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Mapping the basic reproduction number (R_0) for vector-borne diseases: A case study on bluetongue virus

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ABSTRACT

Geographical maps indicating the value of the basic reproduction number, R_0, can be used to identify areas of higher risk for an outbreak after an introduction. We develop a methodology to create R_0 maps for vector-borne diseases, using bluetongue virus as a case study. This method provides a tool for gauging the extent of environmental effects on disease emergence. The method involves integrating vector-abundance data with statistical approaches to predict abundance from satellite imagery and with the biologically mechanistic modelling that underlies R_0. We illustrate the method with three applications for bluetongue virus in the Netherlands: 1) a simple R_0 map for the situation in September 2006, 2) species-specific R_0 maps based on satellite-data derived predictions, and 3) monthly R_0 maps throughout the year. These applications ought to be considered as a proof-of-principle and illustrations of the methods described, rather than as ready-to-use risk maps. Altogether, this is a first step towards an integrative method to predict risk of establishment of diseases based on mathematical modelling combined with a geographic information system that may comprise climatic variables, landscape features, land use, and other relevant factors determining the risk of establishment for bluetongue as well as of other emerging vector-borne diseases.

Introduction

The basic reproduction number, R_0, is defined as the expected number of secondary cases caused by one infectious individual introduced into a naïve population. It is a measure of the success of invasion into a population; if the value of R_0 is higher than 1, an outbreak of the infectious agent is possible, whereas if R_0 is less than 1, the infection will die out (Anderson and May 1991; Diekmann and Heesterbeek 2000). Maps indicating the value of R_0 can be used to identify areas with a higher probability of a major outbreak after an introduction. This concept has been used to develop risk maps for directly transmitted diseases such as foot-and-mouth disease (Ferguson et al. 2001; Keeling et al. 2001), avian influenza (Boender et al. 2007) and classical swine fever (Boender et al. 2008).

R_0 maps for vector-borne diseases could be particularly useful in many applications, including, for example, gauging the effects on disease patterns resulting from changes in climatic and environmental conditions. Climate and local environmental conditions are likely to have a large impact on vector-borne diseases, as survival and development rates of ectothermic animals like ticks and insects are highly sensitive to these factors (Altizer et al. 2006; Kovats et al. 2000). Ultimately, what counts is how these sensitivities translate into changing risk of emergence or spread of diseases. We develop a methodology to create R_0 maps for vector-borne diseases, with bluetongue virus as a case study, to provide a tool for gauging the extent of environmental effects on disease emergence.

Bluetongue virus (BTV) (Reoviridae: *Orbivirus*) is represented by 24 serotypes (BTV-1 to BTV-24) of which most occur in the tropical and subtropical regions of the world between latitudes 35°S and 54°N. The serotypes are transmitted between ruminant hosts, including sheep and cattle, by the bites of female *Culicoides* midges (Diptera: Ceratopogonidae); if the midges are infected with BTV the animal will contract bluetongue (BT). The range of bluetongue in southern Europe expanded dramatically in the last decade partly due to the expansion of the range of the traditional African–Asian BTV vector, *C. imicola* Keiffer and partly due to the increasing involvement in transmission of indigenous European *Culicoides* species, not previously recognized as BTV vectors (Mellor and Wittmann, 2002; Purse et al., 2005, 2007; Savini et al., 2005).

In August 2006, bluetongue disease emerged suddenly in the Netherlands, Belgium and Germany, and spread rapidly to France and

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Luxembourg (Enserink, 2006; Thiry et al. 2006; Toussaint et al., 2006) infecting over 2000 herds and unusually causing severe clinical signs in some cattle herds (Elbers et al., 2008). The virus then successfully overwintered to reappear in 2007, spreading to a further three countries and has caused over 25,000 outbreaks to October 2007 (Elbers et al., 2007). The virus strain, BTV-8, is related to African strains, rather than to strains circulating in Southern Europe and the means of introduction of this strain in North-western Europe in 2006 remains unclear. Animal transport or dispersal of *Culicoides* by wind may have played a role, but only preliminary assessments have been made (EFSA, 2007; Gloster et al., 2007). Despite extensive vector surveillance *Culicoides imicola* Keiffer has not been found in the epidemic area (Meiswinkel et al., 2007), suggesting that introduction through long-distance dispersal of the principal Afro-Asian vector, with vehicles or wind, is improbable, and indicating that other *Culicoides* species must be responsible for transmission.

The epidemic has prompted intensive monitoring for *Culicoides* in all affected countries. In the Netherlands two entomological programmes have been conducted: (i) grid-based light trap sampling of 107 dairy herds over a two-week period in September 2006, and (ii) weekly sampling commencing from November 2006 at 21 sites distributed across the Netherlands to obtain more detailed information on the geographical range and seasonal abundances of vector *Culicoides*. These two sets of data served as inputs for our model.

This work on R_0 maps for bluetongue virus in the Netherlands illustrates how such maps can be used to predict risk of vector-borne disease outbreaks in different seasons or for different climate scenarios. We also illustrate how a well-established method to predict vector species abundance from satellite imagery can be integrated into the more mechanistic R_0 framework as a tool to extrapolate the trapping results to non-sampled areas. In the discussion, we will review the difficulties related to construction of R_0 maps, especially with respect to vector-borne diseases, and indicate where additional research on, notably, vector biology and abundance is needed to ultimately enhance the predictive capability of R_0 maps.

