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Large-scale determinants of intestinal schistosomiasis and intermediate host snail distribution across Africa: does climate matter?

Anna-Sofie Stensgaard[a,b,*], Jürg Utzinger[c,d], Penelope Vounatsou[c,d], Eveline Hürlimann[c,d], Nadine Schur[c,d], Christopher F.L. Saarnak[b], Christopher Simoonga[e], Patricia Mubita[f], Narcis B. Kabatereine[g], Louis-Albert Tchuem Tchuenté[h,i,j], Carsten Rahbek[a], Thomas K. Kristensen[b]

[a] Center for Macroecology, Evolution and Climate, Department of Biology, University of Copenhagen, Universitetsparken 15, DK-2100 Copenhagen Ø, Denmark
[b] DBL, Department of Veterinary Disease Biology, University of Copenhagen, Thorvaldsensvej 57, DK-1871 Frederiksberg C, Denmark
[c] Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, P.O. Box, CH-4002 Basel, Switzerland
[d] University of Basel, P.O. Box, CH-4003 Basel, Switzerland
[e] Ministry of Health, P.O. Box 30205, 10101 Lusaka, Zambia
[f] Department of Community Medicine, University of Zambia, P.O. Box 50110, 10101 Lusaka, Zambia
[g] Vector Control Division, Ministry of Health, P.O. Box 1661, Kampala, Uganda
[h] National Programme for the Control of Schistosomiasis and Intestinal Helminthiasis, Ministry of Public Health, Yaoundé, Cameroon
[i] Laboratoire de Biologie Générale, Université de Yaoundé I, Yaoundé, Cameroon
[j] Centre for Schistosomiasis and Parasitology, P.O. Box 7244, Yaoundé, Cameroon

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ABSTRACT

The geographical ranges of most species, including many infectious disease agents and their vectors and intermediate hosts, are assumed to be constrained by climatic tolerances, mainly temperature. It has been suggested that global warming will cause an expansion of the areas potentially suitable for infectious disease transmission. However, the transmission of infectious diseases is governed by a myriad of ecological, economic, evolutionary and social factors. Hence, a deeper understanding of the total disease system (pathogens, vectors and hosts) and its drivers is important for predicting responses to climate change. Here, we combine a growing degree day model for *Schistosoma mansoni* with species distribution models for the intermediate host snail (*Biomphalaria* spp.) to investigate large-scale environmental determinants of the distribution of the African *S. mansoni-Biomphalaria* system and potential impacts of climatic changes. Snail species distribution models included several combinations of climatic and habitat-related predictors; the latter divided into "natural" and "human-impacted" habitat variables to measure anthropogenic influence. The predictive performance of the combined snail–parasite model was evaluated against a comprehensive compilation of historical *S. mansoni* parasitological survey records, and then examined for two climate change scenarios of increasing severity for 2080. Future projections indicate that while the potential *S. mansoni* transmission area expands, the snail ranges are more likely to contract and/or move into cooler areas in the south and east. Importantly, we also note that even though climate *per se* matters, the impact of humans on habitat play a crucial role in determining the distribution of the intermediate host snails in Africa. Thus, a future contraction in the geographical range size of the intermediate host snails caused by climatic changes does not necessarily translate into a decrease or zero-sum change in human schistosomiasis prevalence.

1. Introduction

Climate change is currently ongoing (IPCC, 2007), and expected to affect biological systems worldwide (Rosenzweig et al., 2008). Hence a better understanding of how climate – particularly rising temperature – affects the frequency and transmission dynamics of infectious diseases is an important public health issue (Haines et al., 2009; Lafferty, 2009; Chaves and Koenraadt, 2010; Yang et al., 2010b). Conventionally, predicted risk profiles of climate-sensitive infectious diseases have emphasised potential increases in disease with climate change, even though recent studies noted range shifts in disease distributions, rather than net expansions (Randolph, 2009; Ostfeld, 2009; Lafferty, 2009). Though complex and fraught with uncertainties, understanding how species involved in disease

* Corresponding author at: Center for Macroecology, Evolution and Climate, Department of Biology, University of Copenhagen, Universitetsparken 15, DK-2100 Copenhagen Ø, Denmark. Tel.: +45 3532 1262; fax: +45 3532 2321.
E-mail address: asstensgaard@bio.ku.dk (A.-S. Stensgaard).

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transmission are likely to respond to climate change is imperative if we are to identify appropriate mitigation, control and adaptation strategies.

Thus far, only few attempts have been made to predict changes in the frequency and transmission dynamics of schistosomiasis in the face of global warming, and reported results are conflicting (Martens et al., 1995, 1997; Yang et al., 2005; Mangal et al., 2008; Zhou et al., 2008). Indeed, the two studies by Martens and colleagues came to different conclusions regarding the extent of schistosomiasis transmission under the scenario of a warmer climate, whereas the investigations made by Yang et al. (2005) and Zhou et al. (2008) for the People's Republic of China (P.R. China) predict a broad north- and westward expansion of schistosomiasis japonica within P.R. China, governed by an expansion in the range of the cold-tolerant intermediate host snail species. The discrepancies in results are linked to the fact that schistosomiasis, like many infectious diseases, are strongly influenced not only by climate, but also by ecological, economic, evolutionary and social factors besides climate (Allotey et al., 2010; Yang et al., 2010a; Utzinger et al., 2011). Of note, the many different snail species involved in schistosomiasis transmission worldwide differ substantially in terms of their biology and ecological requirements. Disentangling how the range of disease transmission is controlled by such factors is of key importance for predicting responses to climate change.

The wide geographic distribution of *Schistosoma mansoni* (Sambon, 1907), a digenetic trematode and parasite that causes intestinal schistosomiasis in humans (Jordan and Webbe, 1969; Gryseels et al., 2006) is first and foremost determined by the occurrence of the intermediate host of its larval stages; freshwater snails of the genus *Biomphalaria* (Preston, 1910). Twelve out of 30 currently recognised species of *Biomphalaria* are found in Africa with a geographical range that covers most of sub-Sahara, northeast Africa, Madagascar and parts of the Middle East (Bandoni et al., 1995; DeJong et al., 2001; Jorgensen et al., 2007). While all 12 species of *Biomphalaria* may be susceptible to *S. mansoni*, it is predominantly transmitted through *B. pfeifferi*, the most widespread intermediate host in sub-Saharan Africa. This species has both a lacustrine and non-lacustrine distribution (Angers et al., 2003), but is rarely found in the Great Lakes, where mainly three other species are currently recognised, namely *B. choanomphala* (Martens, 1879), *B. smithi* (Preston, 1910) and *B. stanleyi* (Smith, 1888). Of note, *B. smithi* is endemic to Lake Edward, *B. stanleyi* is mainly found in Lake Albert and *B. choanomphala* occurs in Victoria, Kyoga and Albert lakes and in Albert Nile and Victoria Nile (Mandahl-Barth, 1957). *Biomphalaria sudanica* (Martens, 1970) is common in rivers, swamps at lake shores or true swamps inland, and is widely distributed across Africa. The current geographical ranges of the snails are believed to be constrained by their climatic tolerances with temperature playing a particularly important role (Appleton, 1978; Appleton and Eriksson, 1984; Brown, 1994). Thus, an intuitively appealing idea is that predicted climatic changes will cause an expansion of the areas potentially suitable for disease transmission. However, to our knowledge, continental-scale environmental controls of African intestinal schistosomiasis and intermediate host snail geographical ranges have not previously been investigated in a quantitative manner.

Ideally, a comprehensive model for future as well as contemporary schistosomiasis distribution and transmission should integrate the essential biology of all implicated life histories, i.e. those of the parasite, the intermediate snail host and the definitive human host. To map out the probable impacts of climate change on schistosomiasis transmission, it is desirable to integrate of two modelling "schools", (i) process-based models, for which parameterisation requires solid knowledge of the life history of the species in questions and the relationships between climate variables and vital rates (but requiring no distribution data) and (ii) an occurrence-based approach, statistically linking spatial data to species distribution records (Elith et al., 2010). The integration of these two models would result in a model that incorporates both the unique ecology of the disease as it operates at small scales, and the specific characteristics of the species climatic niche at larger spatial scales. Such an approach bears resemblance to what has also been demonstrated for predicting the future transmission patterns of schistosomiasis and malaria in P.R. China (Yang et al., 2005, 2010a, 2010b; Zhou et al., 2008).

