% for *Bi. glabrata.* Reductions in the maximum mean number of adult snails were much larger: 48% for *Bi. pfeifferi*, 42% for *Bi. alexandrina*, and 63% for *Bi. glabrata* (Figure 4.10b).

Simulating higher mortality rates reduced both mean snail and adult snail numbers at all temperatures for all snail species, with the exception of the mean number of *Bi. alexandrina* at 20.5°C to 21.5°C, where snail numbers were 0.09% to 2.03% higher in the higher mortality scenario. This occurred as a result of the density dependence functions used in the model, and would not necessarily occur in wild snail populations. The presence and magnitude of the dip depends on the density functions used.

4.3.3.2 Human infection risk

Doubling snail mortality rates had little effect on the relationship between water temperature and infection risk (relative to maximum infection risk in the same scenario), beyond eliminating infection risk at temperatures at which the snail populations were no longer able to survive indefinitely (Figure 4.10c). It did, however, reduce absolute infection risk within the range of temperatures at which simulated snail populations were able to survive indefinitely by 53-65% for *Bi. pfeifferi*, 58-71% for *Bi. alexandrina* and 58-63% for *Bi. glabrata* (Figure 4.10d).

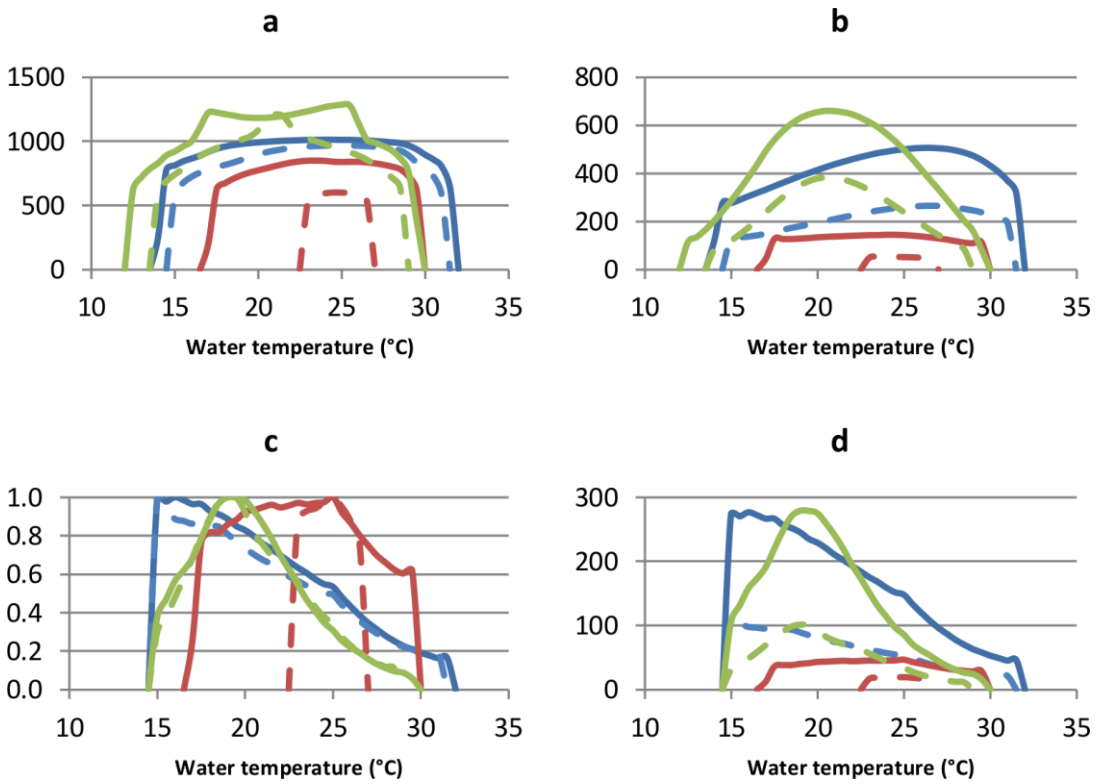

Figure 4.10. Number of snails and adult snails, and relative and absolute infection risk, for different simulated snail species, with high and low snail mortality rates.

a) Mean total number of snails in the model. b) Mean total number of adult snails in the model. c) Infection risk, relative to the maximum risk for the same snail species with the same mortality rates (high or low). d) Absolute infection risk (arbitrary units). Blue lines show *Bi. pfeifferi*, red lines show *Bi. glabrata* and green lines show *Bi. alexandrina*. Solid lines show results with low mortality rates and dashed lines with high mortality rates.

4.4 Discussion

In this chapter, I demonstrate the importance of parameterising mathematical models of water temperature and schistosome transmission to individual species of host snail. The results suggest that *Bi. alexandrina* may be better adapted to slightly cooler water temperatures than *Bi. pfeifferi*, as both the maximum and minimum temperatures at which the simulated populations could survive indefinitely were lower. Simulated *Bi. glabrata* populations could survive indefinitely at a smaller range of temperatures than either *Bi. pfeifferi* or *Bi. alexandrina* populations, and died out at constant temperatures outside

17.0°C to 29.5°C. Simulating diurnal variation of ±5°C reduced the range of temperatures at which simulated *Bi. glabrata* populations could survive indefinitely to only 18.5°C to 28.0°C. Doubling snail mortality rates slightly reduced the range of temperatures at which *Bi. pfeifferi* and *Bi. alexandrina* populations could survive, and slightly reduced mean population size at most temperatures. Doubling mortality rates had a greater effect on *Bi. glabrata*, reducing the range of temperatures at which the population could survive to only 23.0°C to 26.5°C, and reducing maximum population size by 29%.

Compared with when *Bi. pfeifferi* were simulated, infection risk peaked at a slightly higher temperature when *Bi. alexandrina* were simulated (19.0°C compared with 16.5°C), and at a higher temperature still when *Bi. glabrata* were simulated (25.0°C). Doubling mortality rates reduced the temperature at which infection risk peaked to 15.0°C when *Bi. pfeifferi* were simulated, but had no effect on the temperature at which infection risk peaked when *Bi. glabrata* and *Bi. alexandrina* were simulated. Absolute infection risk was lower at most temperatures when *Bi. alexandrina* were simulated, compared with when *Bi. pfeifferi* were simulated, and much lower at all temperatures when *Bi. glabrata* were simulated. Doubling snail mortality rates more than halved absolute infection risk for all three species at all temperatures.

These observations provide support to the idea that it is crucial to consider the species of snail acting as intermediate host(s) in an area when attempting to predict the effects of increasing temperatures on snail numbers and infection risk. They suggest that in many areas where *Bi. pfeifferi* is the main intermediate host for *S. mansoni,* infection risk may fall as temperatures increase. In general, infection risk may also fall in areas where *Bi. alexandrina* is the main intermediate host, although it may increase in areas and/or seasons where mean temperatures are currently below around 19.0°C. Where *Bi. glabrata* is the main intermediate host however, infection risk may increase in a much higher proportion of areas and/or seasons, as the model suggests that infection risk peaks at the much higher constant temperature of 25°C.

The model results also suggests that, all else being equal, infection risk may be lower in areas where *Bi. glabrata* is the intermediate host than in areas where *Bi. pfeifferi* or *Bi. alexandrina* are the intermediate hosts. These results should be interpreted with caution however, for two main reasons. The first is that much of the difference in absolute infection risk is due to the fact that at moderate temperatures simulated *Bi. glabrata* have much higher mortality rates than simulated *Bi. pfeifferi* and *Bi. alexandrina* (Figure 4.6).

Absolute infection risks in the *Bi. glabrata* model with standard mortality rates are much closer to absolute infection risks in the *Bi. pfeifferi* and *Bi. alexandrina* models with mortality rates doubled. The higher mortality rates mean that fewer infected *Bi. glabrata* survive the prepatent period (Figure 4.7c), and that infectious *Bi. glabrata* have a lower median survival time, resulting in them producing far fewer cercariae on average over their lifetime (Figure 4.7d). Mortality rates in the model are estimated from mortality rates in laboratory experiments however, and it is therefore possible that the much higher mortality rates of *Bi. glabrata* were due to different experimental conditions only, and not due to genuine differences between the species.

Secondly, the model does not take into account differences between snail species in susceptibility to *S. mansoni* infection or in cercaria production rates. This is because susceptibility appears to vary as greatly within snail species as it does between species, and there is large variation between individual snails of the same species in cercaria production rates. This should have had no effect on the relationship between water temperature and relative infection risk, and very little effect on numbers of snails, but could have had a large effect on absolute infection risk in the models.

The model was parameterised using the best available data for each snail species. There are a number of limitations of the data used however. Firstly, in the vast majority of the experiments that informed model parameterisation, snails were identified using morphological methods only. This means that it is possible that not all of the data were from the species of snail that they were reported to be from, as there can be discrepancies between the molecular and morphological classification of *Biomphalaria* specimens (Plam, Jørgensen *et al.* 2008).

Secondly, experimental conditions (e.g. snail densities and feeding strategies) will have varied between the different experiments that produced the data used to parameterise the model. The effect of these differences has been minimised by using data from one experiment only to fit each model parameter wherever possible. This means that the overall relationship between water temperature and snail numbers and relative infection risk should not have been affected greatly by the different experimental conditions. Experimental differences may have had a larger effect on absolute snail numbers and infection risk however.

Finally, for a small number of parameters, the data available for *Bi. alexandrina* and *Bi. glabrata* were insufficient for accurate parameterisation. For instance, very few data were available on the duration of the *S. mansoni* prepatent period in *Bi. alexandrina*. In these cases, data from *Bi. pfeifferi* were typically used to help inform model parameterisation. To improve the parameterisation of future models, there is a need for a wider range of experimental studies to be conducted with each species of snail that can act as an intermediate host for human schistosomes. This will allow models of other intermediate host species to be developed, as well as models of *S. haematobium* transmission.

5 Predicting the effects of increasing temperatures on *S. mansoni* transmission in eastern Africa

5.1 Background

It is increasingly recognised that climate change may have large impacts on many aspects of human health. The first assessment report of the Intergovernmental Panel on Climate Change (IPCC), published in 1990 (IPCC 1990), devoted less than four pages to human health. This had increased to an entire chapter by the fourth assessment report, published in 2007 (IPCC 2007). In 2008, the World Health Assembly unanimously adopted a resolution that called on the WHO to strengthen its work on climate change and health, and provided a framework for action for both national governments and the WHO (World Health Assembly 2001).

Diseases with invertebrate vectors or intermediate hosts are one area of health that is likely to be greatly affected by climate change, and changes in the distribution and seasonality of these diseases may be among the first detectable changes in human health (World Health Organization 2003). Indeed there is some evidence that there may have been climate-change driven changes in the transmission of these diseases already. Schistosomiasis transmission now occurs at altitudes above previously defined limits in Uganda (Kabatereine, Brooker *et al.* 2004; Rubaihayo, Moghusu *et al.* 2008), which may be due to higher temperatures. Many studies also suggest a link between increasing temperatures and the spread of malaria in eastern Africa and elsewhere (Patz, Hulme *et al.* 2002; Pascual, Ahumada *et al.* 2006; Chaves and Koenraadt 2010; Cohen, Smith *et al.* 2012), although others dispute this (Mouchet, Manguin *et al.* 1998; Hay, Cox *et al.* 2002; Hay, Rogers *et al.* 2002).

Despite its importance, the implications of climate change for schistosomiasis control and elimination have been largely ignored, and were not mentioned in the WHO's 2012 'Roadmap to implementation' (World Health Organization 2012). This may have been due to a lack of evidence or predictions. Only a few studies have explored the effects of temperature on schistosomiasis transmission (Martens, Jetten *et al.* 1995; Martens, Jetten *et al.* 1997; Mangal, Paterson *et al.* 2008; Zhou, Yang *et al.* 2008; Mas-Coma, Valero *et al.*

2009; Stensgaard, Utzinger *et al.*), and no previous dynamic models have been run using future climate projections. In this chapter, I greatly advance the field by producing, for the first time, high-resolution maps highlighting areas where temperatures may become suitable for increased or decreased transmission, and where schistosomiasis may spread to new areas. I do this using eastern Africa as a case study.

5.2 Methods

5.2.1 Model

The model used in this chapter is described in Chapter 2. To allow schistosomes to become established in the model in new locations, a snail egg was introduced into the model each hour with a probability of 0.00012 (which gives an average rate of one snail egg per model year). As non-temperature-dependent egg mortality is simulated using reduced egg production rates in the model, this is equivalent to a 'real life' egg introduction rate of 10 eggs/year. To reduce model stochasticity, a rate of miracidium introduction of 30/hour was simulated.

5.2.2 Climate projections

An ensemble of regional climate simulations over Africa was used to provide projected daily maximum and minimum temperature data for the eastern African study region. The ensemble consists of three members of the Rossby Centre Regional Climate Model (RCM) - RCA4 (Nikulin, Jones *et al.* 2012) - driven by a coupled atmosphere ocean general circulation model (AOGCM) - EC-EARTH (Hazeleger, Severijns *et al.* 2010). Three sets of climate projections were used, based on RCP2.6, RCP4.5 and RCP8.5. These represent low, moderate and high level of warming respectively. All three regional simulations were made within the African branch of the Coordinated Regional Downscaling Experiment (CORDEX), and have a resolution of around 50km (0.44°). This means that the eastern Africa study region was covered by 1470 (35x42) grid boxes, each with their own projected

temperatures. Climate projections were provided by Grigory Nikulin, Swedish Meteorological and Hydrological Institute.

The mean absolute projected increases in minimum temperatures over the study area over the next 20 years (2026-2035 relative to 2006-2015) were 0.35°C, 0.49°C, and 0.63°C in the low, medium, and high warming projections respectively. The projected increases in maximum temperatures were and 0.33°C, 0.49°C, and 0.68°C. Over the next 50 years (2056-2065 relative to 2006-2035), the mean increases in minimum and maximum temperature were 0.64°C, 1.35°C, and 2.06°C and 0.52°C, 1.25°C, and 1.95°C (Figure 5.1). To prevent confusion, the different climate projections or scenarios are referred to as 'projections' in this thesis, and the term 'scenarios' reserved for the schistosome transmission model scenarios.