Materials and methods

General approach

An R_0 map aims to present the, possibly different, values of the basic reproduction number, R_0, for different areas. The first step is to derive an expression for R_0, tailored to incorporate the relevant features of the disease system concerned. A framework for derivation of R_0 for vector-borne diseases is provided by the next-generation matrix (hereafter NGM) (Diekmann and Heesterbeek, 2000; Diekmann et al., 1990). This NGM method is used to 'average' the expected number of hosts infected by one vector and the expected number of vectors infected by one host. The largest eigenvalue of the NGM is equivalent to the basic reproduction number R_0. Here, analogous to the case of directly transmitted diseases, R_0 represents the expected number of new cases caused by one primary case on a generation basis, regardless of whether the cases are vectors or hosts. A detailed explanation of the derivation of next-generation matrices and of the definition of R_0 for complex disease systems, such as host–vector systems, is provided in Hartemink et al. (2008). Not surprisingly, the resulting formula closely resembles the formulae derived by Lord et al. (1996) for African horse Sickness and by Gubbins et al. (2008) for BTV, but for the sake of clarity we will explain the derivation here in some detail.

First, we consider the types of individuals involved in transmitting the infection: the *Culicoides* (which are considered as one type, because of lack of information on the differences between the species, denoted as type 1) and cattle (type 2) and sheep (type 3). A disease system with three types of individuals involved in the transmission will yield a NGM of size 3 by 3. The elements of this NGM, k_{ij}, represent the expected number of cases of type i caused by one individual of type j, resulting in the following NGM:

$$K = \begin{bmatrix} k_{11} & k_{12} & k_{13} \\ k_{21} & k_{22} & k_{23} \\ k_{31} & k_{32} & k_{33} \end{bmatrix}.$$

For example, element k_{13} should be interpreted as the mean number of *Culicoides* (type 1) infected by one infected sheep (type 3).

Before deriving the expressions for each of the elements, it bears noting the biological framework of this system. Principally, *Culicoides* midges suck blood only once to complete each gonotrophic cycle; the females take one blood meal on a vertebrate host, digest the blood and lay a batch of eggs, after which the gonotrophic cycle repeats. BTV is transmitted via these blood meals from the ruminants (principally cattle and sheep) to midge and vice versa. Hence, *Culicoides* have to take at least two blood meals (one to become infected and one to infect) in order to transmit BTV.

Some elements of the NGM are easy to derive; as there is no published evidence for vertical (transovarial) or venereal transmission of BTV by any *Culicoides* species (Mellor et al., 2000), k_{11} can be assumed to be zero. Transmission between cattle and sheep has also not been reported, so we assume k_{23} and k_{32} also equal zero. Although mother–offspring transmission of BTV in cattle or sheep may play a role (De Clercq et al., 2008; Menzies et al., 2008), especially in overwintering, we regard this presently as a relatively insignificant route of transmission in the onset of the epidemic, and consequently also assume that k_{22} and $k_{33} = 0$.

Now we consider elements k_{12} and k_{13}; the transmission from hosts to midges. The number of midges infected by one infectious host will depend on the infectious period, the number of bites received by the host and the transmission probability per bite (denoted by c). The average duration of infectiousness is denoted by $1/\gamma_c$ for cattle and $1/\gamma_s$ for sheep; infection can be lost either by recovery or by death (the latter especially in sheep). The number of bites received by one individual will depend on the local midge density (denoted by v), the biting rate (a, which equals the reciprocal of the length of the gonotrophic cycle) and the densities of sheep and cattle (h_s and h_c, respectively). Multiplying the biting rate, a, with the vector density, v, yields the total number of bites per day per unit area. Given the absence of information on host preference in the midges, we assumed that this 'burden' is then divided over the available hosts in that area ($h_s + h_c$). The average number of midges infected by one newly infected cow will then equal:

$$k_{12} = \frac{acv}{(h_c + h_s)\gamma_c}.$$

Analogously, the average number of midges infected by a newly infected sheep will equal:

$$k_{13} = \frac{acv}{(h_c + h_s)\gamma_s}.$$

Now we look at elements k_{21} and k_{31}; the transmission from midge to hosts. In order to become infectious, a midge exposed to BTV must live long enough to survive the extrinsic incubation period (EIP) of the virus. When the exponential rates of becoming infectious and the mortality rate are denoted by respectively q and μ, the probability to survive the EIP will be $q/(q+\mu)$. When the vector has become infectious, it infects hosts with a probability b (the transmission efficiency from an infectious midge to a host) with biting rate a—for as long as it remains infectious, which is assumed to be for the rest of its lifespan (i.e., the reciprocal of mortality rate μ). The average number of cows infected by one infected midge is represented by:

$$k_{21} = \frac{h_c}{(h_c + h_s)} \frac{ab\left(\frac{q}{q+\mu}\right)}{\mu},$$

whereas the average number of sheep infected by one infected midge is represented by:

$$k_{31} = \frac{h_s}{(h_c + h_s)} \frac{ab\left(\frac{q}{q+\mu}\right)}{\mu}.$$

For each host type, this term is multiplied by the probability that the host is a sheep or a cow, respectively.

