# A novel approach to mapping and calculating the rate of spread of endemic bovine tuberculosis in England and Wales

Brunton, L. A.[1*], Nicholson, R.[2], Ashton, A.[2], Alexander, N.[3], Wint, W.[3], Enticott, G., Ward, K., Broughan, J.[1] & Goodchild, A. V.[1]

[1]Department of Epidemiological Sciences & [2]Data Systems Group, Animal and Plant Health Agency, Woodham Lane, New Haw, Addlestone, Surrey, KT15 3NB, United Kingdom

[3]Environment Research Group Oxford, Department of Zoology, South Parks Road, Oxford, OX1 3PS, United Kingdom

*Corresponding author email: Lucy.Brunton@apha.gsi.gov.uk

1 **Abstract**

2 After a dramatic reduction in bovine tuberculosis prevalence following an intensive testing

3 programme that started in 1950, the number of herds and animals affected by bTB in England

4 and Wales started to increase in the 1980s in an epidemic manner. Further study reveals

5 areas that are affected by persistent bTB, which should more accurately be considered

6 endemic bTB, and outward spread at the edge of these areas. The aim of this work was to

7 identify and validate a generally applicable mathematical method for estimating the endemic

8 status of bTB in cattle for localities and times and to use this to map the spread of endemic

9 bTB in England and Wales.

10 England and Wales were divided into a grid of 6.25km$^2$ hexagonal cells which were used as

11 the base resolution for our study. Maps were produced for nine overlapping 24 month

12 intervals between 1$^{st}$ September and 31$^{st}$ August spanning 2001/03 to 2009/11. Distance

13 from a farm to each of the ten nearest 'Officially Tuberculosis Free status – Withdrawn'

14 (OTF-W) incidents within the same time period was measured. Following validation of

15 specimen maps by veterinarians with first-hand experience of the location of endemic bTB,

16 endemic areas for each of the two year periods were defined as those hexagons containing

17 farms where the 3$^{rd}$ nearest incident occurred within 7km. The temporal spread of endemic

18 bTB was estimated by overlaying the endemic areas from each time period and creating a

19 contour-like map displaying the spread of endemic bTB over the two-year periods. A

20 boundary displacement approach was used to calculate the rate of spread of endemic bTB

21 across the centre of each hexagon. A rate was obtained for ~2,300 cells and varied between

22 0.04km and 15.9km per year, with a median of 3.3km per year.

23 This novel approach to defining endemicity has allowed the expansion of the endemic fronts

24 of bTB in England and Wales to be mapped, which in turn enables further analysis of the

25 factors associated with this expansion.

26

# Introduction

A disease can be defined as endemic when it is constantly present in a population (Thrusfield 2007) and persists without being reintroduced from outside (Segen 2006). Although the numbers of herds and cattle affected by bovine tuberculosis (bTB) in England and Wales have increased epidemically since the 1980s, closer study reveals substantial areas that are affected by persistent bTB, which should more accurately be considered endemic.

It is evident from time-series maps of the spread of bTB produced using annual surveillance data that the major mode of spread of endemic bTB in England and Wales is by expansion along the edges of existing endemic areas; only rarely do isolated outbreaks become new foci of endemic disease (for example see Figure 2 in Defra 2011). In order to characterise the spread of endemic bTB, we first need to develop a definition of endemicity in this context, and then identify the areas which are defined as endemic and map their expansion.

This is the first time that such an approach has been taken to investigate the spatial epidemiology of bTB. Historically, the progression of bTB has been illustrated by mapping statistical parameters such as incidence and prevalence or the density of animals that react to bTB testing (AHVLA 2013). Although these maps provide valuable information about the spatial distribution of bTB, they do not discriminate between endemic disease and localised outbreaks which are unlikely to persist. Identification of the areas where bTB is endemic will allow better targeting of interventions to control the spread of the disease.

Developmental work explored various approaches to defining endemicity for bTB. We considered approaches using classical measures of incidence such as number of incidents per number of herds or herds tested within a grid cell; and attempts to specify for endemic disease were made by incorporating criteria such as confirmation of disease and recurrence of bTB. It was found that an approach based on proximity to confirmed disease helped

51  eliminate sporadic incidents likely to be the result of long distance cattle movements and was

52  therefore likely to produce the best estimates of the location of truly endemic disease.

