



TECHNICAL REPORT

The climatic suitability for dengue transmission in continental Europe

ECDC TECHNICAL REPORT

The climatic suitability for dengue transmission in continental Europe



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Abbreviations

AIC	Akaike's Information Criterion
AICc	Akaike's Information Criterion Corrected
AUC	Area under the curve
AVHRR	Advanced Very High Resolution Radiometer
BRDF	Bidirectional Reflectance Distribution Function
CDC	United States Centers for Disease Control and Prevention
CRU	Climate Research Unit
DENV	Dengue virus
ECDC	European Centre for Disease Prevention and Control
EU	European Union
EVI	Enhanced Vegetation Index
GAMs	Generalised additive models
GCM	Global climate model
GLIMs	General Linear Models
LST	Land surface temperature
dLST	Daytime land surface temperature
nLST	Night-time land surface temperature
MD	Mahalanobis distance
MODIS	Moderate Resolution Imaging Spectroradiometer
NASA	National Aeronautics and Space Administration
NDVI	Normalised Difference Vegetation Index
NLDA	Non-linear discriminant analysis
PCA	Principal Components Analysis
ROC	Receiver Operating Characteristics
TFA	Temporal Fourier analysis
VBORNET	A network of medical entomologists and public health experts
WHO	World Health Organization

Executive summary

Background

The global incidence of dengue has increased over the past fifty years. Although the main mosquito vector for dengue is *Aedes aegypti*, the species *Aedes albopictus*, which is present in continental Europe, has also been shown to be capable of transmitting dengue, and in 2010, sporadic dengue transmission occurred in continental Europe. This project assesses which areas in Europe could be most amenable for dengue transmission.

Methodology

Data on the global distribution of *Aedes aegypti*, *Aedes albopictus*, and cases of dengue were collected. Using datasets for climate, environmental conditions, geography, and population density, mathematical modelling (non-linear discriminant analysis) was conducted to assess the areas of Europe most climatically suitable for *Ae. aegypti*, *Ae. albopictus*, and dengue transmission.

Results

Climate suitability maps were developed for *Ae. aegypti*, *Ae. albopictus*, and dengue. Europe appears to be at little risk from dengue transmission in comparison with other locations globally. Much of central and Mediterranean Europe is potentially climatically suitable as a habitat for *Ae. albopictus*. For *Ae. aegypti*, there are some areas that could potentially be a suitable habitat, including the Mediterranean areas of Spain, France and Italy as well as south-eastern Europe. Yet, the actual establishment would depend upon the introduction and expansion of the vector, the absence of effective vector control measures, and possible competition with *Ae. albopictus*.

Discussion and conclusion

Suitability maps can be a useful tool for public health planning, but there are many potential sources of error that need to be properly understood. The current risk to Europe from the transmission of dengue appears to be minimal, yet some areas of Europe are more suitable for transmission than others. A sensible strategy is to continue to monitor the spread of *Ae. albopictus* across Europe, to maintain vigilance for *Ae. aegypti*, and to consider expanding vector surveillance in areas particularly suitable for these vectors. Additional research is needed to better understand the ecology of dengue in a European context, and to assess the possible impacts of climate change and other important drivers of dengue on the risk of dengue in Europe.

1 Introduction

Scope and purpose

This report summarises the key findings of a project for which the objectives were to develop a series of risk maps demonstrating the current and potential distribution of dengue in continental Europe, based upon current knowledge of global dengue transmission, as well as of its mosquito vectors, *Ae. aegypti* and *Ae. albopictus*. It is published with the sole intention of informing readers about the findings from this project, so as to inform any subsequent research or public health work addressing dengue transmission in continental Europe. This report is not designed to offer formal guidance or guidelines on the best strategies for preparing for dengue. It has been prepared for public health institutions and scientific experts dedicated to the control of vector-borne diseases. This report should be of particular relevance to those working with vector-borne diseases in European Union (EU) Member States and neighbouring countries, but it may also be relevant to a broader international audience.

The project was commissioned in 2009 in order to conduct a preliminary assessment of the possibility for dengue transmission in continental Europe. Following the outbreak of chikungunya in 2007, European public health officials have become more concerned about possible outbreaks of mosquito-borne diseases, and this project was commissioned in order to compile the best evidence currently available.

The project was financed solely by the European Centre for Disease Prevention and Control (ECDC), and the project was undertaken by the University of Oxford, United Kingdom, in collaboration with ECDC technical staff.

2 Background

The global incidence of dengue, a mosquito-borne arboviral infection transmitted by *Aedes* genus mosquitoes and with humans as sensitive hosts, has increased in recent decades. There are four different types of dengue virus (DENV) that circulate globally with partial cross-immunity. Dengue is an endemic disease in Africa, the Americas, the East Mediterranean, South-east Asia and the West Pacific, with the World Health Organization (WHO) estimating that 2.5 billion people are now at risk [1]. Globally, there are an estimated 50–100 million dengue cases annually [1], including 500 000 cases of severe dengue.

Dengue infections now occur in roughly 100 different countries globally [2]. In recent years, this has included European countries. In 2010, autochthonous dengue transmission occurred in Europe for the first time since 1927–1928, when Greece suffered from a large outbreak [3]. The 2010 transmission, which took place in southern France [4] and in Croatia [5], involved just a small number of cases but has led to concern amongst public health officials about a potential resurgence and spread of dengue in Europe. This possibility is not to be discounted in a highly interconnected and warming world. The rate limiting steps of persistent transmission cycles are the presence of the DENV, sensitive hosts and competent vectors. The Asian tiger mosquito, *Ae. albopictus*, first appeared in Europe in Albania in 1979, and since its introduction into Italy in the early 1990 via trade in used tires [6,7], the mosquito is notably prevalent in the northwest Mediterranean basin (**Figure 1**) [7]. The expansion of the vector in Europe has been driven by global trade and travel between climatically similar regions [8], and some have speculated that future European expansion of *Ae. albopictus* could be further facilitated by climate change, as altered warming and precipitation patterns might increase the number of suitable niches for the vector [9].

It is noteworthy that *Ae. aegypti*, the primary dengue vector, mediated the 1927–28 outbreaks in Greece [10]. Although capable of transmitting DENV, the degree to which *Ae. albopictus* could drive sustained transmission of dengue in Europe is uncertain. As compared to *Ae. aegypti*, *Ae. albopictus* has a wider environmental flexibility, prefers peridomestic over urban environments and feeds on a wider range of terrestrial mammals thereby enhancing its invasiveness. The latter two factors might lessen its propensity to transmit DENV [11]. In the laboratory, *Ae. albopictus* is susceptible to infection and transmits a wide range of arboviruses for which *Ae. aegypti* is the main vector, including dengue and yellow fever flaviviruses and chikungunya alphaviruses [12]. *Aedes albopictus* appears to be more susceptible to DENV infection in the midgut than is *Ae. aegypti*, but as viral dissemination rates from the midgut to other tissues are significantly lower in *Ae. albopictus*, it has been suggested that it is a much less effective epidemic DENV vector than *Ae. aegypti* [13]. However, it must be remembered that viruses have the potential to adapt to secondary vectors, as reported for chikungunya virus in 2005–2006 in the Indian Ocean [14].

Well-known natural experiments appear to confirm this suspicion [11,13,15]. Taiwan has *Ae. aegypti* in its southern extremities, but *Ae. albopictus* throughout the rest of the island. As Taiwan also has a high human population density with generally low herd immunity to DENV, it is noteworthy that the island has witnessed no major dengue outbreaks in the past 60 years in areas where *Ae. albopictus* is present [13]. In both Guam and Hawaii, *Ae. albopictus* replaced *Ae. aegypti* in the 1950s and 1960s [11]. Despite being surrounded by islands that

have suffered from numerous dengue outbreaks (with *Ae. aegypti* as a vector), only one dengue epidemic has been reported in Hawaii in 2001–2002, when 122 autochthonous cases were reported [16]. The cases were believed to have been imported from French Polynesia, where a large outbreak transmitted by *Ae. aegypti* was taking place [16].

