CURRENT AND FUTURE DISTRIBUTION OF A PARASITE WITH COMPLEX LIFE CYCLE UNDER GLOBAL CHANGE SCENARIOS: *ECHINOCOCCUS MULTILOCULARIS* IN EUROPE

Running Head: *Echinococcus multilocularis* distribution in Europe

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GRAPHICAL ABSTRACT

We described the ecological niche of *Echinococcus multilocularis*, a zoonotic cestode with a complex life cycle, identifying four major drivers of its distribution (temperature of the coldest quarter, forest cover, urban cover and precipitation seasonality) and predicted its current and future distribution in Europe. Our analyses showed an increase of habitat suitability at northern latitudes and in the Alpine region and a loss of suitable areas in central Europe. Our results shed light on how complex life cycle parasites respond to global changes.

Figure 4

ABSTRACT

Global change is expected to have complex effects on the distribution and transmission patterns of zoonotic parasites. Modelling habitat suitability for parasites with complex life cycles is essential to further our understanding of how disease systems respond to environmental changes, and to make spatial predictions of their future distributions. However, the limited availability of high-quality occurrence data with high spatial resolution often constrains these investigations. Using 449 reliable occurrence records for *Echinococcus multilocularis* from across Europe published over the last 35 years, we modelled habitat suitability for this parasite, the aetiological agent of alveolar echinococcosis, in order to describe its environmental niche, predict its current and future distribution under three global change scenarios, and quantify the probability of occurrence for each European country. Using a machine learning approach, we developed large-scale (25x25 km) species distribution models based on seven sets of predictors, each set representing a distinct biological hypothesis supported by current knowledge of the autecology of the parasite. The best-supported hypothesis included climatic, orographic and land-use/land-cover variables such as the temperature of the coldest quarter, forest cover, urban cover and the precipitation seasonality. Future projections suggested the appearance of highly suitable areas for *E. multilocularis* towards northern latitudes and in the whole Alpine region under all scenarios, while decreases in habitat suitability were predicted for central Europe. Our spatially explicit predictions of habitat suitability shed light on the complex responses of parasites to ongoing global changes.

INTRODUCTION

Ongoing global change is dramatically influencing species distributions and biology, leading to range shifts and declines in population size and viability, with the most recent estimates predicting that 57–70% of all animal species will be extinct by 2050 (Román-Palacios & Wiens, 2020). Global change also drives the spread and outbreak of many infectious diseases, in both human and wildlife populations (Jones *et al.*, 2008, Kutz *et al.*, 2005, Patz *et al.*, 1996). Since it is estimated that more than 60% of known human infectious diseases, and about 75% of new or emerging infectious diseases are caused by pathogens of animal origin (zoonoses; Jones *et al.*, 2008, Taylor *et al.*, 2001), understanding the impact of the global change on parasite distribution and prevalence is considered of critical public health concern (Moffett *et al.*, 2007).

Increasing evidence suggests that the effect of climate change is even more pronounced in zoonotic parasite species with complex life cycles and tight trophic dependencies (Parmesan, 2006, Tylianakis *et al.*, 2008); that is, the greater the complexity of parasite life cycles, and their relationships with multiple hosts, the higher the risk of extinction of both parasites and their hosts (Rogers & Randolph, 2006). However, although modelling the distribution of complex life cycle parasites is considered urgent, such analyses are often hampered by the lack of reliable occurrence data (Johnson *et al.*, 2019).

Echinococcus multilocularis (Leuckart 1863) (*Em* hereafter) is a complex life cycle parasite and the aetiological agent of alveolar echinococcosis (AE), the third most relevant human food-borne disease worldwide (FAO/WHO, 2014). Extensive, high-quality occurrence data for this species are available in Europe as a result of its medical relevance. Therefore, modelling the distribution of this parasite under various global change scenarios provides the opportunity to investigate how habitat suitability of parasites with complex life cycles might be influenced by environmental changes.

Em is a dixenous parasite with a sylvatic cycle that typically involves foxes (*Vulpes* spp.), wolves (*Canis lupus*), and other canids such as coyotes (*C. latrans*) and golden jackals (*C. aureus*) as definitive hosts, whereas small mammals such as rodents act as intermediate hosts (Rausch, 1967, Romig *et al.*, 2017). Adult worms reproduce in the canid intestine, and the eggs are released in the environment with the faeces after passing through the intestinal lumen. Eggs are then accidentally ingested by an intermediate host, and oncospheres (first larval stage) are released and reach the target organs (mostly lungs and liver) where they develop into the asexually reproducing metacestode (second larval stage; Thompson *et al.*, 2017). At this stage, *Em* causes a tumor-like infiltrative and destructive growth in the liver and other target organs of the intermediate hosts causing severe clinical conditions which are often fatal (Torgerson *et al.*, 2010, Vuitton *et al.*, 2015). Finally, the metacestode larvae mature into protoscoleces (the last larval stage), and the cycle is completed when a canid definitive host preys on an infected intermediate host.

Feral and domestic dogs and cats are also competent definitive hosts (Romig *et al.*, 2017, Thompson *et al.*, 2017), but there are also several aberrant or ‘dead-end’ hosts, including the domestic pig and wild boar, as well as humans (Romig *et al.*, 2017, Wahlstrom *et al.*, 2011). ‘Dead-end’ hosts ingest the eggs accidentally acting as intermediate hosts, but transmission is interrupted as no definitive host is reached by the parasite (Romig *et al.*, 2017).

Em has an extensive geographical range in the northern hemisphere, including an endemic region in central Europe (Austria, France, Germany and Switzerland), northern and central Eurasia, and North America (Thompson *et al.*, 2017). In the last three decades, the distribution of this parasite has expanded considerably, to include many other European countries, such as the

Baltic countries, Belgium, Croatia, the Czech Republic, Denmark, Hungary, Italy, Liechtenstein, Luxembourg, the Netherlands, Norway, Poland and the Slovak Republic (Bagrade *et al.*, 2008, Beck *et al.*, 2018, Casulli *et al.*, 2005, Dán *et al.*, 2018, Eckert & Deplazes, 1999, Romig *et al.*, 2017). However, the ecological processes underlying the expansion of *Em* are still unknown. Several authors have suggested possible causes, including the dispersal of *Em* with red foxes, the expanding distribution of certain intermediate hosts, changes in land use, and improved diagnostics (Vuitton *et al.*, 2015, Vuitton *et al.*, 2003). However, given that the most common definitive host is the red fox, a wide-ranging species present across the whole European continent (Hoffmann & Sillero-Zubiri, 2016), and the great variety of intermediate rodent hosts available as prey to this carnivore, host range is unlikely to be a limiting factor. Climate, instead, is known to influence *Em* distribution (Giraudoux *et al.*, 2013), and a preference for colder regions and/or areas with a higher humidity has been reported from several European countries (*e.g.*, Slovakia, Germany; Miterpáková *et al.*, 2006, Staubach *et al.*, 2001), as well as other areas (*e.g.*, Central Asia; Shaikenov, 2006).