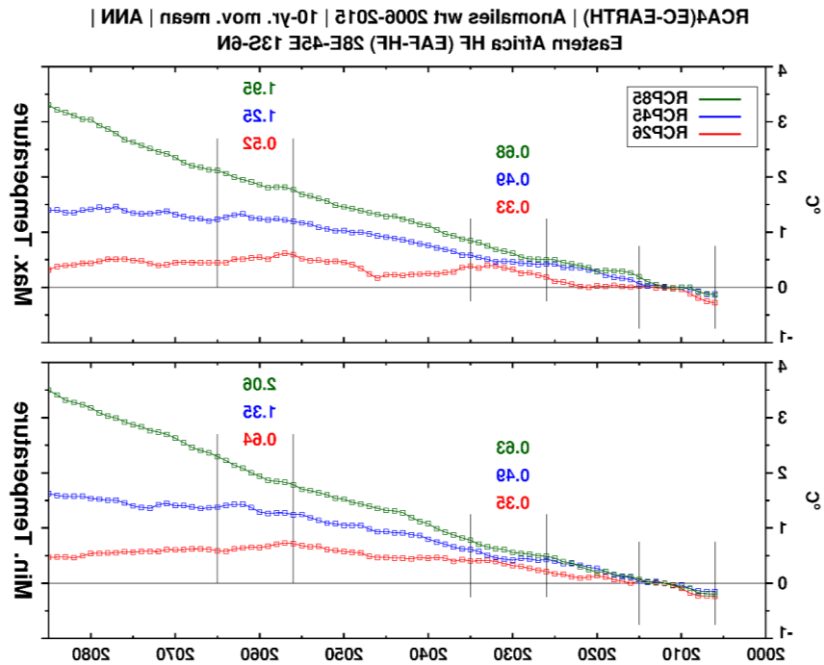

Figure 5.1. Projected changes to daily maximum and minimum temperatures under RCP2.6, RCP4.5 and RCP8.5.

Changes are relative to 2006-2015, are averaged over the eastern Africa study region, and are smoothed using a 10 year moving average. Vertical lines mark 2006-2015, 2026-2035 and 2056-2065. The numbers show the increases in temperature (°C). Figure reproduced with kind permission of Grigory Nikulin, Swedish Meteorological and Hydrological Institute.

5.2.3 Model scenarios

For each set of climate projections, the model was run for eight model scenarios. Four different relationships between air temperature and water temperature were simulated:

1) Daily minimum and maximum water temperatures equal to daily minimum and maximum air temperatures.
2) Minimum and maximum water temperatures 2°C higher.
3) Minimum and maximum water temperatures 2°C lower.
4) Minimum water temperatures 2°C higher, and maximum water temperatures 2°C lower.

These were each simulated using two sets of snail mortality rates: rates estimated from experimental and field data, and double these rates. Therefore, in total, eight model scenarios were simulated for each of three climate projections.

The model was first run using the first two years of the climate projection data (2006-2008) to allow snail numbers to reach plausible initial values. Following this, the model was run using the full climate data between 2006 and 2065. The model was run separately for each of the 1470 grid squares. For each location, the model was run 20 times and the results averaged. Outputs were averaged over each of three 10 year time periods: baseline (2006-2015), 20 years in the future (2026-2035), and 50 years in the future (2056-2065). Kernel interpolation using a fifth order polynomial function was used to produce smooth risk maps for each scenario and time period.

5.2.4 Comparison with empirical prevalence data

Geo-referenced data on the prevalence of *S. mansoni* in human populations in the model output region were extracted from the Global Neglected Tropical Disease (GNTD) database (Hürlimann, Schur *et al.* 2011). For grid squares containing more than one data point, the un-weighted mean of the prevalence estimates was calculated. The mean prevalence for each grid square was then plotted against the mean (across scenarios) model output infection risk for the same square, and the AUC calculated for the ability of the model to predict prevalences of above 0%, 10%, 20% and 50%. AUC is a measure of the

predictive capability of the model, where a value of 0.5 indicates a model that is no better than guessing at random, and 1.0 indicates a perfect model. The analysis was then repeated, restricting the prevalence data to estimates from children, collected from 2004 onwards, and where at least 10 children were tested ('selected data').

5.2.5 Analysis

To facilitate easy interpretation of model results, for each climate projection and future time period, median changes in risk (across model scenarios) were calculated to give a central estimate of the magnitude of changes that may occur. Means were not used as the predicted changes in each scenario were highly skewed in some locations, due to very high relative risks in some areas and scenarios where baseline risks were very low.

The levels of agreement between scenarios in the direction of changes in risk were also explored. For each scenario, climate projection, and future time period, areas were given the value of +1 if risk was predicted to increase from its baseline value, -1 if risk was predicted to decrease, and zero if it was predicted to stay the same. Risk was considered to stay the same if it changed by less than ±10%. The values were then summed over all scenarios for each climate projection and future time period to give an indication of the overall predicted direction of change in risk. For areas where both an increase and a decrease in risk were predicted by one or more scenarios, the number of scenarios that disagreed with the overall predicted direction of change was calculated.

Additional analyses were conducted on each of the model scenarios to explore the possibility of schistosome transmission becoming established at new sites. For these analyses, areas were given the value of +1 if risk was predicted to increase from below to above a cut-off between the two time periods, and zero otherwise. The analysis was conducted for all possible cut-offs between 1% and 99% of the maximum risk in the scenario in any time period, increasing in increments of 1% of the maximum risk. The cut-offs were split into three equal-sized groups (1-33%, 34-66%, and 67-99% of maximum risk), and the mean value was calculated for each group, time period and climate projection.

5.3 Results

5.3.1 Comparison with empirical prevalence data

Prevalence data were available from 2965 records in total, and 594 records when surveys that did not meet the criteria listed above were excluded ('selected data'). Figure 5.2 shows the prevalence data plotted on top of a map of the mean model output infection risk at baseline (2006-2015). The prevalence data gave estimates of prevalence for 19% (279/1470) of grid squares when all data were used, and 7% (100/1470) when selected data were used. Prevalence estimates for each square were calculated from 1-119 (median=4) and 1-37 (median=4) individual estimates when all and selected data were used respectively. When all data were used, 25% of squares with data had a prevalence of zero, 35% had a mean prevalence of >10%, 25% had a mean prevalence of >20%, and 9% had a mean prevalence of >50%. When selected data were used, 34% of squares with data had a prevalence of zero, 22% had a mean prevalence of >10%, 13% had a mean prevalence of >20%, and 4% had a mean prevalence of >50%.

AUC's for the ability of the model to predict prevalences of above 0%, 10%, 20% and 50% ranged from 0.57-0.63 when all data were used, and 0.56-0.76 when selected data were used (Table 5.1). Figure 5.2 shows the mean model output at baseline divided by the maximum model output at any location, plotted against the prevalence data. The mean prevalence is higher than the adjusted model output in 9/279 (3.2%) grid squares when all data were used, and 1/100 (1.0%) grid squares when selected data were used.

	All data (N=279)		Selected data (N=100)	
Prevalence cut-off	**Number above cut-off**	**AUC* (95% CI)**	**Number above cut-off**	**AUC* (95% CI)**
0%	209 (75%)	0.60 (0.52-0.67)	66 (66%)	0.56 (0.45-0.68)
10%	98 (35%)	0.62 (0.55-0.69)	22 (22%)	0.62 (0.47-0.77)
20%	69 (25%)	0.63 (0.56-0.71)	13 (13%)	0.68 (0.50-0.86)
50%	26 (9%)	0.57 (0.46-0.69)	4 (4%)	0.76 (0.39-1.00)

Table 5.1. **Comparison of model output infection risk at baseline (2006-2015) with empirical prevalence estimates.**

***Area under receiver operator characteristic curve

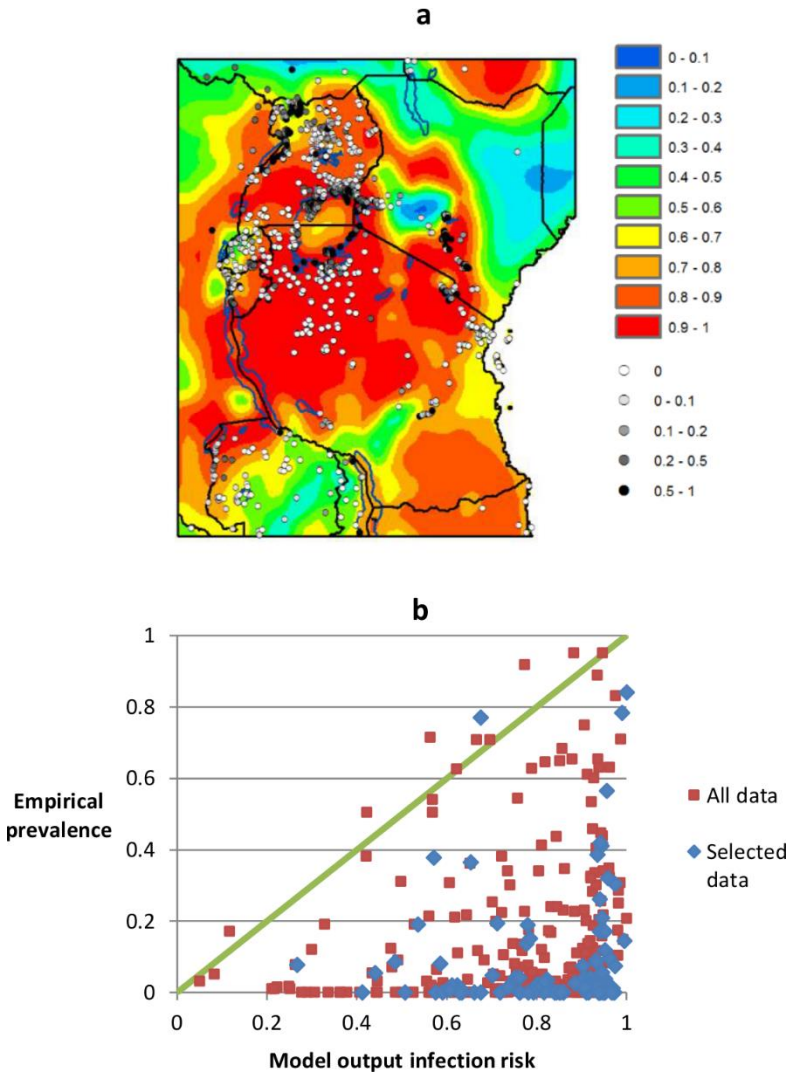

Figure 5.2. Comparison of model output infection risk at baseline (2006-2015) with empirical prevalence estimates.

a) Baseline risk map. Background colour shows the model output infection risk, averaged across scenarios, and translated into proportion of maximum risk. Greyscale circles show empirical prevalence data. b) Model output infection risk plotted against empirical prevalence data. The red squares show mean prevalence for all 279 grid squares for which any prevalence data were available. The blue diamonds show mean prevalence for 100 grid squares for which higher quality and more suitable prevalence data were available. Infection risk has been translated into proportion of maximum infection risk. The green line shows where prevalence and translated infection risk are equal.

5.3.2 Predicted increase in infection risk

Figure 5.3 shows the median predicted change in *S. mansoni* infection risk across scenarios, over the next 20 and 50 years. Figure 5.4 gives an indication of the level of agreement between scenarios in the overall direction of change (increased risk or decreased risk), and the number of scenarios that disagree with the overall direction. There is widespread agreement between scenarios and climate projections that infection risk may increase in Rwanda, Burundi, and eastern Zambia; and over most of Uganda, Tanzania and south-west Kenya over the next 20 years, and that infection risk may decrease in north-east Kenya. A similar picture is found in 50 years' time, with the exception of the high warming scenario where risk is predicted to decrease over larger areas, and where scenarios disagree in the direction of change in risk over much larger areas. In the majority of areas, the median predicted increase in infection risk is less than 20%. In Rwanda, Burundi, south-west Kenya and eastern Zambia however, increases in risk may be greater.

There is widespread agreement between scenarios that infection risk may decrease by more than 50% over the next 20 and 50 years in parts of north and east Kenya, south South Sudan, and east Democratic Republic of Congo. The size of the area over which reductions may occur is larger with higher levels of warming, and in 50 years' time.

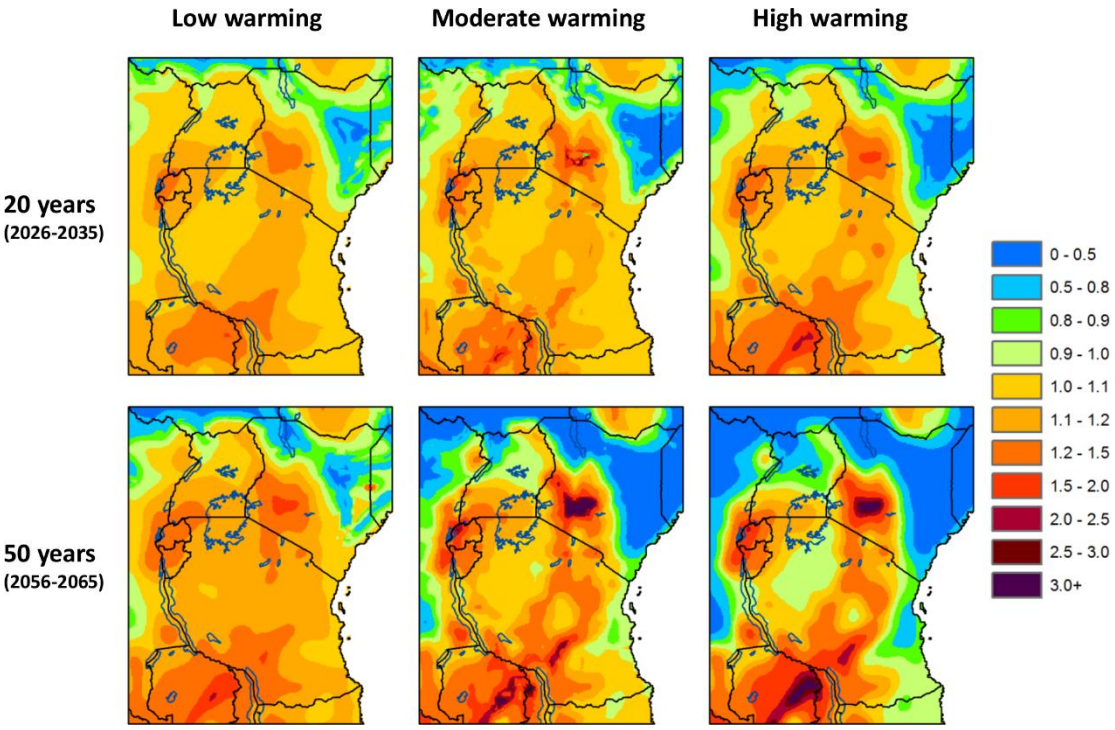

Figure 5.3. Median predicted *S. mansoni* risk in eastern Africa in 2026-2035 and 2056-65, relative to risk in 2006-2015, assuming low, medium, and high levels of warming.