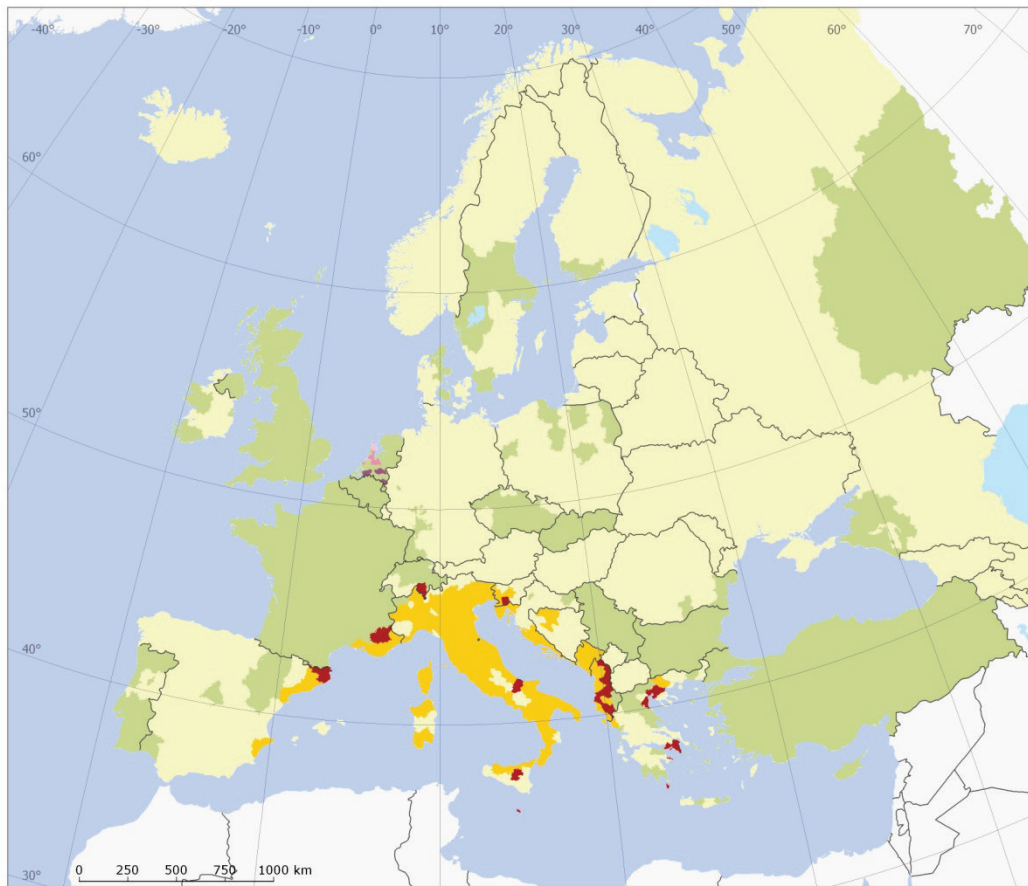
Nonetheless, evidence contrary to the above was supported by a dengue outbreak of around 200 cases mediated by *Ae. albopictus* that took place in the French island La Reunion in 2004 [17]. This vector has also demonstrated its ability to cause outbreaks in Europe during the 2007 outbreak of chikungunya in Italy, in which an infected traveller from India resulted in autochthonous viral transmission, leading to over 200 laboratory-confirmed cases of chikungunya [18]. The high density of *Ae. albopictus* upon arrival of the viremic index case was described as a main driver of the outbreak [19]. These observations, considered alongside the 2010 local DENV transmission in Croatia and France, support the notion of a possible dengue epidemic in Europe transmitted by *Ae. albopictus*. Certainly, there are plenty of opportunities for DENV to come into contact with the vector: in 2008, 526 imported dengue cases were reported by eleven EU Member States¹ [20]. But does a large number of possible introductions of DENV into regions of Europe with *Ae. albopictus* suggest that a dengue outbreak is inevitable, or point to the poor vector competency of the mosquito?

In order to obtain a better understanding of the risk that dengue poses to continental Europe, a series of risk maps were developed describing the climatic suitability for dengue transmission across the world. It is important to note that the possibility of dengue transmission in Europe must be understood by considering a global context, given the very few instances of dengue transmission in Europe. This report describes the climatic suitability within Europe for the two primary dengue vectors as well as for dengue transmission in Europe. All maps were produced via models that were based upon data on the global presence and absence of these vectors and/or of dengue. In addition to climate suitability maps, this report discusses the degree of climatic difference – the Mahalanobis distance (MD) – that exists between Europe and known sites of dengue transmission.

The maps presented in this report provide a basis for developing public health measures that address the spread of dengue and its vectors, but the interpretation of the risk maps must be done by keeping in mind that the risk in Europe is much less than the risk elsewhere based upon current climatic conditions.










¹ The number of reported dengue cases may not perfectly reflect reality due to varying case definitions for dengue and differences in whether dengue or only dengue hemorrhagic fever is reported. Nonetheless, the vast majority of these cases were reported during periods in which *Aedes* mosquitoes were inactive in Europe.

Figure 1. Recorded presence and absence of *Aedes albopictus* at regional administrative levels (NUTS) in continental Europe



Projection : Lambert Azimutal Equal Area © EuroGeographics for the administrative boundaries. © European Centre for Disease Prevention and Control, 2012. Source: Data courtesy of Vboronet (http://ecdc.europa.eu/en/activities/diseases/programmes/emerging_and_vector_borne_diseases/Pages/VEBORNET.aspx).

Legend

- | | | |
|--|---|---|
| <i>Aedes Albopictus</i> |  Indoor presence (2008-2011) |  Borders |
| Surveillance data |  Indoor presence (2011) |  Lakes |
|  Presence (2008-2011) |  Not recorded | |
|  Presence (2011) |  No data | |
|  Indoor presence (2008) | | |



Note: Indoor presence corresponds to presence recorded in greenhouses. Data courtesy of Vboronet.

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3 Methods

3.1 Data collection

Vector distribution data.

Databases of the global distribution of *Aedes aegypti* and *Aedes albopictus* were constructed as a basis for modelling. The PubMed, Web of Science and Promed databases were used. Search terms were '*Aedes aegypti*' and/or '*Aedes albopictus*'. The time span for articles from PubMed and Web of Science was from 1960–May 2009. Promed archives date back to January 1994, and the time span was January 1994 until July 2009.

10 314 original citations were retrieved and each was scanned for likelihood of containing geographical information about the distribution of *Aedes aegypti* or *Aedes albopictus*. Of these, 3 723 citations were identified, of which 3 704 were obtained as PDF files. This led to 6 111 points and 2 550 polygons of *Aedes* presence, from which 5 467 geo-located point records and 571 geo-located polygon records were obtained to complete this database.

A second database, which was used to develop a series of risk maps for *Aedes albopictus* in Europe, was created from the ECDC Tiger Maps project [9]. A third database, for *Aedes albopictus* within the USA only, was made from maps made available through the American Centers for Disease Control and Prevention (CDC) and appearing on a number of websites, or in presentations from CDC personnel that can be found on the internet [21–22]. These maps record the distribution of this species to county level (only) as it spread into the USA. A fourth database was made by amalgamating the points in the first three *Ae. albopictus* databases, above. This database was then augmented with private database records on the Asian range of *Ae. Albopictus* [23].

The core of the database for *Ae. aegypti*, the more important vector of dengue, was the first database described above. A second database for *Aedes aegypti* was derived from a map published in 1965 [24] and supplemented by additional information in 2008 [21]. This map was scanned and registered for data points. The two *Ae. aegypti* databases were combined into a single '*aegypti* database' for modelling purposes.

Dengue distribution data.

