Preventive Veterinary Medicine 149 (2018) 1–9

Contents lists available at ScienceDirect

Preventive Veterinary Medicine

journal homepage: www.elsevier.com/locate/prevetmed

Environmental heterogeneity and variations in the velocity of bluetongue virus spread in six European epidemics

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ARTICLE INFO

Keywords:
Bluetongue
Disease vectors
Spread rate
Spatial epidemiology

ABSTRACT

Several epidemics caused by different bluetongue virus (BTV) serotypes occurred in European ruminants since the early 2000. Studies on the spatial distribution of these vector-borne infections and the main vector species highlighted contrasted eco-climatic regions characterized by different dominant vector species. However, little work was done regarding the factors associated with the velocity of these epidemics. In this study, we aimed to quantify and compare the velocity of BTV epidemic that have affected different European countries under contrasted eco-climatic conditions and to relate these estimates to spatial factors such as temperature and host density. We used the thin plate spline regression interpolation method in combination with trend surface analysis to quantify the local velocity of different epidemics that have affected France (BTV-8 2007–2008, BTV-1 2008–2009), Italy (BTV-1 2014), Andalusia in Spain (BTV-1 2007) and the Balkans (BTV-4 2014). We found significant differences in the local velocity of BTV spread according to the country and epidemics, ranging from 7.9 km/week (BTV-1 2014 Italy) to 24.4 km/week (BTV-1 2008 France). We quantify and discuss the effect of temperature and local host density on this velocity.

1. Introduction

The spread of emerging infectious diseases is influenced by different combinations of socio-economic (Jones et al., 2008; Nicolas et al., 2013), environmental (Patz et al., 2004; Weiss and McMichael, 2004) and ecological (Taylor et al., 2001) factors. However, these are often difficult to disentangle, and studies trying to link disease spread to spatial or temporal factors may often benefit to and from other studies carried out in different regional and environmental conditions.

Bluetongue (BT) is a non-contagious, vector-borne virus infection of ruminants widely distributed across the world. The bluetongue virus (BTV, Orbivirus, Reoviridae), of which 24 classical or historical distinct serotypes exist, and further 4–6 new serotypes more recently discovered, are presently known (Hofmann et al., 2008; Maan et al., 2011; Zientara et al., 2014) is transmitted by the bite of certain *Culicoides* midges species (Diptera, Ceratopogonidae) (Carpenter et al., 2009). It affects domestic ruminants: sheep, cattle (considered as the long-term reservoir (Hourrigan and Klingsporn, 1975)), and goats (to a lesser extent), as well as wild ruminants such as deer. It may cause high morbidity and mortality, and most importantly export bans, resulting in heavy economic losses for the farming sector (Wilson and Mellor, 2009). As such, BT is in the list of notifiable diseases to the World Organization of Animal Health (OIE). In temperate countries, BT epidemics have a clear pattern, with outbreaks mostly occurring from late spring to late fall (Coetzee et al., 2012; Guis et al., 2012; Wilson et al., 2008; Wilson and Mellor, 2008). When the temperature drops, vector activity stops (Purse et al., 2005) but midges can survive during milder winters (Carpenter et al., 2009; Mellor and Wittmann, 2002; Wilson et al., 2008). The spread of BT out of Africa was made possible through a combination of factors including changes in climate that may have influenced the habitat suitability for many *Culicoides* species (Purse et al., 2005), their vector competence and role in transmission (Carpenter et al., 2009), and to possible changes in inter and intra-continental trade networks (Napp et al., 2013).

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https://doi.org/10.1016/j.prevetmed.2017.11.005
Received 30 May 2017; Received in revised form 4 October 2017; Accepted 3 November 2017

Table 1
Summary of datasets.

	Main competent vectors	Strain	Week	Month	Year	Abbr.	Reference
France	*C. obsoletus* (north)	BTV8	28–52	07–12	2007	FR1	Pioz et al. (2011, 2012, 2014)
	C. imicola (Med.basin)	BTV8	14–52	04–12	2008	FR2	
		BTV1	27–53	07/08–01/09	2008 – 09	FR3	
Italy	*C. imicola*,Obsoletuscomplex Pulicaris complex	BTV1	19–52	06–12	2014	IT	
Andalusia	*C. imicola*, *Obsoletus*complex *Pulicaris* complex	BTV1	26–48	06–11	2007	AN	Allepuz et al. (2010), Ippoliti et al. (2013)
Balkans*	*C.obsoletus*	BTV4	17–51	04–12	2014	BK	Purse et al. (2006),unpublished data

BTV: Bluetongue virus; Week: week number of the year in which cases were observed; Month: month of the year in which cases were observed; Breeding: main affecting farm during the epidemic; Name: given name to the dataset; Med.basin: Mediterranean basin; SW: south west.

The presence of BTV in Africa (its most likely origin), Asia, Australia, and America is at least several centuries old (Carpi et al., 2010). In contrast, it was absent from Europe until the end of 1990′s, except a few sporadic invasions in Portugal and Spain (Meiswinkel et al., 2004; Mellor and Boorman, 1995). Since 2000, epidemics were reported on several occasions in the southern fringe of Europe and the whole Mediterranean Basin. In the last decade (since 2006), the disease has extended northwards into previously unaffected European areas, causing the greatest ever-recorded BT epizootic in 2006-9 (Wilson and Mellor, 2009). According to the context of changing European climatic conditions, the emergence of the disease was first attributed to the northwards extension of the distribution of the main afro-tropical vector, *Culicoides imicola*, across the Mediterranean Basin (Mellor and Wittmann, 2002; Purse et al., 2005). It was recently demonstrated that the vector species has a long history in this part of the world (Jacquet et al., 2015; Mardulyn et al., 2013). Moreover, other *Culicoides* species (mainly Obsoletus and Pulicaris complexes) are BTV-competent vectors in northern Europe, in the absence of *C. imicola* (Caracappa et al., 2003; Saegerman et al., 2008; Savini et al., 2005; Takamatsu et al., 2003). Another possible reason for this change in BT epidemiology is the virus ability to overwinter in the apparent absence of adult vectors (Mellor and Wittmann, 2002). This might be related to (i) the virus persistence within surviving adult vectors, (ii) transovarial virus transmission in the vector, or (iii) prolonged/persistent infection in invertebrate hosts (Losson et al., 2007; Purse et al., 2005; Takamatsu et al., 2003). The spread of BT into cooler and wetter areas of Europe would have thus been facilitated by these vectors that carried infection far beyond the range of *C. imicola* (Purse et al., 2006). According to this ecological variability, temporal change of the occurrence of BT cases is related to the phenology and abundance seasonality of vectors (Carpenter et al., 2009; Purse et al., 2005, 2006; Saegerman et al., 2008; Torina et al., 2004).