Median is calculated across eight model scenarios for each map.

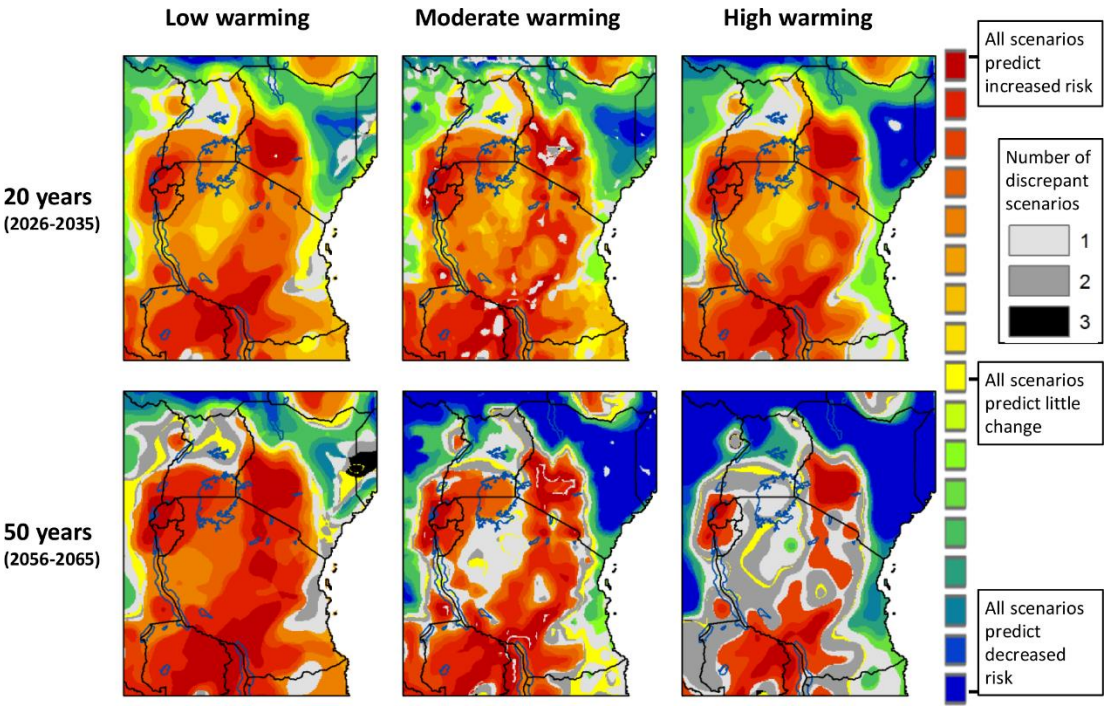

Figure 5.4. Agreement between scenarios in the direction of change in *S. mansoni* risk in eastern Africa over the next 20 and 50 years, assuming low, medium, and high levels of warming. Results are for 2026-35 compared with 2006-2025 (top) and 2056-2065 compared with 2006-2015 (bottom). Areas are shown in yellow if all scenarios agree that increasing temperatures will have little effect on schistosomiasis transmission. Areas are shown in red and blue respectively if there is widespread agreement between scenarios that temperatures will become suitable for increased or decreased schistosomiasis transmission over the next 20 years. Areas are shown in grey if the majority of scenarios predict increasing risk or little change, but one or more scenarios predict decreasing risk, or *vice versa*.

5.3.3 Newly endemic areas and new foci of transmission

Figure 5.5 - Figure 5.7 highlight areas at risk of new transmission foci developing. The maps on the left show areas where the model predicts that cut-offs corresponding to 1-33% of maximum risk will be crossed over the next 20 and 50 years. These cut-offs correspond to temperatures which are suitable for transmission in the model, but not ideal. These cut-offs are therefore most likely to be crossed in areas where both levels of human risk behaviour are high, and where habitats for the snails are good (for instance permanent

habitats with a good supply of food and few predators). The maps on the right show areas where the model predicts that cut-offs corresponding to 67-99% of maximum risk will be crossed. These cut-offs correspond to temperatures which are highly suitable for transmission. Schistosome transmission may therefore newly occur in villages and at potential transmission sites where levels of human risk behaviour are low and/or snail habitats are more marginal.

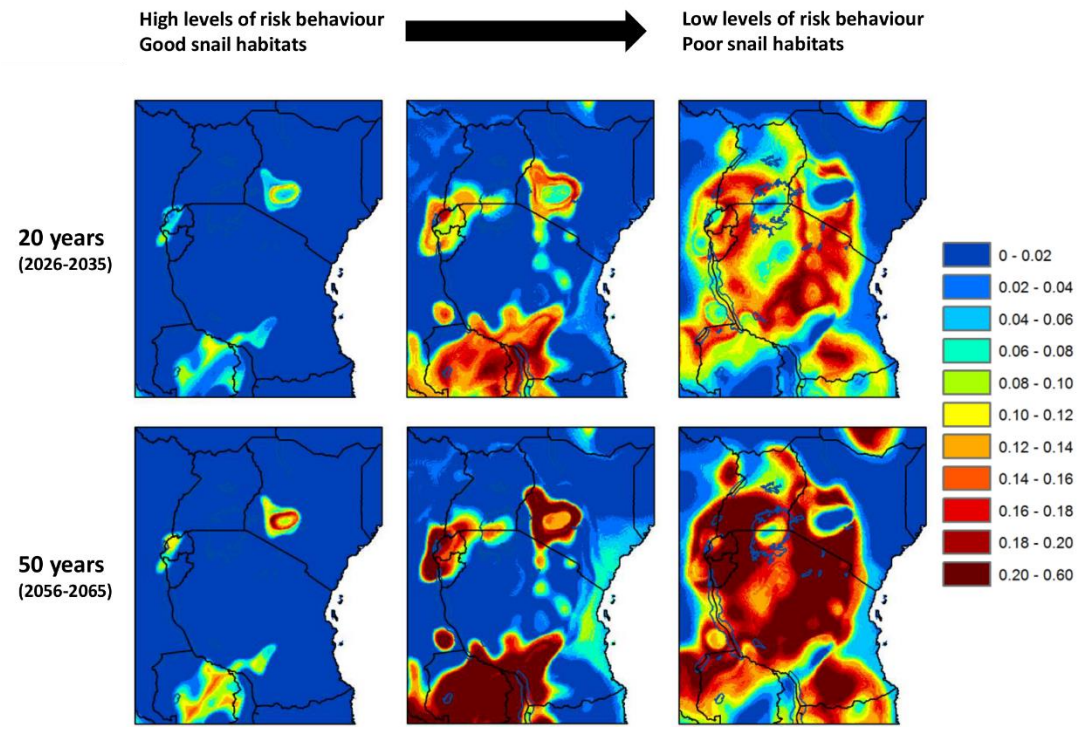

Figure 5.5. Relative risk of new transmission foci developing between 2006-2015 and 2026-2035 (top) and 2056-2065 (bottom) in the low warming scenario.

Blue colours indicate little or no risk. Red colours indicate high risk. The maps on the left show risk in villages with high levels of risk behaviour and good snail habitats. The maps on the right show risk in villages with lower levels of risk behaviour and/or poor snail habitats. The key indicates the proportion of cut-offs that were crossed between baseline and 20 and 50 years' time.

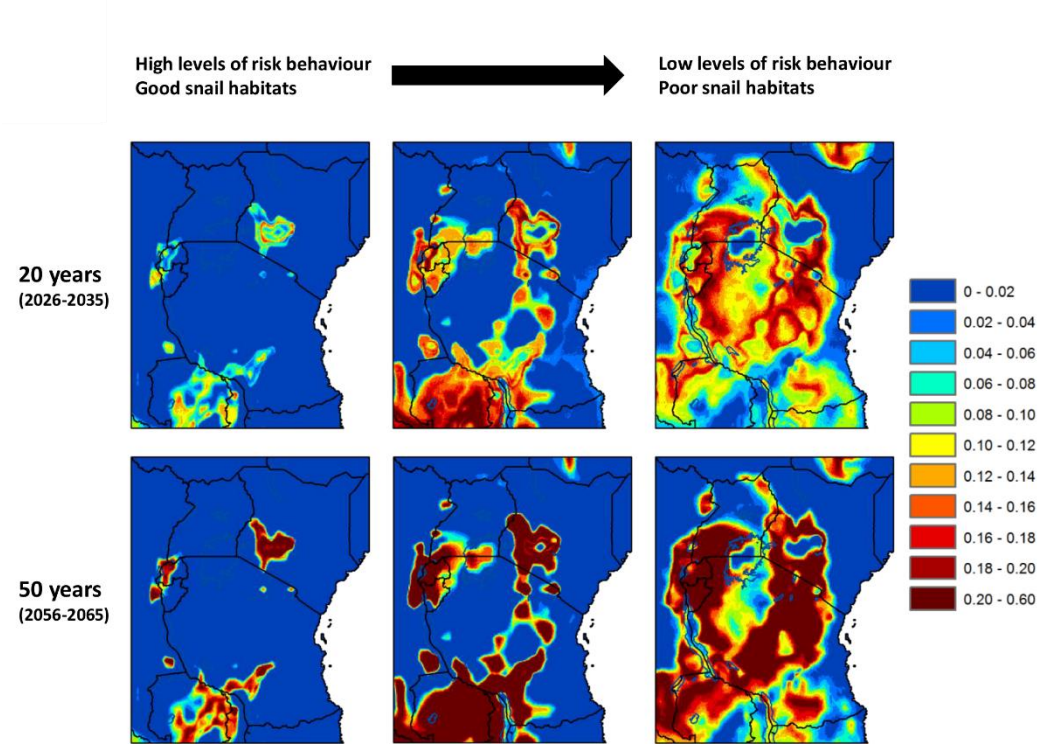

Figure 5.6. Relative risk of new transmission foci developing between 2006-2015 and 2026-2035 (top) and 2056-2065 (bottom) in the moderate warming scenario.

Blue colours indicate little or no risk. Red colours indicate high risk. The maps on the left show risk in villages with high levels of risk behaviour and good snail habitats. The maps on the right show risk in villages with lower levels of risk behaviour and/or poor snail habitats. The key indicates the proportion of cut-offs that were crossed between baseline and 20 and 50 years' time.

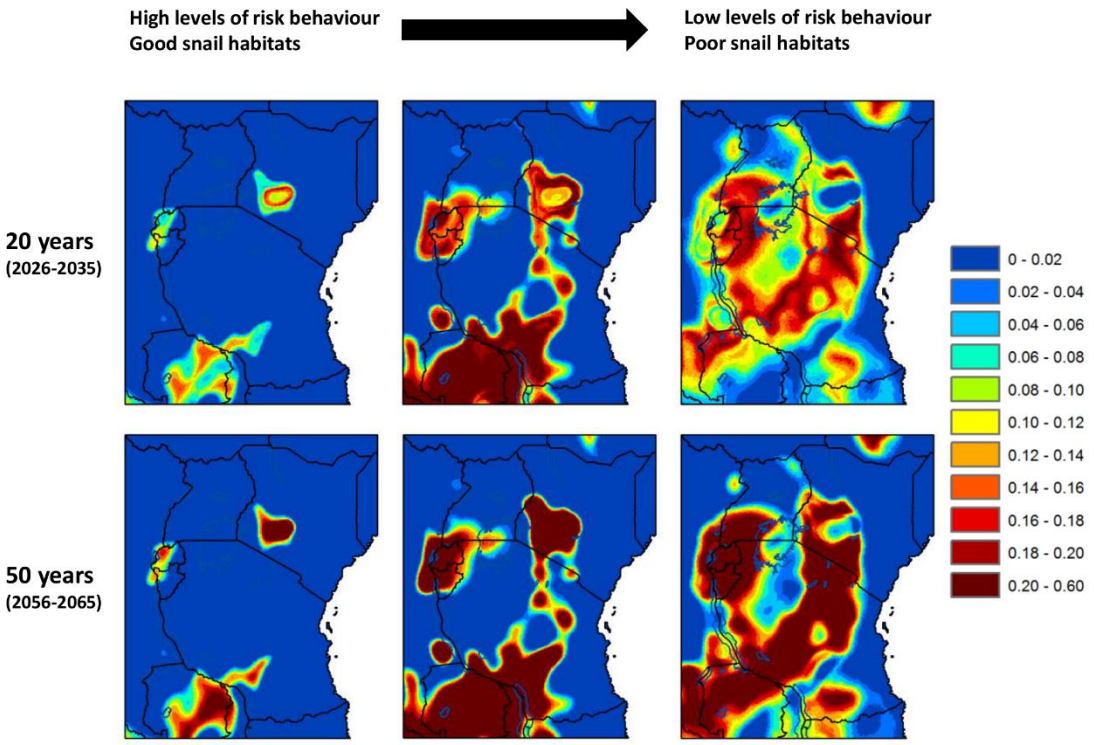

Figure 5.7. Relative risk of new transmission foci developing between 2006-2015 and 2026-2035 (top) and 2056-2065 (bottom) in the high warming scenario.