53  We report a new and generally applicable mathematical method for predicting the endemic

54  status of bTB in cattle for localities and times, and demonstrate how this method can be used

55  to map endemic bTB and calculate the rate at which the endemic areas are expanding in

56  England and Wales.

57

## Methods

### Data handling and map production

Data describing bTB testing and incidence were obtained from surveillance data recorded in the Animal and Plant Health Agency's VetNet database for nine 24 month intervals from 1st September to 31st August (to begin and end at a time when tests were least frequent) and spanning 2001/03 to 2009/11 using Microsoft Access 2003. Geographic data were processed and maps were produced in ArcGIS 10.0 (ESRI 2011). Custom scripts were written in Python 2.6 (Python Software Foundation 2012).

### Spatial resolution

A custom script was used to generate hexagonal grids with cell sizes of 6.25km$^2$ and 25km$^2$. Advantages and disadvantages of hexagonal grids relative to square grids have been reviewed by Birch et al. (2007). Square grids are far more widely used than hexagonal grids, possibly because raster data and smaller grid cells can easily be aggregated into lower resolution grids. Whilst hexagonal grids are less practical in the context of data processing, they minimise the distance between points within the same cell, and all pairs of neighbouring cells share an equal length of edge, meaning that neighbouring hexagons are readily adaptable to smoothing.

### Defining endemicity

Endemicity was defined in three steps.  Firstly, measures related to the two key criteria of endemicity, disease presence and disease recurrence were assessed. Secondly, a range of candidate definitions of endemicity were identified to provide a new measure.  Thirdly, it was necessary to identify a clear and communicable mapping solution to allow the proposed definitions to be understood, assessed and calibrated through expert and non-specialist

81     stakeholder knowledge. The geo-processing workflow is included in the supplementary

82     information.

83     Within each of the 24 month time periods, the distances from each farm holding to the

84     nearest ten 'Officially Tuberculosis Free status – Withdrawn' (OTF-W) incidents were

85     calculated. Data were aggregated by 6.25km$^2$ and 25km$^2$ hexagon cell and then mapped for

86     rapid comparison of each measured distance. The more inclusive measure of the distance to

87     the nearest holding with a bTB incident of any type was also measured and considered but

88     was dropped in preference of distance to confirmed OTF-W incidents.

89     From these maps it was possible to visually define a number of candidate definitions of

90     endemicity using a combination of different distance thresholds (3, 5, 7 or 10km) to ranked

91     nearest incidents (1$^{st}$ to 10$^{th}$). Examples include 10km from the 2$^{nd}$ nearest OTF-W incident,

92     or 3km from the 3$^{rd}$ nearest OTF-W incident.

93     After investigating the outlying areas of endemicity as defined by our candidate definitions

94     and comparing them with data from VetNet, distance to the 3$^{rd}$ nearest OTF-W incident was

95     shown to be the most reliable measure of endemicity. This definition suitably omitted areas

96     where the disease was likely to have been seeded by long distance cattle movements.

97     Discussions with social science collaborators revealed that maps using contour lines were

98     more likely to be understood than hexagon values which tended to obscure patterns at farm

99     or parish level. A series of interpolated contours showing the expansion over time of the

100    endemic area for selected distance thresholds to the third nearest OTF-W holding were

101    produced to communicate the results. These were generated from the hexagonal cell values

102    using an inverse distance weighting (IDW) interpolation.

103    Significant efforts we made to ensure the maps were clear to all non-specialist stakeholders:

104    only expansion (rather than contraction) was shown, towns and major roads were added to

6

105     help identify locations, and colours were optimised to avoid implying risk. These maps were

106     then used in consultation with expert Veterinary Officers (VOs) as part of the validation

107     process outlined in the next section.