In Europe, *C. imicola* is considered to be the main BTV vector in the Mediterranean basin, but other different species have been implicated in BTV transmission. In particular species belonging to the '*Culicoides obsoletus* group', including *C. obsoletus s.s.*, *C. scoticus*, *C. dewulfi* and *C. chiopterus* and species of the Pulicaris complex have been found positive in field and are incriminated to be potential vectors (Caracappa et al., 2003; Savini et al., 2005; Vanbinst et al., 2009; Romón et al., 2012). Many questions remain on the factors influencing the spatial and temporal pattern of the disease. Most previous spatial BT models focused on the distribution of vectors and disease and on the influence of various factors on these distributions (Calvete et al., 2008; Ippoliti et al., 2013; Mardulyn et al., 2013; Pérez et al., 2012). Researches focusing on the identification of factors associated to the velocity of epidemics were scarce and mainly related to the French epidemics (Pioz et al., 2011, 2012, 2014).

The objectives of this study were to quantify the velocity of several bluetongue epidemics that affected different parts of Europe, and to assess the effect of temperature and host density on BTV spread velocity. Temperature was chosen because of its key role in modulating the vector population and virus transmission dynamics, and host density because the absence of hosts may represent a barrier to short-distance virus spread. Six epidemics were analysed in France (BTV-8 2007, BTV-8 2008 and BTV-1 2008–2009), mainland Italy (BTV-1 2014), Andalusia in Spain (BTV-1 2007) and in the Balkans (BTV-4 2014) to include a range of different temperature and host compositions. All these epidemics unfolded in the absence of vaccination, with the exception of BTV-8 2008 and BTV-1 2008–2009 in France. Animal movement ban were implemented to comply the European regulations. Surveillance was also regulated at the European level. It was largely based on the detection and report of clinical outbreaks by farmers and veterinarians (event-based surveillance), complemented the implementation of sentinel animals (programmed surveillance), as well as systematic serological/virological tests done at the occasion of animal movements (Italy, France, Spain).

2. Material and methods

2.1. Data

We compiled several datasets describing BT epidemics which occurred between January 2000 and December 2014 in Andalusia (Spain) (Allepuz et al., 2010), the Balkan countries, France (Pioz et al., 2011, 2012, 2014), and Italy (Conte et al., 2016; Lorusso et al., 2013) (Table 1). The common information extracted from each data set was the date and place of occurrence of BT cases. A BT case was defined as a farm in which at least one animal tested positive with an officially acknowledged laboratory technique. The studied epidemics involved serotypes spreading through new territories. Thus, there was no residual immunity or RNA-emia related to a previous infection. In addition, cattle movements were intense in space and time, in many of the affected areas. Therefore, in a given municipality, the oldest (i.e. the first) positive laboratory tests on samples from traded livestock were likely to detect recent infections, as sentinel animals did. Each case was described by its report date and geographic coordinates. When the premise location was unknown, we took the municipality centroid coordinates. The locations latitude and longitude were converted into the European Lambert Azimuthal Equal Area coordinate reference system (projection ETRS89, epsg 3035), and the full database was converted at the pixel level at a spatial resolution of 1 km. Each pixel could potentially include more than one positive case, so for each pixel, we estimated the first day of invasion as being the date of the earliest positive case recorded in the pixel in the given epidemics.

BTV epidemics are driven by the population dynamics of their main vector species, who differ in their seasonal activity according to the eco-climatic conditions. In 2014,BTV-1 in Italy affected areas where *Culicoides* species belonging to the Obsoletus and Pulicaris complexes were the main vectors (Conte et al., 2016; Goffredo et al., 2015). BTV epidemics were mainly related to *C.imicola* populations in Andalusia (Calvete et al., 2008) and in Corsica, and to *C. obsoletus* populations in the Balkans (Purse et al., 2006) and northern France (Balenghien et al., 2010) (Table 1). Temperature is an important factor influencing the population dynamics of *Culicoides* vector species (Ippoliti et al., 2013; Losson et al., 2007; Mellor et al., 2000; Purse et al., 2008; Saegerman et al., 2008), alongside other weather conditions. For example, rainfall

and wind can also influence the flight behaviour and the *Culicoides* species' capacity to transmit the disease, and rainfall and soil conditions may combine to offer varying conditions for breeding site. However, we focussed on temperature because this factor alone explains a very large part of the seasonal variations in populations, including in the Mediterranean context (Rigot et al., 2012). It is the main factor explaining the decay of epidemics in late autumn, winter and/or early springs. To account for this driver of epidemics in our analysis for each infected pixel, and for its first date of invasion in the considered epidemics, we extracted two temperature variables from the E-obs database: i) the mean temperature on the day of the first invasion, and ii) the mean of the daily mean temperature in the preceding week.

The host population structure markedly differed in the three studied areas. For example, the population of ruminant in Italy (Sardinia excluded) in 2014 was composed of 5 million sheep and goats and 5.7 million cattle (source: Italian National Database for Animal Identification and Registration, accessed on:19th April 2017). In Andalusia, sheep and goats also represented the majority of ruminants with 2.7, 1.1 and 0.6 million sheep, goat and cattle (Pérez et al., 2012). In contrast, there were 19.4 million cattle in France, as well as 7.2 million sheep (mainly in the South) and 1.3 million goats. A strong variation in the species composition was observed in the Balkans where the range of sheep, goat and cattle populations was [0.2;9.8], [0.06;4.0], and [0.06;14.0] million heads. we extracted cattle, sheep and goats density from the Gridded Livestock of the World data base (GLW3) (Nicolas et al., 2016; Robinson et al., 2014) at a spatial resolution of 1 km.