Blue colours indicate little or no risk. Red colours indicate high risk. The maps on the left show risk in villages with high levels of risk behaviour and good snail habitats. The maps on the right show risk in villages with lower levels of risk behaviour and/or poor snail habitats. The key indicates the proportion of cut-offs that were crossed between baseline and 20 and 50 years' time.

5.4 Discussion

In this chapter, I show that a mathematical modelling approach can be used to generate risk maps highlighting areas where temperatures may become suitable for increased schistosome transmission, and where there is a risk of new endemic areas developing. The results suggest that, all else being equal, *S. mansoni* infection risk may increase across much of eastern Africa as temperatures increase over the next few decades. In most areas, the predicted increases are less than 20%. Increases may be much larger in Rwanda, Burundi, south-west Kenya, and eastern Zambia however. Infection risk may decrease by more than 50% in parts of north and east Kenya, south South Sudan, and east Democratic Republic of Congo. The results also highlight areas where schistosome transmission may occur at new sites. The left hand maps in Figure 5.5 - Figure 5.7 show areas where the model predicts that temperatures are suitable for little or no schistosomiasis transmission at baseline, but will become more suitable over the next 20 and 50 years. These are areas where schistosomiasis may become newly endemic in whole new areas or districts, which are likely to fall outside any current control programs. The right hand maps show areas where temperatures may already be suitable for schistosome transmission, but where infection risk is predicted to increase. Areas highlighted in the right hand maps only may be endemic for schistosomiasis already, however new, small-scale foci of transmission may still develop in these areas.

The results indicate changes in risk that are attributable to increasing temperatures only. Other climatic changes, such as changes in patterns of rainfall, flooding and droughts, will also have an impact on future prevalence (McCreesh and Booth 2013). Similarly, non-climatic changes will play a large role in determining future prevalence and infection intensity. These include changes in land use, water contact behaviour and sanitation. They also include control programs such as mass treatment with praziquantel and snail control. For these reasons, the model results should not be taken as predictive of future schistosomiasis prevalence as such, but instead as indicative of areas where risk may fall even in the absence of effective control, and of areas where control efforts may need to be increased to obtain the same results.

There is considerable variation in the relationships between air and water temperature in different types of water body and in different seasons. Compared with minimum and maximum air temperatures, minimum and maximum water temperatures may be both

higher (Jacobs, Heusinkveld *et al.* 2008; Paaijmans, Jacobs *et al.* 2008), both lower (Jacobs, Heusinkveld *et al.* 2008), or may be higher and lower respectively (Adebisi 1981; Jacobs, Heusinkveld *et al.* 2008). Furthermore, snails may be capable of escaping above optimum water temperatures by moving to deeper water where temperatures may be cooler, or by burrowing in mud (Klumpp, Chu *et al.* 1985). For these reasons, a number of scenarios were simulated, with different relationships between air temperature and water temperature. Scenarios with high and low snail mortality rates explored the effect of differences between different types of habitat further. With the exception of the medium and high warming projections in 50 years' time, there is little disagreement between scenarios in the direction of change in risk, suggesting that the model results are robust to variations between snail habitats. The eight scenarios also act as a form of sensitivity analysis, as shifting temperatures and keeping snail and parasite temperature preferences constant is equivalent to keeping the temperatures constant but altering model parameterisation.

Validation of the model is challenging, as the model produces an estimate of the contribution of temperature to infection risk, and the only data that are available to validate it against are empirical prevalence data. These prevalences may have been affected by local temperatures, but will also have been affected by a range of other factors including the presence or absence of suitable snail habitats, water contact behaviour, and sanitation. In addition, the prevalence data were collected for a wide range of different purposes, at different times, in different age groups, using different sampling methods, and using different tests with widely varying sensitivities. Locations where temperatures were believed to be unsuitable for schistosomiasis may have been under-sampled, and these are the areas where the model output could be expected to correspond most closely to the prevalence data. Nevertheless, a comparison of model output at baseline with prevalence data gives AUC's of around 0.6 (Table 5.1), which suggests that temperatures do play some role in determining empirical prevalence (and that the model is able to capture that role), but that other factors are also important. Figure 5.2 shows clearly that zero or low prevalences of schistosomiasis can occur in any area, regardless of temperatures, but that higher prevalences only occur in areas where temperatures are suitable for higher levels of transmission. In other words, suitable temperatures are necessary but not sufficient for both schistosome transmission, and for high prevalences of schistosomiasis.

Snail eggs are introduced into the model at an average rate of one a year. This is necessary to allow simulated snail populations to become established in areas where conditions

become newly suitable. In real snail populations, this may occur through movement of snails from interconnected water bodies or during flooding (Wu, Zhang *et al.* 2008), or through live snails being transported short distances on objects such as fishing nets. These events are all extremely stochastic, and the 'newly endemic' model results should therefore be taken to indicate areas that may become newly suitable for the establishment of schistosome transmission only, and not as a definite guide to the spread of schistosomiasis. The exception to this is cooler areas where snails are found but schistosome transmission does not currently occur, where new transmission foci could quickly become established.

Taking regional climate simulations made by only one regional climate model, downscaling one global circulation model (under different RCPs) is not enough to assess the full range of uncertainties in future climate projections. However, the main focus of this study is to provide a range of plausible future changes in schistosomiasis risk, suitable for public health planning purposes, and to explore the effect of uncertainties associated with the transmission model and its parameterisation. Using a wider range of different climate projections (from different RCMs downscaling different AOGCMs) is unlikely to have any real effect on the public health consequences of the findings. As the main focus of the study was the transmission modelling, there was also no bias correction applied to the RCM data.

To maximise the potential utility of my results for public health purposes, I used 10 year time periods for the analysis: 2006-2015 (reference), 2026-2035 and 2056-2065. Using 10 year time periods can lead to errors if natural multi-decadal variability is attributed to the global warming signal. However I do not believe that this was the case for my study, as climate projections for daily maximum and minimum temperatures in eastern Africa averaged over 10 years were robust and consistent across the three RCP trajectories (Figure 5.1).

The model is parameterised using data from *Bi. pfeifferi* snails. These are the most widespread intermediate host snail species in sub-Saharan Africa (Stensgaard, Utzinger *et al.* 2013). Other species of host snail are found at many transmission sites however, and as I show in Chapter 4, the species of snail used in parameterising a model can have a large effect on the relationship between water temperature and infection risk. Simulating different relationships between air temperature and water temperature goes some way towards testing the sensitivity of the model to the choice of snail species, as the higher and

lower simulated temperatures could also be viewed as alterations in minimum, maximum, and optimum temperatures for snail survival and reproduction. The widespread agreement between scenarios therefore suggests that the model is not very sensitive to small differences in temperature preferences between snail species. Nevertheless, experimental work with the different species of intermediate host snail found in eastern Africa would increase confidence in the model results by allowing the model to be explicitly parameterised to other species of snail.

6 Discussion

The overall aims of this thesis were to use mathematical modelling to investigate the effects of water temperature on *Biomphalaria* population dynamics and *S. mansoni* transmission, and to develop a model that can be used to inform policy makers of the potential effects of climate change on schistosome transmission.

In Chapter 2, I describe the structure of the model, and the data and the techniques used to parameterise it to *S. mansoni* and *Bi. pfeifferi*. I also discuss the advantages and limitations of both the model structure and the data.

In Chapter 3, I explore in detail the dynamics of the model structure. I show that when constant temperatures are simulated, human infection risk is highest at 16°C, and that simulated *Bi. pfeifferi* snail populations cannot survive at temperatures outside 14.0-31.5°C. Simulating diurnal variation in temperature of ±5°C increased the temperature at which infection risk was highest to 18°C. The type of water body may be an important modifier of the relationship between temperature and infection risk. Approximating conditions in flowing water, by simulating additional temperature-independent miracidium and cercaria mortality rates, increased the temperature at which infection risk was highest. Simulating a temperature gradient, such as that found in deeper water bodies, allowed the snail population to survive and transmission to occur at temperatures as high as 35.5°C.

In Chapter 4, I demonstrate the importance of parameterising dynamical models of water temperature and schistosome transmission using data from a single species of intermediate host snail. Simulating *Bi. alexandrina* and *Bi. glabrata* increased the temperature at which infection risk was highest in the model by 3.5°C and 8.5°C respectively, to 19.0°C and 25.0°C.

Finally, in Chapter 5, I describe the results from running my model using climate projections for eastern Africa over the next 20 and 50 years. I show that temperatures may become suitable for increased transmission over much of the region over coming decades, and highlight areas at risk of becoming newly endemic.

6.1 Model structure

In my thesis, I describe a new dynamical model of water temperature and schistosome and intermediate snail host lifecycles. There are four main features of the model that distinguish it from previous models, resulting in a greater understanding of snail and schistosome population dynamics, and improved predictions of the effects of climate change on *S. mansoni* transmission:

1) My model uses an agent-based approach, which allows it to track individual attributes of each snail and schistosome stage. This increases model accuracy when realistic, diurnally and seasonally fluctuating temperatures regimens are simulated, when the temperatures experienced by agents born or created only short periods of time apart may be very different.
2) The model has a time-step of only one hour. This allows the short-living miracidia and cercariae to be explicitly simulated, and their temperature-dependent production, mortality, and infectivity rates to be accurately incorporated. It also allows me to run the model using diurnally fluctuating temperatures, as opposed to using mean daily temperatures which introduce model error when non-linear relationships exist between water temperature and model parameters.
3) The model is parameterised separately to different individual species of intermediate host snail. In particular, the main version of the model (described in Chapter 2) is parameterised using data from *Bi. pfeifferi*, the most widespread intermediate host species in sub-Saharan Africa. The importance of this is demonstrated in Chapter 4.
4) The model is designed to be run using actual climate projections, over defined geographical areas. This allows risk maps to be produced, highlighting areas where temperatures may become more or less suitable for schistosome transmission, or where temperatures may become newly suitable. This step is crucial if model predictions of the effects of climate change on schistosomiasis are to be used to inform policy and the design of control programs.

6.2 Uncertainties in model parameterisation and predictions

There are a number of sources of uncertainty in the data that were used to parameterise the model. For the main model, data that were used came from experiments on *Bi. pfeifferi* wherever possible, however a lack of suitable data meant that data from other species of *Biomphalaria* were used for a small number of parameters. In addition, in the majority of experiments, snails were identified using morphological methods only, and in many cases data were presented solely in graphical form. These issues are discussed in Section 2.3. For many parameters, data were available from one study only. For parameters where data were available from multiple different experiments, there were often substantial differences between experiments in observed rates. For this reason, absolute results (e.g. the proportion of snails that are infectious at 20°C in the model) should be considered as less reliable than relative results (e.g. the proportion of snails that are infectious at 20°C, relative to at 25°C), and results are therefore given as relative results throughout this thesis. This issue is discussed further in Section 4.4.

An additional source of uncertainty is introduced by the limited range of different temperatures at which most empirical experiments which informed model parameterisation were conducted. Only parameterising the model to the very small number of temperatures for which a good range of data were available would have greatly limited the potential applications of the model, preventing the simulation of diurnally varying temperatures, and preventing the model from being run using climate projections. For this reason, parameter values were estimated for all real temperatures. This was done by fitting a range of different relationships (e.g. linear or quadratic) through the available data points. For some parameters, data were available at many temperatures, and a high level of confidence can be placed in the shape of the fitted relationship (e.g. egg development rates, Section 2.2.3.3.). For other parameters, data were sparser and the fitted relationships may be less reliable (e.g. infectious snail mortality rates, Section 2.2.3.4). Inaccuracies in measured temperatures, and temperatures which fluctuated around the stated mean temperatures, may have further reduced the reliability of fitted relationships.

The effect of uncertainties in model parameterisation is to introduce uncertainty into model results. These are explored to some degree in the sensitivity analyses conducted in Chapters 3-5. In Chapter 3, the effects of simulating different miracidium and cercaria

mortality rates, and different density dependence functions, were investigated. In Chapter 4, the effects of increasing snail mortality rates for each simulated snail species were determined. Finally, in Chapter 5, the different simulated snail mortality rates and different simulated relationships between air and water temperature act as a sensitivity analysis (see Section 5.4). A more comprehensive sensitivity analysis was not conducted for two reasons. The first is that estimates of variance were not given for many of the data used in model parameterisation, preventing the accurate calculation of distributions from which to sample parameter values. The second is that, while there were a number of important advantages to using an agent-based model approach (see Section 2.3), agent-based models are often computationally intensive, preventing a comprehensive sensitivity analysis.

The sensitivity analyses conducted in Chapters 3-5 give an indication of the effects that uncertainties in the data may have had on model results. Simulating different miracidium and cercaria mortality rates, in additional to different degrees of diurnal variation in temperature, had a substantial effect on the estimated temperature at which human infection risk was highest. In the different simulated scenarios, the estimated optimum temperatures for transmission ranged from 16.5°C to 25.0°C. In reality, there will not be a single optimum temperature at all transmission sites, with the optimum temperature depending on a range of factors including the type of water body, and the evolutionary history of the snail population. For most transmission sites, it is probable that the optimum temperature for transmission falls within the range estimated in the different scenarios.

Six different model scenarios were simulated in Chapter 5, with different relationships between air and water temperatures, and different snail mortality rates. As Figure 5.4 shows, there was substantial agreement between the different scenarios in the direction of change in risk in 20 and 50 years' time with low and moderate levels of warming, and in 20 years' time with high levels of warming. While the main purpose of the different scenarios was to explore the effect of different habitat types on the predicted effects of increasing temperatures on *S. mansoni* transmission, they also act as a form of sensitivity analysis. They demonstrate that uncertainties in the data used to inform model parameterisation are likely to have had little effect on predictions of the effects of climate change on *S. mansoni* transmission in eastern Africa.

