Applying regional climate change projections for spatio-temporal risk analyses of vector-borne diseases

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“*The planet has a fever. If your baby has a fever, you go to the doctor. If the doctor says you need to intervene here, you don’t say, ‘Well, I read a science-fiction novel that told me it’s not a problem.’ If the crib’s on fire, you don’t speculate that the baby is flame-retardant.*”

Albert Arnold “Al” Gore

Table of contents

List of pictures

Glossary of used abbreviations

Arboviruses	“Arthropod-borne viruses”
AUC	”Area under the receiver operator characteristic curve” (Model quality criteria; e.g. article 4)
CCLM	Regional climate model “COSMO-CLM” that is hosted by the CLM community COSMO = Consortium for Small-scale Modelling CLM = Climate Limited-area Model
CDC	“Centers for Disease Control and Prevention”
CIA	“Central Intelligence Agency” (see article 7)
DKRZ	German Climate Computing Centre (“Deutsches Klimarechenzentrum”)
DWD	Germean Weather Service (“Deutscher Wetterdienst”)
ECDC	“European Centre for Diseae Control and Prevention”
ECHAM	Global climate model, developed by the the Max Planck Institute for Meteorology
EIP	“Extrinsic Incubation Period” (Interval between the acquisition of an infectious agent by a vector and the vector's ability to transmit the agent to other susceptible vertebrate hosts; see article 2).
EKBM	“Expert knowledge based model” (model that is derived by selection of variables using already understood species´climatic constraints; see article 4)
GARP	“Genetic Algorithm for Rule Set Production” (Software to model species distribution)
GCM	“Global climate model” (syn. General circulation model)
IPCC	“Intergovernmental Panel on Climate Change”
Maxent	Software to model species distribution based on maximum entropy approach (see articles 4-6)
MESS	“Multivariate Environmental Similarity Surface” (see articles 4 to 7)
MRPP	“Multiresponse Permutation Procedure” (see article 4)
Phleboviruses	Viruses belonging to the Bunyaviridae. Vectors are either phlebotomine sandflies (*Phlebotomus* fever viruses) or ticks (Uukuniemie group)
RCM	“Regional climate model”
REMO	“Regional Model” (Regional climate model, developed by the Max Planck Institute for Meteorology)
RKI	“Robert-Koch Institut” (see article 7)
SBM	“Statistic based model” (model that is derived by selection of variables using statistical test of variable´s importance; see article 4)
STAR	“Statistisches Regionalisierungsmodell” developed by the Potsdam Institut for Climate Impact Research
VBD	“Vector-borne disease” (used in article 7)
WETTREG	“Wetterlagen-basierte Regionalisierungsmethode“, developed on advise of the German Federal Ministry ofor the Environment, Nature Conservation and Nuclear Security
WHO	“Word Health Organization”

1. Compendium

1.1 Summary

This thesis addresses the topic of climate change effects on vector-borne diseases. Disease vectors gather the pathogen from an infected host (usually mammals), become infected but usually do not fall sick. They are capable to transmit the pathogens between hosts. Most of the vector-borne diseases are considered to be climate-sensitive. This has several reasons: First of all, the majority of the vectors belong to ecto-thermic arthropods which cannot regulate their body temperature. In addition, pathogen development within the vector is dependent on temperature constraints.

Data concerning expected climate change during the 21st century are provided by climate models in different spatial and temporal resolutions. Projections of future climate include emission scenarios of greenhouse gases. In this thesis the use of regional climate projections with special respect to their capacity for being implemented in spatio-temporal risk analyses of vector-borne diseases is presented. Regional climate models are recommended for risk analyses of vector-borne disease on smaller spatial scales, due to their remarkably better performance in comparison to global climate models. Possible applications and opportunities of regional climate projections are introduced (article 1). Within this thesis, data obtained by the regional climate models REMO and COSMO-CLM are used for risk analyses. Both models were derived by a dynamical downscaling procedure. They are nested within the well-established global model ECHAM5, in the latest versions.

In the first methodological part (articles 2 and 3) the transfer of already understood vector and/or pathogen temperature constraints to expected future conditions is addressed. By using this approach, the required temperatures for dengue virus amplification within the primary vector *Aedes aegypti* are compared with expected future European conditions. Results indicate a growing threat for Europe in a twofold manner. First of all, a spatial range expansion of regions, which offer the window of opportunity for dengue-virus amplification, is projected. Starting from southern parts of Europe in the upcoming years, also Central Europe will provide suitable temperature conditions from mid-century onwards. Furthermore, the inter-annual season of possible virus amplification in Europe will increase remarkable (article 2). On a further example, the threat of autochthonous transmission of visceral leishmaniasis, the most severe sandfly-borne disease is determined. Therefore the temperature constraints of vector (genus: *Phlebotomus*) and pathogen (*Leishmania infantum* complex) are projected to future conditions on the regional example of Germany. The results for projected

vector and pathogen requirements are finally overlaid with the aim to generate risk classes of potential establishment of visceral leishmaniasis. Western and southern German regions will be at risk, expectedly from mid-century onwards. At the end of the 21st century, the establishment of this disease can no longer be excluded for large parts of Germany (article 3).

In the second part (articles 4 to 6), regional climate change projections are implemented within species distribution models for vector species. For this approach, statistical analyses are applied in order to determine species´ preferred bioclimatic niches. Once the specific climatic niches of species are identified, these can be transferred to future climatic conditions. Based on this approach it is indicated that the climatic suitability will increase for the invasive mosquito *Aedes albopictus* (vector of several human-pathogenic viruses) in most European regions. Especially in Western Europe (e.g. in France) suitability will increase. With temporal delay also central and eastern parts of Europe will provide favourable conditions, while the suitability will decrease in some Mediterranean areas (article 4). On the example of sandfly species (vectors of the *Leishmania* complex), the results of the species specific niche modelling show that climatic suitability can be expected to increase in Central Europe within this century and especially for Germany. Potential future dispersal pathways for the species in a rapidly changing environment are identified via least-cost analysis. This indicates that the studied sandfly species will hardly be able to occupy all of their potentially suitable future areas due to their limited dispersal ability (articles 5 and 6).

In different case studies it is already shown that European climate change within the 21st century will probably support a spread or at least range expansions of the mentioned disease vectors and vector-borne diseases. As a general tendency for Central Europe it can be expected that the risk will increase especially for the outgoing 21st century. This may be due to the fact that the applied regional climate models indicate a more rapid warming in the second half of the 21st century, regardless the chosen scenario.

To conclude, it is worth mentioning that further factors beyond climate change additionally facilitate the potential spread and new-establishment of vector-borne diseases. The influence of these factor (“drivers”) on vector-borne diseases, however, depends on the considered spatial and temporal scale. Therefore, a scale-dependent risk assessment for vector-borne diseases is proposed. Starting at broader scales, climatic risk assessments can be initiated to identify risk areas. Then, the relevant factors must be identified on smaller scales for the detected risk areas and integrated in follow-up studies (article 7). The results can then support more efficiently the development and implementation of surveillance strategies for vector-borne diseases. This enables to initiate counteractions against spreading vector-borne diseases - or supports societal adaptations to this novel threat.

1.2 Zusammenfassung

Bei vorliegender Dissertation handelt es sich um eine Abhandlung zu vektor-assoziierten Krankheiten in Zeiten des Klimawandels. Bei vektor-assoziierten Krankheiten wird ein Pathogen durch einen Vektor (Überträger), auf ein Wirtstier übertragen. Als Vektor agieren meist Arthropoden die sich mit dem Pathogen infizieren können, jedoch meist nicht selbst erkranken. Aus verschiedenen Gründen gelten diese übertragbaren Infektionskrankheiten als besonders sensibel hinsichtlich klimatischer Veränderungen. Entscheidend ist, dass Arthropoden ihre Körpertemperatur nicht selbst regeln können und zudem bestimmte Temperaturansprüche zur Pathogenentwicklung im Vektor erfüllt sein müssen.

Das Klimaänderungssignal des 21. Jahrhunderts wird von Klimamodellen in verschiedenen räumlichen und zeitlichen Auflösungen wiedergegeben. Die Projektionen beruhen auf Emissionsszenarien klimawirksamer Treibhausgase. In der Arbeit werden die Einsatzmöglichkeiten von regionalen Klimamodellen zur Gefährdungsabschätzung anhand verschiedener Fallbeispiele aufgezeigt. Die deutlich bessere Performance regionaler Klimamodelle im Vergleich mit globalen Modellen, empfiehlt diese für genauere Gefährdungsanalysen von vektor-assoziierten Krankheiten auf kleineren räumlichen Skalen. Der Nutzen und die Einsatzmöglichkeiten regionaler Klimamodelle werden einführend aufgeführt (Artikel 1). Für die Risikoanalysen werden in dieser Arbeit die regionalen Klimamodelle REMO und COSMO-CLM angewandt, die durch dynamisches „Downscaling" globaler Modelle generiert wurden. Beide sind in ihrem neuesten Prozesslauf in das globale Modell ECHAM5 eingebettet.

Der direkte Übertrag bekannter Temperaturansprüche von Vektor und/oder Pathogen auf künftig zu erwartende Bedingungen stellt den ersten methodologischen Schwerpunkt dieser Arbeit dar. Eine Amplifikation des Dengue-Virus im Überträger der Stechmücke *Aedes aegypti* könnte demnach zunächst in Südeuropa, im weiteren Verlauf des 21. Jhd. aber auch in weiteren europäischen Regionen möglich sein und damit eine zunehmende Gefährdung darstellen. Ab der Jahrhunderthälfte kann das Risiko beispielsweise auch für Mitteleuropa nicht mehr länger ausgeschlossen werden. Weiterhin verdeutlichen die Ergebnisse, dass sich auch das Zeitfenster einer potentiellen Übertragung des Dengue-Virus verlängern kann (Artikel 2). Durch das Überlagern der bekannten Temperaturansprüchen von Sandmücken

(Gattung *Phlebotomus*) und der von ihnen übertragbaren Erreger - *Leishmania infantum* Komplex - können potentielle Regionen Deutschlands identifiziert werden, in denen einer autochthone Übertragung der Leishmaniose möglich ist. Es ist zu erwarten, dass ab Mitte des Jahrhunderts ein solches Risiko in südwestlichen und westlichen Regionen Deutschlands bestehen wird. Für das ausgehende 21. Jhd ist anzunehmen, dass sich auch für eher nördlich und östlich gelegene Regionen das Risiko erhöhen wird (Artikel 3).

Der zweite innerhalb dieser Arbeit gewählte methodologische Ansatz (Artikel 4 bis 6) zeigt die Einsatzmöglichkeiten regionaler Klimaprojektion für die bioklimatische Nischenmodellierung von Krankheitsüberträgern auf. Die anhand statistischer Verfahren ermittelte bioklimatische Nische der jeweiligen Art wird hierbei auf zukünftig zu erwartende klimatische Bedingungen übertragen. Anhand dieser Analyse kann aufgezeigt werden, dass sich die klimatische Eignung für die invasive Stechmücke *Aedes albopictus* (Überträger mehrere humanpathogener Viren) zunächst in westlichen Regionen Europas (insbesondere Frankreich) verbessern wird und ab Mitte des Jahrhunderts auch größere Bereiche Mitteleuropas klimatisch gesehen für eine Etablierung der Art geeignet erscheinen. Ende des Jahrhunderts werden sich osteuropäische Regionen geeignete Bedingungen bieten, während das Klima in Teilen der Mittelmeerregion eher ungeeigneter wird (Artikel 4). Der Transfer der ermittelten spezifischen klimatischen Nische ausgewählter Sandmücken-Arten (u.a. Überträger der zum *Leishmania*-Komplex zählenenden Pathogenen) auf künftige Bedingungen lässt vermuten, dass deren klimatische Eignung in Mitteleuropa - abgesehen von alpinen Regionen - zunehmen wird. In Deutschland werden die günstigsten klimatischen Bedingungen voraussichtlich Ende des 21. Jhd. gegeben sein. Künftige potenzielle Ausbreitungswege der Sandmücken in einer sich verändernden Umwelt, werden via “least-cost analysis“ ermittelt. Die Ergebnisse deuten darauf hin, dass aufgrund der eingeschränkten natürlichen Ausbreitungsfähigkeit, einige der künftig potenziell geeigneten Lebensräume nicht erreicht werden (Artikel 5 und 6).

In den verschiedenen Fallstudien kann gezeigt werden, dass die zu erwartenden klimatischen Veränderungen im 21. Jhd. eine mögliche Ausbreitung der in dieser Arbeit adressierten Vektoren und vektor-assoziierter Krankheiten in Europa begünstigen werden. Als einheitliche Tendenz kann speziell für Mitteleuropa festgehalten werden, dass sich die Gefährdung, Ende des 21.Jhd. erhöhen wird. Dies begründet sich höchstwahrscheinlich durch die projizierte raschere Erwärmung in der zweiten Jahrhunderthälfte.

Abschließend bleibt jedoch festzuhalten, dass es neben klimatischen Veränderungen weitere Faktoren für die Ausbreitung bzw. Neuetablierung von Vektoren und den damit verbundenen übertragbaren Infektionskrankheiten ausschlaggebend sind. Der Einfluss einzelner Faktoren auf die Etablierung bzw. Ausbreitung vektor-assoziierte Krankheiten variiert auf raum-zeitlichen Skalen. Insofern wird eine skalen-abhängige Risikoabschätzung vorgeschlagen, an deren Beginn klimatische Risikoanalysen gestellt werden sollten. Für die ermittelten klimatisch-abgeleiteten Risikogebiete müssen in Folgestudien auf kleineren Skalen wirksam werdenden Faktoren integriert werden (Artikel 7). Diese Ergebnisse können wiederum die Entwicklung von Surveillance- und Monitoringprogramme unterstützen, um somit Maßnahmen gegen die Ausbreitung von vektor-assoziierten Krankheiten initiieren zu können bzw. falls nötig, dabei helfen sich rechtzeitig an diese Gefährdung zu adaptieren.

2. Introduction

2.1. Climate models and projections of climate change

Due to anthropogenic impacts, the world's climate appears to change at an unprecedented rate (IPCC 2007). The economical behaviour and development of human societies is the main driving force for the emission of greenhouse gases into the planetary atmosphere. Since the installation of the first general circulation model (GCM) - by Phillips et al. 1956 - a multitude of such models were developed and used in order to forecast weather, predict the current climate or project climate change. A general circulation model (global climate model) is based on a three-dimensional rotating atmosphere in which fluid motion as well as physical and chemical processes are included accounting especially for the ocean-athmospere interaction (e.g. Stute et al. 2001). The model projections of future climate change are dependent on emission scenarios of greenhouse gases prepared by the Intergovernmental Panel on Climate Change (IPCC 2000) and used in the latest Assessment Report (IPCC 2007). These scenarios, which represent different storylines of expected emission of greenhouse gases with the respective consequences for climate change, were designed to substitute the previous scenarios of the second assessment report (see IPCC 1995).

One of the main limitations of the global climate models is the coarse horizontal resolution which ranges usually between 100 and 200 km. These models are then insufficient to address the spatial structure of temperature and precipitation in areas of complex topography and land use distribution (e.g. the Alps, the Mediterranean, Scandinavia) and the depiction of regional atmospheric circulations adequately (Christensen et al. 2008). In order to account for this limitation of the global climate models, procedures have been developed in order to cope with the required higher spatial resolution of climate projections. The first regional climate models were successfully developed for the western parts of the United States by Dickinson et al. (1989) and by Giorgi and Bates (1989). Since then, much effort has been devoted to the development and application of regional climate models. In the following the two main procedures for the development are highlighted.

2.1.1 Regional climate models based on statistical downscaling

Statistical downscaling methods are used to determine the relationship between large scale climate variables and the actual conditions measured at one particular place (e.g. Wilby et al. 1998). If the relationship is known for the current climate, the projections derived from the global climate model for the future climate can be used to project how climate will change at this specific place (Wilby and Wigley 1997). For European regions, two principles have successfully been used:

a) The first one can be considered as statistical downscaling based on linear regressions of observations for a respective time-period (Orlowsky and Fraedrich 2009). This method offers the opportunity that future projections are constrained only by the parameters of a linear regression line for a characteristic climatic variable and not from various further features given from complex global climate models as driver (Werner and Gerstengarbe 1997). This guarantees physically consistency respecting both, the combinations of different climatic variables and their spatial distribution in time (Orlowsky et al. 2008). Using this approach, STAR (**STA**tisitical **R**egional model) was developed (Werner and Gerstengarbe 1997). This principle is, however, limited by its own empiricism and by the availability of data sets of adequate quality (Giorgi and Mearns 1991).

b) Another method uses weather-pattern dependent downscaling principles, in which significant circulation patterns are identified using cluster analysis from the upper air fields of the troposphere from a driving global model (Enke and Spekat 1997). The respective episodes from the current climate were then recombined, based on surface data from weather stations, in order to synthesize time series under the conditions of an altered climate. This is conditioned by the requirement to reproduce the changing frequency distribution of the various global models` circulation patterns from the previous stage (Enke et al. 2005a). Then, a conditional (weather pattern-dependent) stepwise screening regression analysis is performed for each weather element and climate regions. In comparison to the previously described method, this offers the opportunity to leave the envelope of the current climate (Enke et al. 2005b). By using this principle WETTREG (**WETT**erlagen-basiertes **REG**ionalisierungsverfahren) has been developed (Enke et al. 2005a).

2.1.2 Regional climate models based on dynamical downscaling

In this thesis, however, projections are based on data provided by dynamically downscaled regional climate models. The main advantage of these models is a more physical consistent way of development than those with statistical procedures (Giorgi and Mearns 1991). Hence, they can display feedback processes that are not anticipated with statistical methods.

Atmospheric processes at the boundary given by the global model are used as input driver for the regional climate model. By nesting a smaller model into a global driving model, the spatial extent of the regional climate model is decreased into a smaller, limited region of interest with a higher spatial resolution (e.g. Wang et al. 2004). On the regional scale of Europe, two established and well-documented models are addressed here in more detail. These are the ones that are used for climatic projections in this thesis.

a) COSMO-CLM (COSMO Climate Local Model):

COSMO-CLM is a non-hydrostatic regional climate model developed from the Local Model (LM) of the German Weather Service (DWD) (Rockel et al. 2008). Non-hydrostatical component offers the opportunity to include convective (vertical) movements. Previously, the LM has been developed for operational weather forecast. Meanwhile it is used and further developed by several other weather services organized in the **CO**nsortium for **S**mall-scale **MO**delling (COSMO). It has been demonstrated that the impact of the driving data has a larger impact on simulation results than further factors such as changing resolution or physical parameterizations (Meissner et al. 2009). The errors given by the global model at the boundaries biases the regional climate projections. Consequently, COSMO-CLM is driven by the well-established global model ECHAM5 (Rockel et al. 2008). COSMO-CLM covers whole Europe and the African regions bordering the Mediterranean Sea. It provides data not only for the land surface but also for water bodies (Mediterranean Sea, parts of the Atlantic - especially the North and the Baltic Sea). The spatial resolution is about 18 km² (Smiatek et al. 2009). Data of this model are used for the analyses of the articles 2, 4, 5 and 6, where data are required for the complete European continent or at least bigger parts of it. Projected climatic changes are based on the two emission scenarios A1B and B1 (see articles 2 and 4 for details).

b) REMO (Regional Model):

REMO is based on the “Europa-Model” which was the main weather forecast model of the German Weather Service (Deutscher Wetter Dienst “DWD”). In advance to this primary model, REMO offers the opportunity of using the same physics as the global climate model (ECHAM3) into which it is nested to assess the scale dependence of physical parameterizations within the same dynamical framework (Jacobs and Podzun

1997). The newest version of REMO is driven by ECHAM5. The spatial resolution of the model is about 12 km^2. REMO has performed quiet well in comparison to further regional climate models and simulated current climatic conditions in mountainous regions better than for instance COSMO-CLM due to the higher spatial resolution (Smiatek et al. 2009). However, data given by REMO are just available for Central European regions (completely for Germany, Switzerland and Austria including Liechtenstein, as well as parts of Belgium, Luxembourg, the Netherlands, Poland and the Czech Republic). Therefore data of temperature change projected by REMO are used in article 2, where the spatial focus is directed to Germany. Applied are the two scenarios A1B and A2 (see article 3 for details).

2.2 Climate change effects on vector-borne diseases

Anthropogenic climate changes do significantly impact not only physical but also biological systems, ranging from local to global scale (Rosenzweig et al. 2008). The velocity of expected climate change in the 21st century will be extraordinary fast with severe consequences for species and ecosystems (Loarie et al. 2009). If species are not capable to adapt, the ranges of organisms, their spatial distribution areas, need to move in order to keep up with recent climate change (Walther et al. 2002, Parmesan and Yohe 2003). In general, climate change is assumed to enable those potentially “invasive” species to expand spatially to regions where they previously could not survive or establish (Walther et al. 2009).

Of special interests are moving species that constitute serious consequences for human or animal health. The caterpillars of the oak processionary (*Thaumetopoea processionea*) for instance are meanwhile found in several European countries causing lepidoptermis in humans by contacting the hairs of the caterpillars (Gottschling and Meyer 2006). This health problem is expected to increase in temperate European regions such as the Netherlands in the face of climate change (van Oudenhoven et al. 2008).

Starting in the 90ies of the last century it has been realized that climate change affects occurrences and transmission cycles of vector-borne diseases (e.g. Rogers and Packer 1993, Martens et al. 1995, Binder et al. 1999, Gratz 1999). The disease vectors, which are mainly arthropods, but sometimes also rodents, are capable to transmit the pathogens (microorganisms or viruses) to a host, which are in most cases mammals. Vector-borne diseases are sensitive to climate change due to several reasons: Temperature directly influences pathogen evolution and hence efficiency of pathogen transmission (Gould and Higgs 2009). Furthermore, changing spatial patterns of temperature and precipitation can affect the characteristics of vector arthropod life cycles, alter vector habitats and hence cause geographic and temporal variations in their occurrences due to their dispersal (Githeko et al. 2000, Gould and Higgs 2009).

Since these relationships were noticed, scientific and consequently also public and political awareness on this topic grows rapidly. Assumedly, emerging and resurging vector-borne diseases that are supported by climate change will cause significant morbidity and mortality in humans and animals (McMichael et al. 2006, Eisen and Eisen 2011). Consequently, this group of emerging infectious diseases must be considered as one of the world´s most devastating maladies of the future. It can be expected that it will become one of the main societal issues during the 21st century (LaBeaud and Aksoy 2010).

Leishmaniasis is a striking example of a recently spreading vector-borne disease that is already threatening the European population (Ready 2008, Ready 2010). Detailed information concerning vector and disease are provided in chapter 2.3 of this thesis. In the Old World, sandflies of the genus *Phlebotomus* serve as vectors. Their European distribution has been thought to be limited to the Mediterranean. In Italy, a northward directed spread of leishmaniasis has been realized which was very likely related to warming (Maroli et al. 2008). Moreover, *Phlebotomus mascittii* was recorded for the first time in the Upper Rhine Valley (Southwest Germany on the frontier to France) (Naucke and Pesson 2000) and in southern parts of Austria (Naucke et al. 2011). *P. perniciosus* seems to have established permanent populations in the German state of Rhineland-Palatinate (Naucke and Schmitt 2004). This corresponds to cases of assumed autochthonous origin in Germany that are reported from humans and horses (Bogdan et al. 2001, Koehler 2002, Mueller 2009).

The Asian tiger mosquito (*Aedes albopictus*), native to Southeast Asia, is a very successful global invader due to the global shipping of goods (Reiter 1987, Benedict et al. 2007, Enserink 2008). *Ae. albopictus* is competent to transmit several viruses; most severe for human health are the dengue and Chikungunya virus (Gratz 2004; see chapter 2.3 of this thesis for more details). In Europe, the mosquito is meanwhile established in almost all countries bordering the Mediterranean Sea. In a recent study, potential range expansions of the species due to climate change effects has been pointed out for Northern Italy (see Roiz et al. 2011).

A further wake-up call for Europe was the surprising outbreak of the bluetongue virus transmitted by midges and affecting ruminants in the Netherlands and surrounding regions.

The outbreak took place in summer of 2006 when the July was the hottest month on record in the Netherlands (Enserink 2006). Generally, in the case of animal health, it can be expected that climate change will raise the risk of incursion for several vector-borne diseases, listed by the World Organization for Animal Health, for European regions: Most strongly the effects will very likely benefit the tick-borne disease Crimean-Congo haemorrhagic fever as well as the mosquito-borne diseases African horse sickness, and the West Nile fever (Gale et al. 2010).

The health concern of the emerging West Nile virus is not exclusively focused to animals (horses) but also to humans. The virus was firstly isolated in 1937 from humans in the West Nile district of Uganda (Smithburn et al. 1940). *Culex spp.* (e.g. *Culex modestus* and *C. pipiens*) are generally considered as principal vectors (Reiter 2010). The tremendous speed and related health care problems has been demonstrated after initial establishment of the virus in the northwest of the United States in 1999 (Lanciotti et al. 1999) and the rapid spread across the North-American continent (Murray et al. 2010). Europe is aware: In Northern Italy, the West Nile virus re-emerged in humans after ten years in 2008 (Calistri et al. 2010). In 2010, West Nile virus outbreaks in human populations are documented from the south-eastern European countries of Greece (Papa et al. 2010) and Romania, where weather conditions favoured the establishment and increase of mosquito populations (Sirbu et al. 2011). The European human population will probably be threatened more intensively by the virus in the upcoming decades (Reiter 2010).

2.3 Short medical entomology of the addressed disease vectors

In this thesis, organisms that serve as disease vectors are studied. The phylum “Arthropoda” is characterised by a three-segmented body (Head-Thorax-Abdomen) with exoskeleton. They are ecto-thermic and hence depend in the maintenance of body functions on the thermic conditions of their environment. The estimates of the real number of species of Arthropoda are manifold (e.g. the initial estimation of 30 million arthropod species by Erwin 1982 and the reduction to 4-6 million by Novotny et al. 2002, due to the detected low host specifity of tropical herbivores). “Insecta” is the most diverse class belonging to the arthropods (e.g. reviewed by Dettner and Peters 2003). About one million insect species are described, which represent taxonomically more than half of all known living organisms. As many of them build up large populations, partly with social interaction, their abundance is even more pronounced.

The studied species within this thesis belong to the order "Diptera". This order contains about 85000 described species which typically exhibit one pair of wings that is used for the flight (two-winged) and a second pair as reduced knobs for the flight balance (Crosskey 1993, Dettner and Peters 2003). Due to their medical importance the focus of this study is directed to aedine mosquito species and phlebotomine sandflies.

2.3.1 Mosquito species

Mosquitoes ("Culicidae") have perhaps attained greater public notoriety than any other arthropod, which may be due to the fact that they are almost unrivalled as irritating biting pests and moreover capable to transmit several human pathogenic parasites (Service 1993). The females require proteins obtained by blood sucking to mature their eggs. Of special interest are the transmittalbe arboviruses (arthropod-borne viruses) are sucked up by the females from an infected host. They multiply in the stomach of the host and are passed within a few days across the stomach wall into the haemocoel (Service 1993). Development of a sufficient virus dose helps to overcome internal "barriers" and leads to a mitigation to the salivary glands (DeFoliart et al. 1987). The virus then can be inoculated into a host by a new blood meal. The period between pathogen acquisition by a vector to the time when the vector is infective (capable to transmit the pathogen) to a host is called "extrinsic incubation period" and is generally temperature-dependent (see e.g. Watts et al. 1987 for the example of dengue virus amplification).

Within the Aedini, the largest tribe of Culicidae, more than 1000 species are described. The ranking of taxa as genera and/or subgenera is subjective and differs remarkable between traditional phenetic classification (mainly based on the work of Edwards 1932) and classifications based on phylogenetic relationships (e.g. Reinert et al. 2004). The two species with the most severe consequences for human health are addressed within this thesis.

a) *Aedes albopictus* (Skuse, 1894):

The Asian tiger mosquito, *Aedes albopictus* (syn. *Stegomyia albopicta*), was first described by Frederick Askew Skuse in 1984 as *Culex albopictus* but was later assigned to the genus *Aedes* (Edwards 1920). The subgenus *Stegomyia* was recently compiled to genus by Reinert et al. (2004). However, especially medical entomologists recommend using the previous classification of the Aedini (see e.g. Savage 2005), due to concerns regarding the cladistic analysis of Reinert et al. (2004), in order to keep a stable nomenclature and to facilitate communication and information exchange among professionals.

The global invader *Ae. albopictus* is an epidemiologically important vector for the transmission of many viral pathogens (at least 22 human-pathogenic viruses), most importantly for the Chikungunya and dengue but also for e.g. the St. Louis encephalitis, West Nile and Yellow fever virus (Gratz 2004).

Picture 1:

Female *Aedes albopictus* mosquito on human skin starting with the blood-meal.

Source: James Gathany/CDC
on

http://phil.cdc.gov/phil/home.asp

(Pic number: 1866)

The tiger mosquito is characterized by its black and white striped legs and the white stripe at his back side (see Picture 1). Interestingly, the female lays her eggs near water or on the water surface but not directly into it (Hawley 1988). Any open container that is temporally flooded with water may therefore be sufficed for larvae development (Estrada-Franco and Craig 1995). Native to Southeast Asia, this ability supported the mosquito in his very successful invasion process.

In Europe, *Ae. albopictus* caused the unexpected local Chikungunya epidemic in the region of Ravenna, Northern Italy (Rezza et al. 2007, Boniluari et al. 2008). Furthermore the tiger mosquito acted as vector of the recent cases of dengue infections in Europe. In Nice, France, two men became infected with the virus (La Ruche et al. 2010). Due to the case report of a German traveller infected with dengue after returning from Croatia (Schmidt-Chanasit et al. 2010), the health professionals in Croatia initiated a screening programme. 15 persons with evidence of recent dengue infections of autochthonous origin were identified (Gjenero-Margan et al. 2011). Up to now there is no vaccination available against dengue virus. *Ae. albopictus* species is addressed in detail within this work in article 4.

b) *Aedes aegypti* (Linnaeus, 1762)

The Yellow fever mosquito, *Aedes aegypti* (syn. *Stegomyia aegypti*, proposed by Reinert et al. 2004 and critisized by e.g. Savage 2005) is native to Africa (Mousson et al. 2005) but is now found in several (sub-) tropical regions around the globe. In Europe the mosquito was present until Second World War but disappeared thereafter probably due to the use of DDT (Holstein 1967). Recently the mosquito was found in the continental of Europe (Scholte et al. 2010). However, permanent populations are just observed for Madeira, Portugal (Almeida 2007). This species is also a container-breeding mosquito and can be recognized by white markings on legs (see Picture 2) and - in contrast to *Ae. albopictus* - a marking in the form of a lyre on the thorax (Phillips 2008). The mosquito is active throughout the day, but the females usually prefer to bite at dusk and dawn. With the spread of *Ae. aegypti*, several health concerns are related, such as yellow and dengue fever but also Chikungunya epidemics that could arise.

Picture 2:

Female *Aedes aegypti* mosquito aquiring blood-meal from a human host.

Source: Paul I. Howell/Frank Hadley Collins/CDC on http://phil.cdc.gov/phil/home.asp

(Pic number: 9533)

Although, further mosquitoes such as *Ae. albopictus* are competent vectors, yellow-fever transmission in Africa and South-America is most closely related to *Ae. aegypti* occurrences, wherefrom the common (non-scientific) name yellow-fever mosquito is derived. Moreover, *Ae. aegypti* is considered as primary vector of the dengue virus due to higher vector competence in comparison to *Ae. albopictus* (Lambrechts et al. 2010). Globally, this mosquito is hence the main vector responsible vector for dengue transmission (Phillips 2008). However, a spread of *Ae. albopictus* may lead to a decline of *Ae. aegypti* populations (O´Meara et al. 1995) which may be a result of competitive displacement (Lounibos 2007). The mosquito is addressed in article 2 (extrinsic incubation period for dengue virus amplification within *Ae. aegypti*).

2.3.2 Phlebotomine sandflies

Sandflies (family: “Psychodidae”) are delicate, hairy flies (see Picture 3) with long slender legs (Lane 1993). Adults obtain a body size of not more than 3 mm. Sandflies do not require aquatic habitats as breeding sides such as mosquitoes (Culicidae). Instead, oviposition happens in moist soils (Feliciangeli 2004). From the five genera, only *Phlebotomus* (Old World) and *Lutzomyia* (New World) are anthropophagous and hence of medical importance (Lane 1993). Of the 700 species only about ten percent are thought to be involved in pathogen transmission to humans. Within this thesis *Phlebotomus species*, occurring in Europe were considered for risk analyses (article 3, 5 and 6). Especially, the following species are studied in more detail (compare article 6):

- *Phlebotomus ariasi* (Tonnoir, 1921)
- *Phlebotomus mascittii* (Grassi, 1908)
- *Phlebotomus neglectus* (Tonnoir, 1921), syn. *Phlebotomus major s.l.*
- *Phlebotomus perfiliewi* (Parrot, 1930)
- *Phlebotomus perniciosus* (Newstead, 1911)

Picture 3:

Female phlebotomine sandfly aquiring blood-meal from a human host.

Source: Frank Hadley Collins/CDC on

http://phil.cdc.gov/phil/home.asp

(Pic number: 10277)

Sandflies are crepuscular and nocturnal. When seeking for food, sandflies usually have a characteristic short hopping flight near the ground (Killick-Kendrick 1999). Only females suck blood, which very likely accelerates the maturation of their eggs. However, this blood meal may be facultative, as autogeny has been observed (Johnson 1961). Due to the fact that the blood sucking can last up to five minutes, sandflies are constrained by sleeping blood victims. The preferred hosts of *Phlebotomus* and *Lutzomyia* species are humans and dogs and in less extent also rodents (Lindgren and Naucke 2008). Sandflies are capable to transmit several kinds of Phleboviruses, the bacteria *Bartonella baciliformis* and most importantly *Leishmania* (Protozoa). Vertical transmission of the different *Leishmania* complexes from an infected female sandfly to the offspring is possible.

Leishmaniasis is found in all continents, excepting Oceania, with spatial hotspots of occurrences in Southern America, the Middle East as well as European and African regions bordering the Mediterranean Sea. It needs to be mentioned that *Phlebotomus mascittii* which has recently been found in Germany and Austria has not yet been confirmed as a vector of *Leishmania infantum*, but its competence is strongly suspected (Naucke et al. 2008). The life-cycle of *Leishmania* protozoa comprises two developmental stages. In a first stage the female sandflies ingests the *Leishmania* as amastigote during feeding from vertebrate reservoir hosts, mainly dogs and rodents. Over a period of up to 25 days the amastogotes undergo a transformation into flagellated promastigotes within the sandflies (Neuber 2008). When the now infected sandfly feeds on fresh source of blood, it passes the promastigotes into the new host and complete the life cycle (Cunningham 2002). Generally, *L. infantum* and *L. donovani* (Old World) and *L. chagasi* (New World) cause the visceral form of leishmaniasis which affect the internal organs and, if left untreated, can end with the death (WHO 2010). *L. major* and *L. tropica* (Old World) as well as *L. braziliensis* (New World) cause mainly the cutaneous leishmaniasis, which is in most cases self-limiting with scarring (WHO 2010). *L. braziliensis*, however, can also cause a more severe mucocutaneous form, which needs to be treated (Neuber 2008). To date, there exists no vaccine against leishmaniasis despite the substantial efforts of laboratories (Kedzierski 2010).

3. Synopsis of the thesis

3.1 General objectives and outline

The overall motivation of this thesis can be divided into three main issues:

(1) Identifying the main climatic factors affecting occurrences of disease vectors and vector-borne diseases.

(2) Investigating the risk of emerging/resurging disease vectors or vector-borne diseases for European regions under current climatic conditions.

(3) Evaluating the temporally changing spatial patterns of risk exposure for European regions during the 21st century.

In order to cope with these challenges, regional climate change projections are used for exploration. The topic on the relevance of climate change effects on vector-borne diseases is introduced and the possible application of data provided by regional climate models is given (article 1).

Firstly, the research focus is directed to disease vectors that were recently (re-) introduced to Europe. Here, the invasive mosquito species *Ae. albopictus* and *Ae. aegypti* and the dengue virus as their probable most severe transmittable pathogen is of special interest. Secondly, phlebotomine sandflies as group of disease vectors which can be considered as native to the European continent and their most severe transmittable pathogens belonging to the *Leishmania infantum* complex are addressed. Europe or specific Central European regions are defined as spatial target to apply the spatio-temporal risk analyses. Research work is divided into two approaches in which the opportunities of regional climate change projection for spatio-temporal risk analyses of vector-borne diseases are presented.

In a first approach, the main known temperature constraints of pathogens or vectors, derived by experiments and observations, are used to transfer to future conditions. Climatic constraints for dengue virus amplification within the primary vector *Ae. aegypti* were taken from two laboratory experiments. Using projected temperature data in a daily resolution, European risk zones are identified that fulfil the requirements. Furthermore, the longest potential duration of dengue transmission is determined (article 2). Analyses for vector and pathogen requirements in combination are carried out exemplary for sandflies and *Leishmania infantum*. The projections for the main known temperature constrains of vector and pathogen are overlaid to detect potential temperature-derived future risk areas in Germany (article 3).

These two studies illustrate the opportunity of regional climate models for direct climate impacts studies of vector-borne diseases.

In a second - rather statistical - approach it is demonstrated how regional climate change projections can be integrated in species distribution models. Vector-borne pathogens do just occur within the vector or hosts, respectively. Due to this reason, relating environmental variables to spatial occurrences of pathogens would probably fail. Therefore, the purpose of species distribution models was solely practiced for the disease vectors.

The bioclimatic niche for the invader *Ae. albopictus* is determined by relating geographically explicit vector species presences with current bioclimatic conditions. Here, the effects of different selections of variables and training regions are evaluated. Then, the determined niches - representing best the current occurrence - are transferred to the expected future conditions by using data of the regional climate model COMO-CLM. This enables identifying future climatic suitability for the mosquito in Europe (article 4).

In general, projected climatic suitability does not necessarily imply vector occurrences in the respective region. For this reason, it is shown how conventional niche modelling can be improved by integrating species natural dispersal ability. Due to the fact that the dispersal of *Ae. albopictus* to climatically suitable habitats is mainly supported by human activities and hence happens by chance, this approach was practiced on disease vectors with mainly natural dispersal. Therefore, firstly, future climatically suitable habitats are projected for phlebotomine sandflies. Then artificial landscapes are generated in which the movement of the species will take place. The landscapes are characterised by both, stable environmental conditions but also changing landscape elements due to climatic changes. This methodological task enables to project species future occurrences (articles 5 and 6).

Finally, the use of regional climate projections for risk assessments of vector-borne diseases is brought into a bigger scientific context (article 7). Therefore, a framework is proposed that attempts to include geographical expertise in risk analyses. The main knowledge and surveillance gaps concerning vector-borne diseases are identified. New approaches are presented with the ability to close these gaps and the aim to support epidemiological studies of vector-borne diseases.

3.2 Articles´ purposes, histories and authors´ contribution

Article 1:

Fischer D., Thomas S., Beierkuhnlein C. (2010): Climate change effects on vector-borne diseases in Europe. Nova Acta Leopoldina 112(384), 99-107.

Article´s purpose and history:

In article 1 the main facets of climate change effects on several vector-borne diseases are given. This article provides an overview about recent trends and emergence of vector-borne diseases with a spatial focus on Europe. A methodological task to determine future vector occurrences by using regional climate change projections with bioclimatic envelope modelling is introduced. The article is published in a special issue of the "Nova Acta Leopoldina". This issue is based on lectures given at the international congress "Continents under climate change" as event of the Humboldt-Universität zu Berlin on its 200th anniversary, held in April 2010.

Authors´ contribution:

Dominik Fischer and Carl Beierkuhnlein developed the idea of the manuscript. Dominik Fischer wrote the manuscript and prepared the figures. Stephanie Thomas evaluated the findings of a literature search in the ISI Web of Knowledge and summarized the results in the table. She gave valuable comments on the manuscript. Carl Beierkuhnlein edited the paper.

Article 2:

Thomas S.M., Fischer D., Fleischmann S., Bittner T., Beierkuhnlein C. (2011): Risk assessment of dengue virus amplification in Europe based on spatio-temporal high resolution climate change projections. Erdkunde 65, 137-150.

Article´s purpose and history:

The extrinsic incubation period indicates the time in which an infected vector becomes infectious (capable to transmit the pathogen). This is one of the main factors regulating transmission of a vector-borne disease, assuming a competent vector is present. In this study, two laboratory findings concerning temperature thresholds for dengue virus amplification within the vector *Ae. aegypti* are used. The risk analyses are based on projected temperature data in daily resolution obtained from the regional climate model COSMO-CLM. European regions, where dengue virus amplification can be expected and the longest potential season for virus amplification are identified.

Authors´ contribution:

Stephanie Thomas and Dominik Fischer contributed equally to this work. Stephanie Thomas had the idea of the paper and searched for profound studies concerning the extrinsic incubation period of the dengue virus. She wrote mainly the introduction with biological-ecological background of the study and the discussion. Dominik Fischer developed the code for the analysis in GIS and arranged the figures 1-4. He mainly wrote the methods, results and the conclusion. He pre-processed the climatic data with Stefanie Fleischmann. Stefanie Fleischmann practiced the final analysis in GIS based on the developed code and wrote a first draft (in German) as her Bachelor-thesis. Torsten Bittner prepared scripts written in Python and R in order to standardize the procedure in GIS. He additionally arranged figure 5. Carl Beierkuhnlein was the supervisor of Bachelor-thesis of Stefanie Fleischmann, gave critical comments and edited the manuscript.

Article 3:

Fischer D., Thomas S.M., Beierkuhnlein C. (2010): Temperature-derived potential for the establishment of phlebotomine sandflies and visceral leishmaniasis in Germany. Geospatial Health 5, 59-69.

Article´s purpose and history:

The aim of this paper is to determine risk classes for the potential establishment of visceral leishmaniasis in Germany in the face of climate change. For this purpose, the main known temperature constraints for the establishment of the disease vectors (phlebotomine sandflies) and the pathogen (*Leishmania infantum*) within the vector were are identified and projected to future conditions. A final overlay of the suitability maps for vector and pathogen leads to the temperature-derived risk classes for potential establishment of visceral leishmaniasis in Germany. Projections for the 21st century are based on temperature data of REMO.

Authors´ contribution:

Dominik Fischer had the idea for this study, did the analysis and wrote the manuscript. He prepared figures and tables. Stephanie Thomas commented the paper critically. Carl Beierkuhnlein helped in searching the target journal and edited different versions of the paper (from submission stadium to the final draft).