2.2. Analysis

The steps of this analysis are summarized in SI Fig. 1, taking as an example the BTV8 outbreak of 2008 in France. First, we built a mask of the main affected areas using a kernel density smoothing of the case locations, with a bandwidth of 25 km, and at a spatial resolution of 1 km: we only kept pixels with a smoothed density > 0.5 for France, > 1.5 Andalusia, > 0.03 for Balkans and > 0.2 for Italy. The bandwidth and density threshold were selected based on a visual examination of their effect on the spatial pattern of the mask. They were chosen as a trade-off between including the majority of cases in the study area, and excluding areas with no, or only few isolated and remote cases (Fig. 1). In order to derive the spread rate, we used the methodology identified by Tisseuil et al. (2016) as providing the best estimates, based on simulated and empirical data sets. The first time of invasion was interpolated for each cell within the 1 km resolution mask using thin plate spline regression (TPSR) (Tisseuil et al., 2016) (Fig. 2). The local friction, i.e. the slope of the TPSR surface (units of time per pixel) and its inverse, the spread rate (units of pixels per time), were derived from the interpolated values by measuring the average differences between each cell of the TPSR raster and its surrounding cells, weighted by the distance of each cell to the central pixel. This weighted average distance was smoothed using a 25 km radius circular moving-windows mean filter to prevent the occurrence of a local null friction, which would result in an infinite local spread rate.

2.3. Statistical analyses

Multiple linear regression was used to assess the association between the log-transformed spread rate (as the dependent variable) and the predictors: linear and quadratic terms for daily mean temperatures or mean temperature on the week before the cases report, month and season of cases report, and livestock density (cattle, goat, sheep). The week number, with its quadratic term, was added to the predictors to account for possibly remaining seasonal trend. A stepwise procedure based on the Akaike Information Criterion (AIC) was used to select the best model.

In addition, the approach proposed by Crase et al. (2012) was used to account for residuals autocorrelation. We computed the local mean of the residuals, and re-fitted the model with this autoregressive term as an additional predictor variable to obtain new parameter values and significance. The radius of the autoregressive local mean was chosen to match the range of the correlogram of the model residuals. We checked the residuals of the final model did not show any spatial autocorrelation.

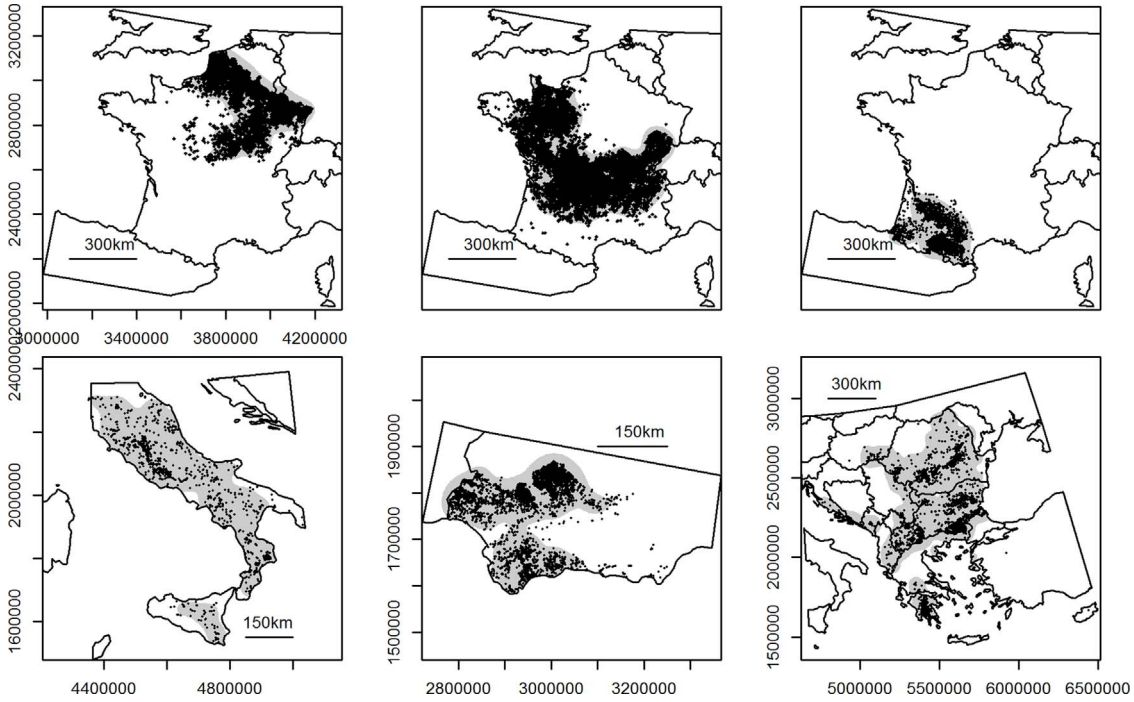

Fig. 1. Distribution of farms with recorded BTV infections in the six epidemics in France, Italy, Andalusia and in the Balkans. The study mask appears in grey.