6.3 Comparison of model results using diurnally varying temperatures and climate projections

There is an apparent contradiction between the relationship between water temperature and infection risk when the model is run using constant temperatures (Chapter 3), and the predicted changes in the suitability of temperatures for *S. mansoni* in eastern Africa (Chapter 5). When run using constant temperatures, human infection risk is highest (above 90% of its maximum) between temperatures of around 15.0-19.0°C. Simulating ±5°C diurnal variation in temperature increases the temperatures at which risk is highest to 17.5-20.0°C. These temperatures are low in comparison to mean temperatures in parts of eastern Africa, with mean temperatures ranging from 19-24°C over much of the region (Glunt, Blanford *et al.* 2013). It may therefore be supposed that increasing temperatures would decrease risk over much of the region. Minimum night time temperatures can be much lower than mean temperatures however, and there is a sharp drop in the suitability of temperatures for *S. mansoni* transmission as temperatures drop below optimum. Even occasional, seasonal drops in night time temperature to below around 15°C can have a large effect on overall infection risk. These drops in temperature are predicted to decrease over coming decades, contributing to the overall predicted increase in risk over much of the region.

6.4 Predicting the effects of climate change on schistosomiasis prevalence and mean intensity of infection

The output of the model is something I refer to as 'infection risk'. It is calculated as the number of cercariae in the model, adjusted for their decreasing probability of successfully causing infection with increasing age. It can be viewed as a measure of the relative suitability of temperatures for *S. mansoni* transmission to humans.

In producing risk maps for *S. mansoni* transmission in eastern Africa, I do not attempt to translate infection risk into estimates of schistosomiasis prevalence or infection intensity. This is because the relationship between the model output infection risk and prevalence and infection intensity will vary depending on human behaviour, such as water contact and

sanitation behaviour. These behaviours can vary greatly, even on a very small scale. For instance, in a single village on the shores of Lake Albert, adult men from the Bagungu ethnic group were observed to spend a mean of 251 minutes in contact with the lake water over the course of around 10 months, compared with a mean of 31 minutes for Alur men (Pinot de Moira 2008). The two ethnic groups lived at separate ends of the village, and the majority of water contact occurred near to people's residences. Assuming that defaecation also mostly occurred near to people's homes, then the village contained two largely isolated transmission cycles. This resulted in very different prevalences of infection in Bagungu and Alur (prevalences of 58% and 30% respectively in adult men 12 months after treatment), despite almost identical water temperatures. This kind of detailed information on human behaviour is only available from a limited number of sites, preventing the translation of infection risk into prevalence or infection intensity over a wide area.

Due to the difficulties of translating infection risk at any particular time point into more directly interpretable measures, I present my results as future risk relative to estimated risk during a baseline period. Assuming no non-climatic changes such as changes in sanitation or mass treatment coverage, a doubling of infection risk would lead roughly to a doubling of mean infection intensity. Feedback between increased levels of human infection and a higher rate of miracidium introduction (which is explored in Chapter 3) could potentially lead to mean intensity of infection being more than doubled with a doubling of infection risk. On the other hand, increased immunity with higher burdens of infection could potentially lead to lower increases in mean infection intensity. In general, a doubling in infection risk would result in smaller increases in prevalence, particularly in areas with higher baseline prevalences, due to the non-linear relationship between mean worm burdens and prevalence (De Vlas and Gryseels 1992).

6.5 Climate-driven changes to snail habitats and ecosystems

Biomphalaria and *Bulinus* snail populations do not exist in isolation, but as part of complex ecosystems. Changes in water temperature will not only affect the snail populations directly, but also indirectly, through changes to their wider ecosystems. This includes food sources, predators, and other parasites (in addition to *Schistosoma*). It also includes other

snail species, which may compete with *Biomphalaria* and *Bulinus* snails for food or egg laying surfaces, or may act as 'miracidium sponges' – attracting *Schistosoma* miracidia away from snails that are capable of acting as intermediate host (Laracuente, Brown *et al.* 1979).

Biomphalaria and *Bulinus* snails feed on decaying macrophyte tissue, colonial diatoms and smaller green algae (Thomas, Nwanko *et al.* 1985). Much of the work that has been conducted into the potential effects of climate change on freshwater phytoplankton has focused on cyanobacteria, due to their toxicity to humans (Elliott 2012). Optimum temperatures for the growth of the majority of cyanobacterium species are higher than the optimum temperatures for most other algae groups, and it is predicted that their relative abundance will increase in many water bodies as temperatures rise (Haande, Rohrlack *et al.* 2011; Elliott 2012). Cyanobacterium blooms have been observed in a wide range of African water bodies, and in some cases it has been suggested that their appearance or growth may be partially attributable to climate change (Haande, Rohrlack *et al.* 2011; Muir and Perissinotto 2011; Krienitz, Dadheech *et al.* 2013; du Plooy, Smit *et al.* 2014). It is unclear what effect an increase in the relative abundance of cyanobacteria will have on *Biomphalaria* and *Bulinus* snails. *Nostoc* sp. of cyanobacterium are non-toxic to *Biomphalaria*, and can be used as a food source for rearing juvenile snails in a laboratory (Vasta, LeSage *et al.* 2011). On the other hand, toxins from some cyanobacteria are being considered as potential molluscicides (Pereira, Etzbach *et al.* 2011), and 5/86 extracts from cyanobacterium investigated in one study were found to be harmful to *Biomphalaria glabrata* (Jaki, Orjala et al. 1999). The effects on *Biomphalaria* and *Bulinus* populations of climate-change driven changes to phytoplankton communities are therefore likely to depend on the species of cyanobacterium found in a water body.

S. mansoni and *S. haematobium* are not the only parasites of *Biomphalaria* and *Bulinus* snails. One study in Benin found *Bulinus* snails infected with non-*Schistosoma* furcocercariae, lophocercariae, and xiphidiocercariae parasites (Ibikounlé, Mouahid *et al.* 2009). *Biomphalaria* and *Bulinus* snails also act as intermediate host for a number of species of *Echinostoma* (Huffman and Fried 2012). As some species of *Echinostoma* are of medical or veterinary importance, they are better studied than many other species of snail parasites, however data on the effects of temperature on *Echinostoma* infections of snails are still sparse. One study suggested that the transmission efficiency of *E. recurvatum* was highest at temperatures between 15-25°C (McCarthy 1999). Another found that the effects of increasing swimming speed and decreasing lifespan with increasing temperatures largely

cancelled out for *E. caproni* cercariae, resulting in temperature having little effect on infectivity (Meyrowitsch, Christensen *et al.* 1991).

In practice, the presence of other parasites is only likely to have much effect on the overall relationship between increasing temperatures and *S. mansoni* transmission if the prevalence of the other parasites is high, or if a substantial proportion of *S. mansoni* infected snails are co-infected with other parasites. In general, the prevalence of (detectable) parasite infections is low in wild *Biomphalaria* and *Bulinus* populations (<10%), however co-infections may be more common than would be expected by chance (Wright, Rollinson *et al.* 1979; Loker, Moyo *et al.* 1981; Hussein and Bin-Dajem 2008). *S. mansoni* and *Echinostoma* co-infected *Biomphalaria* have been shown to release fewer, less infectious *S. mansoni* cercaria than snails with *S. mansoni* infections only (Jourdane, Mounkassa *et al.* 1990; Sandland, Rodgers *et al.* 2007). If rising temperatures increase the prevalence of co-infections in snails, then increases in human infection risk with increasing temperatures may be overestimated. Conversely, if rising temperatures decrease the prevalence of co-infections, then increases in human infection risk may be underestimated.

Biomphalaria and *Bulinus* snails are eaten by a wide range of different predator species, which includes fish, insects, crustaceans, and other snails (Demian and Lutfy 1966; McKaye, Stauffer *et al.* 1986; Armúa de Reyes and Estévez 2006; Savaya Alkalay, Rosen *et al.* 2014). The range and abundance of many of these species may be affected by climate change over coming decades, reducing or increasing the predation pressure on *Biomphalaria* and *Bulinus* populations in different water bodies. In the case of certain predators, increasing temperatures may even affect the rate at which they consume snails. The rate at which *Marisa cornuarie* snails fed on *Bu. truncatus* in a laboratory setting increased with increasing temperatures up to 30°C, before decreasing slightly (Demian and Lutfy 1966). Like the effects of climate-change driven changes to phytoplankton communities, the effects of climate-driven changes to predator populations on *Biomphalaria* and *Bulinus* snails are likely to depend on the species of predators found in a water body, with increasing temperatures resulting in a higher levels of predation in some water bodies, and lower levels in others.

Changes in water temperatures may also affect other abiotic properties of the water, which in turn may have an effect on the snails or *Schistosoma* miracidia and cercariae. The direct effects of this are likely to be minimal, as differences in the chemical contents of water bodies appear to have little effect on snail populations (Brown 1994). The exception to this

is calcium concentrations (see Section 1.3.4), however water temperature has only a small effect on calcium carbonate solubility within the range of temperatures suitable for snail populations (Coto, Martos *et al.* 2012). Indirect effects of changes in the abiotic properties may be larger if other species in the snails' ecosystems are more sensitive to water chemical content.

Some or all of these factors may alter the relationship between increasing temperatures and changes in the suitability of a water contact site for *Schistosoma* transmission. It is uncertain what effect they will have, and the effect is likely to be different in different water bodies.

6.6 Predicting the effects of changes in precipitation and extreme climatic events on *S. mansoni* transmission

In addition to increasing temperatures, patterns of precipitation and extreme climatic events are predicted to change over coming decades (Stocker, Qin *et al.* 2013). These changes are likely to have an impact on the distribution and intensity of *S. mansoni* transmission, however their impact may be difficult to predict. Figure 6.1 summarises the most likely effects of different climatic changes on the distribution and intensity of schistosomiasis.

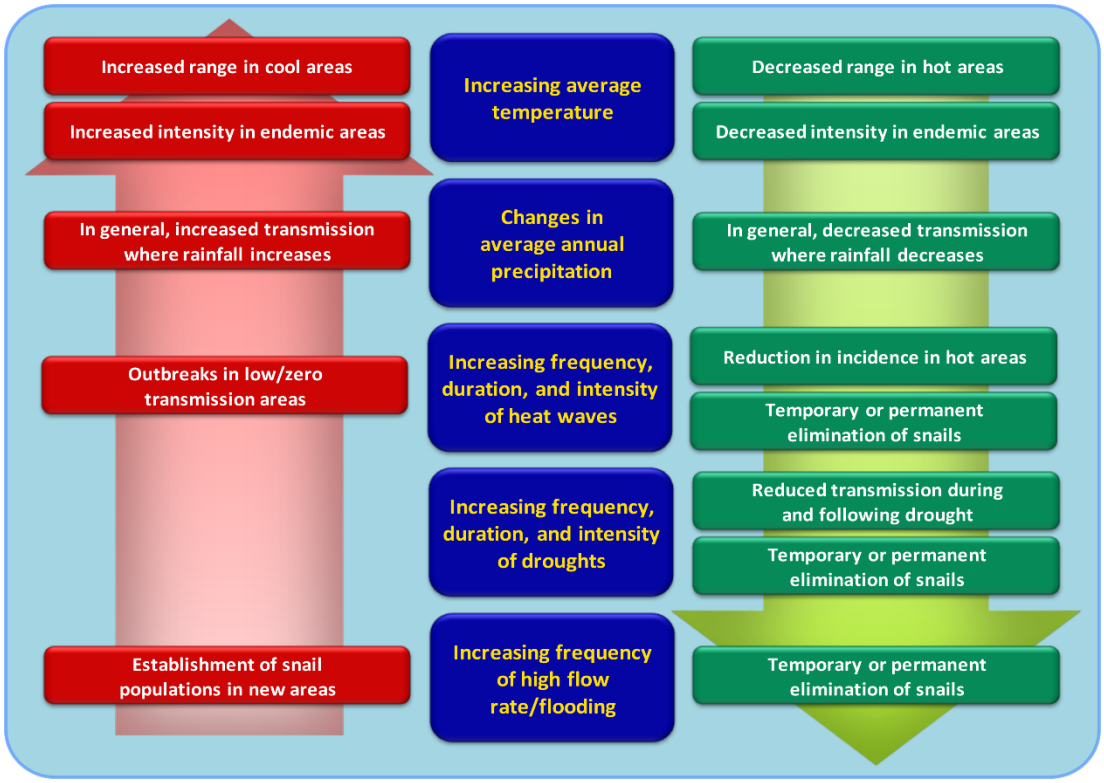

Figure 6.1. Potential effects of climate change on schistosomiasis and schistosome intermediate host snails.

The flow chart summarises the most likely effects of projected climate changes on the ecology of intermediate host snails and schistosome transmission. The central column lists climate change events. The left and right hand columns relate each climate event to the natural history of schistosomiasis. The left hand column corresponds to increased transmission potential, and the right hand column to decreased transmission potential.

6.6.1 Precipitation

It is more difficult to predict the effect of changes in rainfall on schistosomiasis transmission than it is to predict the effect of changes in temperature. Statistical models of the distributions of five *Biomphalaria* species in Africa did not find any precipitation variable to be an important predictor of distribution for any of the species (Stensgaard, Utzinger *et al.* 2013). This does not necessarily mean that precipitation does not have a large effect on schistosomiasis transmission. The lack of a strong Africa-wide relationship in the statistical models may indicate that the relationship between rainfall and snail

abundance is different in different habitats. For instance, the amount and seasonality of rainfall may be much more important for snails living in temporary water bodies than for snails living in permanent lakes. Both this and the geographical variation and uncertainty in predictions of future precipitation are likely to impede the development of any large scale models of precipitation change and schistosomiasis (see also section 6.7). The difficulties are likely to be further increased by the gaps in our knowledge of the different ecological requirement of different snail species.

Stronger relationships between precipitation and snail numbers or schistosomiasis prevalence have been found by studies looking at smaller geographical areas, and it may therefore be simpler to predict the effect of changes in rainfall on schistosomiasis in these areas. Kabatereine *et al.* found that little or no *S. mansoni* transmission occurred in Uganda in areas where total annual rainfall was less than 900mm (Kabatereine, Brooker *et al.* 2004). Increased rainfall may therefore increase the range of schistosomiasis in Uganda, and decreased rainfall may decrease it. In Bahia State, Brazil, a significant negative relationship was found between the length of the dry period and the prevalence of *S. mansoni* in a municipality (Bavia, Hale *et al.* 1999). The projected increased risk of extended periods with little rainfall may therefore mean that schistosomiasis risk is reduced in the area (Stocker, Qin *et al.* 2013).