Article 4

Fischer D, Thomas S.M., Niemitz F., Reineking B., Beierkuhnlein C. (2011): Projection of climatic suitability for *Aedes albopictus* Skuse (Culicidae) in Europe under climate change conditions. Global and Planetary Change 78, 54-64.

Article´s purpose and history:

Within this paper the current bioclimatic niche of *Ae. albopictus* is modelled for the native range and the entire (invaded) global range using maximum entropy approach. The effects of different selections of bioclimatic variables (expert knowledge vs. statistic based) are evaluated. Niche similarity between the native and the global range is analysed. The global models (regardless the chosen bioclimatic variables) fitted best with the recent regions of occurrence of the mosquito and were hence used to project species future climatic suitability in Europe. Projections are based on data provided by the regional climate model COSMO-CLM. Potential failure of projections due to non-analogue climate is excluded via Multivariate Environmental Similarity Surface analysis.

Authors´ contribution:

Stephanie Thomas, Franziska Niemitz and Carl Beierkuhnlein had the initial idea of climate change projections for *Ae. albopictus* with the regional focus of Bavaria. Franziska Niemitz practiced these previous analyses and wrote a first draft (in English) as Master thesis. She organized an initial data set of species presence records. Stephanie Thomas completed this data set with a search for additional infestations of the species from the year 2003 onwards and provided these references in the Supplemental Material. She wrote main parts of the introduction, especially the parts concerning species ecology. Dominik Fischer practiced the species distribution models and future projections for whole Europe and tested of non-analogue climatic conditions by Multivariate Environmental Surface analysis. He wrote the main parts of the results, discussion and conclusion and prepared the figures. Dominik Fischer and Björn Reineking wrote the methodology chapter and generated the tables. Additionally, Björn Reineking tested the different data sets for niche similarity and provided expertise for further issues concerning the modelling procedure. Björn Reineking and Carl Beierkuhnlein (both supervisors of the Master thesis from Franziska Niemitz) gave both critical comments on the manuscript and were responsible for the final editing.

Article 5:

Fischer D., Thomas S.M., Beierkuhnlein C. (2011): Modelling climatic suitability and dispersal for disease vectors: the example of a phlebotomine sandfly in Europe. Procedia Environmental Sciences, in press.

Article´s purpose and history:

The paper provides a methodological background on enhancing conventional bioclimate envelope modelling of species distribution with species specific dispersal ability. The calculations of the different compartments to generate the least-cost path (cost surface, distance and backlink) as most likely way of species dispersal are presented on the example of the sandfly species *Phlebotomus perniciosus*. This description provides the supporting methodological information for article 6. The special issue of Procedia Environmental Sciences is based on contributions of participants of the “1st conference on Spatial Statistics: Mapping Global Change” held in March 2011 in Enschede, the Netherlands.

Authors´ contribution:

Dominik Fischer had the idea of the manuscript and wrote it. He practiced the analysis and prepared the figures. Stephanie Thomas commented the paper critically. Carl Beierkuhnlein finally edited the paper.

Remark: Published in Procedia Environmental Sciences (Volume 7, 164-169).

Article 6:

Fischer D., Moeller P., Thomas S.M., Naucke T.J., Beierkuhnlein C. (2011): Combining climatic projections and dispersal ability of phlebotomine sandflies: A methodological task to estimate vector responses to climate change. PLoS Neglected Tropical Diseases, under review (submitted 18th of July, 2001).

Article´s purpose and history:

This article is based on the previous paper (article 5) and supports the proposed methodological task with concrete results. Within this paper, firstly, bioclimatic niches of five *Phlebotomus* species are modelled and projected to future conditions of Central Europe (Austria, Germany and Switzerland). Projections of climatic suitability are enhanced by analysis concerning potential natural dispersal pathways. Therefore, species potential movement through artificial (future) landscapes is analysed. Those landscapes are attributed by different cost factors representing the different landscape features. The least-cost paths, which correspond to the least effort for species movement, are calculated throughout the 21st century. Combining the two approaches - niche modelling and dispersal analysis - allows distinguishing between climatically suitable regions which can be occupied by the species from those that are unreachable by natural dispersal. The editorial board invited the authors to submit the paper for full consideration (review process) after initial pre-submission inquiry.

Authors´ contribution:

Dominik Fischer had the idea and wrote the paper. He practiced the analysis and prepared figures and tables. Philipp Moeller processed the data and practiced previous species distribution models with the data for his Bachelor thesis. Stephanie Thomas commented the paper critically. She had the idea for figure 1. Torsten Naucke provided the sandfly occurrence data from his literature database and own field collections. He gave valuable hints how to integrate expert knowledge on sandfly ecology for the least-cost analysis. Carl Beierkuhnlein (supervisor of the Bacherlor thesis of Philipp Moeller) edited the final version.

Remark: Published in PLoS Neglected Tropical Diseases (Volume 5, e1407) after minor revisons and changed title: “Combining climatic projections and dispersal ability: a method for estimating the responses of sandfly vector species to climate change”.

Article 7:

Fischer D., Thomas S.M., Beierkuhnlein C. (2011): Vector-borne diseases in a rapidly changing world - Geography needs to become infected! The Geographical Journal, submitted (3rd of August, 2011).

Article´s purpose and history:

Within this paper a framework to include geographical expertise in research and surveillance of vector-borne diseases is provided. In the previous case studies applications of regional climate projections for spatio-temporal risk analysis are demonstrated. Here, the focus is a more conceptual one by offering a scale-dependent proposal for risk analysis of vector-borne diseases under global change conditions. It is shown how regional climate change projections can be integrated in this framework as a first step in risk assessment. This consequently demands for follow-up studies for the detected climatic risk zones. The linkage between research and surveillance of vector-borne diseases is given.

Authors´ contribution:

Dominik Fischer had the idea of the manuscript and prepared the figures. Stephanie Thomas commented the paper. Dominik Fischer and Carl Beierkuhnlein wrote the manuscript. Carl Beierkuhnlein finally edited the manuscript.

Remark: Editor of “The Geographical Journal” instructed for major revisions after receiving reviewers’ comments.

4. Critical reflection and outlook

4.1 Concerns about the use of climate projections for risk analyses

Vector-borne diseases are ranked as one of the most severe emerging infectious diseases (Morens et al. 2004). In a global perspective, however, there is no evidence that solely climate change in the 20th century has supported vector-borne diseases (Kovats et al. 2001). Although, in particular Reiter (2008) stated that climate change alone has not affected the spread of vector-borne diseases alone, there is no doubt concerning climate change effects on vector-borne diseases. However, large-scale orientated human activities may superpose climate change effects. Especially in the case of Malaria, probably one of the most severe human pests in the modern age, a global recession during the 20th century has been identified (Gething et al. 2010). In that case, for instance, the generous use of DDT has probably caused the recession.

The effects of climate change do not act everywhere in the same manner neither at the same time, the same intensity nor on the same spatial scale. Especially on the example of mosquito disease vectors it has been demonstrated that the suitability of environmental habitat conditions would increase under climate change conditions for some regions, while also decrease for others (Peterson 2009). Within this thesis, the spatial focus is directed to Europe. The addressed European regions can be as the potential northernmost limit of distribution, where, consequently, mainly climatic conditions regulate the maximal extension of suitability for the addressed vector-borne diseases. The aim of this thesis is not to determine the intensity but rather the potential occurrences of specific diseases vectors or vector-borne diseases, respectively. Therefore, the previously mentioned concerns about climate change effects are legitimate but cannot be seen as counter-argument to the topic of this thesis.

The presented risk analyses are related to climatic projections. Those projections are based on assumptions, for instance concerning the choice of emission scenario which is used. Hence, there necessarily exists a chance that the future developments will not exactly take place as assumed. Due to this reason, the developed risk maps should not be interpreted as factual forecasts of emergency of a disease vector or of the transmittable disease. Instead, the results indicate possible future developments, assuming the chosen assumptions will come true. Generally, the intrinsic problem with projections about the future is that they are not testable. In order to cope with the critic of some scientists that future projections are hence non-scientific (see Randolph 2009), it is advisable to take evidence from the past or test the analysis on the current situation. Then projections are expedient and more reliable. Therefore, expert knowledge from observations or experiments was taken in the first part of this thesis and species distribution models were tested on the current condition, in the second part.

4.2 Development of novel climate models and a new generation of scenarios

Although regional climate models can be seen as powerful tool for climate impact studies, the models still fail to capture temporarily and spatially small-scale local specifics (Harte 2008). The quality of projections concerning climatic extreme events is biased by the spatial resolution the climate models. While spatial resolutions of 10-20 km (used in these studies) are proper for projections for climatic long-term trends, they failed for projections of short-term events. Due to this spatial limitation of occurring weather extremes, reliable projections requires a further downscaling from the regional level to the local one. Here, generalizations across scales are inappropriate as the effects on vector-borne diseases are often dependent on the specific of the event itself (Ivers and Ryan 2006).

Despite of the required embedding of extreme events in climate models, scientists are currently working on novel emission scenarios (Moss et al. 2010, Overspeck 2011). Up to now, the development of the IPCC scenarios was based on a sequential approach. Only a group of specialist determined the respective reaction of developed emission scenarios of greenhouse gases in analyses and their reactions of the atmosphere. Various scientific disciplines which required future projection for their climate impacts studies were not involved in the process of development (Moss et al. 2010). Therefore, concerns and suggestions of the users could not be integrated in the stage of development.

The novel scenarios which are currently under development can be seen as a parallel approach in which various scientific disciplines are involved. In this completely new paradigm, traditional climate research is joined with research on climate adaption, services and assessment (Overspeck 2011). They will all give input for the calculation of the feedback of the climate system. It is aimed to provide analysis and advice that comprehensively addresses all or at least many aspects of the climate change issue (Sarofim and Reilly 2011). Consequently, these novel scenarios are much more complex in development. Nevertheless the new generation of scenarios offers two main advantages: First of all, embedding different scientific disciplines that are all working on systems influencing the climate at the early progress promises a higher quality (Moss et al. 2010). Secondly, the required data are more understandable for a broad interdisciplinary audience and can then be reported more promptly (Overspeck 2011).

4.3 Proposal for future research activities

Elucidating expert knowledge e.g. via field observations or laboratory experiments supports quantification of climate change impacts on vector-borne diseases (Gale 2010). Especially projections, based on previously determined influence of weather extremes for instance on vector survival, may provide valuable support for the detection of future tendencies. Here, new experiments with regard to e.g. species frost or heat tolerance have to be generated which then could be applied for the novel climate change scenarios on different spatial scales.

Furthermore, while several European regions can expect increasing climatic suitability for various vector species (shown in the different case studies) a special focus should be directed to biotic interactions such as competitive behaviour and niche similarity between the species. In comparison to most mosquitoes, the knowledge concerning sandfly biology and ecology is rather scarce. There exist only few fundamental works on this topic (e.g. Killick-Kendrick 1999, Feliciangeli 2004). Much more is required in order to support and enhance model projections by expert knowledge.

In the case of introduced mosquito-borne diseases, the primary focus should be directed to potential introduction pathways due to the globalized travel and trade activities. From the introduction harbours the invaders manage to spread via highway traffic. The collected eggs of *Ae. albopictus* at a resting place of the highway A5 near the city of Rastatt in the southwest of Germany hints on introduction of the species from southern parts of Switzerland or northern parts of Italy across the Alps (Pluskota et al. 2008). The continuous and ongoing introduction and establishment of mosquitoes to Europe is not only limited to *Ae. albopictus*. The Yellow fever mosquito (*Ae. aegypti*) has recently been founded in the in the Netherlands (Enserink 2010) where intensified mosquito control activities avoid an infestation (Scholte et al. 2010). The Asian bush mosquito ("*Aedes japonicus*", syn. *Ochlerotatus japonicus*) is meanwhile established in the Central European regions of northern Switzerland (Schaffner et al. 2009) and southern Germany (Becker et al. 2011).

Pathogen introduction, instead, is mainly related to infected travellers coming from endemic regions by air planes. This is how the Chikungunya-virus was introduced to Europe (Rezza et al. 2007) and the West-Nile virus to United States (Lanciotti et al. 1999). Consequently, future research should attempt to take such invasion and dispersal pathways into account in the face of global exchanges. Here, data concerning the import of container import at the main European harbours as well as data from the airline companies regarding travellers from endemic countries can be included in risk analysis. The proposed research activities would be a further step towards an accurate risk assessment of climate-sensitive vector-borne diseases, which Europeans should not longer consider as “exotic tropical diseases”.

4.4 Concluding remark

Finally, I would like to give a personal statement by taking up the previously noted concern of Al Gore about “the planet [that] has a fever”. Indeed, he is right that rising global temperatures cause a fever of our planet. But this is not the only fever on the earth. Increasing number of cases of vector-borne diseases, resulting mainly in illness with high temperatures in human beings can cause a second fever. This fever is probably closely related to the first one and can be expected to increase and get worse in the same manner for European regions during the 21st century.

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6. Articles

6.1 Article 1:

Climate change effects on vector-borne diseases in Europe

With 1 Table and 2 Figures.

Abstract

The most dangerous infectious diseases occur in tropical or subtropical regions. Climate change, however, will be associated with the spread of vector-borne diseases to higher latitudes. Here, the resulting bio-risks for Europe are presented in more detail. Knowledge on suitable future habitat for disease vectors in Europe is scarce. Here, one approach - the modeling of bioclimatic envelopes - is presented. By combining these envelopes with explicit regional climate change simulations, maps of future suitable climatic conditions for disease vectors can be developed. In addition to climatic drivers, globalization might also contribute to the spread of disease vectors in Europe.

High invasive capacity combined with travel and trade has turned several disease vectors into “global players”. Conceivably, climate change might create the ideal conditions at sea- and airports, from which imported vectors could then go on to conquer other areas in Europe. Nevertheless, vector establishment does not always equate to disease outbreak. For this, additional factors such as the abundance of reservoir hosts and pathogen requirements (e.g. thermal constraints) must be fulfilled.

As a matter of fact, European health care is challenged by novel threats for which it must be prepared. This will require both interdisciplinary research and close links between policy and science in order to become proactive and if necessary to adapt monitoring systems in time.

Zusammenfassung

Die gefährlichsten Infektionskrankheiten treten in tropischen bzw. subtropischen Gebieten auf. Der Klimawandel wird jedoch mit sich räumlich ausbreitenden vektor-übertragenen Krankheiten in höhere Breiten in Verbindung gebracht. Die dadurch auftretenden Biorisiken werden im Folgenden für Europa näher beleuchtet. Bisher ist sehr wenig

darüber bekannt, welche europäischen Regionen künftig gefährdet sein werden. Als erster Ansatz kann das Modellieren der bioklimatischen Nische, die der Vektor unter aktuellen klimatischen Bedingungen bevorzugt, verstanden werden. Die ermittelte Nische kann mithilfe regionaler Klimaszenarien auf künftig veränderte Bedingungen übertragen werden.

Neben klimatischen Faktoren begünstigten intensivierte Handels- und Reisetätigkeiten die weltweite Ausbreitung invasiv auftretender Krankheitsüberträger. Ausgehend von großen europäischen See- und Flughäfen, könnten die importierten Vektoren weitere, für sie klimatisch geeignete, Gebiete besiedeln. Neuauftretende und sich etablierende Krankheitsüberträger sind jedoch nicht gleichbedeutend mit Krankheitsausbrüchen. Hierzu müssen zusätzliche Faktoren wie die thermischen Anforderungen des Erregers erfüllt sein, damit dieser zwischen Wirtstieren zirkulieren kann.

Das europäische Gesundheitssystem wird unausweichlich mit dieser neu bzw. wieder auftretenden Gefährdung konfrontiert werden. Dies erfordert den interdisziplinären Wissenschaftsaustausch sowie enge Verknüpfungen zwischen Wissenschaft und Politik. Mithilfe frühzeitig angepasster Überwachungsmaßnahmen könnten die Risiken somit minimiert werden.

1. Vector-borne diseases: Risk for human health

From an ethical point of view, human health should generally be an issue that is given priority in science, policy, and in particular in climate change research. According to regional climate models, Central Europe will be subjected to above-average warming and its precipitation regimes are expected to change in a patchy and non-uniform way, thus creating irregular regional conditions (Kysely and Beranova 2009). In 2003 human mortality rates were found to respond to climatic extremes. A more hidden and latent health threat from climate change is related to vector-borne diseases, where organisms and pathogens are highly sensitive to the climate. Recent occurrence has been strongly controlled by the climatic constraints of the biota constituting a chain of infection: pathogen, vector, reservoir and host (Fischer et al. 2009a).

Here, we briefly highlight the potential effects of climate change on vector-borne diseases, which could provoke the (re-)emergence of hazardous bio-risks within Europe in the 21st century. We identify potential risk vectors that are expected to expand their range or become invasive in Europe. We present methodological tools for estimating the tendency to spread and finally, we suggest additional drivers that are contributing to the supposed spread of vector-borne diseases.

Tab. 1: Selected major vectors and their transmitted pathogens that may cause zoonotic diseases in Europe. Abbreviations behind vector species means: mosquitoes (M), ticks (T) and sandflies (S). Assumed but unproven vector competence is marked with A, while proven Laboratory competence is marked with L. Pathogens, with few occurrences in Europe are marked with *.

Spread of endemic vectors and their transmitted pathogens	
Ixodes ricinus (T) northward trend	Anaplasmataceae, *Babesia divergens, Bartonella, Borrelia (afzelii, burgdoreri, garnii, valaisiana*), Central European and Tick-borne Encephalitis, *Coxiella burnetii, Francisella tularensis, Rickettsia helvetica*
Phlebotomus mascittii (T) northward trend (Germany)	*Leishmania infantum* ^{A}
Phlebotomus perniciosus (S) north-eastward trend (France, Germany)	*Leishmania infantum*, Arbia and Toscana virus
Widespread European vectors and their possible transmitted emerging pathogens	
Aedes vexans (M)	Eastern Equine Encephalitis, Rift Valley fever (subspecies: *Ae. vexans arabiensis*) and West Nile Virus
Culex pipiens pipiens (M)	Rift Valley fever and West-Nile Virus (enlargement)
Spreading tendencies of endemic vectors and their possible transmitted emerging pathogens	
Dermacentor marginatus (T)	Crimean-Congo Haemorrhagic Fever Virus*
Possible emerging vectors and their transmitted pathogens	
Aedes albopictus (M) recently introduced (Italy 1990)	Chikungunya, Dengue and further 20 arthropod-borne viruses!
Aedes japonicus (M) recently introduced (Switzerland 2007)	Eastern Equine^{L},- Japan B^{L} and St. Louis Encephalitis^{L}, West Nile Virus
Possible re-emerging vectors and their transmitted pathogens	
Aedes aegypti (M) disappeared in the last century	Dengue and Yellow Fever Virus
Anopheles maculipennis complex (M)	*Plasmodium ssp.* *

2. Disease vectors in the light of a changing European climate

Disease vectors are carriers that transmit pathogens from one host to another. The majority of vectors are ectothermal arthropods. They are unable to regulate their body temperature and depend directly on their environment. Hence, they react promptly to changing thermal conditions as a survival strategy. The competence of vectors has been compiled in Table 1 for selected species.

In the light of climate change, northward and altitudinal spread has been observed for ticks such as *Ixodes* and *Dermacentor* species (Lindgren and Gustafson 2001, Gray et al. 2009) with warming leading to increased winter activity, as has been observed for *Ixodes ricinus* in a Berlin forest (Dautel et al. 2008).

Risks from regionally restricted infectious diseases, such as sandfly-borne diseases (e. g. Leishmaniasis), are still underrepresented in European science and policy (Dujardin et al. 2008). Although the basis of knowledge on future trends assumed for native and alien disease vectors in Europe is limited there is some cause for alarm: Recently, a northward expansion of sandflies has become increasingly more apparent (Aspöck et al. 2008, Naucke et al. 2008).

3. Projecting the future: Bioclimate envelope modeling of disease vectors

The establishment of vector-borne diseases directly depends on the presence of disease vectors. While several studies and observations provide general information on the preferred habitats of vectors, only very little is known about the role of spatio-temporal variation in resource availability. Advanced and more sophisticated bioclimatic models may close this gap as they aim at defining the bioclimatic envelope (Fig. 1) that best describes the limits of a species' spatial range. Species records are correlated with selected bioclimatic variables (Heikkinen et al. 2006) and those variables are selected that best describe the current distribution pattern.

Projections of species' biogeographical ranges for the future are conveyed by simulating future distributions for selected climate change scenarios (Hijmans and Graham 2006). Data on projected climate change in the 21st century are supplied on global and regional scales by climate models (e.g. Jacob 2008). In contrast to their driving global models, regional climate models (RCM) are capable of taking topography into account at the meso-scale. They simulate climate change at a much higher spatial resolution, which is crucial in very structured relief such as European high mountain regions. The fine grain of regional projections improved the quality of impact studies on human health (Giorgi and Diffenbaugh 2008). Furthermore, assessments on the dispersal of vector organisms in the face of climate change benefit in particular from a high spatial resolution (Jacob 2008, Fischer et al. 2009b).

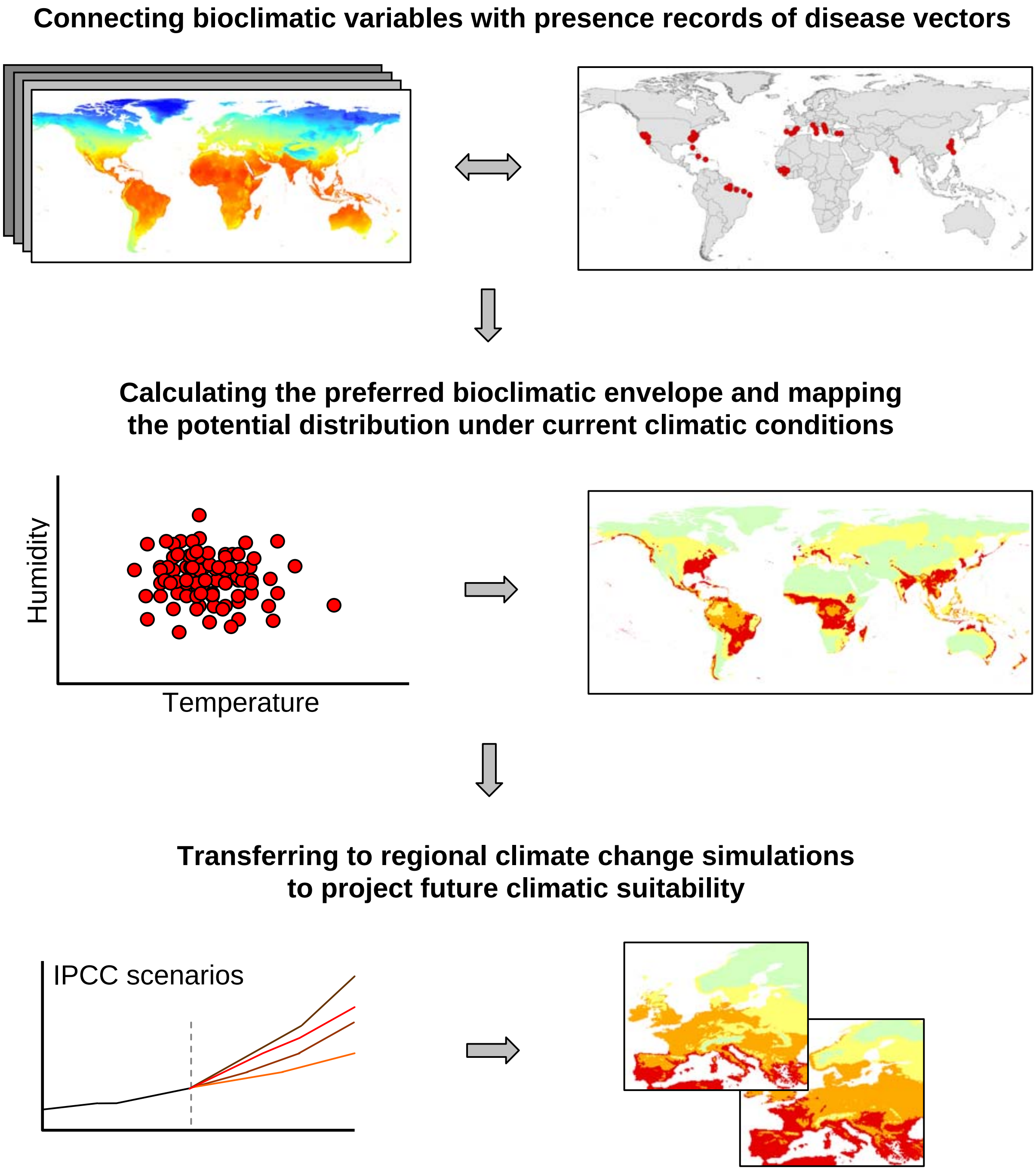

Fig. 1: Principle of bioclimatic envelope modeling of climate-sensitive disease vectors in regional climate change investigations

An intrinsic problem that is apparent in climate models is also a problem in regional models: climatically extreme and thus extraordinary phases are difficult to distinguish from statistical noise and modeling artifacts. In particular, forecasts on precipitation are still rather unreliable. Projections vary strongly between scenarios and, more importantly, between regions (Beniston et al. 2007).

We realize that other environmental variables (e.g. land use change) contribute to the successful establishment of vectors. Here, uncertainties are striking. Even when limitations are taken into account, we are convinced that bioclimatic envelopes remain a powerful tool for estimating the potential responses of vector distribution to climate change (Fischer et al. 2009c). Hence, the investigation of spatio-temporal climatic suitability of disease vectors in Europe can be considered to be a first step in detecting potential risk areas.

4. Climatic constraints of pathogens and climatic effects on reservoir hosts

The presence of vectors does not necessarily imply disease outbreaks. Moreover, risk analysis on vector-borne diseases in a rapidly changing European environment requires profound knowledge on the thermal constraints of pathogens.

Several mosquitoes (genus *Anopheles*) with vector competence for Malaria are now even endemic to Europe. These species do not only establish in the Mediterranean but also in temperate regions. Serendipitously, neglecting a few individual autochthonous cases (Kampen et al. 2003), the pathogen *Plasmodium vivax* is not established in Europe. Jetten and Takken (1994) called this the phenomenon of “Anophelism without malaria in Europe”. These authors stated that these mosquitoes require more than 100 days with a mean temperature of at least 14.5 °C to become infectious. However, rising temperatures may exceed these constraints in the future.

Common European vectors such as Aedes vexans and Culex pipiens pipiens could function as vectors for other emerging pathogens such as Eastern Equine Encephalitis (endemic to the USA) and the Rift Valley Fever Virus (currently endangering African populations) (Tab. 1). Unfortunately, there is not much knowledge available on pathogen constraints in general let alone on sustainable strategies. Microorganisms and viruses usually perform with high turn-over rates and undergo mutation to adapt to a changing environment.

The Hantavirus (Bunyaviridae) for instance, used to only occur in limited regions of South-East Asia but is now present in many areas of the world. The different strains, which are named according to the regions where they first occurred (e.g. Hantaan, Dobrava, Puumala, Korea, Sin-Nombre), are closely related to specific interactions with rodent hosts. Puumala Virus, the most common Hantavirus in Europe, is carried by the bank vole (*Myodes glareolus*). Humans contract the virus by inhaling aerosols or the dust particles of rodent excreta that are contaminated with the virus.

The infectious capacity of reservoir hosts is an additional factor contributing to the performance of a vector-borne disease. Based on the Hantavirus mode of transmission and circulation in nature, it seems reasonable to assume that climate change might influence Hantaviruses through impacting their reservoir host populations (Klempa 2009). Drought and heat waves, experienced by Europeans in 2003 as a memorable example of climatic extremes, are expected to increase both in amplitude and frequency under a changing climate (Jentsch et al. 2007, Jentsch and Beierkuhnlein 2008). They may also cause intensified fructifications of deciduous trees. Such mast years combined with anthropogenically-created or storm-related sparse forests may cause an increase in rodent populations and hence increase the risk of human infections with the Hantavirus (Beierkuhnlein and Foken 2008, Clement et al. 2009).

Furthermore, the spatial pattern of some infectious diseases (e.g. the West-Nile Virus) is related to the routes of migratory birds, which carry the pathogen as reservoirs over short and long distances. The West Nile Virus, originally identified in the West Nile district in Uganda, was commonly considered as a minor risk, inducing a fundamentally non-symptomatic disease or a mild influenza-like illness in humans. However, over the last 15 years, several infections of humans were reported with fatal cases of encephalitis. These cases were mainly related to elderly people in Southern Europe i.e. Romania 1996, Italy 1998, and France 2000 (Zeller and Schuffenecker 2004).

Empirical evidence suggests that climate change alters the speed, timing and typical routes of bird migration (Hedenström 2007). Research on the potential reduction of bird migrations, resulting in less pathogen transport to higher latitudes is valuable for risk analysis.

5. Global change factors contributing to the spread of vectors and diseases

The Asian tiger mosquito (*Aedes albopictus*) is native to South-East Asia. Obviously, the spread of the species has been assisted by human introductions and has not only responded in its global pattern to climatic constraints or favorable conditions (Fischer et al. 2009a). Meanwhile the mosquito has been introduced to almost all continents including Europe due to the global shipping of goods (Fig. 2) and its high adaptive capacity (Enserink 2008). However, as its introduction to Europe already took place in Albania in 1979 and in Italy in 1990, climate change is thought to be assisting in its dispersal across the continent (ECDC 2009).

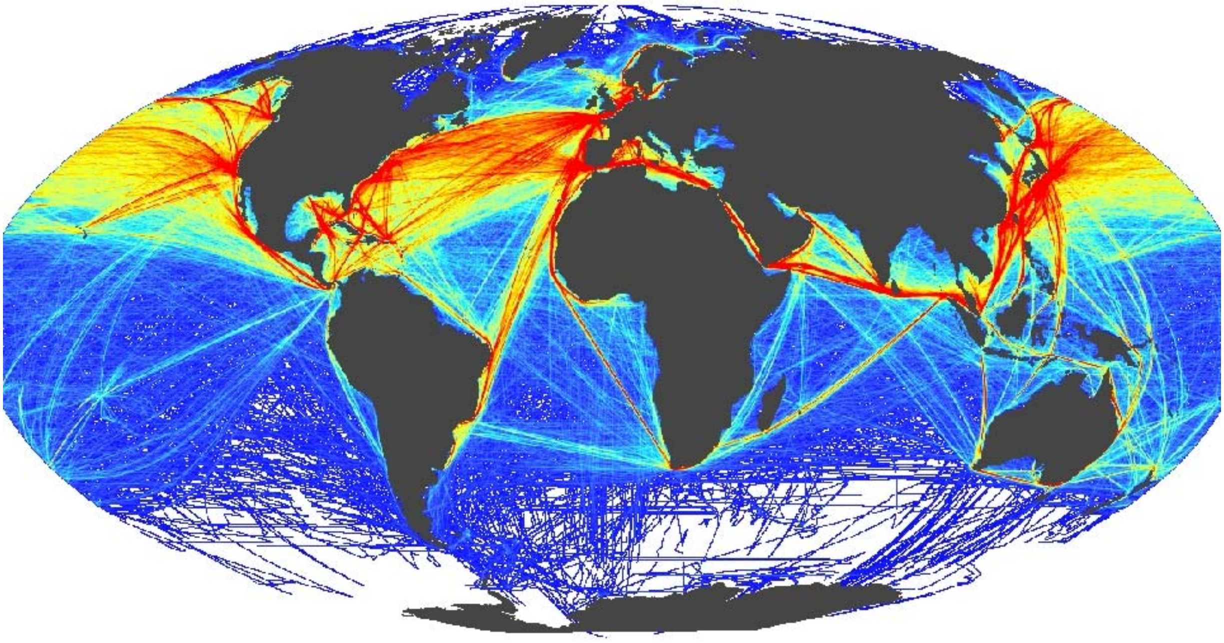

Fig. 2 Global shipping net. Frequency is coloured from blue (low) to red (high). Hence Europe is closely connected with almost all continents. Endangered are therefore many European harbours. Biosecurity controls at European harbours may help to avoid accidental introductions of harmful organisms. Adapted from Halpern et al. (2008).

Long-distance transport and travel enhance the risk of global invasions from vector-borne diseases and have become important supporting mechanisms for their non-linear spread. Infected people from endemic areas may carry "exotic" pathogens to Europe. As a consequence of increased international travel, an increasing number of cases of Malaria and Dengue Fever have been reported at higher latitudes. Returning travelers become infected in endemic areas for instance and transport the pathogen back to Europe.

Still, most pathogen's thermal constraints have prevented them from establishing near European airports. However, one cannot entirely rely on this theory, as the Chikungunya-virus was introduced by an Indian traveler to Northern Italy (near Ravenna) and caused a local epidemic. In addition to the introduction of the pathogen and a fulfillment of the thermal requirements, a competent vector for Chikungunya (*Aedes albopictus*) was present. Hence, this invasive species was able to transmit the pathogen in the summer between (human!)

reservoir hosts. Such an unexpected disease outbreak documents the complex interactions that have to be considered.

Trade and the import of pets (especially dogs) - regardless of whether these are legal or illegal - can also become a serious health problem. Many Europeans take pets from their preferred holiday destination - the Mediterranean. These pets (in most cases dogs) could be infected, in particular with the *Leishmania* species. The imported dogs then constitute a lasting reservoir. Sandflies appear to be undertaking climatically-induced range shifts towards the northern and eastern regions in Europe. These insects feed on mammals and can contract pathogens and transmit the disease to humans (Tab. 1). In this case, the introduction of the pathogen could be controlled efficiently by avoiding the trade and transportation of dogs. Sandflies are not very mobile and will perform rather diffusive and slow range shifts.

6. Adaptation strategies - from monitoring to biosecurity

It is very likely that new kinds of climate-driven natural hazards will occur. In addition to abiotic responses such as avalanches, floods, storms, and drought, the ecological responses to changes in temperature and precipitation regimes have to be considered.

Taking into account the post-Copenhagen political environment, a great deal of uncertainty is constituted in deviating international politics. Nevertheless, there are options for a variety of latent and previously not experienced responses in ecosystems and organisms. Pest outbreaks may damage forests and crops. However, the most serious threat to humans is related to the probable occurrence and spread of vector-borne diseases. In particular vector-borne diseases without any options for a vaccination or a cure should be given high priority.

In the face of potentially novel climate-driven biorisks, adaptation strategies are urgently required. Preventative strategies may contribute to minimizing the consequences of climate change on human health. However, coping with uncertainty is difficult when large scales and severe consequences are involved. Many climatically-controlled vector-borne diseases (e.g. Leishmaniasis) are still not eminent in European countries, even if they constitute serious health hazards. As a result of their expected surge, standardized notification regulations are required to detect any tendency of spread and direction as well as local kernels of establishment. Improved knowledge on the biology and ecology of the species is needed. In addition to laboratory experiments, geographical analyses, correlations, and models all represent promising approaches. In terms of monitoring efforts, an interdisciplinary cooperation with traditionally low interaction ranging from entomology, to ecology, microbiology, virology, climatology, geography, and medicine must be implemented (Fischer et al. 2009c). Studies on the economic repercussions of spreading vector-borne diseases will also become imperative. Research needs are evident, but incentives from the scientific community are lacking.

Due to globalization, continental and oceanic barriers are easily overcome. Biosecurity is recognized as being essential for islands that host sensitive endemic species with low competitive capacity and not occupying ecological niches. Continents, in contrast, are perceived to be more or less ecologically saturated and in equilibrium. If this was an illusion in the past, it is ignorance in the future. Climate change is increasingly contributing to the development of novel habitats and to potential invasions.

Implementing efficient biosecurity measures at European airports and harbors may reduce the risk of accidental introductions of exotic disease vectors and pathogens. Strict import and immigration controls of the oceanic islands (e.g. Hawaii, New Zealand) serve as role models. Australia managed to avoid the establishment of *Aedes albopictus* although climatically suitable habitats occur. This stresses the importance of detecting the preferred bioclimatic suitable habitats of disease vectors. Specific monitoring systems can then be concentrated in the respective regions.

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6.2 Article 2:

Risk assessment of dengue virus amplification in Europe based on spatio-temporal high resolution climate change projections

With 1 Table and 5 Figures.

Summary

During the last decades dengue incidences are emerging significantly around the globe. Currently, about one fifth of the human population lives in dengue risk zones, which are mainly located in (sub-) tropical regions of Southeast Asia and the Western Pacific. Dengue infections in European population mainly referred to returning travellers from tropical endemic regions. Nevertheless, vector establishment in Europe already took place and therefore the risk increases. Currently, autochthonous cases of dengue fever have been reported in Europe.

Studies estimating the risk of dengue epidemics regarding changing climatic conditions in Europe are missing. Therefore, we close this gap by using the temperature constraints for virus amplification within the vector *Aedes aegypti* from two laboratory experiments. We transfer these findings to the changing European climate based on data provided from a regional climate model (COSMO-CLM; A1B and B1 scenario). Daily mean temperature were averaged for the time-steps 2011-2040, 2041-2070 and 2071-2100 in order to reduce natural variability but rather point out climatic trends for risk assessments. For both scenarios the strongest increase of temperature is projected after mid-century.

Results indicate a growing threat of virus amplification in Europe especially towards the end of this century. Larger parts of the Mediterranean will be at risk. The southwest of the Iberian Peninsular appears to be especially threatened. Even in some parts of Central Europe, such as Southwest Germany, dengue virus amplification can no longer be excluded at the end of the century. However, it is unlikely that *Aedes aegypti* will serve as an efficient vector in Europe. In fact, it is *Aedes albopictus* that is an invasive species in Europe and potential differences in extrinsic incubation period between *Ae. aegypti* and *Ae. albopictus* have to be identified. Policy and public health authorities have to consider these emerging biorisks in order to establish surveillance systems and develop counteraction strategies. Hence, we strongly

emphasize the need for a growing European awareness in the face of biological hazards that are responding to climatic changes.

Zusammenfassung

Dengue-Fieber ist eine durch Stechmücken übertragene Infektionskrankheit, deren Gefährdungspotenzial innerhalb der letzten Jahrzehnte dramatisch zunahm. Mittlerweile lebt ein Fünftel der Weltbevölkerung in Dengue-Risikogebieten, welche sich insbesondere in den (sub-) tropischen Gebieten Südostasiens und dem Westpazifik befinden. Regelmäßig wird das Dengue-Virus von infizierten Reisenden aus Endemiegebieten nach Europa importiert. In jüngster Vergangenheit treten auch vereinzelte autochthone Fälle in Europa auf. Ein kompetenter Überträger hat sich in Südeuropa bereits Ende des letzten Jahrhunderts etabliert (*Aedes albopictus*); ein Weiterer ist sporadisch wieder neu aufgetreten (*Aedes aegypti*).

Zu Risikoabschätzungen möglicher Dengue-Epidemien in Europa fehlen allerdings bislang Studien. Für eine thermisch abgeleitete Gefährdungsabschätzung nutzen wir Temperaturanforderungen des Virus zur Entwicklung im Vektor (*Ae. aegypti*) aus zwei verschiedenen Laborexperimenten. Diese Anforderungen der sogenannten extrinsischen Inkubationsperiode des Virus werden auf die projizierte Erwärmung Europas im 21. Jahrhundert übertragen. Hierzu bereiten wir das projizierte Klimaänderungssignal der Szenarien A1B und B1 des Regionalen Klimamodells COSMO-CLM in täglicher Auflösung auf. Um signifikante klimatische Trends herauszufiltern und Unsicherheiten in den Projektionen der täglichen Durchschnittstemperaturen zu minimieren, werden diese für die Zeitabschnitte 2011-2040, 2041-2070 und 2071-2100 gemittelt.

In beiden Szenarien wird eine stärkere Erwärmung ab Mitte des Jahrhunderts und speziell gegen Ende des Jahrhunderts projiziert. Insofern steigt die thermische Eignung im Verlaufe des 21. Jahrhunderts abhängig von der verwendeten extrinischen Inkubationsperiode an. Ende des Jahrhunderts ist eine Amplifikation des Virus in den wärmsten Regionen Mitteleuropas wie dem Oberrheingraben im Südwesten von Deutschland nicht mehr auszuschließen. In weiteren Studien bleibt zu klären, ob sich die extrinsische Inkubationsperiode in *Ae. albopictus* im Vergleich zu *Ae. aegypti* unterscheidet. Frühzeitig erkannte potenzielle Gefährdungsgebiete verhelfen politischen Entscheidungsträgern und dem Gesundheitssektor dazu, rechtzeitig Adaptions- bzw. Gegenmaßnahmen initiieren zu können. Unsere Ergebnisse verdeutlichen, dass Europa gewappnet sein muss, um nicht von Epidemien scheinbar exotischer Tropenkrankheiten überrascht zu werden.

Keywords

Dengue fever, emerging infectious disease, GIS, global change, global warming, mosquito-borne disease, surveillance, vector-borne disease

1. Introduction

Globally, the importance of vector-borne diseases has increased significantly during the last decades. Today, this group represents about one third of all outbreaks of emerging infectious diseases (Jones et al. 2008). Changing spatial patterns of occurrence are observed. The reasons for such changes are manifold, ranging from globalization of travel and trade to environmental and climatic changes or modified human behaviour (e.g. Maier 2003; Sutherst 2004; Fischer et al. 2009; Fischer et al. 2010a; Pfeffer and Dobler 2010; Randolph and Rogers 2010).

The dengue virus is mainly transmitted by the mosquitoes *Aedes aegypti* and *Ae. albopictus*. The latter ranks among the first 100 of the “World’s Worst” invaders (Crans 2008) and has been mostly introduced by trade of goods, especially used tires (Mitchell 1995). A distinction is drawn between different cycles of dengue: a primitive enzootic transmission cycle which involves lower primates, an epidemic transmission cycle in rural villages and the urban endemic/epidemic cycle in large urban centres, which is most relevant for public health (Gubler 1998). Four closely related serotypes of the arbovirus occur (DENV-1 to DENV-4), with specific geographical distribution and pathogenity (Halstead 2008). Furthermore, different dengue genotypes (American and Asian DENV-2) show different ability of the virus to grow in mosquitoes (Halstead 2007). Dengue fever is characterised either by mild fever or high fever combined with severe headache, pain behind the eyes, muscle and joint pains and rash. Patients that suffer a secondary infection with another dengue virus serotype have a significantly higher risk for developing dengue haemorrhagic fever (DHF). Especially young children are concerned (Halstead1988; Guzman et al. 2002). Clinical features of DHF are high fever, often with liver enlargement and in severe cases accompanied by circulatory failure. The number of countries that experienced DHF epidemics has quadrupled between 1970 and 1995. Without intensive care, affected human population can exceed mortality rates of 20% (WHO 2009; Cummings 2010).