In the case of *Em*, the overwintering egg stage are highly resistant to temperatures ranging from -18 to 4°C and high humidity, but not extreme temperatures or dry conditions (Veit *et al.*, 1995). Primary terrain attributes, such as elevation, and land use are also known to influence the distribution and biology of *Em* (Thompson *et al.*, 2017). A recent review suggested that a combination of host characteristics and assemblages, differential virulence in different hosts, and climate conditions might be acting in limiting *Em* distribution compared to other species of the *Echinococcus* genus (Massolo *et al.*, 2022).

In addition to the impact of climate, the environmental niche of *Em* in Europe has never been characterized, and spatially explicit predictions of current and future habitat suitability for the species in Europe are still missing despite their usefulness for surveillance efforts (Atkinson *et al.*, 2013). Large-scale eradication of this parasite is deemed unlikely and instead, local scale anthelmintic baiting campaigns in foxes are recommended in areas of high transmission to reduce environmental contamination with parasite eggs (Hegglin & Deplazes, 2013). Hence, identifying the environmental drivers affecting its current and future distribution might help to deploy cost-effective interventions.

The objectives of this study were then to:

i) describe the currently reported and potential presence of *Em* in Europe;

ii) characterize and model the large-scale environmental niche of *Em* in Europe by building and testing models based on different sets of predictors and representing contrasting biological hypotheses;

iii) predict *Em* distribution in Europe in the near future (2041-2060) under three global change scenarios;

iv) inform the assessment of the zoonotic transmission risk of *Em* for each European country under current and future conditions.

MATERIALS AND METHODS

Echinococcus multilocularis presence data

Presence data for *Em* were compiled from georeferenced records from across Europe. Of these, 212 were downloaded from the freely accessible EmsB Website for *Echinococcus* Typing – EWET Project (https://ewet-db.univ-fcomte.fr/) developed by (Knapp *et al.*, 2017), a database of the microsatellite profiles of *E. multilocularis* covering 12 European countries. In addition, an exhaustive literature search performed on the 6th February 2020 in the SCOPUS and Google Scholar databases provided the remainder of the occurrence records. The search was performed using the keywords "*Echinococcus multilocularis*" AND "Europe", resulting in a set of publications from which we selected those that: i) reported the presence of the parasite in the most common definitive host, *V. vulpes*, and; ii) indicated the precise coordinates, or at least the municipality where infected foxes were collected. If only municipality was available, we used Google Maps to calculate the coordinates of the center of the municipality for a particular record. Since the red fox is the most highly cited definitive host for *Em* (Romig *et al.*, 2017), and studies of intermediate and other hosts are scarce, to guarantee the coherence of the dataset, we excluded studies involving hosts other than red fox (*e.g.,* humans, companion animals, intermediate hosts or rare definitive hosts).

To remove spatial sampling bias from the occurrence records, which could have resulted in an over-representation of the associated environmental parameters and, consequently, a biased prediction of *Em* distribution, the area of Europe between 24°W to 44°E longitude and 30°N to 80°N latitude was divided into 57,120 raster cells (0.25° resolution; *i.e.*, ~ 25x25 km) using the Geographic World Geodetic Survey 1984 (WGS_84) Coordinate System (GCS). One biological record of *Em* for each grid cell was randomly selected and spatial filtering in R (version 3.6.3; R Core Team 2020) was performed, selecting 75 % of data while maximizing the distance between records. This filtering process was essential to reduce spatial autocorrelation, as well as to avoid higher omission errors (false negatives) and commission errors (false positives; Kramer-Schadt *et al.*, 2013).

Environmental characterization

To model the potential distribution of *Em* in Europe, we selected two time periods: i) 1970-2000, to describe the parasite's environmental niche and current distribution; and ii) 2041-2060, to predict the future distribution of *Em*, and for which climate and Land-Use/Land-Cover (LULC) predictions are available. Since we wanted to test the effect of climatic variables, which are typically defined over a 30-year period (Matthews *et al.*, 2021), we decided to use this time period, rather than a shorter interval that matched the temporal distribution of occurrences.

Nineteen bioclimatic variables known to be drivers of species distributions (Hijmans *et al.*, 2005) were used to describe the climatic components of the parasite environmental niche, representing annual trends (*e.g.*, mean annual temperature, annual precipitation), seasonality (*e.g.*, annual range in temperature and precipitation) and extreme or limiting environmental factors (*e.g.*, temperature of the coldest and warmest month, precipitation of the wet and dry quarters). We downloaded current climatic indices (computed over the period 1970-2000) from the WorldClim 2 dataset (Fick & Hijmans, 2017). The bioclimatic data for the 2041-2060 period were based on three Representative Concentration Pathways (RCPs; Moss *et al.*, 2008, Weynat *et al.*, 2009), or climate scenarios: RCP2.6 (optimistic scenario), RCP4.5 (moderate scenario) and RCP8.5 (pessimistic scenario). To represent the components of uncertainty in future projections, we used three General Circulation Models retrieved from the WorldClim Coupled Model Intercomparison Project - Phase 5 dataset (Taylor *et al.*, 2012): HadGEM2-ES, IPSL-CM5A-LR, MIROC5 (Sanderson *et al.*, 2015). Results from the most recent CMIP6 were not used as they did not include all three climatic scenarios selected above. Climatic data were downloaded at a 10 min resolution (~ 18.5 km) and resampled at a 25 km resolution with the 'resample' function in the *raster* R package (Hijmans & van Etten, 2012). Although at continental and global scales, climate is the major factor driving species distributions (Pearson & Dawson, 2003), primary terrain attributes, such as elevation and slope, can also influence the distribution and biology of *Em*, especially in heterogeneous montane zones such as the Alps (Romig *et al.*, 2017). Hence, median elevation raster data at a 30 arc-second resolution were obtained from the Global Multi-resolution Terrain Elevation Data (GMTED) 2010 (United States Geological Survey - available at https://topotools.cr.usgs.gov). Slope, aspect, roughness, Topographic Position Index (TPI) and Terrain Ruggedness Index (TRI) raster layers were then generated from median elevation raster data with the 'terrain' function of the *raster* R package (Hijmans & van Etten, 2012) in R 3.6.3 (R core Team 2020) and used to provide information on the geomorphology of the landscape, which served as a proxy for terrain complexity.