Negative relationships have also been found between rainfall and schistosomiasis transmission. In an irrigated agricultural region in Ethiopia, researchers found a significant negative correlation between monthly precipitation volume and the number of patients seeking treatment for *S. mansoni* at lags of one and two months (Xue, Gebremichael *et al.* 2011). They suggest that this may be caused by intense rainfall causing fast flowing water which kills cercariae, and/or by intense rainfall lowering the water temperature and interrupting the optimal infective conditions for cercariae. It may also be caused by the rainfall having a negative impact on the snail populations. In Lake Victoria, Uganda snail numbers are lowest during the middle of the rainy season. This is most likely due to high water velocities along the lakeshore when rainfall is intense (Odongo-Aginya, Kironde *et al.* 2008). If this explanation is correct, then snail numbers may fall in the future at the two sites as rainfall events become more intense.

In addition to affecting snail populations, changes in rainfall may affect the proportion of schistosome eggs that enter a water body. Because of this, Liang *et al* included seasonal variation in rainfall in their mathematical model of *S. japonicum* transmission in China, with

the amount of rainfall determining the proportion of schistosome eggs that entered the model's aquatic component (Liang, Maszle *et al.* 2002). How much effect changes in rainfall will have on numbers of schistosome eggs entering water bodies will vary locally, depending on factors such as sanitation practices.

6.6.2 Heat waves

The frequency, duration and intensity of heat waves are predicted to increase over coming decades (Stocker, Qin *et al.* 2013). The effect of heat waves on schistosomiasis transmission in an area will depend on where more typical maximum water temperatures are in relation to the optimum temperatures for the snail hosts and parasite. In areas that are normally well above the optimum temperature, schistosomiasis incidence may be greatly reduced both while the heat wave is ongoing and for some time afterwards. Sufficiently long or hot heat waves may even temporarily or permanently eliminate the host snails from the area, particularly if additional snail control measures are implemented while the snail population is vulnerable.

In colder areas, heat waves could potentially increase the transmission potential of the schistosome parasite, and the incidence of schistosomiasis. This may result in outbreaks occurring in areas which normally experience little transmission. In areas that are normally too cold for the parasite to develop, but where suitable host snails are found, transmission may occur if the parasite is introduced into water bodies.

6.6.3 Drought

More intense and longer lasting droughts have occurred in many areas of the world since the 1970s, particularly in the tropics and subtropics. It is likely that the proportion of the world that is affected by droughts will continue to increase over coming decades (Stocker, Qin *et al.* 2013).

Biomphalaria and *Bulinus* snails are aquatic and will only reproduce in water. Some or all species are able to aestivate however, enabling them to survive short-term drying up of water bodies (Brown 1994). This is a common occurrence for species that live in temporary

ponds and streams, which can regularly dry up for several months at a time (Brown 1994; Vera, Bremond *et al.* 1995; Erko, Balcha *et al.* 2006). Droughts can both lengthen the time that temporary water bodies are empty, and dry up normally permanent water bodies. The abilities of different species of snail to survive different lengths and severities of desiccation in natural conditions are not well understood. Survival rates will depend on many factors including the species of snail, whether habitats dry up gradually or rapidly, soil moisture, and relative humidity (Appleton 1978). Survival may be lower for snail populations with little history of previous desiccation (Appleton 1978).

Regardless of the snail species and environmental conditions, it is likely that the extended drying up of water bodies will be harmful to the survival of any resident snail populations. One South African lake contained an estimated 47,000 *Bu. globosus* before it began to dry up. Only around 2000 emerged from aestivation when water returned four months later (Shiff 1964a). Repeated failure of rains over multiple years will be particularly detrimental if the snail populations are unable to fully recover their numbers between each dry season. Droughts of a sufficient length and severity may even lead to the temporary or permanent elimination of the snail population from a site. This is particularly likely in areas that are marginal for snail survival. Snail surveys were conducted in 1966 and 1995 in Kruger National Park, South Africa. A number of droughts occurred over the 29 year period, and a large number of snail species, including *Biomphalaria* and *Bulinus* species, disappeared from many sites between the two surveys (De Kock and Wolmarans 1998). There is evidence from historical records that *S. haematobium* transmission occurred in many parts of the Eastern Cape of South Africa between the early 1860s and late 1890s, but there is little evidence that it occurred between around 1900 and 2002 (Appleton and Naidoo 2012). It has been suggested that the elimination was caused by a severe drought in the area between 1895 and 1920.

6.6.4 Flooding

It is predicted that rainfall events will become more intense over coming decades. This is likely to lead to an increase in flooding in many parts of the world (World Health Organization 2003). In general, the species of snail that act as intermediate hosts for schistosomiasis are unable to tolerate water flows of over around 0.3 ms^{-1} (Appleton and

Stiles 1976). Intense rainfall and flooding may therefore greatly reduce the number of snails found at a transmission site. In one river in Zimbabwe, above average intense rainfall and seasonal flooding during one rainy season decreased the abundance of *Bu. globosus* by 99.9% (Woolhouse and Chandiwana 1990b).

While the majority of snails that are washed away by fast flowing water will not survive, some snails may end up in favourable habitats, and could potentially establish new colonies. Flooding in the Yangtze River valley, China has been shown to re-introduce snails and schistosomiasis into areas where they had previously been eliminated (Wu, Zhang *et al.* 2008). Between 1979 and 2000, in years where floods occurred, the average annual re-emerging areas and newly snail-infested areas were 2.6 and 2.7 times larger than in years with normal hydrologic conditions. This appears to have led to an increase in human schistosomiasis. On average, 2.8 times more cases of acute schistosomiasis were observed in flood years compared with normal years. In addition to reintroducing snails and schistosomiasis to areas from which they had previously been eliminated, flooding could also facilitate the spread of snails, including infected snails, to areas that are newly suitable for snail populations and/or schistosomiasis development. Flooding may therefore play a large role in determining the actual range of schistosomiasis, as opposed to its potential range, over coming decades.

6.6.5 The effect of not simulating changes in precipitation on predictions of the effects of climate change on *S. mansoni* transmission in eastern Africa

I chose not to include the effects of rainfall and changes in rainfall in the model for two main reasons. Firstly, as described above, the effects of changes in rainfall on snail populations will vary on a small scale between different habitats. While this does not prevent the inclusion of the effects of changes in rainfall into a model designed to represent a specific, well studied transmission site, it does present challenges to their inclusion in large-scale models. Secondly, there is substantial disagreement between different climate models in projected changes in rainfall in eastern Africa over the next few decades, with different models predicting overall increases or decreases in precipitation (Figure 6.2 and Figure 6.3) (van Oldenborgh, Collins *et al.* 2013). In addition, projected long term changes are small compared with inter-annual variability.

Only simulating changes in temperatures, as opposed to all climatic changes, may have had an impact on my predictions of the effects of climate change on *S. mansoni* transmission in eastern Africa. The overall impact is likely to have been small however, and the implications of the results for control and elimination policy are unlikely to have been greatly affected by the omission of changes in precipitation.

In Chapter 5, I show maps highlighting areas where the model predicts that temperatures will become more or less suitable for *S. mansoni* transmission (Figure 5.3), and where there is a risk of new transmission foci developing (Figure 5.5 - Figure 5.7). Of most interest to policy makers are the regions where it is predicted that schistosomiasis risk may increase greatly, or where schistosomiasis may become newly endemic in whole new areas. As the predicted increases in risk with increasing temperatures are so large in these areas, it is highly probable that the overall effects of climate change will be to increase risk, even if changes in rainfall make the area less suitable for snail populations.

Over much of the rest of eastern Africa, the model predicts that climate change will (all else being equal) increase *S. mansoni* transmission by up to around 20% over the next 20 years. Changes in patterns of rainfall may have a more important effect on overall changes in risk in these areas, as they are less likely to be of negligible magnitude compared with the effects of increasing temperatures. CMIP5 ensemble multi-model medians suggest that there may be a slight increase in rainfall in some areas of eastern Africa over the next 20 and 50 years, and slight decreases in others (Figure 6.2 and Figure 6.3). 25^{th} and 75^{th} percentiles of the ensemble results are compatible with increases or decreases in rainfall over most areas. In general, and averaged over large areas, it is probable that increases in rainfall will increase schistosomiasis transmission, and decreases in rainfall will decrease it. By not allowing for changes in rainfall, I may therefore have slightly over- or under-estimated the future impacts of climate change on schistosomiasis transmission.

The omission of changes in rainfall from the model may have a much larger impact on a smaller scale, as increases or decreases in rainfall may greatly alter the suitability of some individual habitats or transmission sites for snail populations. Temporary, seasonal habitats are likely to be most strongly affected by changing precipitation patterns, however these habitats are not generally favoured by *Biomphalaria* in sub-Saharan Africa. Temporary habitats are discussed in more detail in Section 6.7. Sheltered bays in fast flowing rivers may also be greatly affected by changes in rainfall, disappearing in some places and newly forming in others. This may have a large effect on the distribution of snails, but may have

less effect on *S. mansoni* transmission if humans seek out slower flowing water for household activities and recreation.

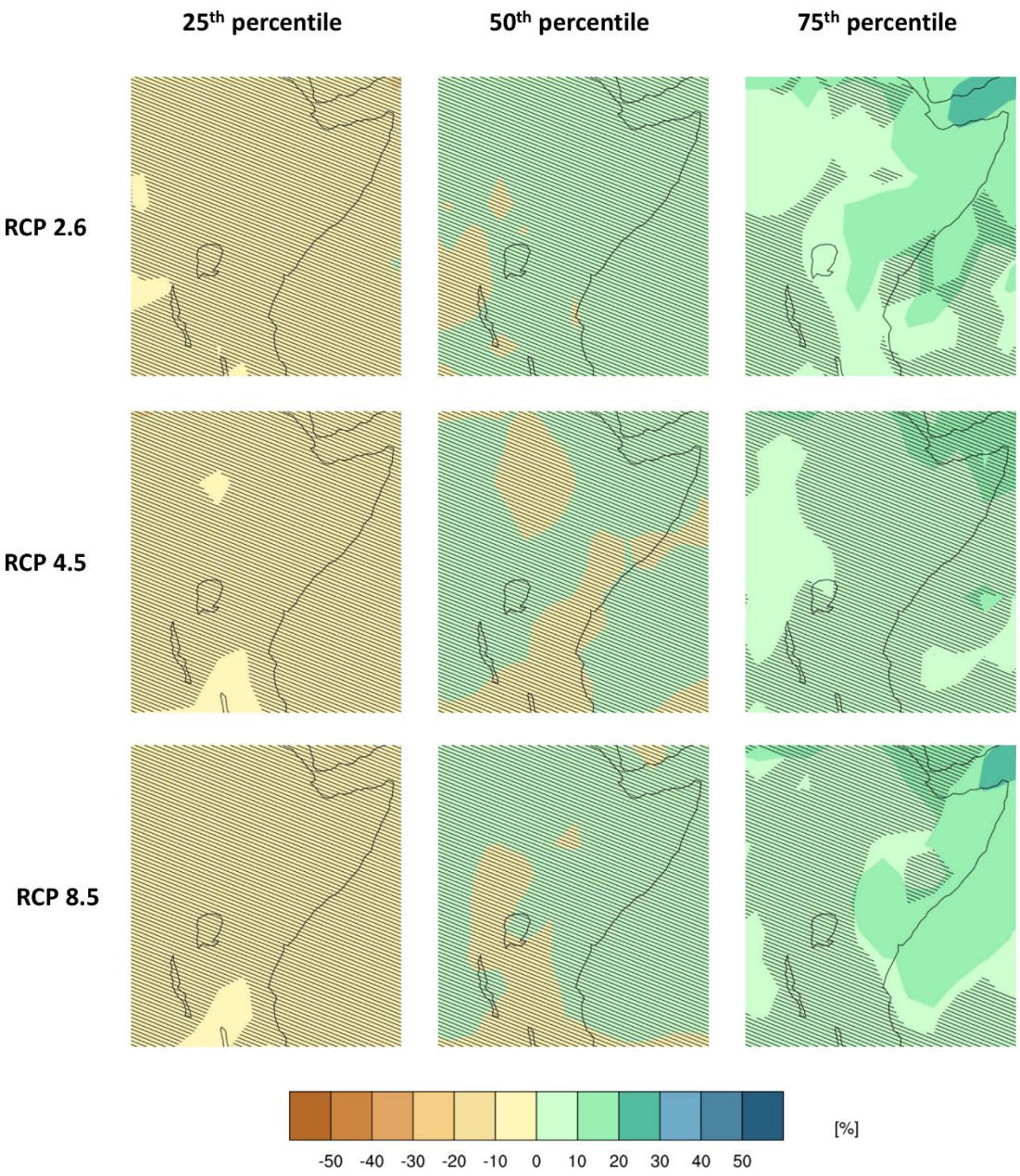

Figure 6.2. Projected change in precipitation in 2026-2035 relative to 2006-2015 (%).
From left to right, maps show the 25th, 50th and 75th percentiles of the distribution of the full CMIP5 ensemble. The hatching represents areas where the signal is smaller than one standard deviation of natural variability. Data were extracted from the KNMI Climate Explorer web application (van Oldenborgh).