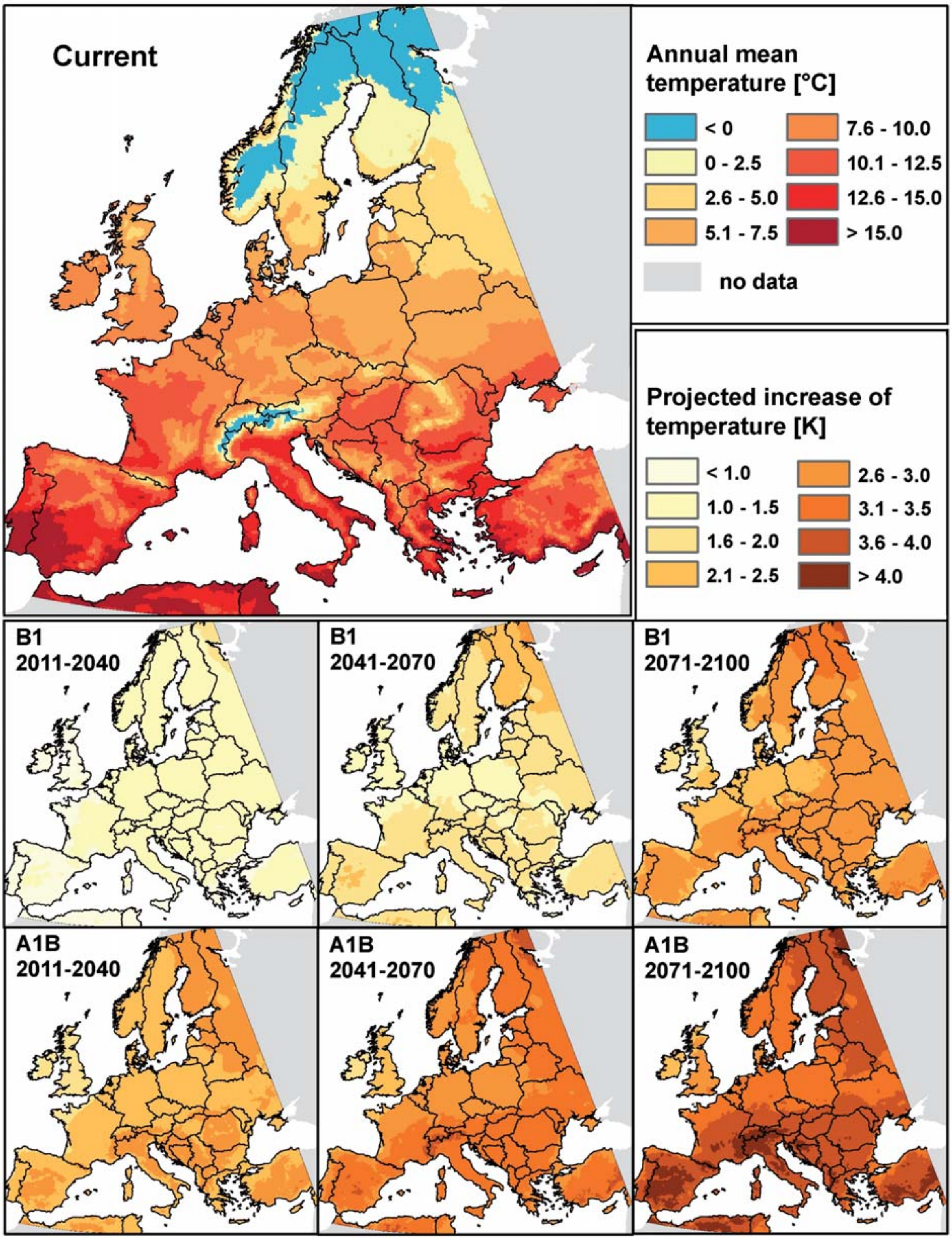

Fig. 1: Current annual mean temperature in Europe and projected warming in Kelvin during the 21st century based on two IPCC emission scenarios. Projections are based on the regional climate model COSMO-CLM. Generally, projected warming is less severe for the B1 scenario than for A1B. Highest increase in annual mean temperature is projected for Central parts of the Iberian Peninsular, the Alps and the northernmost parts of Scandinavia. Instead, the British Isles seems to be less affected by the projected increase of annual mean temperature.

In Northern America, outbreaks have arisen along the Texas-Mexican border for about three decades (Reiter et al. 2003). Recently, locally acquired dengue infections were reported for Florida (CDC 2010). Up to now, Europeans tend to consider dengue as a travel-related disease only. Southeast Asia, especially Thailand, is the most important region of travel-related dengue infections, followed by Latin America, the Indian subcontinent, the Caribbean and Africa (Heddini et al. 2009; Jelinek 2009). The last dengue epidemic in Europe occurred in Greece during the years 1927 and 1928. At that time, *Ae. aegypti* was transmitting the virus (DENV-1) (Rosen 2006). During the following decades, dengue was no longer established in Europe. However, exotic arbovirus are thought to become a future public health concern in Europe (Pfeffer and Dobler 2009). In September 2010, the French Ministry of Health reported the first cases of dengue fever from autochthonous origin in Europe (La Ruche et al. 2010). Furthermore, a dengue virus infection was reported for a German traveller returning from Croatia (Schmidt-Chanasit et al. 2010) and there upon autochthonous cases were found in Croatia too (Gjenero-Margan et al. 2011).

The potential rate of transmission depends on the daily survival rate and duration of the gonotrophic cycle of the mosquito (including searching for a host, blood feeding, blood meal digestion, eggs maturation, and oviposition). Virus amplification is determined by the extrinsic incubation period (EIP). EIP is defined as the time interval between the acquisition of an infectious agent (pathogen) by a vector and the vector's ability to transmit the agent to a susceptible vertebrate host. The EIP includes virus replication, maturation and migration within the mosquito body to its salivary glands. Females remain infective during their entire life. Temperature is considered to be the main factor regulating the EIP and thus warmer temperatures shorten the EIP (Watts et al. 1987; Barbazan et al. 2010). If minimum temperature thresholds for the EIP are not exceeded, the virus can not accomplish its amplifycation inside the vector and transmission, for instance to humans, can be excluded (Ooi and Gubler 2010).

It is known that favourable meteorological conditions significantly influence dengue incidences in endemic regions such as South America (Luz et al. 2008) and Southeast Asia (Shang et al. 2010). Evidence suggests that global warming increases the latitudinal and altitudinal range as well as intensity of dengue transmission (Jetten and Focks 1997). At the end of the 21st century, about 5-6 billion people can be expected to live in risk areas of potential dengue transmission including present-day's temperate regions (Hales et al. 2002).

Identifying the climatic constraints of the organisms that are involved in a chain of infection on spatio-temporal scales is the first step in determining risk areas (Fischer et al. 2010b).

Although the WHO (2009) declared dengue as one of the main public health concerns, it is surprising that no study exists that geographically analyzes the risk of dengue for Europe. Especially the availability of highly resolved regional climate models, both in terms of spatial and temporal resolution, gives us the option to detect possible developments in the run-up to climatic changes.

There is no doubt that Europe will be confronted with increasing temperatures in the 21st century (Fig. 1). The question arises whether climate change will assist a potential re-establishment of dengue in Europe. Here, we survey the risk of virus amplification by using the EIP. Our aim is to explore:

i.) Which areas will provide suitable temperature conditions?

ii.) At what time will these regions be at risk?

iii.) Which longest seasonal duration of risk has to be expected?

2. Material and methods

First we took documented temperature requirements for EIP from literature. Then, we prepared climatic data of a regional climate model in a daily resolution for the 21st century and transferred the determined temperature requirements to three time-steps and two scenarios. We detect areas at risk in the 21st century and identify the longest temperature-dependent intra-annual season of potential dengue virus amplification in Europe.

2.1 Temperature constraints

In this study we applied the temperature relationship for the EIP of the dengue virus. *Ae. albopictus*, a known vector of dengue virus, is already established at the European continent (mainly in Italy and the eastern shore of the Adriatic Sea). Studies on the EIP of this species are actually missing. Therefore, experiment-derived knowledge of EIP and temperature relationships was taken for *Ae. aegypti* (Blanc and Caminopetros 1930; Watts et al. 1987). This mosquito was already endemic in Europe up to the Second World War and extinct thereafter. Currently, *Ae. aegypti* is established in Madeira (Portugal) (Almeida et al. 2007). The species was also introduced into the Netherlands (Scholte et al. 2010). This gives rise to concern regarding a re-establishment of this dengue vector in continental Europe. Knowledge on temperature thresholds for virus amplification in *Ae. aegypti* generates from two experimental studies:

a) Blanc and Caminopetros (1930) detect an EIP of eight days with temperatures of at least 22 °C for dengue virus amplification. They aimed to identify the required EIP with special respect for Europe. For this laboratory study *Ae. aegypti* mosquitoes were taken from the Greek outbreak of dengue in 1927/28.

b) In contrast to this, Watts et al. (1987) found temperature requirements for dengue virus amplification in a Bangkok strain of *Ae. aegypti* of at least 30 °C mean temperature at twelve consecutive days for mosquitoes with low virus dose or seven consecutive days with daily mean temperature between 32 and 35 °C for those with a high virus dose.

As these studies yielded remarkably differing results, we compared projections based on both studies, respectively. Additionally, we evaluated both temperature requirements found by Watts et al. (1987) in order to determine, whether the frequency of highest daily mean temperatures over short time-periods (seven consecutive days between 32-35 °C) increases more rapidly than those of moderate high temperatures over a longer time-period (twelve consecutive days of at least 30 °C) in regional climate model projections.

2.2 Application of regional climate change projections

2.2.1 The regional climate model COSMO-CLM

Spatially explicit data on projected climate change are supplied by climate models on regional to global spatial scales. In contrast to their driving global models, regional climate models are capable to consider topography and further landscape features. They offer a much higher spatial resolution which enhances especially the quality of climate impacts studies (Rummukainen 2010). Consequently, such regional projections can be applied to impact studies on human health (Giorgi and Diffenbaugh 2008) and to assessments of climate-sensitive vector-borne diseases (Jacob 2008).

Our projections refer to the regional climate model COSMO-CLM (CCLM), which is driven by ECHAM5 and dynamically downscaled for Europe (Rockel et al. 2008). The quality of the driving data has a larger impact on simulation results than spatial resolution or physical parameterization (Meissner et al. 2009). CCLM addresses the scenarios A1B and B1, which both expect continuous human population growth until mid-century in a global oriented homogeneous world.

The A1B scenario is characterized by an equal use of fossil and non-fossil energy resources and the introduction of efficient technologies. The moderate and hence rather optimistic B1 scenario supposes a development towards service orientated societies with regional focus on ecological changes by introduction of renewable energies. Hence, projected temperature increase is less severe in B1 than in A1B (Fig. 1). Both were considered as marker scenarios that best illustrate the respective storyline (IPCC 2007). The B1 scenario matches well with the European Union target of keeping global anthropogenic warming below two Kelvin above industrial level (Jacob and Podzun 2010).

2.2.2 Pre-processing of the data

In our calculations, the original model output for projected daily mean temperature data was applied for both scenarios and for the complete 21st century in the binary net.cdf format (network common data form). We used the data stream D3 (run 2), which is the only one that organises on a regular grid and does not require conversion from the usually used rotated grid. This data stream was previously also used for model evaluation (Smiatek et al. 2009). The spatial resolution is 0.2°, which is about 18 km.

In order to reduce statistical noise and natural variability and to detect significant climatic trends in both scenarios we averaged the daily values separately for the time-steps 2011-2040, 2041-2070 and 2071-2100. By calculating the averages over the time-intervals we receive more robust and veritable hints for the expected temperature increase of every day in the year. Averaging of daily temperature data as well as interpolation of the available binary format net.cdf to a horizontal grid as text files was done via Climate Data Operators code (Schulzweida et al. 2009). This resulted in text files incorporating temperature data for each julian day for the respective time-step and scenario. Each text file was then attributed with an identical header indicating the spatial resolution and geographical extent. Hence, the text files could be imported by conversion to raster files for further processes in ArcGIS 9.3.1. In a second step the raster of the first of January for each scenario and time-step and scenario was converted to a point shapefile, locating points at the centre of each raster cell. These point shapefiles were used to extract the raster files representing other days of the year (January 2 - December 31) for the respective time-step and scenario.

The conversions of the text files to raster grids and the extraction of the raster values for each day via the point shapefiles were standardized and carried out with scripts written in Python 2.5.5 and R 2.11.0 (R Development Core Team 2010).

2.3 Modelling the spatio-temporal risk of dengue virus amplification

We received point shapefiles for each time-step and scenario including the daily temperatures of the whole year for Europe. This allowed a selection via attributes. We generated three selection codes to determine at which locations temperature requirements are fulfilled for:

- eight consecutive days with temperatures of at least 22 °C (Blanc and Caminopetros 1930)
- twelve days of at least 30° C (Watts et al. 1987)
- seven days with temperatures between 32-35 °C (Watts et al. 1987)

for the respective time-step and scenario.

The selection principles was a moving temporal window beginning on the first of January (and consecutive days), while the second selection then started on the second of January and the last ended on the 31st of December. Those points were selected where the mentioned temperature requirements are at least fulfilled one time. In a second step, the longest potential intra-annual period, where the temperature requirements for virus amplification are fulfilled, was identified for the three time-steps and two scenarios separately. The beginning and the end was recorded for those points with the longest temporal fulfilment of temperature requirements without interruptions. Resulting selections were exported and converted to raster grids with the usual raster grid size of 0.2° (10 arcminutes) for cartographical visualization. We quantified areas at risk for three countries that represent a climatic gradient in Europe (Spain, France and Germany). Risk areas were calculated in comparison to the total country area.

Selection codes to model the spatial risk of virus amplification and to determine the longest intra-annual period as well as calculating percentages of areas at risk, for specific countries were performed in ArcGIS 9.3.1.

Tab. 1: Area (in per cent) at risk of dengue virus amplification for a climatic gradient across Spain, France and Germany. Novel threats are projected to be most important for Spain and France. Germany will be at risk only if the extrinsic incubation period that was determined by Blanc and Caminopetros (1930) (eight consecutive days with minimum temperatures of 22 °C) is relevant, but not if applying the findings of Watts et al. (1987) (twelve consecutive days of at least 30 °C or seven consecutive days between 32–35 °C.

	Time-step	Area at risk per country in per cent					
		Spain		France		Germany	
		B1	A1B	B1	A1B	B1	A1B
8 days ≥ 22 °C	2011-2040	74	76	22	23	-	-
	2041-2070	83	85	46	54	< 1	< 1
	2071-2100	86	94	70	83	1	12
12 days ≥ 30 °C	2011-2040	5	5	-	-	-	-
	2041-2070	18	16	-	-	-	-
	2071-2100	21	35	-	< 1	-	-
7 days ≙ 32-35 °C	2011-2040	1	1	-	-	-	-
	2041-2070	5	4	-	-	-	-
	2071-2100	8	21	-	-	-	-

3. Results

3.1 Areas at risk according to dengue virus amplification

Apparently, the risk of virus amplification is likely to generally increase in the course of the 21st century, regardless of the chosen EIP and climate change scenarios. The highest percentage of areas located in risk zones is identified for the end of the century due to the projected increase in daily mean temperature from mid-century onwards in both scenarios (Tab. 1). For the A1B scenario the total areas at risk does exceed the risk areas for the B1 scenario. Remarkable differences in the results for virus amplification are conspicuous between EIP determined by Blanc and Caminopetros (1930) and Watts et al. (1987). Following the constraint of Blanc and Caminopetros (1930) with temperature requirements of eight consecutive days with at least 22 °C for virus amplification, big parts of Europe would provide suitable temperature conditions during the 21st century (Fig. 2). This is true for both scenarios, even if the A1B scenario entails larger areas. The spatial hotspots are the same for both scenarios. For the period 2011-2040, almost the whole Mediterranean region and countries in the Southeast bordering the Black Sea seem to meet the temperature requirements.

In addition, the Rhone valley in France will already be suitable. During the mid of the century there is a considerable increase of risk areas in Western Europe, especially in France. There, the area at risk is nearly doubled in the period 2041-2070 in comparison to the time-step 2011-2040 (Tab. 1). Temperature requirements will be met during this period also in parts of Central Europe, for instance in the Southwest of Germany. At the end of the century, larger parts of Belgium and the North of France will provide suitable temperature conditions for the A1B but not for the B1 scenario as well.

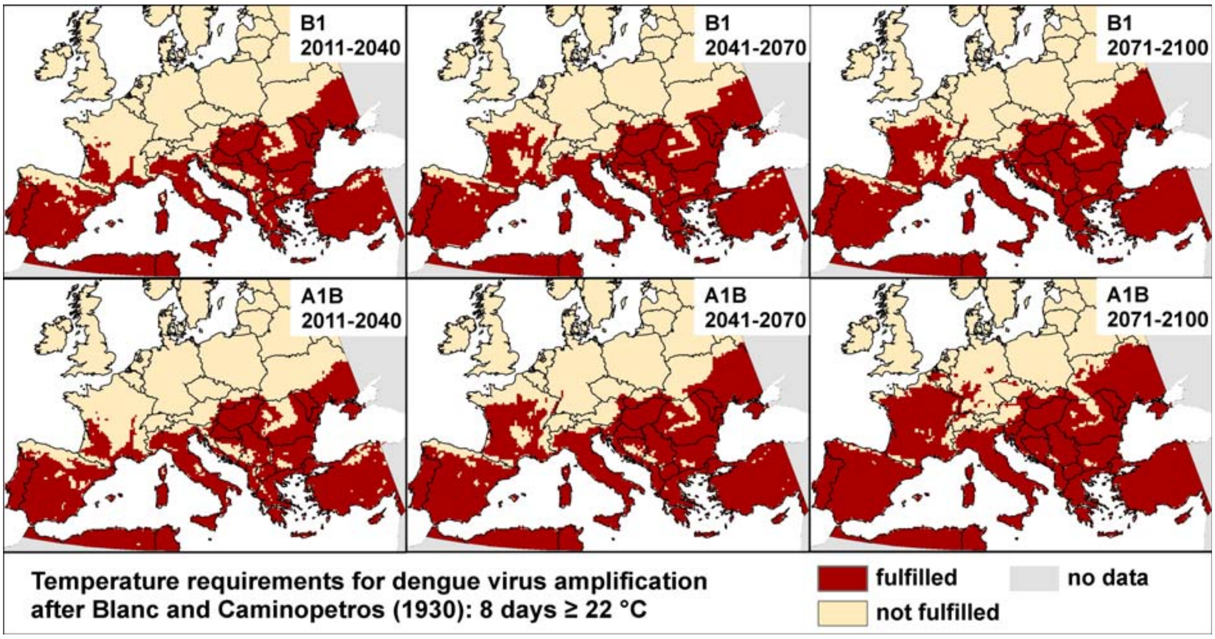

Fig. 2: Projection of the extrinsic incubation period for dengue virus amplification within the vector *Aedes aegypti*, determined by Blanc and Caminopetros (1930) with eight consecutive days of at least 22 °C.

When assuming an EIP of 12 days above 30 °C (Watts et al. 1987), the Southwest of the Iberian Peninsular (Valleys of Tajo, Guadalquivir and Guadiana) and Sicily are exposed to high risks during the time-step 2011-2040 (Fig. 3). During the following decades, the risk areas increase further in the Southwest of Europe and additionally spatially limited areas will be threatened in Greece (region of Thessaly) and coastal zones of Turkey. Furthermore, confined areas in Southeast Europe are expected to exceed thresholds. Between 2071 and 2100 considerable parts of Italy will also be appropriate.

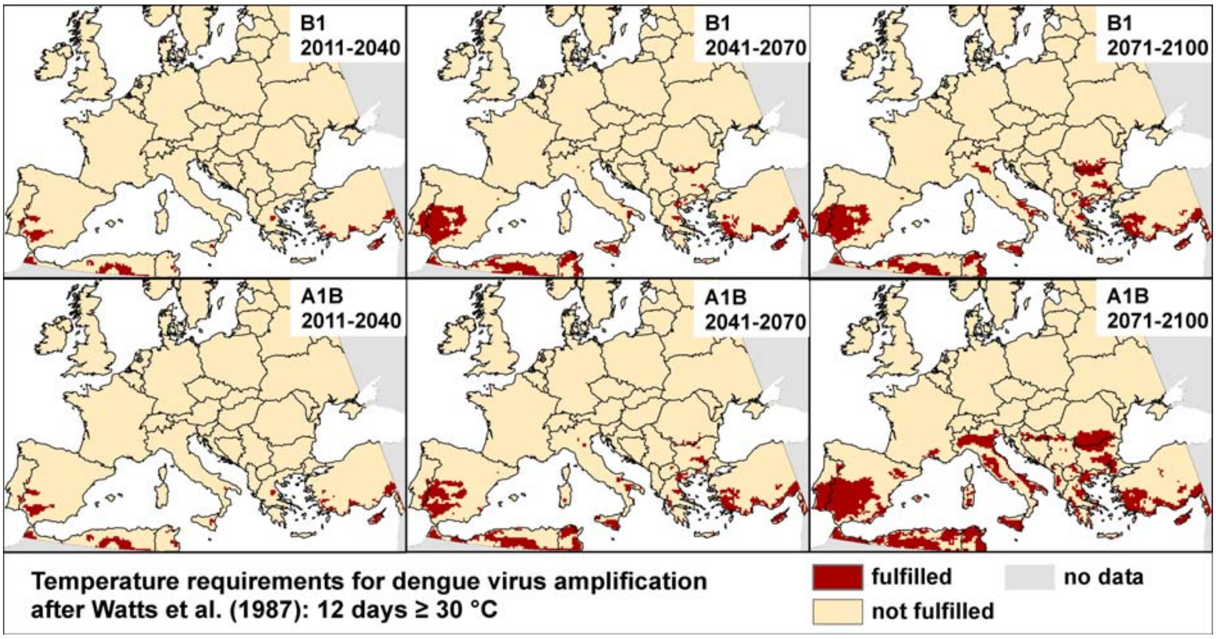

Fig. 3: Projection of the extrinsic incubation period for dengue virus amplification within the vector *Aedes aegypti*, determined by Watts et al. (1987) with twelve consecutive days of at least 30 °C.

The temperature constraints with daily mean temperatures between 32-35 °C (Watts et al. 1987) are rather extreme and only few regions will achieve daily mean temperatures between 32-35 °C over seven consecutive in the 21st century (Fig. 4). Following these assumptions, for Seville and regions along the Tajo River in the Southwest of Spain, dengue virus amplification can be assumed already during the first half of the 21st century. The risk area would extend slightly within the time-step 2041-2070 and reach up to 20% (A1B) of the total area of Spain. At the end of the century spatially limited risk is projected for the Italian regions (Apulia, Lombardy, Piedmont and Venetia). In south-eastern Europe, the valley of the Danube in Romania and the Aliakmon in Greece as well as the coastal region of Turkey will provide suitable temperatures.

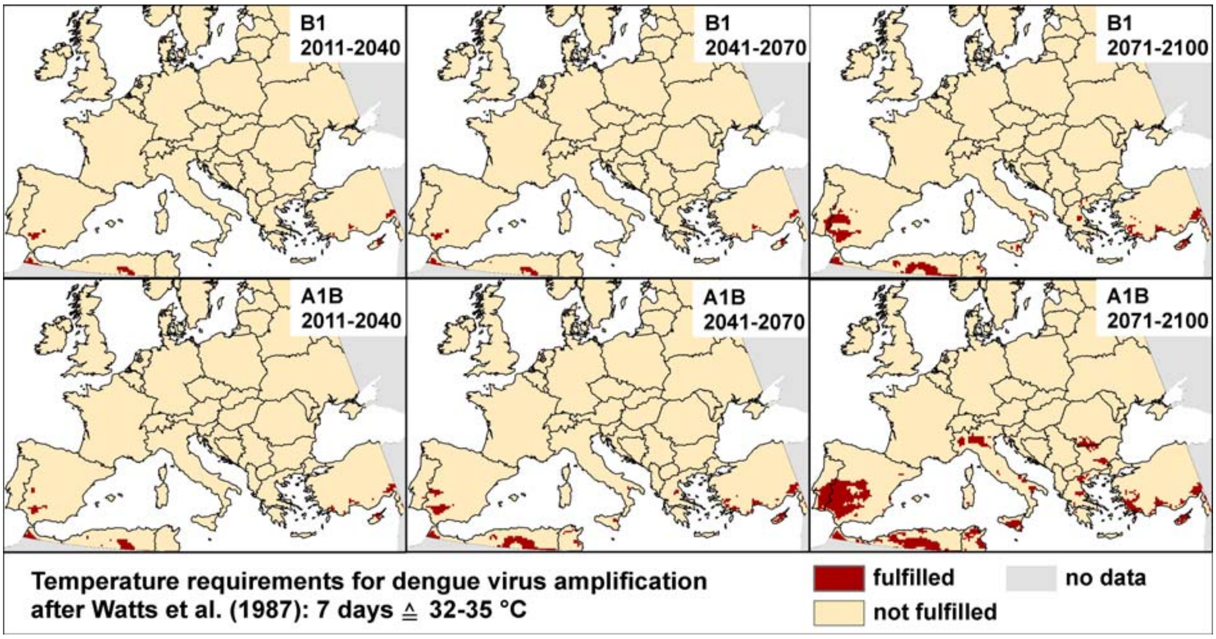

Fig.4: Projection of the extrinsic incubation period for dengue virus amplification within the vector *Aedes aegypti*, determined by Watts et al. (1987) with seven consecutive days between 32-35 °C.

3.2 Longest potential period of dengue virus amplification

The longest suitable period is detected in the southwest of the Iberian Peninsula - the region around Seville. We expect the annual duration of periods that are providing suitable temperatures for virus amplification to increase during the 21st century in general and especially towards the end of the century (Fig. 5).

This is true for all temperature requirements, time-steps and scenarios. As expected, the duration of the longest period mainly depends on the chosen EIP. Moreover, the longest intra-annual period of virus amplification varies more between time-steps than between scenarios. On the regional example of southwest Europe, the longest duration with suitable temperature conditions are noted:

Virus amplification based on the findings of Blanc and Caminopetros (1930) can last 146 days (A1B) or 136 (B1) during the coming decades (2011-2040). The increase of the length of suitable intra-annual periods from the early 21st century to mid-century is surprisingly higher for the B1 scenario. As consequence, at mid-century, the maximum temporal range for virus amplification will last up to 160 days in both scenarios. However, differences in the projections of the two scenarios are again from mid-century onwards to the end of the century, when a further increase of up to 179 days is projected in the A1B scenario, while the B1 scenario is characterised by a slight decrease to 157 days.

Concerning the EIP found by Watts et al. (1987) of at least 30 °C mean temperature over twelve consecutive days, the longest potential period is limited to 70 days (A1B) or 58 days (B1) within the years 2011 to 2040. The period for dengue virus amplification is longer in B1 scenario (88 days in comparison to 80 days in A1B scenario) for the years 2041 to 2070. A temporal extension can be expected (A1B: 93 days, B1: 90 days) for the last time-step.

When applying the finding of Watts et al. (1987) with daily mean temperatures of 32 to 35 °C over seven consecutive days, we identify the shortest window for virus amplification. Regarding the A1B scenario, the period will last longer in all time-steps than in B1 scenario. Starting at 2011-2040 the maximum period will last 41 (A1B) or 34 (B1) days respectively. At mid-century a period of 59 (A1B) or 48 days (B1) can be expected, while the virus amplification will be extended up to 85 days in A1B and 72 days in B1 scenario.

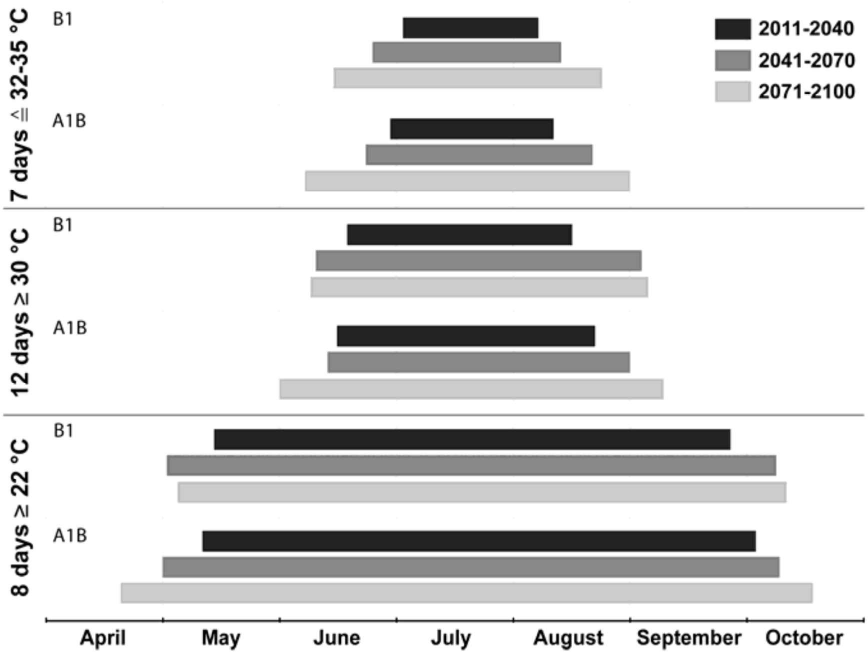

Fig. 5: Longest possible intra-annual period of dengue virus amplification in Europe.

4. Discussion

4.1 General tendencies in projected temperature thresholds

In this study, we used temporally high resolved data (daily resolution) from a regional climate model. We detect where and when dengue virus amplification can be expected to take place with respect to climate change in Europe. We indicate increasing areas at risk for all temperature requirements of dengue virus in both scenarios. Especially towards the end of the century the negative trend that we find is expected to speed up.

The results are based on experimentally identified temperature constraints. Differences between these laboratory studies are considerable. First of all, the temperature ranges for dengue virus transmission via *Ae. aegypti* is influenced by the titer of the mosquito-infecting virus dose. In the classic study, Blanc and Caminopetros (1930) experimentally infected mosquitoes by feeding them on infected humans at subsequent days of illness with low virus dose. Using low virus dose in monkey blood, Watts et al. (1987) determined extended EIP in comparison to high virus dose. Applying the comparatively low temperature threshold determined by Blanc and Caminopetros (1930) resulted consequently in an earlier threat and more European areas at risk, than in the projections based on the much higher temperature requirements that were detected by Watts et al. (1987). Comparing the results for the two alternative temperature regimes of Watts et al. (1987), most European regions would not achieve these extremely high daily mean temperatures (corresponds to EIP found for high virus dose) over short periods. More regions will experience lower but nevertheless rather high temperatures over longer periods (corresponds to EIP found for low virus dose).

4.2 Other factors for dengue transmission and comparison of aedine dengue vectors

Various factors and processes are contributing to the performance of mosquito-borne diseases besides climatic constraints. Thus, our results should not be misinterpreted as factual risk maps but rather as temperature-derived risk maps for dengue virus amplification, assuming the presence of a competent vector.

For the potential introduction of dengue virus in Europe, increasing risks are related to increasing intercontinental travel and trade (Kuno 1995; Reiter 2008). The number of virus-carrying human hosts in Europe increases due to close connections with endemic (sub-) tropical regions (Randolph and Rogers 2010; Reiter 2010). Socioeconomic factors play an important role in dengue transmission, as shown in Texas, where human behaviour (use of air-conditioning, evaporative coolers) lowers dengue prevalence (Reiter et al. 2003).

Regarding the risk of transmission, the mean age and the life expectancy of the mosquito population have to be taken into account, as older females show higher probability to transmit the virus (Holmes and Birley 1987; Carbajo et al. 2001).

Ae.aegypti, which is one main vector of the dengue virus, was recently introduced and established in Madeira (Almeida et al. 2007). Mosquito control actions inhibited an establishment in the Netherlands (Scholte et al. 2010), whereas *Ae. albopictus*, also a potential vector, is already established in Southern Europe. This invasive species is observed to rapidly spread into warm regions of the continent (Knudsen et al. 1996; Benedict et al. 2007). Survival during wintertime will be crucial regarding the further expansion of *Ae. albopictus* in Europe. Depending on the origin of the species, cold tolerance and the production of diapausing eggs differ (Hawley 1988). Moreover, diapause apparently evolved from nondiapause or non-photoperiodic ancestors (in Brazil), whereby a diapause reduction could be observed presumably due to rapid local selection (in USA) (Lounibo set al. 2003). Furthermore, a distinct competitive advantage is found for *Ae. albopictus* compared with *Ae. aegypti* especially in the larval stadium (Brakset al. 2004).

Unfortunately, studies on temperature thresholds for the EIP of the dengue virus in *Ae. albopictus* are missing. As a consequence, our study is based on the temperature constraints for the EIP in *Ae. aegypti* only. These two mosquito species differ in habitat preference, desiccation resistance of eggs (Sota et al. 1992) and, most notably, in feeding patterns. Female *Ae. aegypti* take more than one blood meal during each gonotrophic cycle and prefer feeding on humans. Feeding rates of *Ae. aegypti* vary geographically depending on climatic conditions (Scott et al. 2000). Also the oral receptivity of *Ae. aegypti* to dengue is significantly higher than that of *Ae. albopictus*. Generally, colonisation of these vectors in laboratory increases their susceptibility for dengue virus (Vazeille et al. 2003). Moreover, differences in feeding patterns and susceptibility of both aedine mosquitoes could lead to different dengue incubation times.

Both vectors are capable of transmitting the dengue virus transovarial (vertical) to the offspring, which determines the starting point for further infections (Rosen et al. 1983; Rosen 1987; Shroyer 1990). *Ae. albopictus* and *Ae. aegypti* are also capable of transmitting various other virus such as chikungunya, Rift-Valley, Ross-River, West Nile and yellow fever (Gratz et al. 2004). Recently, invasive populations of *Ae. albopictus* were involved in a chikungunya outbreak in the region of Ravenna, Northern Italy (Rezza et al. 2007). After more than six decades autochthonous dengue cases have been reported in Europe again (Southern France La Ruche et al. 2010, Croatia Gjenero-Margan et al. 2011).

4.3 Previous models regarding the role of changing temperature in dengue transmission

Focks et al. (1995) provided a dengue simulation model with EIP as the most influencing parameter in the transmission dynamics in areas with suitable vector habitat conditions. Even slight fluctuations in temperature significantly affect the EIP and hence seasonal risk of dengue transmission. In contrast, further parameters such as the length of gonotrophic cycle or the probability of multiple feeding stay more or less unchanged (Patz et al. 1998).

Based on this previous study, Patz et al. (1998) applied global climate change effects to project the basic reproduction rate (R_O) originally representing the vectorial capacity multiplied by the length of time that a person remains pathogenic. Hence, R_0 is interpreted as the average number of secondary human infections produced from one infected person among a susceptible human population. In their study Patz et al. (1998) excluded the multiplication by duration of a pathogenic person assuming this factor as relatively constant in the case of dengue. They indicate an increasing risk of potential seasonal dengue transmission for temperate regions at mid 21st-century. This is in accordance with the projections based on global climate change of Haleset al. (2002) who additionally integrated further climatic factors and projections of human population.

As temperature effects on EIP have previously been pointed out as crucial factor, our approach to project EIP via spatio-temporal highly resolved climate change projections allows a more detailed characterization of potential areas at risk for Europe, which is currently missing. In addition, our methodological proposal offers the opportunity to calibrate recently proposed dengue models (e.g. Barbazan et al. 2010; Degallier et al. 2010; Erickson et al. 2010) to the expected regional climate change in Europe. Those regional climate change projections are also applied in order to project the risk of malaria transmission in Germany using a R0-model, although not in a daily resolution (Holy et al. 2011).

4.4 Data quality of the regional climate model

In order to cope with uncertainties regarding future climate change (IPCC 2007), we focused on two scenarios (A1B and B1) integrated into the regional climate model CCLM. This is driven by the global model ECHAM5 (Rockel et al. 2008). An accurate downscaling of the spatial resolution of ECHAM5 improves model performance (Roeckner et al. 2006). Hence, the uncertainty that is related to the boundary conditions of a regional climate model is reduced (Déqué et al. 2007; Meissner et al. 2009).

Comparing the observed present-day climate with the current conditions simulated by CCLM, a cold summer bias becomes obvious for Western and Central Europe (Brockhaus et al. 2008; Jaeger et al. 2008). This leads to an underestimation in the longest continuous period of summer days with maximum temperatures above 25 °C (Roesch et al. 2008). A potential underestimation in the projected longest period of dengue virus amplification for Europe may occur in our study, although we used daily mean instead of maximum temperatures. Nevertheless, these biases are documented - and even more pronounced - for other state-of-the-art models of European regions (Christensen et al. 2007; Jacob et al. 2007; Jaeger et al. 2008).

The earlier version (CLM) was nominated as a community model for the German climate research by the steering committee for the German Climate Computing Centre (DKRZ) in 2005 (Rockel et al. 2008). Additionally, CCLM offers the advantage of including the entire area of Europe. Therefore, in this study CCLM is used.

4.5 Impact of weather extremes

As it has been stressed for ecological impact studies in the face of climate change (Jentsch et al. 2007; Jentsch and Beierkuhnlein 2008), also for the evaluation of risks related to mosquito-borne diseases in Europe, studies are needed on the relevance of short-term weather extremes and increasing climatic variability. During the 21st century, the continental interior of Europe is very likely to experience a rapid increase in the intensity of extreme temperatures (Beniston et al. 2007). However, projections for temperature and precipitation extremes differ significantly between models (Kjellströmet al. 2007). Only if this uncertainty is reduced in the climate models, both climatic trends and weather extremes can be considered. This would improve the risk assessments for mosquito-borne diseases.

5. Conclusions

Here, we identified potential future risk areas for dengue virus amplification. Climate change can be connected with spatial as well as temporal extension (longer potential intra-annual period for dengue transmission) of this novel threat for European regions. Our proposed methodological task to integrate climate change data in daily resolution seems promising to benefit impact studies on mosquito-borne diseases. Such projections necessarily require profound knowledge on climatic constraints of vectors or/and pathogens. Therefore experimental studies should take this issue into account in future research in order to reduce uncertainties in projections.

Climate change is expected to cause repercussions in the distribution of pathogens and vectors resulting in novel threats for human societies and challenges for healthcare. The recent example of an outbreak of chikungunya virus in Italy was a first wake-up call in Europe. Obviously, infectious diseases that were thought to be restricted to tropical regions can expand northwards.

Introduction of virus and vector already took place at certain European gateways, such as harbours and airports. Obviously, the expected spread of mosquito-borne diseases refers not solely to climatic changes. Other aspects of globalization have to be taken into account as well and strict biocontrol may help to delay or even avoid further accidental carry-overs. Policy and public health authorities urgently require profound knowledge on the potential responses of mosquito-borne diseases to climatic changes for decision making. The design of specific monitoring and surveillance systems can only be efficient if it can be concentrated to risk areas.

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6.3 Article 3:

Temperature-derived potential for the establishment of phlebotomine sandflies and visceral leishmaniasis in Germany

With 2 Tables and 4 Figures.

Abstract

Climate change is expected to manifest in the shift of organisms to regions where they were not present in the past, potentially entailing previously unseen biological risks. However, studies evaluating these future trends are scarce. Here, an important group of vectors (sandflies) and the pathogen transmitted *(Leishmania infantum* complex) causing the infectious disease visceral leishmaniasis is investigated, focussing on potential establishment in Germany during the 21st century.

As the most important habitat factor, temperature requirements of pathogen and vector were derived from the literature and compared with recent climate records provided by worldclim and climate change scenarios. Climate data from the Regional Climate Model REMO were obtained and averaged over the time periods 20112040, 2041-2070 and 2071-2100. Projected temperature changes (based on the A1B and A2 scenarios) were correlated with the constraints of vector and pathogen. Simulated potentially suitable habitat areas for vector and pathogen were merged to generate a temperature-derived risk map of visceral leishmaniasis. Temperature conditions seem to become suitable for the vector across large swaths of Germany.

Nevertheless, temperature constraints for the pathogen may defer the establishment of the parasitic disease, particularly during the first half of the 21st century. Long-lasting epidemics of visceral leishmaniasis are therefore not expected in Germany during the next few decades, although during extremely warm years an increase in autochthonous cases of leishmaniasis may occur. The southwest (Upper Rhine Valley) and west (Cologne Bight) of Germany are identified as risk areas. The time of potential establishment and corresponding rise in biological risk varies between scenarios, due to differences in the predicted rate of temperature increase.

Keywords

climate change, global warming, Europe, leishmaniosis, kala-azar, *Phlebotomus*, vector-borne disease.

1. Introduction

Regional climate change has been linked with potential impacts on human health in various ways (Patz et al., 2005), such as those health-related problems and hazards (e.g. water shortages or floods) associated with an expected increase in extreme climatic conditions including heat waves, drought and heavy rainfall (Jentsch and Beierkuhnlein, 2008). Besides these meteorological stress situations with direct impacts on human and animal health, organism and ecosystem responses to climate change are also expected to entail indirect impacts on public health (Fischer et al., 2010).

As a prominent example, vector-borne infectious diseases may spread from subtropical or tropical regions to higher latitudes and altitudes (e.g. Shope, 1991; Fischer et al., 2009). Infectious diseases such as malaria or dengue occur on several continents. Increasing human population density, global trade and climatic changes are all likely connected to the increased numbers of reported cases (Sutherst, 2004).

However, as people are unfamiliar with diseases that were previously confined to specific regions, their potential expansion has been widely neglected or even ignored. The documented spread of leishmaniasis (Shaw, 2007; Maroli et al., 2008) is one such problem demanding more attention in terms of both science and policy (Dujardin et al., 2008). Formerly restricted to South America, India, the Middle East and the Mediterranean, the annual incidence of leishmaniasis is approximately 2 million cases, while about 350 million people reside temporarily or permanently in leishmaniasis risk areas (Reithinger and Dujardin, 2007). Pathogens belonging to *the Leishmania infantum* complex (*L. infantum* complex; endemic in Europe) or *Leishmania donovani* complex (endemic in Asia) both cause visceral leishmaniasis in humans and animals (Gramiccia and Gradoni, 2005).

In Europe, sandflies of the genus *Phlebotomus* serve as vectors, transmitting these obligate intracellular parasites to new hosts where they infect internal organs such as the liver and spleen (Neuber, 2008). *Phlebotomus* spp. are located in rural as well as urban environments in close proximity to humans and their domestic animals, largely dogs which are the main reservoir of the *L. infantum* complex (Camargo and Langoni, 2006). These small insects (length = 2-3 mm) are strongly dependent on specific environmental conditions (e.g. Cross and Hyams, 1996; Aspoeck et al., 2008). The first documented sandfly catches (*Phlebotomus mascittii* and *P. perniciosus*) in Germany came from the south-west on the border with France (Naucke and Pesson, 2000; Naucke et al., 2008). Conceivably, the species had already reached central Europe from Mediterranean refugial areas during the Holocene optimum (approximately 6,500 years ago), survived in very small areas and due to global warming is now spreading (Aspoeck, 2008; Aspoeck et al., 2008).