Since correlation often occurs within or between bioclimatic and GMTED layers (Cruz-Cardenas *et al.*, 2014, Merow *et al.*, 2013, Warren *et al.*, 2014), we applied a Principal Components Analysis (PCA) to the 19 climatic and five orographic variables to remove collinearity among predictors. PCA was performed with the varimax rotation method in the *jmv* R package version 1.6 (available at https://cran.r-project.org/web/packages/jmv/index.html; Selker *et al.*, 2022). Since correlation among variables may vary in in different time periods, and as models fitted with PCs may behave erratically when transferred to different scenarios (Warren *et al.*, 2014), we avoided the direct use of the PCs as predictors in the models; instead, for every PC, we selected the variable with the highest coefficient. Correlation among the chosen variables was then tested using the *stats* R package (Version 4.1.0; available at https://stat.ethz.ch/R-manual/R-devel/library/stats/html/stats-package.html).

For the parasite cycle to persist in a particular area, both the definitive and intermediate hosts must be present. Therefore, we included a subset of LULC categories considered proxies of environments where *Em* hosts are usually found as environmental variables in the model. LULC categories for the current time were described using the CORINE Land Cover Map of Europe (European Commission, European Environment Agency and European Topic Centre on Land Cover 1994) for 2018. We reclassified the original 0.1 km resolution map to obtain a set of layers describing the percentage cover of different LULC classes at the 28 km resolution, focusing on three categories that best represent habitats of red fox and their rodent prey according to literature (see Romig *et al.*, 2017 for a review of the ecology of the parasite): I) Open, which included the subcategories I-i) Land under a rotation system, I-ii) Pastures, I-iii) Land principally occupied by agriculture, with significant areas of natural vegetation, I-iv) Natural grasslands, I-v) Moors and heathlands; II) Forest, which included II-i) Broad-leaved forest, II-ii) Coniferous forest, II-iii) Mixed forest; III) Urban, with subcategories III-i) Continuous urban fabric, III-ii) Discontinuous urban fabric. To represent the future conditions for LULC variables, we used the GCAM dataset provided by (Chen *et al.*, 2020), covering three representative SSP scenarios: SSP1 'Sustainability', SSP3 'Regional rivalry', and SSP5 'Fossil-fueled development' (Di Marco *et al.*, 2019, Kim *et al.*, 2018). Hence, our projections described three SSP-RCP scenarios: SSP1-RCP2.6 (low climatic impact), SSP3-RCP4.5 (medium climatic impact), SSP5-RCP8.5 (severe climatic impact).

Machine learning modelling

Due to unplanned sampling in the collection of presence data, and lack of homogeneity in temporal and spatial sampling effort, we chose the Maximum Entropy algorithm (Maxent; Version 3.4.1; Phillips *et al.*, 2006), a machine learning technique developed to classify the probability of species occurrence as a function of a set of environmental variables. Maxent is considered among the best-performing methods for modelling species distributions and allows fine-tuning of model complexity (Muscarella *et al.*, 2014).

We formulated seven biological hypotheses with appropriate combinations of environmental layers to be included in the model (Table 1) and developed a cycle of models for each one. To find the appropriate balance between the goodness-of-fit and model complexity, we generated 360 candidate models for each hypothesis running Maxent with the *ENMeval* R package (Muscarella *et al.*, 2014). Since the regularization multiplier β is a means to reduce collinearity and the risk of overfitting (Phillips *et al.*, 2006, Rodriguez-Merino *et al.*, 2018, Warren *et al.*, 2014), and it is advisable to adjust the value of β as the default settings may not match the empirical conditions of all systems (Phillips & Dudik, 2008), we varied β from 0 to 1 in increments of 0.1 and from 1 to 10 in increments of 0.5. The algorithm was run using six possible combinations of feature classes (linear = L, quadratic = Q, product = P, threshold = T, hinge = H): I) L; II) LQ; III) H; IV) LQH; V) LQHP; VI) LQHPT (Table S1). The models were run with 10,000 random background points. To ensure a robust test of model performance, we used a block cross-validation procedure (Muscarella *et al.*, 2014) where data are split into *k* geographically independent blocks and *k* models are developed using *k*-1 blocks for training, and the remaining for testing (Muscarella *et al.*, 2014). We developed this procedure using the *ENMeval* R package with *k* = 4. Within each cycle of models elaborated using the different combinations of environmental variables, the model with the lowest Akaike Information Criterion (AIC; Burnham & Anderson, 2004) value was selected as the best model of the cycle.

The Area Under the Receiver Operating Characteristic (ROC) Curve computed on test data (AUCtest; Fielding & Bell, 1997), and the difference between the AUC computed on training and test data (AUCdiff; Radosavljevic & Anderson, 2014) were also computed for the seven best-performing models to evaluate predictive ability according to the most widely used measure of SDM performance (AUC_{test}), as well as to quantify overfitting (Radosavljevic & Anderson, 2014). Within the seven best-performing models, we identified the model showing the best trade-off among the three evaluation metrics (*i.e.*, AIC, AUC_{test}, AUC_{diff}), and used it to gauge support for the corresponding biological hypothesis on the drivers of *Em* distribution, project current habitat suitability for the species, and examine the response curves of the environmental factors. Response curves represent the relationship between the predicted relative probability of species occurrence and the values of each environmental predictor and are useful for checking the ecological validity of a model (Elith *et al.*, 2005), as well as to characterize the ecological niche of the modelled species.

Future projections

Future projections (hereafter, raw projections) for the period 2041-2060 were developed for each GCM and the mean among the three projections was used to represent future habitat suitability for a given SSP-RCP scenario. The standard deviation between the three projections was computed to describe the uncertainty deriving from the different scenarios (Beaumont *et al.*, 2008, Porfirio *et al.*, 2014). The genetic diversity of *Em* is higher in the endemic area of central Europe compared to surrounding areas (Knapp *et al.*, 2009). Therefore, an increased adaptive potential might buffer the negative effects of unfavorable climatic conditions (Hamann & Aitken, 2013). To account for the likely permanence of the parasite in these areas and hence provide a more biologically realistic prediction, for each SSP-RCP scenario, we produced a projection of future habitat suitability that considered the maximum between current and future habitat suitability values as probability of *Em* occurrence for each cell (hereafter, combined projection). Finally, to highlight the changes in habitat suitability, for each cell and under every SSP-RCP scenario, we computed the difference in suitability between future (according to the raw projection) and current conditions.