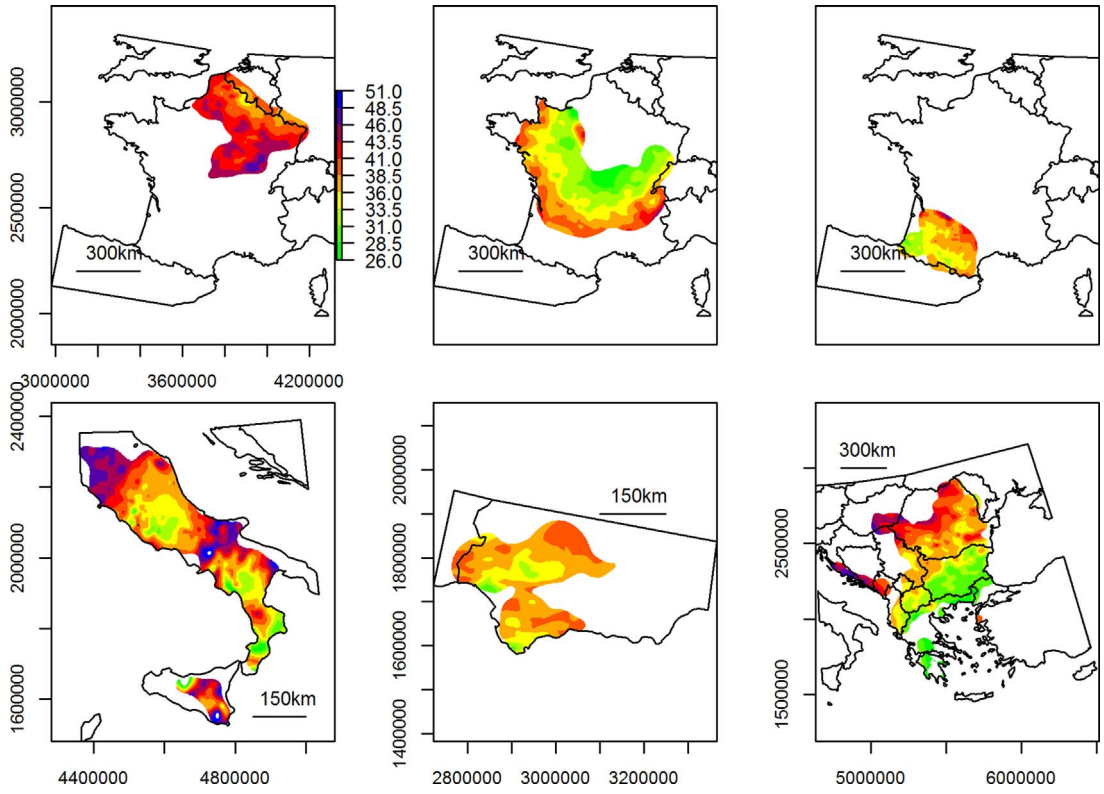

Fig. 2. Interpolated week of first report of BTV infection in the six epidemics. March to May (w 10–22); June to August (w 23–35); September to December (w 36–52); January to February (w 1–9).

3. Results

The six BT epidemics had contrasted spatio-temporal patterns (Fig. 1). As they covered different regions and seasons (Fig. 2), they corresponded to varying temperature conditions between and within epidemics (Tables 2 & 3). Their respective waves of invasions are presented in Fig. 2, showing the interpolated time of first invasion.

The BTV-8 was first reported in northern France in Autumn 2006, with 28 serological, and 2 laboratory-confirmed clinical cases. After overwintering, the epidemic restarted in July 2007 and spread in the country from the North-East to the South-West till late fall. The epidemic resumed in April 2008, following a similar direction.

In January 2008, the first BTV-1 cases were reported in the south west of France, in the Pyrenees (Spain border), consecutively to the well-documented northward spread of the BTV-1 Iberic epidemic (Wilson and Mellor, 2009). A mean temperature of 14.7 °C [-4.2;27.3]

Table 2
Seasonal and overall spread rate in the studied countries. The values of the spread rates are expressed in km/week.

Dataset	season	n	Twmean	T	SR_{median} (CI 95%)
FR1	All	4440	11.6 (−4.0.20.1)	11.6 (−4.2, 21.9)	18.4 (9.9 – 36.6)
	Summer	217	16.2 (14.7, 20.1)	17.0 (14.1, 21.9)	14.3 (9.3 – 23.5)
	Autumn	3934	11.8 (−1.6, 17.3)	11.8 (−4.0, 18.6)	18.8 (9.9 – 37.1)
	Winter	289	4.1 (−4.0, 9.8)	4.7 (−4.2, 10.9)	17 (9.8 – 28.6)
FR2	All	6347	17.0 (−1.9, 22.9)	16.3 (−3.4, 26.0)	24.4 (11.5– 61.4)
	Summer	4419	18.5 (12.4, 22.9)	17.8 (10.1, 26.0)	25.3 (9.3 – 23.5)
	Autumn	1875	13.8 (−0.7, 20.5)	13.1 (−0.5, 21.7)	21.4 (9.9 – 37.1)
	Winter	46	3.4 (−1.9, 8.2)	3.9 (−3.4, 9.6)	16.0 (9.8 – 28.6)
FR3	All	1560	17.7 (−0.2, 24.1)	17.8 (−0.5, 27.3)	15.8 (9.5 – 26.6)
	Summer	652	19.4 (12.1, 24.1)	19.6 (11.9, 27.3)	17 (9.9 – 27.5)
	Autumn	906	16.6 (−0.2, 23.8)	16.5 (−0.5, 25.9)	15.0 (9.3 – 26.0)
IT	All	1159	18.9 (1.7, 27.2)	18.9 (0.18,28.6)	8.11 (3.8 – 18.2)
	Summer	397	23.2 (15.9, 27.2)	23.1 (13.4, 28.6)	7.9 (3.9 – 18.3)
	Autumn	675	19.1 (8.3, 24.3)	18.3 (7.5, 25.5)	8.2 (3.9 – 18.1)
	Winter	81	9.9 (1.7, 16.8)	9.0 (0.18, 17.37)	9.0 (2.9 – 17.1)
AN	All	4327	22.2 (11.2, 31.2)	22.1 (10.7, 33.0)	16.5 (9.6 – 40.2)
	Summer	1094	25.3 (21.3, 31.2)	25.3 (19.6, 33.0)	13.1 (8.2 – 25.7)
	Autumn	3233	21.2 (11.2, 27.8)	21.0 (10.7, 28.9)	18.2 (10.1 – 41.9)
BK	All	1968	18.7 (−2.6, 26.6)	18.6 (−3.2, 27.5)	21.0 8.2 – 48.7)
	Summer	975	22.1 (13.4, 26.6)	22.2 (11.7, 27.5)	22.0 (10.9 – 48.7)
	Autumn	982	15.4 (−2.6, 23.1)	15.3 (−3.2, 24.2)	18.4 (7.3 – 47.3)
	Winter	11	10.1 (3.6, 15.1)	9.9 (3.1, 15.5)	19.5 (12.6 – 64.0)

T_{wmean}: mean temperature on the week of case report given in °C; T: recorded temperature on the day of report; SR: spread rate given as the median and the first and last quartile of the distribution.