Until now, most cases of infection reported from Germany have been allochthonous, associated with imported pets (i.e. dogs), especially from the Mediterranean region, and travelling humans (Harms et al., 2003; Weitzel et al., 2005). However, Bogdan et al. (2001) reported the first case of autochthonous visceral leishmaniasis in a German child, while the number of autochthonous cases of canine leishmaniasis has also increased. In total, 11 cases with assumed autochthonous origins have been diagnosed in humans and animals in Germany (Naucke et al., 2008). This is the ominous “smoking gun” suggesting that infected sandflies must be present at least periodically in Germany.

Spatio-temporal models may become crucial components of leishmaniasis risk analyses (Ready, 2008). Compared with other diseases and their vectors, only a few studies have investigated leishmaniasis and sandflies with an environmental-climatic focus via species distribution models (e.g. Peterson and Shaw, 2003; Nieto et al., 2006; Chamaille et al., 2010), geographical information system (GIS) and remote sensing techniques (Rossi et al., 2007). Aspoeck et al. (2007) estimated the risk of autochthonous leishmaniasis in Austria, identifying temperature as the most important variable.

The northern limit of sandflies in Europe is closely related to the 10 °C annual mean temperature isotherm (Naucke, 2007; Lozán et al., 2008). Sandflies require an average monthly temperature of at least 20 °C during the warmest month, which corresponds with their activity phase (WHO, 1984). Winter temperatures may not be as crucial to their occurrence, since diapause enables overwintering in tunnels and holes (Killick-Kendrick and KillickKendrick, 1987).

Evidence suggests that the *L. infantum* complex is prevalent only in areas with average temperatures ranging between 5-10 °C during the coldest month and 20-30 °C during the warmest month (Kuhn, 1999). Based on the detected constraints imposed on vectors and pathogens by temperature, potential future risk zones can be identified. Until now, no study has investigated the future risk of visceral leishmaniasis for regions north of the Alps. Regarding these known temperature requirements for vector and pathogen suitability in the light of projected climate change for Germany during the 21st century, the following questions arise:

(i) When will climatic vector requirements be fulfilled?

(ii) When will climatic pathogen requirements be fulfilled?

(iii) Which specific regions will be exposed to this novel threat?

2. Materials and methods

2.1 Climatic data

Present-day vector and pathogen temperature constraints (annual mean temperature and temperature of the warmest and coldest months) were established at 5 arc-minutes resolution from data published in Hijmans et al. (2005) for recent climatic conditions in Germany. Projected temperature change during the 21st century was derived from the regional climate model REMO (UBA project, datastream 3), which is driven by the global climate model ECHAM5 (Jacob, 2008). REMO also integrates regional details through the use of highly resolved dynamic downscaling and as a result is able to project climatic change at the regional scale of Central Europe more precisely (Déqué et al., 2007). Regional climate change simulations are therefore more powerful tools for the detection of future risks of climate-sensitive vector-borne diseases (Jacob, 2008; Fischer et al., 2010).

The climate change simulations used in this study were based on theoretical IPCC (2007) emission scenarios for greenhouse gases. The A1B scenario is characterised by rapid economic growth and technological change towards the balanced use of all energy resources, while the A2 scenario projects regionally-oriented economic development and diversification of energy use. Both of these selected scenarios are accepted to represent realistic potential developments.

Following typical climatological procedure, projected monthly and annual mean temperatures from REMO were averaged over 30-year intervals to reduce uncertainty in deriving climatic trends. Periods considered in the analysis of projected trends were: 2011-2040, 2041-2070 and 20712100. Analysis of each scenario was carried out separately. Projected values of annual mean temperature, selected warmest and coldest month were taken for further analysis. Current and projected temperature data were incorporated at a spatial resolution of 6 km, in order to overlay and accurately compare results for recent and projected conditions. The area of Germany was then extracted for analysis. The climatic data provided by Hijmans et al. (2005) were already available as raster data, but projected climatic data derived from REMO had to be prepared using climate data operators (CDO) codes, before finally being transformed to raster format for further analysis in ArcGIS (version 9.1).

2.2 Temperature suitability for organisms and risk classes of visceral leishmaniasis

First, four temperature-derived suitability classes for vector and pathogen were established separately, taking into account the overlay of their temperature constraints (Table 1). Classes were generated from the comparison of current and projected temperature conditions with vector and pathogen constraints. The results produced represent temperature-derived areas in Germany suitable for Phlebotomus spp. (Fig. 1) and the *L. infantum* complex (Fig. 2).

Classified habitat suitability data for vector and pathogen were then combined to generate temperature-related risk classes for the establishment of visceral leishmaniasis. By analysing the fulfilment of vector and pathogen requirements under current conditions and throughout the time periods of both scenarios, risk was classified on a range from excludable to likely (Table 1).

By overlaying the classified raster cells of each single map, calculated risk classes of visceral leishmaniasis for each individual time period and scenario were then compared with each other. This was done in order to identify significant temporal trends and differences between scenarios. The specific area of every leishmaniasis risk class was also calculated for each individual time period and scenario. These analyses were carried out in ArcGIS.

Tab. 1: Classification of current and projected temperature conditions with regard to vector and pathogen requirements. Annual mean temperature of at least 10 °C (Naucke, 2007; Lozán et al., 2008) and average monthly temperature of more than 20 °C during the warmest month (WHO, 1984) are considered to be suitable for the vector. Pathogen suitability classes are based on the fulfillment of temperature requirements during the coldest month (5-10 °C) and warmest month (20-30 °C) (Kuhn, 1999). More than one combination of vector and pathogen suitability classes resulting in one risk class for the disease establishment are possible. Dotted lines separate the possible combination of one pathogen suitability class with two vector suitability classes.

Establishment of visceral leishmaniasis	Pathogen requirements		Vector requirements	
	Coldest month	Warmest month	Annual mean temperature	Warmest month
1 excludable	< 4° C	< 19 ° C	< 9° C	< 19° C
	not fulfilled		not fulfilled	
			< 9° C	≥ 20° C
			partially fulfilled	
2 unlikely	< 4° C	< 19 ° C	9° C	≥20° C
	not fulfilled		almost fulfilled	
	4° C	19° C	< 9° C	≥ 20° C
	partly fulfilled		partly fulfilled	
			9° C	≥20° C
			almost fulfilled	
3 rather unlikely	< 4° C	≥ 20° C	≥10° C	≥ 20° C
	partly fulfilled		fulfilled	
	4° C	≥20° C	9° C	≥20° C
	almost fulfilled		almost fulfilled	
4 possible	4° C	≥ 20° C	9° C	≥20° C
	almost fulfilled		fulfilled	

3. Results

3.1 Temperature-derived suitability for *Phlebotomus* species

Currently, the climate of south-west Germany almost satisfied the temperature demands of Phlebotomus spp. (Fig. 1). This spatial pattern corresponds with documented sandfly presence in the region (Naucke et al., 2008). In this area of Germany, it is extremely likely that vector temperature constraint will be exceeded at some stage between 2011 and 2040. During this time period, vector requirements will also be fulfilled in some western (Cologne Bight) and eastern areas, depending on the prediction model.

During the mid-21st century, most parts of Germany can be expected to experience annual mean temperatures exceeding the lower threshold for sandfly establishment which is 10 °C. However, maximum summer temperatures of above 20 °C will remain restricted to southern and eastern (continental) regions, and thus large areas of Germany may not be fully suitable for these insects until the end of the century. By the end of the 21st century, many regions of Germany will have become suitable for phlebotomine sandflies, with only the Alps, low mountain ranges and northern areas not satisfying their thermal requirements.

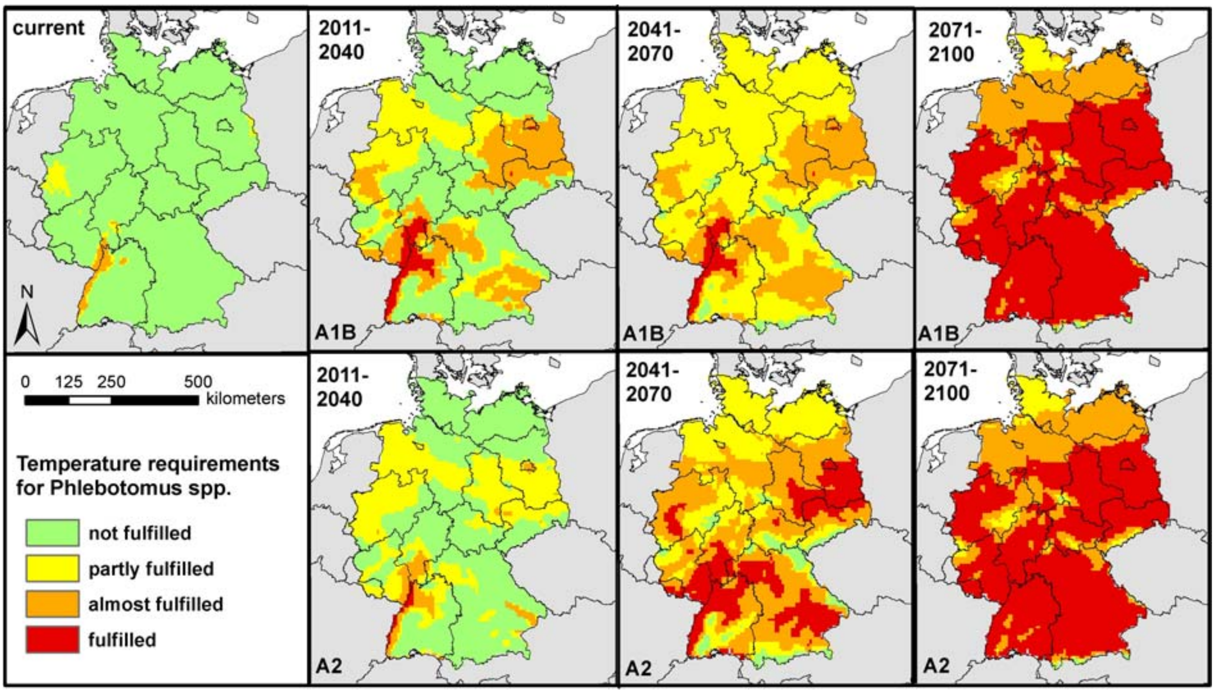

Fig. 1. Temperature-derived suitability for Phlebotomus spp. in Germany under current and projected temperature conditions represented by two IPCC climate change scenarios (A1B and A2). Calculations were based on 30-year average values.

3.2 Temperature-derived suitability for *L. infantum* complex

Temperature requirements of the pathogen will very likely not be achieved in Germany until the mid-21st century (Fig. 2). By then, it can be expected that the south-west will (nearly) experience suitable temperature conditions for pathogen prevalence, with some western regions also characterised by near-fulfilment of thermal suitability during this period. Eastern and south-eastern areas will achieve required summer but not winter temperatures, due to the projected gradient of decline in winter warming towards the east (Déqué et al., 2007; Jacob, 2008). Permanent establishment of the pathogen in eastern parts of Germany can be virtually excluded.

Surprisingly, by the end of 21st the century some northern regions will provide higher suitability than the south-east. Large parts of the west of Germany and the Upper Rhine Valley in the south-west are projected to be warm enough for pathogen activity. According to these trends, western Germany seems to fulfil the climatic needs of the *L. infantum* complex earlier.

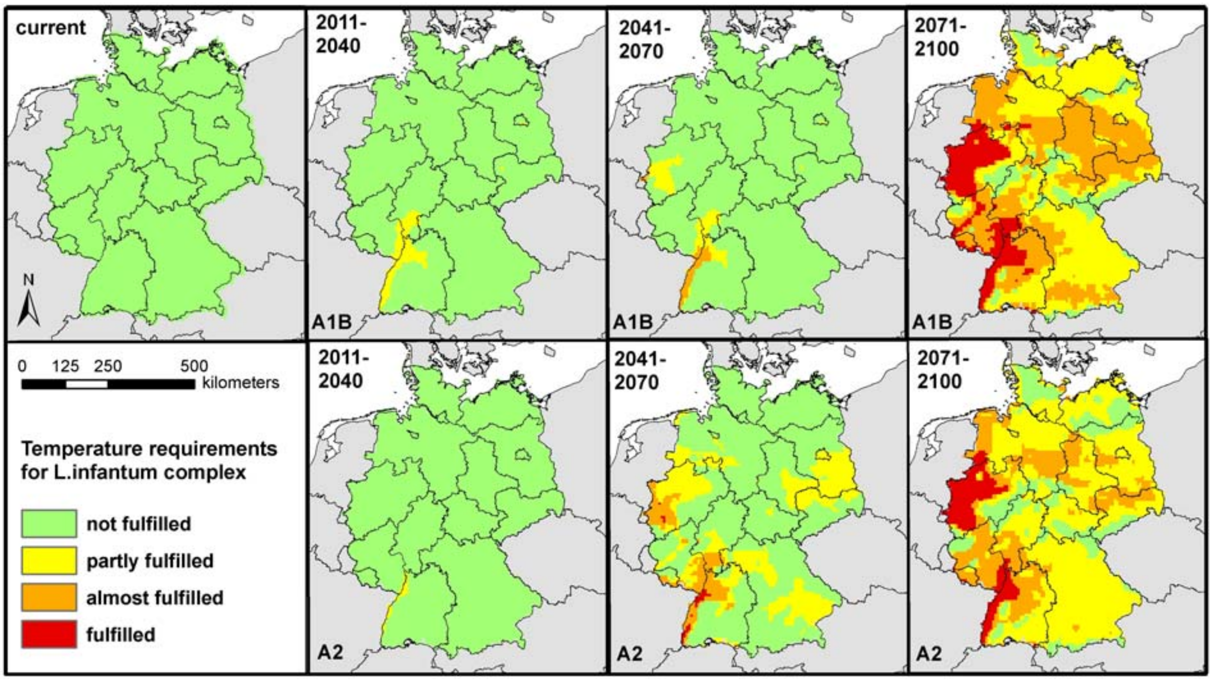

Fig. 2. Temperature-derived suitability for L. infantum complex in Germany under current and projected temperature conditions represented by two IPCC climate change scenarios (A1B and A2). Calculations were based on 30-year average values.

3.3 Temperature-derived establishment of visceral leishmaniasis

Due to the combined temperature constraints facing both, vector and pathogen (Fig. 3), visceral leishmaniasis has been prevented from becoming endemic in Germany. As this is unlikely to change during the early 21st century, the permanent occurrence of this infectious disease can be almost completely excluded during the next few years. However by the mid-21st century, model projections detect small areas in the south and south-west as potential risk areas. These regions, offering suit able thermal conditions for vector as well as for pathogen, may increase in extent by the end of the 21st century. Regions where potential establishment seems to be completely implausible by the end of the 21st century are the northernmost parts of Germany and the Alps in the south.

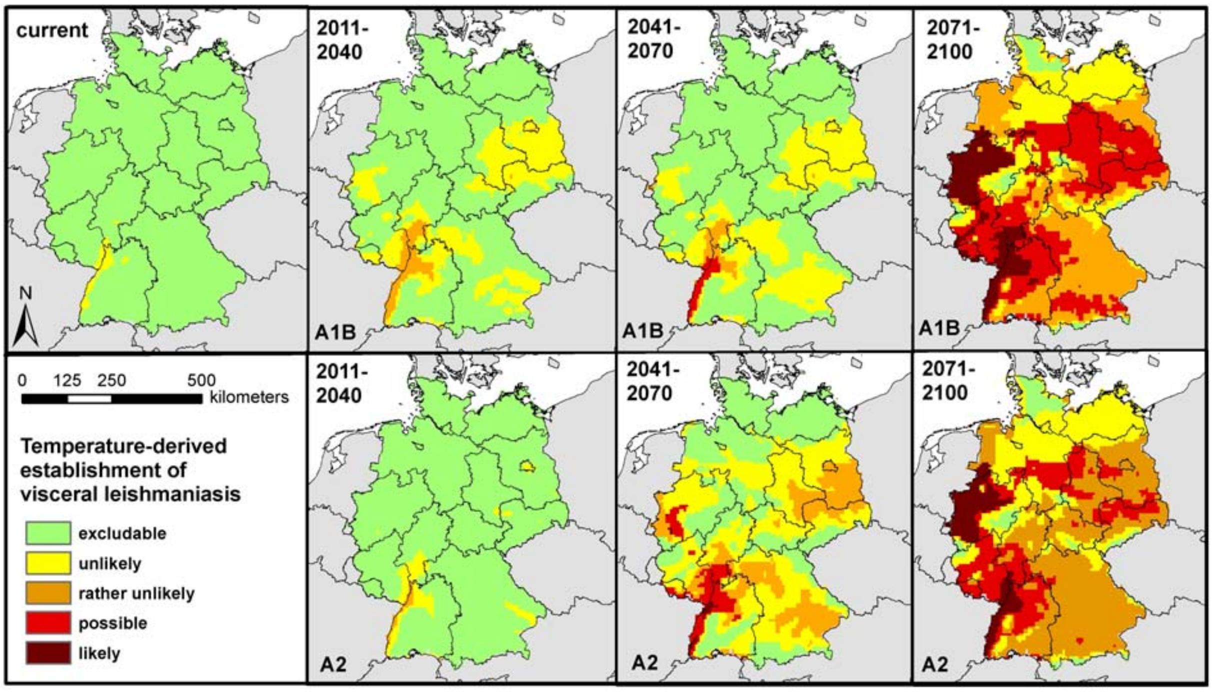

Fig. 3. Temperature-derived risk classes of visceral leishmaniasis in Germany under current and projected temperature conditions represented by two IPCC climate change scenarios (A1B and A2). Calculations were based on 30-year average values.

3.4 Time-steps and scenarios

Climatic simulations based on the A1B scenario yield higher temperatures for the first time period (2011-2040) than simulations of the A2 scenario. Consequently, some eastern areas will almost satisfy vector habitat requirements in the A1B projection but not in the A2 scenario. However in both scenarios, pathogen, and hence disease establishment, can be excluded during this period.

Tab. 2: Classified risk areas for potential autochthonous occurrence of visceral leishmaniasis. Risk areas are denoted as percentages of the total area of Germany separately for each time period and scenario. Regions at risk increase during the 21st century in both scenarios.

Establishment of visceral leishmaniasis		Current	2011-2040		2041-2070		2071-2100	
			A1B	A2	A1B	A2	A1B	A2
1	Excludable	98.5	72.0	94.7	67.9	37.1	3.6	4.7
2	Unlikely	1.5	24.6	4.6	28.6	39.8	23.0	26.6
3	Rather unlikely	-	3.4	0.7	2.2	17.7	30.0	42.0
4	Possible	-	-	-	1.3	4.9	31.9	19.1
5	Likely	-	-	-	-	0.5	11.5	7.6

Remarkable differences in classification are projected for the second time period (2041-2070). Midcentury temperature conditions will permit disease establishment in western and south-western Germany in the A2 scenario, while this will be rather unlikely under A1B conditions. The risk of establishment also differs for eastern Germany. At the end of the century, both scenarios resemble each other more strongly with respect to vector, pathogen and consequently, disease requirements, than in the earlier periods. However some differences are still conspicuous. Areas providing climatic suitability will be fewer and more isolated especially in the east according to the A2 projection compared to the A1B scenario. Spatio-temporal variation in classification results for each scenario concerning the risk of temperature-derived establishment of visceral leishmaniasis are summarised in Table 2.

Increases in the risk of visceral leishmaniasis establishment vary significantly over time (Fig. 4). During the next few decades the potential threat increases faster in the A1B scenario than in A2, but by mid-21st century increases in risk become more apparent in the A2 projection. Generally, warming will be more rapid from the middle to the end of the 21st century. Accordingly, transitions in risk class are highest within this period for both scenarios.

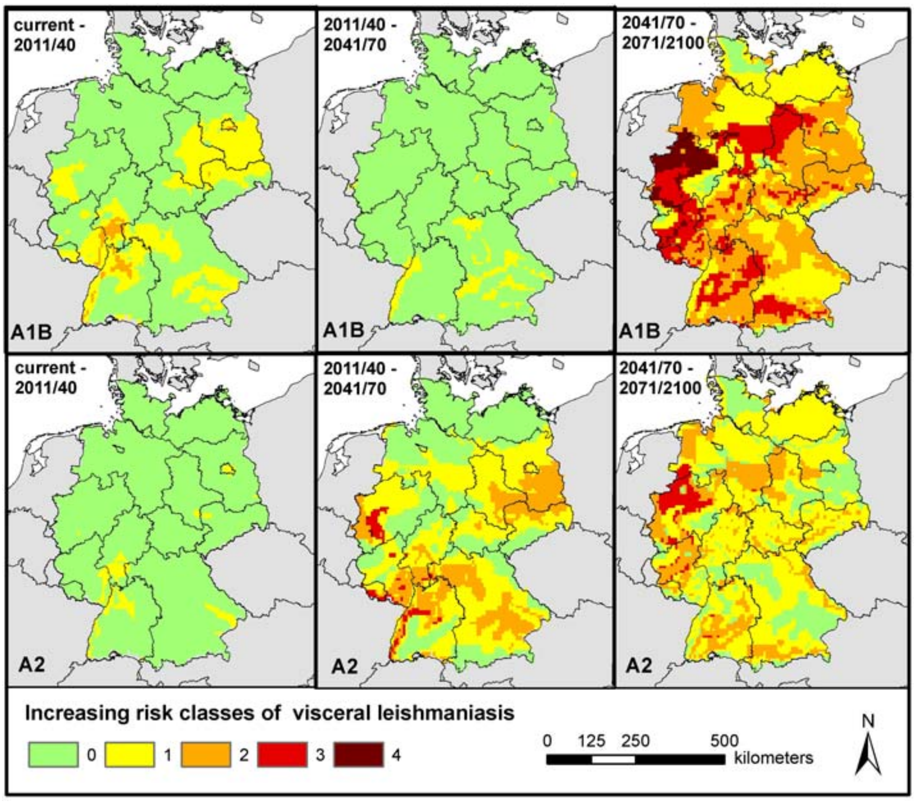

Fig. 4. Temporal variation in classification results for visceral leishmaniasis. Classified results for each time period (30-year averages) were subtracted from the following one for each scenario separately, in order to detect temporal trends in risk class variation.

4. Discussion

In this study, potential effects of the expected change in European climate on phlebotomine sandflies and visceral leishmaniasis are elucidated. During the 21st century, temperature conditions will favour the occurrence of sandflies in Germany. Temperature requirements of the *L. infantum* complex will also be fulfiled, albeit with some delay, with thresholds for pathogen survival not expected to be surpassed before mid-century. Establishment of visceral leishmaniasis is therefore not predicted during the first half of the 21st century. Afterwards, an increasing risk of infections is detected for Germany, where leishmaniasis does not presently occur. However, zones of elevated risk will be limited to certain regions.

The Upper Rhine Valley and Cologne Bight regions will be the first and most strongly exposed to this emerging biological risk according to two IPCC scenarios under consideration (A1B and A2). Nevertheless, the temporal dynamics of risk exposure vary between scenarios. Climate change projections are therefore associated with uncertainties. Even though two plausible scenarios (IPCC, 2007) were chosen, it is not certain that either will occur, as they are still theoretical and based on a number of assumptions. This consequently leads to uncertainty when attempting to predict the establishment of vector-borne diseases.

We identified areas in the north-west of Germany which seem to become suitable for the pathogen earlier than those in the south-east (Bavaria). The former are characterised by maritime climatic conditions with mild winters due to the influence of the Gulf Stream, while the south-east is associated with a more continental climate typified by colder winters and strong seasonality. Additionally, mountains in the south (e.g. Black Forest, Swabian Mountains) may restrict the eastward spread of vector and disease. Northern parts of Germany do not contain such barriers. In the east, risk of infections would rise during the projected increasingly hot summers. The important role of climate variability in the establishment of leishmaniasis has previously been pointed out by Cardenas et al. (2006) as well as Chaves and Pascual (2006).

Our analyses are based on the concordant tem perature requirements of vector and pathogen. However, studies are currently limited to general constraints of the genus *Phlebotomus* and cannot, as yet, consider requirements at the species level. Knowledge regarding the specific temperature and moisture constraints regulating the presence of single *Phlebotomus spp.* is scarce. The species may differ subtly in their ecological requirements, particularly with regard to moisture and humidity (Lindgren and Naucke, 2008). Further studies are required in order to clarify the effects of climatic change on individual

Phlebotomus spp. Attention must also be concentrated on the variant transmission capacities of the species, with proof of the vector competence of *Phlebotomus mascittii* especially required (Naucke and Pesson, 2000).

The capacity of reservoir hosts is an additional factor affecting the permanent occurrence of a vector-borne disease. Approximations of the total number of leishmaniasis-infected dogs in Germany, which are mostly imported from the Mediterranean Region, range from 20,000 (Lozán et al., 2008) up to 150,000 (Harms-Zwingenberger and Bienzle, 2007). This constitutes an appreciable reservoir from which phlebotomine sandflies can gather pathogens in the detected risk zones.

There is currently no vaccine available against visceral leishmaniasis. The most efficient method of protection for humans and animals is to avoid sandfly bites for instance via the use of insecticides (Maroli and Khoury, 2006). Surveillance and control of vectors and disease has proven difficult (Killick-Kendrick, 1999; Gramiccia and Gradoni, 2005). The introduction of potentially infected dogs must therefore be tightly monitored and restricted.

5. Conclusion

Leishmaniasis is not currently eminent in Germany, even if it does constitute a serious health hazard of increasing importance. We demonstrate here that the spread of a (sub-) tropical disease (i.e. visceral leishmaniasis) to previously non-endemic regions constitutes a risk in the 21st century. We project differentiated spatial and temporal patterns for the probability of occurrence and local establishment of visceral leishmaniasis in Germany.

Favourable regions for both vector and pathogen are situated close to unsuitable areas, with human mobility and transport links bridging these barriers between isolated habitats. However, vector dispersal ability, density of reservoir hosts and further environmental and anthropogenic factors must be better understood and included in future risk analyses. Feasible proactive adaptation strategies can then be implemented in order to delay or even avoid regional establishment of vector-borne diseases.

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6.4 Article 4:

Projection of climatic suitability for *Aedes albopictus* Skuse (Culicidae) in Europe under climate change conditions

With 3 Tables and 5 Figures in the main text as well as one Reference list and 7 Figures in the Supplemental Material.

Abstract

During the last decades the disease vector *Aedes albopictus* (*Ae. albopictus*) has rapidly spread around the globe. The spread of this species raises serious public health concerns. Here, we model the present distribution and the future climatic suitability of Europe for this vector in the face of climate change. In order to achieve the most realistic current prediction and future projection, we compare the performance of four different modelling approaches, differentiated by the selection of climate variables (based on expert knowledge vs. statistical criteria) and by the geographical range of presence records (native range vs. global range).

First, models of the native and global range were built with MaxEnt and were either based on (1) statistically selected climatic input variables or (2) input variables selected with expert knowledge from the literature. Native models show high model performance (AUC: 0.91-0.94) for the native range, but do not predict the European distribution well (AUC: 0.70-0.72). Models based on the global distribution of the species, however, were able to identify all regions where *Ae. albopictus* is currently established, including Europe (AUC: 0.89-0.91).

In a second step, the modelled bioclimatic envelope of the global range was projected to future climatic conditions in Europe using two emission scenarios implemented in the regional climate model COSMO-CLM for three time periods 2011-2040, 2041-2070, and 2071-2100. For both global-driven models, the results indicate that climatically suitable areas for the establishment of *Ae. albopictus* will increase in Western and Central Europe already in 2011-2040 and with a temporal delay in Eastern Europe. On the other hand, a decline in climatically suitable areas in Southern Europe is pronounced in the Expert knowledge based model.

Our projections appear unaffected by non-analogue climate, as this is not detected by Multivariate Environmental Similarity Surface analysis. The generated risk maps can aid in

identifying suitable habitats for *Ae. albopictus* and hence support monitoring and control activities to avoid disease vector establishment.

Keywords

Asian tiger mosquito, dengue, global change, global warming, species distribution model, invasion, vector-borne disease

Research highlights

- We model the current climatic suitability for the disease vector *Aedes albopictus*.
- We assess the potential of the mosquito to establish in Europe under climate change.
- Increasing areas for the establishment are pointed out for Western and Central Europe.
- Risk maps may support monitoring activities to avoid disease vector establishment

1. Introduction

The invasive disease vector *Aedes albopictus* (*Ae. albopictus*) has recently received much attention (e.g. Benedict et al., 2007; Enserink, 2008; Medley, 2010). The mosquito has been ranked among the first 100 of the Worlds´ worst invaders (Crans, 2008). It has spread from its original distribution area in South-east Asia (Hawley, 1988) to at least 38 countries in North and South America, Africa, Oceania and even Europe (Benedict et al., 2007), likely by global transport of goods (e.g. Lounibos, 2002; Tatem et al., 2006; Fischer et al., 2010a). The first European invasion of *Ae. albopictus* was reported in 1979 from Albania (Adhami and Reiter, 1998). Upon its second arrival in Europe in 1990 the mosquito managed to establish permanent populations in Italy (Sabatini et al., 1990) and is now found across the Mediterranean area (Spain, France, Slovenia, Croatia and Greece; see Suppl. Reference list).

The spread of *Ae. albopictus* raises serious public health concerns. Under experimental conditions *Ae. albopictus* is able to transmit 22 viruses (Gratz, 2004). In nature it is mainly known to be an important vector of dengue, chikungunya and West Nile. Also Yellow fever virus and eastern equine encephalitis virus (North America), Ross River virus (Australia), Usutu virus (Italy) and the heartworms Diofilaria immitis and D. repens (Italy) were isolated from specimens collected in the field (Mitchell et al., 1987; Cancrini et al., 2003a,b; Calzolari et al., 2010). Due to its rapid spread (Lounibos, 2002), broad ecological plasticity (Delatte et al., 2008b) and high population density, this species has the potential to serve as an epidemic vector. Furthermore, its capacity to vertically transmit dengue and La Crosse (Tesh and Gubler, 1975; Rosen et al., 1983) enhances the possibility of establishing diseases in new areas (Delatte et al., 2008a). In Europe, the medical relevance of *Ae. albopictus* was highlighted in 2007 when the occurrence of the species was related to a chikungunya-epidemic in Northern Italy in the region of Ravenna (Rezza et al., 2007). Recently, autochthonous cases of dengue fever were diagnosed in Southern France for the first time (La Ruche et al., 2010) where *Ae. albopictus* serves as vector. Furthermore, autochthonous dengue virus infections were reported from Croatia (Schmidt-Chanasit et al., 2010; Gjenero-Margan et al., 2011).

Even under conservative and optimistic scenarios, future climate change is likely to increase air temperatures. At the end of this century the number of hot days in Central Europe is projected to reach conditions that are currently experienced in Southern Europe. While heavy summer precipitation is expected to increase in north-eastern parts of Europe, it is likely to decrease in the south (Beniston et al., 2007). In addition, changes in annual cold extremes are projected, whereby the largest relative warming is expected for North-eastern Europe (Goubanova and Li, 2007). These climatic changes may support a range shift and further regional establishment of *Ae. albopictus*.

As an ectothermal arthropod, *Ae. albopictus* is unable to regulate its body temperature. Hence the species directly depends on the thermal conditions of its environment. Under laboratory conditions, changes in temperature and precipitation affect the population dynamics of *Ae. albopictus*, which suggests that climate change is likely to extend the limits of its northern distribution (Alto and Juliano, 2001). Regarding a northward shift, especially temperature constraints in the cold period and decreasing photoperiod are of outmost interest, because these factors determine diapause of eggs and thus the survival of the species. The 10 °C coldest-month isotherm coincides with the separation between continuously breeding populations and those that must undergo a period of dormancy to survive cold periods in winter (Mitchell, 1988). Larval surveillance in Northern Japan shows that the mean temperature of the coldest month below -2 °C is potentially lethal there (Kobayashi et al., 2002). Nawrocki and Hawley (1987) state that the -5 °C coldest-month isotherm describes the maximum northward expansion of *Ae. albopictus* in continental Asia and, presumably, also in North America. A risk of establishment in Europe is considered for areas with 0 °C or higher as cold-month isotherm (Mitchell, 1995; Knudsen, 1995).

But, it is not only the limitation by low temperatures that has to be considered; warm temperatures, too, play an important role for *Ae. albopictus*. Pumpuni et al. (1992) pointed out that higher temperatures greatly reduce or prevent diapause incidences in *Ae. albopictus* specimen that were exposed to critical photoperiods. Results from natural foci in Southern Brazil demonstrate that diapause apparently evolved from nondiapause or non-photoperiodic ancestors, whereby in southern parts of USA a diapause reduction was observed presumably due to rapid local adaptation (Lounibos et al., 2003). Sufficient precipitation or perhaps more generally a suitable local moisture regime is an additional prerequisite for the occurrence of the species. Moisture directly controls the availability of breeding sites and the relative humidity is an important factor for egg survival (Juliano et al., 2002). Annual precipitation is reported to be higher than 500 mm in the species' habitats in the Mediterranean area (Mitchell, 1995).

Previous approaches to map suitable climatic conditions for the establishment of *Ae. albopictus* in Europe mostly focused on the risk of invasion under current climatic conditions. Considering rainfall beside other factors (photoperiod, temperature and humidity), Mitchell (1995) developed a risk map for the Mediterranean Basin by comparing the climatic conditions of the region with the estimated climatic envelope of *Ae. albopictus*. Knudsen et al. (1996) investigated the distribution of *Ae. albopictus* in Italy and projected the risk for a broader distribution throughout Europe. This projection is based on climatic criteria identified by Nawrocki and Hawley (1987) including winter mean temperature, mean annual rainfall, and mean summer temperature. Eritja et al. (2005) used the same climatic limits as Mitchell (1995) and generated a detailed risk map for Spain, which considered regional climatic conditions. For the United Kingdom, Medlock et al. (2006) developed a GIS based model using mean monthly temperature, annual rainfall and photoperiod to assess the overwintering survival, spring hatching and production of overwintering eggs in autumn.

The European Centre for Disease Prevention and Control (ECDC) produced risk maps that are aiming to predict climatic suitability of *Ae. albopictus* for the years 2010 and 2030 (ECDC, 2009). On a global scale, Benedict et al. (2007) investigated the regional risk of invasion by *Ae. albopictus*. Their analysis was carried out using eleven environmental data layers of the present climate. Recently, Medley (2010) investigated environmental (including climatic) niche shifts during the global invasion of the species, by modelling niches separately for each continent. Notably, most of the relevant literature is concerned with the present distribution and risk of invasion by *Ae. albopictus* under current climatic conditions. However, the predicted increase in temperature that is based on climate change scenarios will probably extend the spatial availability of breeding sites and also enhance mosquito survival (Woodward et al., 2001).

Our analysis starts from the assumption that *Ae. albopictus* will colonise climatically suitable niches around the world. We want to identify areas that could serve as potential habitat for the species today and in the future. Here, we assess the potential of *Ae. albopictus* to establish in Europe under projected climatic trends in the 21st century. In order to account for uncertainty in the selection of presence records and environmental variables, we (1) compare projections based on the species' former native range to those based on its recent entire global range, and (2) apply variable selection by expert knowledge as well as variable selection by an automated statistical procedure.

2. Material and methods

We created distribution models with MaxEnt, using species occurrences of the native range and of the entire range across the globe. For both training areas (global and native) two sets of bioclimatic data were prepared as input variables. One set was selected using expert knowledge on species climatic constraints. The second set was selected using solely statistical criteria. The future climatic suitability of *Ae. albopictus* in Europe was projected for two climate change scenarios. In addition, niche similarity between global and native regions and climatic similarity between projections was analysed.

2.1. Spatial distribution and presence records of *Aedes albopictus*

Presence records of *Ae. albopictus* at the global scale were taken from Benedict et al. (2007). Additionally, a literature search of scientific articles and reports of mosquito surveillance was conducted for the years 2003 onwards to consider additional infestations (see Supplemental Reference list). Reported occurrences of *Ae. albopictus* without evident establishment were excluded from the dataset.

This resulted in a global dataset that consists of 6347 occurrence points with 4683 occurrence points just for Brazil, due to a detailed monitoring system in South America. Presence records for the United States are available on county level but not as precise geographical coordinates. Therefore the 1033 counties with documented presence records were converted to points by digitising the centroids for each of the counties. Considering that worldwide, apart from the USA and Brazil, less than 1000 coordinate pairs were available, a random set of ten percent of the data were extracted for Brazil and the USA. Hence, the density of presence records for Brazil and the USA was reduced to levels that correspond to the density of documented presence points in other regions with maybe less intensified mosquito monitoring systems. Without this stratified sub-sampling, the results would have been biased towards the climatic conditions of South and North America (Medley, 2010). Additionally, duplicate species records within one raster cell of the training area (described in Section 2.2) were removed. The total global number of presence records used for modelling was 1199 (including 241 records in the native range).

2.2. Selection and pre-processing of climatic data

Current bioclimatic data (19 bioclimatic variables) were taken at a spatial resolution of 5 arcmin (http://www.worldclim.com). These bioclimatic variables are derived from monthly temperature and rainfall values in order to generate more biologically meaningful variables, which are recommended to use in ecological niche modelling (Hijmans et al., 2005). Higher spatial resolution would not correspond to the spatial accuracy of occurrence data for *Ae. albopictus*. Two climatic datasets with different spatial extent were generated. The global climatic conditions of the land surfaces were used to model the global distribution. For the definition of the “native range” models, each native presence record was buffered with a circle of 1000 km radius. The native range then included all areas which were located in at least one of the circles. Hence, this range included a climatic gradient within Asia, in order to yield a clear delineation of the species' climate niche, but excluded areas that may be too far from the realised distribution, such that geographical factors rather than climate are dominant in limiting the species' distribution.

We used two sets of variables as input for global and native models. The first set is based on expert knowledge on the climatic requirements of the target species (e.g. Mitchell, 1995). Those variables are the same for the native and for the global range. Most variables represent thermal constraints (Table 1). In this model, some variables show substantial collinearity: Annual mean temperature (Bio1) is correlated with mean temperature of the warmest and coldest quarter (Bio10 and Bio11) in the native and the global range higher than r = 0.7 (Pearson correlation coefficient). Nevertheless, as a pre-selection of variables based on expertise is often useful (Elith and Leathwick, 2009), we kept these variables in our analyses, and chose a modelling approach that is known to be robust against collinearity (see Section 2.3). Hereafter, we will refer to this set as the expert knowledge based model (EKBM).

Tab. 1: Selected bioclimatic variables of native and global models, referring either to expert knowledge based or statistic based model. Listed are the training gains for the selected bioclimatic variables measured by Jackknife test. Variables without mentioned training gain were not part of the selected data set. Training gains were calculated for a single variable if used solely for the modelling procedure and additionally for the remaining dataset if this variable has been dropped from the set. Both aspects must be considered for a statistical selection of variables. For instance, altitude as variable achieved comparatively low values for the training gain is used as the single variable for modelling procedure, but training gain of the dataset decreases remarkable, if altitude is removed. Therefore it is advisable to keep this variable within the set. After selection of the variables, training gain was calculated for modelling with all selected variables. Training gain for the complete selected dataset is highest for the native datasets (expert knowledge based: 1.67, statistic based: 1.69). Training gain of the global dataset is 1.42 for the expert knowledge based selection and 1.34 for the statistic based selection.

Training gain of selected bioclimatic variables and altitude		**Expert knowledge based**				**Statistic based**			
		global		Native		global		native	
		without variable	with only variable	without variable	with only variable	without variable	with only variable	without variable	with only variable
BIO1	Annual mean temperature	1.35	0.67	1.42	0.80	0.99	0.66	-	-
BIO4	Temperature seasonality	-	-	-	-	-	-	1.43	0.84
BIO10	Mean temp. (warmest quarter)	1.27	0.70	1.42	0.72	-	-	-	-
BIO11	Mean temp. (coldest quarter)	1.33	0.64	1.42	0.90	-	-	1.50	0.91
BIO12	Annual precipitation	1.20	0.71	1.35	1.00	1.17	0.72	1.51	1.00
BIO17	Precipitation (driest quarter)	-	-	-	-	-	-	1.42	0.66
BIO18	Precipitation (warmest quarter)	-	-	-	-	1.23	0.31	-	-
BIO19	Precipitation (coldest quarter	-	-	-	-	1.21	0.48	-	-
ALT	Altitude	1.157	0.16	1.24	0.74	1.18	0.16	1.36	0.75

The second set of variables was selected by using a statistical procedure for native and global range separately. First, the importance of each variable was quantified with a Jackknife test implemented in MaxEnt (Elith et al., 2011). Variable importance is calculated in a two-fold manner based on the training gain for all variables in isolation and for the remaining set of variables when the isolated variable is dropped from the set (Yost et al., 2008). To reduce collinearity in the set of statistically selected variables (Dormann et al., 2008) variables were removed that had a Pearson correlation coefficient $r \geq 0.7$ with any other higher-ranking variable in the results of the Jackknife test. We applied the variable selection procedure separately for the native and global range. The statistically derived sets of variables consist mainly of variables that represent the precipitation regime for the global range and identical number of temperature and precipitation variables for native range (Table 1). Models based on this set of variables are henceforth called statistic based model (SBM).

We projected the best models (determined by AUC-value, Section 2.3) to the future European climate. Projections of climate change in the 21st century refer to the scenarios for greenhouse gas emissions implemented within global or regional climate models. A1B and B1 scenario, which were considered as marker scenarios that best illustrate the respective storyline (IPCC, 2007), were applied for our projections of the future climate suitability for *Ae. albopictus* in Europe. In short, the A1B scenario is characterised by rapid global oriented economic growth and technological change towards the balanced use of fossil and non-fossil energy resources. The B1 scenario projects a more rapid change towards a service information economy with the introduction of resource efficient technologies while assuming a similar economic growth. It matches well with the European Union target of keeping global anthropogenic warming below two Kelvin above the pre-industrial level (Jacob and Podzun, 2010). Hence warming tendencies are projected to be stronger in the A1B scenario.