The present project benefited from a pre-existing dengue database made from the on-line published literature up to 2006. This previous database had not included any records for continental USA or for Puerto Rico. For the present project, therefore, the previous search was brought up to date (to September 2009), and the USA and Puerto Rican records were added. Wherever noted by the original authors, the database recorded the disease either as 'dengue fever' or as 'dengue haemorrhagic fever'. This database involved an original search of a total of 7 778 dengue citations (4 304 from the previous study and the remainder from the present study), the selection of a total of 3 010 of these for further investigation, 2 838 of which were obtained as PDFs, in which 3 399 point and 5 371 polygon records were identified, of which 435 point and 5 308 polygons could be geo-located.

Environmental, climate, geographic and population density data.

Time series of nominal 1 km spatial resolution Moderate Resolution Imaging Spectroradiometer (MODIS) data from the National Aeronautics and Space Administration (NASA) Terra satellite were downloaded from NASA's Earth Observing System data gateway [25] for five complete years, January 2001 to December 2005. A MODIS digital elevation surface dataset was also used. Satellite-derived rainfall estimates from the CPC MORPHing technique project² and meteorological station derived WORLDCLIM climate surfaces at 1/120th degree resolution³ [26].

The Hadley Centre Coupled Model, version 3 (HADCM3) synoptic monthly dataset, a global climate model (GCM) produced by the Hadley Centre, was used at a resolution of 3.75 degrees of longitude by 2.5 degrees of latitude. This was downloaded from the Intergovernmental Panel on Climate Change data distribution centre [27].

A dataset on surface of estimated human population density per square km was obtained from the Global Rural-Urban Mapping Project "GRUMP" project [28].

Further details about the data collection and MODIS data can be found in Annex 1 and Annex 2, respectively.

² http://www.cpc.noaa.gov/products/janowiak/cmorph_description.html

³ <http://www.worldclim.org/>

3.2 Data processing

Multi-temporal environmental data were processed using temporal Fourier analysis (TFA), which produces descriptors of environmental signals that are both robust statistically and meaningful biologically [29–30]. Most data were TFA processed at their original resolution (i.e. 1km for MODIS data, 1/6th degree for the Climate Research Unit high resolution data), except in the case of the HADCM3 data that were spline-interpolated to 0.5 degrees resolution before TFA processing. The TFA-ed 1/6th degree Climate Research Unit (CRU) meteorological data and the 0.5 degree HADCM3 data were used at these resolutions in a number of models, yet, in the case of the MODIS and WORLDCLIM data, the fine resolution TFA data were first aggregated to coarser spatial resolution, by spatial averaging, to 1/15th of a degree. Similarly, the human population density surface was aggregated to 1/15th degree. Global models for the current distribution of dengue and its vectors were then developed at this resolution.

3.3 Modelling

Model selection

The sets of data on vector and disease distribution derived from the literature are unique objects and it is impossible to justify the application of many traditional ('frequentist') statistical methods to them. So little is known about the real determinants of most species' distributions that it is necessary to start with a much larger dataset of potential predictor variables (the danger of data dredging), and then decide which ones might be important. The selection of variables during model fitting is an often neglected part of model building. Some modelling approaches (including much-favoured Bayesian methods) have no obvious way of selecting from a list of candidate predictor variables a subset that actually describes well the distribution of the species under study. Such models often end up using all variables; a good fit to the data may be obtained, but at the cost of parsimony and, usually, any possible understanding of the biological processes underlying species' distributions. To avoid these twin pitfalls, the models developed here use as few variables as possible, selected in a step-wise inclusive manner using one or more accuracy measures (most frequently κ , the kappa statistic, or the corrected Akaike's Information Criterion, AICc).

Generation of pseudo-absence points

Non-linear discriminant analysis requires both presence and absence data; the models then aim to discriminate between these two categories using the predictor variables available. Databases only rarely record absences, and rarely a sufficient number of them, so 'pseudo-absence' data points must first be generated from the presence data. A first round of model building was carried out choosing pseudo-absence points simply on the basis of geographical distance. A single model was run using all the presence and absence data and predictor variables were selected in a step-wise fashion. At the end of this first model run a new image was created of the MD of all pixels in the image to the nearest presence cluster. The MD is a co-variance adjusted measure of environmental distance, here calculated using the key predictor variables for each mosquito vector or disease dataset. Thus the MD image shows how far each point is in environmental, rather than geographic space from any presence area. Subsequently, all models are then involved in selecting pseudo-absence points on the basis of both geographic and MD criteria. Points which were either too close geographically or too close environmentally were not selected as pseudo-absences.

The frequency distribution of the MDs of sites known and classified as being presence sites were compared to the frequency distributions of sites known to be present but classified as absent; sites assumed to be absent but classified as present; and sites assumed to be absent and classified as absent in the confusion matrix. The aim was to identify a threshold MD value that reduced as far as possible the classification errors, without creating new errors in those points currently correctly classified. Once these thresholds were decided upon, a new set of pseudo-absence points were generated from each database and combined with that database's presence points. The satellite and other data were then extracted for all the points, thus creating the training set used in all subsequent models.

Model implementation

All maps were produced through the following steps:

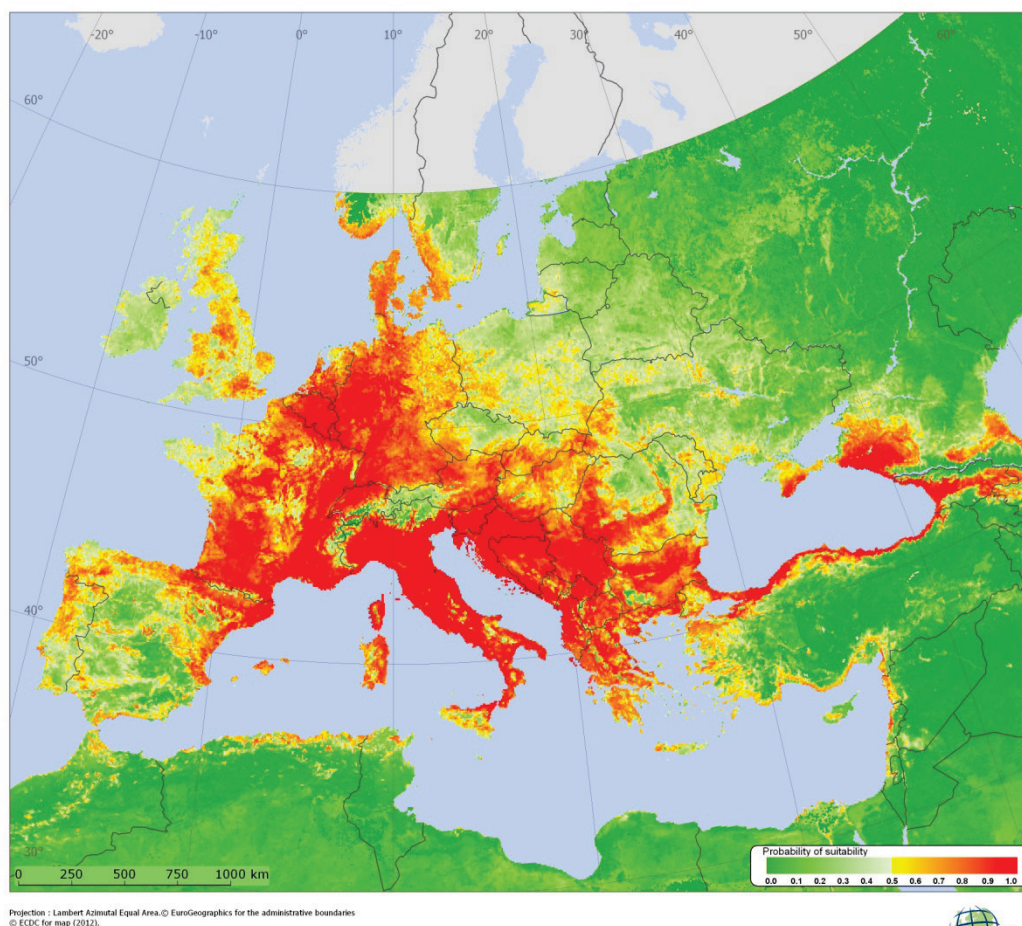
- The entire training set of data was subjected to k -means cluster analysis within SPSS™, to show cluster membership of each data-point for presence clusters and absence clusters. During the clustering process, SPSS first allocated all the points to one or other clusters, and then examined the entire dataset for outliers, i.e. points which were more than six standard deviations away from their cluster means. These outliers were then excluded and the clustering was repeated, thus generating a series of clusters which could be regarded as multi-variate normal. Outliers were identified in the output file, and were not subsequently used in modelling.
- One hundred bootstrap samples, with equal numbers of presence and absence points, were taken at random, with replacement, from the training set. Using equal numbers of presence and absence points ensures greater model accuracy[31], and sampling with replacement makes it more likely that the relationship of the bootstrap sample to the training set is similar to that between the training set and the real world, of which it is a sample.
- Within each bootstrap model, ten variables from the entire set of available predictors were selected in a step-wise inclusive fashion, on the basis either of minimising the corrected AIC and maximising the kappa statistic, κ .
- For each bootstrap model an output image file, a climate suitability map, was produced using the model results applied to the selected input data layers for that particular model. Output was expressed in terms of posterior probabilities on the scale of 0 to 1. Discriminant analytical models calculated the position of each point on the multi-variate surfaces determined by the input data. The underlying assumption of multi-variate normality ensured that the outputs are real probabilities in the statistical sense (they are the probabilities that each point 'belongs' to each cluster in the model, on the basis of the similarity of its environmental conditions to those of each cluster).
- The 100 maps produced from the 100 bootstrap samples were averaged to produce the final output prediction – the final risk maps. The outputs of the 100 bootstrap models also produced 100 images of the MD of every pixel from the nearest (in environmental space) dengue presence area. The MD neatly allows comparisons to be made between models, more or less regardless of the predictor variables used within them.