108     **Validation of the definition of endemicity used for the maps**

109     To assist with validation of the geospatial definition of endemicity and to determine the

110     appropriate distance threshold to use to create the contour polygons, two methods of

111     validation were used. The first approach consisted of a focus group in collaboration with

112     social scientists in which VOs with local knowledge of bTB spread were consulted to obtain

113     their view of how endemic bTB is spreading in their areas. They were shown four versions of

114     the temporal contour maps created with a distance threshold of 3km, 5km, 7km or 10km.

115     The second, mathematical, approach was also intended to discriminate between areas with

116     endemic bTB and other areas which may be subject to sporadic bTB. The method calculated

117     the effect of distance threshold and N-number (i.e. the $N^{th}$ nearest OTF-W incident) on the

118     sensitivity and specificity of apparent endemicity.

119     The reference standards for endemicity and sporadicity were two subsets of the 141

120     "Stevenson districts" into which England and Wales can be divided. These districts had been

121     designed by Stevenson *et al.* (2005) to analyse BSE incidence, each of them containing

122     around 20,000 cows. The districts were ranked according to the incidence of bTB in herds

123     between September 2002 and August 2011, divided into six groups of 23 and merged. In the

124     23 districts that had the highest bTB incidence, the range of incidence (by district) was 7.4 to

125     13.3 OTF-W incidents per 100 herds per year. These districts, containing 453 $25km^2$

126     hexagons, were considered to have unambiguous endemic bTB. The 23 districts with the

127     lowest incidence contained 323 hexagons and were assumed to be affected by bTB

128     sporadically, if at all: the incidence was no more than 0.34 OTF-W incidents per 100 herds

129     per year. The method was also applied to $6.25km^2$ hexagons with similar results. At least

130  85% of the herds in each hexagon were required to fit into the merged districts.

131  The estimates of sensitivity and specificity were calculated for a series of threshold distances
132  and N-numbers. First, geometric mean distances to OTF-W incidents were calculated for
133  each N-number, September – August year and hexagon. Sensitivity was the average
134  proportion of years in which hexagons in the highest incidence districts had smaller mean
135  distances than the threshold. Likewise, specificity was the average proportion of years in
136  which hexagons in the lowest incidence districts had mean distances that were greater than
137  the threshold. The optimum threshold distance was assumed to be the threshold that gave
138  commensurate values for sensitivity and specificity. In order to be sure that a hexagon was
139  affected by endemic bTB, specificity of discrimination was considered to be slightly more
140  important than sensitivity.