In the present study, we aimed to identify key climatic and non-climatic determinants of the African continental-scale parasite-intermediate host snail distribution, and then investigated potential impacts of climate change. We focus on three overall classes of environmental determinants that all have been indicated to influence intermediate host snail distribution patterns (Appleton, 1978; Brooker and Michael, 2000); namely (i) climate (temperature and precipitation); (ii) natural habitat conditions (water bodies and soil conditions); and (iii) human impacted habitat conditions (anthropogenically influenced habitat, i.e. water development projects and human "presence"). To predict current distributions and assess the relative contributions of explanatory factors, we used a species distribution modelling method, MaxEnt (Phillips et al., 2006; Phillips and Dudik, 2008), which is widely and effectively employed in ecology (Elith et al., 2006). These models were then combined with a process-based growing degree day (GDD) model for *S. mansoni*. Model predictive performance was evaluated against a comprehensive compilation of historical *S. mansoni* parasitological survey records (Hürlimann et al., 2011). Finally, future projections of the best performing model combination were examined under two climate change scenarios of increasing severity for the year 2080.

2. Materials and methods

2.1. Malacological and parasitological data

Biomphalaria occurrence data were mainly compiled from two sources, namely (i) the dry and wet freshwater snail collection maintained at the Mandahl-Barth Research Centre for Biodiversity and Health at DBL (Copenhagen, Denmark) and (ii) Brown's collection maintained at the Natural History Museum (London, UK). The data were furthermore supplemented with specimens collected by partners of the European Union (EU)-funded CONTRAST project (http://www.eu-contrast.eu) within the past 4 years. The majority of the data first had to be digitised and then georeferenced following the Global Biodiversity Information Facility's guidelines to best practice (Chapman and Wieczorek, 2006). Data were available for 10 out of the 12 currently accepted species acting as *S. mansoni* intermediate host snails in Africa, but only five species had sufficient number of georeferenced localities according to our modelling criteria (i.e. at least 30 point records). As of early November 2010, the collective database contained 1,485 records and the occurrence points for these five species are displayed in Fig. 1A.

Parasitological data of *S. mansoni* infection prevalence in humans and occurrence were extracted from the readily available, open-access global neglected tropical disease (GNTD) database (Hürlimann et al., 2011). Parasitological data in this GNTD database were obtained from a systematic review of peer-reviewed journals and 'grey literature', ministries of health records and data hand-searched from research institutions in schistosomiasis-endemic countries. Details on number of individuals surveyed, age profiles of study populations, diagnostic approaches taken, and exact location of surveys were included. All data are georeferenced. The entire data repository is freely available under http://www.gntd.org. On 10 January 2011, the database contained 12,388 georeferenced

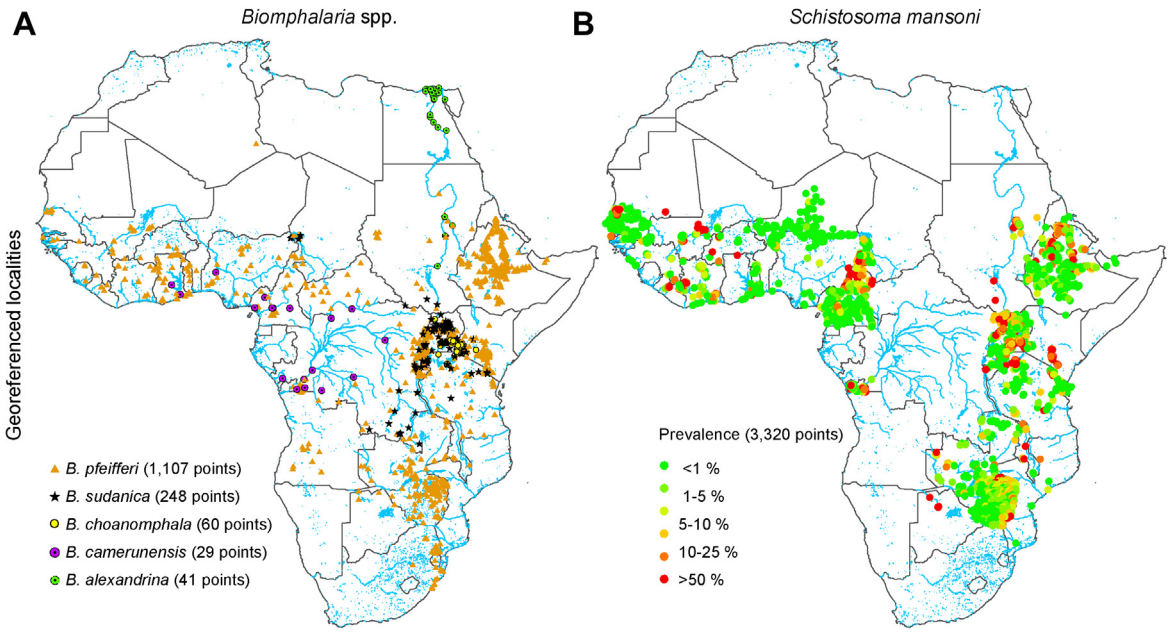

Fig. 1. Maps of Africa with georeferenced locations of *Biomphalaria*, the intermediate host snail of intestinal schistosomiasis, including information on the available number of georeferenced point locations for each of five snail species (left) and *S. mansoni* prevalence rates in humans (right).

survey locations for schistosomiasis from 35 African countries, and 40.8% of these data pertained to *S. mansoni*. Data were filtered according to the following criteria: (i) school- or community-based surveys (no case reports or hospital records); (ii) at least 10 individuals surveyed; and (iii) age class 5–19 years. After filtering, 3320 unique records for *S. mansoni* remained for the current study, as shown in Fig. 1B. The filtering was done to ensure the best possible confidence in the infection level estimates and comparability throughout the continent.

2.2. Predictor variables

The climatic and non-climatic predictor variables were selected based on their perceived biological relevance for intermediate host snail distributions. To represent climatic controls, three temperature parameters and three rain-related variables were downloaded from the Worldclim global dataset hosted at: http://www.worldclim.org (Hijmans et al., 2005). Regarding temperature, the diurnal temperature range was chosen to account for the demonstrated importance of fluctuating temperatures, as previously shown for *B. pfeifferi* (Appleton and Eriksson, 1984). Moreover, temperature of the warmest and coldest quarter was included to account for the sensitivity of *Biomphalaria* snails to temperature extremes (Appleton, 1977a, 1977b; Pflüger, 1981). Measures of seasonal variation in precipitation were used as indirect measures of the availability of suitable temporary water bodies that *Biomphalaria* snails are known to inhabit.

Natural habitat was represented by distance to nearest permanent surface water body, soil pH and forest cover (Hansen et al., 2003). The two latter variables were considered, as it has been indicated that soil type and pH in water bodies (influenced by soil pH and to some extent forest cover) influence some species of *Biomphalaria* snails (Bavia et al., 1999; Kloos et al., 2004). It has also been observed that *B. pfeifferi* prefer habitats with only small amounts of shade (Ndifon and Ukoli, 1989), and hence forested landscapes might provide unfavourable habitats for these snails. Importantly, not only natural habitat is important for many of the intermediate host snail species. For example, anthropogenic impacts, such as the expansion of irrigated agricultural lands into previously undisturbed regions has been shown to increase the risk of schistosomiasis transmission (Steinmann et al., 2006). Interestingly, water resources development projects seem to create favourable habitat for *Biomphalaria* snails, which might explain outbreaks or increased levels of intestinal schistosomiasis transmission. We selected three proxies to represent "human impacted" habitat types, namely (i) distance from nearest (large) dam; (ii) percentage of irrigated area; and (iii) the so-called anthromes or anthropogenic biomes (Ellis and Ramankutty, 2008). The latter describe the terrestrial biosphere in its contemporary, human-altered form using global ecosystem units defined by global patterns of sustained direct human interaction with ecosystems.

To minimise problems induced by collinearity among predictors, a correlation (Pearson's test) matrix was constructed based on 10,000 randomly extracted pixel values for each of the environmental predictor variables, with variables above a threshold of $r > 0.75$ not allowed to enter the same model. Data source, spatial resolution and maximum correlation r values to any other predictor variable are summarised in Table 1.