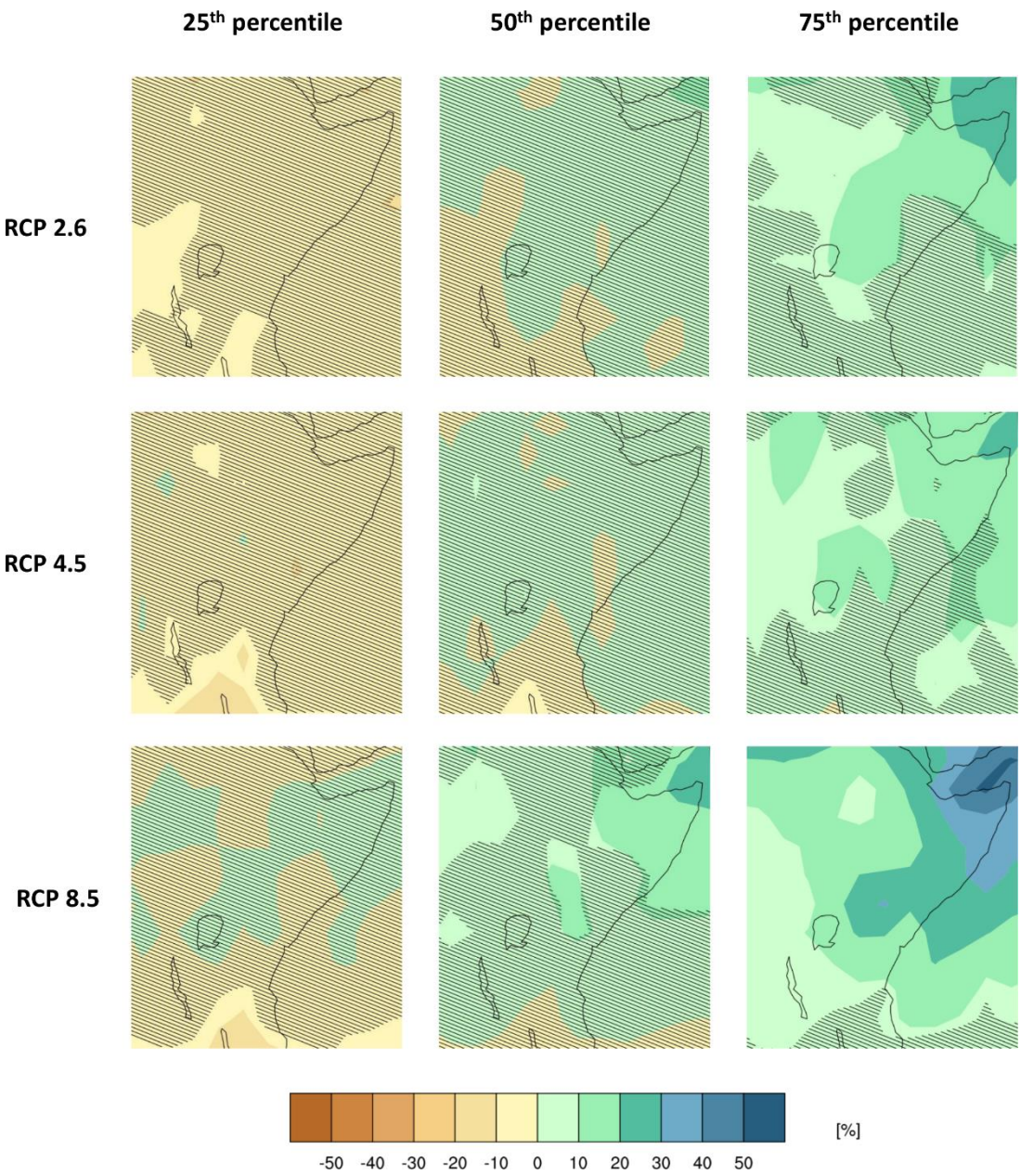

Figure 6.3. Projected change in precipitation in 2056-2065 relative to 2006-2015 (%).

From left to right, maps show the 25th, 50th and 75th percentiles of the distribution of the full CMIP5 ensemble. The hatching represents areas where the signal is smaller than one standard deviation of natural variability. Data were extracted from the KNMI Climate Explorer web application (van Oldenborgh).

6.7 Predicting the effects of non-climatic changes on *S. mansoni* transmission

In addition to changes in climate, changes in a range of other factors are likely to have large effects on the future distribution and intensity of *S. mansoni* transmission. The scale up of mass drug administration programs in particular may greatly reduce the intensity of transmission in many areas. Elimination campaigns may also alter the distribution of *S. mansoni*, as described in Section 1.5.4.

Sub-Saharan Africa is becoming increasing urbanised. It is estimated that only around 27% of the region's population lived in urban areas in 1990. This had increased to 37% in 2014, and is predicted to increase to 55% by 2050 (United Nations 2014). People living in urban areas are generally at low risk for schistosomiasis, due to an absence of suitable snail habitats (Mwakitalu, Malecela *et al.* 2014). Increasing urbanisation may therefore reduce the proportion of people at risk of schistosomiasis in Africa. Absolute numbers may increase however, due to population growth in rural areas. The rural population of sub-Saharan Africa is projected to increase by 62% between 2014 and 2050, an increase of nearly 359 million people (United Nations 2014). Furthermore, schistosome transmission has been shown to occur in some urban areas (Mungomba and Michelson 1995; Firmo, Costa *et al.* 1996), and people living in unplanned slums without access to safe water and adequate sanitation may be at risk (Mwakitalu, Malecela *et al.* 2014).

The building of irrigation systems, reservoirs and dams has resulted in large increases in schistosomiasis in a number of areas, through the development and expansion of suitable snail habitats (Steinmann, Keiser *et al.* 2006). Despite large uncertainty in projected changes in precipitation volume in Africa over coming decades, it is generally agreed that rainfall will become less predictable, with fewer, more intense precipitation events. (Stocker, Qin *et al.* 2013). This, in combination with an increasing population size, means that large increases in irrigated agriculture may be necessary to produce sufficient food for the continent (Calzadilla, Zhu *et al.* 2013). In addition, the construction of new reservoirs may be necessary to reduce the impact of droughts (Steinmann, Keiser *et al.* 2006). These changes may result in the development of new high intensity transmission sites, and migration to areas with improved agriculture may further increase the number of people at risk of high worm burdens.

6.8 Predicting the effects of climate change on *S. haematobium* transmission

In my thesis, I use mathematical modelling to investigate the potential effects of increasing temperatures on *S. mansoni* transmission in eastern Africa. In theory, the same approach could be used to predict changes in *S. haematobium* transmission. In practice, poorer data availability and *Bulinus* habitat preferences mean that any results and conclusions drawn would necessarily be more tentative.

In Chapter 4, I demonstrate that it is crucial to consider the species of intermediate host snail found in an area when designing and parameterising mathematical models of water temperature and schistosomes. In sub-Saharan Africa in general, and eastern Africa in particular, multiple different species of *Biomphalaria* are involved in *S. mansoni* transmission (Brown 1994). Nevertheless, one particular species of snail (*Bi. pfeifferi*) is widely considered to be the most important *S. mansoni* intermediate host, due to its widespread distribution (Brown 1994; Rollinson 2011; Stensgaard, Utzinger *et al.* 2013). This both allows the development of a model which can be applied over a large geographical scale, and means that a wide range of data were available on a single species of snail.

There is no corresponding 'obvious' choice of snail to use in developing a model of water temperature and *S. haematobium* transmission in sub-Saharan Africa. While *Bu. globosus* has been described as "*probably the most important intermediate host for* S. haematobium *in tropical Africa*" (Brown 1994), other species of *Bulinus* are as or more important in many areas, reducing the range over which a model parameterised to *Bu. globosus* could be reliably applied. The dominance of different species in different areas also dilutes the availability of data on the effects of water temperature on different aspects of the snails' lifecycles. Despite extensive searching, I could not find sufficient existing data to accurately parameterise the model to any single species of *Bulinus*.

The habitat preferences of *Bulinus* snails also reduces the reliability of any models of climate change and *S. haematobium* transmission that do not incorporate changes in patterns of rainfall. While some species of *Biomphalaria* can be found in temporary water bodies in some areas, *Biomphalaria* snails are more commonly found in permanent water bodies in sub-Saharan Africa. In contrast, seasonal water bodies are frequently exploited by *Bulinus* snails, and these sites may be far more important for the transmission of *S. haematobium* than *S. mansoni*. Changes in rainfall will alter the length of time for which

temporary water bodies are dry each year, increasing or decreasing length of time available for snails to breed. This will interact with changes in temperature. In warmer areas, increasing temperatures may reduce snail survival and fecundity, but this may not result in reduced *S. haematobium* transmission if increased rainfall increases the duration of the transmission season.

Incorporating the effects of changes in precipitation into a large-scale model of *S. haematobium* transmission presents many challenges. Crucially, the effects of the same changes in rainfall on snail population dynamics may be very different in different snail habitats. For instance, a greater amount of precipitation falling in less regular, less frequent, and more intense downpours may result in one seasonal pond containing water for a longer period each year, increasing length of the potential transmission season. In another pond, the same changes in rainfall may result in snails emerging from aestivation too early, and dying when the water dries up again shortly afterwards. The likelihood of the latter occurring may also depend on the species of snail. *Bu. nasutus* (Webbe 1962) and *Bu. senegalensis* (Goll and Wilkins 1984) aestivate on the margins of temporary ponds, where they are unlikely to be stimulated to emerge by isolated showers. In contrast, *Bu. globosus* and *Bu. truncatus* aestivate on the bottom of pools, and it has been suggested that unpredictable rainfall may be responsible for *Bu. globosus*'s limited distribution in northern Nigeria (Betterton, Ndifon *et al.* 1988).

6.9 Application of the model to areas outside eastern Africa

I have run my model using climate projections for eastern Africa. *Bi. pfeiffferi* are a common *S. mansoni* intermediate host throughout much of sub-Saharan Africa (Stensgaard, Utzinger *et al.* 2013), and the same model and methods could therefore be used to predict climate-driven changes in infection risk across large areas of the continent.

In addition to *Bi. pfeiffferi*, I have fitted my model to two additional species of intermediate host: *Bi. alexandrina* and *Bi. glabrata*. *Bi alexandrina* is the main intermediate host in Egypt and parts of Sudan (Brown 1994), and the model could therefore be used to predict the effects of increasing temperatures on schistosomiasis transmission in these areas. Egypt is close to achieving the elimination of schistosomiasis however, and there are no high altitude areas where schistosomiasis may become newly endemic in either country. The

practical implications of modelling the effects of changes in temperature are therefore limited. *Bi. glabrata* is one of several species of *Biomphalaria* found in South America and the Caribbean, and is thought to be the most important *S. mansoni* intermediate host species (Scholte, Carvalho *et al.* 2012). *Bi. glabrata* are more commonly found in seasonal water bodies than most species of *Biomphalaria* however (Brown 1994), and therefore the reliability of predictions made without considering the effect of changes in rainfall may be low.

6.10 Comparison with the results of other studies

Three previous studies have attempted to predict the effects of climate change on *S. mansoni* transmission. Details of two of the studies, which used a mathematical modelling approach, are given in Section 1.7.1 (Martens, Jetten *et al.* 1995; Martens, Jetten *et al.* 1997; Mangal, Paterson *et al.* 2008), and details of the third study, which used a statistical modelling approach, are given in Section 1.9 (Stensgaard, Utzinger *et al.* 2013).

Martens *et al.* estimated that schistosomiasis epidemic potential is highest at constant temperatures of 16-18°C, decreases sharply at below optimum temperatures, and decreases more gradually at above optimum temperatures (Martens, Jetten *et al.* 1995; Martens, Jetten *et al.* 1997). This is very similar to the relationship between water temperature and *S. mansoni* risk at constant temperatures in the 'lake' scenario shown in Figure 3.6. There are many differences between Martens *et al*'s model and the model described in Chapter 2, however there are two main differences that are likely to have a large effect on the relationship between water temperature and infection risk at constant temperatures. These are that Martens *et al*. did not simulate an increase in cercaria production with increasing temperature, and that they assumed that infection would have the same relative effect on snail mortality rates at all temperatures. These two differences cancel out to some extent, with Martens *et al* predicting longer mean survival but lower cercaria production rates by infected snails at higher temperatures. This may explain why results at constant temperatures were similar between the two models. Other differences in the structure and parameterisation of the models are likely to be of more importance when more realistic, varying temperatures are simulated.

Using a model largely parameterised using data from *Bi. alexandrina*, Mangal *et al*. estimated infection risk at constant temperatures of 20°C, 25°C, 30°C, and 35°C, and determined that the mean worm burden per person was highest at 30°C and lowest at 20°C (Mangal, Paterson *et al.* 2008). This is in contrast to the current model results when the model parameterised to *Bi. alexandrina* was run using constant temperatures (Chapter 4), where I found that infection risk was highest at around 19°C. A major difference between the two models is that Mangal *et al* simulated temperature-dependent worm mortality rates, with adult worms living for a median of 22 days at 20°C, increasing linearly to 87 days at 35°C. These lifespans are much lower than the mean lifespans of 3-5 years estimated from empirical data (Anderson and May 1991), and there are no empirical or theoretical reasons for assuming that adult worm mortality rates are affected by external temperature. It is plausible that this difference between the two models is responsible for much of the difference in the predicted optimum temperature for transmission.

Stensgaard *et al* used statistical modelling to produce risk maps showing where the range of *S. mansoni* in Africa may expand or contract by 2080 (Stensgaard, Utzinger *et al.* 2013). They predict that the range may decrease slightly in certain parts of eastern Africa, and in particular in parts of Kenya and two areas of Tanzania. Stensgaard *et al*'s predicted area of contraction in Kenya matches closely with areas where my model predicts that infection risk will greatly decrease (Figure 5.3). The predicted contractions in Tanzania match my model output to some extent: my model predicts decreased risk in both areas of Tanzania in 50 years' time in the high warming scenario, and in one of the areas in medium warming scenario. It is not clear if the differences between the two models' results are due to genuine differences between model predictions, or to differences in the climate projections used and/or the baseline and future time periods chosen. Stensgaard *et al* do not predict any expansion in potential range in eastern Africa. This may reflect a limitation of statistical models fitted to existing non-randomly distributed prevalence data: sites thought to be unsuitable for schistosomiasis, for instance due to cold temperatures, may be greatly under-sampled, leaving statistical models underpowered to detect the effects of cold temperatures on schistosomiasis prevalence.

6.11 Healthy Futures

My PhD thesis forms part of a larger body of work conducted as part of the EU FP7 funded 'Healthy Futures' project. The overall aim of Healthy Futures is to construct disease risk mapping systems for schistosomiasis, malaria, and Rift Valley fever in eastern Africa, taking into account changes in climate and socio-economic conditions. The model results presented in Chapter 5 provide estimates of the suitability of current and projected future temperatures for schistosome transmission. These estimates will be combined with estimates of the vulnerability of populations to schistosomiasis to produce maps illustrating areas where the burden of schistosomiasis disease may be highest, and areas where climate change may have the largest impact on population health. Areas that are too dry to support *Biomphalaria* populations will be masked using a measure of the normalized difference vegetation index.