Based on the above, we find the following NGM:

$$K = \begin{bmatrix} 0 & \frac{acv}{(h_c + h_s)\gamma_c} & \frac{acv}{(h_c + h_s)\gamma_s} \\ \frac{h_c}{h_c + h_s} \frac{ab\left(\frac{q}{q+\mu}\right)}{\mu} & 0 & 0 \\ \frac{h_s}{h_c + h_s} \frac{ab\left(\frac{q}{q+\mu}\right)}{\mu} & 0 & 0 \end{bmatrix}.$$

The largest eigenvalue of this matrix,

$$R_0 = \sqrt{\frac{a^2 bcqvh_c}{\gamma_c (h_c + h_s)^2 \mu(q+\mu)} + \frac{a^2 bcqvh_s}{\gamma_s (h_c + h_s)^2 \mu(q+\mu)}}.$$

Some parameters in this expression for R_0 are assumed to be constant in time and space (such as transmission efficiencies b and c), whereas other parameters will vary over space (such as cattle and sheep densities h_c and h_s) or with time, as for example reflected by varying temperature (such as biting rate a, extrinsic incubation period or vector density). As a result, the value of R_0 can vary for specific areas and different seasons.

Applications

Based on the expression for R_0 derived above, three applications for the R_0 map were developed: 1) a simple R_0 map, 2) species-specific R_0 maps based on predictions derived from satellite data, and 3) monthly R_0 maps throughout the year to express seasonal differences. All parameters in the R_0 expression are assumed to be constant over space, except for the vector densities and the host densities. Cattle and sheep densities (h_c and h_s) were obtained for each post-code area from the Dutch national farm animal registration database. The approach to estimate vector densities, which is different for each application, is explained below. Calculations were performed, and maps were generated, using ArcMap 9.2 (www.ESRI.com).

Application 1: A general R_0 map

The midge density is estimated from the 'snapshot' samples collected in September 2006 at 107 locations that were evenly distributed over the Netherlands in a 20 by 20 km grid. The details of the collections are described in Meiswinkel et al. (2008). Each location was sampled for one night. The number of midges caught in a Onderstepoort blacklight trap is assumed to reflect 1% of the local midge density. For each of the locations, the value of v (number of midges per km^2) is assumed to be 100 times the number of midges in the trap. The transmission efficiencies, b and c, and the recovery rates, γ_c and γ_s, are assumed to be temperature independent, the estimates are given in Table 1.

The temperature-dependency of biting rate a and mortality rate μ are taken into account by applying algorithms derived from laboratory experiments and field data (Gerry and Mullens, 2000; Mullens et al., 2004) that relate these rates to temperature. The mean temperatures (i.e. the mean of 24 hourly measurements) of ten Dutch weather stations are used to calculate an average mean temperature for each month (see Fig. 1). This mean temperature is then used to calculate the values of these temperature-dependent parameters (see Table 1).

The duration of the EIP is also temperature-dependent. This duration reflects accumulated thermal time; higher temperatures lead to a shorter EIP. The rate of becoming infectious (q) is calculated by applying the algorithm in Table 1 to the daily maximum temperature (i.e. the maximum of the 24 hourly measurements) and then averaging these daily values for q to obtain a value for each month. Whereas we used mean temperatures in the algorithms for biting rate a and mortality rate μ (midges are thought to be most, but not exclusively, active at dawn and dusk, and mean temperatures thus seem to be most appropriate), we choose to use the maximum temperature for q in order to best reflect the accumulation of *'thermal time'*.

Application 2: Species-specific R_0 maps based on satellite-data based predictions

In this application, the value of R_0 is calculated for each of the 4003 four digit postal code areas in the Netherlands. The vector abundance in the non-sampled areas is predicted using a method described in detail in Rogers (2006) and Scharlemann et al. (2008). In short, patterns in seasonality of important climate conditions such as air temperature and vegetation are extracted from Fourier Transformed satellite images across the sampled area and matched statistically to patterns in vector abundance using non-linear discriminant analytical methods. These relationships are then used to predict vector abundance in other, non-sampled, areas. The environmental data are derived from time-series of 1 km resolution transformed MODIS images from 2001 to 2005 extracted for the centroid of each of the 107 trap site postal code areas and include Channel 03 (Middle Infrared), Daytime Land Surface Temp (dLST), Night-time Land Surface Temp

Table 1
R_0 parameters.

Non-temperature-dependent parameters			
Description	Symbol	Point estimate (range)	Source
Transmission efficiency midge to host	b	1 (0.8–1)	O'Connell (2002)
Transmission efficiency host to midge	c	0.05 (0.01–0.20)	Carpenter et al. (2006a), Gerry et al. (2001) and Venter et al. (1998)
Sheep recovery and death rate	γ_s	0.125 (0.033–0.25)	Luedke (1969)
Cattle recovery rate	γ_c	0.04 (0.0167–0.1)	Bonneau et al. (2002), Luedke et al. (1969) and Singer et al. (2001)
Temperature-dependent parameters			
Description	Symbol	Point estimate September 2006	Algorithm relating parameters to temperature in degrees Celcius
Midge biting rate	a	0.17	$a = 0.0002\ T\ (T - 3.7)\ (41.9 - T)^{1/2.7}$ (Mullens et al., 2004)
Rate of becoming infectious (1/EIP)	q	0.09	$q = 0.0003\ T\ (T - 10.4)$ (Mullens et al., 2004)
Midge mortality rate	μ	0.16	$\mu = 0.009\ e^{(0.16\ T)}$ (Gerry and Mullens, 2000)

Rates are per day. Average mean temperature in September 2006 was 18 °C and the average maximum temperature was 22.6 °C.