2.3. Snail species distribution models

Species distribution modelling was implemented using the MaxEnt approach proposed by Phillips et al. (2006), which has been shown to perform well compared to other predictive algorithms in a recent comparative study (Elith et al., 2006). MaxEnt is constructed by the distribution of the presence records in contrast to the background environmental conditions. MaxEnt estimates species' distributions by finding the distribution of maximum entropy subject to the constraint that the expected value for each environmental variable under this estimated distribution matches its empirical average (Phillips et al., 2006). MaxEnt can fit complex relationships to environmental variables through the use of, for example, threshold and hinge features interactions between environmental variables. However, such complex models are often difficult to specify *a priori* based on ecological theory, and we therefore chose to only fit linear, quadratic and product relationships for the snail models. For each snail species, a full model using all occurrence records for training were

Table 1
Overview of environmental predictors used to model the distribution of *Biomphalaria* spp., the intermediate host snail of intestinal schistosomiasis.

Name	Description	Source	Resolution	Correlation (max)
Bioclim2	Mean Diurnal Range	http://www.worldclim.org/bioclim	30″ (~1 km^2)	0.52
Bioclim10	Mean Temperature of Warmest Quarter	–	30″ (~1 km^2)	0.52
Bioclim11	Mean Temperature of Coldest Quarter	–	30″ (~1 km^2)	0.62
Bioclim12	Annual Precipitation	–	30″ (~1 km^2)	0.73
Bioclim15	Precipitation Seasonality (Coefficient of Variation)	–	30″ (~1 km^2)	0.46
Bioclim17	Precipitation of Driest Quarter	–	30″ (~1 km^2)	0.73
Irrigation_ar	Percentage of area equipped for irrigation	http://www.fao.org/geonetwork/Global Map of Irrigated area	5′ (~8 km^2)	0.29
Anthromes	Terrestrial biomes based on global patterns of sustained, direct human interaction with ecosystems	http://www.ecotope.org: Anthropogenic Biomes of the World	5′ (~8 km^2)	0.59
DistDams	Distance grid measuring distance to the nearest dam	http://www.fao.org/geonetwork/Database of African dams	30″ (~1 km^2)	0.72
DistSWB	Distance grid measuring distance to the nearest Surface Water Bodies	http://www.fao.org/geonetwork/: SRTM Surface Water Body Linear Outlines	30″ (~1 km^2)	0.72
SoilpH	Top soil pH, derived from the ISRIC-WISE soil database (vs 3.0)	http://www.isric.org/	0.5° (~50 km^2)	0.31
MODISVCF	A measure of percentage tree cover derived from Moderate Resolution Imaging Spectroradiometer (MODIS) data	http://www.landcover.org/data/vcf/	~500 m^2	0.59

developed for mapping and used with the biology-based GDD model for *S. mansoni*.

To address our study questions with regard to the relative importance of climate and habitat variables for snail distributions, we ran five models with different combinations of predictor variables for each species. The models can be summarised as follows: (i) climate (CLIM) only; (ii) habitat, including both natural (NATHAB) and human-impacted habitat (HUMHAB) variables; (iii) climate and natural habitat variables (CLIM + NATHAB); (iv) climate and human-impacted variables (CLIM + HUMHAB); and (v) a full model (CLIM + NATHAB + HUMHAB) with all 12 predictors.

The relative performance of each model was evaluated by a 10-fold cross-validation procedure, by randomly dividing the snail occurrence data in training and test data sets and using 10,000 randomly selected pseudo-absences from the whole study area. Models were calibrated on the training data and evaluated on the test data using a threshold-independent assessment measure, the area under the receiver operating characteristic (ROC) curves (AUC), which measures the accuracy of predictive distribution models (Lobo et al., 2008). For example, an AUC value of 0.5 indicates that the model predicts no better than a random model, while AUC values >0.75 are considered in the "best" model category (Phillips and Dudik, 2008). However, comparing models across species using AUC scores is problematic, as AUC is influenced by species' prevalence (Lobo et al., 2008). This issue was alleviated by only comparing AUC values among models within species. Additionally, we addressed the study questions by testing if certain classes of predictor variables contributed the strongest predictor variables for a species more often than expected by chance. This was assessed by classifying the most important variable (i.e. variable with the highest contribution to the training gain) for each species in the best performing model into pairs of mutually exclusive groups (climate *versus* habitat), and testing the group frequencies against the null expectation based on the number of variables in a group. Goodness of fit tests for whether the observed frequency of the most important predictor variable for each *Biomphalaria* species was implemented using the G-test adjusted using Williams' correction for the two-cell case (G_{adj}). To facilitate quantitative analysis of the potential change in species range size under future climate change scenarios, the modelled probability maps for the snail species were furthermore converted into Boolean presence/absence maps, using the threshold indicating maximum training sensitivity plus specificity (Liu et al., 2005).

All grid outputs from MaxEnt were subsequently handled in ArcGIS version 9.3 (ESRI; Redlands, USA) with the Geospatial Modelling Environment extension (*Geospatial Modelling Environment*: http://www.spatialecology.com). The statistical analysis was carried out in STATA/SE version 10 (StataCorp LP; College Station, USA) and Revolution R Enterprise version 4.0 (Revolution Analytics; Palo Alto, USA).

2.4. Parasite GDD models

The thermal development requirements of *S. mansoni* have been studied in detail (Pflüger, 1980, 1981). In brief, minimum and maximum temperatures for development of the parasite were established, as well as the number of GDD required to complete one life cycle within the intermediate host snail. The temperature–growth relationship was described by a hyperbola given in Eq. (1):

$$y = \frac{268}{x - 14.2} \tag{1}$$

with y representing the minimum time from miracidial infection to cercariae shedding (expressed in days), x denoting the mean temperature, 14.2 (expressed in °C) considered the theoretical temperature threshold, and 268 indicating the number of GDD that must be accumulated to complete one generation. The optimum temperature lies between 20 and 27 °C, while there is an upper threshold of approximately 35 °C. The developmental rate within this range was shown to follow a linear function of the mean environmental temperature (Pflüger, 1980, 1981).

GDD for each month of the year were calculated as the number of degrees above 14.2 °C, the minimum temperature required for development of *S. mansoni* multiplied by the number of days per month. Values were then summed over the year to give the accumulated GDDs for *S. mansoni* (AGDD). The AGDD value for each map pixel is calculated according to Eq. (2):

$$\mathrm{AGDD} = \sum_{j=1}^{12}\sum_{k=1}^{N_f}(T_{\mathrm{mean}(j)} - T_0)\mathrm{I}\{T_{\mathrm{mean}(j)} > T_0\} \tag{2}$$

where T_{mean} is the estimated minimum temperature required for parasite development and N_f the number of days in a given month. The number of potential generations per year that could occur for each grid can be calculated based on the number of GDDs that must

be accumulated to complete one generation. This measure has been phrased potential transmission index (PTI), following the nomenclature of Zhou et al. (2008), which gives an indication of where, in theory, one might expect schistosomiasis transmission to occur. As shown in Eq. (3), PTI is calculated as follows:

$$\mathrm{PTI} = \frac{\mathrm{AGDD}}{268} \tag{3}$$

2.5. Combining parasite GDD and intermediate host snail distribution models

Naturally, transmission of schistosomiasis will only occur if both the intermediate host (snail) and the definitive host (humans) are present, facilitated through human water-contact patterns. To account for this, we combined the GDD model with the intermediate host snail models. When the potential transmission index is weighed by the snail distribution models (the probability surface for snail species m), one gets an indication of the "degrees that count" for the parasite, i.e. fast generations of parasites are only relevant when the probability of the presence of the intermediate host snails is high. The weighed PTI is calculated according to Eq. (4):

$$\mathrm{PTI}_m = \mathrm{PTI} \times P_m \tag{4}$$

where P_m is the modelled snail habitat suitability (probability) for each of the m species of *Biomphalaria*. Weighed PTI was calculated based on all five model combinations (i to v) of climate and habitat variables for comparison.