On http://www.worldclim.com data of the projected climate change are provided for the global climate models CCCMA and HADCM, which originally have very coarse spatial resolution (about 250km). Climatic changes were interpolated to the high grid resolution of the current climatic conditions. As a consequence, this simple downscaling procedure does not account for climatic changes at small scales. In order to achieve more realistic projections of future climatic suitability for *Ae. albopictus* in Europe, we instead used data of climate change provided from the regional climate model COSMO-CLM (CCLM). Near-scale physical processes integrated in CCLM (spatial resolution about 18 km) are fitted at the boundaries with large-scale conditions given by the global model ECHAM5 (Rockel et al., 2008). Such a dynamical downscaling procedure enhances the quality of climate impact studies on vector-borne diseases due to integrated small-scale specifics such as topography or further landscape features (Jacob, 2008).

Climatic data were separately averaged over time periods 2011- 2040, 2041-2070 and 2071-2100 for each scenario. Bioclimatic variables for modelling future climate projections were calculated in the same way as the original variables for current conditions. The spatial resolution of CCLM was resampled to the 5 arcminutes used for the current conditions. The pre-processing of the CCLM data was done via climate data operator codes (Schulzweida et al., 2009). The spatial extension of Europe for the current and future projections is adjusted to the defined space of the CCLM data.

2.3. Species distribution models

Species distribution models were built with MaxEnt. MaxEnt is a machine-learning technique combining species occurrence data with detailed climatic and environmental datasets in order to predict species distribution (Phillips et al., 2006; Phillips and Dudik, 2008). MaxEnt is favoured among other (pseudo) presence-only species distribution models due to high predictive power across all sample sizes (Elith et al., 2006; Wisz et al., 2008). In addition, variable selection in MaxEnt is less affected by correlated variables than e.g. step-wise regression, so there is less need to remove such correlated variables or, for instance, pre-process covariates by calculating principal components (Elith et al., 2011). Model residuals were tested for spatial autocorrelation using Morans I (Dormann et al., 2007).

Several parameter settings affect MaxEnt performance: Regularisation modifiers, which reduce the likelihood of overfitting and thus increase the predictive ability of modes beyond the training region (Phillips and Dudik, 2008), were set to 1. Increasing the number of model training iterations beyond the default value of 500 enhanced model performances, and the maximum number of iterations was therefore set on 2000 for all models. Furthermore, models were run with following settings: feature types were automatically selected depending on the training sample size (auto feature), convergence thresholds were 0.00001, maximum number of background points were 10000 as more background points do generally not enhance model quality criteria, but extend running time (Phillips and Dudik, 2008).

The model performance was quantified using the area under the receiver operator characteristic curve (AUC), a threshold-independent quality criterion (e.g. Elith et al., 2006). AUC-values can be interpreted as the probability that the model assigns a higher occurrence probability to a randomly selected presence location than to a randomly selected absence location. In order to yield unbiased estimates of model performance, we employed a standard split-sample strategy. Models were trained using a random subset (70%) of occurrence data and then tested on the remaining 30% (see also Araujo et al., 2005). This procedure was replicated 100 times and finally averaged. Both native models were additionally projected onto current climatic conditions of Europe.

Those models were further analysed that yielded high model quality criteria when tested with European presence records (Table 2). Additionally, prediction quality was visualised with maps of current climatic suitability for the entire range, for the native range, and for Europe (Figs. 2-3). Climate change projections were made for three time periods at high spatial resolution for Europe in order to identify regions with future climatic suitability for the mosquito.

2.4. Niche similarity and climatic similarity

We tested for differences in environmental conditions at the occurrence points using Multiresponse Permutation Procedure (MRPP) with 999 replicates. Occurrence points were assigned to one of three groups: the native range, the invasive non-European range, or the invasive European range. The MRPP was repeated for all three sets of environmental variables that were used in the modelling, i.e. those of the EKBM, the native SBM, and the global SBM. Additionally, we tested for niche differences between models trained on the native or on the global range, using a randomization test based on a method by Warren et al. (2008). Niche overlap between two model predictions is quantified with the *I* statistic (Table 3).

Since our main regional interest is Europe, we evaluated niche similarity for Europe only. The test compares the niche overlap of the original data with the niche overlap of randomised data, where we randomised the assignments to the regions (native and global), for both occurrence and background points. In order to keep the number of presence records constant in both regions, we separately randomised the region assignments for occurrence points and for background points. We used a one-sided test, with the null hypothesis that niche similarity is smaller or equal in the randomised data than in the original data; 199 randomisations were performed.

Furthermore, potential non-analogue climatic conditions between all projections in space and time were calculated. If non-analogue climate is detected, this requires caution in the interpretation of the results (Fitzpatrick and Hargrove, 2009). We determined potential non-analogue climate by using Multivariate Environmental Similarity Surface (MESS) analysis (Elith et al., 2010) for all of our projections in space and time. The MESS analysis measures the similarity between those environments used to train the model and the new projected environments for any grid cell (Elith et al., 2011). Regions with dissimilar values of the used variables, representing values that are outside the range of environmental training area, can be detected (Elith et al., 2010).

Preparation of presence records, current and projected climatic data was executed in ArcGIS 9.3.1 and R 2.11.0 (R Development Core Team, 2010). Correlation analysis of bioclimatic variables and Moran's I test were done in R. This software was also used to perform MRPP using the package “vegan” (Oksanen et al., 2011), while the package “phyloclim” (Heibl, 2011) was used for calculating *I* statistics (Warren et al., 2008). Species distribution models and MESS as well as calculation of variables contribution and Jackknife tests were carried out in MaxEnt 3.3.3e.

3. Results

3.1. Bioclimatic envelope and current distribution

Regarding the bioclimatic envelope, the occurrence of the mosquito mainly refers to regions that exhibit more than 500 mm of average annual precipitation and annual mean temperatures above 10 °C (Fig. 1). This is found to be true for both, the native and the invasive range. Within its invasive distribution the mosquito established in areas with annual mean temperatures between 10 and 25 °C and annual precipitation that ranges from 500 mm up to 2000 mm. The native range of *Ae. albopictus* is characterised by slightly higher temperatures and rainfall compared to the invasive range. Notably, the invaded range in Europe achieved the lowest values of annual mean temperature and annual precipitation.

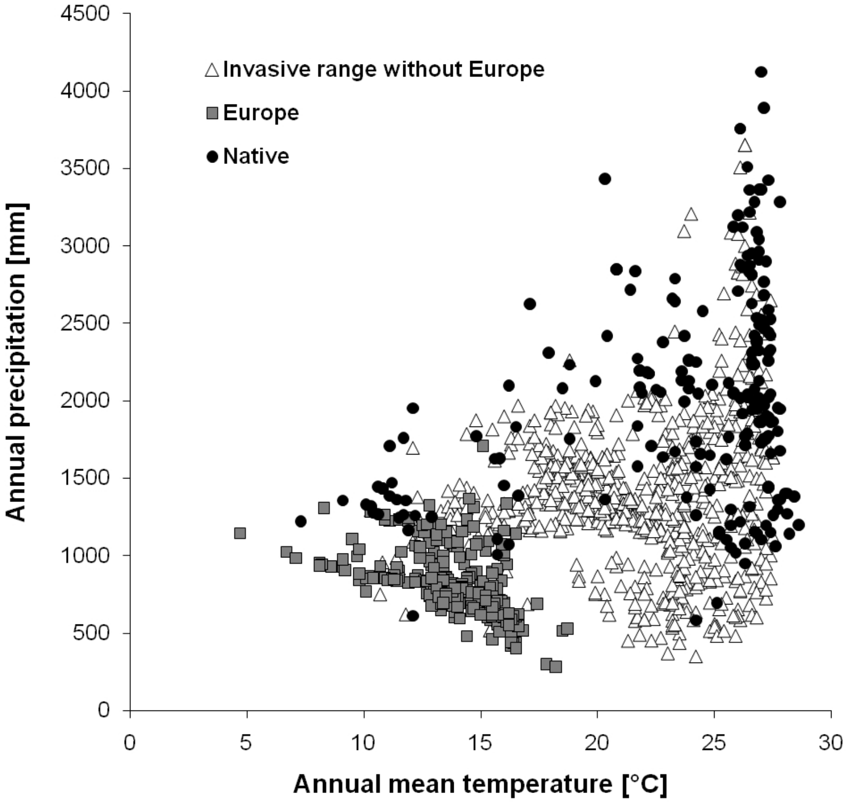

Fig. 1: Bioclimatic envelope for *Aedes albopictus* (native and invasive range), derived by geographically explicit overlay of presence records with annual bioclimatic variables. Annual mean temperature is highest in the native range (South-east Asia) with an average value of 23.7 °C (± 5.1 standard deviation) and the invasive range excluding Europe with 21.7 °C (±3.7), but lowest in Europe with 13.8 °C (± 2.2). High values of annual precipitation are characteristic for the native range (2028 mm ± 691) and for the invasive range without Europe (1392 mm ± 496). Invaded European regions obtain an average of 831 mm (± 218) of annual precipitation. Globally, the averaged annual mean temperature for regions with occurrence of the species is 20.3 °C (± 5.2) and averaged annual precipitation is 1392 mm (±632). The climatic conditions at the occurrence points differ significantly between the native range, the invaded European range, and the invaded non-European range (significance level of 0.001, Multiresponse Permutation Procedure with 999 replicates; the result holds for all three sets of environmental variables used in this study).

The EKBMs were mainly built on temperature variables. Results of the Jackknife test for the selection of meaningful variables for the SBM differ for the global and the native range: While the global-driven SBM mainly includes hydrological variables, the native-driven SBM reflects equally thermal and hydrological constraints. Altitude and annual precipitation were the only variables used in both EKBMs and SBMs, regardless of the chosen training region (Table 1).

Tab. 2: Evaluation of model performance based on the area under the curve for the receiver-operator characteristic (AUC). AUC-values range from 0 to 1 (perfect discrimination); useful models have AUC-values above 0.7, excellent models achieve AUC-scores above 0.9. AUC values were calculated on randomly selected test and training data; the split into training and test data was replicated 100 times, reported are mean and, in brackets, standard deviation. Both global models performed best and were used for further analysis.

Evaluation of model quality via AUC-scores	Native model (trained and tested in native range)		Native model (trained in native range, tested in European range		Global model (trained and testedin global range)	
	Expert knowledge based	Statistic based	Expert knowledge based	Statistic based	Expert knowledge based	Statistic based
Training data	0.93 ($^{+}$/- 0.01)	0.94 ($^{+}$/- 0.01)	0.94 ($^{+}$/- 0.01)	0.94 ($^{+}$/- 0.01)	0.91 ($^{+}$/- 0.01)	0.90 ($^{+}$/- 0.01)
Test data	0.91 ($^{+}$/- 0.01)	0.91 ($^{+}$/- 0.01)	0.72 ($^{+}$/- 0.02)	0.70 ($^{+}$/- 0.02)	0.90 ($^{+}$/- 0.02)	0.89 ($^{+}$/- 0.01)

Both native and both global models showed high model performance for their respective training region (Table 2). The global EKBM and SBM delivered a realistic representation of the global range (Fig. 2). Interestingly, large parts of the continental west coasts of South America (Chile), Mexico and the United States (California, Oregon and Washington) as well as Europe (France, Portugal) are determined as climatically suitable, although there are currently no presence records. Furthermore the eastern side of Australia has been predicted as climatically suitable in both global models where the species is not established. The SBM made better predictions of the distribution of the mosquito in India. European areas with current distributions are successfully predicted with both global models (Figs. 2,4,5).

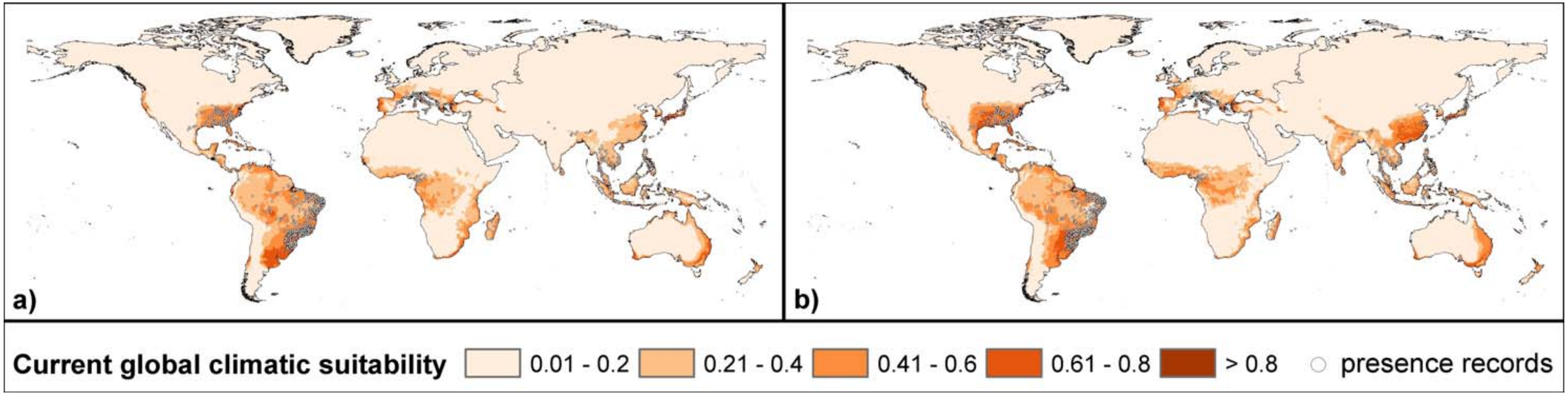

Fig. 2: Global climatic suitability, modelled based on global occurrence data under current conditions. MaxEnt suitability values range from zero to one. High values represent favourable climatic conditions for the species; values close to zero indicate unfavourable climatic conditions. Results are mapped for the global-driven: a) expert knowledge based model and b) statistic based model.

3.2. Projected climatic suitability for *Aedes albopictus* in Europe

The modelled niches for Europe differed significantly between models based on native and global occurrence records (Table 3).

Table 3: Niche similarity based on *I* statistic (Warren et al., 2008) for the different models, evaluated for the regional example of Europe. In all comparisons, a randomisation test indicates significant differences in the pairs of modelled niches ($p < 0.05$).

Model comparison	Niche similarity
Global expert knowledge based vs. global statistic based model	0.91
Native expert knowledge based vs. native statistic based model	0.85
Global expert knowledge based vs. native expert knowledge based	0.72
Global expert knowledge based vs. native statistic based	0.65
Global statistic based vs. native expert knowledge based	0.74
Global statistic based vs. native statistic based	0.66

Both native models that are based on records of South-east Asia do not predict the recent distribution of *Ae. albopictus* in Europe well (Table 2, Fig. 3). While the native-driven EKBM projected the north-western part of Europe (British Isles and north-west of France) as a preferable region for mosquito establishment, the SBM additionally detected Denmark and the northern part of Germany as climatically suitable.

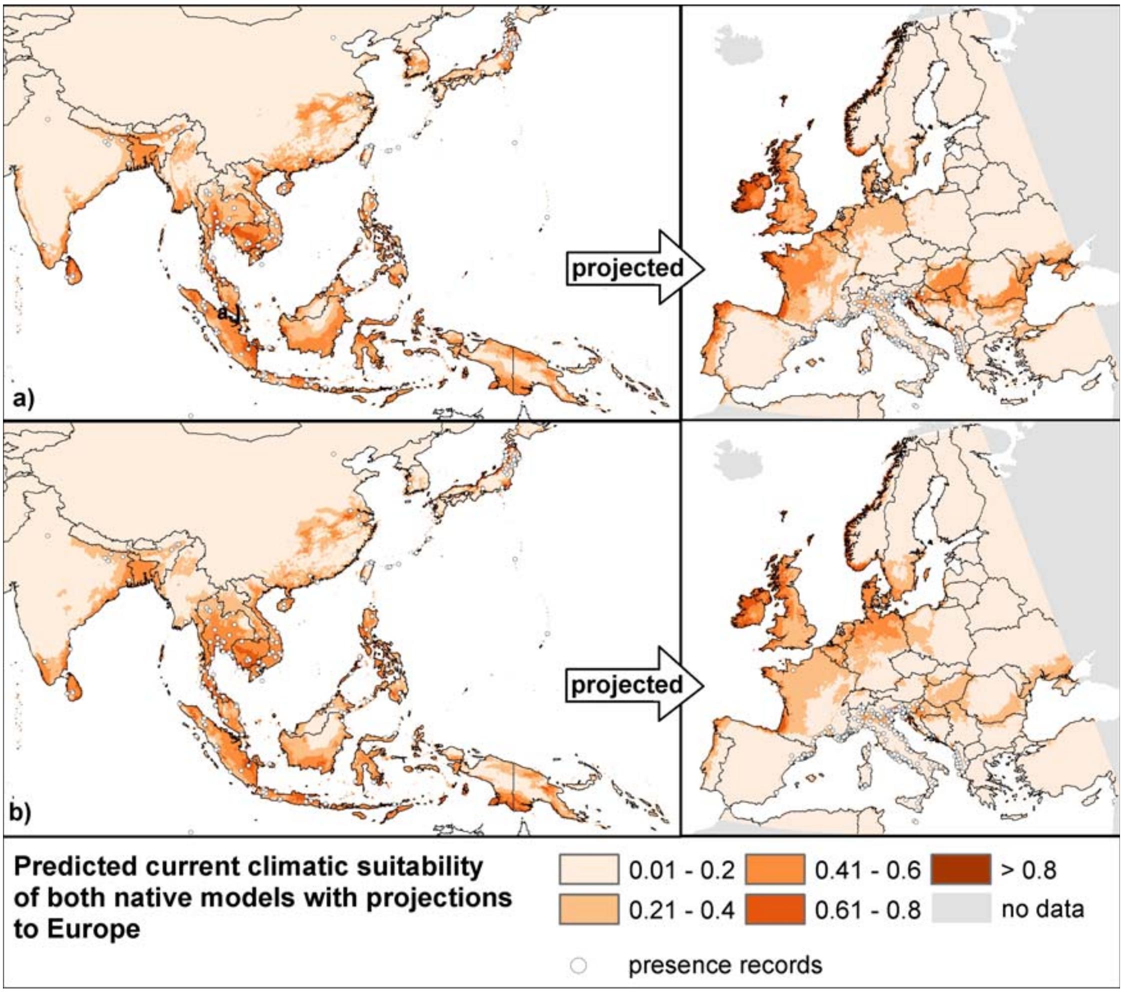

Fig. 3: Current climatic suitability modelled based on the species' occurrences in the native range and projected to the European continent. Results are mapped for the global-driven a) expert knowledge based model and b) statistic based model. Both native models failed to predict the current distribution of *Aedes albopictus* in Europe.

Only the north-east of Italy and some eastern coastal Mediterranean regions are correctly predicted as climatically suitable in both native-driven models. As a consequence, European climatic suitability of *Ae. albopictus* in the 21st century was projected using the current global range of distribution as training region.

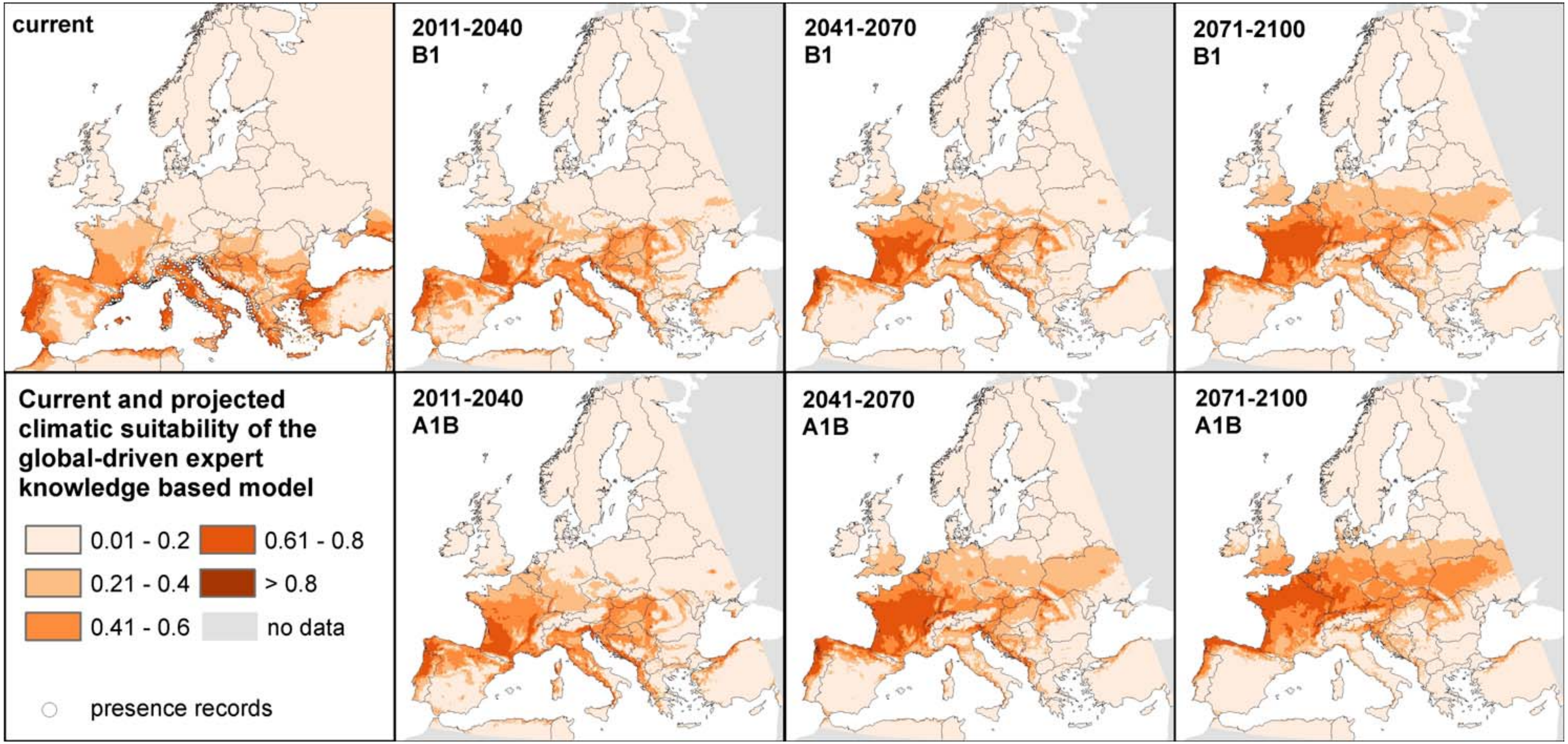

Fig. 4: Current and projected climatic suitability for *Aedes albopictus* in Europe derived from the global-driven expert knowledge based model.

Italy provides highest climatic suitability under current climatic conditions in both global models. The western Atlantic coast of Portugal, Spain and France are pointed out as climatically suitable as well, though records from these regions are still missing. Both models already project a slight decrease of climatic suitable areas in Southern Europe for 2011-2040 (Figs. 4-5). The decrease is more pronounced in south-western parts of Europe. However, Italy and south-eastern parts of Europe will still provide suitable climatic conditions for the mosquito. Passing the mid-century the Mediterranean coast of Spain seems to become unfavourable for *Ae. albopictus*.

On the other hand, climatic suitability in Western Europe is projected to increase considerably. France can be expected to become the country with the best climatic suitability, regardless of the applied model or scenario. At the end of the century, our results suggest that especially some western parts of the Mediterranean such as Spain seem to develop towards a climatically unsuitable direction for the species. Today's temperate regions of Europe will be characterised by a continental gradient of climatic suitability, with Central Europe becoming a more and more suitable habitat. The United Kingdom will be exposed to the establishment and spread of *Ae. albopictus* as well. Scandinavia is projected to remain outside of the bioclimatic niche, with the exception of Denmark, where a limited suitability is indicated at the end of the century.

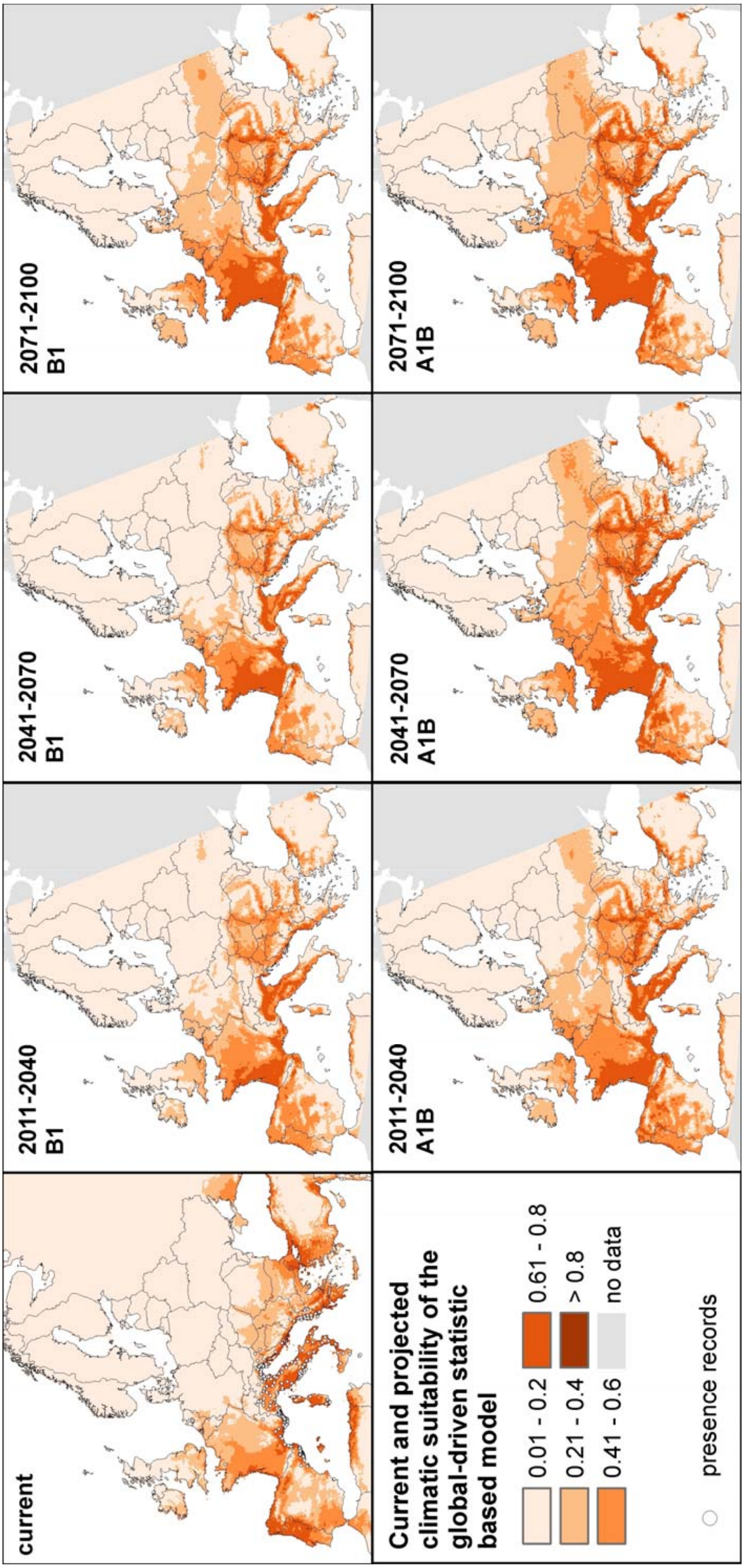

Fig. 5: Current and projected climatic suitability for *Aedes albopictus* in Europe derived from the global-driven statistic based model.

3.3. Comparison of model results

Even though the decreasing climatic suitability in the south and the increasing suitability in Central Europe are highlighted by both scenarios and models, this tendency is more pronounced in the EKBM. Notably, this model tends to attribute Central and Eastern Europe with substantially higher values of suitability throughout the 21st century than the SBM (Suppl. Fig. 1). The SBM, however, pointed out better habitat conditions for the south-west, south and south-east of Europe and additionally for the United Kingdom than the EKBM. This is true for both scenarios.

Differences between climate change scenarios are worth mentioning (see also Suppl. Fig. 2). Generally, higher values of climatic suitability for *Ae. albopictus* in both models refer to the A1B scenario. This becomes especially apparent in the SBM for Central Europe, Eastern Europe, and for the British Isles (time periods 2011-2040 and 2041-2070) and in the EKBM in the later period (2071-2100). Regionally limited areas of the Iberian Peninsula and France are detected to be more suited following the B1 scenario.

Regarding the changing climatic suitability we compare trends across different time periods. Clear temporal trends of the changing climatic suitability in projections of the EKBM exist, with a stronger emphasis in the A1B scenario (Suppl. Fig. 3). Western, Central and Eastern Europe are characterised by an increase in climatic suitability throughout the 21st century, while climatic suitability decreases in the south from one period to the following. Nevertheless, projections of the SBM do not show such a clear tendency (Suppl. Fig. 4). Although suitability also decreases generally in Southern Europe, some spatially limited regions in Central Spain and Northern Italy show increasing climatic suitability, when the time period 2011-40 is compared with current conditions. For the southern parts of Europe generally only small changes in climatic suitability are projected from the time period 2011-40 to 2041-70 in both scenarios. Instead, increasing suitability at higher latitudes is projected for the end of the century.

3.4. Climatic similarity and non-analogue climate

Climatic similarity between regions was determined by MESS analysis (Elith et al., 2010) ranging theoretically from 100 (maximum similarity) to zero (minimal similarity). Negative values represent non-analogue climatic conditions. Non-analogy may be caused either by e.g. completely divergent relationships between the chosen climatic variables in training and projected area or by completely novel relationships of the variables in the projections across space and/or time (Fitzpatrick and Hargrove, 2009). Projections of a species' climatic suitability must then be expected to be biassed. In none of our projections non-analogue climate can be identified (Suppl. Figs. 5-7). For projections of the native models to current European climate (Suppl. Fig. 5), the climatic variables selected of the EKBM show higher similarity. Regions with lowest similarity in both projections are the north-east of Italy, the coastal areas of Belgium, the Netherlands, the north-west of Germany and parts of Scandinavia as well as mountainous regions in general.

Non-analogue climate must not only be a phenomenon occurring between regions but also between time periods. But again, no European region was found to exhibit non-analogue climatic conditions in temporal projections of the two global models. The lowest values of similarity are detected in the highest mountainous regions (Alps and Pyrenees), the north-eastern parts of Italy, the coastal areas of the North Sea and the coast of Norway. Projections of the EKBM (Suppl. Fig. 6) generally result in higher values of similarity. However, these projections tend to perform dispersed spatial patterns of similarity. Using the SBM projection (Suppl. Fig. 7) France, the Iberian Peninsula and Turkey reach considerably lower values of similarity compared to the EKBM projection. Only slight deviations between scenarios and time periods were found in the results for both global climatic datasets that were used for projection.

4. Discussion

4.1. Reflection of the results and comparison to previous studies

Our aim was to identify areas that can serve as a potential habitat for *Ae. albopictus*, today and under future climate change. Two sets of bioclimatic variables were used to detect the influence of variable selections on spatio-temporal patterns of model output. In addition, we tested if records of occurrence of the former native or of the recent global range are more appropriate for predicting the current distribution in Europe.

Particularly in early stages of the invasion process, niche models are usually trained with data from the native range and applied to areas that are novel for the potentially invasive species (Mau-Crimmins et al., 2006). As invasive species are known to be adaptive (Eritja et al., 2005; Juliano and Lounibos, 2005), the habitat preferences of the species may change during the invasion process (e.g. Pearman et al., 2008; Medley, 2010). In that case, the ecology of the species in its native range cannot be directly transferred to the invaded area. On the other hand, the native range may not necessarily cover a species' entire fundamental niche (Broennimann et al., 2007).

Modelling potential spread and range dynamics based on the native habitats of a species alone has limits that can be overcome when additional data from recently occupied locations are integrated into the analyses (Broennimann and Guisan, 2008). Hence, we built native and global models in order to assess the influence on the estimated environmental niches of the invasive species. Since the global models use presence records of Europe, it was expected that they showed good results concerning the current European distribution. *Ae. albopictus* has the potential to adapt to local conditions during or after the invasion process (Medley, 2010). Hence, even using all existing species occurrence data does not guarantee per se accurate predictions of species current distribution.

We applied the regional climate model CCLM for climate projections of Europe. CCLM projects Europe to experience only a moderate warming during the first half of the century (annual mean temperature and mean winter temperatures). As mean temperature is projected to increase significantly from the midcentury onwards, certain regions reach the temperature threshold found by the global climatic envelope of the species. Precipitation, however, may be overestimated during all seasons and therefore the largest number of consecutive dry days may be higher than projected (Roesch et al., 2008), resulting in reduced habitat availability and survival rates.

An expansion of climatically suitable habitats over time could be observed in both model projections. The results raise concerns of a serious risk for the establishment of *Ae. albopictus* in Western and Central Europe. Once the species arrives there, it will be able to survive and establish permanent populations (Takumi et al., 2009). Annual mean temperature and annual precipitation are the only climatic variables that are applied in both global-driven models. Nevertheless, annual mean values should be considered as proxy-values, because the species is not active throughout the whole year in all established regions.

The risk of invasion of *Ae. albopictus* under current climatic conditions was examined in previous approaches for European countries (Knudsen et al., 1996), the Mediterranean Basin (Mitchell, 1995), and Spain (Eritja et al., 2005). In comparison to the previously hypothesised suitable areas for establishment of *Ae. albopictus* in Spain (Eritja et al., 2005), we found a greater extent of suitable climatic conditions in the north-west (Galicia) and south-west of Spain (Western Andalucía). The European risk map of Knudsen et al. (1996) is categorised in three classes at country level: high, moderate and low risk. This does not enable for a detailed detection of suitable areas. Benedict et al. (2007) present a global risk map for the establishment of *Ae. albopictus* under current climatic conditions. When focusing on the European part of this global map it is noticeable, that the south-western areas of the United Kingdom and Ireland show a higher climatic suitability than we found in our investigation.

We observe a "coast phenomenon" beyond the one described in Benedict et al. (2007): The coastal areas of invaded continents seem to be climatically suitable for *Ae. albopictus*. This is especially true for the Americas (Pacific coastline of Washington, Oregon, California, Mexico and Chile), Europe (Atlantic coastline of Portugal, Spain and France), Africa (Atlantic coastline of Ghana, Cote d'Ivoire and for the Indian Ocean coastline of Mozambique), and for Australia (southern and western coastline). But no occurrences have yet been documented in these areas. Certainly, some of these regions have implemented pronounced mosquito monitoring and control programmes. On the one hand, these findings may indicate that introduction of the species has not yet occurred or has been avoided. On the other hand, further climate factors could play a role under oceanic climatic conditions, which contribute to suppress the mosquito populations, such as wind, sea salt aerosols, or humidity.

ECDC (2009) practised ensemble forecasting for specific years (2010 and 2030) by embedding different scenarios to detect future possible risk areas for the establishment of *Ae. albopictus* in Europe. In contrast, we used climatic averages over longer time periods, which handicap the direct comparability of the results. Nevertheless, under current conditions our global-driven models seem to project higher climatic suitability for the south-west of France and Portugal and lower suitability for Spain compared to the ECDC statistical model. Even the minimal impact scenario of the ECDC-projections (2030) determines more European regions to be climatically suitable, especially France, Belgium, Luxembourg, the Netherlands, Germany and Greece. The tendencies of the projected eastward expansion in climatic suitability in this study are in agreement with our findings.

4.2. Limitations

As with all climate impact studies, uncertainties connected to future climate projections must be taken into account (Beaumont et al., 2008). To minimise this limitation we applied two scenarios that document the respective storyline best: A1B and B1 (IPCC, 2007). Apart from overall climatic conditions, microclimate and habitat availability will strongly influence the success of *Ae. albopictus* (Romi et al., 2006; Lounibos et al., 2010). Regions that display unsuitable annual rainfall in general might nevertheless supply the mosquito with hydroponic facilities when ambient conditions are dry (Romi et al., 2006). In the same way indoor hibernation could protect the mosquito from cold extremes. Such aspects are difficult to account for on the regional scale (Kysely and Beranova, 2009). The short-term availability of suitable conditions at small scales can be responsible for local establishment events under very special conditions. In the Netherlands, *Ae. albopictus* was monitored in greenhouses of companies that imported “Lucky Bamboo” (*Dracaena sanderiana*) (Scholte et al., 2007). However, such anthropogenic factors cannot be covered with our analysis. Nevertheless, the number of records used in this study as well as the large geographical extent of data provides a sound basis for the detection of robust large scale patterns.

In addition to spatial aspects of uncertainty, temporal variability is relevant. Besides changes in climatic trends, extreme weather events are also expected to increase in magnitude and frequency (Semmler and Jacob, 2004; Jentsch and Beierkuhnlein, 2008), so that a temporal window of opportunity for an invasive vector could arise. Up to now, both aspects can hardly be reflected and projected accurately in climate models (Beniston et al., 2007).

Using only climatic variables as explanatory variables for scenarios may be problematic (Dormann, 2007; Wiens et al., 2009): Land use and land cover can modify the realised ecological niche in a certain region, but become more important for modelling species distribution on smaller spatial scales (Pearson and Dawson, 2003). Knowledge on interspecific competition, predation as well as quantitative life history traits may improve the understanding of the invasion processes (Juliano et al., 2004; Juliano and Lounibos, 2005; Armbruster and Conn, 2006; Armistead et al., 2008; Juliano, 2009) and could provide input data for process-based models of invader spread. As the mosquito adapts rapidly to its environment the ecological niche models will have to be updated iteratively. Mutations and even epigenetic responses have to be considered. However, this kind of knowledge is not available yet.

On a more technical level, a further source of uncertainty stems from spatial autocorrelation, which MaxEnt - at least currently - cannot take into account. Spatial autocorrelation in the residuals may for example bias parameter estimates, and lead to optimistic estimates of model performance. Based on Moran's I, we detected statistically significant spatial autocorrelation in the residuals for all models. However, estimates of AUC using 32-fold spatially structured cross-validation (e.g. Reineking et al., 2010), which is expected to be less affected by spatial autocorrelation, were only slightly lower than those by the 70/30 splitting approach. This indicates limited bias in our estimates of model performance.

4.3. Relevance

Even when considering the limits of extrapolative niche modelling, environmental envelope models remain a powerful tool to envisage potential responses in species distribution to climate change (Wiens et al., 2009).

Our projections refer to the regional model CCLM, which is integrated into the well established global simulations of ECHAM5 (Rockel et al., 2008). In comparison to their driving models, regional models project patterns of climate change at a higher spatial resolution. This is especially relevant in climate impact studies on human health, where precise geographical information is needed (Giorgi and Diffenbaugh, 2008). In particular, small-scale heterogeneity has to be considered in studies on vector-borne diseases (Jacob, 2008; Fischer et al., 2010b). We detected those regions of Europe that are especially endangered regarding a potential establishment of *Ae. albopictus* under current conditions. Subsequently, we projected for the first time geographic patterns of climatic suitability for the mosquito that can be expected to develop during the entire 21st century. These risk maps of potentially suitable areas for the establishment may serve as a valuable support for the design of monitoring and control activities. These can contribute to avoid the further spread of the disease vector and prevent the human population from unexpected disease outbreaks. Knowledge of potential future occurrences of the vector *Ae. albopictus* becomes especially relevant regarding the increasing European areas that are expected to provide suitable temperatures for dengue-virus amplification in the 21st century (Thomas et al., 2011).

Projections of species distribution in regions of non-analogue climate are a common, but still a rarely addressed problem in species distribution modelling. The consequences can be ecologically and statistically invalid studies (Fitzpatrick and Hargrove, 2009). To assess the problem of non-analogue climate, we re-analysed our dataset using the MESS analysis (Elith et al., 2010). No regions with nonanalogue climate were detected.

5. Conclusions

Our findings indicate an increasing risk of establishment by *Ae. albopictus* especially for the Atlantic Coast of the Iberian Peninsula and for the south-west of France. In addition to the detection of already potentially appropriate areas, we find additional areas of potential future establishment of *Ae. albopictus*. It is possible that the mosquito has already colonised larger areas than noticed. Large areas of Western and Central Europe that are inappropriate for the species today are projected to change during the 21st century towards a climate that can support the survival of the species. Once the species is established, it is very difficult to control.

However, unintended anthropogenic introduction (e.g. by shipping goods) can be expected as a constant source of insecurity and will very likely contribute consistently to the introduction of mosquito populations especially close to the hubs of infrastructure (harbours and large railroad terminals). Therefore, we believe in efficiency of monitoring schemes for Europe, in order to be able to limit the spread of *Ae. albopictus* and the diseases that can be transmitted by this vector.

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Supplemental - Reference list

Collected dataset of *Aedes albopictus* with worldwide occurrence points from the year 2003 onwards. Benedict et al. (2007) conducted a database with occurrences of *Ae. albopictus* up to the year 2003. This consists of 206 occurrence points located in the native Asian range and additionally 181 records on the worldwide arrivals or establishments of the species. For the United States, the presence of the mosquito is documented from 1033 counties. An additional dataset exists for Brazil with 4683 presence records. Upon requesting, the authors Mark Q. Benedict, Rebecca S. Levine and their collaborator Joselita Maria Mendes dos Santos, they kindly agreed to pass on this data. We conducted a literature search in order to detect further infestations of the mosquito from the year 2003 onwards. These references are listed below.