Country-wise analysis

Describing suitability for the species in each European country can help to quantitatively assess the risk of transmission and hence drive epidemiological surveys (Mwima *et al.*, 2017). We standardised the projections by reclassifying the probability of presence into three classes of occurrence probability: level 0 (0-0.33, low probability), level 1 (0.33-0.66, moderate probability) and level 2 (0.66-1, high probability), and quantified the number of raster cells in each category, separately for each European nation. Furthermore, we computed the percentage difference between current and future cells for all classes of occurrence probability and every country. The overall modelling workflow is described in more detail in the Overview, Data, Model, Assessment and Prediction (ODMAP) protocol (Zurell *et al.*, 2020; Appendix S1).

RESULTS

Echinococcus multilocularis presence data

The bibliographic search identified 1,567 scientific papers, from which we were able to obtain the coordinates of 1,959 *Em* records in red fox in Europe and combine them with the 212 from the EWET database (for a total of 2,171), spanning the period 1985 – 2020. After retaining a maximum of one record per grid cell and performing the spatial filtering, 449 occurrence points were obtained and used to build the Maxent model (Figure 1).

Environmental variables selection and Maxent modelling

The PCA on the bioclimatic variables resulted in four PCs explaining the 91% of the total variance of the 19 layers. As for the orographic variables, once variables with low communality were removed, the PCA extracted a first PC explaining the 87% of the variance alone. Based on PC loadings, the variables with the greater loading for every PC were selected: these proved not to be highly correlated ($0.06 < r < 0.51$). The set of environmental variables selected for the climatic set included: mean temperature of the coldest quarter, precipitation of the wettest month, precipitation seasonality and temperature annual range, whereas from the orographic set of variables, roughness and TPI were included in Maxent models.

The comparison of the best models of the different biological hypotheses obtained from Maxent (Table 1) indicated that the first biological hypothesis run with the complete set of environmental variables (mean temperature of the coldest quarter, precipitation of the wettest month, precipitation seasonality, temperature annual range, roughness, TPI, open, forest and urban) produced the best performing model, and was used to describe *Em* potential current distribution (Figure 2) projected under different scenarios.

Environmental niche

The proxies of habitat suitability for *Em* included in the best performing model were mean temperature of the coldest quarter (percentage contribution: 59.2), percentage of forest cover (percentage contribution: 11.0), percentage of urban cover (percentage contribution: 8.5) and precipitation seasonality (percentage contribution: 6.8). A unimodal relationship between habitat suitability and mean temperature of the coldest quarter was noted, with maximum temperature suitability between -10 and 10 °C, whereas a negative linear relationship with precipitation seasonality was detected (Figure 3). The percentage of forest cover showed a unimodal relationship with suitability for *Em*, with a peak at 40-60 % cover, whereas suitability increased with the percentage of urban cover up to an asymptote at a relatively low cover (Figure 3).

Current probability of occurrence

The probability of *Em* presence in Europe was higher in central and eastern Europe (Figure 2), a historical endemic zone for the cestode, and decreased towards areas with more extreme climates, either hot and dry (*e.g.*, western France, Spain, Southern Italy, Greece) or very cold (*e.g.*, Fennoscandian peninsula) conditions. At the southern margin of the historical endemic zone, the match between areas of high suitability and occurrence points was low (Figure 2).

Future projections

Raw projections for *Em* highlighted a shift in suitable areas from the central European endemicity area (north-eastern France, Switzerland, Germany) towards northern latitudes, in particular Great Britain and the Fennoscandian peninsula (Figure 4a). A high increase in suitability was also reported in the Alps, an area largely unsuitable at present, but entirely suitable according to future projections (Figure 4a). Besides the central European endemicity area, suitability is also predicted to decrease in the three Mediterranean peninsulas (Iberia, Italy, Balkans), as well as in eastern Europe.

The three climatic-LULC scenarios influenced predictions (Figure 4a). That is, as the severity of scenarios increased, suitability was predicted to undergo stronger reductions in the central European endemicity area and in eastern Europe (in the latter case particularly under SSP 5 – RCP 8.5, Figure 4). Instead, the predicted expansion of suitable areas in northern Europe and the Alps was similar under all scenarios (Figure 4a).

Combined projections predicted an expansion of suitable areas towards higher altitudes and latitudes (Figure 4b), with patterns similar to those described for future projections; *i.e.*, the probability of occurrence increased towards northern latitudes (Great Britain, Fennoscandian peninsula) and in the Alps (Figure 4b).

The agreement between raw predictions was low for different General Circulation Models in the central European endemic area (particularly in Germany and Belgium), in Denmark and along the coasts of Sweden (Figure 5a). Under more severe scenarios, the agreement was lower although similar patterns of spatial uncertainty were reported (Figure 5a).

The analysis of cell-wise change of habitat suitability depicted similar patterns of change under all scenarios, although more marked changes were reported for the SSP 5 – RCP 8.5 scenario and in the central and eastern European areas (Figure 5b). In all scenarios, the Alps were expected to undergo a marked increase in habitat suitability and central and eastern Europe were predicted to experience low to marked decreases in suitability (Figure 5b). Small increases were instead predicted for most of the Fennoscandian peninsula, with some areas of marked increase (Figure 5b).

Country-wise analysis

The countries with the highest percentage of cells in the ‘high occurrence probability’ class were mainly located in central Europe, *e.g.*, Germany (71.4 % of national geographical area with a high occurrence probability), Poland (55.8 %), Switzerland (56.3 %), Austria (42.9 %) and Czechia (61 %) (Table S2). Outside this core area of endemicity, an extensive area of suitability for *Em* was also reported for Belgium (44.8 %) and Lithuania (47.1 %) (Table S2).

Under future conditions, a general decrease of occurrence probability was reported, especially in the endemic area, *e.g.*, in the intermediate scenario (SSP 3 – RCP 4.5), the percentage of highly suitable geographical areas was 7.8 % for Germany, 9.6 % for Poland and 14.8 % for Austria (Tables S3 – S5). The predicted decrease was higher according to more severe scenarios, *e.g.*, for Germany the percentage of high occurrence probability cells changed from 14.0 % (SSP1 – RCP2.6) to 7.8 % (SSP 3 – RCP 4.5) to 1.6 % (SSP 5 – RCP 8.5) (Tables S3 – S5). Some countries highly suitable for *Em* were reported in northern Europe, *e.g.*, under the SSP 3 – RCP 4.5 the percentage of highly suitable cells was 59.9 % for Lithuania and 39.4 % for Latvia (Tables S3 – S5).

