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RISK ASSESSMENT OF DENGUE VIRUS AMPLIFICATION IN EUROPE BASED ON SPATIO-TEMPORAL HIGH RESOLUTION CLIMATE CHANGE PROJECTIONS

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With 5 figures and 1 table
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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

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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 tyres (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 (Halstead 1988; 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).

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 thereupon 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 amplification 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).

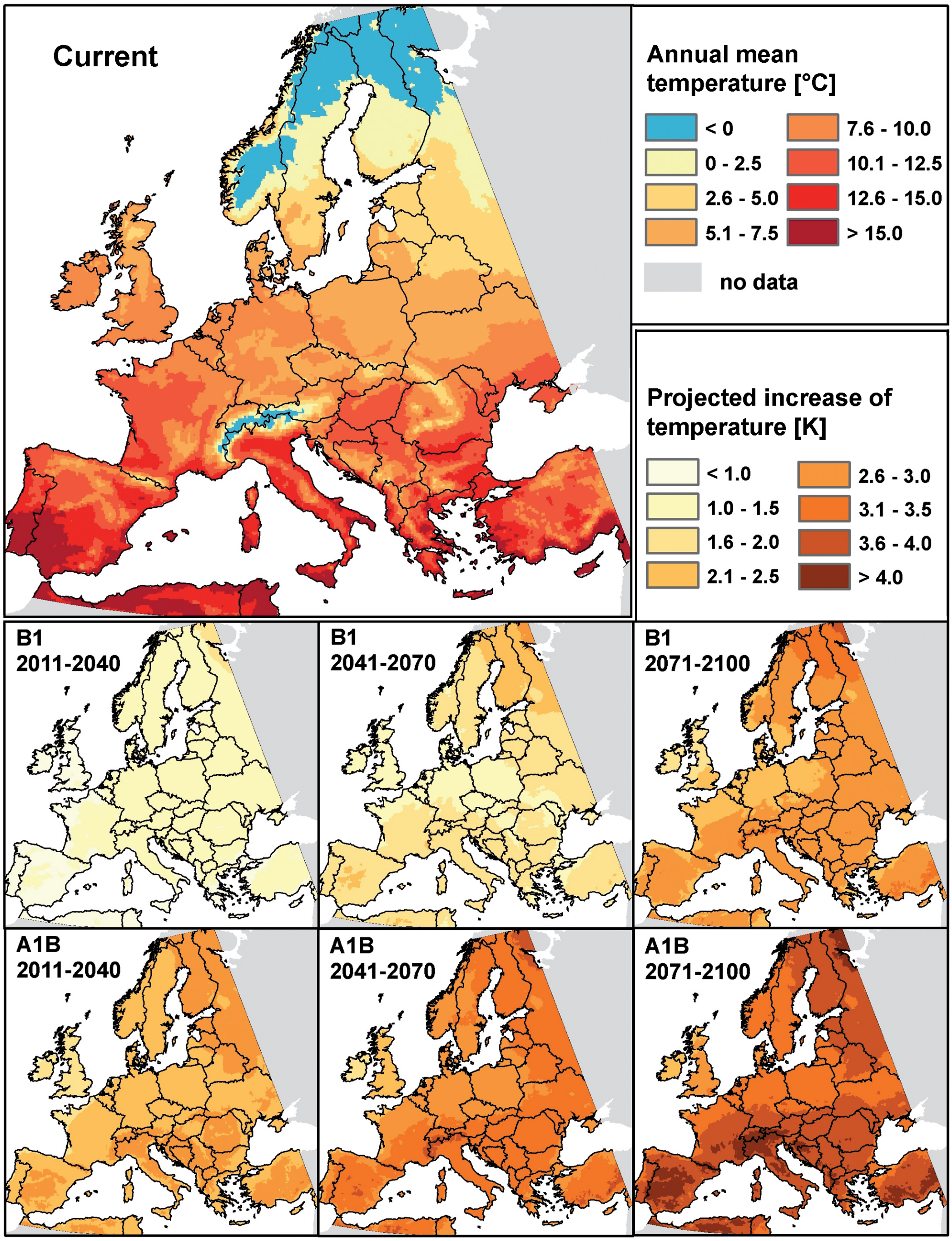

Fig. 1: Current annual mean temperature in Europe and projected warming in Kelvin during the 21st century based on two IPCC emission scenarios. Projections are based on the regional climate model COSMO-CLM. Generally, projected warming is less severe for the B1 scenario than for A1B. Highest increase 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.

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.