4 Results

4.1 *Aedes albopictus* map for continental Europe

Models were run for each of the individual *Ae. albopictus* databases described in 3.1 of the Methods section and, as described in section 3.3 of the Methods, produced based upon averages from 100 bootstrap models. The outputs from all of these models were then combined to produce the final map, which presents the estimated areas of environmental suitability for *Ae. albopictus* in continental Europe (Figure 2).

Figure 2. Climatic suitability for *Aedes albopictus* in Europe



Note: This map was produced by combining the outputs of all the *Ae. albopictus* models using a non-linear discriminant analysis. The probability scale is from zero to 1.0:

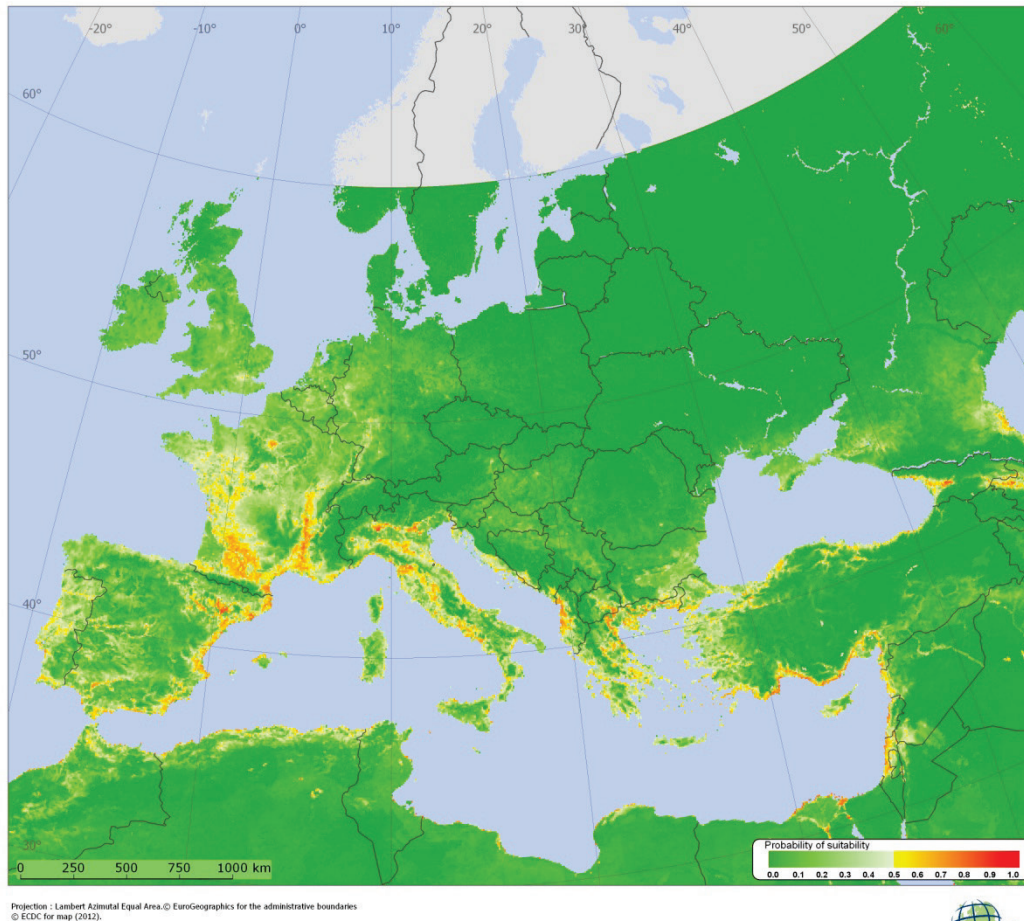
Probabilities from [0–0.49] are coloured green (darker to lighter) and indicate conditions not suitable for the vector (or gradual predicted absence of the vector).

Probabilities from [0.5–1] are coloured yellow through to red, indicating conditions increasingly suitable for the vector (or gradual predicted presence of the vector).

4.2 *Aedes aegypti* map

Models were run for each of the individual *Ae. aegypti* databases described in Methods and produced based upon averages from 100 bootstrap models. The outputs from all of these models were then combined to produce the final map, which presents the estimated areas of environmental suitability for *Ae. aegypti* in Europe (Figure 3).

Figure 3. Climatic suitability *Aedes aegypti* in Europe



Note: This map was produced by combining the outputs of all the *Ae. aegypti* models using a non-linear discriminant analysis. The probability scale is from zero to 1.0:

Probabilities from [0–0.49] are coloured green (darker to lighter) and indicate conditions not suitable for the vector (or gradual predicted absence of the vector).