2.6. Validation of PTI models against parasite prevalence data

To determine which of the model combinations fitted the parasite prevalence data described in Section 2.1 best, we fitted a suite of Bayesian logistic regression models in OpenBUGS version 3.1.1 (Imperial College & Medical Research Council; London, UK) (Lunn et al., 2009), using the snail and/or PTI model output as the explanatory variables. Let N_i be the number of individuals tested at location l_i, $i = 1,.., n$, Y_i the number of those found to be infected with *S. mansoni* and $\mathbf{X}_i = (X_{i1}, X_{i2},.., X_{ip})^T$ be the vector of p associated co-variates observed at location l_i. We assumed that Y_i arose from a Binomial distribution, that is $Y_i \sim Bin(N_i, p_i)$ with parameter p_i measuring infection risk at location l_i and model the relation between the *S. mansoni* infection risk and covariates $\mathbf{X}_i$ via the logistic regression $\mathrm{logit}(p_i) = \mathbf{X}^T\boldsymbol{\beta}$, where $\boldsymbol{\beta} = (\beta_1, \beta_2, \ldots, \beta_p)^T$ are the regression coefficients. To account for extra-binomial variation, a set of location-specific error terms (exchangeable random effects) $\boldsymbol{\varepsilon} = (\varepsilon_1, \ldots, \varepsilon_n)^T$ were included in the model. They are assumed to be independent, arising from a normal distribution $\varepsilon_i \sim N(0, \tau^2)$, where τ^2 accounts for the extra binomial variation in the infection risk data. The model can thus be written as shown in Eq. (5):

$$\log it(p_i) = \sum_{j=1}^{n} x_{ij} \times \beta_j + \varepsilon_j \tag{5}$$

To complete Bayesian model specification, we chose vague normal prior distributions for the regression coefficients, with mean 0 and variance 100, and an inverse gamma distribution for τ^2. Markov chain Monte Carlo simulation was applied to fit the models. We run a single chain sampler with a burn-in of 2000, followed by 20,000 iterations. Convergence was assessed by inspection of the ergodic averages of the model parameters. A suite of 14 logistic regression models representing different combinations of PTI and snail models were constructed, and the models were ranked based on their complexity and fit, compared using the deviance information criterion (DIC) (Spiegelhalter et al., 2002). The best performing models are considered the ones with the lowest DIC value. We then calculated the difference between each model's DIC and the DIC of the top-ranked model (Δ_i). The strength of evidence for any particular model is evaluated based on Spiegelhalter et al. (2002) suggestion that models with Δ_i values between 1 and 2 are as strongly supported as the "best" model, those with DIC values between 3 and 7 of the 'best' are only weakly supported and models with a Δ_i DIC more 7 higher are substantially inferior to the "best" model.

The PTI maps were furthermore converted to binary presence/absence of endemic transmission areas using a threshold of ≥ 1 (representing one "potential generation per year"). In the snail weighed PTI maps, endemic transmission was considered in areas that fulfilled both the PTI threshold and presence of at least one intermediate host snail species.

2.7. Climatic change scenarios

To evaluate the effect of climate change on the distribution of *Biomphalaria* snails, we used projections for the climatic normal period 2070–2099, hereafter referred to as 2080, derived from a widely used global circulation model (GCM), from the Hadley Centre for Climate Prediction and Research (HADCM3) (Gordon et al., 2000). This was chosen from a variety of GCMs (with their respective versions) that have been developed, tested and their results have been made available to the public by the Intergovernmental Panel on Climate Change (IPCC) (IPCC, 2007). Although GCM predictions are also available for earlier time points into the future (e.g. 2020 and 2050), we chose to focus on 2080 due to the spatio-temporal extent of our historical input data and the scale of analysis.

We used projections of the Wordclim climate parameters derived from two carbon dioxide (CO_2) emissions scenarios, A2 (medium-to-high emissions) and B2 (low-to-medium emissions) that corresponded to the IPCC Special Report on Emissions Scenarios (IPCC, 2007). Statistically disaggregated data at 5′ resolution were downloaded from CIAT (http://gisweb.ciat.cgiar.org/GCMPage/#). We used the MaxEnt snail species distribution models developed earlier to project the future climate distribution for each snail species to 2080. For the habitat variables, as no reliable future projections of changes in these exist, we made an assumption of no change for these predictors. We furthermore adopted a full dispersal scenario that assumes that a species can track its shifting suitable climatic space, and colonize all locations that are predicted to become suitable.

To assess the influence of projected future temperature rises on the parasite development rate, we repeated our calculations of GDDs based on the projected T_{mean} for 2080 (A2 and B2 scenarios), and produced a map of the future PTI. The changes in range sizes of the snail species and of endemic transmission of schistosomiasis areas were based on the thresholded presence/absence maps and calculated as $((R_{2080}/R_{\mathrm{current}}) - 1) \times 100$, where R represents the number of pixels where the species is predicted to be present.

3. Results

3.1. Snail species distribution models

Maps representing the current distributions, modelled with various combinations of environmental predictors, are displayed in Fig. 2 for the five considered *Biomphalaria* species in Africa.

Overall model performance based on AUC was very good ranging from 0.836 to 0.997. The combined CLIM + HAB model almost always had better predictive ability as measured by AUC compared to models based on either climate (CLIM) or habitat variables (HAB) alone (Table 2).

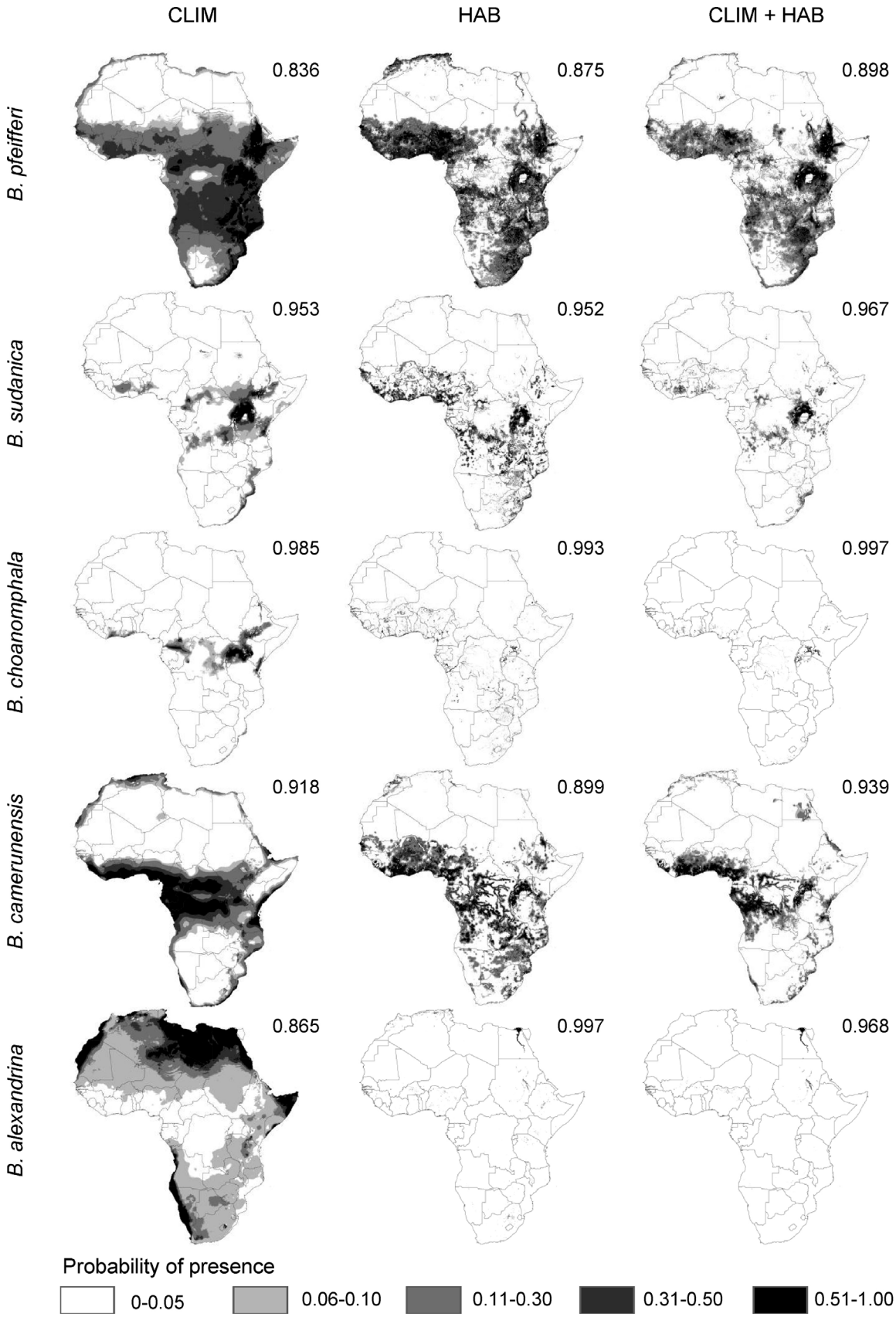

Fig. 2. *Biomphalaria* snail habitat suitability maps as modelled by MaxEnt. Maps for each of the five species of intermediate host snails are show for three selected combinations predictor variables (CLIM, climate variables only; HAB, habitat related variables only; CLIM + HAB, combining all predictor variables.) The area under the curve of the receiver operating characteristic (AUC) values for the individual models are shown in the top right corners of the maps.