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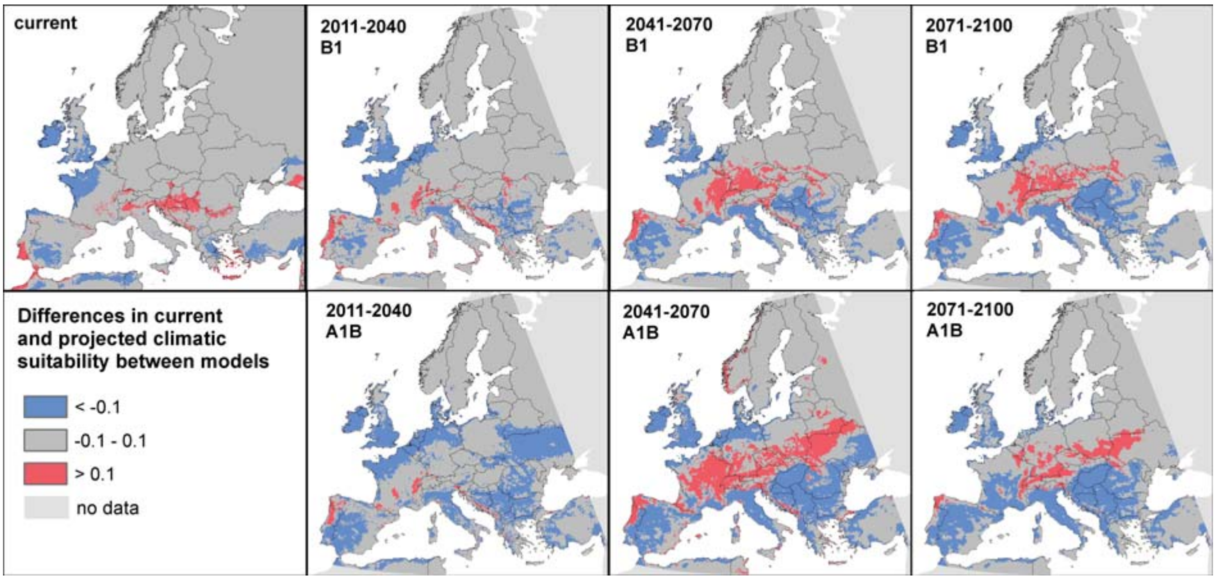
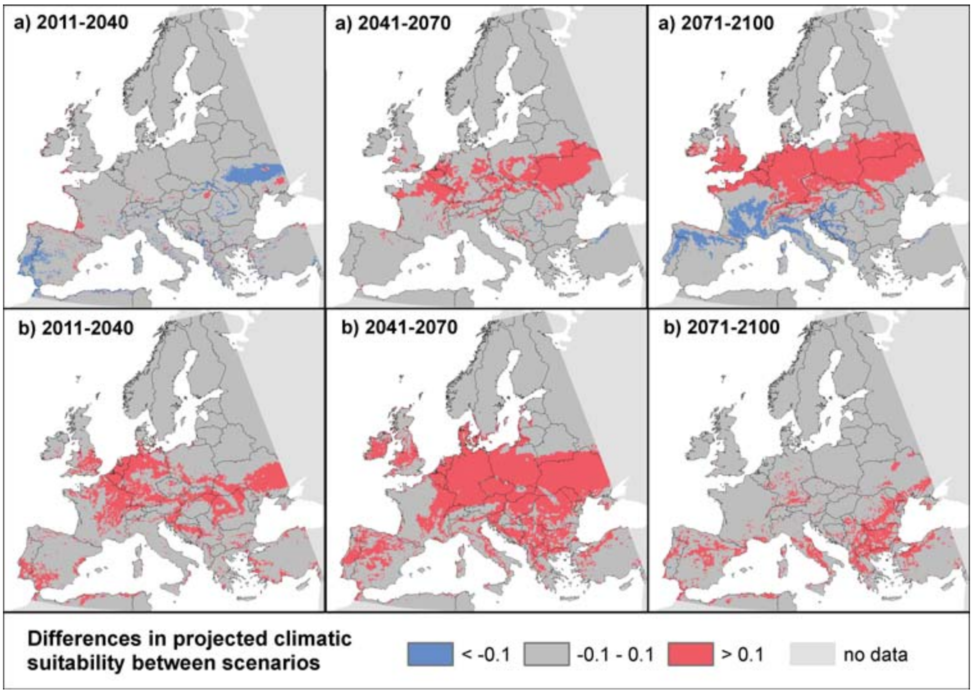
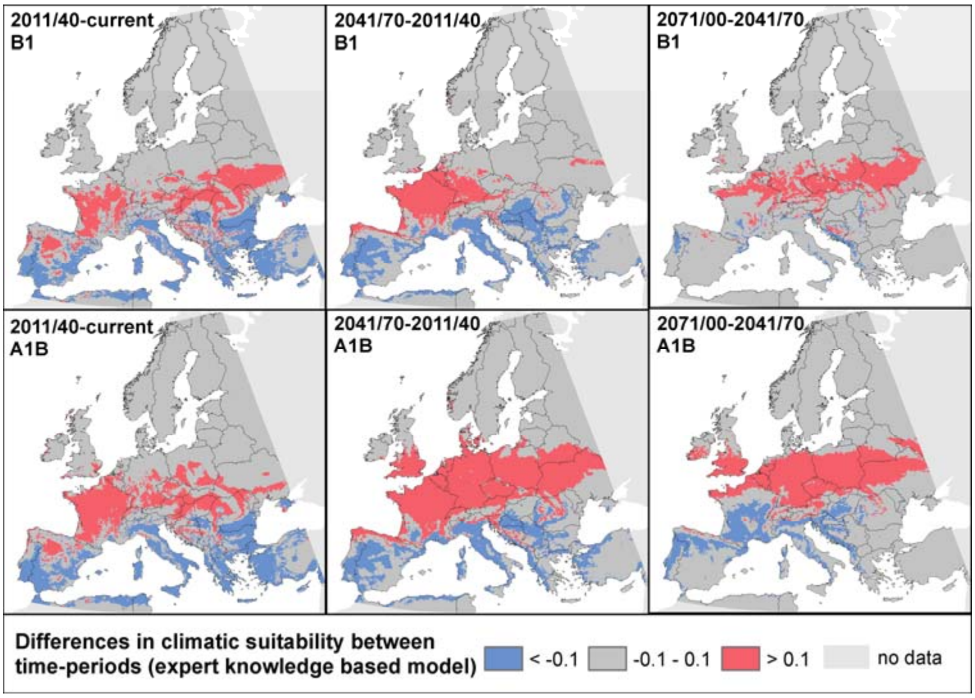
Supplemental Material Figures



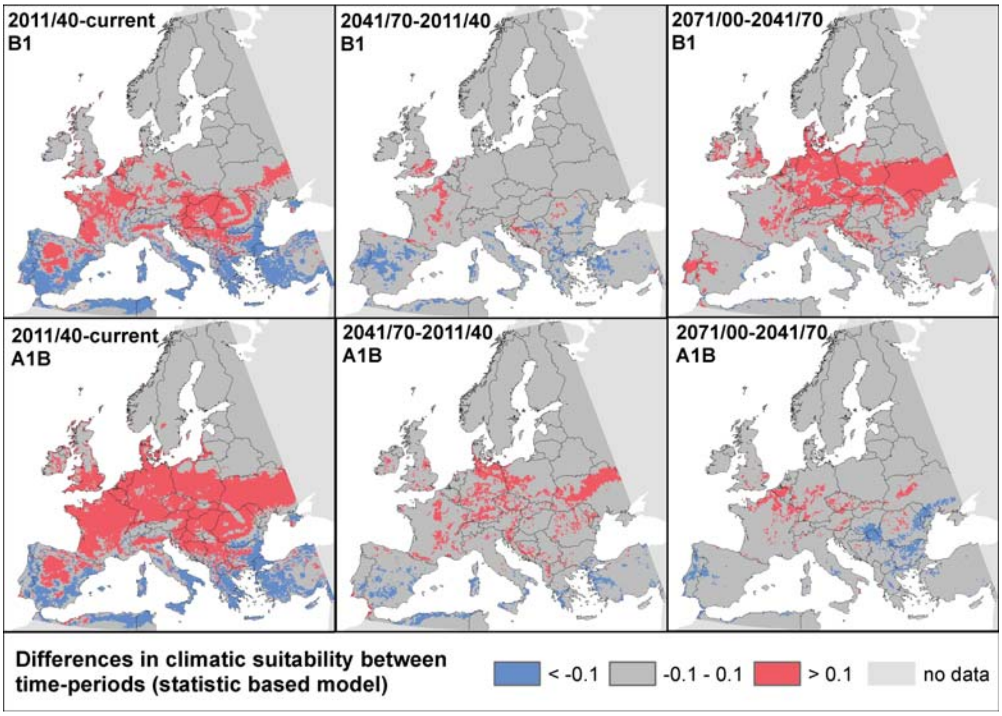
Suppl. Fig. 1: Differences in results between global-driven models. The computed values of climatic suitability from the statistic based model were subtracted from the results of the expert knowledge based model for each scenario and time period separately.



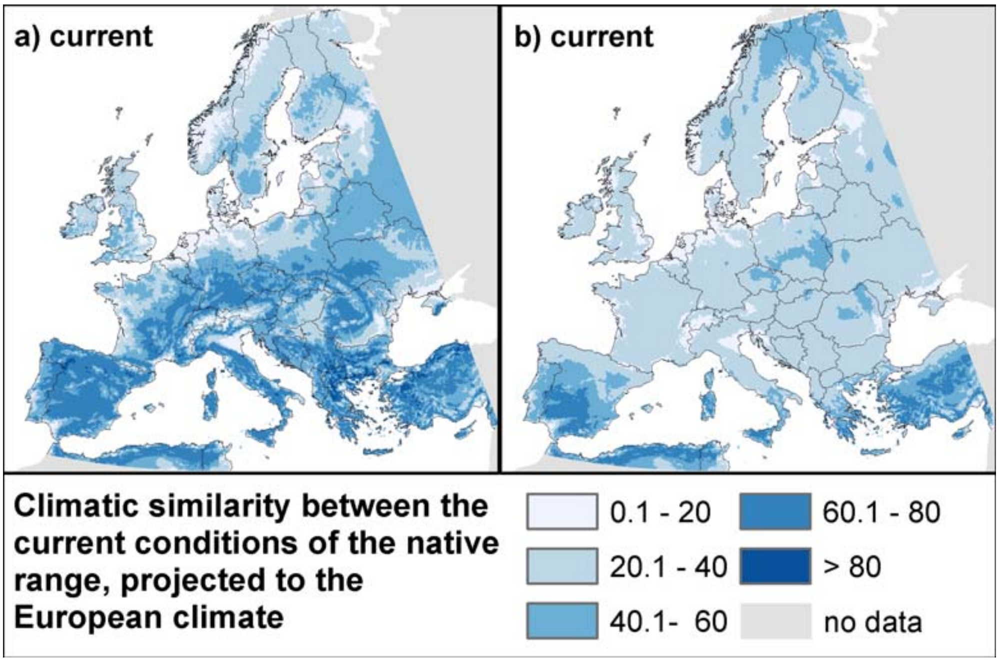
Suppl. Fig. 2: Differences in results between scenarios of global-driven models. The computed values of the climatic suitability for the B1 scenario were subtracted from the results of the A1B scenario for each model and time period separately. Differences are mapped for the a) expert knowledge based model and b) statistic based model.



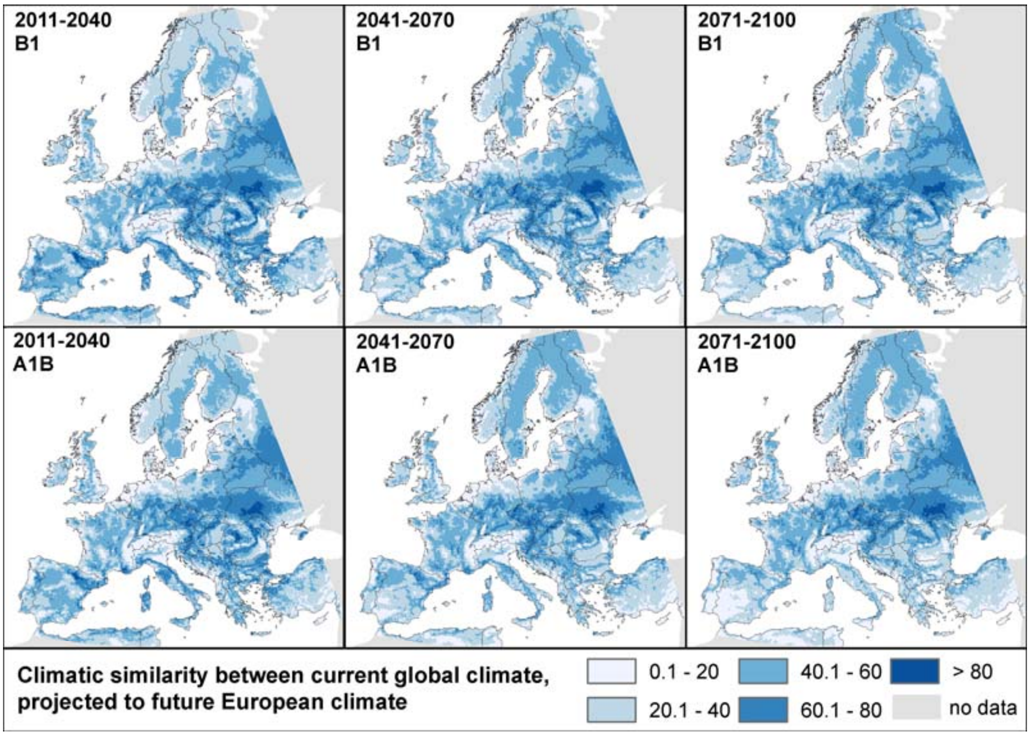
Suppl. Fig. 3: Changing climatic suitability in Europe, comparing the different time periods, calculated for the global-driven expert knowledge based model. The computed values for each time period were subtracted from the following one for each scenario separately.



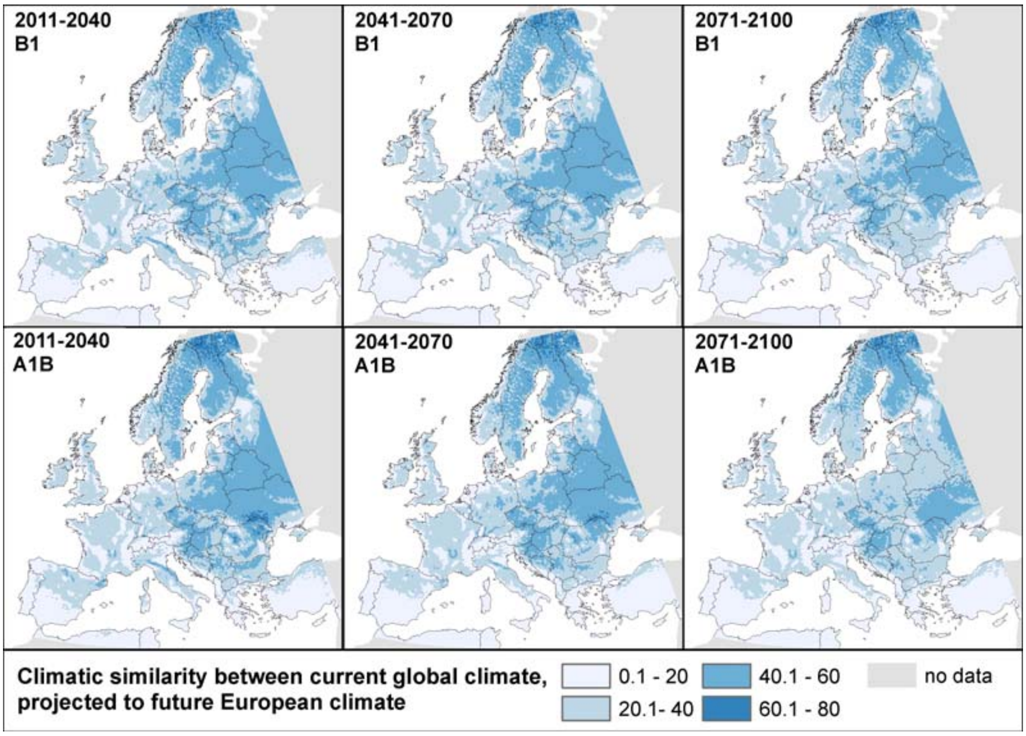
Suppl. Fig. 4: Changing climatic suitability in Europe, comparing the different time periods, calculated for the global-driven statistic based model. The computed values for each time period were subtracted from the following one for each scenario separately.



Suppl. Fig. 5: Climatic similarity detected via Multivariate Environmental Similarity Surface analysis by projecting the a) expert knowledge based and the b) statistic based native models to the current European conditions. High values represent high climatic similarity. Non-analogue climate was not detected.



Suppl. Fig. 6: Climatic similarity detected via Multivariate Environmental Similarity Surface analysis by projecting the global expert knowledge based models to future European climatic conditions. High values represent high climatic similarity. Non-analogue climate was not detected.



Suppl. Fig. 7: Climatic similarity detected via Multivariate Environmental Similarity Surface analysis by projecting the global statistic based models to future European climatic conditions. High values represent high climatic similarity. Non-analogue climate was not detected.

6.5 Article 5:

Modelling climatic suitability and dispersal for disease vectors: the example of a phlebotomine sandfly in Europe

With 1 Table and 2 Figures.

Abstract

Climate change is thought to assist spreading vector-borne diseases. During the last years, ecological niche modelling has been increasingly applied to predict the current distribution of disease vectors and their potential responses to climate change. However, sandflies and their transmitted diseases are only scarcely investigated via niche modelling.

Here, we propose a methodological approach to combine specific dispersal pathways for a sandfly species (*Phlebotomus perniciosus*) with the shifting climatic niche in the face of climate change. Current climatic suitability for the species was determined. Future projection is based on data of a regional climate change model. We defined a cost-surface assigned by the changing climatic suitability and expert knowledge on species dispersal ability. The derived travel costs correspond to the effort for the species to move across the landscape to climatically suitable habitats.

In future steps, least-cost paths will be calculated for this and further sandfly species with assumed spreading tendencies to Central Europe in the 21st century. Challenges are the integration of wind speed and biotic interactions.

1. Background: Sandflies as disease vectors in the light of climate change

Globally, vector-borne diseases pose a serious and increasing problem to public health. Today, almost one third of the emerging cases of infectious diseases are vector-borne [1]. Most of the disease vectors are ectothermal arthropods which cannot regulate their body temperature themselves. Therefore, climate change may be associated with spatio-temporal variations in occurrences of vector-borne diseases [2].

While mosquito-borne diseases such as Malaria and Dengue-fever attract much attention in science and policy, sandfly-borne diseases are often neglected. Nevertheless, especially leishmaniasis constitutes a serious human and animal health concern [3]. In Europe, phlebotomine sandflies have been thought to be restricted to the Mediterranean. However, in recent years a northward spread of the disease vector is documented in Italy [4]. Sandflies have recently even been caught north of the Alps in Central Europe [5], where they have not been recorded before. This may either indicate spreading tendencies from the Mediterranean or range expansions from potential small Central European refugial areas. It is noticed that even moderately increasing temperatures in the 21st century would provide further suitable areas for the infestations of sandflies in Germany [6]. Based on these findings the question arises which regions exlicitedly could provide suitable climatic habitats in the near future and whether sandflies are capable to disperse to these potential climatically suitable areas.

2. Ecological niche modelling of sandflies and sandfly-borne diseases

Correlative ecological niche models refer to the algorithms relating observed presences (and absences) of a species to values of ecological variables at those sites. The aim is to determine a species' known and inferred distribution in the environmental space. They have become increasingly important due to advanced modelling techniques for determining spatial distribution patterns of species and their potential responses to environmental changes [7]. The organisms (pathogen, vector and reservoir/host) involved in a chain of infection of a vector-borne disease are dependent on a specific environment. Therefore, niche modelling can be expected to be a useful tool for projecting occurrences of vector-borne diseases.

We conducted a literature survey (January 2011) in the ISI Web of Knowledge (literature databases: Web of Science, BIOSIS Previews and Medline) to search for peer-reviewed articles dealing with ecological niche models and their application to sandflies and sandfly-borne diseases. We found ten articles addressing explicitly this topic (Table 1).

Possible application of niche modelling for leishmaniasis or sandflies without concrete research was found in four articles [8]-[11]. In those reviews or reports, climate change is noticed to affect vector and disease occurrences, but without mentioning whether it will benefit spreading tendencies or not. Concrete modelling approaches are used in six original research papers [12]-[17]. America is addressed in the majority of the research articles as study area. Those authors who integrate climate change scenarios point out a potential spread of sandflies [12][17]. Nevertheless, for some *Lutzomyia* species (*L. intermedia* and *L. migonei*) endemic in South America only subtle improvements in climatic conditions are projected [16]. Europe is solely addressed in the work of Chamaille et al. (2010) [15]. There, ecological variables refer to the occurrence of canine leishmaniasis. Until today, explicit modelling of the current distribution of *Phlebotomus* species and of their potential shifts in spatial patterns of occurrence in the face of European climate change is missing.

Tab. 1: Peer-reviewed articles dealing with the topic of sandflies or/and sandfly-borne diseases and ecological niche modelling.

Reviews or reports	Vector/reservoir/disease	Climate change		
Peterson (2006) [8]	Sandflies/further vectors	Effect		
De la Roque et al. (2008) [9]	Leishmaniasis/further diseases	Effect		
Ready (2008) [10]	Sandflies/Leishmaniasis	Effect		
Colacicco-Mayhugh et al. (2009) [11]	Sandflies/further vectors	Effect		
Research	Vector/reservoir/disease	Climate change	Region	Software
Peterson and Shaw (2003) [12]	Sandflies	Positive effect	Brazil	GARP
Peterson et al. (2004) [13]	Sandflies	Not addressed	Brazil	GARP
Nieto et al. (2006) [14]	Leishmaniasis	Not addressed	Brazil	GARP
Chamaille et al. (2010) [15]	Leishmaniasis	Not addressed	France	MaxEnt
Colacicco-Mayhugh et al. (2010) [16]	Sandflies	Not addressed	Middle East	MaxEnt
Gonzales et al. (2010) [17]	Sandflies and reservoir	Positive effect	North America	MaxEnt

3. Case study: Combining climatic suitability and dispersal ability of *Phlebotomus perniciosus*

3.1. Current and projected climatic suitability for *Phlebotomus perniciosus*

Maximum entropy algorithm implemented in MaxEnt software [18] was used for modelling the current and projected distribution of *Phlebotomus perniciosus* (*P. perniciosus*) in this case study. MaxEnt is found to be superior in performance in comparison to other algorithms that are capable to handle presence-only data [7]. Recently, MaxEnt has successfully been applied to model the ecological niche of leishmaniasis as well as sandflies and substituted GARP as preferred modelling software (Table 1).

Bioclimatic variables [19] were used to predict the current distribution of *P. pernicosus*. The climatic niche was then transferred to the expected climatic conditions for the upcoming time-period (2011-2040; IPCC A1B scenario). The climatic projection is based on data of the regional climate model COSMO-CLM that covers entire Europe and is nested into the global model ECHAM5 [20]. Regional climate models integrate regional structures of land cover and topographical specifis in the dynamically downscaling procedure of their driving model [21]. Hence, studies concerning vector-borne diseases in climate change investigations benefit in particular from applied spatio-temporal highly resolved climate change projections [2][21]. Results are shown using the example of Bavaria (Southeast Germany).

Currently, no part of Bavaria provides suitable climatic conditions for *P. perniciosus* (fig. 1). Only in a small region in the outermost Northwest, climatic requirements of the species are almost fulfilled. Applying the A1B scenario for the next time-period (2011-2040), the river valley of the Main in the Northwest of Bavaria offers climatically suitable conditons. Then, also further parts in western Bavaria and central parts along the the river valleys Danube and Isar will almost fulfill climatic requirements. Mountaineous regions such as the Alps in the South and the Bavarian Forest in the East will persist to be completely climatically unfavourable for vector establishment.

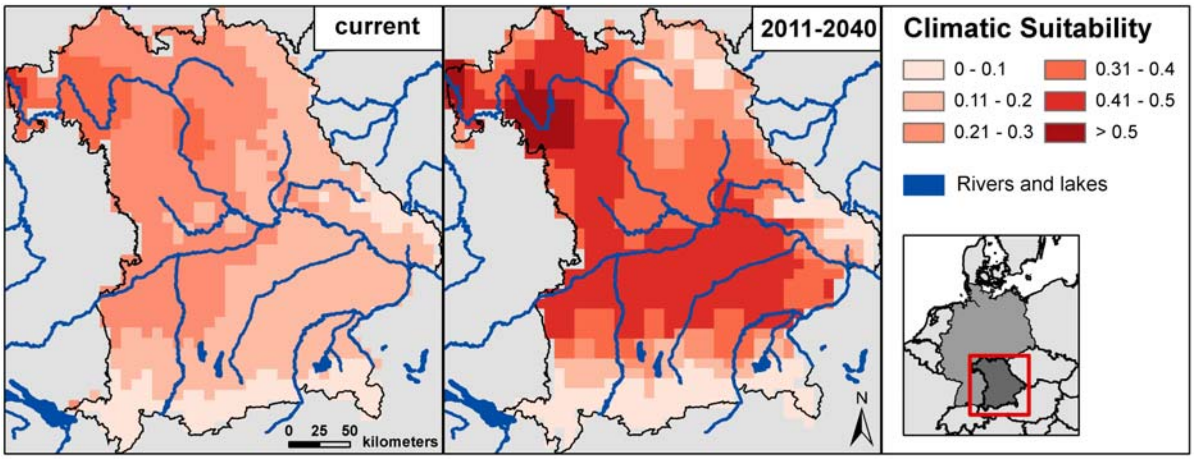


Fig. 1: Current and projected (2011-2040; A1B scenario) climatic suitability for *Phlebotomus perniciosus* in Bavaria (Southeast Germany). Values for climatic suitability range theoretically from zero to one. Establishment generally seems unlikely in regions with unfavourable conditions (values < 0.3). Climatically suitable regions are labelled by values > 0.5. Climatic suitability was modelled with MaxEnt based on a statistical selection of significant bioclimatic variables. 70% of the 271 spatially explicit species presence records were used to train the model. The remaining occurrence points were used to test model quality. The model was run 100 times and the results were averaged. The AUC value for the test data was 0.92 ($^{+}$/- 0.01) and indicated high model quality. An AUC value of 1 would represent a perfect fit.

3.2. Cost analysis and dispersal ability for *Phlebotomus perniciosus*

Least-cost analysis helps to identify the potential dispersal pathway, which is directed to climatically suitable habitats. The path function is based on graph theory and determines the shortest cost distance in a landscape between a specified origin and a target area. In ecology, least costs correspond to the least effort for a species that is moving through a landscape, assuming the species is capable to take the optimal dispersal pathway [22]. We defined a cost surface (fig. 2, a) that must be crossed by *P. perniciosus*. The cost surface includes, firstly, changing climatic suitability between the current conditions and the subsequent time-period (2011-2040; A1B) and, secondly, further expert knowledge on sandfly ecology and ability to disperse, such as flight range, topography and their depency on landcover [23]. River valleys for instance are attributed as prefered dispersal pathways (no costs), lower mountaineous regions exhibit a reduced ability to be crossed (mid to high costs; depending on altitude) and the highest regions above 2000 m above sea level are efficient barriers that exclude dipersal.

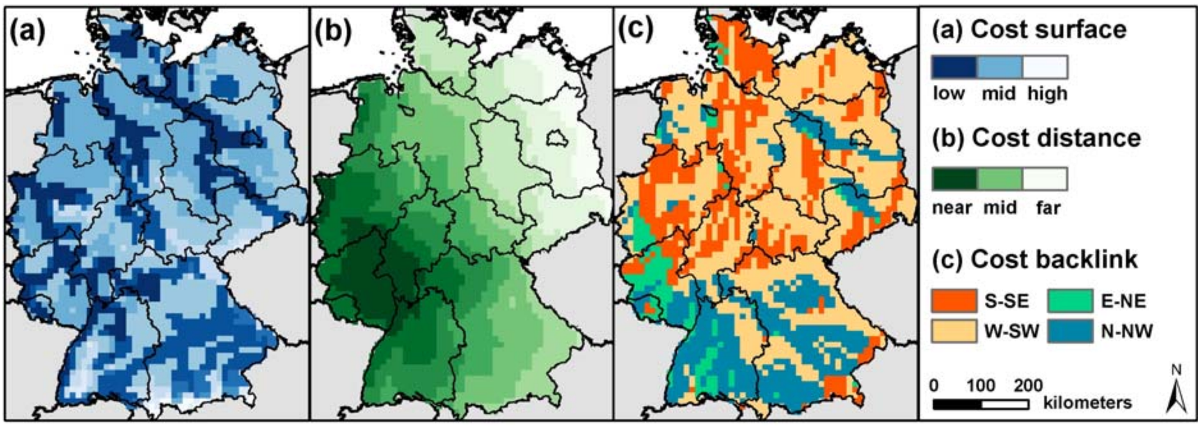


Fig. 2: Cost analysis for *Phlebotomus perniciosus*, aiming to estimate the species' dispersal probability in Germany. Least-cost path requires the following input. Initially, a cost surface is generated (a), where travel costs are indicated. Then, a specific cost distance (b) that is based on defined occurrence points and the cost surface to be crossed is determined. The cost backlink (c) is a qualitative expression and indicates for each raster cell, to which of the neighboring raster grids the costs are lowest. Based on the occurrence points as start, a defined target area and the calculated cost distance and backlink, the final path of least-cost can be defined.

Based on the cost surface, we calculated the cost distance (CD) (fig. 2, b) as accumulated shortest weighted distance ("travel costs") for movement between raster cells with CS_1 as first cost value of the starting grid cell defined by the cost surface and CS_n as end point. For vertical and horizontal movement CD was calculated by:

$$CD_{orth} = (CS_1+CS_2)/2 + (CS_2+CS_3)/2 + ... + (CS_{n-1}+CS_n)/2$$

and for diagonal movement in the same manner (but with length correction) by:

$$CD_{diag} = ((CS_1+CS_2)/2 + (CS_2+CS_3)/2 + ... + (CS_{n-1}+CS_n)/2))\ 1.414214.$$

Cost distance and spatial distance are not necessarily similar (fig. 2, b). The cost distance is for instance relatively far to southeastern Bavaria, although *P. perniciosus* is present in northern Italy. Here, the Alps cause high costs to cross. The species is furthermore located in western and southwerstern parts of Europe. As a consequence, the cost distance is nearest to western Germany as there are only little cost barriers for species movement. Values of cost distance increases to northeastern Germany. The cost backlink (fig. 2, c) of each raster cell is determined by the neighbouring raster cell to which costs are cheapest and marked in direction to this cell. Central, northern and northeastern Germany mainly show backlinks to western, southwestern and southern directions. Only few southern and norhtern Bavarian areas indicate a backlink to southern direction, although many records are documented in northern Italy (not presented here). Most parts of Bavaria, especially the central parts, show backlinks to western and northwestern regions. Hence, it is likely that *P. perniciosus* may disperse from western Europe towards Bavaria. A direct northward spread from Italy may be blocked by the Alps.

4. Discussion and outlook

Here, we propose a method to improve conventional niche modelling with integrated species-specific dispersal ability. Based on this, the least-cost path as most likely spatial trajectory of the species dispersing to Bavaria can be calculated on basis of the cost distance and cost backlink for *P. perniciosus*. Climate change alters dispersal and movement patterns of insects. It has to be acknowledged that the direction of movement may not be optimal in all cases. Especially, dispersal behaviour of individuals between populations may differ from the general tendency of the metapopulation level [22].

Nevertheless, ecological niche modelling in combination with least-cost path analysis offers the opportunity to detect whether sandflies are able to occupy their potential suitable habitats by natural dispersal. It is uncertain, if humans assist the migration of sandflies directly. Hence, such potential accidental carry-overs are not considered in this study. Spreading tendencies for other *Phlebotomus* species can be assumed as well. Probably, these species may also disperse to Central Europe. Knowledge concerning biotic interactions and the competitive ability of the species in particular is missing. Therefore, experiments and field observations must be intensified in order to reduce uncertainty. Integrating biotic interactions into environmental niche modelling under climate change conditions would yield more realistic projections [24].

Comparing climate change scenarios and model algorithms will reduce the uncertainties of species range shifts [25]. Moreover, wind speed as well as differences in potential flight ranges have to be considered. Wind is not a mere vector but affects the behaviour of the species. Sandflies reduce their flight acitivity with increasing wind speed [26]. Generally, future research and in particular modelling approaches will require more knowledge on sandfly ecology and biology. Our approach represents a powerful tool for detecting regions with potential infestations and establishment of disease vectors. Already early stages of risk exposure can be identified. Hence, efficient monitoring and surveillance activities can be specifically directed to these target areas.

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6.6 Article 6:

Combining climatic projections and dispersal ability of phlebotomine sandflies: A methodological task to estimate vector responses to climate change

With 3 Tables and 3 Figures in the main text as well as 1 Table 2 Figures in the Supplemental Material.

Abstract

Background

In the Old World, sandflies of the genus *Phlebotomus* are known vectors of *Leishmania*, *Bartonella* and several viruses. Recent sandfly catches and autochthonous cases of leishmaniasis hint on spreading tendencies of the vectors towards Central Europe. However, studies addressing potential future distribution of sandflies in the light of a changing European climate are missing.

Methodology

Here, we modelled bioclimatic envelopes using MaxEnt for five species with proven or assumed vector competence for *Leishmania infantum*, which are either predominantly located in south-western (*Phlebotomus ariasi, P. mascittii* and *P. perniciosus*) or south-eastern Europe (*P. neglectus* and *P. perfiliewi*). The determined bioclimatic envelopes were transferred to two climate change scenarios (A1B and B1) for Central Europe (Austria, Germany and Switzerland) using data of the regional climate model COSMO-CLM. We detected the most likely way of natural dispersal ("least-cost path") for each species and hence determined the accessibility of potential future climatically suitable habitats by integrating landscape features, projected changes in climatic suitability and wind speed.

Results and relevance

Results indicate that Central European climate will become increasingly suitable especially for those vector species with a current south-western focus of distribution. In general, highest suitability of Central Europe is projected for all species in the second half of the 21st century, except *P. perfiliewi*. Nevertheless, we show that sandflies will hardly be able to occupy their whole provided climatic niche due to limited dispersal ability. A northward spread of species with south-eastern focus of distribution may be constrained but not completely avoided by the Alps. Our results can be used to install specific monitoring systems to the projected risk zones of potential sandfly establishment. This is urgently needed for adaptation and coping strategies against the emerging spread of sandfly-borne diseases.

Authors' summary

Growing evidence exist on the emergence of sandfly-borne diseases in the light of climate change. Determining the principle responses of phlebotomine sandflies to climatic changes supports our understanding of future regions that will be threatened by new-establishments of this important group of disease vectors.

The aim of this paper is to combine projected climatic suitability for five *Phlebotomus* species in Central Europe (Austria, Germany and Switzerland) for different time-periods during the 21st century with their potential spreading capacity to disperse to climatically suitable areas. We indicate that Central European climate will develop towards the preferred bioclimatic niche of the species, especially from mid-century onwards. Nevertheless, we also elucidate within this study, that sandflies will hardly be able to occupy the whole areas which will provide suitable climatic conditions due to their limited natural dispersal ability.

Our approach provides a framework to combine statistical modelling techniques with expert knowledge on species ecology. Indications of future occurrences of disease vectors may help to initiate surveillance systems in specific regions at an early stage of risk exposure. Hence, the threat of the climate-driven spatial extension of disease vectors and consequently of potentially emerging vector-borne diseases can be counteracted.

Keywords

global change, global warming, leishmaniasis, species distribution model, vector-borne disease

1. Introduction

Globally, the number of vector-borne infections in humans and animals increases rapidly, meanwhile causing almost one third of all cases of emerging infectious diseases [1]. In the Old World, sandflies of the genus *Phlebotomus* (*Phlebotomus spp.*) serve as vectors for sandfly-borne pathogens such as *Leishmania*, *Bartonella* and several viruses (e.g. *Phlebovirus*, *Vesiculovirus* and *Orbivirus*) [2, 3, 4]. Sandfly-borne diseases and in particular visceral leishmaniasis are a main public health concern [5], which demands more attention in science and policy [6]. While the spatial distribution of leishmaniasis seems to expand in southern parts of Europe [7, 8], first cases of autochthonous origin are recently reported from Central Europe [9, 10, 11], where this disease was not endemic in the past.

The presence of sandflies as vectors is mainly regulated by the species' climatic requirements on temperature and humidity or soil moisture, respectively [3, 12, 13, 14, 15]. Temperature and humidity are also the main factors regulating the altitudinal structure of sandfly occurrences [16]. It is known that sandflies react very sensitive to wind speed and prefer breeding sites sheltered from wind [17, 18, 19, 20]. Beyond that, high wind speed decreases or even excludes flight activity [17, 21].

As climate is expected to change rapidly in the 21st century, sandflies are forced to react promptly. For this purpose, the advantages of ecological niche modelling to infer geographic distribution for sandflies have been demonstrated on the example of *Lutzomyia* species (*Lutzomyia spp.*) in the New World [22]. For the first time, Peterson and Shaw [23] integrated climate change scenarios in order to project future distribution of *Lutzomyia spp.* in Brazil. Recently, range expansions for sandflies of the genus *Lutzomyia* have also been projected for North America in the face of climate change [24].

For Europe, surprisingly, only few studies estimated the risk of potential range expansions of sandflies in the face of climate change [e.g. 25, 26]. The need for such studies is supported by the first sandflies catches in Central Europe. *P. mascittii* has been caught in Austria on the frontier to Slovenia [26]. Furthermore, *P. mascittii* is reported from the Upper Rhine Valley in the outermost southwest of Germany near the French border [28]. *P. perniciosus* seems to be established in the German state of Rhineland Palatinate [29]. These findings may either indicate spreading tendencies from the Mediterranean or range expansion from small Central European refugial areas, which may have already been occupied by the species during the Holocene climate optimum about 6 500 years ago [30]. Possibly sandflies has occupied more areas in the past than it was noticed.

For Austria, establishment of sandflies in formerly non-endemic areas can be expected already by moderately increasing temperatures in the 21st century [25]. Recently, Fischer et al. [26] estimated potential temperature-derived establishment of sandflies in Germany by transferring the required temperature during their activity phase and annual mean temperature for persistence to the expected future climate conditions in Germany using data of a spatio-temporal highly resolved regional climate model. But up to now, projections of the current and climate-driven potential future distribution of *Phlebotomus spp.* which additionally consider species-specific dispersal ability are missing. Here, we close this gap and hypothesize:

1) Climatic suitability for *Phlebotomus spp.* will generally increase within the 21st century. The climatic requirements for sandflies with current (south-) western European regions of distribution are supposed to be fulfilled in the south-westernmost parts of Central Europe in the 21st century. Otherwise, species with a south-eastern focus of distribution are thought to find favourable conditions in the south-easternmost Central European regions.
2) Species with current (south-) western focus of distribution may spread north-eastwards as they are not hampered by natural dispersal barriers. Instead, the Alps will restrict a direct range expansion for species that are currently distributed in the (south-) east of Europe.

2. Methods and material

2.1 Bioclimatic envelope modelling of species distributions

2.1.1 Species presence records and climatic variables

Documented presence records of *Phlebotomus* species were taken from literature. Most of the occurrence data were provided by Artemiev and Neronov [31]. This was done by digitizing their analogue maps of presence records. Additional presence records were taken from peer-reviewed articles by searching within the literature databases ISI Web of Science, Medline and Biosis Previews from 1984 onwards. Number of presence record are listed in Table 1.

Current bioclimatic data were taken from http://www.worldclim.org [32] in 5 Arcmin resolution. The 19 bioclimatic variables are derived from monthly temperature and rainfall values. Higher spatial resolution would not correspond to the spatial accuracy of occurrence data for sandfly species. We extracted the area of Europe, the Middle East and northern Africa (regions that contain our presence records) from all bioclimatic variables.

Selection of the most important bioclimatic variables was done via Jackknife test. We considered results of the Jackknife tests for the model training gain for all variables in isolation and for the remaining set of variables when the isolated variable is dropped from the set [33]. To reduce collinearity in the data set [34] those variables that had a Pearson correlation coefficient $r > 0.7$ with any other higher-ranking variable in the results of the Jackknife test variables were removed. We applied the variable selection procedure separately for each species.

The high-resolution regional climate model COSMO-CLM (CCLM) was applied for future projections in Europe. This dynamically downscaled model is nested into the global model ECHAM5 [35]. In contrast to their driving global models, regional climate models integrate topography and can project climate change at a much higher spatial resolution. This enhances the quality of studies on climate change impacts on disease vectors and vector-borne diseases in general and disease vectors in particular [36]. Our future projections refer to the IPCC A1B and B1 emission scenarios for greenhouse gases [37]. In short, the A1B scenario is characterized by a rapid economic growth in an integrated world with a balanced technological emphasis on fossil and non-fossil energy sources. The B1 scenario is based on the same economic growth as in A1B but with a more rapid change towards a service and information economy. Consequently, warming tendencies are projected to be stronger in the A1B scenario. Climatic data were averaged over time periods 2011-2040, 2041-2070 and 2071-2100 for each scenario separately. Bioclimatic variables for modelling future climate projections were calculated in the same way as they are provided by http://www.worldclim.org [32] for current conditions.

Non-analogue climatic conditions are a problematic issue in projections [38]. We used a Multivariate Environmental Similarity Surface (MESS) analysis introduced by Elith et al. [39] to detect regions where projections are inappropriate due to dissimilarity in values of the used variables for training and projecting the model [40]. The MESS analysis measures the similarity between those environments used to train the model and the new projected environments for any grid cell [39, 40].

Occurrence records and climatic data were prepared in ArcGIS 10.0, correlation analysis was performed in PASW Statistics 18, Jackknife test to measure the variable's importance is implemented in MaxEnt 3.3.3e.

Tab. 1: Number of species presence records, AUC-values, and training gain determined by Jackknife test for the selected bioclimatic variables. AUC-values are a threshold-independent model quality criterion and range from 0 to 1 (perfect fit). Useful models yielded in AUC-values above 0.7, where excellent models achieve at least AUC-scores above 0.9. Training gains for the selected variables by using only this variable for the model (upper value) and if the specific variable is removed for the rest of the variable set (lower value). For the species with current (south-) western focus of distribution (*P. ariasi*, *P. mascittii* and *P. perniciosus*) BIO 11 (Mean temperature of the coldest quarter) represents the most important variable. This is indicated by the highest training gain of the model by using only this variable and the lowest training when this variable is removed from the set of variables. The drop of BIO 10 (Mean temperature of the warmest quarter) from the set of variables instead seems to lower training gain most for the species with (south-) eastern focus of distribution. BIO 13 (Precipitation of the wettest month) is identified as most important variable when used in isolation for *P. neglectus*, while BIO 11 seems to be most influencing factor in isolation regarding the occurrences of *P. perfiliewi*.

		P. ariasi	***P. mascittii***	***P. perniciosus***	***P. neglectus***	***P. perfiliewi***
Presence records		79	66	273	90	124
AUC (Training data)		0.94	0.97	0.92	0.92	0.96
AUC (Test data)		0.93	0.93	0.90	0.89	0.95
Model training gain for variables used in isolation (upper value), and for the remaining data set if the specific variables is dropped from the set (lower value)						
BIO 10	Mean temperature of the warmest quarter	1.50 0.51	1.91 0.57	1.18 0.65	0.98 0.16	0.81 0.10
BIO 11	Mean temperature of the coldest quarter	1.35 1.15	1.74 1.24	1.30 0.67	0.70 0.67	0.87 0.49
BIO 12	Annual precipitation	- -	1.94 0.95	- -	- -	0.88 0.24
BIO 13	Precipitation of the wettest month	- -	- -	1.35 0.73	- -	- -
BIO 16	Precipitation of the wettest quarter	- -	- -	1.36 0.70	- -	- -
BIO 17	Precipitation of the driest quarter	1.43 0.61	1.88 0.78	- -	0.97 0.29	- -
BIO 18	Precipitation of the warmest quarter	1.45 0.73	- -	- -	0.98 0.32	0.86 0.32
BIO 19	Precipitation of the coldest quarter	1.38 0.73	1.85 0.78	1.29 1.00	0.94 0.43	0.93 0.33

2.1.2 Model runs

All models were generated using the maximum entropy algorithm. Maximum entropy basically is a machine-learning technique combining species occurrence data with detailed climatic and environmental datasets [41, 42]. This algorithm implemented in MaxEnt software computes a probability distribution covering the study area that satisfies a set of constraints which are derived from environmental conditions at species presence records. The algorithm then chooses a distribution with maximum entropy within all possible distributions [41]. MaxEnt generally performs better than other presence-only or pseudo-presence-only models [41, 43, 44], which becomes especially apparent by using small numbers of species occurrence records [45, 46, 47]. Furthermore, the influence on spatial errors in species occurrences on model performance of MaxEnt due to e.g. inaccurate georeferences is less severe in comparison to other algorithms [48].