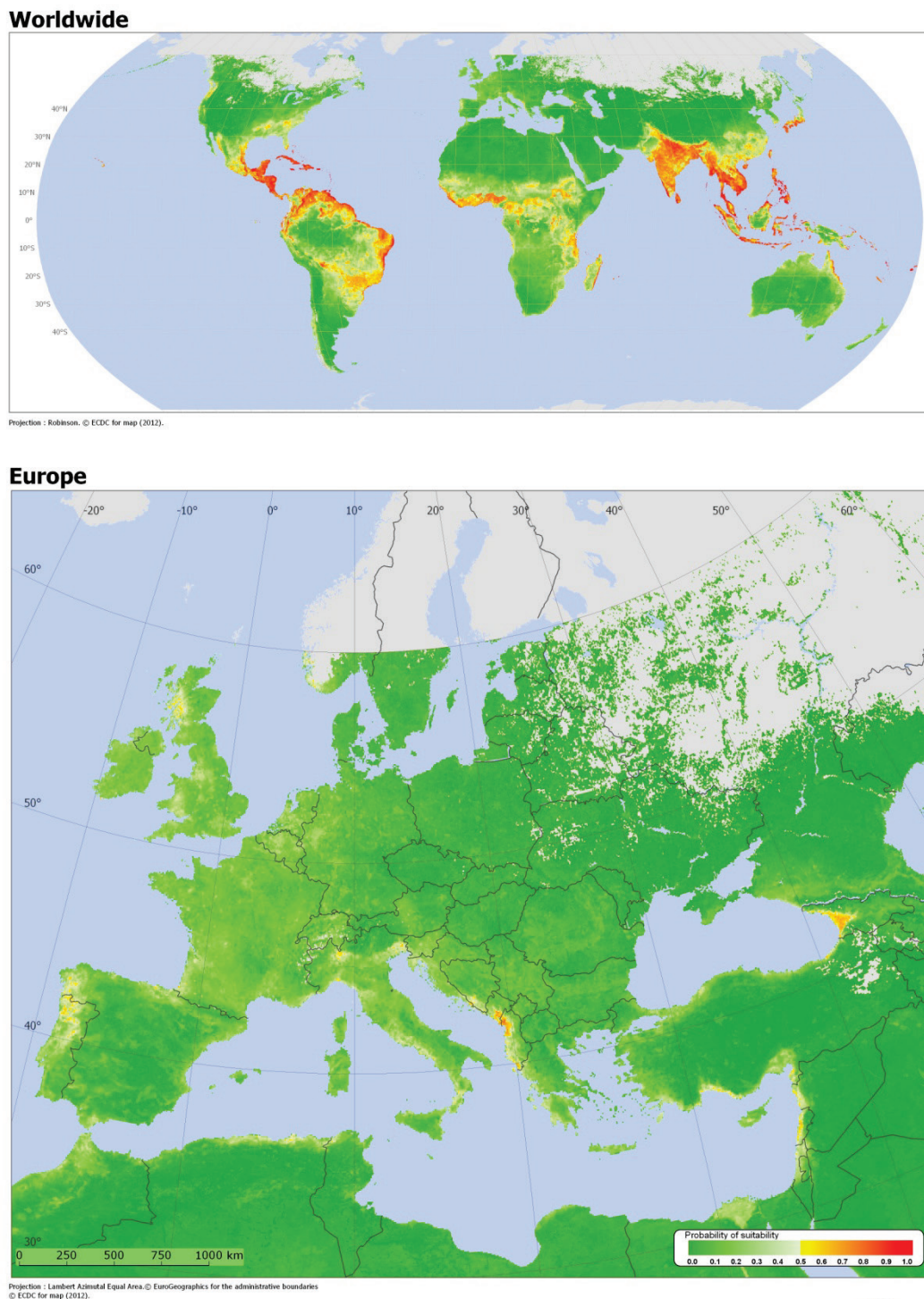
Probabilities from [0.5–1] are coloured yellow through to red, indicating conditions increasingly suitable for the vector (or gradual predicted presence of the vector).

4.3 Global climatic suitability for dengue transmission

The climate suitability maps for dengue were based upon models which assessed the combined database of recorded dengue fever and severe dengue (Figure 4). The maps presented in Figure 4 represent the average of 100 bootstrap models, each one using 600 absence and 600 presence sites selected at random, with replacement from the training set database which had a total of 2 926 presence and 14 997 absence points.

The top two variables are the means of the two rainfall variables, CMORPH and WORLDCLIM. The second important variable was mean land-surface temperature.

Figure 4. Climatic suitability of Dengue fever transmission



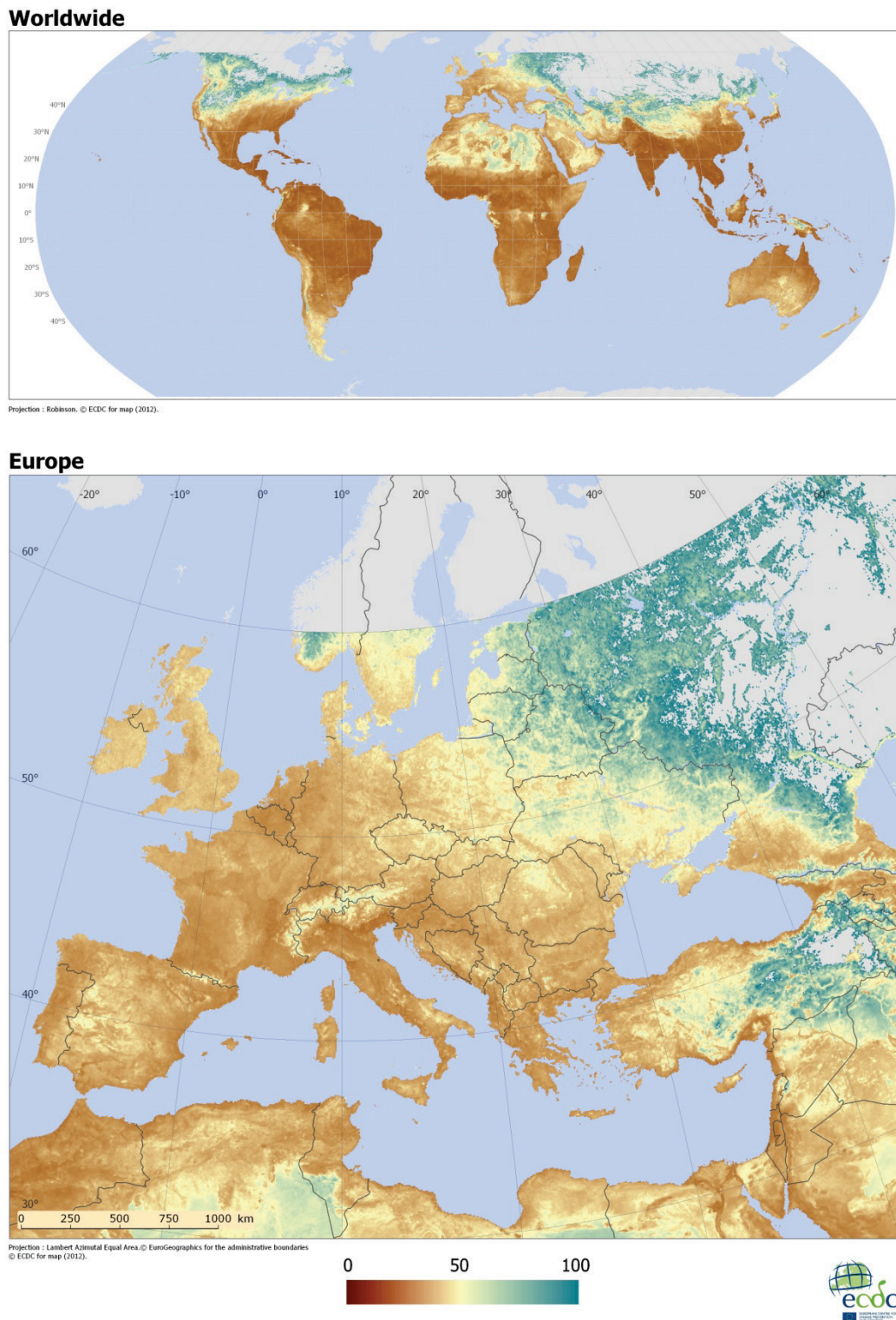
Note: This map was produced by combining the outputs of all the Dengue fever models. The probability scale is from zero to 1.0: Probabilities from [0–0.49] are coloured green (darker to lighter) and indicate conditions not suitable for the vector (or predicted absence of the vector). Probabilities from [0.5–1] are coloured yellow through to red, indicating conditions increasingly suitable for the vector.

4.4 Mahalanobis distance assessment

Mahalanobis distance can be used to assess the vulnerable areas for Europe for dengue i.e. those areas most similar environmentally to known dengue areas worldwide. Mahalanobis distance is a metric used to calculate the distance between any two points using a co-variance adjusted measure of environmental distance. Mahalanobis distance therefore neatly allows comparisons to be made between models more or less regardless of the predictor variables used within them. The average MD image from the 100 bootstrap models does give some idea of the similarity of areas in Europe to dengue areas as the same predictor variables are used within each model. The shorter the MD distance is, in other words the lower the MD value, the more climatically similar the location is to those locations where dengue has been recorded.