Table 3
Inter-country variability of spread rate and temperature in the Balkans area.

Country	n	Twmean	T	S_{median}(CI 95%)
Albania	22	19.4 (17.5, 23.6)	19.7 (15.7, 24.13)	23.0 (16.1–38.8)
Bulgaria	672	22.6 (9, 26.6)	22.8 (11.0.16.1)	27.3 (11.2 – 56.8)
Croatia	56	12.0 (4.2, 18.6)	12.1 (3.1, 18.9)	27.5 (12.7 –66.3)
Greece	287	21.1 (18, 25.3)	21.2 (16.3, 25.9)	22.5 (12.4 – 51.8)
Hungary	43	9.3 (3.1, 18.2)	9.3 (1.8, 21.0)	20.1 (12.1 –39.8)
Montenegro	24	10.6 (6.4, 18.6)	10.4 (4.8, 19.5)	18.3 (17.1 – 19.5)
Romania	838	15.7 (−2.6, 23.6)	15.6 (−3.2, 24.7)	18.5 (6.8–36.1)
Serbia	47	17.6 (15.1, 20.8)	17.8 (14.7, 21.0)	42.7 (15.5–73.9)
YRM	205	20.9 (12.8, 26.1)	20.6 (12.8, 27.1)	23.0 (10.4–36.8)

* YRM: The former Yugoslav Republic of Macedonia; Twmean: given as the mean (minimum, maximum) temperature on the week of case report; n: recorded number of infected farm; $S_{mean,min,max}$: respectively, mean, minimum and maximum spread rate on the infected pixel.

was recorded on that 2-year outbreaks (11.6 °C and 16.3 °C in 2007 and 2008 BTV-8 outbreaks, 17.8 °C for 2008 BTV-1) (Table 2). By the end of the three epidemics in 2007 and 2008, BTV-8 had invaded most of France. BTV-1 epidemic was limited to the southwestern part of the country (at the exception of a new cases in Brittany (north-western France) related to illegal cattle trade). For those outbreaks, reported cases peaked in September with temperature ranging from 10 to 15 °C.

In Italy, the patterns of invasion suggested the virus was introduced in three different areas. The mean temperature was 15.2 °C [14; 16.2] at the time of first invasion (June). The reported of cases peaked in September with a mean temperature of 19.2 °C.

In Andalusia, the BTV-1 epidemic started in late June with three different introductions at distant locations (Fig. 2). A mean temperature of 22.1 °C [10.7;33] was recorded at the first time of invasion.

Finally, the Balkans BTV-4 epidemic occurred from late April to late December (Table 1), with a clear pattern starting from the most southern region, then gradually spreading northward, with a mean temperature of 18.6 °C at times of first invasion (Table 2). The range of temperature conditions changed while the epidemic wave was moving northward (Table 3).

The spread rate (SR) varied considerably between countries, epidemics and conditions (Table 2). Some areas showed relatively lower spread rate even at times of intense transmission, such as Italy (median SR 8.2 km/week). Conversely, somewhat high spread rates were observed during reduced transmission periods (e.g. France 2007 median SR of 17 km/week in the winter). Also, within the Balkans, the median SR ranged from 18.3 km/week in Romania, to 27.5 km/week in Croatia, and 42.7 km/week in Serbia.

In France, the median SR peaked in September-October 2007, and in July 2008 for the BTV-8 and BTV-1 epidemics. It decreased afterward, alongside temperature. In Italy, it reached a peak in September. In Andalusia, it peaked in September-October, with a slower SR during the former months. In the Balkans, the median SR was maximal in August, and then gradually decreased.

The best models as quantified by their AIC were those including the mean temperature on the week before the report instead of the temperature of the day of the BTV record (Table 4, M1 vs. M2 and M3 vs. M4) and the models were improved by the inclusion of a quadratic term (Table 4, M4 vs. M2). The addition of the month or week number also improved the AIC (Table 4 M5 or M6 vs. M4). The effect of temperature and season were difficult to disentangle, because these variables were strongly correlated. However, models had better AICs once the week number was included, in addition of the temperature. The relationship between SR and temperature, estimated from model 4 (with constant week number), varied across the epidemics, with a trend to peak between 15 and 20 °C (Fig. 3).

In most epidemics, we found a negative association between cattle density and SR, except for the BTV-1 epidemics in France (Table 5). The association between sheep density and SR was mostly positive, with the exception of the first epidemics in France. Finally, the SR showed varying associations with goat density. However, the distribution of cattle, sheep and goats markedly differed between those regions (Fig. 4).

Table 4
AIC values calculated for the studied models of the BTV spread rate in a given pixel.

	M1	M2	M3	M4	M5	M6
FR1	−3225	−3217	−3343	−3295	−3351	**−3375**
FR2	−1122	−1149	−1163	−1203	−1245	**−1268**
FR3	−1807	−1811	−1815	−1821	−1864	**−1877**
IT	−456	−456	−479	−484	−502	**−533**
AN	−2787	−2869	−2785	−2867	−2983	**−3028**
BK	−537	−533	−533	−550	−575	**−611**

Models: **M1**:SR ~ T + Ct + Sh + Gt; **M2**: SR ~ T_{wmean} + Ct + Sh + Gt; **M3**: SR ~ T + T^2 + Ct + Sh + Gt; **M4**: SR ~ T_{wmean} + T^2_{wmean} + Ct + Sh + Gt; **M5**: SR ~ T_{wmean} + T^2_{wmean} + month + $month^2$ + Ct + Sh + Gt; **M6**: SR ~ T_{wmean} + T^2_{wmean} + week + $week^2$ + Ct + Sh + Gt.
SR: spread rate; **T**: recorded temperature on the day of report; $\mathbf{T_{wmean}}$: mean temperature on the week of record; **Sh, Gt, Ct**: respectively Sheep, Goat and Cattle density; **month**: month of record; **week**: week of record.