We used the following settings for model runs: Regularisation modifiers were set to 1. Maximum number of iterations was set on 15500. A higher number did not enhance mode quality criteria. Feature types were automatically selected depending on the training sample size (auto feature) and the convergence thresholds were 0.00001. The maximum number of background points was set to 10 000 as more background points do generally not enhance model quality criteria [42]. For each species, models were replicated 100 times for each species and the results were finally averaged. To evaluate model accuracy we randomly selected 70 % of the occurrence data to train each model and used the remainder to test each model as suggested by Araujo et al. [49]. Most of the settings have been adapted from a previous study concerning projections of climatic suitability for *Aedes albopictus* in Europe [50].

We used both, threshold-dependent as well as threshold-independent quality criteria. Eleven binary omission rates were calculated as the proportion of test respective training points that were not predicted at a threshold probability that equalled the minimum probability on any pixel containing an occurrence point [42]. Those were tested using one-sided p-values for the null hypothesis that test points are predicted no better than by a random prediction with the same fractional predicted area. This was practiced previously for the evaluation of model results for *Lutzomyia spp*. [24]. Furthermore, model performance was evaluated using area under the receiver operator curve (AUC) statistics, which compares how likely a random presence site will have a higher predicted value in the model than a random absence [43]. The receiver operator curves appeals to be independent on a user-defined threshold for determining presence versus absence. We limited the study area to the geographic extent of the sampling distribution (see Section 2.1.1) in order to avoid inflated AUC scores that are associated with geographical extents that go beyond the presence environmental domain [51, 52]. All models were built in the latest available version (MaxEnt 3.3.3e).

2.2 "Least-cost path" for species dispersal

Species´ dispersal ability varies strongly with landscape structure [53]. We used a least-cost path analysis based on graph theory [54, 55, 56] to determine the most likely way for *Phlebotomus spp.* to move across a spatio-temporal changing landscape. The path function indicates the least efforts ("costs") for a species in moving through any particular cell in the respective landscape [57, 58, 59]. Least-cost path analyses are frequently used to determine potential dispersal pathways for mammals [60, 61, 62, 63] but has also been practiced for insects [58].

2.2.1 Definition of cost surfaces and calculation of distances and backlinks

Our aim was to identify the species-specific least-cost pathway for potential movement of the five *Phlebotomus spp.* to each of the modelled climatically suitable habitats in the 21st century for the time-periods and for each scenario, respectively. Therefore we created three different species-specific cost surfaces. The first cost-surface was generated for costs arising for the species movement to climatically suitable habitats of the upcoming time-period (2011-2040). The second one was built for the movement up to mid-century (2041-2070) and finally to the end of the century (2071-2100). The respective cost factors are listed in Table 2. Each cost surface includes temporarily stable and varying environmental land-scape features.

Tab. 2: Cost factors within the defined cost surfaces for *Phlebotomus* species. Factors are surfaces were generated by considering both, spatio-temporal stable and variable environmental conditions within the 21st century. Two cost factors are stable within the 21st century: River valleys are considered as the preferred breeding sides for sandflies [2]. Hence, regions which include river valleys are attributed with costs. Sea as absolute barrier cannot be crossed. Beyond, an altitudinal cost structure was developed in accordance to the preferred elevation of sandflies [2]. Two factors vary in the 21st century: MaxEnt-values of climatic suitability range theoretically from 0 (unfavourable conditions) to 1 (perfect conditions). These values are classified and attributed with costs in accordance to the suitability; the lower the suitability the higher the costs. This factor is species-specific. Cost factors for wind speeds are related to the observations concerning wind-speed dependent flight activity. They are taken from findings of Lane [94] concerning the highest flight activity up to 1.5 m/s; from Quate [95] who observed a reduced flight activity between 1.5 - 2.5 m/s and Roberts [96] who noticed no flight activity above wind speeds of 3.5 m/s. Climatic suitability and wind speed were averaged over two subsequent time-periods.

Landscape feature	Value or area	Cost factor
Altitude [m.a.s.]	0 - 800	0
	801 - 1200	1
	above 1201	2
Further landscape features	River valleys	0
	Non-valleys	4
	Sea	-
Climatic suitability (averaged over two subsequent time-periods)	0.81 - 1.0	0
	0.61 - 0.8	1
	0.41 - 0.6	2
	0.21 - 0.4	3
	0.01 - 0.2	4
Wind speed (averaged over two subsequent time-periods)	0.01 - 1.5	0
	0.76 - 2.5	1
	2.51 - 3.5	2
	above 3.5	3

a) Environmental landscape features that do not to change in the 21st century were consequently considered as constant (stable) cost factors in all created cost surfaces: River valleys provide the preferred breeding sites due to high temperatures and moist and humid soils [64, 65] and can hence be considered as preferred dispersal corridors. We buffered this features with a distance of ten kilometres for consistency with the climatic data and attributed it without costs. Only the surrounding landscape was addressed with costs. Additionally, increasing altitude was attributed with rising costs [2]. Sea surfaces and high mountains were considered as "absolute barriers" which cannot be crossed. The costs were the same in all cost surfaces throughout the 21st century and for all species.

b) Within the cost surfaces temporally varying environmental landscape features in the 21st century (due to climatic effects) were integrated: The species-specific changing climatic suitability of an area between two subsequent time-steps (current-2011/2040, 2011/2040-2041/2070, 2041/2070-2071/2100) was integrated as a further cost factor in the respective cost surfaces. For this purpose the projected climatic suitability was averaged over two subsequent time-periods. The values of climatic suitability were taken from MaxEnt-models. Regions that have to be overcome between two time-periods but would persist to remain outside of the preferred bioclimatic niche were attributed with higher costs. We furthermore integrated wind speed in the cost surface as sandflies react very sensitive to high wind speed by reducing flight activity [17, 21]. Data of current and projected wind speed (for A1B and B1 scenario) are taken from CCLM. Data were averaged for the equivalent time-periods, which were already used to model climatic suitability for the single sandfly species (2011-2040, 2041-2070 and 2071-2100). It is realized that sandflies predominantly prefer to be active near the soil surface (up to one meter above the ground) and usually do not exceed two meters above the ground [64]. The provided data of wind speed, however, are given for a height of ten meters above the ground. In consequence, we applied the wind profile power law that is derived from the logarithmic wind profile equation for the lower atmosphere in order to relate wind speeds given at one height to another [66]. The equation to calculate wind speed in one meter was calculated for each time-period by:

$V_{1m} = V_{10m} * (h_{1m}/h_{10m})^{RF}$,

with V_{1m} representing wind speed in one meter, V_{10m} representing the (given) wind speed in ten meter above the ground, $h_{1m}/h_{10m} = 0.1$ (height in meter you want to obtain the velocity, divided by the height for which the velocity is given) and RF (roughness factor). Land cover decreases the near surface wind speed due to the roughness of the landscape features. The RF should not be considered as constant as it varies for different surface obstacles, which must be taken into account [67]. Therefore, we integrated land cover data provided by http://earth.esa.int [68] for the calculation of the near-surface wind speed. We reclassified the provided map of land cover in Europe into three classes (with different RF) proposed by Kleemann and Meliss [69]. In our study, land cover is considered not to change during the 21st century:

1. Low RF (=0.16): cropland, grassland vegetation, bare areas
2. Mid RF (=0.28): different types of forests, vegetation dominated by trees and rural communities
3. High RF (=0.40): urban areas

Then, the wind speeds were averaged over two subsequent time-periods of species movement as it was done for the modelled climatic suitability. For all species, the development in wind speed was attributed with equal costs (Table 2). Due to these temporal factors (changing climatic suitability and wind speed) different cost surfaces were generated.

2.2.2 Determining the least-cost path based on the generated cost surfaces

Determining the least-cost path requires cost distance and cost backlink calculations as inputs which are both assigned on the basis of the defined cost surfaces. Cost distances were calculated in order to account for the minimal accumulated travel costs that accrue by travelling with increasing distance from the source to the target area [63]. The cost backlinks indicate the direction for each grid cell to which direction the costs are cheapest. Details on calculations of cost distance and assignment of cost backlink can be found elsewhere [see 70].

Our initial source grid for species occurrences as starting points included all areas with documented current European presence records. As destination area we defined Central Europe (Austria, Germany and Switzerland) for all species throughout the 21st century. The natural dispersal ability of sandflies is limited. Generally, the flight range around their breeding area is about one kilometre [71]. The flight range for *P. ariasi*, however, reaches two kilometres [17]. In the Mediterranean, sandflies are able to establish up to three generation each year [2]. Therefore we limited the maximal range expansion for *P. ariasi* to six kilometres per year (180 km/30 year time interval) and for the other sandfly species to three kilometres per year (90 km/30 year time interval) for moving through any particular cost surface.

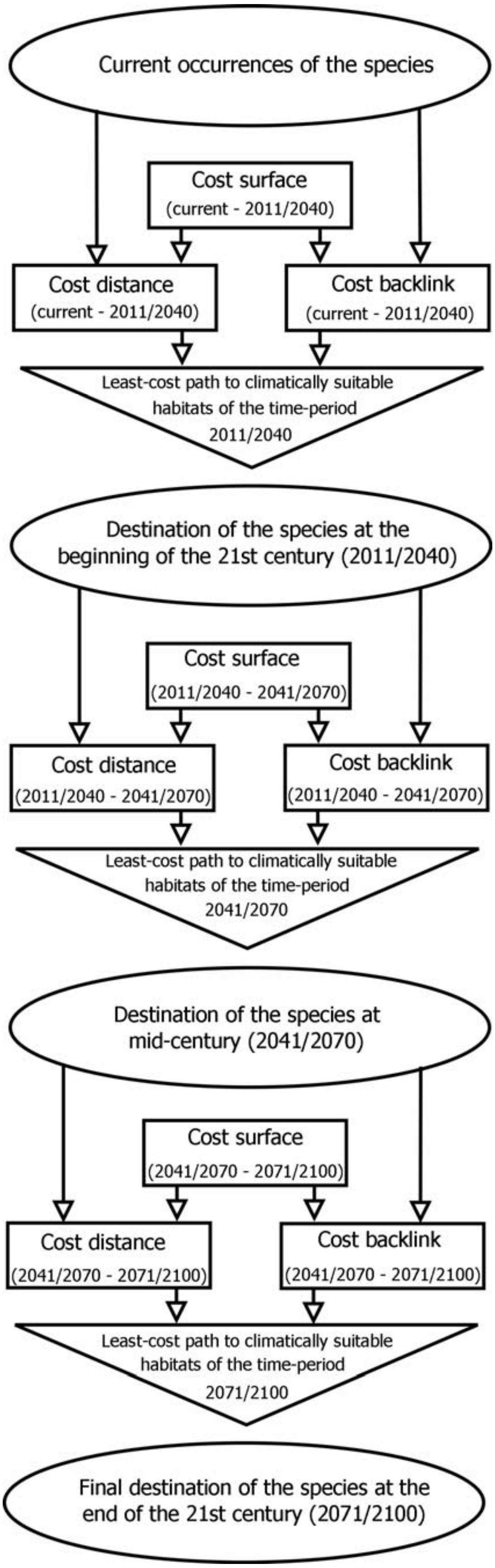

Fig. 1: Principle of the least-cost analysis to determine the most likely way of natural dispersal for the species.

In our study, species are able to establish in climatically suitable habitats indicated by values higher than 0.5 of the MaxEnt models. This typically corresponds to values of the climatic suitability on the respective presence records [42]. Therefore those regions were indicated as species occurrences of the subsequent time period (2011-2040) that overtop the threshold of suitability and that are connected via the initial least-cost path. Those areas were defined as new starting points for the least-cost path to the expected climatically suitable habitats at mid-century (2041-2070). This procedure was repeated for a third time in order to determine reachable location of the sandfly species at the end of the 21st century (2071-2100). The principle is illustrated in Figure 1.

Least-cost analyses were performed using distance functions within the "Spatial Analyst Tool" implemented in ArcGIS 10.0 after using the "Raster Calculator" for the definition of the cost surfaces.

3. Results

3.1 Model results for species´ climatic suitability

AUC-values yielded in high scores for five species (Table 1). Binominal tests indicated that tests points are predicted better by the model than a random prediction with the same factional predicted area at the significance level $p < 0.01$. Our projections seem not to be affected by non-analogue climate as this was not detected by MESS analysis.

In general, climatic suitability can be expected to increase for all species in the 21st century (Table 3, Figure 2, Supplemental Material Table 1 and Supplemental Material Figure 1). This is in accordance with the first part of our first hypothesis assuming increasing climatic suitability for the species in Central Europe. Nevertheless, we cannot completely verify the second part of our first hypothesis of more favourable conditions in the (south-) western parts for species with (south-) western focus of distribution and the opposite for species which are currently distributed in (south-) eastern Europe (see Sections 3.2.1 and 3.2.2).

Overall, projections based on the A1B scenario represent higher suitability for species in comparison to projection of the B1 scenario (Table 3 and Supplemental Table 1). Nevertheless, the spatial patterns of potential climatically suitable habitats remain to be the same for both scenarios. The detailed annotation of climatic suitability in the following refers to the A1B scenario.

Tab. 3: Current and projected mean values of climatic suitability for Central Europe with standard deviation in brackets. Projections refer to the A1B scenario.

		P. ariasi	*P. mascittii*	*P. perniciosus*	*P. neglectus*	*P. perfiliewi*
Central Europe	current	0.14 (+/- 0.10)	0.28 (+/- 0.19)	0.25 (+/- 0.14)	0.23 (+/- 0.10)	0.10 (+/- 0.06)
	2011-2040	0.32 (+/- 0.13)	0.30 (+/- 0.20)	0.35 (+/- 0.19)	0.31 (+/- 0.15)	0.10 (+/- 0.13)
	2041-2070	0.38 (+/- 0.17)	0.40 (+/- 0.23)	0.46 (+/- 0.20)	0.38 (+/- 0.14)	0.19 (+/- 0.17)
	2071-2100	0.54 (+/- 0.17)	0.47 (+/- 0.25)	0.52 (+/- 0.22)	0.49 (+/- 0.16)	0.33 (+/- 0.23)
Austria	current	0.02 (+/- 0.02)	0.26 (+/- 0.17)	0.09 (+/- 0.10)	0.18 (+/- 0.13)	0.04 (+/- 0.03)
	2011-2040	0.17 (+/- 0.22)	0.22 (+/- 0.19)	0.17 (+/- 0.20)	0.23 (+/- 0.20)	0.22 (+/- 0.22)
	2041-2070	0.29 (+/- 0.19)	0.28 (+/- 0.24)	0.26 (+/- 0.23)	0.36 (+/- 0.20)	0.28 (+/- 0.28)
	2071-2100	0.39 (+/- 0.21)	0.28 (+/- 0.23)	0.33 (+/- 0.26)	0.46 (+/- 0.20)	0.36 (+/- 0.32)
Germany	current	0.17 (+/- 0.08)	0.32 (+/- 0.18)	0.31 (+/- 0.10)	0.24 (+/- 0.08)	0.12 (+/- 0.05)
	2011-2040	0.36 (+/- 0.11)	0.36 (+/- 0.16)	0.42 (+/- 0.14)	0.34 (+/- 0.11)	0.07 (+/- 0.06)
	2041-2070	0.43 (+/- 0.11)	0.48 (+/- 0.18)	0.53 (+/- 0.12)	0.38 (+/- 0.09)	0.17 (+/- 0.12)
	2071-2100	0.60 (+/- 0.10)	0.55 (+/- 0.18)	0.60 (+/- 0.12)	0.49 (+/- 0.12)	0.34 (+/- 0.20)
Switzerland	current	0.07 (+/- 0.08)	0.21 (+/- 0.18)	0.13 (+/- 0.15)	0.23 (+/- 0.17)	0.05 (+/- 0.04)
	2011-2040	0.18 (+/- 0.24)	0.12 (+/- 0.14)	0.10 (+/- 0.17)	0.30 (+/- 0.30)	0.17 (+/- 0.26)
	2041-2070	0.11 (+/- 0.15)	0.14 (+/- 0.16)	0.15 (+/- 0.23)	0.40 (+/- 0.28)	0.17 (+/- 0.20)
	2071-2100	0.39 (+/- 0.29)	0.15 (+/- 0.19)	0.19 (+/- 0.26)	0.53 (+/- 0.31)	0.29 (+/- 0.30)

3.1.1 Climatic suitability for species with current (south-) western focus of distribution

Results for species with current (south-) western focus of distribution (*P.ariasi, P. mascittii* and *P. perniciosus*) show - regardless to the slight differences - a similar tendency in spatial patterns of projected climatic suitability for the upcoming time-period (Figure 2 and Supplemental Material Figure 1). Expectedly, these species achieve highest values of current and projected climatic suitability in the westernmost parts of Germany and Switzerland. Projections for the conditions from mid-century onwards, however, indicate increasing suitability for the eastern parts of the countries. Interestingly, moderate suitability is indicated for *P. perniciosus* on western parts of Germany and the coast of the North Sea for the current climatic conditions. In those regions no presence of the species is documented up to now. Favourable conditions for *P. mascittii* and *P. perniciosus* can be expected in north-eastern Germany at the end of the century and in less extent also for *P. ariasi*. Instead, *P. ariasi* will achieve highest values of climatic suitability in Switzerland. Nevertheless it is worth mentioning that favourable conditions can be expected for all species in certain river valleys in the northern and north-eastern parts of Switzerland on the border to France and Germany and along the Danube valley. This becomes especially apparent regarding the projections for the end of the 21st century.

For *P. mascittii* climatic suitability will persist in eastern (including south-eastern and north-eastern parts) of Austria. For *P. ariasi* and *P. perniciosus* suitability can be expected to increase in those regions. Alpine Austrian regions remain to persist outside the preferred niche of the species throughout the 21st century.

3.1.2 Climatic suitability for species with current (south-) eastern focus of distribution

The results of the current and projected climatic suitability for the two species with (south-) eastern focus of distribution (*P. neglectus* and *P. perfiliewi*) differ remarkable. For *P. neglectus,* moderate suitable habitats in Upper Austria along the border to Germany and Switzerland in the Lake Constance region are pointed out for current conditions. For the upcoming time-period, it can be expected that especially the Upper Rhine Valley in the south-west of Germany will provide suitable climatic conditions. Starting at mid-century, almost all regions in Germany will provide favourable conditions for species establishment. At the end of the century, additionally, northern and southern parts of Switzerland will achieve excellent climatic conditions. Then, only the highest Alpine regions will remain unfavourable for the establishment of *P. neglectus*.

The modelled climatic suitability for *P. perfiliewi* differs from the overall tendency. Currently, climatic requirements of the species will not be fulfilled in Central Europe. Favourable conditions can be expected for the up-coming time period and mid-century higher in spatially limited areas for southernmost parts of Switzerland - canton Ticino - and (south-) eastern parts of Austria. Germany remains unfavourable for species establishment until the end of the century. Then, the river valley of the Rhine and Danube will provide preferable climatic conditions for *P. perfiliewi*.

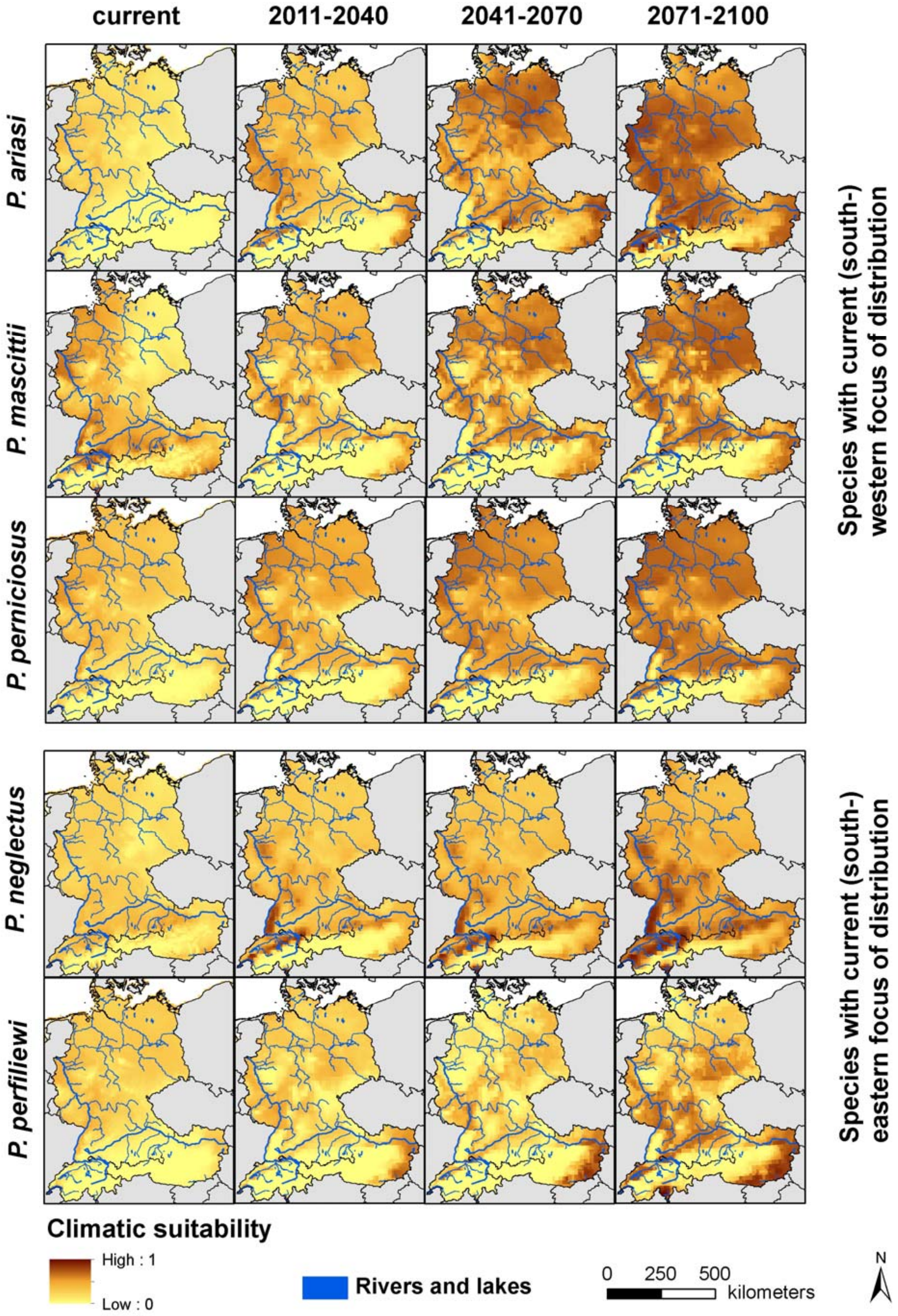

Fig. 2: Current and projected climatic suitability for five *Phlebotomus* species. Values of climatic suitability range theoretically from 0 (unfavourable conditions) to 1 (perfect conditions). Projections refer to the A1B scenario.

3.2 Least-cost path analysis

In general, projections hint on spreading tendencies for all studied *Phlebotomus spp*. to areas where they have not occurred so far in both scenarios (Figure 3 and Supplemental Material Figure 2). Nevertheless, sandfly species will not be able to become established in all climatically suitable areas of Central Europe according to the limited natural dispersal ability. The detected dispersal pathways show some differences between the two applied scenarios, in contrast to the modelled climatic suitability, where just temporal but no spatial variations are pointed out.

We can affirm the first part of our second hypothesis that species with current (south-) western focus of distribution will disperse eastwards only for *P. perniciosus* but not for *P. ariasi* and for *P. mascittii* see Section 3.3.1). We cannot keep with the part of the second hypothesis that the Alps will prohibit completely a northward spread for the species which are currently distributed in (south-) eastern European regions. However, the Alps will very likely decelerate the range expansion (see Section 3.3.2).

3.2.1 Least-cost path for species with current (south-) western focus of distribution

In contrast to the similar tendency in climatically suitable habitats, dispersal pathways for these species will differ. *P. ariasi* is characterized by the highest dispersal ability and seems to spread to Switzerland and Germany from recent occurrences in France. Consequently, the western parts of these countries can be expected to be occupied already in the upcoming time-period. From then on, the species seems to spread along the border of Germany and Switzerland to Bavaria in the southeast of Germany until the end of the century. Additionally, *P. ariasi* will spread to north-eastern parts of Germany until the end of the century in A1B but not in the B1 scenario. A further dispersal pathway is detected starting from Croatian and Slovenian occurrences directed to the (south-) eastern parts of Austria. Up to the end of the century, *P. ariasi* will also be able to occupy eastern and north-eastern parts of Austria.

Two pathways are detected for *P. mascittii* starting from the Upper Rhine Valley in the southwest of Germany, which are either directed northwards or southwards (to the northeast of Switzerland). Additionally, a direct spread from France to Switzerland is identified. As two pathways are directed to northern parts of Switzerland, this region seems to be especially endangered regarding species establishment, expectedly from mid-century onwards. The north-eastern expansion for *P. mascittii* in Germany is solely indicated in A1B scenario. Additionally two pathways are found from Carinthia in Austria. There a northward spread to the river valley of the Danube and a westward spread along the Slovenian and Italian boarder can be expected in both scenarios.

From the recent occurrences of *P. perniciosus* in the southwest of Germany, potential pathways are determined mainly to southern and eastern directions. Across southernmost parts of Germany species will disperse to the southeast of Germany (Bavaria) until the end of the 21st century. Beyond that, western parts of Germany will be reached from an expected species movement from French regions across Belgium. The range expansion is more pronounced in A1B scenario. Switzerland and Austria seem not to be endangered by a direct northward spread from the species across the Alps.

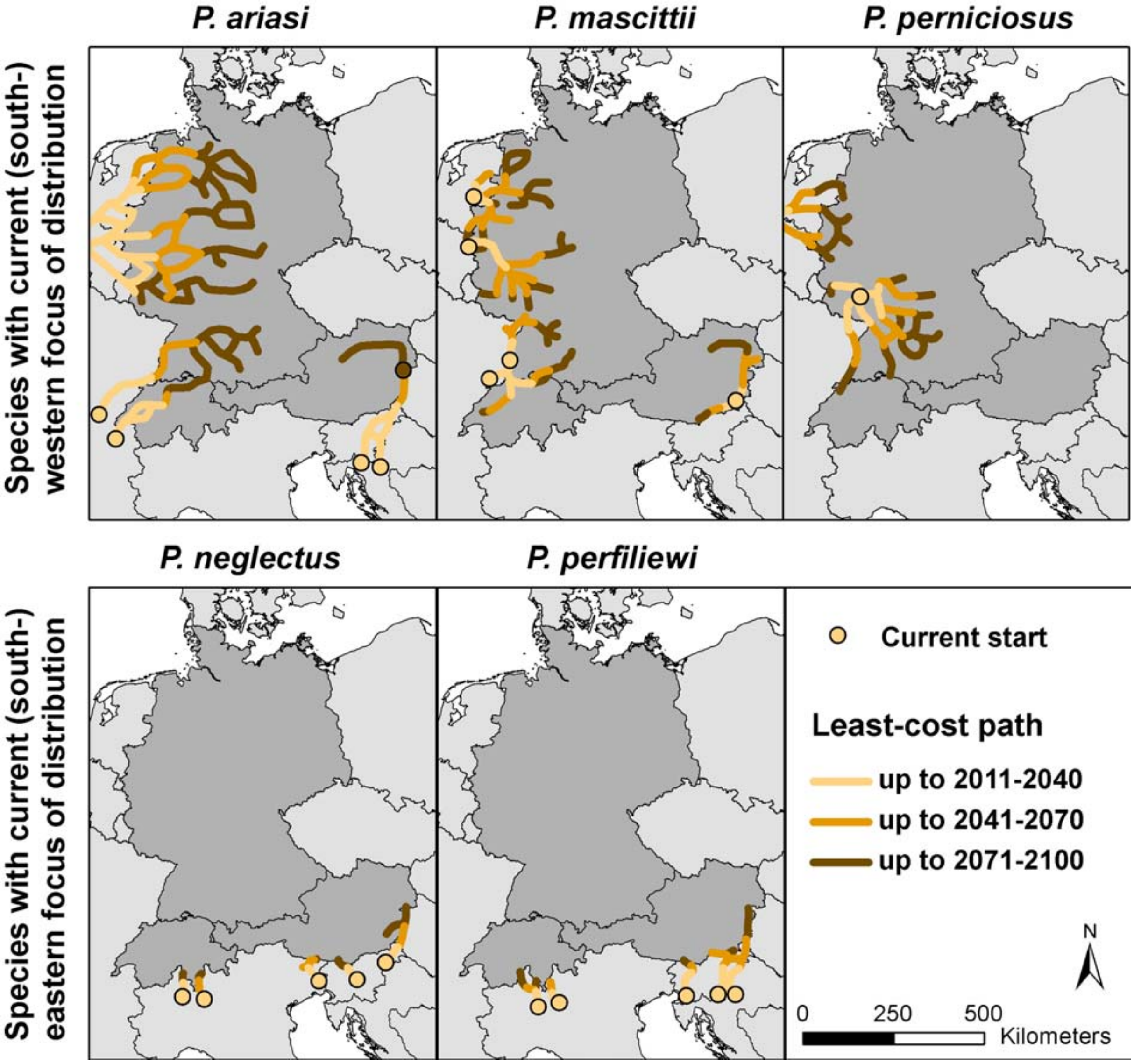

Fig. 3: Least-cost path for *Phlebotomus* species indicating direction of spread in the 21st century. Spatio-temporal varying (climatic) conditions included in the cost surface that must be crossed by species in the 21st century refer to the A1B scenario.

3.2.2 Least-cost path for species with current (south-) eastern focus of distribution

The detected least-cost paths for *P. neglectus* are rather disperse. Several pathways indicate a northward spread to different locations in Switzerland (from Italy) and Austria (from Slovenia). Expectedly at mid-century, the southern parts of Switzerland and Austria will be achieved by the specimen. Only in A1B scenario, *P. neglectus* will be able to spread to eastern regions of Austria and become established there. There is no evidence that species may move further northwards to Germany.

P. perfiliewi is currently established in northern Italy. Species will only spread to southern areas of Switzerland and Austria from recent locations within the upcoming time-period. Up to mid-century and more pronounced to the end of the century, range expansions to eastern Austria can be expected. Instead, further dispersal in regions of Switzerland is unlikely. Germany seems not be endangered by species movement and establishment within this century.

4. Discussion

4.1 Relevance and generality of the study

Our aim was to determine future occurrences for five *Phlebotomus spp.* with assumed spreading tendencies in the face of a changing climate. Knowledge concerning the potential future presence of disease vectors is a first step towards an accurate risk assessment of vector-borne diseases [72]. Conventional and rather static bioclimatic niche modelling can be improved by novel avenues for instance regarding species ability to disperse [73]. Therefore, we integrated species-specific dispersal pathways to the detected climatically suitable habitats. The results suggest that Central European climate will become suitable for phlebomine sandflies generally but more pronounced in the second half of the 21st century. We project sandfly establishment in formerly non-endemic areas. This will additionally increase the risk of emerging sandfly-borne diseases in Central Europe. Nevertheless, sandflies will not be able to occupy their provided climatically suitable habitats entirely.

4.2 Limitations

Assuming climate is suitable, the presence of *Phlebotomus spp.* is mainly dependent on land cover [74, 75]. However, the importance of land cover and land use to model species distribution becomes generally more important on smaller spatial scales [76, 77]. Nevertheless, in this analysis we integrated river valleys and elevation in least-cost path analysis. In order to recalculate wind speed we additionally integrated land cover data. Land cover and land use changes depend in general on complex interactions of decision makers under heterogonous political and economical developments [78] and are hence rather difficult to project in a long-term perspective. Therefore those factors were considered as temporarily constant.

In general, biotic interaction under climate change conditions is a crucial factor to determine species´ distribution [79]. The modifications of the ecological links or networks of an organism can substantially alter the realised niche of species population [80]. In Germany, *P. perniciosus* and *P. mascittii* do not co-exist at the same locations [29]. This can be a result of diverging invasion pathways or of competitive exclusion in the respective regions. Unfortunately, knowledge on biotic interactions of sandflies is scarce. However, such information would enhance model projection power remarkably. Furthermore, one has to bear in mind that presence of phlebotomine sandflies is dependent on humans and their social factors, for instance living conditions [81, 82]. Sandflies are located in rural as well as urban environments in close connection to humans and their domestic animals such as dogs and horses [5], which provide the preferred blood meal for the gravid females [83].

Further uncertainties refer to the current occurrences of the species and dispersal behaviour of sandfly species. Comparing the reports for cases of autochthonous leishmaniasis in regions that were considered as being non-endemic [e.g. 9] with documented presence records of sandflies leads to the assumption that sandflies may be wider distributed than realized. However, as it is unknown which species acted in such region as vector, only documented presence records of the *Phlebotomus spp.* can be integrated.

Concerning the least-cost analysis for species movement it has to be noted that the attributed costs are based on assumptions and/or preliminary observations and hence may not include all of the relevant factors [55, 61]. For instance, it is questionable whether humans assist in the spread of sandflies. Nevertheless, in comparison to mosquitoes, direct human effects on dispersal are of minor importance. Furthermore, the species movement behaviour must not necessarily be optimal or well adapted in human-modified landscapes [53]. Especially dispersal behaviour of individuals between populations may differ from the general tendency of the metapopulation level [58].

Besides the effects of changes in long-term climatic conditions used in this study, extreme weather events are expected to increase in Europe [84]. This will influence organisms and ecosystems remarkably [85, 86]. It has been shown that climatic variability in general and extreme weather events such as floods particularly affect sandfly occurrences [87, 88]. In order to integrate weather extremes in a satisfactory quality within climatic projections, a further downscaling of their spatial resolution to the local scale is required [89]. This is the only way to integrate the contribution of weather extremes on disease vectors in risk analysis.

4.3 Strengths

Bioclimatic envelope models are powerful tools to envisage potential responses in species distribution to climate change from regional to global scales [76, 90]. They can be seen as a useful first filter for approximations of the impact of climate change on the species distribution [76, 91]. The necessity of using a well-adapted modelling approach to project climate change effects on species is realized [44]. Therefore, we selected MaxEnt as preferred algorithm, due to better performances in comparison with further presence-only and (pseudo) presence-only algorithms (see Section 2.1.2 for details). Results yielded in high model quality criteria, emphasized by threshold-dependent and independent criteria for *Phlebotomus spp*.

In order to cope with the general uncertainty in species distribution modelling regarding the climatic evolvement [79], we projected the climatic suitability based on two IPCC [37] scenarios (A1B and B1) that best illustrate the respective storyline. We choose bioclimatic variables that are considered to be biologically meaningful variables for model input. Our projections of future climatic suitability refer to data of the regional climate model CCLM, which is nested into the well-established global climate model ECHAM5 [35]. In comparison to their driving global models, regional patterns of climate change are projected more precisely, which enhances the quality of climate impact studies [36]. Global climate models failed particularly in replication of observed wind speeds. Obviously, projections of changes in wind speed require an accurate downscaling to the regional level [92].

Evidently, the consideration of the dispersal capacity of insects in a changing climate improves the quality of projections of species distribution [93]. Hence, we combined projected climatic suitability in the 21st century with dispersal ability for five *Phlebotomus spp.*. We practiced a least-cost analysis for future movement patterns by including temporarily stable (elevation, landscape features) and variable factors (wind speed and development of climatic suitability). This allows integrating and combining expert knowledge on sandfly ecology and biology with statistical methods. In doing so, species-specific dispersal pathways can be pointed out. This offers the opportunity to distinguish between climatically suitable habitats that are reachable for invasive species and those that are not.

5. Conclusions

Here, we provide a powerful methodological approach to improve conventional bioclimatic envelope modelling of disease vectors by species specific dispersal ability. Our findings promise more realistic projections concerning the vector species´ future distributions. We identify those Central European regions that are especially exposed to the emerging threat of spreading disease vectors in the light climate change. For the modelling of hitherto neglected vector-borne- connected risks, expertise from various scientific disciplines has been taken into account.

Proactive monitoring activities and development of feasible adaptation strategies are required before the establishment of disease vectors may take place. This enhances first of all counteractions directed against the suggested spread of disease vectors and consequently reduces the risk of disease transmission in formerly non-endemic areas. Once the disease vectors such as sandflies are established, vector control and disease prevention have proven to be difficult.

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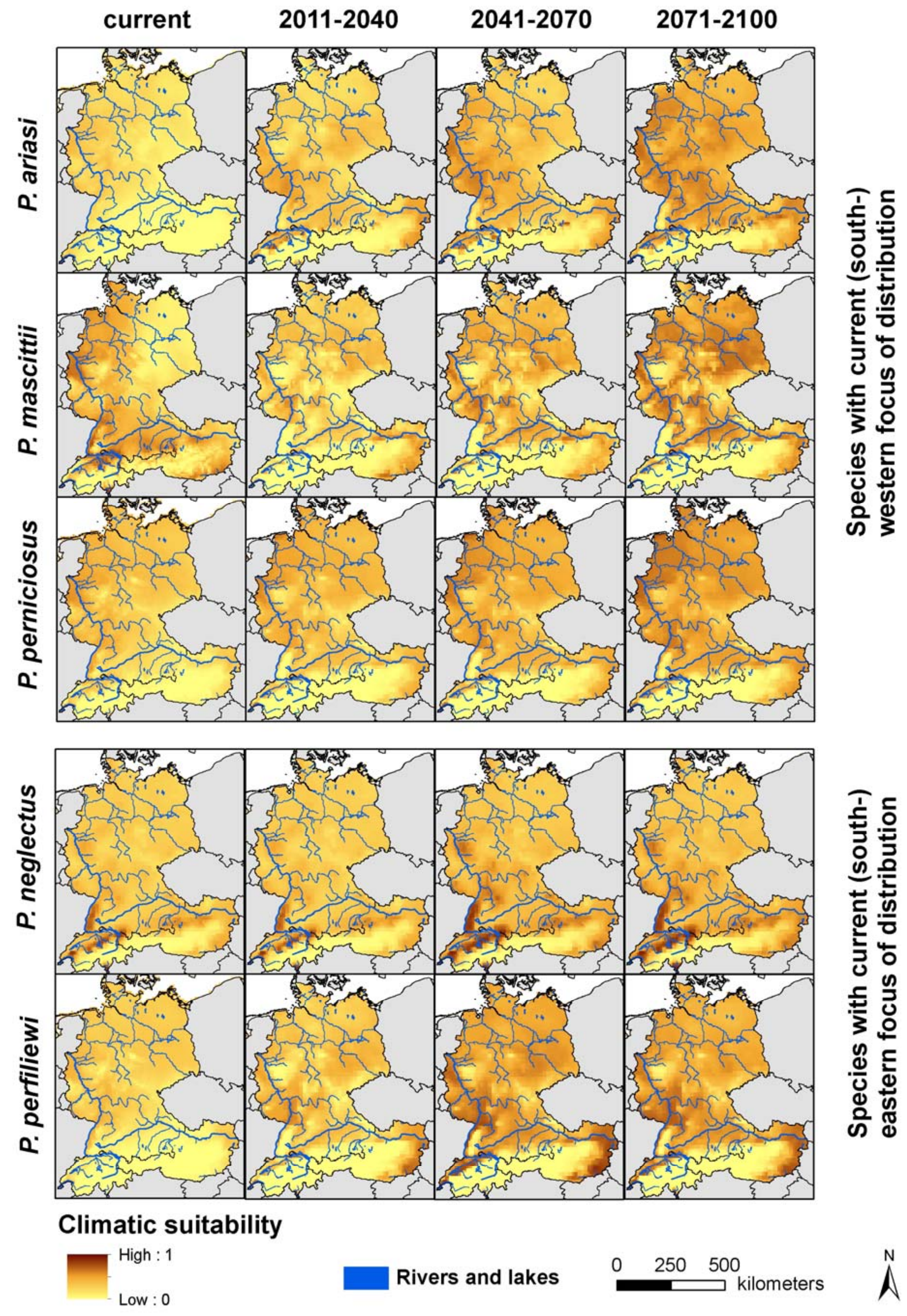
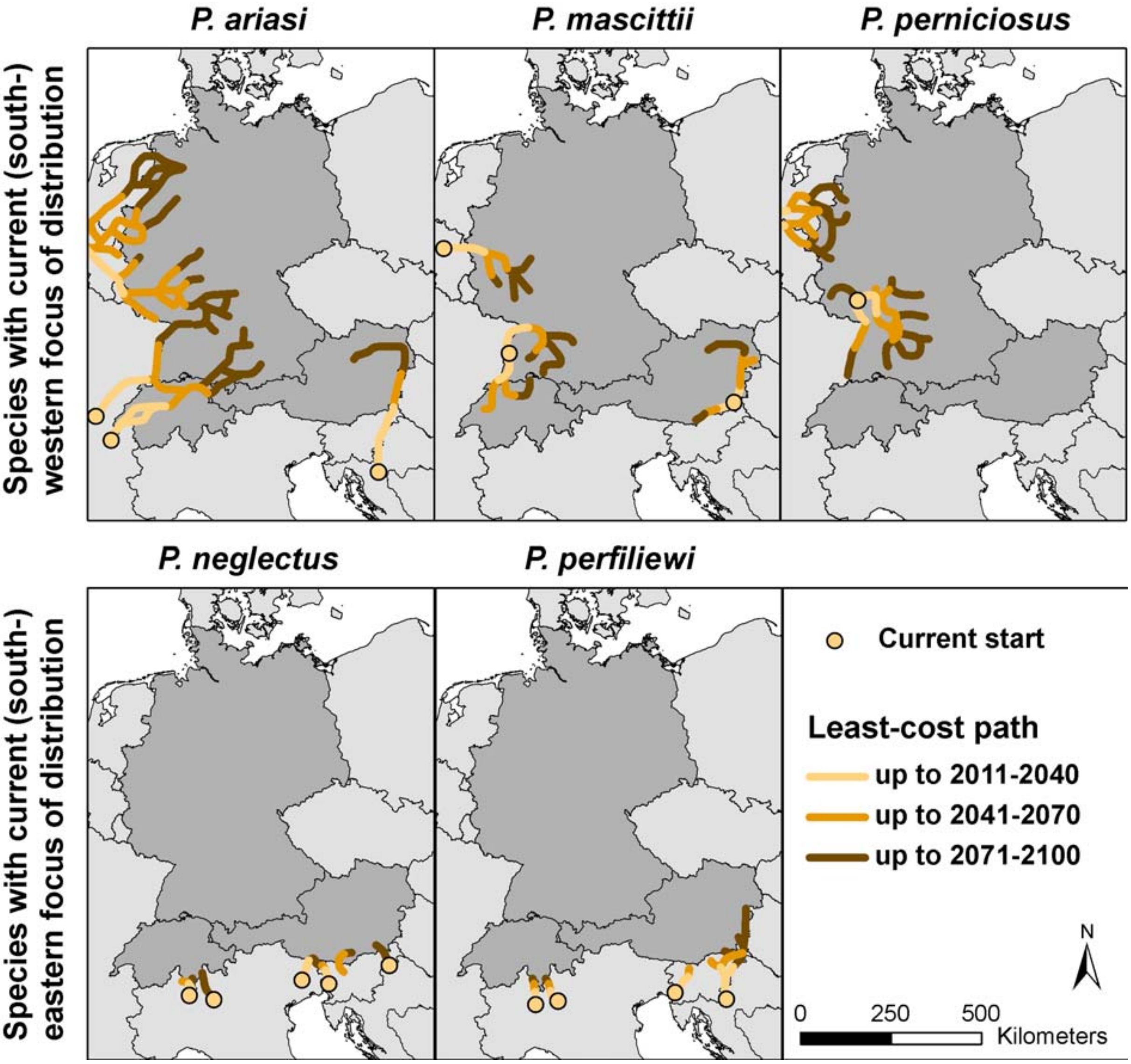
Supplemental Material Table and Figures

Suppl. Mat. Tab. 1: Current and projected mean values of climatic suitability for Central Europe with standard deviation in brackets. Projections refer to the B1 scenario.