Table 2
The predictive ability as measured by the area under the curve (AUC) values for the following snail models: (i) CLIM (six climate variables only); (ii) NATHAB + HUMHAB (natural and human-influenced habitat variables); (iii) CLIM + HUMHAB (climate and human-influenced habitat); (iv) CLIM + NATHAB (climate and natural habitat variables); and (v) CLIM + NATHAB + HUMHAB (all environmental predictors). Mean AUC* values ± 1 standard error are presented for 10 replicate models for each species of *Biomphalaria*. AUC should only be compared within a species, based on the different sets of predictors, and not between species.

#	Model	Intermediate host snail species				
		B. pfeifferi	*B. sudanica*	*B. choanomphala*	*B. alexandrina*	*B. camerunensis*
(i)	CLIM	0.836 (0.020)	0.953 (0.025)	0.985 (0.009)	0.865 (0.134)	0.918 (0.026)
(ii)	NATHAB + HUMHAB	0.875 (0.017)	0.952 (0.027)	0.993 (0.004)	0.997 (0.003)	0.899 (0.079)
(iii)	CLIM + HUMHAB	0.882 (0.009)	0.969 (0.017)	0.997 (0.002)	0.963 (0.092)	0.953 (0.044)
(iv)	CLIM + NATHAB	0.891 (0.015)	0.955 (0.024)	0.992 (0.007)	0.966 (0.088)	0.952 (0.027)
(v)	CLIM + HUMHAB + NATHAB	0.898 (0.020)	0.967 (0.019)	0.997 (0.001)	0.968 (0.089)	0.939 (0.066)

A closer look at the contributions to model training gain of each environmental predictor revealed that habitat-related predictors more often than climatic predictors were among the top three contributors (Fig. 3). In particular, human-impacted habitat predictors consistently were ranked in the top three for each of the five *Biomphalaria* species investigated, with the highest impact revealed on *B. pfeifferi* distribution (52% contribution to model training gain). The goodness of fit tests (adjusted G-test) of the relative importance of habitat predictors *versus* climate predictors based on full model (CLIM + NATHAB + HUMHAB), furthermore supported a predominance of habitat over climate predictors as the most influential predictor class across species ($G_{adj} = 16.5$, $p < 0.001$).

3.2. Snail species distribution models under future climate change

The best performing (highest AUC value) and most parsimonious model for each *Biomphalaria* species was projected onto the predicted situation in 2080, using two different climate change scenarios (A2 and B2). The resulting maps of probability of intermediate host snail occurrence were also thresholded into Boolean presence/absence maps, and the percentage change in range size for each species calculated (Figs. 4 and 5).

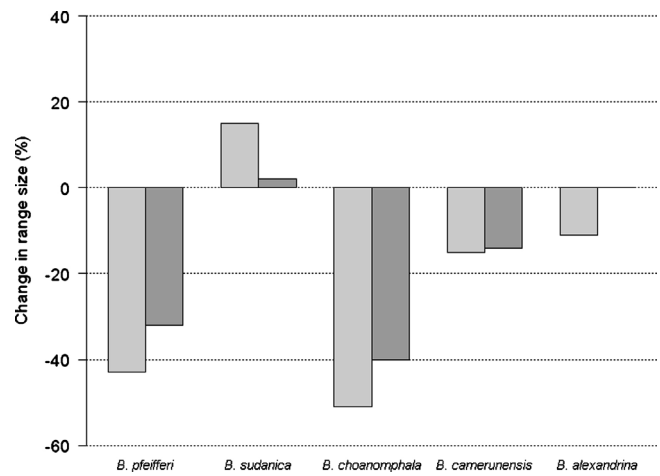

Fig. 4. Percent change (overall contractions or expansions) in range size predicted for five *Biomphalaria* species acting as intermediate host snails for *S. mansoni*. Predictions are based on the global circulation model HADCM3 for two scenarios (A2 (light grey) and B2 (dark grey)) in 2080.

3.3. PTIs of S. mansoni under current and predicted future climates

The maps of PTI across Africa are shown in Fig. 6. The first column represents the current conditions, and there is a substantial effect on the PTI pattern after weighing the maps with the modelled intermediate host snail distributions. Weighing the PTI with the snail models based on climatic data only (CLIM), "moves" the high transmission zone of intestinal schistosomiasis from the hot Sahara zone, south to more realistic ranges as known from the current distribution, but still predicts transmission in desert regions where transmission currently does not occur. Weighing the PTI by the snail models developed with both climate and habitat variables (CLIM + NATHAB + HUMHAB), further refines the distributional patterns of intestinal schistosomiasis transmission.

The bivariate logistic regression analysis showed that all combinations of snail models (alone or combined with PTI) were all significantly positively correlated with observed *S. mansoni* prevalence (data not shown). Un-weighed PTI on the other hand showed

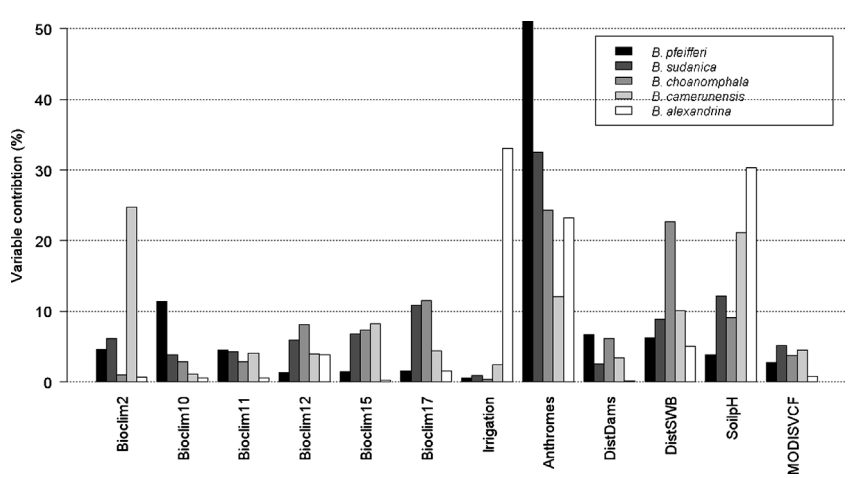

Fig. 3. Relative variable contribution to model training gain (based on the full CLIM + HAB model) per *Biomphalaria* snail species (average contribution in percent) in 5 × 10 replicate MaxEnt models.