4. Discussion

There was a high variability in SR, but their range remained relatively stable between countries. Almost all epidemics, except for Italy, had SR ranging from10 to 40 km/week. This spread rate measurement was found in a similar range in France by Pioz et al. (2011), who reported spread rate ranging from 2 to 9 km/day for BTV8 (2007 and 2008), and 1–126 km/day for BTV-1 (2008) (Pioz et al., 2014).The BTV-1 epidemics in Italy in 2014 had an apparently lower SR than other epidemics. The implementation of animal movement bans after cases report may have contributed to a reduction of the SR. However this factor alone cannot necessarily explain this difference because such bans were also implemented in France, for example. These differences might be partly explained by anisotropic SR. The long shape of Italy, as compared to France, might have constrained the spread in a specific direction, different from the main axis of the Italian country shape. More generally, though European regulations imposed animal movement restrictions upon BTV case detection the actual implementation of these measures might have been different according to the country. For example, delays in outbreak detection and consecutive movement restriction zones would reduce their effectiveness in reducing the SR. In addition, reduction in the local level of compliance with these restrictions may also lead to higher SR. So, variations on the timing of outbreak detection and effectiveness of movement restrictions may result in increased variability in SR that cannot be predicted using the variables considered in this analysis.

Out of the high SR variability (Fig. 3), only a low fraction was explained by the predictor variables, ranging from 0.05 to 0.22. Measurement errors (case date of occurrence/location), and under reporting related to imperfect disease surveillance might result in biases in SR mean and variance. The measurement method itself (TPSR) may have contributed to spurious variability in SR. However, the variables considered in this analysis are only few of the many factors that may influence patterns of spread, and these variables should all be considered in both space and time, and possibly interacting with each other. If a farm is infected in week 40, for example, it makes sense to match the SR of epidemic frontline at that farm with the climatic conditions (temperature, rainfall, wind) of that specific week. However, the interactions between these variables during that specific week may be more important than their individual values. For example, the temperature and host composition at a specific location and in a particular week may be perfectly suitable for BTV transmission. Should heavy rainfall and/or

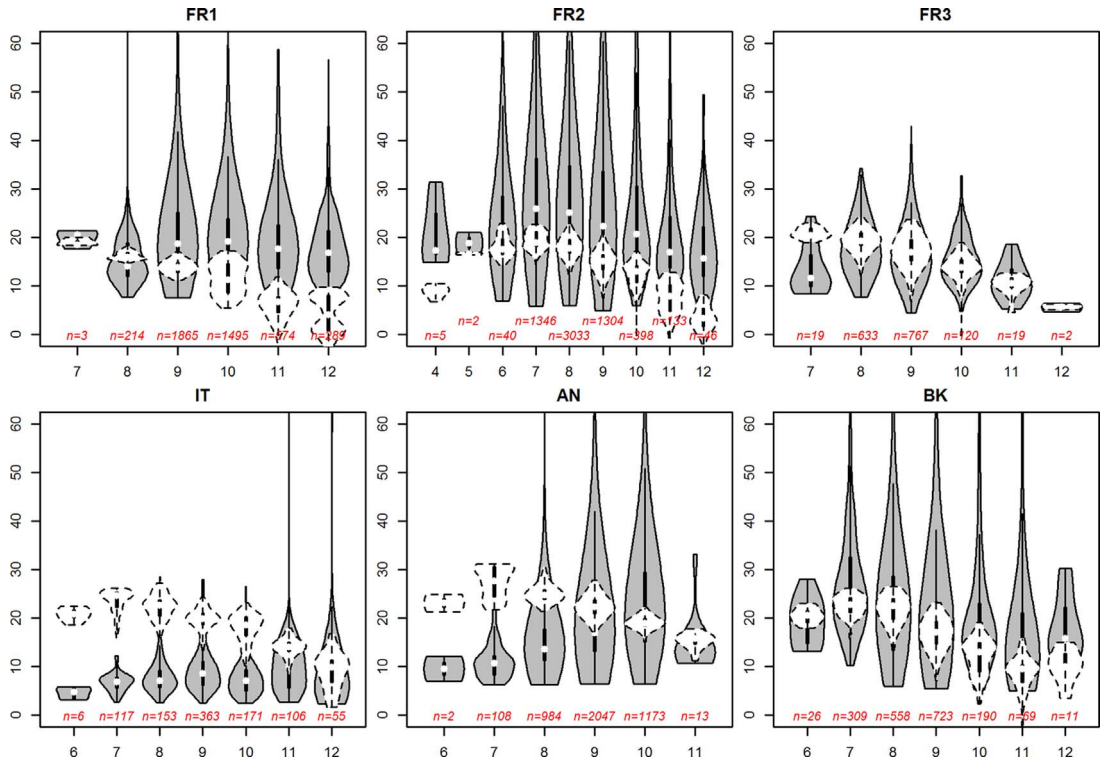

Fig. 3. Spread rate and average temperature at the time of invasion. grey: spread rate; white: mean temperature. From top left to bottom right: France (BTV8 2007, BTV8 2008, BTV1 2008), Italy, Andalusia, Balkans. Sample size are given in red (n).

strong wind occur at the same time, the vector flight would impaired during that week, with little possibility of BTV transmission. As a consequence, the estimated SR would be low, regardless of the suitable temperature conditions. This issue was already identified by Pioz et al. (2012) in their study of the factors influencing the spread of BTV-8 in France: the interaction between temperature and rainfall was an important predictor.