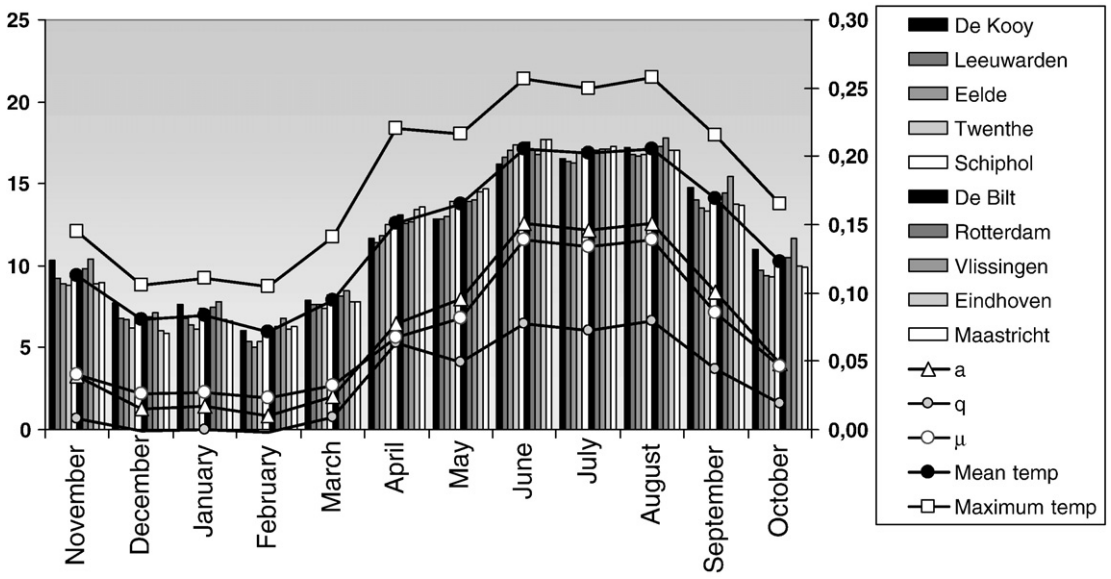

Fig. 1. Mean temperatures at different weather stations per month in the period November 2006–October 2007 in The Netherlands. The average of these temperatures is used to estimate the values of parameters a (biting rate) and μ (mortality rate). Daily maximum temperatures are used to calculate the value of q (the reciprocal of the EIP). Source: Royal Netherlands Meteorological Institute, http://www.knmi.nl.

(nLST), Normalised Difference Vegetation Index (NDVI) and Enhanced Vegetation Index (EVI). Step-wise non-linear discriminant analysis was used to identify the best predictor variables for vector abundance and the most parsimonious models were selected using the kappa statistic (Rogers, 2006).

This method can best be applied to individual species, as different species may have different habitat preferences. The *Culicoides* trapped at the 107 locations in September 2006 have been identified down to the species or species-complex level (EFSA, 2007). For the analysis, the abundance data were categorized into 5 categories (Absent, 1–9, 10–99, 100–999, >1000). The *Culicoides* species trapped in the Netherlands include the following taxa: the Obsoletus complex (consisting of *C. obsoletus sensu stricto* and *C. scoticus*), *C. chiopterus*, *C. dewulfi* and the Pulicaris complex (consisting of six species, i.e. *C. pulicaris*, *C. punctatus*, *C. newsteadi*, *C. impunctatus*, *C. lupicaris* and *C. halophilus*). *C. impunctatus* was found at only one location and could not be modelled. Kappa coefficients for the model fit (a measure of the agreement between the input and predicted outcome) ranged from 0.47 to 0.87, indicating a moderate to good agreement. The resulting predictions are a series of pixel-resolution maps which are then summarized by postal code area by taking the frequency weighted mean values of abundance for all pixels falling within each postal code area. This method provides predictions for vector abundance for non-sampled areas. We interpreted the predictions as if they were trap results and treated them in exactly the same way as we used the trap results; they were used as input for parameter v, in the R_0 model, where, except for the vector densities, the parameter values are the same as in Application 1. Areas with few hosts (usually urban zones) were removed from the analysis (if the number of host was less than ten, risk was set to zero), because division by these low numbers would yield very high risk estimates though such low numbers of hosts will most likely not be sufficient to maintain infection in midges.

The results are species-specific R_0 maps based on prediction maps for the abundance of each candidate vector species. The underlying principle here is to assume one species (or complex) at a time as the (primary) vector of BTV.

Application 3: Seasonal R_0 maps

In temperate regions, the value of R_0 for BTV will not be constant throughout the year, as some of the parameters depend on temperature or other climatic factors. Provided sufficient data are available, a risk map can be created for any specific moment. We illustrate this by constructing a series of R_0 maps reflecting the risk of establishment of BTV in each month. To this end, the results of weekly samplings made at 21 locations from November 2006 to September 2007 (same method as for the 'snapshot' taken in September 2006), were aggregated per month and used to calculate a seasonally and spatially variable estimate for the vector density, v, as input for the R_0 model. Not all catches have been identified down to species level yet, thus total numbers of *Culicoides* were used. Though we acknowledge the limitations of this approach, given the differing vector competences, this should at least give an impression of the abundance and the activity of the *Culicoides* throughout the year. These vector data were not modelled spatially using the satellite-data based method data as in Application 2; hence Application 3 is a seasonal version of Application 1.

Not only does the vector density change throughout the year; some other parameters, such as the biting rate, the *Culicoides* mortality rate and the duration of the extrinsic incubation period (EIP) are known to be temperature-dependent. Higher temperatures shorten the duration of the EIP and induce higher activity and quickened rate at which the gonotrophic cycle is completed (resulting in a higher biting rate), and have been shown to improve the transmission efficiency in other *Culicoides* species, but these effects are counteracted by mortality increases with increasing temperatures (Carpenter et al., 2006b; Wittmann et al., 2002), thus shaping a complicated relationship between temperature and R_0. There is little information available on the relationship between temperature and BTV and midge parameters and the way to implement the relationship (as degree-days or as a function of minimum, maximum or mean temperature) is not straightforward (Baylis 2008; Wilson et al. 2007, 2008), so it has to be kept in mind that the parameter values are merely used to illustrate the approach, not to give an exact risk profile for each month.