Vulnerability estimates have been produced by Michael Hagenlocher and Stefan Kienberger, University of Salzburg. They combine a number of indicators of disease susceptibility and lack of resilience into a single, spatially explicit composite indicator. Indicators of susceptibility include density of school aged children, and measures of poverty and sanitation. Indicators of resilience include education level and distance to the nearest health care facility. This approach has previously been applied to malaria vulnerability in the same region (Kienberger and Hagenlocher 2014) and to dengue fever in Columbia (Hagenlocher, Delmelle *et al.* 2013). Predicted changes in gross domestic product will be used to estimate future changes in vulnerability for each country.

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8 Appendices

8.1 Model parameter values

Rate (per hour) [varies with]	**Source(s)**	**Range of data**	**Fitted model**	**Equation/ Parameters**	**Behaviour outside range of data**
Relative increase in mortality in infectious snails [water temperature (T_w)]	Foster (1964)	23-28°C	Exponential	0.3073 * e ^ (0.1002 * T_w)	Line extended backwards to 11.2°C where it takes the value of 1. Below 11.2°C, the relative increase in mortality is taken to be equal to 1. Line extended forwards above 28°C.
Relative increase in mortality [number of snails in model N_s]	-	-	Linear	If N_s < 600: 1 If N_s ≥ 600: (N_s – 600) / 500 + 1	Lines used for any number of snails in model
Relative egg production rate [number of snails in model N_s]	Loreau and Baluku (1987a)	Data from tanks with 8.6 snails/l and 85.7 snails/l only	Gompertz	If N_s < 300: 1 If N_s ≥ 300: e ^ (0.005 * (1 – e ^ ((N_s - 300)/100)))	Lines used for any number of snails in model
Relative egg production rate [Cumulative number of degree hours above 27°C,	Appleton and	0-5065 degree hours above 27°C, above a threshold of 39	Exponential	e ^ (-0.00031 * d)	Line extended to higher values of d

above a threshold of 39 degree hours above 27°C/day, during a juvenile snail's development period *(d)*]	Eriksson (1984)	degree hours above 27°C/day			
Miracidium biological age gain [water temperature (T_w)]	Anderson, Mercer *et al.* (1982)	5-40°C	Piecewise linear	If T_w < 15°C: 0 If T_w ≥ 15°C: 0.0530 * T_w - 0.349	No biological age gain occurs below 15°C. The line is extended forwards above 40°C
Miracidium mortality rate if T_w ≥ 15°C [miracidium biological age (hours) (M_a)]	Anderson, Mercer *et al.* (1982)	Miracidium birth to 100% mortality of cohort	Exponential	1 - (1 - (0.0083 * e ^ ((-0.35 + 0.032 * 25) * M_a)))	Line used to determine mortality rate at all biological ages
Miracidium mortality rate if T_w < 15°C [water temperature (T_w)]	Anderson, Mercer *et al.* (1982)	Miracidium birth to 100% mortality of cohort	Linear	-0.0192 * T_w + 0.2911	Line used to determine mortality rate for all water temperatures < 15°C
Relative miracidium infection rate [miracidium biological age (hours) (M_a)]	Anderson, Mercer *et al.* (1982)	Miracidium birth to 100% mortality of cohort	Weibull	(0.196 * e ^ ((-2.18 * 10^{-6} / D$6) * M_a ^ 8.33)) / 0.196	Line used to determine relative infection rate at all biological ages
Relative miracidium infection rate [water temperature (T_w)]	Anderson, Mercer *et al.* (1982)	15-35°C	Piecewise exponential	If T_w < 15°C: 0 If 15°C ≤ T_w ≤ 25°C: 0.135 * e ^ (0.0572 * T_w)	Lines extended to higher and lower temperatures

				If T_w > 25°C: 2.28 * e ^ (-0.0544 * T_w)	
Relative miracidium infection rate [number of snails in model N_s	-	-	1 - exponential	1 – e ^ (-N_s / 3000)	Line used for any number of snails in model
Relative cercaria production rate [time of day (hours since midnight h)]	Kazibwe, Makanga *et al.* (2010)	9.00-17.00	Quadratic	-0.0578 * h^2 + 1.501 * h - 8.84	No cercariae production occurs between 17.00 and 9.00
Cercaria production rate [water temperature (T_w)]	Fried, LaTerra *et al.* (2002)	12-35°C	Linear	0.02 * (14.2 * T_w - 159.2)	Line extended in both directions. No cercariae production occurs below 11.2°C where the line meets the x-axis
Cercaria biological age gain (hours) [water temperature (T_w)]	Lawson and Wilson (1980)	15-40°C	Exponential	0.199 * e ^ (0.069 * T_w)	Lines extended to higher and lower temperatures
Cercaria mortality rate [cercaria biological age (hours) (C_a)]	Lawson and Wilson (1980)	Cercaria birth to 100% mortality of cohort	Gompertz	1 – (1 – e ^ (-e ^ (1.75 – 0.056 * C_a))) ^ (*cercaria age gain*)	Line used to determine mortality rate at all biological ages

Relative cercaria infection rate [cercaria biological age (hours) (C_a)]	Ghandour and Webbe (1973)	2-24 hours	Exponential	0.829 * e ^ (-0.0675 * C_a)	Line used to determine relative infection rate at all biological ages

Table 8.1. Model rates common to all three snail species (*Bi. pfeifferi*, *Bi. glabrata* and *Bi. alexandrina*)

Rate (per hour) [varies with]	**Source(s)**	**Range of data**	**Fitted model**	**Equation/ Parameters**	**Behaviour outside range of data**
Juvenile heat unit gain* [water temperature (T_w)]	De Kock, Van Eeden *et al.* (1981) and Kariuki (1994)	17-32°C (laboratory) and 25.6°C (field)	Lactin	0.54 * Lactin model with parameters: ρ = 0.161 λ = -0.032 Δ = 6.20 T_{max} = 34.0°C	Line extended to 6.1°C and 33.6°C where the model meets the x-axis. No heat unit gain occurs outside this range.
Egg production rate [water temperature (T_w)]	De Kock, Van Eeden *et al.* (1981) and Kariuki (1994)	17-32°C (laboratory) and 17.9-23.5°C (field)	Lactin	0.1 * 0.22 * Lactin model with parameters: ρ = 0.105 λ = -1.687 Δ = 7.72 T_{max} = 34.5°C	Line extended to 13.8°C and 32.1°C where the model meets the x-axis. No egg production occurs outside this range.
Egg heat unit gain* [water temperature (T_w)]	De Kock, Van Eeden *et al.* (1981) and Kariuki (1994)	17-32°C (laboratory) and 19.7-25.6°C (field)	Linear	0.0259 * T_w - 0.152	Line extended in both directions. No egg heat unit gain occurs below 5.9°C where the line meets the x-axis

Egg mortality rate [water temperature (T_w)] De Kock and van Eeden (De Kock, Van Eeden *et al.* 1981)	De Kock, Van Eeden *et al.* (1981)	17-32°C	Piecewise constant and linear	If T_w < 29°C: 0.000283 If T_w ≥ 29°C: 0.000564 * T_w - 0.0161	Lines extended to higher and lower temperatures
Mortality rate at 19°C	Loreau and Baluku (1987b)	-	-	0.000285	-
Relative mortality rate between 13-32°C (relative to rate at 19°C) [water temperature (T_w)]	De Kock, Van Eeden *et al.* (1981)	17-32°C	Linear	0.0485 * T_w + 0.0776	See rows below
Mortality rate below 13°C [water temperature (T_w)]	Joubert, Pretorius *et al.* (1984)	0-6°C	Quadratic	0.000141 * T_w^2 - 0.00388 * T_w + 0.0268	Line extended below 0°C
Mortality rate above 32°C [water temperature (T_w)]	Joubert, Pretorius *et al.* (1986)	34-40°C	Exponential	$1.30 * 10^{-14}$ * e ^ (0.76 * T_w)	Line extended above 40°C
Parasite heat unit gain within snail* [water temperature (T_w)]	Foster (1964) and Pfluger (1981)	18-32°C (constant temperature) 12-39°C (as	Piecewise linear, quadratic and exponential	If T_w < 17°C: (0.005 * e ^ ((T_w - 4.7) / 5))	Line extended in both directions. No parasite heat unit gain occurs

		part of a fluctuating regimen)		If $T_w \geq 17$°C and $T_w < 32$°C: 0.0119 * T_w - 0.143 If $T_w \geq 32$°C: 0.87 * (-0.0080 * T_w^2 + 0.52 * T_w - 8.18)	above 38.4°C where the line meets the x-axis

Table 8.2. *Bi. pfeifferi* model rates

*Number of heat units necessary to complete stage set to 100

Rate (per hour) [varies with]	**Source(s)**	**Range of data**	**Fitted model**	**Equation/ Parameters**	**Behaviour outside range of data**
Juvenile heat unit gain* [water temperature (T_w)]	Sturrock and Sturrock (1972)	20-30°C	Lactin	Lactin model with parameters: ρ = 0.070 λ = -0.14 Δ = 13.8 T_{max} = 38.2°C	Line extended to 6.5°C and 33.6°C where the model meets the x-axis. No heat unit gain occurs outside this range.
Egg production rate [water temperature (T_w)]	Pimentel-Souza, Barbosa *et al.* (1990) and Jobin (1970)	17.5-27.5°C (laboratory) and 23°C (field)	Lactin	0.1 * 0.31 * Lactin model with parameters: ρ = 0.18 λ = -0.35 Δ = 5.4 T_{max} = 31.0°C	Line extended to 11.7°C and 30.4°C where the model meets the x-axis. No egg production occurs outside this range.
Egg heat unit gain* [water temperature (T_w)]	Joubert and Pretorius (1985)	14-34°C	Lactin	Lactin model with parameters: ρ = 0.051 λ = -1.42 Δ = 11.3 T_{max} = 46.0°C	Line extended to 13.8°C and 40.0°C where the model meets the x-axis. No egg heat unit gain occurs outside this range.

Egg mortality rate [water temperature (T_w)]	Joubert and Pretorius (1985)	14-34°C	Piecewise quadratic and linear	If $T_w \leq 32$°C: 0.000019 * T_w^2 - 0.00088 * T_w + 0.011 If $T_w > 32$°C: 0.0074 * T_w - 0.23	Lines extended in both directions.
Uninfected and prepatent snail mortality rate between 16-33°C [water temperature (T_w)]	Pfluger (1980)	16-33°C	Constant	0.00067	See rows below
Uninfected and prepatent snail mortality rate below 16°C [water temperature (T_w)]	Joubert and Pretorius (1985)	0°C	Exponential	0.070 * e ^ (-0.29 * T_w)	Line extended to lower temperatures
Uninfected and prepatent snail mortality rate above 33°C [water temperature (T_w)]	Pfluger (1980) and Joubert and Pretorius (1985)	34-40°C	Exponential	0.000000000000003 * e ^ (0.79 * T_w)	Line extended to higher temperatures
Parasite heat unit gain within snail* [water temperature (T_w)]	Pfluger (1980) and	16-36°C	Piecewise linear,	If $T_w < 17$°C: 0.0037 * e ^ ((T_w - 4.7) / 5)	Line extended in both directions. No parasite heat unit gain occurs

	Pfluger (1981)		exponential and quadratic	If $T_w \geq 17$°C and $T_w < 32$°C: (100 / 24) * (T_w - 14.2) / 268) If $T_w \geq 32$°C: -0.0080 * T_w^2 + 0.52 * T_w - 8.18	above 38.4°C where the line meets the x-axis

Table 8.3. *Bi. glabrata* model rates

*Number of heat units necessary to complete stage set to 100

Rate (per hour) [varies with]	**Source(s)**	**Range of data**	**Fitted model**	**Equation/ Parameters**	**Behaviour outside range of data**
Juvenile heat unit gain* [water temperature (T_w)]	El-Hassan (1974) and El-Emam and Madsen (1982)	18-30°C	Lactin	Lactin model with parameters: ρ = 0.159 λ = -0.023 Δ = 6.27 T_{max} = 31.5°C	Line extended to 5.2°C and 31.1°C where the model meets the x-axis. No heat unit gain occurs outside this range.
Egg production rate [water temperature (T_w)]	El-Hassan (1974)	12.5-30.0°C	Lactin	Lactin model with parameters: ρ = 0.149 λ = -0.017 Δ = 6.72 T_{max} = 31.1°C	Line extended to 10.0°C and 31.0°C where the model meets the x-axis. No egg production occurs outside this range.
Egg heat unit gain* [water temperature (T_w)]	El-Hassan (1974)	12.5-35.0°C	Quadratic	$-0.000825 * T_w^2 + 0.0576 * T_w - 0.497$	Line extended to 10.1°C, where the model meets the x-axis, and to higher temperatures. No egg heat unit gain occurs below 10.1°C
Egg mortality rate [water temperature (T_w)]	El-Hassan (1974)	15.0-35.0°C	Quadratic	$0.0000019 * T_w^2 - 0.000091 * T_w + 0.0011$	Line extended to higher and lower temperatures

Uninfected and prepatent snail mortality rate [water temperature (T_w)]	El-Hassan (1974)	10.0-37.0°C	Quadratic	0.0000053 * T_w^2 - 0.00020 * T_w + 0.0021	Line extended to higher and lower temperatures
Parasite heat unit gain within snail* [water temperature (T_w)]	Foster (1964) and Pfluger (1981)	18-32°C (constant temperature) 12-39°C (as part of a fluctuating regimen)	Piecewise linear, quadratic and exponential	If T_w < 17°C: (0.005 * e ^ ((T_w - 4.7) / 5)) If T_w ≥ 17°C and T_w < 32°C: 0.0119 * T_w - 0.143 If T_w ≥ 32°C: 0.87 * (-0.0080 * T_w^2 + 0.52 * T_w - 8.18)	Line extended in both directions. No parasite heat unit gain occurs above 38.4°C where the line meets the x-axis

Table 8.4. *Bi. alexandrina* model rates

*Number of heat units necessary to complete stage set to 100