The percentage change of high occurrence probability cells was notable for central Europe where losses were reported, *e.g.*, in Germany (- 88.9 % under the SSP 3 – RCP 4.5 scenario), Austria (- 65.4 %), Poland (- 82.6 %) and Czechia (- 92.1 %) (Tables S6-S8). Instead, an increase was indicated for northern European countries like Norway (+ 52.4 % under the SSP 3 – RCP 4.5 scenario) and the Great Britain (+ 1000 %, although only 10 cells were gained) (Tables S6-S8).

The countrywide analysis for combined projections reported a higher suitability for *Em* in the core endemic area (Tables S9 - S11). Under the SSP 3 – RCP 4.5 scenario, the percentage of cells with high suitability values in Germany was 72.0 %, with 53.2 % in Austria, 58.6 % in Poland and 75.4 % in Switzerland (Tables S9 - S11). The percentage change was similar to that reported for raw predictions, although central European countries had small gains (*e.g.*, 0.8 % for Germany under the SSP 3 – RCP 4.5 scenario) (Tables S12 – S14).

DISCUSSION

Using publicly available records of *E. multilocularis* in red fox, and a hypothesis-based evaluation of alternative species distribution models generated using these data, we identified the main environmental drivers of habitat suitability for *Em* in Europe at large scale (25x25km) and produced spatially explicit projections of current and future suitability for the parasite.

Among the suite of developed models, the one with the highest performance, which employed the full set of variables, predicted a marked decrease in habitat suitability for *Em* in central Europe (Germany, Poland, Switzerland, Austria, Czechia), but increases towards higher altitudes (the Alpine region) and latitudes (Great Britain and the Fennoscandian peninsula).

A mechanistic explanation for these predictions has been proposed (Atkinson *et al.*, 2013); that is, the survival of eggs is severely impaired by high temperatures and desiccation (Federer *et al.*, 2015), so *Em* is often found in cold and humid areas (Shaikenov, 2006); therefore, rising temperatures might reduce egg survival in lower latitudes and altitudes, causing a shift of suitable areas towards northern countries. The negative impact of high temperatures on egg survival might also explain why the observed reduction of *Em* probability of occurrence in Central Europe under all global change scenarios was far more extensive than its increase at higher latitudes.

Another possible mechanistic explanation for our predictions is linked to changes in the distribution of key intermediate hosts (Massolo *et al.*, 2022), as definitive hosts are widespread and cannot explain large-scale patterns of *Em* distribution and its changes (Hoffmann & Sillero-Zubiri, 2016). However, intermediate hosts might not always be able to track suitable habitats under global change scenarios as a result of dispersal and biogeographical limitations. Hence, the projected expansion of *Em* at higher latitudes might be limited by intermediate host availability.

The role of temperature in shaping *Em* distribution has been highlighted in several regions (Miterpakova *et al.*, 2006, Tolnai *et al.*, 2013), and the preference for relatively cold winter temperatures that we highlighted is consistent with this environmental preference. The negative relationship with precipitation seasonality also confirms a possible negative impact of drought periods on egg survival and *Em* transmission.

The positive relationship of suitability with urban areas is also well known for *Em* (Deplazes *et al.*, 2004, Liccioli *et al.*, 2015), and it is probably explained by the urbanization of red foxes in Europe, as reported in the city of Zurich (Hofer *et al.*, 2000), Vienna (Duscher *et al.*, 2005) and Brussels (Brochier *et al.*, 2007), as well as in other types of *urbes* (*sensu* Liccioli *et al.*, 2015). In addition, the extensive occurrence of human-occupied areas in the historically endemic rural areas of eastern France might also explain this pattern (Knapp *et al.*, 2018). In these rural landscapes, forested areas interspersed with urban settlements and open spaces result in a landscape that is highly conducive to the transmission of this parasite (Knapp *et al.*, 2018). The unimodal relationship of suitability with forest cover (with a peak at intermediate cover) suggested by our best model appears to reflect this phenomenon.

Our raw projections suggested there will be a marked loss of suitability in central Europe regardless of the considered scenario. Furthermore, combined predictions indicated a spreading of the parasite out of the core endemicity area and towards higher altitudes and latitudes. Future northern shifts in preferred habitat have already been projected for some parasites (ticks and lungworms: Jore *et al.*, 2014, Kafle *et al.*, 2020), and future latitude/altitude shifts in others (viruses and haemosporidians: Harrigan *et al.*, 2014, Perez-Rodriguez *et al.*, 2014).

Our country-wise predictions of transmission risk provide a useful guide for surveillance and pre-emptive efforts towards areas where the risk is high or predicted to increase. However, current predictions at the range margins (*e.g.*, northern Italy) do not match actual occurrence records, possibly reflecting the preponderance of data from the historically endemic areas in the definition of species-environment relationships. Suitable areas for peripheral populations are often poorly described by continental models built at a large coarse scale (Vale *et al.*, 2014); therefore, future work should aim to determine the fine-scale determinants of habitat suitability for *Em* along its range margins. Future research might also aim to integrating a wider set of GCMs (Thuiller *et al.*, 2019), following an increased availability of corresponding LULC scenarios. Although we used presence data of parasites in their main definitive host, assuming that environmental conditions at the occurrence sites were conducive to all stages of the life cycle, a better mechanistic understanding of the autecology of each life cycle stage and of the hosts might help to detect mismatches in host-parasite responses to global change (Cizauskas *et al.*, 2017, Pickles *et al.*, 2013).

As extensive intraspecific genetic variation might buffer the negative impacts of global change via local adaptation (Razgour *et al.*, 2019, Valladares *et al.*, 2014), we cannot rule out that areas where the parasite is currently highly endemic might continue to host viable parasite populations despite the predicted loss of habitat suitability. More refined ways to account for this phenomenon in species distribution models for *Em* should therefore be developed. In addition, the integration of other factors into our models, such as the distance of an occurrence record from endemic areas, could be used to weigh the probabilities of presence of the parasite between areas which are equally environmentally suitable, but not yet reached by the parasite. In addition, since our analyses were conducted on data collected in Europe, the results may not apply elsewhere, and predictions of occurrence probability for *Em* outside Europe should be developed to attain a more thorough understanding of the response of this species to global changes.