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

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	-	-	-	-

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–

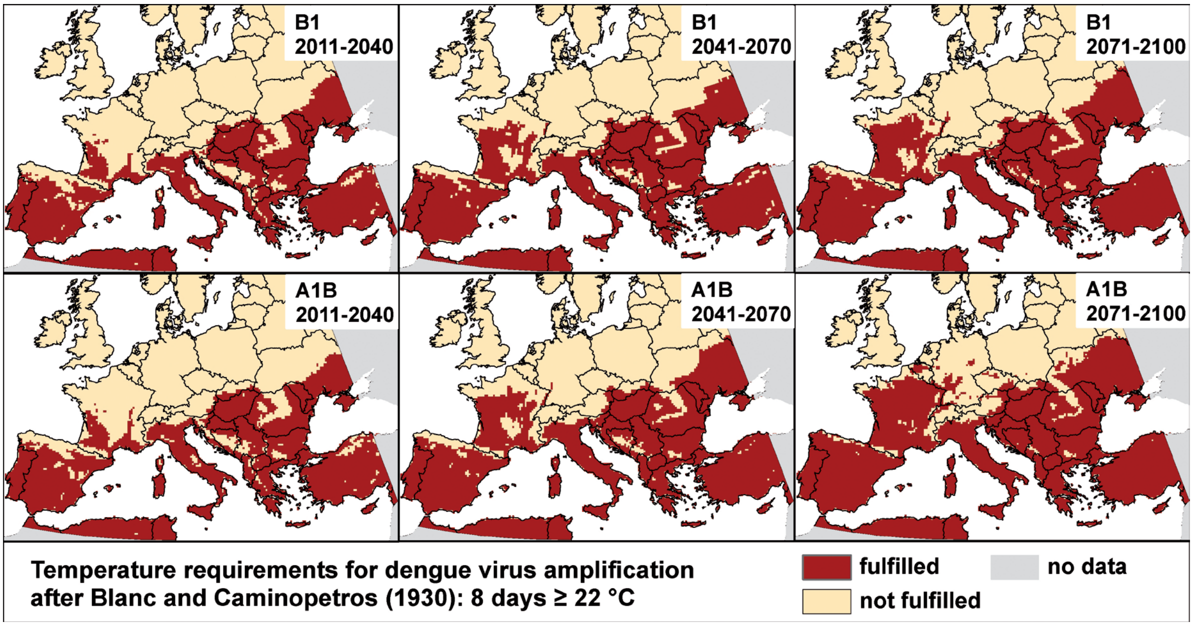

Fig. 2: Projection of the extrinsic incubation period for dengue virus amplification within the vector *Aedes aegypti*, determined by Blanc and Caminopetros (1930) with eight consecutive days of at least 22 °C

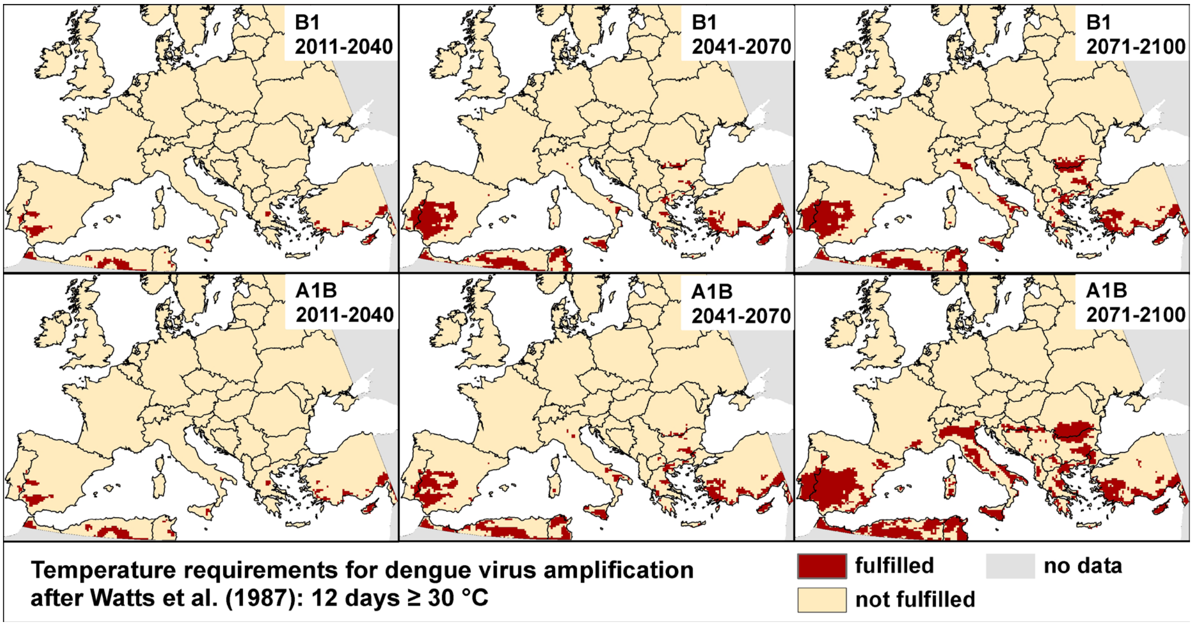

Fig. 3: Projection of the extrinsic incubation period for dengue virus amplification within the vector *Aedes aegypti*, determined by Watts et al. (1987) with twelve consecutive days of at least 30 °C

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.