Results

Application 1: A simple R_0 map

A first R_0 map (Fig. 2) is based on the 2006 snapshot data and parameters estimates in Table 1. There is considerable variation. The area of introduction triggering the initial 2006 outbreak indeed has

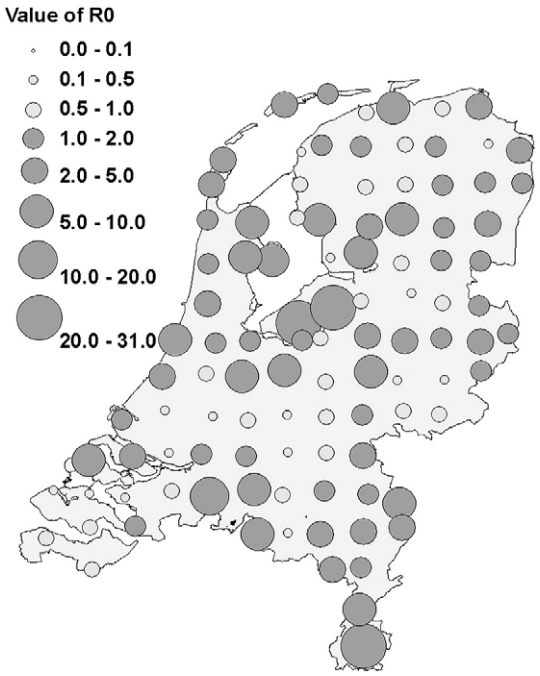

Fig. 2. The general R_0 map. The values of R_0 are estimated for each of the 107 locations sampled in September 2006. Colors indicate whether the value of R_0 is below 1 (light) or above 1 (dark).

high values of R_0. The presented results should be interpreted as a proof-of-principle rather than as a fully realised risk map ready to use for veterinary public health predictions. We want to emphasize that the interpretation of the value of R_0 at a certain time and place is the expected number of new cases arising from an average newly infected case introduced at that time and place in a susceptible population. Hence an R_0 map aims at predicting where a pathogen may be able to establish after a single introduction, it should not been seen a risk map to predict where BTV can occur in the long run, because multiple introductions may lead to an outbreak even at places where R_0 is below 1.

Application 2: Species-specific R_0 maps2

During the recent outbreaks in northern Europe, BTV was detected by RT-PCR in wild caught adults of the Obsoletus complex in Germany (Mehlhorn et al. 2007) and from *C. dewulfi* (Meiswinkel et al., 2007) and *C. chiopterus* (Dijkstra et al., 2008) in the Netherlands. Prior to 2006, BTV had been detected in southern Europe in both the Obsoletus complex (De Liberato et al., 2005; Savini et al., 2005) and the Pulicaris complex (Caracappa et al., 2003). Overall, there is insufficient information to determine the relative levels of competence of midge species for BTV transmission. Hence, we show R_0 maps for the two complexes, the Obsoletus complex (Fig. 3a) and the Pulicaris complex (Fig. 3b) and for the species *C. dewulfi* (Fig. 3c) and *C. chiopterus* (Fig. 3d). The emerging patterns reflect the distribution of *Culicoides* as well as the distribution of hosts. Since all other parameters are kept the same, differences between maps reflect differences in abundance predictions for the various species. Some of the patterns within the maps reflect the host density. Given the uncertainty in the results, we cannot incriminate a specific species as a probable vector; we show the results as a proof-of-principle.

Application 3: Seasonal R_0 maps

An R_0 map is plotted for every month between November 2006 and October 2007 (see Fig. 4). As expected, we see a pattern of very low values for R_0 in winter, and higher values from April until October. This is a combined effect of higher midge abundances in the warmer months and a temperature-induced increase of the biting rate and the shortening of the EIP. The effect of increased midge mortality at higher temperatures is not strong enough to counteract these effects.

There are fewer trapping locations and hence fewer data points than in Application 1, however, the number of observations per location is substantially higher.

Conclusions and discussion

This paper presents a framework to explore spatial variation in the risk of establishment of vector-borne diseases, using bluetongue in the Netherlands as a case study. Combining the next-generation matrix method, based on mechanistic descriptions of the biological processes, with spatially varying parameters and a geographical information system, this framework allows for full use of existing knowledge to predict whether a major outbreak may occur, should the pathogen be introduced in an area. Earlier published risk maps for BTV were derived from statistical models of vector distribution and abundance (see Baylis et al. (2001), Purse et al. (2004a,b) and Tatem et al. (2003)). In our framework, based upon the expression for R_0, both the quantity of R_0 and the parameters involved have a clear biological and epidemiological interpretation and the mechanistics of the processes involved are explicitly modelled. Using this kind of model allows us to gauge the effect of changing values of various biological determinants on the risk of an epidemic following introduction of the pathogen. Furthermore, the outcome of the oft-opposing effects of temperature on transmission parameters can be studied. The predicted risk of outbreaks in terms of an R_0, needs to be interpreted as a prediction of the local probability that a major outbreak will result when the vector-transmitted pathogen is introduced from outside into that area. Comparing the map in Fig. 2 to the early stages of the outbreak in 2006, we observe that the area in the south of the Netherlands, where the introduction into the Netherlands occurred, is predicted to have a high probability of a major outbreak.