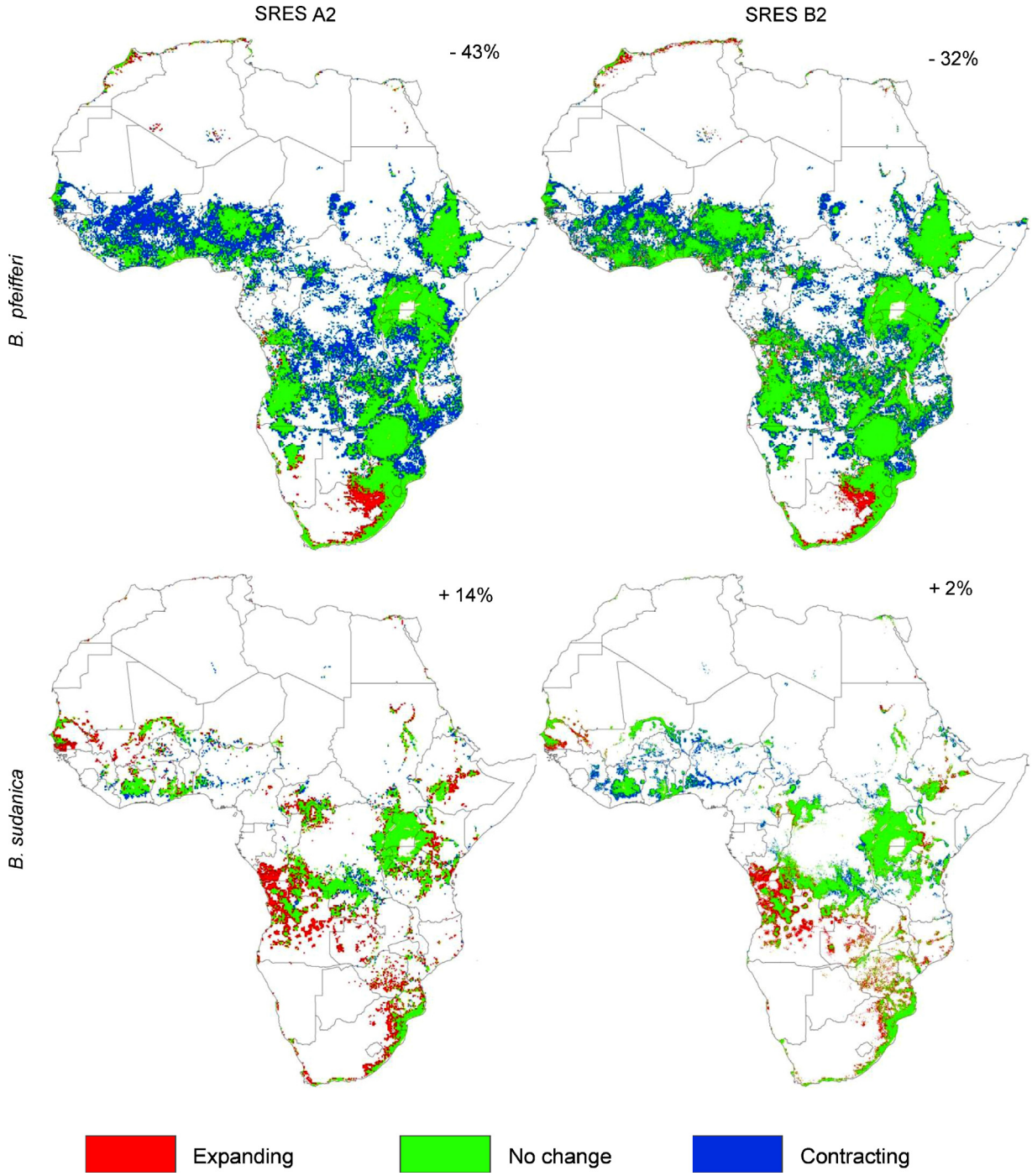

Fig. 5. Potential future expanding and contracting ranges of *B. pfeifferi* and *B. sudanica* under either the A2 or B2 emission scenarios (for 2080) put forth by the Intergovernmental Panel on Climate Change (IPCC). The maps are produced based on the thresholded versions of the full MaxEnt (climate and habitat) models. Red indicates new potential distribution by 2080, green shows areas of status quo between current and future climate scenarios and blue illustrates areas predicted to be unsuitable for the snails by 2080. The change in percentage (negative or positive) is given in the top right corner for each map.

no significant association with *S. mansoni* prevalence data. The Bayesian random effects model showed similar results. When interpreting our results it is important to bear in mind that our models do not take into account geographical dependence between survey locations. However, disease cases tend to cluster due to underlying common environments, and when spatially correlated data are analysed ignoring this correlation, the statistical significance of the covariates may be over- or under-estimated (Cressie, 1993). A common approach to explicitly account for this spatial autocorrelation in geostatistical data is to introduce another random effect based on the distance between locations (Diggle et al., 1998). However, due to the large number of locations in the current dataset this poses computational challenges (Lunn et al., 2000) that currently cannot be overcome. We thus refrain from interpreting on the size and significance of the parameter estimates and focus on the relative performance of each model combination.

The DIC for the multivariate logistic regression model are given in Table 3 together with the difference between this and the DIC for every other model. The first nine models compare the unweighed PTI model to various snail and snail-weighed PTI models to

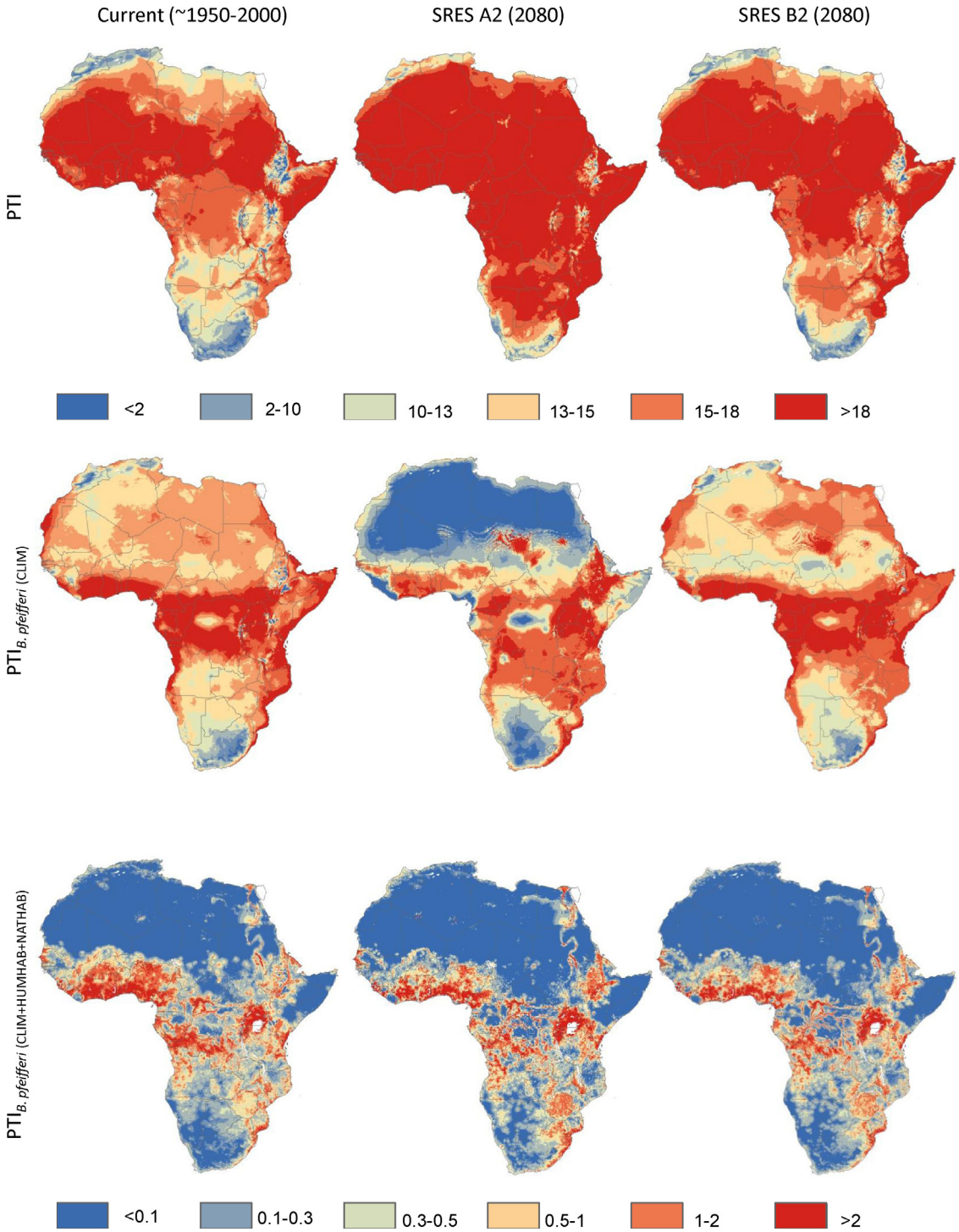

Fig. 6. Potential transmission index (PTI) for *S. mansoni* under current conditions and under two climate change scenarios proposed by the Intergovernmental Panel on Climate Change (IPCC). The first row of the maps illustrates the changes in PTI under the assumption that temperature alone is the limiting factor for the potential generations of *S. mansoni* over the year. The second row shows PTI, as weighed by snail SDM models based only on climatic variables (CLIM models), whereas the last row shows PTI weighed by the full (CLIM + NATHAB + HUMHAB) intermediate host snail models.

investigate whether, by adding the various snail species the model fit improved. The snail distribution model outputs included in these models are the best performing according to AUC (highlighted in Table 2). Between models 1-9, the model with PTI weighed by *B. pfeifferi* and *B. choanomphala* showed the best fit (smallest DIC). To test the extent to which this particular model was influenced by the environmental predictor classes used to develop the snail distribution models for these two species, five more models were developed and compared (model numbers 10–14). The model that best fitted the observed parasite prevalence data is the PTI weighed with modelled snail habitat suitability based on the full set of predictors (CLIM + NATHAB + HUMHAB).