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.

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.

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-

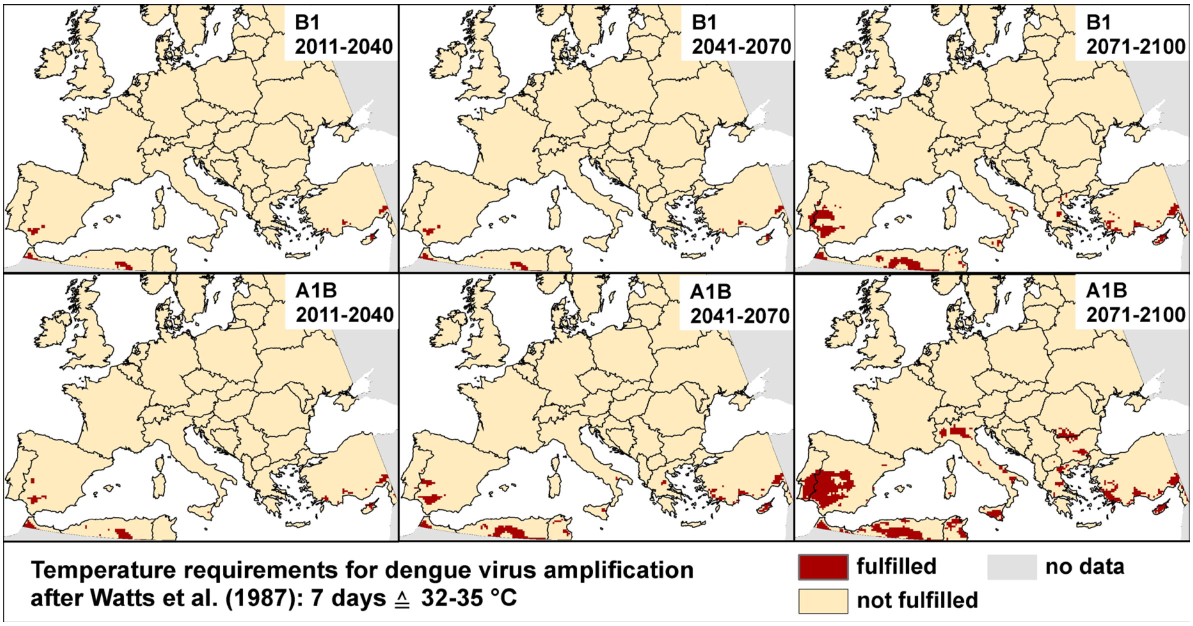

Fig. 4: Projection of the extrinsic incubation period for dengue virus amplification within the vector *Aedes aegypti*, determined by Watts et al. (1987) with seven consecutive days between 32–35 °C

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.

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 tempera-

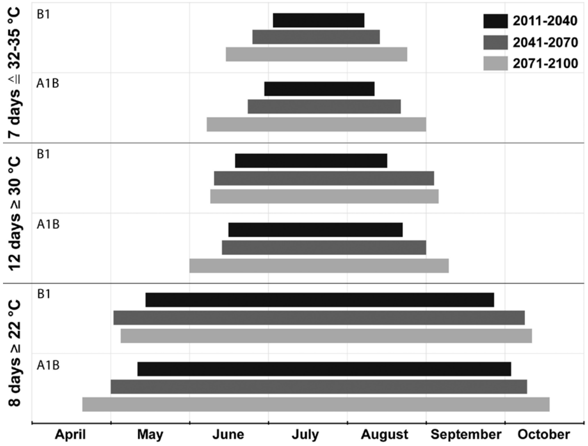

Fig. 5: Longest possible intra-annual period of dengue virus amplification in Europe

ture 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 nonphotoperiodic ancestors (in Brazil), whereby a diapause reduction could be observed presumably due to rapid local selection (in USA) (Lounibos et al. 2003). Furthermore, a distinct competitive advantage is found for *Ae. albopictus* compared with *Ae. aegypti* especially in the larval stadium (Braks et 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_0) 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 Hales et 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 R_0-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 (Kjellström et 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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