By exploiting the large availability of high-quality occurrence data for *Em* in Europe, we modelled its current and future occurrence probability in this continent, providing insights on how habitat suitability for complex life cycle parasites is expected to vary under global change. Our hypothesis-driven modelling framework should prove useful to model spatial patterns of occurrence probability for other trophically-transmitted parasites with a complex life cycle. Indeed, despite the complexity of the ecology of this parasite, our framework allowed us to rapidly test biological hypotheses on the drivers of *Em* distribution and to obtain robust predictions of current and future occurrence probability, accounting for both climate and LULC. Furthermore, in the case of zoonotic parasites, our framework could be employed to provide rapid, reliable assessments of parasite occurrence probability to aid the prevention of pathogen outbreaks.

DATA ACCESSIBILITY

The data that support the findings of this study are openly available in Dryad at https://doi.org/10.5061/dryad.dv41ns230.

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LIST OF TABLE LEGENDS

Table 1. Combinations of environmental factors included in the Maxent model for *Echinococcus multilocularis* in Europe according to different biological hypotheses. A grey block indicates that the variable/set of variables has been included in the models representing a given hypothesis. The performance of the best model selected for each hypothesis is reported according to three performance measures: the Area Under the Receiver-Operating Characteristic Curve computed on the test data (AUC_{test}), the difference between the AUC computed on the train data and the AUC_{test} (AUC_{diff}), and the Akaike Information Criterion corrected for a small sample size (AIC_c). In bold: performance measurements of the model used to predict the current and future probability of occurrence for the species. Variable names are abbreviated as follows: Bio = Bioclimatic predictors (Temperature annual range, Mean temperature of the coldest quarter, Precipitation of the wettest month, Precipitation seasonality), Rou = Roughness, TPI = Topographic Position Index, Urb = Urban, Dis = Discontinuous, For = Forest, Rot = Rotation, Pas = Pastures, R_p = Rotation and pastures, G_m = Grasslands and moorlands. References are numbered as follows: [1]Craig et al., 2000, [2]Danson et al., 2003, [3]Danson et al., 2004, [4]Deplazes et al., 2004, [5]Giraoudoux et al., 2003, [6]Giraudoux et al., 2013, [7]Hegglin et al., 2015, [8]Liccioli et al., 2015, [9]Marston et al., 2014, [10]Pearson & Dawson, 2003, [11]Raoul et al., 2015, [12]Romig et al., 2006, [13]Umhang et al., 2013, [14]Veit et al., 1995. Hp = Hypothesis; Refs = References.

Table 2. Relative contribution (%) of the environmental variables in the Maxent model used to predict the current and future probability of occurrence of *Echinococcus multilocularis* in Europe as a function of climatic, topographic and land-use/land-cover variables.

Table 1.

Hp	Variables											AUC_{test}	AUC_{diff}	AIC_c	Refs
	Bio	Rou	TPI	Urb	Dis	For	Open	Rot	Pas	R_p	G_m				
1	▨	▨	▨	▨		▨	▨					**0.825**	**0.028**	**7546.7**	(Giraudoux *et al.*, 2003, Marston *et al.*, 2014, Pears
2	▨											0.819	0.033	7814.3	(Marston *et al.*, 2014, Tackmann *et al.*, 2001)
3	▨					▨		▨	▨			0.835	0.026	7613.0	(Craig *et al.*, 2000, Danson *et al.*, 2003, Giraudoux 2003, Veit *et al.*, 1995),
4	▨					▨		▨	▨		▨	0.826	0.031	7594.1	(Danson *et al.*, 2004, Giraudoux *et al.*, 2013, Pearso *et al.*, 2001, Veit *et al.*, 1995)
5	▨					▨				▨	▨	0.841	0.029	7586.1	(Danson *et al.*, 2004, Giraudoux *et al.*, 2013, Pearso *et al.*, 2001, Veit *et al.*, 1995)
6	▨	▨	▨			▨	▨					0.813	0.019	7582.2	(Giraudoux *et al.*, 2003, Romig *et al.*, 2002, Tackm 1995)
7	▨	▨	▨		▨	▨						0.819	0.048	7567.8	(Deplazes *et al.*, 2004, Giraudoux *et al.*, 2003, Licc 2002, Tackmann *et al.*, 2001, Veit *et al.*, 1995)

LIST OF FIGURE CAPTIONS

Figure 1. Occurrence records of *Echinococcus multilocularis* in Europe, used to model its current and future probability of occurrence as a function of climatic, topographic and land-use/land-cover variables. Data from a bibliographic search were combined with data from the EmsB Website for *Echinococcus* Typing (EWET) database (updated to 6th February 2020). Map lines delineate study areas and do not necessarily depict accepted national boundaries.

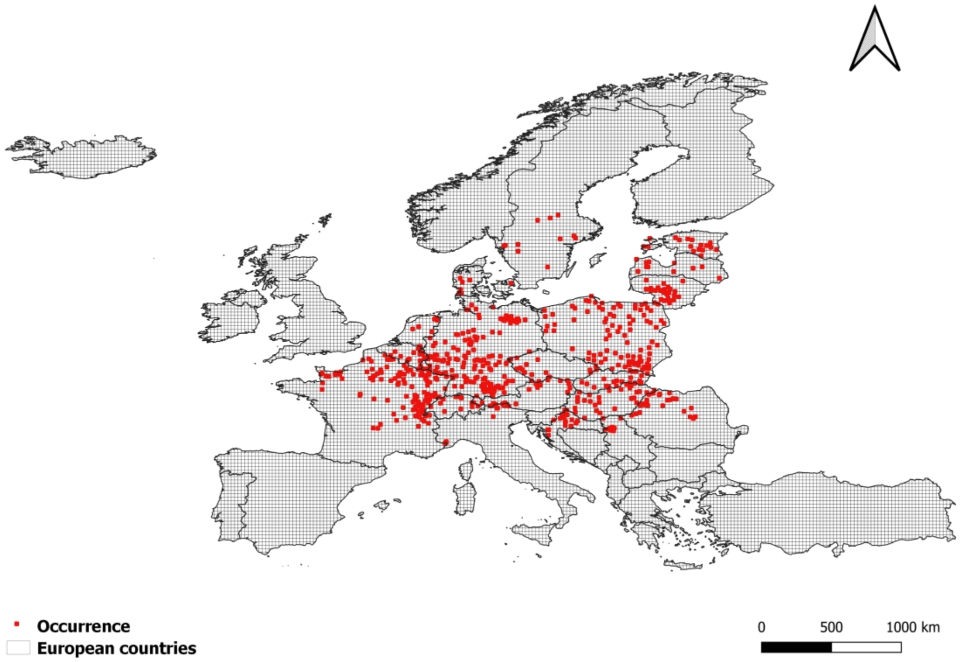
Figure 2. Current probability of occurrence for *Echinococcus multilocularis* in Europe as estimated by the best performing Maxent model. Points represent presence points used to calibrate the model. The probability of occurrence is reported in five classes of increasing value from dark green to red. Map lines delineate study areas and do not necessarily depict accepted national boundaries.