		P. ariasi	*P. mascittii*	*P. perniciosus*	*P. neglectus*	*P. perfiliewi*
Central Europe	current	0.14 (+/- 0.10)	0.28 (+/- 0.19)	0.25 (+/- 0.14)	0.23 (+/- 0.10)	0.10 (+/- 0.06)
	2011-2040	0.26 (+/- 0.10)	0.34 (+/- 0.20)	0.30 (+/- 0.16)	0.23 (+/- 0.10)	0.10 (+/- 0.06)
	2041-2070	0.32 (+/- 0.15)	0.36 (+/- 0.22)	0.36 (+/- 0.18)	0.36 (+/- 0.15)	0.15 (+/- 0.15)
	2071-2100	0.02 (+/- 0.02)	0.26 (+/- 0.17)	0.42 (+/- 0.20))	0.38 (+/- 0.14)	0.21 (+/- 0.18)
Austria	current	0.02 (+/- 0.02)	0.26 (+/- 0.17)	0.09 (+/- 0.10)	0.18 (+/- 0.13)	0.04 (+/- 0.03)
	2011-2040	0.19 (+/- 0.18)	0.21 (+/- 0.20)	0.16 (+/- 0.17)	0.25 (+/- 0.17)	0.20 (+/- 0.23)
	2041-2070	0.21 (+/- 0.18)	0.21 (+/- 0.19)	0.19 (+/- 0.19)	0.33 (+/- 0.20)	0.22 (+/- 0.25)
	2071-2100	0.30 (+/- 0.21)	0.30 (+/- 0.21)	0.23 (+/- 0.21)	0.36 (+/- 0.20)	0.27 (+/- 0.28)
Germany	current	0.17 (+/- 0.08)	0.32 (+/- 0.18)	0.31 (+/- 0.10)	0.24 (+/- 0.08)	0.12 (+/- 0.05)
	2011-2040	0.28 (+/- 0.10)	0.33 (+/- 0.12)	0.36 (+/- 0.12)	0.29 (+/- 0.07)	0.15 (+/- 0.11)
	2041-2070	0.36 (+/- 0.11)	0.37 (+/- 0.15)	0.43 (+/- 0.12)	0.37 (+/- 0.11)	0.14 (+/- 0.10)
	2071-2100	0.48 (+/- 0.09)	0.46 (+/- 0.17)	0.49 (+/- 0.12)	0.38 (+/- 0.10)	0.19 (+/- 0.14)
Switzerland	current	0.07 (+/- 0.08)	0.21 (+/- 0.18)	0.13 (+/- 0.15)	0.23 (+/- 0.17)	0.05 (+/- 0.04)
	2011-2040	0.19 (+/- 0.22)	0.10 (+/- 0.10)	0.09 (+/- 0.14)	0.28 (+/- 0.25)	0.13 (+/- 0.21)
	2041-2070	0.20 (+/- 0.23)	0.12 (+/- 0.16)	0.11 (+/- 0.17)	0.40 (+/- 0.30)	0.11 (+/- 0.20)
	2071-2100	0.21 (+/- 0.23)	0.13 (+/- 0.17)	0.14 (+/- 0.21)	0.14 (+/- 0.21)	0.14 (+/- 0.21)



Suppl. Mat. Fig. 1: Current and projected climatic suitability for five *Phlebotomus* species. Values for suitability range theoretically from 0 (unfavourable conditions) to 1 (perfect conditions). Projections refer to the B1 scenario.



Suppl. Mat. Fig. 2: Least-cost path for *Phlebotomus* species indicating direction of spread in the 21st century. Spatio-temporal varying (climatic) conditions included in the cost surface that must be crossed by species in the 21st century refer to the B1 scenario.

6.7 Article 7:

Vector-borne diseases in a rapidly changing world - Geography needs to become infected!

With 3 Figures.

Abstract

Vector-borne diseases constitute one of the main striking issues regarding human and animal health. Disease vectors, which are mainly arthropods, transmit pathogens between mammal hosts. In the first part of this paper, we highlight the main effects of natural and/or human forced changes on vector-borne diseases. Climate and environmental change as well as globalization contribute to modified spatial patterns of occurrences and transmission cycles of vector-borne diseases, resulting in a growing threat for humans. In general, the sensitivity of vector-borne diseases to the main natural or human-forced changes of their environment is manifold.

In the second part, we point out recent developments in research concerning occurrences and spatial patterns of vector-borne diseases. Furthermore uncertainties and research challenges are identified. Especially political recommendations demands supporting information, which consider the varying risk of potential (re-)emerging vector-borne diseases on different spatio-temporal scales. We provide a framework to include geographical expertise in research as well as surveillance systems in order to close this gap. Humans are involved in both, cause and effects of this emerging public health hazard. This emphasizes the necessity to cope with the complexity of this emerging threat by integrating various scientific disciplines.

Keywords

global warming - global change - environmental change - emerging diseases - public health

1. Introduction

Global change encompasses a variety of processes, which differ in scale, intensity and severity. The contributing processes are driven mainly by the technological and demographic development of human societies (e.g. globalisation of trade, emission of greenhouse gases). However, also natural mechanisms such as the melting of glaciers or the modification of ocean currents can be stimulated and intensified. In all cases, the complexity of the processes and interactions that contribute to these large scale changes and their effects is high. A novel quality of the contributing processes is attributed to their speed and spatial extension in comparison to natural dynamics.

In the context of a rapidly changing world, human health is a vital attribute that should be given priority in science and policy (Fischer et al. 2010a). Several infectious diseases are transmitted via specific disease vectors, which are capable to transmit pathogens from one host to another. Hence, the geographical distribution of a vector-borne disease (VBD) is directly connected to the availability of vectors, which are mainly arthropods (e.g. bugs, flies, fleas, mosquitoes and ticks) but also rodents. In general, the fulfilment of suitable environmental conditions for all species involved in the transmission cycle is the prerequisite for the occurrence and spatial distribution of VBD. Pathogens, vectors and reservoir hosts must coexist spatially and temporarily, and interact (Peterson 2008).

Since anthropogenic global and regional changes manifested themselves at the end of the 20th century, VBDs have responded significantly and meanwhile constitute an emerging biological risk for humans (Sutherst 2004). Globally, the number of VBD related outbreaks has increased remarkably within the last decade, being meanwhile responsible for almost 30% of all cases of infectious diseases (Jones et al. 2008). Due to the fact that humans are both responsible and aggrieved, these topics are in equal measure of interest for several scientific disciplines. The reasons for changes in organismic and viral distribution patterns resulting in emergent or resurgent outbreaks of a VBD are manifold and complex.

Here, the main driving forces affecting emergencies of VBDs are discussed in the first part of this article. In the second part, recent methodological developments for the detection of risk areas of VBDs are highlighted. Furthermore, uncertainties and research challenges are identified. A scale dependent research agenda to include geographical expertise in research as well as surveillance systems is provided.

2. The complexity of global change effects on vector-borne diseases

2.1 Climate change, variability and weather extremes

Human impacts on climate change are unquestionable. However, magnitude, velocity and intensity are still uncertain depending on many factors including political decisions, technological progress and the economy (IPCC 2007). The expected global warming in the first half of the 21st century is mapped in Figure 1.

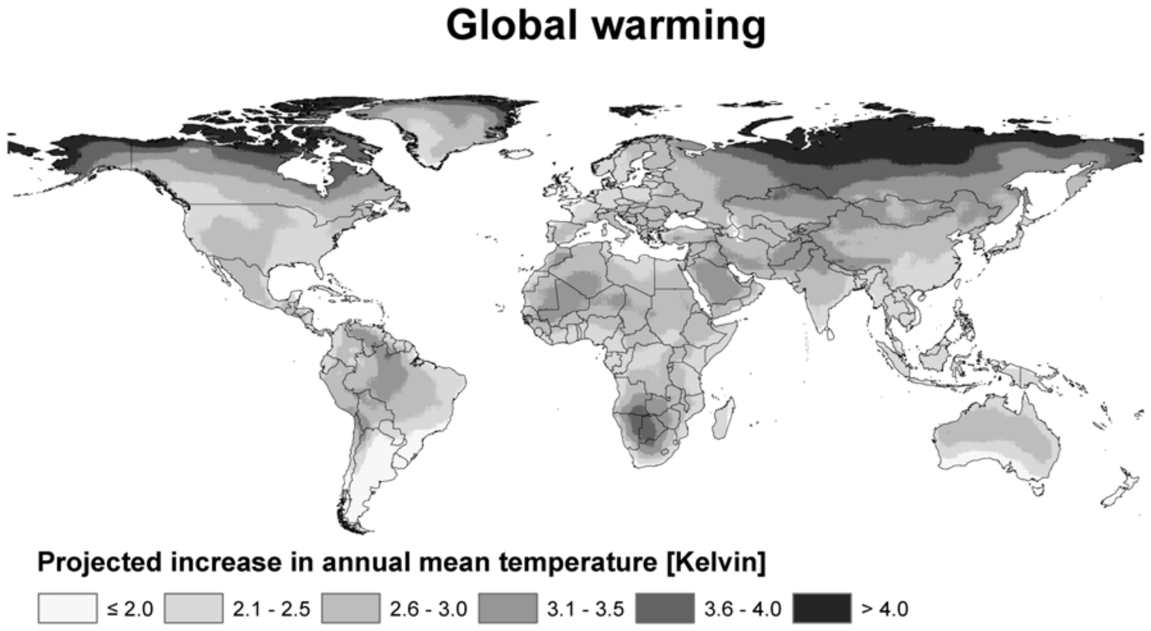


Fig. 1: Global warming. Illustrated is the projected increase in annual mean temperature from the current situation to the mid-century (2050ies). Projections in temperature are obtained from the global climate model ECHAM5 (see Giorgetta et al. 2006) and based on the A1B emission scenario. This scenario is characterised by a rapid economic growth in a globalized world with a balanced emphasis on all energy sources and a decline in human population after an expected peak in 2050 (IPCC 2007). Highest warming is projected for boreal and polar regions in the northern hemisphere. Furthermore the Kalahari dessert, located in the southern part of Africa, seems to be especially affected by rising temperatures during the next decades.

Changing long-term average conditions can affect the spread of VBDs. Arthropod vectors are ecto-thermic and hence depend directly on their surrounding environment. As a consequence of warming, the colonisation of new habitats of regionally unknown vectors and the extension of diseases into formerly unsuited areas have to be expected. Climate-driven spatial expansions of VBDs have been already detected in recent years (Epstein and Mills 2005). The observed northwards expansion of tick-borne diseases, for instance, may result besides other factors also from global warming (Gray et al. 2009). Milder winter temperatures and drier summers may drive tick-borne encephalitis or Lyme borreliosis not only to higher latitudes but also to higher altitudes in specific European regions (Lindgren et al. 2000; Randolph 2001; Lindgren and Jaenson 2006). Ticks perform extraordinary complex life cycles and they combine this with low mobility. Interactions with natural hosts such as various species of wild mammals impede observation and monitoring. In addition, ticks can host a large variety of pathogens.

However, most arthropod vectors are less difficult to assess. Regarding the climatic projections of the 21st century, a spread of leishmaniasis - the most severe sandfly-borne disease - can be expected not only for Central Europe (Fischer et al. 2010b) but also for temperate regions of North America (Gonzáles et al. 2011). Furthermore, re-emerging autochthonous cases of malaria in Germany cannot be excluded. The vectors (*Anopheles*-species) are already present. Assuming pathogen (*Plasmodium vivax*) introduction will take place, the risk of malaria establishment in Germany can be expected to increase under climate change conditions during the 21st century (Holy et al. 2011).

VBDs may also display year-to-year variations dependent on climatic variability. The most dominant feature is probably the El Niño and La Niña phenomenon characterized by anomalous weather conditions in the Pacific region (Yeh et al. 2009). For mosquito-borne diseases occurring in the southern hemisphere and most importantly for malaria, correlations of transmission cycles with the El Niño Southern Oscillation Index have been found (see Kovats et al. 2003). It is expected that frequency as well as characteristics of El Niño events will change significantly in the 21st century (Yeh et al. 2009).

Generally, global warming is associated with increased energy turnover in the atmosphere facilitating weather extreme events. Weather extremes may either accelerate or attenuate activity phases of diseases vectors and consequently alter the transmission cycles of VBDs in endemic areas. Hydrological events such as heavy rainfalls and resulting flooding may create windows of opportunity for the invasion and establishment of mosquitoes (Landesman et al. 2007; Hubálek 2008). Extraordinary hot summers with heat waves such it was recorded for Europe in 2003 caused the largest mast production by deciduous trees in the autumn of 2004 (a so-called mast year). This caused an extremely high rodent survival rate in the European winter 2004/2005. Several of the rodent species are vectors and hosts for the different strains of the hanta-virus. In Belgium, the highest incidences of humans with hanta-virus infections were therefore recorded in 2005 (Clement et al. 2009), probably due the high abundance of rodents. Especially the closer contact of rodents with humans is considered as main factor for increased human infections with the hanta-virus (Jonsson et al. 2010). However, climate change alone cannot explain the recent epidemiology of VBDs (e.g. Gething et al. 2010; Randolph 2010).

2.2 Trade and travel as dispersal mechanisms and the growing connectivity between vulnerable regions and societies

Beyond climatic change effects on VBDs, the complex interplay of globalisation and regional climatic or environmental changes is of special relevance (Sutherst 2001). As long as the target area exhibits only unsuitable habitats for disease vectors no outbreak after pathogen or vector introduction can occur. However, conceivably, climate and further environmental changes may provide suitable habitats for potential vectors in the target area, which then might result at least in local epidemics. Human-induced carry-overs (trade and transport) are increasingly promoting the dispersal, establishment and epidemics of VBDs (Randolph and Rogers 2010). This can either be facilitated by human-forced invasions of vectors or by pathogen introduction by mobile hosts (e.g. birds).

2.2.1 Human support of vector invasions

Trade and transport of goods and materials (mainly by sea) around the world were responsible for the long distance dispersal of several disease vectors in the last century (Tatem et al. 2006). Especially invasions of mosquitoes that require only small water bodies during their larval and pupal stages are responsible for the most notable invasions and range expansions. Such conditions are given even in containers and other devices for the transport of goods (Lounibos 2002). The number of container ships per country involved in the global shipping of goods is illustrated in Figure 2.

The most prominent example in recent times is probably the global invasion of the Asian tiger mosquito (*Aedes albopictus*) (Enserink 2008). This species has left its native region in Southeast Asia during the last decades causing serious public health concerns in various places of the world. The tiger mosquito is capable of transmitting at least 22 viruses to humans (Gratz et al. 2004). The most severe consequences accompanied by the spread of this insect are surely the establishment of dengue, Chikungunya and West-Nile virus infections in regions where these diseases were unknown until then. The yellow fever mosquito (*Aedes aegypti*) that went extinct in continental Europe in the 1950ies, recently reappeared in the

Netherlands (Enserink 2010). However, intensified mosquito could very likely avoid an infestation of the Yellow fever mosquito (Scholte et al. 2010).

In general, mosquito introduction is not only a phenomenon of recent years. The devastating introduction of *Anopheles gambiae*, the most efficient vector of *Plasmodium falciparum* malaria, from West Africa to Eastern Brazil by either steamship or aircraft happened already in the 1930ies (Lounibos 2002).

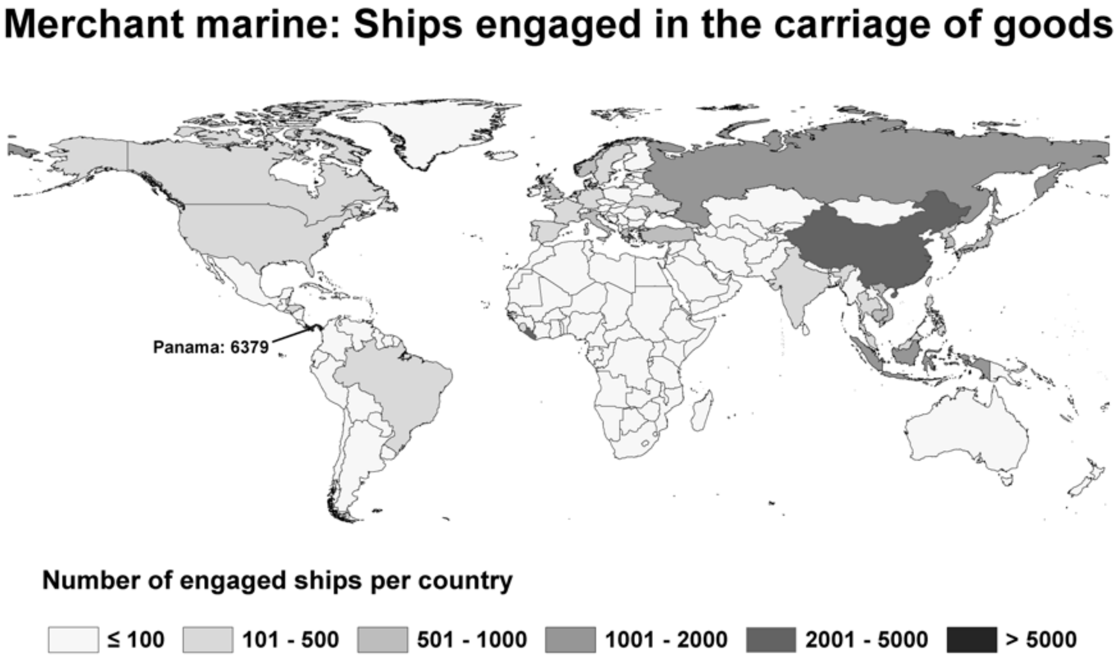


Fig. 2: Merchant marine in 2010. Illustrated is the number of ships engaged in the carriage of goods for each country based on data of the CIA (2011). Note that many ship owners register their ship in a sovereign state different from their own in order to avoid taxes and regulations ("flag of convenience"). Therefore, especially Panama, but also Liberia contains an unexpected high number of engaged ships. The transport of goods from (-sub) tropical regions to temperate regions enables mosquito species to become established in new regions and continents.

2.2.2 Human support of pathogen introduction

Beside the incidental transport of vectors, infected humans act increasingly as mobile hosts. Humans can become infected in (sub-) tropical touristic destination regions and carry pathogens accidentally to formerly non-endemic areas (Tatem et al. 2006; Cosner et al. 2009). The West-Nile virus was very likely introduced to the United States from Israel by airplane and transmitted via local *Culex* mosquitoes in the region of New York (e.g. Lanciotti et al. 1999). Thereafter it spread rapidly across the North American continent. This spread was supported by highly mobile birds that can also act as hosts. This disease became a common problem for instance in the Mid-West and can not be eradicated there any more. Another striking example is the introduction of the Chikungunya virus by an Indian traveller to Italy. In the region of Rimini introduced the Asian tiger mosquitoes incorporated the Chikungunya virus from this person leading to a local epidemic (Rezza et al. 2007).

In addition, trade and migration of infected domestic animals and pets, which can also act as reservoir hosts, may support epidemic outbreaks in formerly non-endemic regions (Dantas-Torras 2007; Menn et al. 2010; Pfeffer and Dobler 2010). For many Europeans, the Mediterranean Region is the preferred holiday destination. The travel and import of dogs from the Mediterranean is connected with the transport of pathogens beyond previously experienced endemic regions. A pathogen screening of imported dogs to Germany found a high proportion of dogs that were infected by tick-borne pathogens but also for by sandfly-borne pathogens such as *Leishmania infantum* (Menn et al. 2010).

2.3 Poverty, demography and resulting human-altered landscapes

The emergence of VBDs depends furthermore on societal aspects such as demography and population pressure or social behaviour and activities (Morens et al. 2004; Vora 2008). Population growth is concentrated to certain regions of the world, especially to Africa, Asia and South-America. This correlates with the poorest regions of the world (Cohen 2003). Amongst VBDs, mosquito-borne diseases are connected with the highest lethality rates in the respective regions (WHO 2004). Unfortunately, no vaccine is available against the most severe mosquito-borne diseases such as malaria or dengue, although recent developments are promising (e.g. Cech et al. 2011).

Poor countries do often exhibit weak health care systems, insufficient medical infrastructure, less developed educational systems, high numbers of malnourished people and other societal stressors that can amplify the effects on biological threats. Conceivably, malaria recurrence in the East African highlands may be most likely a result of missing effective disease treatments as well as decreases in vector control activities (Hay et al. 2002; 2005). Two main concerns exist regarding to land use and cover changes that are associated to human population pressure:

1. Not only in recent times, cities and megacities attract rural population by allegedly providing better options in education, jobs, food and water supply as well as health care. Increasing urbanization tendencies may constitute an appreciable (human) reservoir for different kind of VBDs (Gubler 2010).

2. High human population growth rates especially of the African continent are causing an increased demand for food. This alters vector habitats (Sutherst 2004). The replacement of forests by croplands may create supportive habitats for vectors (Patz et al. 2000). Furthermore, in subtropical and tropical climates, irrigation of agricultural fields is common creates increasing breeding sites for vector mosquito. Whether an irrigations system also triggers an increase in mosquito-borne diseases such as malaria depends on the single project and further contextual determinants (Keiser et al. 2005). Nevertheless, in Western Australia it has been observed, that endemic *Culex* mosquitoes do breed year round - including the driest season - in irrigation facilities. This is connected with a growing risk of Ross-River virus infection (Jardine 2004).

3. Defining the scope: A novel research agenda

3.1 Advances of improved risk analysis with geographical implications

Geo-statistics and ecological niche modelling provide new qualities for the detection of emerging and resurging VBDs (Aagaard-Hansen 2009). Risk analyses are furthermore supported by freely available spatial data e.g. for different types of vectors (flies, mosquitoes and ticks) on platforms such as http://www.vectormap.org (initiated by Foley et al. 2010). This supports the application of GIS-based monitoring tools. Of course, these databases are constantly evolving and to date far from being complete. Nevertheless, novel options can be implemented in order to make science more efficient and to support improved results:

a) Multivariate and geo-statistical approaches allow identifying environmental relationships on different scales (e.g. Eisen and Eisen 2008). The different environmental factors account on changing spatial and temporal scales with varying intensity on VBDs (Fig. 3). Therefore, we are convinced that addressing the adequate scale is substantial to understand the mechanisms of relevant drivers. Beyond simple correlation analyses, especially multiple linear or logistic regression analyses contribute to identify those environmental factors that best predict species distribution and potential range expansion (e.g. de Souza et al. 2010; Roiz et al. 2011). Beginning on larger spatial and temporal scales, especially climate is the major factor regulating the establishment of a VBD. Once specific risk areas are detected, analyses have to be translated to the local level by accounting for further influences. Environmental factors such as changing vegetation and land use, were found to be most relevant on local to regional spatial scales (see the example of Schwarz et al. 2009 for environmental factors determining occurrences of the tick *Ixodes ricinus* in a German nature reserve). Smaller scales demand necessarily for a higher spatial and temporal resolution in order to account for local patterns or variations.

b) Non-apparent spatial or temporal patterns of vectors and VBDs can be characterised and identified (e.g. Peterson 2008; Winters et al. 2010). Once the main environmental drivers affecting vectors or VBDs have been identified, statistical niche modelling incorporated into GIS frameworks offers the opportunity to generate predictive or potential risk maps. They are built on known or inferred distributions in the environmental space (e.g. Peterson 2007). To detect short-term (seasonal) variations, the integration of remotely sensed data has proven to qualify for mapping mosquito populations (e.g. Tran et al. 2008). Time-series of images can moreover be used to monitor the dynamics of vector breeding sites via change detection analyses. However, evidence from previous rather "historical" outbreaks can also be derived from reports. In doing so, Endfield et al. (2009) could relate past environmental, climatic and social factors to the epidemics of sleeping sickness (a disease caused by the tse-tse flies) in East Africa for the years 1900 to 1920.

The appraisal of future tendencies of VBDs concerning their climatic suitability would then probably be the next step (Fischer et al. 2010a). The data are obtained from climate models ranging from regional to global scales. Regional climate models provide a much higher spatial resolution than their driving global models. This enhances the quality of climate impact studies for limited areas with differentiated landscape features (Jacob 2008). Recently, regional climate change projections have been used to assess the future distribution of disease vectors (e.g. Fischer et al. 2011), to project the temperature-dependent pathogen development (Thomas et al. 2011) or to combine vector and pathogen constraints under climate change conditions, respectively (Fischer et al. 2010b; Holy et al. 2011).

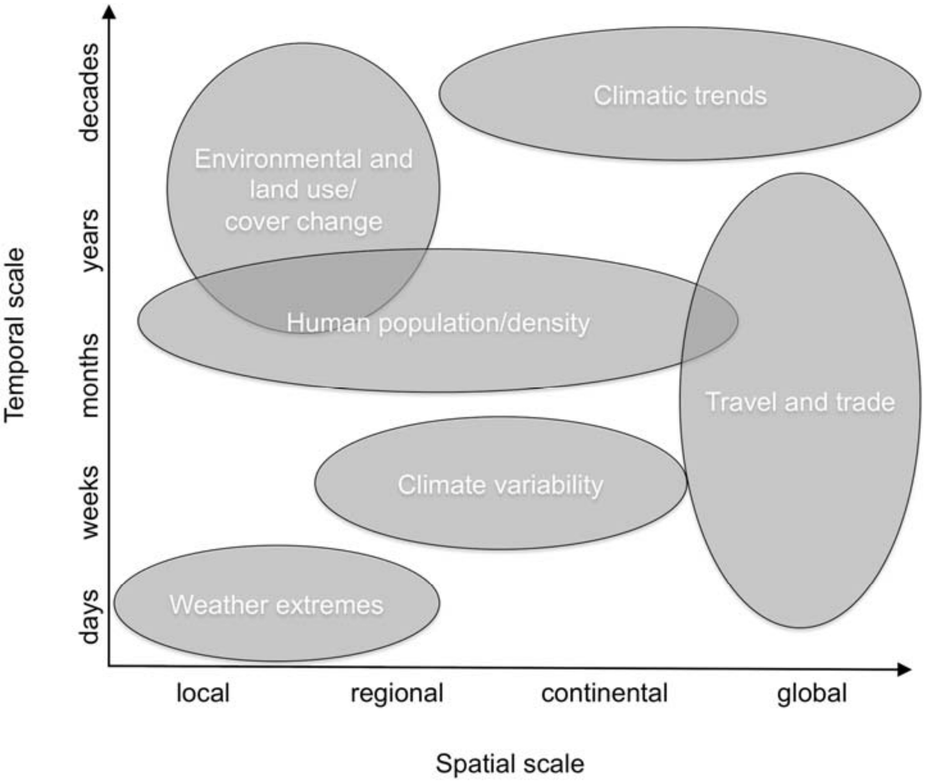


Fig. 3: Different factors determining introductions, occurrences and establishments of vector-borne diseases on varying spatial and temporal scales. This is due to the fact that some of these factors are more restricted in space and time than others. On the other side, an “unrestricted” global and long-term phenomenon becomes negligible in its effect on a vector-borne disease when regarding the smallest scale.

3.2 Research challenges

3.2.1 Problems in projection approaches

One of the major problems concerning projections in space and/or time is related to potential non-analogue environmental conditions (Fitzpatrick and Hargrove 2009). Non-analogue environments represent either novel conditions or novel environmental interrelations. In the case of novel environments, species responses under such conditions have not been observed so far and cannot be projected. New statistical approaches such as Multivariate Environmental Similarity Surface Analysis enable to detect the similarity between regions and to identify regions with upcoming novel and incomparable conditions (Elith et al. 2010). Nevertheless, to date, the issue concerning projections to regions with novel environments has not been resolved.

A further challenge arises regarding potential changing environmental requirements during species invasion processes. Some vector species such as the Asian tiger mosquito are capable to perform niche shifts during the invasion process (Medley 2010). Hence, it is essential to detect what kind of spatial data - native, invaded or entire range - is used as a basis for the calculation of projections via niche analysis (Fischer et al. 2011). This is not exclusively restricted to disease vectors. Also rapid genetic variation in pathogens demands for intensified research. Recently, it has been pointed out that the adaptability of pathogens is higher during range expansions than during host shifts (Dennehy et al. 2010). Consequently, adaptive emergence may preliminary occur at the edge of a pathogen's ecological or geographical range.

Further uncertainties are related to the projections of extreme weather events and their effects on VBDs. The ecological consequences of increasing extreme events can be disproportionate (Jentsch and Beierkuhnlein 2008). Nevertheless, these extremes are - in comparison to gradually changing long-term conditions - difficult to tackle (Beniston et al. 2007; Hegerl et al. 2011). As the related processes generally take place on comparatively small spatial scales, downscaling of regional climate models to the local level is required.

3.2.2 Data availability and quality

Restrictions in data quality are found to be a major obstacle for modelling efforts (Eisen and Eisen 2007). Explicit knowledge is needed that is directly related to the environmental requirements of VBDs. For instance, spatially inclusive and comprehensive screenings of vector occurrences are missing. Only few taxonomists are able to identify species and to monitor their temporal or seasonal emergence. In temperate regions, disease vectors are not active all-the-year. Therefore, non-detection of a vector in a respective region does not imply its absence.

Furthermore, data acquisition is a crucial factor determining quality and accuracy of research. In the United States, the majority of data concerning pathogen or vector distribution is documented on county level, which obscures the occurrence patterns within each administrative unit (Eisen and Eisen 2007). In order to model the climatic suitability of the Asian tiger mosquito, Fischer et al. (2011) transferred the centroids of each county with reported presence of vectors to point data. As the mosquito is mainly distributed in the south-eastern regions of the United States, this approach would be problematic for the western parts, where counties cover more spacious areas (Eisen and Eisen 2007).

3.2.3 New concepts of human vulnerability

Investigating whether the human vulnerability refers more to the capacity to prevent and adapt or to increases in disease transmission is a geographical topic (Sutherst 2004). Up to now, concepts of human vulnerability focus on direct exposures. Climatic events such as floods, storms and heat waves are part of the public awareness and of decision makers (Patz and Kovats 2002). However, the growing threat by VBDs is more diffuse and less obvious.

The most severe consequence for human societies surely refers to lethal cases caused by VBDs. But moreover, VBDs may restrict the ability of societies to pursue and maintain regular functioning (Sutherst 2001). Until now, studies on economic effects of VBDs are rare. On the example of dengue fever in Taiwan, it becomes apparent that non-productive time of the economy increased during dengue outbreaks (e.g. Tseng et al. 2009). Economic damage is obvious in the case of animal diseases. This is impressively highlighted by the bluetongue disease in ruminants - transmitted by *Culicoides* mosquitoes. In 2006 and 2007, this animal disease occurred initially in the Netherlands and neighbouring regions (e.g. van Wuijckhulse et al. 2006). There, the epidemic outbreak caused dramatic financial losses in pasture-based livestock farming (Velthuis et al. 2010).

4. Communication and knowledge transfer

4.1. Strengthening the public awareness

Limiting VBD burdens is an overall goal (Eisen and Eisen 2011). However, the impact of VBDs is still not adequately captured in disease burden assessments (Dujardin et al. 2008). These diseases are often excluded from top-level discussions on disease control priorities, although they constitute a serious and growing threat (LaBeaud and Aksoy 2010). Also, the knowledge that is needed for the efficient design of coping strategies is scarce. There are probably two explanations for this deficit: First of all, there is a disconnection between research and the practical use of the results for prevention and control purposes. The transfer of knowledge from the scientific community into operational vector and diseases control programs must be emphasised (Eisen and Eisen 2011). Secondly, the public understanding of inextricable links between global changes and vector-borne diseases is still rudimental. Growing public awareness on this emerging issue would enhance the pressure on politicians and stakeholders to make decisions.

This in consequence requires the evaluation of spatial information that is needed for different stakeholders in order to make practical use of it (Eisen and Eisen 2011). Then, especially virtual globes - e.g. Google Earth^{TM} and Google Maps^{TM} - may help to share data for the management and control of VBD (Steensgard et al. 2009). More advanced are data management system software packages that support data entry, storage and query, as it was recently proposed for dengue and malaria by Eisen et al. (2011).

4.2 Surveillance: Bottom-up approach

Spreading VBDs are a global problem. Solutions, however, have to be implemented locally (Lambrechts et al. 2009). Surveillance must be based on systematic and continuous observation with the aim to a timely support of political decisions by detecting spatial anomalies in the distribution of VBDs such as emergent cases in formerly non-endemic areas (Jansen et al. 2008).

Germany, for example, may serve as a role model for rapid communication of certifiable diseases via bottom-up approach (from the local via regional to the national public health authorities). The German Infection Protection Act, enacted in 2001 and modified 2007, regulates the prevention and abatement of 47 pathogens and 14 diseases that laboratories and clinicians have to notify to local health departments (Jansen et al. 2008). Via SurvNet software the case-base datasets of each local health department are directly transmitted to the state health department and finally to the federal “Robert Koch Institut” (Krause et al. 2007). The database is updated weekly and freely available on http://www3.rki.de/SurvStat.

In the case of recent EHEC (*Escheria coli*) infections in Germany with an unusual high number of HUS (Haemolytic uraemic syndromes) it was shown that surprising events can hardly be counteracted in time. Nevertheless, the rapid exchange of information, strains and DNA fingerprints within national and international public health networks has been vital in the quick assessment of public health significance (Scheutz et al. 2011). Surprising epidemics are not limited to such a food-borne disease but can also occur in the case of a VBD.

The spread of VBDs is not limited by administrative borders. Recent developments in data exchange are promising, but the overall integration into supranational frameworks is still missing. This requires a standardisation of certifiable VBDs. Without clear regulation concerning notification, the number of infections would probably be underestimated. Decisions which diseases should be certifiable must be built on agreements regarding the risks and efforts for management. For certifiable VBDs then a clear task for the health authorities arises: They must distinguish between those cases that are real emergencies and those that result from increased reporting.

5. Conclusions

The influence of global change on the spread of VBDs around the globe is of increasing importance. Still, gaps in knowledge and surveillance are inhibiting efficient detection of vulnerable regions and populations at an early stage of exposure. Even industrial countries in the temperate zones of Europe and Northern America, where VBDs were not a big issue during the last decades, have been caught napping. Hence, there is a need for in-depth research and the design of sophisticated risk assessments. Transdisciplinary cooperation is required in epidemiological studies. Neither the humanities, nor social, medical or natural sciences are capable to cope with the complexity of these emerging threats alone.

As different spatial and temporal scales have to be addressed and various qualities of drivers have to be considered, it is time especially for geography to become “infected” and provide its expertise. In this rapidly changing world, public health authorities and political decision support are urgently needing spatio-temporal analyses of risks that are related to VBDs. Generalisations across scales are inappropriate. Spatially explicit information is required.

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8. Curriculum vitae

Dominik Fischer was born on the 14th of August 1981 in Lahr (Schwarzwald), Germany. After attending the “Max-Planck-Gymnasium” in Lahr 2001, he passed the basic military service in Sigmaringen. In October 2002, he started his studies in Geography at the University of Heidelberg, where he specialised in human-environmental interactions. His Diploma thesis dealt with applications of GIS and remote sensing applications to detect geo-ecological spatial patterns on the regional example of Fogo (Cape Verde). He obtained his Diploma degree in October 2007.

In August 2008, he started as research assistant and doctoral candidate at the Department of Biogeography, University of Bayreuth. He is research member of the collaborative research project: “Vector-borne Infectious Diseases in Climate Change Investigations” (VICCI-Study) that was launched in summer 2008. The project is funded by the Bavarian State Ministry for Environment and Public Health and coordinated by the Bavarian Health and Food Safety Authority. Within this interdisciplinary research consortium expertise of the Sections “Infectiology, Parasitology and Epidemiology as well as the “National Reference Centre for Borrelia (NRZ)” belonging to the Bavarian Health and Food Safety Authority is joined with the project partners. These are the Institute of Comparative Tropical Medicine and Parasitology (LMU Munich), the Bundeswehr Institute of Microbiology (Neuherberg), the Institute of Microbiology, Immunology and Hygiene (University Medical Centre Erlangen), the Bavarian Forest National Park (Grafenau) and the Department of Biogeography at the (University of Bayreuth).

Dominik Fischer is assigned with subproject 7 “Biogeographical analysis of health-relevant species and projection of their spreading tendencies under changing climatic conditions in Bavaria”. He presented his work at several national and international conferences on climate change, (vector) ecology, entomology, GIS-applications, medical geography and spatial statistics in oral and poster presentations.

9. List of publications

9.1 Articles of this thesis

9.1.1 Published articles

Fischer D., Moeller P., Thomas S.M., Naucke T.J., Beierkuhnlein C. (2011): Combining climatic projections and dispersal ability of phlebotomine sandflies: A methodological task to estimate vector responses to climate change. PLoS Neglected Tropical Diseases 5, e1407.

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Thomas S.M., **Fischer D**., Fleischmann S., Bittner T., Beierkuhnlein C. (2011): Risk assessment of dengue virus amplification in Europe based on spatio-temporal high resolution climate change projections. Erdkunde 65, 137-150.

9.1.2 Submitted article

Fischer D., Thomas S.M., Beierkuhnlein C. (2011): Vector-borne diseases in a rapidly changing world - Geography needs to become infected! The Geographical Journal, (submitted: 3rd of August, 2011, major revisions).

9.2 Further publications to the topic climate change effects on vector-borne diseases

9.2.1 Reviewed journals (by editor):

Fischer D., Stahlmann R., Thomas S., Beierkuhnlein C. (2009): Global warming and exotic insect borne diseases in Germany - Novel threats and scenarios, Geographische Rundschau (international edition), 5(2), 32-38.

Fischer D., Thomas S., Stahlmann R., Beierkuhnlein C. (2009): The propagation of exotic insect-borne diseases in Bavaria as a consequence of global warming, Forum der Geoökologie, 20(1), 51-53.

9.2.2 Peer-reviewed book chapters:

Fischer D., Thomas S., Stahlmann R., Beierkuhnlein C. (2009): Der Klimawandel als Herausforderung für biogeographische Analysen von Krankheitsvektoren - Szenarien für Bayern. In: Strobl J., Blaschke T., Griesebner G. (eds.): Angewandte Geoinformatik: Beiträge zum 21. AGIT-Symposium. Wichmann: Salzburg, 208-217.

Fischer D., Thomas S., Beierkuhnlein C. (2010): Einsatz regionaler Klimasimulationen in der Medizinischen Geographie: Möglichkeiten und Grenzen am Beispiel einer vektorübertragenen Infektionskrankheit. In: Strobl J., Blaschke T., Griesebner G. (eds.): Angewandte Geoinformatik: Beiträge zum 22. AGIT-Symposium Salzburg, Wichmann: Berlin, 248-257.

Remark:

Pdf-versions of the articles that are listed in chapter 9.2 were provided in the appendix of the submitted thesis as supplemental information for the examinations board.

9.3 Additional publications to other topics

9.3.1 Peer-reviewed journal:

Olehowski C., Naumann S., **Fischer D.**, Siegmund A. (2008): Geo-ecological spatial pattern analysis of the island of Fogo (Cape Verde). Global and Planetary Change 64, 188-197.

9.3.2 Book chapter:

Olehowski C., Naumann S., **Fischer D.**, Siegmund A. (2010): Vulnerabilitäts- und Degradationsanalyse semiarider Inselökosysteme der Randtropen am Beispiel der Insel Fogo (Kapverden). In: Dittman A., Jürgens U.: Entwicklungsforschung: Beiträge zu interdisziplinären Studien in Ländern des Südens (Reihe 9). Wissenschaftlicher Verlag: Berlin, 245-260.

9.3.3 Non-peer-reviewed journal:

Olehowski C., **Fischer D.**, Naumann S., Siegmund A. (2009): Satellitenbildgestützte Landbedeckungs- und Landnutzungsklassifikation der Insel Fogo (Kapverden). Zentralblatt für Geologie und Paläontologie - Teil 1- Jahrgang 2007(3-4), 345-355.

Erklärung

Hiermit erkläre ich an Eides statt,
dass ich vorliegende Arbeit selbständig verfasst habe, andere als die von mir angegebenen Quellen und Hilfsmitten nicht benutzt habe und die den benutzten Werken wörtlich oder inhaltlich entommenen Stellen als solche kenntlich gemacht habe.

Hiermit erkläre ich an Eides statt,
dass ich weder die vorliegende noch eine gleichartige Doktorprüfung an einer anderen Hochschule endgültig nicht bestanden habe.

Dominik Fischer Bayreuth, im August 2011