We illustrated how R_0 maps can be used to investigate the general patterns of risk areas (Application 1), study the role of individual vector species in disease transmission (Application 2) and study the changes in risk of establishment over time (Application 3). Moreover, Application 2 provides an illustration of the use of satellite-derived data in R_0 estimations, predicting of vector abundance in non-sampled areas. For Applications 1 and 3 we reported values of R_0 for the postal code areas where trapping had taken place, but for many (public health or economic) applications, a risk map will have to cover all areas, not just the sampled areas. The technique used in Application 2 provides a useful tool for inter- and extrapolation between sampling sites.

In the models presented here, there are several important sources of potential error. First of all, vector density estimates are based on either single measurements at 107 locations (Applications 1 and 2) or on weekly measurements at 21 locations (Application 3) in the Netherlands. A large amount of uncertainty is introduced by the meagre seasonal coverage and the large distances between trapping locations relative to the fine scales over which vector abundance can vary over time and space (Baylis et al., 1997; Bouayoune et al., 1998; Sarto i Monteys and Saiz-Ardanaz, 2003). Furthermore, there is little knowledge on how trap catches relate to the actual number of bites experienced by the ruminants. Recently, a comparison of trapping results from drop-catches and light traps indicated that light traps may not accurately reflect the actual biting midge population (Carpenter et al., 2008). Also, past research indicates that some *Culicoides* species are not only active at dawn and dusk, but also during the day, meaning that abundances may be underestimated as they are based on light traps that only attract *Culicoides* during the night. Nonetheless, our results are based on the best data currently available,

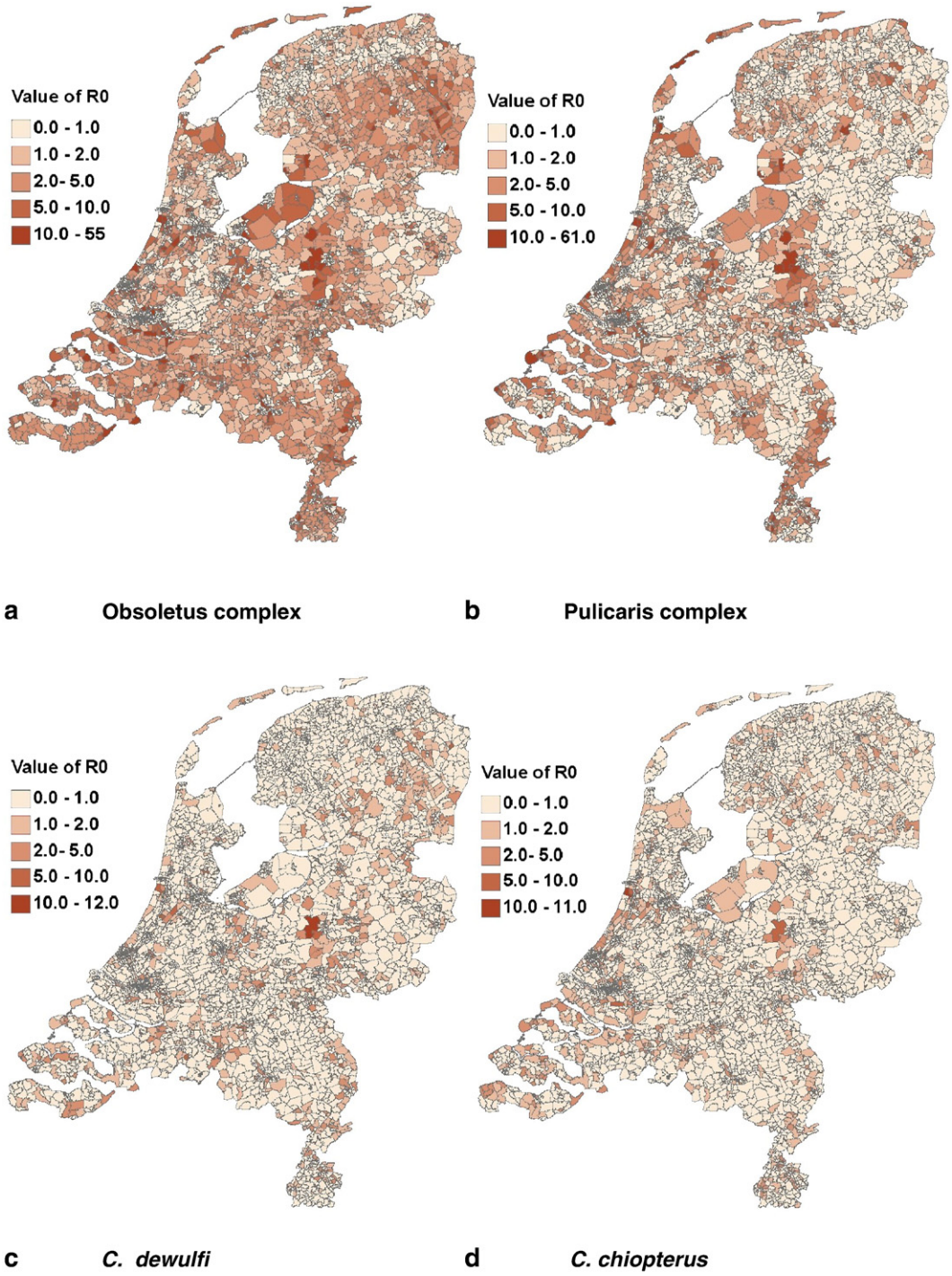

Fig. 3. Species-specific R_0 maps. R_0 map based on the assumption that the principal vector of BTV in the Netherlands is (a) Obsoletus complex, (b) Pulicaris complex, (c) *C. dewulfi*, (d) *C. chiopterus*. The vector densities are estimated for each of the postal code areas using predictions based on satellite-derived data.