Figure 3. Response curves of the Maxent model representing *Echinococcus multilocularis* probability of occurrence against the top four environmental predictors. **a)** Mean temperature of coldest quarter - expressed in °C; **b)** Percentage of forest cover; **c)** Percentage of urban cover; **d)** Precipitation seasonality - expressed as the coefficient of variation.

Figure 4. **a)** Projections of future habitat suitability for *Echinococcus multilocularis* under three global change scenarios of increasing severity (Shared Socioeconomic Pathway 1 - Representative Concentration Pathway 2.6; SSP3 - RCP 4.5; SSP5 - RCP 8.5). As future projections are developed over averaged 2041-2060 climate and land-use/land-cover

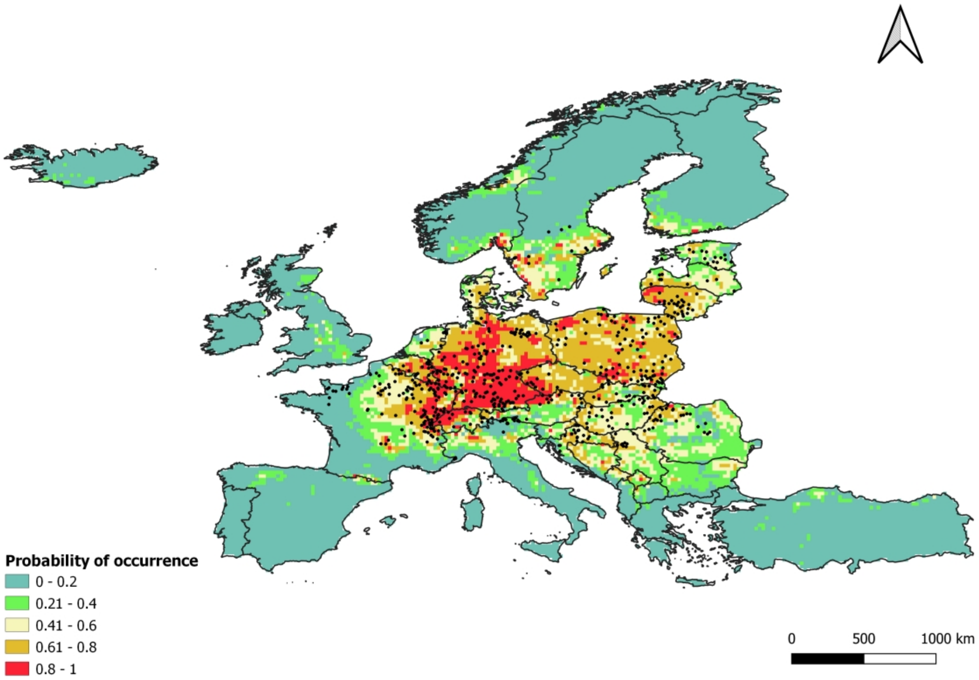
conditions, we assumed these maps to represent *E. multilocularis* distribution around 2050. **b)** Maps combining current and future predictions of habitat suitability for *Echinococcus multilocularis* under three global change scenarios of increasing severity (Shared Socioeconomic Pathway 1 - Representative Concentration Pathway 2.6; SSP3 - RCP 4.5; SSP5 - RCP 8.5). For each grid cell, the maximum predicted value between current and future predictions is retained. These maps account for the plausible persistence of *E. multilocularis* in historically endemic Central European areas due to a higher adaptive potential, despite the predicted reduction in occurrence probability. Map lines delineate study areas and do not necessarily depict accepted national boundaries.

Figure 5. a) Standard deviation among habitat suitability projections for *Echinococcus multilocularis* in Europe developed with three General Circulation Models: HadGEM2-ES, IPSL-CM5A-LR, MIROC5. **b)** Predicted change of habitat suitability for *Echinococcus multilocularis* in Europe under three global change scenarios of increasing severity (Shared Socioeconomic Pathway 1 - Representative Concentration Pathway 2.6; SSP3 - RCP 4.5; SSP5 - RCP 8.5). Areas with a suitability less or equal to the Minimum Training Presence under both current and future scenarios are reported in grey. Map lines delineate study areas and do not necessarily depict accepted national boundaries.



Occurrence records of *Echinococcus multilocularis* in Europe, used to model its current and future probability of occurrence as a function of climatic, topographic and land-use/land-cover variables. Data from a bibliographic search were combined with data from the EmsB Website for *Echinococcus* Typing (EWET) database (updated to 6th February 2020). Map lines delineate study areas and do not necessarily depict accepted national boundaries.

754x533mm (118 x 118 DPI)



Current probability of occurrence for *Echinococcus multilocularis* in Europe as estimated by the best performing Maxent model. Points represent presence points used to calibrate the model. The probability of occurrence is reported in five classes of increasing value from dark green to red. Map lines delineate study areas and do not necessarily depict accepted national boundaries.