141  **Rate of spread**

142  A custom script was written in Python for ArcGIS 10.0 to calculate rate of spread using data
143  generated for the purpose of mapping the expansion of the endemic front. The mapping work
144  focused on the ten year period from September 2001 to August 2011. However, for the
145  purpose of calculating rate of spread, data were generated for a slightly longer time period,
146  from September 2001 to August 2012. The process by which rate of spread was calculated is
147  summarised in Figure 1. Where possible, rate of spread was calculated based on time
148  periods 2 years apart (e.g. September 2003 – August 2005 compared with September 2001 –
149  August 2003). If rate of spread could not be calculated due to lack of contiguity between
150  endemic areas for different 24 month periods, time periods 3 years apart (e.g. September
151  2004 – August 2006 compared with September 2001 – August 2003) were used. Once rate of
152  spread had been calculated for all cells where spread had clearly occurred, results for
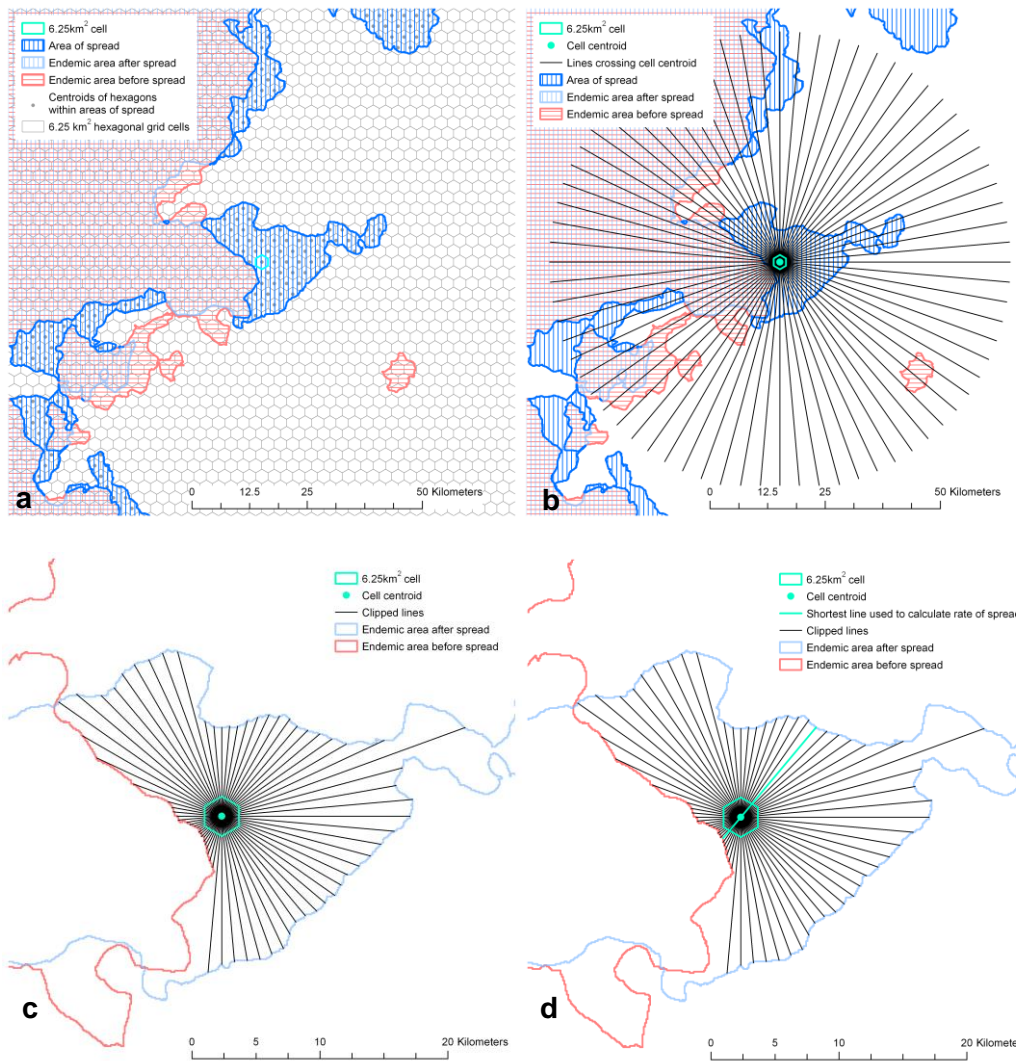153  different years were combined.

Figure 1: Step by step overview of the process by which rate of spread was calculated. (a) Areas of spread were identified as the difference between areas for two non-overlapping 24 month time periods. (b) If the centroid of a 6.25 km$^2$ hexagon was located within an area of spread, lines crossing the centroid were created at 5° intervals. (c) The lines were clipped in order to retain only the segments linking the boundaries of the endemic areas before and after the time period for which rate of spread was calculated. (d) The shortest segment was identified and its length was divided by the number of years between the two time periods to obtain a value for rate of spread.