as systematic sampling only started in 2006. Prior to 2006, occasional sampling was conducted in the context of insect hypersensitivity in horses (see Van Grevenhof et al. (2007) and Van der Rijt et al. (2008)). On the effect of differences between species, we can only speculate; we do know that *C. dewulfi* and *C. chiopterus* live in close association with cattle, as they breed in cattle dung. This could mean that these dung-breeding and pasture-associated species may actually bite more frequently on cattle than we would deduce from the trapping results and hence pose a bigger threat than Fig. 3 suggests, compared to the Obsoletus and Pulicaris complexes. It is clear that more research is needed to reveal the actual.

Using host data at postal code area level is another source of error. Hosts are assumed to be spread out evenly over the areas, and no seasonal or other variation in the hosts was taken into account. Furthermore, sheep and cattle are assumed to be the only hosts for the blood feeding midges. Feeding on wild hosts, such as deer, is not likely to play a major role in the Netherlands, with very limited deer populations. Midges are known to feed on horses (van der Rijt et al. 2008), for which unfortunately no spatially explicit abundance data are available. However, as the overall number of horses is an order of magnitude lower than the number of sheep and cows (source www.CBS.nl, 2008), the error in host abundance is probably negligible

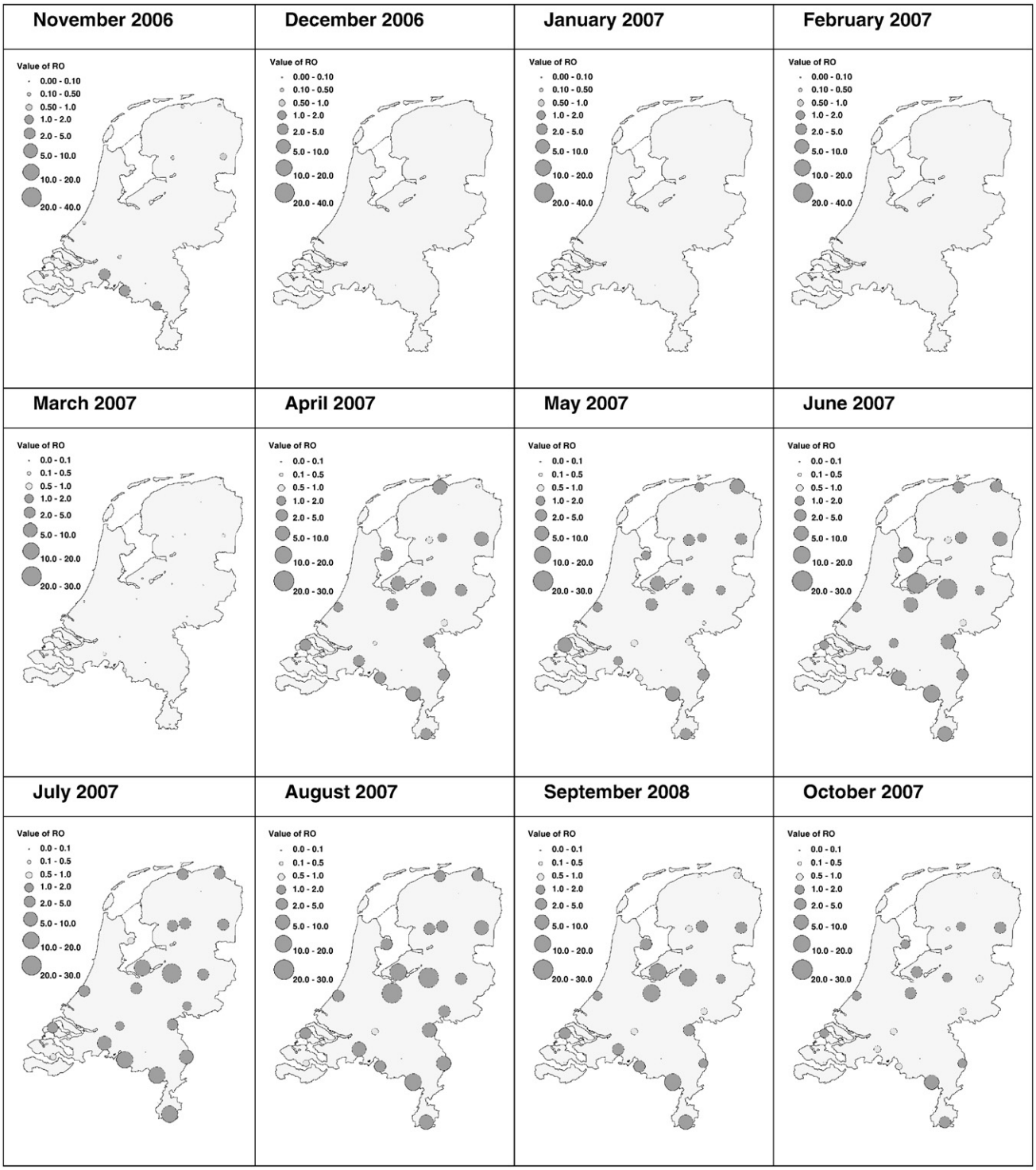

Fig. 4. Seasonal R_0 maps. For each month, the values of R_0 are estimated for the 21 trapping locations, based on the local host and vector densities, and the parameter values corresponding to the particular month (see Fig. 1).

compared to the error introduced by the lack of accuracy in measuring midge densities.