In the MD assessment, Europe's climate is being compared with, for example, South-East Asia. The final maps (Figure 5) identify the most vulnerable areas of Europe for dengue transmission; i.e. those areas most similar environmentally to known locations of dengue transmission globally. This figure shows the mean MD (i.e. the distances in covariance-adjusted multi-variate space), of each pixel from the sites where dengue has been recorded globally. The legend shows the colour scale for MD. Areas in Europe environmentally similar to dengue sites globally are the areas coloured dark brown; areas are increasingly distant in a multivariate space to global dengue sites as MD increases through the colour scale from brown, pale yellow, and blue. Note that grey corresponds to no prediction possible.

Figure 5. Mean Mahalanobis distances for dengue transmission in Europe



Note: Greater MD (i.e. towards the blue end of the spectrum on the scale used in the maps) means less environmental suitability for dengue transmission. Mahalanobis distance is a relative scale, and the European map should be compared with the Worldwide map in order to place the European map in context. Areas in Europe environmentally similar to dengue sites globally are the areas coloured dark brown; areas are increasingly distant in a multivariate space to global dengue sites as MD increases through the colour scale from brown, pale yellow, and blue. Note that grey corresponds to no prediction possible

5 Discussion

The maps presented in this report have assessed the probability that a given location within continental Europe is climatically suitable as habitats for the two mosquito vectors of dengue, *Ae. albopictus* (Figure 2) and *Ae. aegypti* (Figure 3), as well as whether these locations are climatically suitable for dengue transmission (Figures 4–5). As such, these maps help to identify the regions within Europe that are relatively more likely to be favourable for dengue transmission than other regions within Europe. However, they do not provide a calculation of the absolute risk of dengue transmission. Ultimately, this risk will be dependent not only on climatic circumstances, but also numerous other factors, such as the frequency of introductions of dengue into Europe via trade or travel; the presence or absence of vector surveillance and vector control activities; and the ability of public health systems to quickly identify and control any potential dengue outbreak.

5.1 European climatic suitability for *Aedes albopictus* and *Aedes aegypti*

Each of the maps in Figures 2 and 3 shows different areas suitable for the two *Aedes* species. Whilst global databases (e.g. the WDM *Aedes* database) are very good starting points, records for individual regions or continents, such as for both species in the USA, or for *Ae. albopictus* in Europe, show additional areas that these species can inhabit. Although these two examples are on or near the edge of the two species' current global distribution, it is precisely these sorts of regions that are of interest for the current project. What the risks are that *Ae. albopictus* will spread further in Europe, or that *Ae. aegypti* will survive and become established in Europe after its introduction.

By the same token, the use of global data contributed to the production of these regional maps. Building a statistical risk map for any invading species such as *Ae. albopictus* in Europe, solely on the basis of records for this species within Europe to date, does probably not reflect the full range of environments that the species can occupy. The species' global distribution can reveal the climatic conditions in which this species can inhabit elsewhere. If European climates are similar to these it is reasonable to expect that *Ae. albopictus* may be able to survive or establish in them, if it manages to reach them. However, it must always be remembered that other factors, such as the presence of vector control activities, land-use changes, or niche competition between different mosquito species, will also ultimately influence the ability of a vector to survive in a given area.

In this project, risk maps were created for these two dengue vectors with a special interest in the European region. In order to use as much of the information as possible within the risk maps, the final risk maps for both *Aedes* species presented here are the combined final outputs from several models.

Although *Ae. aegypti* has only been sporadically observed in continental Europe since the second world war, these findings indicate that some areas of southern Europe could indeed be suitable habitats. It is noteworthy, therefore, that *Ae. aegypti* is present in the Portuguese territory Madeira [32], not to mention numerous other areas of the world for which extensive trade and travel links with continental Europe exist. Numerous potential opportunities for the re-introduction of the vector therefore exist. Vector surveillance activities, particularly in Albania, France, Greece, Italy, Montenegro and Spain, should at the least be vigilant for potential introductions of the principal dengue vector.

5.2 The potential climatic suitability for dengue transmission in continental Europe

The findings from this study address the question: 'Where in Europe are conditions most similar to those where dengue occurs elsewhere?' Although very little of continental Europe appears to be highly compatible for dengue transmission, there are some areas within Europe that warrant attention, which is supported by the observed 2010 transmission of dengue in Croatia and France. These incidences certainly highlight the need for vigilance of sporadic dengue transmission in Europe, but they do not fundamentally challenge the models presented in this report. This is because most global data of dengue fever and severe dengue relates to transmission mediated by *Ae. aegypti*. There are simply not enough known instances of dengue outbreaks mediated mostly or only by *Ae. albopictus* to permit an accurate global model based upon these alone. It is the research team's general opinion however that the vectorial capacity of *Ae. albopictus* would most likely have to change (through an adaptation of dengue viruses to this vector) before it could become a serious threat for dengue transmission in Europe. Based upon laboratory experiments, such changes appear to be more likely for chikungunya virus than for dengue viruses.

5.3 Potential sources of error and limitations

Working with models involves uncertainties. In the case of this study, the most likely inaccuracies are false positives, in which presence of dengue or its vectors is wrongly predicted, and false negatives, in which absence is wrongly predicted. As concerns the former, it is important to note that it is a common ecological observation that not all suitable sites for any organism are actually occupied by it. For geographical reasons the organism may never have arrived there, or for historical reasons it may have experienced a population decline and become (temporarily) extinct there by the time the training set sample was taken. The same applies to diseases, especially those that are spreading within new continents. It takes time for a disease or a vector to spread so as to occupy all suitable niches. In the meantime, risk maps are likely to show many false positives. These do not necessarily indicate errors in the modelling and should therefore not be used to conclude that the model is inaccurate.

False negative predictions also give cause for concern. When a disease occurs in an area predicted to be unsuitable for it, there is a misclassification in prediction, and probably therefore the underlying model. False negative predictions form a much firmer basis for questioning the accuracy of any predictive model. It is a limitation of the study that the modelling is based on pseudo-absence points rather than recorded absence points to adopt a probabilistic approach for overcoming the lack of real-life absence data.

The risk maps presented in this study are based upon the hypothesis that distributions of animals in environmental, as opposed to geographical, space are multi-variate normal. It is often the case that predictor variables are not multi-variate normal, as not only may areas of presence and absence differ in their environmental characteristics, but different parts of a species range may also show more subtle differences, requiring separate multi-variate descriptions of their climatic conditions. A separate cluster analysis is required to render such data multivariate normal, grouping it into clusters. Each cluster (either for presence or absence) is then treated as a separate multi-variate normal distribution, with its own co-variance characteristics, and the posterior probabilities are calculated by summing across all distributions. To such cluster it is then possible for discriminant analytical methods to be successfully applied through non-linear discriminant analysis (NLDA).

A final source of error can be the data upon which modelling exercises are based. Moreover, both regional and global data were important for this exercise, as they complement each other. It would be unwise, for example, to build a statistical risk map for *A. albopictus* in Europe solely on the basis of records for this species within Europe, as the vector is relatively new to Europe and has likely not spread to all of its suitable niches there. The species' global distribution can reveal the sorts of climate this species can inhabit elsewhere, and if European climates are similar to these, it is reasonable to expect that *Ae. albopictus* could survive and become endemic in them if it were to reach them. Similarly, European data on *Ae. albopictus* can broaden the global picture of where the mosquito might find suitable habitats. Although the analysis of this project has focused on the risk of dengue to Europe, the global dengue maps may also be suitable for assessing the risks in other regions of the world.

6 Conclusion

Considering the climatic conditions suitable for dengue transmission globally is an effective strategy for assessing where in Europe dengue transmission might be more likely. The outputs from this project suggest that the current climatic suitability for dengue transmission in Europe is minimal but not non-existent.

An important limitation of this study is the exclusion as dengue 'presence' points the transmission in Europe in 2010. Most global data on dengue relates to transmission mediated by *Ae. aegypti*. There are not enough known instances of dengue outbreaks mediated by *Ae. albopictus* to permit an accurate global assessment based upon these alone, and plotting the small number of data points relating to recent dengue transmission in Europe could be misleading.