Based on the thresholded PTI maps, we calculated the percentage change in endemic *S. mansoni* transmission areas for two different scenarios for the year 2080. We visualised the areas where disease ranges are expected to contract or expand, by subtracting the current and future maps. Maps showing the geographical change from the current to the A2 and B2 scenarios of PTI

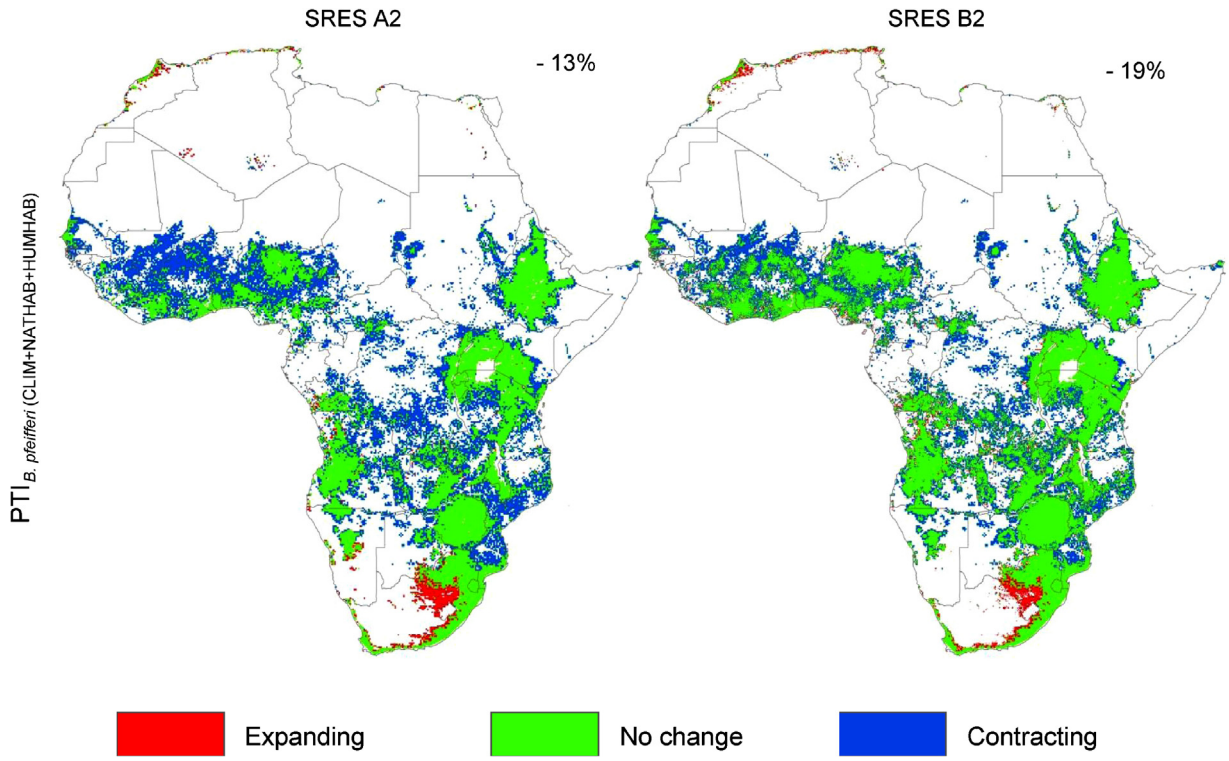

Fig. 7. Potential future expanding and contracting areas of intestinal schistosomiasis transmission based on either the A2 or B2 emission scenarios proposed by the Intergovernmental Panel on Climate Change (IPCC). Red indicates new potential areas by 2080, green shows areas of status quo between current and future climate scenarios and blue illustrates areas predicted to be unsuitable for substantial transmission by 2080.

(weighed by the 2080 snail CLIM + NATHAB + HUMHAB models) are shown in Fig. 7.

4. Discussion

Contrary to conventional wisdom that diseases are prone to expand their geographical ranges in the face of global warming (Epstein, 2000, 2010), our forecasts indicate an overall future contraction of suitable intermediate host snail habitat for four out of five modelled *Biomphalaria* species that are responsible for *S. mansoni* transmission in Africa. By combining an intermediate host snail model for the most important host species, *B. pfeifferi*, with a GDD model for parasite development, results suggest that climate change is likely to cause net contraction of 13–19% of the current transmission area for *S. mansoni* by 2080. However, while some areas in Africa are prone to experience a contraction (West and Central Africa), others in southern regions are likely to experience an expansion, emphasising the importance of a two-tailed hypothesis testing of disease shifts with climate changes (diseases can go up and down) (Lafferty, 2009).

The results of our study highlight three important issues in climate change impact studies of infectious diseases, namely (i) climate change will not unilaterally increase disease; (ii) climate *per se* is not the only important driver of current patterns,

Table 3
Deviance information criterion (DIC) values for various snail and PTI model combinations together with the difference between this and the DIC for every other model. The best performing models are considered the ones with the lowest DIC value. Δ_a DIC is the difference between a given model and the best performing model (comparing models 1-9), and Δ_b DIC is the difference in DIC to the best performing overall model. The first nine models compare the un-weighed PTI model to various snail and snail-weighed PTI models (based on the snail models with the best AUC scores) to investigate whether adding the various snail species to the model improved model fit. Then, based on the model with the highest DIC (model 7), a series of five models were developed to assess if the various snail model environmental predictor classes had an effect on the PTI-weighed model performance (i.e. snail model combination *i*–*v*).

#	Model (covariates)	DIC	Δ_aDIC	Δ_bDIC
1	PTI	16,179.4	199.0	209.5
2	$P_{B.pf}$	16,051.3	70.9	81.4
3	$P_{B.pf}$, $P_{B.sud}$, $P_{B.alex}$, $P_{B.cho}$, $P_{B.cam}$	16,070.1	89.7	100.2
4	$PTI_{B.pf}$	16,019.9	39.5	50.0
5	$PTI_{B.pf}$, $PTI_{B.sud}$	16,019.8	39.4	49.9
6	$PTI_{B.pf}$, $PTI_{B.alex}$	16,019.2	38.8	49.3
7	$PTI_{B.pf}$, $PTI_{B.cho}$	**15,980.4**	0.0	10.5
8	$PTI_{B.pf}$, $PTI_{B.cam}$	16,109.8	129.4	139.9
9	$PTI_{B.pf}$, $PTI_{B.sud}$, $PTI_{B.alex}$, $PTI_{B.cho}$, $PTI_{B.cam}$	16,071.2	90.8	101.3
10	$PTI_{B.pf(CLIM)}$, $PTI_{B.cho(CLIM)}$	16,080.3	110.4	110.4
11	$PTI_{B.pf(NATHAB+HUMHAB)}$, $PTI_{B.cho(NATHAB+HUMHAB)}$	16,169.5	199.6	199.6
12	$PTI_{B.pf(CLIM+NATHAB)}$, $PTI_{B.cho(CLIM+NATHAB)}$	16,001.1	31.2	31.2
13	$PTI_{B.pf(CLIM+HUMHAB)}$, $PTI_{B.cho(CLIM+HUMHAB)}$	16,009.7	39.8	39.8
14	$PTI_{B.pf(CLIM+NATHAB+HUMHAB)}$, $PTI_{B.cho(CLIM+NATHAB+HUMHAB)}$	**15,969.9**	0.0	0.0

B.pf, *B. pfeifferi*; B.sud, *B. sudanica*; B.alex, *B. alexandrina*; B.cho, *B. choanomphala*; B.cam, *B. camerunensis*.

and thus not of future distributions; and (iii) taking the distribution of the intermediate host (or vectors in case of vector-borne diseases) explicitly into account is essential.