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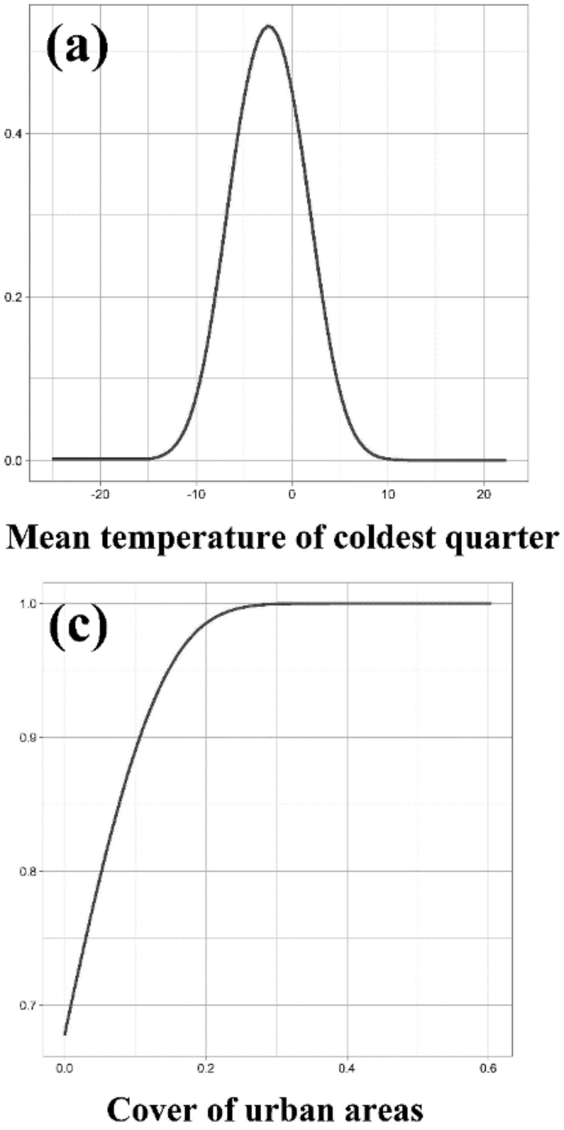
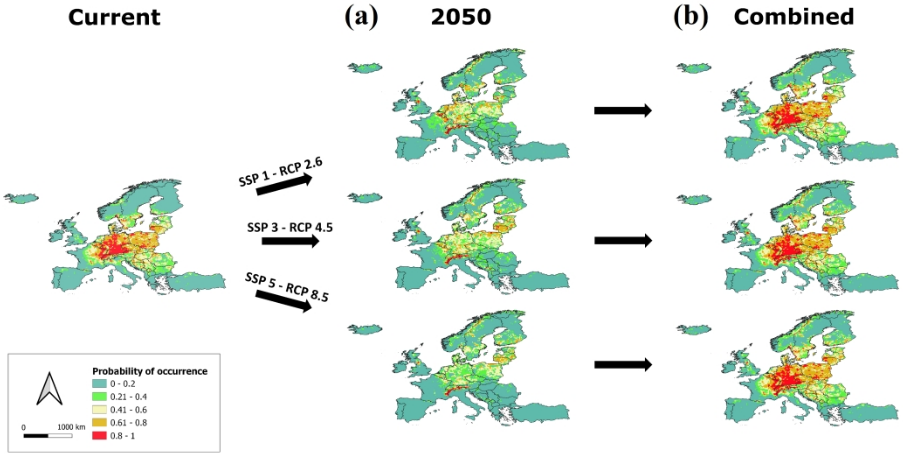
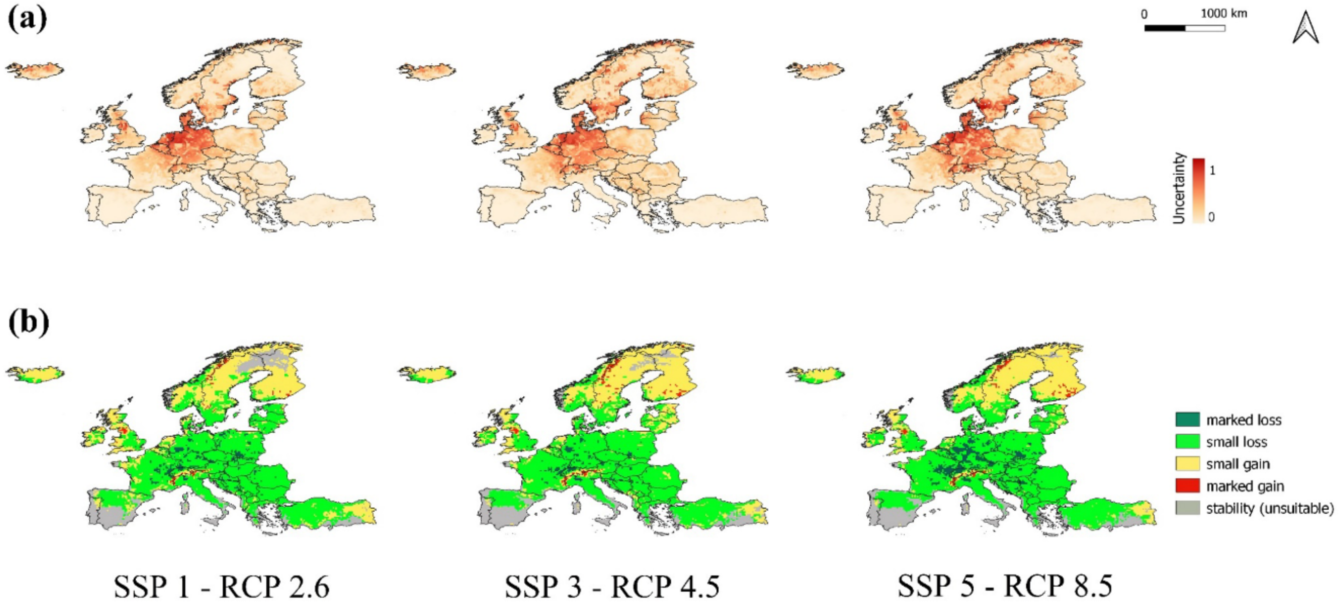


Response curves of the Maxent model representing *Echinococcus multilocularis* probability of occurrence against the top four environmental predictors. a) Mean temperature of coldest quarter - expressed in °C; b) Percentage of forest cover; c) Percentage of urban cover; d) Precipitation seasonality - expressed as the coefficient of variation.



a) Projections of future habitat suitability for *Echinococcus multilocularis* under three global change scenarios of increasing severity (Shared Socioeconomic Pathway 1 - Representative Concentration Pathway 2.6; SSP3 - RCP 4.5; SSP5 - RCP 8.5). As future projections are developed over averaged 2041-2060 climate and land-use/land-cover conditions, we assumed these maps to represent *E. multilocularis* distribution around 2050. b) Maps combining current and future predictions of habitat suitability for *Echinococcus multilocularis* under three global change scenarios of increasing severity (Shared Socioeconomic Pathway 1 - Representative Concentration Pathway 2.6; SSP3 - RCP 4.5; SSP5 - RCP 8.5). For each grid cell, the maximum predicted value between current and future predictions is retained. These maps account for the plausible persistence of *E. multilocularis* in historically endemic Central European areas due to a higher adaptive potential, despite the predicted reduction in occurrence probability. Map lines delineate study areas and do not necessarily depict accepted national boundaries.

879x410mm (118 x 118 DPI)



a) Standard deviation among habitat suitability projections for *Echinococcus multilocularis* in Europe developed with three General Circulation Models: HadGEM2-ES, IPSL-CM5A-LR, MIROC5. b) Predicted change of habitat suitability for *Echinococcus multilocularis* in Europe under three global change scenarios of increasing severity (Shared Socioeconomic Pathway 1 - Representative Concentration Pathway 2.6; SSP3 - RCP 4.5; SSP5 - RCP 8.5). Areas with a suitability less or equal to the Minimum Training Presence under both current and future scenarios are reported in grey. Map lines delineate study areas and do not necessarily depict accepted national boundaries.