There are two major conclusions from the maps presented in this report. First, monitoring the spread of *Ae. albopictus* across Europe and for possible introductions of *Ae. aegypti*, appear to be important public health priorities. This is especially important given that these vectors transmit other viruses, such as chikungunya, relevant for public health in Europe. To facilitate work in this area, ECDC has established VBORNET, a network of medical entomologists and public health experts to coordinate vector surveillance activities and provide regular updated distribution maps of the exotic vector species observed in Europe.

The second conclusion is that additional research needs to be pursued to develop dengue transmission models. Questions that need addressing include:

- How would the risk maps change if additional instances of dengue transmitted by *Ae. albopictus* occurred in Europe?
- What would happen if some DENV adapted so as to be more amenable to transmission by *Ae. albopictus*?
- What more can be learned about the ecology of dengue in Europe?
- How will environmental changes, and climate change in particular, affect the risk of dengue transmission in Europe in the future?

ECDC plans on pursuing projects aimed at addressing these questions. VBORNET will coordinate vector surveillance activities at the European level. A project mapping the impact of climate change on chikungunya transmission in Europe has been recently launched, and the development of the European Environment and Epidemiology (E3) Network will facilitate further research linking environmental variables with the transmission of mosquito-borne diseases in Europe.

Annexes

Annex 1 Summary of information extracted for *Aedes* and dengue.

Aedes

Table 1. Breakdown by species of citations retrieved from each database

Total	PubMed	WoS	Citations 1	Citations 2	PDFs 1
<i>Aedes aegypti</i>	4 607	6 607	7 813	2 913	n/a
<i>Aedes albopictus</i>	1 700	1 856	2 302	632	n/a
Total	PubMed	WoS	Citations 1	Citations 2	PDFs 1
<i>Aedes</i>	6 307	8 463	10 314	3 723	3 704

Literature search:

The PubMed, Web of Science and Promed databases were used for the literature search. In all instances, the search terms *Aedes aegypti* and *Aedes albopictus* were used. The search of the PubMed and Web of Science databases was performed in May 2009 and covered the period from 1960 to the date of search. The Promed archives go back only to January 1994, and all relevant records were examined up to the search date of July 2009.

The Web of Science and PubMed databases allow literature searches to go back to 1920. The decision to have the cut-off search date of 1960 was determined by the available resources for this project. Retrieving literature pre-1960 is very time consuming and costly. In the case of all the libraries to which we have access, pre-1960 material is stored offsite and strict limitations are placed on the volume of requests that can be placed on such material.

Table 1 gives a breakdown by species of the citations retrieved from each database. The Promed figures have not been included until the Citations 1 and Citations 2 columns, because Promed Endnote records must be created manually rather than generated on request by the electronic catalogues.

The figure in the Citations 1 column represents the number of records remaining in the Endnote library once the citations from each database have been merged and duplicate records removed. The figure in the Citations 2 column represents the number of citations that remain in the Endnote library once the abstracts have been read and irrelevant citations have been deleted.

Literature retrieval:

The 10 314 citations were first filtered for relevance by reading their abstracts. References unlikely to produce any geographical information were discarded, leaving a total of 3 723 citations that were felt likely to contain such information. Online and direct approaches to the papers' authors resulted in obtaining 3 049 PDFs. Visits to the Oxford University libraries, the London School of Hygiene and Tropical Medicine Library, the Cambridge University libraries and the British Library retrieved a further 340 PDFs. The inter-library loan system was used to retrieve the remaining citations, yielding a further 116 PDFs. The search was abandoned for the remaining 19 citations, which were deemed too difficult to obtain. The Promed records resulted in a further 199 PDFs being added to the database.

Table 2. Literature retrieval for *Aedes aegypti* and *Aedes albopictus*.

Total	PDFs 2	PDFs 3	Points1	Points2	Polygons 1	Polygons 2
<i>Aedes aegypti</i>	n/a	1 237	4 499	3 973	1 872	490
<i>Aedes albopictus</i>	n/a	662	1 612	1 494	678	81
Total	PDFs 2	PDFs 3	Points1	Points2	Polygons 1	Polygons 2
<i>Aedes</i>	3678	1 628	6 111	5 467	2 550	571

PDF naming:

All PDFs were allocated a label which started with the word *Aedes*, followed by the record number of the citation in the Endnote library. The decision to label the PDFs with the single generic term of *Aedes*, rather than distinguishing the two species by using different prefixes, was taken because many articles refer to both species; using the single generic *Aedes* allows cross reference to the same article from each species' separate geographical database.

Data extraction:

Of the 3 704 PDFs retrieved, data from 3 678 (PDFs2 column) was able to be extracted. The remaining 26 were unable to be processed as the staff team did not have the language skills to extract data from these PDFs. The figure in the PDFs3 column represents the number of PDFs that had relevant geographical data that contributed to the final maps. 271 PDFs had data for both species.

Language restrictions:

All Chinese, English, French, German, Italian, Spanish and Portuguese PDFs were processed by the data extraction team. The team did not have the language skills to extract the data from the Dutch, Japanese or Russian PDFs. The literature search had also identified one Polish article, but this article was unable to be found during the literature retrieval process.

Points and polygons:

The figures in the Points1 and Polygons1 columns represent the numbers of point or polygon records within the PDFs, often identified by a site name, such as a village (point), or by an administrative or health region name (polygon). Not all points or polygons could be located using the geo-referencing tools; such records appear within the database without latitude or longitude coordinates. These records do not appear on the maps, but the information from the studies may still be read directly from the PDFs. The figures in the Points2 and Polygon2 columns in Table 2 represent the number of data points and polygons that do have coordinates. All such points should appear on the final maps.

Staffing:

The *Aedes* phase of the EU ECDC project was completed in approximately 2 000 project staff hours. Seven people were employed during this time. This part of the project benefited from several months' of work previously carried out, in 2007, by two full-time staff members who began an *Aedes* database. This early work significantly reduced the burden of literature search and retrieval for the present project.

Dengue

The second phase of the EU ECDC project started in September 2009. This built on a previously completed dengue project from 2006.

Table 3. Dengue records used in this project.

Total	Pubmed	WoS	Citations 1	Citations 2	PDFs 1
DE	unavailable	unavailable	4 304	1 848	1 823
Old DE + USA	-	-	1 749	127	-
DE 2009	414	2 100	1 725	1 035	1 015
Total	-	-	7 778	3 010	2 838

Literature search:

As before, the PubMed, Web of Science and Promed databases were searched for relevant literature. The search terms 'dengue fever' and 'dengue hemorrhagic fever' were used in all three databases. To avoid duplication, the citations were merged into one Endnote library and all duplicate records were deleted.

As the project built on previously collected dengue data, it was only necessary to search literature from April 2006 to the date of the literature search, September 2009.

For various reasons the previous dengue project did not collect data for the United States of America, including Puerto Rico. This omission was corrected for the present project by performing searches from 1960 to the present day using the terms 'dengue' + 'America' and 'dengue' + 'Puerto Rico', yielding a further 127 citations from a possible 1 749 for this project.

Literature retrieval:

Of the 1 725 dengue citations, 1 035 were identified as likely to yield geographical data. Endnote records for 837 of these were retrieved from online sources or from libraries. The remaining 178 were Promed records that were manually entered into Endnote.

Due to their recent publication dates, 792 PDFs were found online. Only a few of the remainder were found at the Oxford University Libraries, and the rest were requested via the inter-library loan system. It was not possible to find 20 of the requested articles within the limited time available for this project.

Data extraction:

Of the 1 015 PDFs retrieved, relevant geographical data were found in 1 004 of them (see table 4). The four Chinese PDFs were not processed as they were not received until after the data extraction cut off point, as well as seven more PDFs in a range of languages which were unable to be translated by the team.