There is an additional effect in relation to vector density and host density estimates. In the formula for R_0, a higher host density leads to a lower R_0, as the vector density is divided by the host density to obtain 'the number of vectors per host'. This is not as counterintuitive as it may seem, as a relatively low number of midges per host will at least theoretically lead to fewer bites per host and lower transmission risk. However, in the field, the population of midges that can be sustained will most probably increase with the host population size, and a higher density of hosts reduces the distances that have to be crossed to find new hosts, so that risk will increase with host density. This only emphasizes the importance of more research on the relationship between numbers of midges caught in traps and the actual biting rates on ruminants. Field studies in North-western Europe have only just started; we hope that in the near future the results can contribute to obtaining better quantitative estimates.

The discriminant analysis of Fourier transformed satellite data that has been used to predict the abundance of the different *Culicoides* species for each postal code area in Application 2 has proven to be

successful in predicting *Culicoides* abundances in Southern Europe (Baylis et al., 2001; Purse et al., 2006, 2004b) and the distribution of mosquito vectors for malaria and tsetse flies in Africa (Rogers et al., 1996, 2002; Rogers and Robinson, 2004). In this study the predictive power of the method may be hampered by the fact that traps were all placed at farms (and hence in agricultural areas), meaning that landscape features are not very variable amongst trapping sites.

At this stage, successful prediction of patterns in BTV transmission by modelling seems to be primarily limited by the shortage of knowledge of the biology of European *Culicoides* species. These species are much less well-studied than *C. imicola*, the traditional African–Asian vector. Their breeding site preferences, seasonality and competence for bluetongue virus as well as the factors driving their abundance from local to regional scales is lacking. This is difficult to solve given the difficulties in identifying *Culicoides* to species level and also in colonising most *Culicoides* species in the laboratory. Continuing development of new tools for molecular identification of species will at least assist with the former problem (Nolan et al., 2007; Pages and Sarto i Monteys, 2005).

Accurate knowledge of the relationship between climatic factors and vector biology is needed before better predictions can be made. Relationships between temperature and *Culicoides* survival, activity and the EIP that have been determined under laboratory conditions and for species different to those involved in the Northern European BTV epidemic, and may be different in the field. The transmission efficiency, *b*, might also vary with temperature (Paweska et al., 2002), but insufficient information is available at this moment. Further work using field data, live trapped and laboratory reared *Culicoides* of different species are necessary to better understand the effects of climate and vector-borne diseases like BT.

Altogether, the results presented should be interpreted with care. The difficulties and caveats in creating R_0 maps presented here are not specific for this case study—insufficient data and data available on different aggregation levels will most likely cause problems in any attempt to create R_0 maps. Maps are generally easy to interpret, but the uncertainty in the output may be easily overlooked. Maps may appear more informative than the data upon which they are based (Kitron, 2000).

This paper aims at explaining and illustrating an approach to map the values of R_0 for vector-borne diseases. The ultimate aim is to have a framework to construct maps to inform policy makers on the risk of establishing of emerging vector-borne diseases, in the absence of the disease or in the very beginning of an epidemic, and to predict the effect of environmental changes, such as climate change, on this risk. This type of map, when aiming at informing policy makers, should be accompanied not only by a list of assumptions, but also by clear instructions on how to interpret the map; the conclusions that can be drawn from it, and the conclusions that cannot be drawn from it. The requirements are hence quite different than for a scientific paper.

The uncertainty of the estimates could also be expressed in the map itself. In the case of raster maps or maps with polygons where the R_0 value is indicated by a colour, the intensity (light–dark) could be used to indicate the uncertainty in the estimation. The same would apply for maps where the value of R_0 is indicated by the size of a circle or any other shape; the amount of uncertainty can be expressed by the intensity of the colour or even by using a box plot for each point.

The uncertainty in an estimate due to uncertainty in the input parameters can be assessed by using Latin Hypercube sampling or a similar technique (Sanchez and Blower, 1997). For each parameter in the expression, a value is sampled from a range, and each sample provides a point estimate for R_0. Sampling 1000 times yields a cloud of 1000 point estimates for R_0. In this case, however, LHS is not very helpful, as most of the variation arises from the trapping results and we do not have a range, or difference in the ranges between the sites.

Notwithstanding all the caveats, we feel R_0 maps are a useful tool especially for exploring the changing risk for emerging vector-borne diseases, in dependence of environmental conditions (Altizer et al., 2006). The effect of, for instance, changes in climate can be explored by linking parameters such as vector survival probabilities or biting rates to climatic factors. The concept of temperature-dependent R_0 maps, used in Application 3, can be extended toward full climate dependent parameterized models that can be used for prediction of risk of establishment of diseases under different climate scenarios, and hence for simulating the effect of climate change for any relevant vector-borne disease. Altogether, this is a first step towards an integrative tool to predict risk of establishment of diseases based on mathematical modelling combined with a geographic information system that may comprise climatic variables, landscape features, land use, and other relevant factors determining the risk for establishing for bluetongue as well as of other emerging vector-borne diseases. The paper also highlights the most important data needs for this kind of models; systematic and fine scale measurements of vector abundance combined with accurate knowledge on the relationship between numbers in traps and actual biting rates.

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