Conversely, with similar temperature and host density, a sunny week, with moderate wind, could result in long-distance BTV transmission and a fairly high SR in the following week. In addition, short and long-distance transmission through animal movements (before a ban was applied) would still add variability that could not be caught by the models. So, given that (i) the SR integrated the interactions between processes influenced by many climatic variables and farming practices (were the animals inside a barn? in the pastures? Were they transported?) and (ii) our analyses only captured these through simplified predictors, the low level of variability in SR explained by these predictors is not so surprising.

The effect of weekly temperature also varied between epidemics. In addition to the climatic factors that may interact with temperature, and which may differ in the study regions, the species composition of the *Culicoides* population, and their abundance and relative roles in transmission may also vary between the regions. For instance, *C. imicola* is the main vector under hot and dry Mediterranean climatic conditions, such as in Andalusia and Greece. Even within those regions, its distribution is not homogeneous. In mainland Italy BTV is potentially transmitted by species from the Obsoletus and Pulicaris complex (Goffredo et al., 2015), because *C. imicola* is only found in significant numbers in Sardinia along the coast of Tuscany, and along the south east coast of Calabria (Conte et al., 2009). Different species from the Obsoletus and Pulicaris complex have different dispersal, seasonality and peaks in abundances. So, as the travelling wave of BTV infection progresses through the landscapes, it encounters different patterns of vector species, at times that may, or may not, correspond to peaks in their abundance, thus altering the local speed of the travelling wave. In addition, differences in vector BTV competence between *Culicoides* species, or even between populations of the same species could also support variations in the epidemic SR. Similar differential effects of vector populations may have influenced the pattern of spread in the epidemics taking place in other countries. Longitudinal surveillance of active *Culicoides sp*. populations showed very different timing of peaks of active vector in north eastern and southern France (Balenghien et al., 2010). Also, differences in main vector species composition and peaks in abundances are expected between the Balkans countries. In Andalusia, where *C. imicola* is assumed to be the main competent vectors, species distribution models of *C. imicola* and Obsoletus complex showed

Table 5
Multivariate linear model and significance of the parameters. Note that the R^2 was estimated form models without the autoregressive term.

	Intercept	Temp (quadratic)	Week(quadratic)	Cattle	Goat	Sheep	AR	R^2
FR1	1.139	$-1.314\ 10^{-3NS}$ ($9.428\ 10^{-5NS}$)	$4.095\ 10^{-3NS}$ ($-3.224\ 10^{-5NS}$)	$-3.224\ 10^{-4***}$	$1.983\ 10^{-2***}$	$-1.645\ 10^{-3***}$	1.186***	0.06
FR2	1.692	$4.186\ 10^{-3NS}$ ($-1.369\ 10^{-4*}$)	$-1.451\ 10^{-2***}$ ($1.521\ 10^{-3**}$)	$-1.846\ 10^{-4***}$	$-6.373\ 10^{-4***}$	$1.870\ 10^{-4***}$	1.168***	0.05
FR3	1.366	$-7.035\ 10^{-3NS}$ ($-1.661\ 10^{-4NS}$)	$-1.457\ 10^{-3NS}$ ($-3.133\ 10^{-5NS}$)	$6.924\ 10^{-4***}$	$-8.775\ 10^{-3***}$	$3.491\ 10^{-5NS}$	1.458***	0.10
IT	$8.984\ 10^{-2}$	$-5.387\ 10^{-3NS}$ ($1.924\ 10^{-4NS}$)	$5.776\ 10^{-2***}$ ($-8.027\ 10^{-4***}$)	$-3.235\ 10^{-3***}$	$-1.967\ 10^{-3***}$	$3.712\ 10^{-4***}$	1.071***	0.19
AN	0.119	$-4.569\ 10^{-2***}$ ($7.783\ 10^{-4***}$)	$9.933\ 10^{-2***}$($-1.427\ 10^{-3***}$)	$-6.449\ 10^{-4***}$	$2.149\ 10^{-4***}$	$1.551\ 10^{-3***}$	1.323***	0.22
BK	1.803	$-1.219\ 10^{-2***}$ ($3.858\ 10^{-4***}$)	$-1.166\ 10^{-2NS}$ ($2.534\ 10^{-5NS}$)	$-4.079\ 10^{-3***}$	$-1.315\ 10^{-4NS}$	1.587^{*}	1.047***	0.12

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$; NS: not significant; AR: Autoregressive term.