Language restrictions:

All English, French, German, Portuguese and Spanish PDFs were processed by the data extraction team. The languages the team were unable to work with were Japanese, Korean and Norwegian. A Chinese speaker was available, but the Chinese papers were very late in coming through, and it was not possible to process them in time.

Table 4. Total number of dengue records.

Total	PDFs 2	PDFs 3	Points1	Points2	Polygons 1	Polygons 2
DE	1 760	1 166	2 892	2 738	1 537	1 536
Old DE + USA	1 762	1 167	2 920	2 761	1 579	1 546
DE 2009	1 004	554	479	435	3 792	3 762
Total	2 766	1 721	3 399	435	5 371	5 308

Points/Polygons:

As with the *Aedes* figures, the Points1 and Polygons1 columns represent the number of points and polygons found in the PDFs, marking the site of data relevant to the study. As with the *Aedes* database, not all points or polygons could be located; the figures in the Points2 and Polygon2 column represent the number of data points and polygons that were geo-referenced. This will not necessarily correspond to the number of points marked on the maps as some disease records were for travellers returning, infected, from abroad, and diagnosed in their home countries. This was especially noticeable for some of the dengue records for Japan, Australia and the United States of America.

USA data from previous project:

Dengue publications for the USA, excluded from the original dengue search, were processed for the present project, as outlined above, yielding the additional information recorded in the 'Old DE + USA' row of Table 4.

Staffing:

The dengue part of the EU ECDC project was completed in approximately 900 staff hours. Six people were employed during this time, the majority on a part-time basis.

Annex 2 Details of MODIS data and processing.

The following are extracts from: Scharlemann JPW, Benz D, Hay SI, Purse BV, Tatem AJ, et al. Global Data for Ecology and Epidemiology: A Novel Algorithm for Temporal Fourier Processing MODIS Data. PLoS ONE 2008. 3(1):e1408.doi:10.1371/journal.pone.0001408

MODIS data are produced in the Sinusoidal projection (MODLAND Sinusoidal Grid) and made available as 460 tiles covering the Earth, each tile measuring 10° x 10° and consisting of 1200 x 1200, 0.859 km² (926.63 m x 926.63 m) pixels. All available images per time interval (as of 8 January 2007), called granules, were acquired for 229 tiles, including all tiles between 90°N and 60°S, except for 129 oceanic tiles and 62 tiles containing small islands, for two data sets: MODIS/Terra Land Surface Temperature/Emissivity 8-day L3 Global 1 km SIN grid (MOD11A2, version 4, [42]) and MODIS/Terra Nadir Bidirectional Reflectance Distribution Function (BRDF)-Adjusted Reflectance 16-day L3 Global 1 km SIN grid (MOD43B4, version 4). MODIS data sets are provided in Hierarchical Data Format, and were imported to ERDAS Imagine 9.0 (Leica Geosystems, Norcross, GA) and converted to ERDAS LAN format.

The MOD11A2 data set comprises eight-day composited land surface temperature (LST) for daytime (dLST) and night-time (nLST) overpasses. A complete time series for each tile of the MOD11A2 data would therefore consist of 46 granules at eight-day intervals for each of five years, or 230 granules in total.

The MOD43B4 data set provides nadir BRDF-adjusted reflectances for Terra MODIS spectral bands 1–7, computed with the mean solar zenith angle of each 16-day interval over which data were composited. The BRDF removes directional effects of view angle and illumination, providing reflectance values as if every pixel were viewed from nadir. Pre-processing excluded pixels with unreliable BRDF corrections, identified by quality control flags provided with the data set (QC Word 2 value > 10). For each pixel a MIR channel (MODIS band 7, 2105–2155 nm) was extracted and the Normalised Difference Vegetation Index $([\text{near infrared (NIR)} - \text{RED}] / [\text{NIR} + \text{RED}])$, where NIR is MODIS band 2 and RED is band 1, 841–876 nm and 620–670 nm, respectively) and the Enhanced Vegetation Index (EVI) $(2.5 * [[\text{NIR} - \text{RED}] / [\text{NIR} + 6.0 * \text{RED} - 7.5 * \text{BLUE} + 1.0]])$, where BLUE is MODIS band 3, 459–479 nm) were calculated. The MIR band was selected as being similar to band 3 in Advanced Very High Resolution Radiometer (AVHRR), which has been shown to correlate with a number of vegetative processes including forest re-growth. A complete MOD43B4 data set for each tile consists of 23 granules at 16-day intervals for each of five years, or 115 granules in total. Although finer resolution data are available for Normalised Difference Vegetation Index (NDVI) and EVI (MODIS/Terra Vegetation Indices 16-day L3 Global 250 m resolution, MOD13Q1), MIR and LST data are only available at 1 km resolution. For consistency across products, and given the much greater time involved in processing higher resolution data on a global scale, 1 km resolution data were therefore used throughout.

After temporal Fourier processing (described below), outputs for all five products were mosaicked and geo-referenced. Ocean pixels in all output layers were masked using the MODLAND Digital Elevation Model (DEM) and land/water mask version 4, downloaded from ftp://landsc1.nascom.nasa.gov/pub/outgoing/dem_sin_old for all 229 tiles and processed in ERDAS Imagine 9.0 and ArcInfo 9.1 (ESRI, Redlands, CA). Since the MOD11A2 data set had been masked by the version 4 land/water mask prior to production, and this mask did not match the later version 5 mask extents based on MOD43B4 reflectance data, the version 4 mask was used throughout. Information on inland water and ephemeral water bodies was also extracted from the MODLAND version 4 land/water mask.

In 2006 NASA began to use a new MODIS data processing algorithm, overcoming what were felt to be errors in version 4 MODIS data. The algorithm was applied to all subsequent MODIS data and then retrospectively to all previous data, so that the entire time series is now known as 'MODIS v5'. At time of writing it was hoped that the version 5 data would be available for modelling. Whilst this turned out to be the case, inspection of the version 5 processed data showed that various quality control and other flags in the new NASA algorithm are making worse regional problems identified in the version 4 products in areas that are frequently cloud-covered. Quality control rejects so many images that there are too few left in certain areas to get any measure at all of the various MODIS variables. These areas end up masked out in the processed imagery and the masked areas were bigger in version 4 than in version 5 MODIS products. Therefore the present report continues to use the MODIS v4 data for 2001 to 2005 only. Though relatively short, this period of time should be enough to capture important spatial differences in global habitats.

Annex 3 Further reading

Below is a list of useful publications for readers interested in learning more about the methodologies used in this project.

Temporal Fourier processing

Robinson TP, Rogers D, and Williams B. Mapping tsetse habitat suitability in the common fly belt of Southern Africa using multivariate analysis of climate and remotely sensed vegetation data. *Medical and Veterinary Entomology*. 1997. 11: 235–245.

Rogers DJ, Hay SI, and Packer MJ. Predicting the distribution of tsetse flies in West Africa using temporal Fourier processed meteorological satellite data. *Annals of Tropical Medicine and Parasitology*. 1996. 90(3): 225–241.

Rogers DJ. Satellites, space, time and the African trypanosomiasis. *Remote Sensing and Geographic Information Systems in Epidemiology*. 2000. Hay SI, Randolph SE, & Rogers DJ. London, Academic Press: 129–171.

Non-linear discriminant analysis and disease mapping

Green PE. *Analyzing Multivariate Data*. 1978. Hinsdale, Illinois, The Dryden Press.

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Krzanowski WJ, and Marriott FHC. *Multivariate Analysis Part 2. Classification, covariance structures and repeated measurements*. 1995. London, Arnold.

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Tatsuoka MM. *Multivariate Analysis: Techniques for Educational and Psychological Research*. 1971. New York, John Wiley & Sons.

Assessing model accuracy

Burnham KP, and Anderson DR. *Model Selection and Multimodel Inference: a Practical Information-Theoretic Approach*. 2002. New York, Springer.

Fielding AH, and Bell JF. A review of methods for the assessment of prediction errors in conservation presence/absence models. *Environmental Conservation* 1997.24(1): 38–49.

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