The net effect of climate change on a complex life cycle disease system such as schistosomiasis will reflect the differential effects of e.g. temperature on all life history stages of both intermediate hosts and parasites. In the current study, when the distribution of the intermediate host snails and their dependence on suitable aquatic habitats is not accounted for, the geographical areas with high potential parasite generation time, and thus transmission, is predicted to expand substantially in Africa under the two IPCC climate change scenarios considered here (Fig. 6). Given that the majority of the intermediate host snails are predicted to experience a reduction in area of occupancy (e.g. 43% for *B. pfeifferi*) underscores the importance of combining our knowledge of the biology and ecology of both parasites and intermediate hosts (Fig. 5).

There is considerable geographical heterogeneity in our model predictions, with some areas becoming increasingly suitable for some species but not for others and *vice versa*. In South Africa, for example, *B. pfeifferi* is likely to expand its current distribution with global warming, but only if the current absence of snails and disease transmission truly reflect unfavourable climatic space rather than lack of otherwise suitable freshwater habitats. That this could indeed be the case, is supported by a more than 30-year-old observation that large parts of the areas in southern Africa, from which *Biomphalaria* is absent, contain apparently suitable snail habitats and consequently it seems that unfavourable climatic temperature is likely to be a factor of overriding influence in excluding the snails (Brown, 1978). Unfavourable climatic temperature has also been established as an important limiting factor for the occurrence of schistosomiasis japonica in P.R. China. However, in P.R. China, predicted occurrence seems to be determined by the lower temperature threshold for parasite and snail development, and hence the distribution of the disease is likely to expand as temperature increases (Yang et al., 2005, 2010b; Zhou et al., 2008). The seemingly contradictory results from Africa and P.R. China again highlight the importance of incorporating knowledge of intermediate host snail life history. In P.R. China, the intermediate host snail, *Oncomelania* spp., are not only another genus, they also have a very different life history (e.g. amphibious rather than aquatic in the case of *Biomphalaria*). Even within countries the ecological requirements and climatic tolerances between host snail species of the same genus vary considerably (Stensgaard et al., 2006).

As when modelling any future impacts, there are naturally several assumptions and limitations to keep in mind and numerous interacting factors will influence the future distribution and prevalence of intestinal schistosomiasis. First and foremost, there are acknowledged problems with many current methods for predicted future responses of species to climate changes, and relatively few technical advances have been made to overcome these issues (Elith et al., 2010). Our models are based solely on climate change scenarios (changes in temperature and rainfall) with the well-known associated uncertainties—and thus an assumption of "unchanged" natural and man-made habitat related factors in 2080. Our results in particular point to the latter factors as important determinants of the contemporary distribution of the snail–parasite system, leading to poor predictive power under warming scenarios. The importance of man-made habitats for intermediate host snails and schistosomiasis transmission has been demonstrated several times, and examples of how construction and operation of intense water resources development schemes have created suitable *Biomphalaria* snail habitats and enhanced *S. mansoni* transmission are numerous (Steinmann et al., 2006). Predictions of potential contractions or expansions of disease are thus strongly dependant on future scenarios of human activities that impact or create snail habitats, and for which we currently have no future scenario to include in our models. With the increasing human demands placed on the world's supplies of freshwater, pervasive changes have, and are likely to occur in tropical freshwater habitats that influence *Biomphalaria* and consequently *S. mansoni* (UNFCCC, 2006).

Secondly, our snail distribution models indicate differing responses of intermediate host snail species to climate change with the second most widespread intermediate host, *B. sudanica*, predicted to expand its range size. We know very little about the abiotic requirements of this snail, but clearly our results warrant further studies in this regard. In general, a complex parasite-snail system such as schistosomiasis, with multiple intermediate hosts (and parasite strains) interacting to shape the current patterns of disease, render it difficult to make accurate species-specific predictions. It is essential to embark on more experimental work using species-specific host–parasite combination over a range of temperatures, to validate and improve on the accuracy of the predictive models.

Intriguing insights into the flexibility of schistosomes to parasitize a wide variety of species might also be gained, by considering the co-evolutionary history of parasite and snail (Morgan et al., 2001). The parasites might be expected to evolve faster than their intermediate hosts in response to climate change, due to their typically shorter generation times (Raffel et al., 2008). This has implications for predicting schistosome range shifts in response to climate change, because the parasites might be more capable of adapting to new climatic conditions compared to their intermediate snail hosts. Therefore, parasites might be more limited by dispersal, or by the ability of their hosts to adapt and/or disperse, than by their ability to adapt to new environmental conditions.

However, it has been suggested that rather than co-evolving with a single host, *S. mansoni* is expanding its host range (Després et al., 1992). History suggests that *S. mansoni* has a large potential for a wider scope of intermediate host species as indicated by the recent (and on-going) colonization of the South American continent (Morgan et al., 2001). Thus, while currently specific mainly to *B. pfeifferi* in Africa, a contraction in range size of this species might not necessarily mean less transmission potential for *S. mansoni* in Africa in the long run.

Finally, it is important to note that the current study naturally is unable to explicitly account for the small-scale focality in prevalence of schistosomiasis (before and after preventive chemotherapy, now as well as in future). We are duly aware that although sharing many common umbrella predictors such as temperature and rainfall, this focality is largely determined by social–ecological contexts, hence local aquatic and non-terrestrial environmental factors, interplaying with local levels of human sanitation, behaviour and hygiene infrastructures (Standley and Stothard, 2010; Utzinger et al., 2011). However, the purpose of the study is not local-scale precision mapping of schistosomiasis risk for spatial targeting of control interventions. For that purpose national or sub-national study scales are more suitable, which has been described in detail elsewhere (Raso et al., 2005; Clements et al., 2008; Vounatsou et al., 2009; Schur et al., 2013; Standley et al., 2013).

5. Conclusions and outlook

Forecasting the future distribution of species and disease systems is inherently complex and uncertainty levels are high, but necessary if we are to plan ahead in disease control efforts. To make prediction models for schistosomiasis truly holistic, important drivers such as socio-economic and impacts of on-going disease control must be integrated. The continued application of chemotherapeutic control measures and a hoped-for overall rise in the standard of living in the developing world can be expected to lower both intensity and prevalence of infection. In future

studies, by combining more species-specific details and knowledge of the complex of ecological, societal and evolutionary aspects of schistosomiasis transmission, we hope to be able to deliver better predictions of both current and future disease transmission.

While our results indicate the reverse of the conventional wisdom, it is consistent with the increasingly accepted view that climate change is likely to reduce biodiversity. The coming years will prove to be fascinating in deciphering the net impact of the many contrary trends impacting schistosome parasites and their intermediate and definitive hosts. Understanding how these myriad of factors interact to shape the global distributions of schistosomiasis and other human infectious diseases with complex life cycles now and in the future – be they parasites or otherwise – and ultimately mediate their impact on human well-being is a daunting, but important challenge.

Conflicts of interest

All authors declare that they have no conflict of interest concerning the work reported in this manuscript.

Contributors

A.S. Stensgaard designed the study, analysed the data and drafted the manuscript. A.S. Stensgaard, T.K. Kristensen and P. Mubita collated the snail data. E. Hürlimann, P. Mubita, N. Schur and A.S. Stensgaard collated the parasitological data. J. Utzinger, P. Vounatsou, C.F.L. Saarnak, C. Simoonga, C. Rahbek and T. K. Kristensen revised the manuscript. N.B. Kabatereine and L.A. Tchuem Tchuenté gave critical input and re-appraisal in the manuscript. All authors read and approved the final version of the manuscript prior to submission. A.S. Stensgaard and T.K. Kristensen are guarantors of the paper.

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