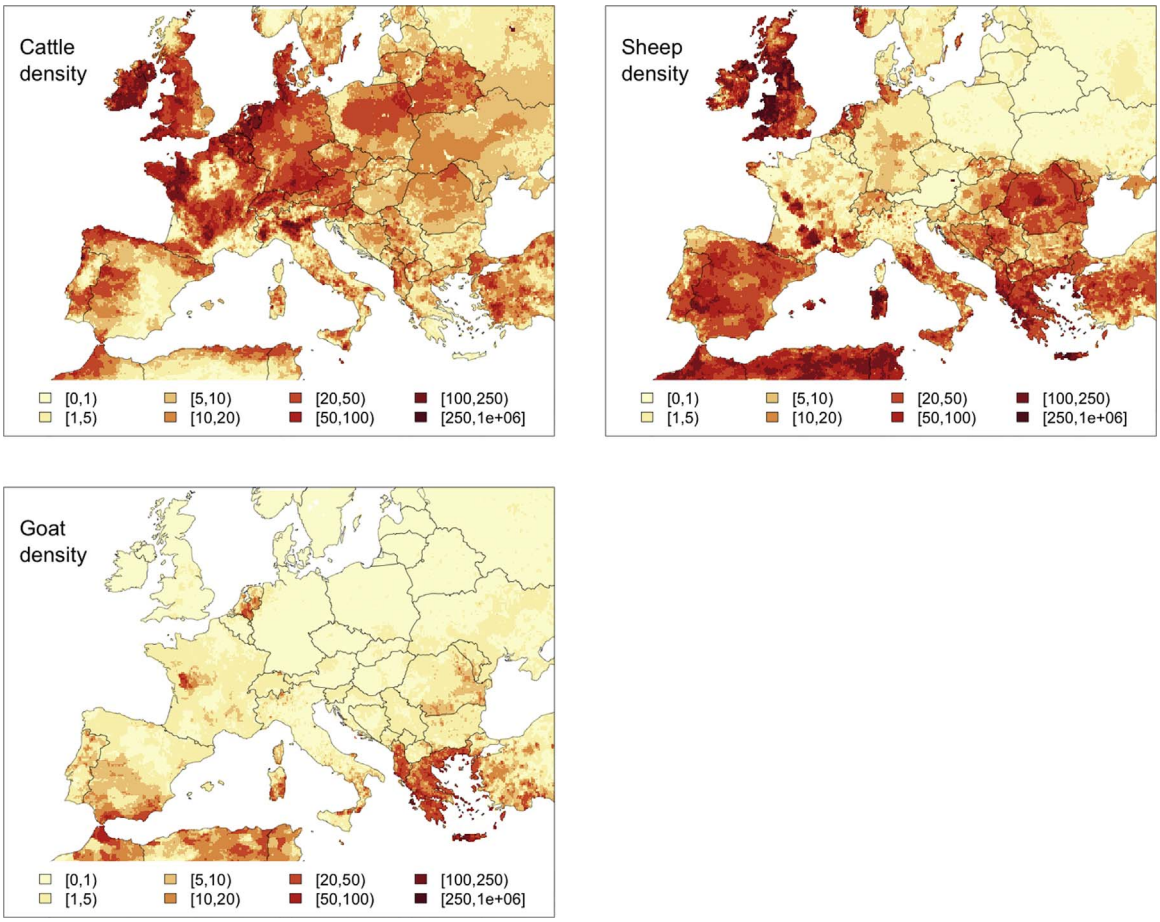

Fig. 4. Distribution of cattle, sheep and goat density in Europe according to the Gridded Livestock of the World (GLW) database.

their population ratio is likely to differ in the different parts of Andalusia (Calvete et al., 2008). Indeed, Allepuz et al. (2010) observed these areas of overlapping *C. imicola* and Obsoletus complex distribution were at high risk of being BTV positive, which may relate to a complementarity in the timing of their population peaks or vector competence.

In terms of host density, SR was in general associated negatively to cattle density (5 out of 6 epidemics), and positively to sheep (5/6 epidemics). Goats showed more variable results. A negative association with dairy cattle density was also found by Pioz et al. (2012) in France for the BTV-8 epidemic. Conversely, beef cattle was positively associated with BTV-1 spread rate in France in 2008 (Pioz et al., 2014). One should note, however, that even in landscapes largely dominated by cattle farming, such as for example in north eastern France, the SR remained fairly high, so the SR reduction in associated with high cattle density was relatively minor. However, spatial location of farming system across France and management practices may have influenced the association. While dairy cattle are kept close to farms, creating clusters in the spatial distribution and discontinuous pattern of host (less favourable to BT spread), beef cattle tend to be scattered throughout the landscape, facilitating the spread (Pioz et al., 2012, 2014). For sheep, the association with SR was more frequently positive, except during the first BTV-8 epidemics in France.

Regarding small ruminants, high densities were previously found negatively associated with BTV-1 and BTV-8 spread rates in France (Pioz et al., 2012, 2014). However, these analyses either pooled the two BTV-8 epidemics together (Pioz et al., 2012), or pooled sheep and goats in a single small-ruminants category (Pioz et al., 2014), so these results are in fact difficult to compare. The positive association between SR and sheep density may be related with the more frequent and apparent clinical signs in sheep than in other domestic ruminant species. Thus, BT outbreaks are easier to detect in sheep than in cattle and goats with event-based surveillance system. In contrast, positive cattle are most often detected in sentinel-based surveillance systems or when tests are done in the frame of exportations. Though both systems were implemented in the affected countries to comply with European regulations, the sensitivity of event-based surveillance was probably better than the sentinel-based surveillance. In addition, the density of goats is low in all countries concerned by the epidemics studied here, except in the Balkans, where the association with SR was found to be not significant.

We did not account for the possible effect of vaccination against BTV. In the French BTV-1 2008 epidemics, vaccination was associated to a slower spread rate (Pioz et al., 2014). However, no vaccination was implemented in the Balkans, Italy and Andalusia at the time of the epidemic (vaccination program occurred only for Sardinia in BTV-1 2013 epidemic, at the end of 2007 in Andalusia, and after the epidemic wave in Italy in 2014). In the epidemics from France, previous results of Pioz et al. (2012) reported fairly low reductions in spread rates linked to vaccination during the 2007–2008 epidemics, ranging form 1.05–1.54 km/week, which probably adds to the unexplained variability in our model. For the BTV-1 2008 epidemics, Pioz et al. (2014) found a stronger effect, with a reduction of up to 11.7 km/week, and this may be linked to the fact that this epidemics had the lowest median spread rate, if we set the Italy epidemic aside.

Further investigations on the SR drivers should focus on the mechanisms involved in the spatio-temporal vector population dynamics. For example, the model built by Rigot et al. (2012) for Sardinia might be extended to midge species from the Obsoletus and Pulicaris complexes. The predicted population abundance might then be combined

with climatic conditions influencing flying conditions, such as wind or rainfall, to assess the vector potential for spatial spread in a specific location and time.

Acknowledgement

We thank the Regional Ministry of Agriculture and Fisheries of the Government of Andalusia for providing the data. This study was partially funded by EU grants FP7-261504 EDENext and FP7-613996 VMERGE. It is catalogued by the VMERGE Steering Committee as VMERGE022 (http://www.vmerge.eu). The contents of this publication are the sole responsibility of the authors and don't necessarily reflect the views of the European Commission. Raw bluetongue outbreak data were initially provided by the National Veterinary Services of each country involved in this survey.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.prevetmed.2017.11.005.

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