## Results

### Definition of endemicity

Figures 2a and 2b illustrate the distance from farms to the $N^{th}$ nearest OTF-W incident in 2005-2007 for values of N between 1 and 6. Increasing the number of breakdowns required within given distances was effective at filtering out the influence of isolated incidents, which are likely to be the result of long-distance cattle movements from bTB-endemic areas (Gopal et al. 2006). However, requiring larger numbers of incidents to be within the threshold distance resulted in less consistency and spatial continuity in areas considered likely to correspond to recent and current spread based on the results of developmental work using incidence. Distance to $N^{th}$ nearest OTF-W incident had the advantage of producing consistent patterns across different cell sizes, and was readily adaptable to farm level, cell level or raster analysis. It had the disadvantage of being a continuous variable, making it difficult to define a clear cut off between endemic and non-endemic. Distances from holding to $N^{th}$ nearest holding were very much smaller than distances from holding to incident: excluding two isolated holdings, one located in central London and one located in the Welsh Mountains, the maximal distances to $N^{th}$ nearest holding for N1, N2, N3, N4, N6 and N10 were 5.3, 6.1, 6.4, 7.1, 7.7 and 9.3km respectively. Distance from holding to $N^{th}$ nearest incident (with a constant herd incidence) may nevertheless be biased towards areas with higher herd density. The 3$^{rd}$ nearest incident was selected as the optimal threshold of N based on the consistency of the core area produced compared with that produced using smaller values of N, and the reduction in the influence of sporadic cases.
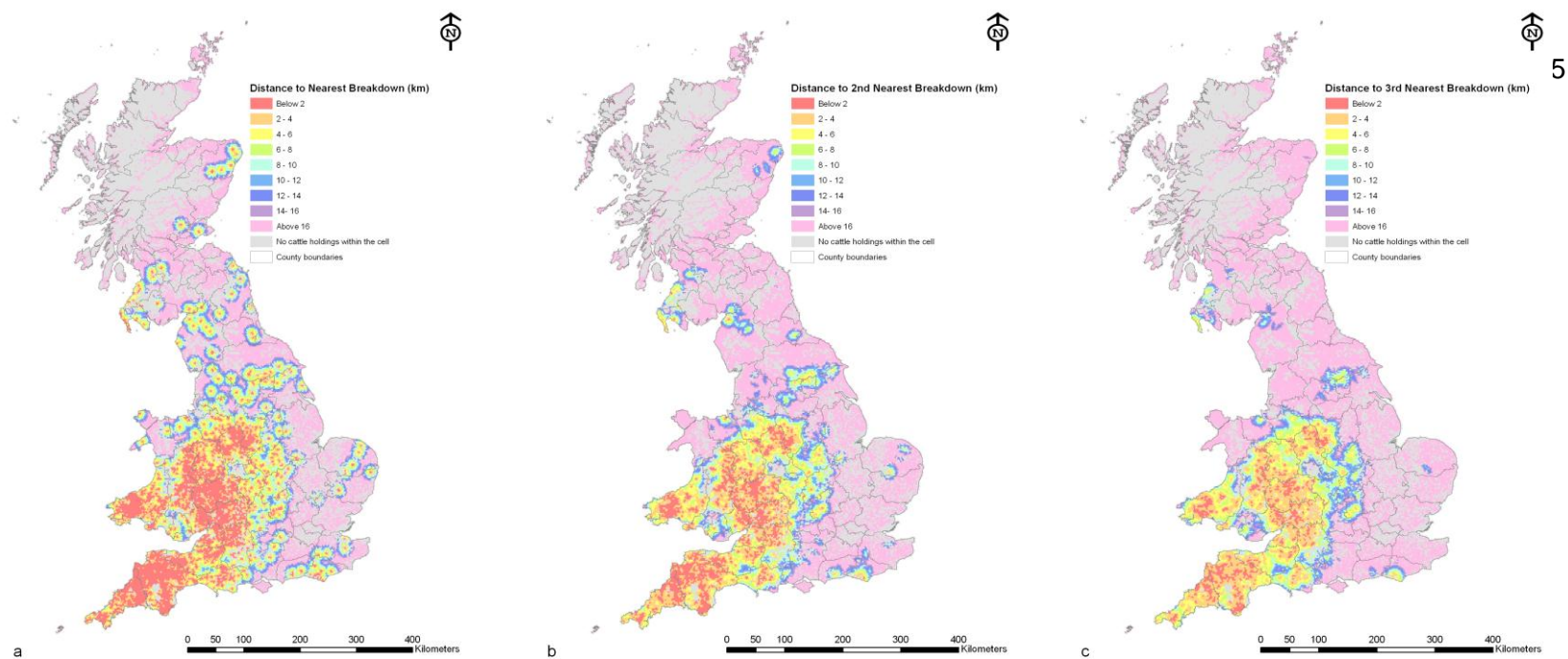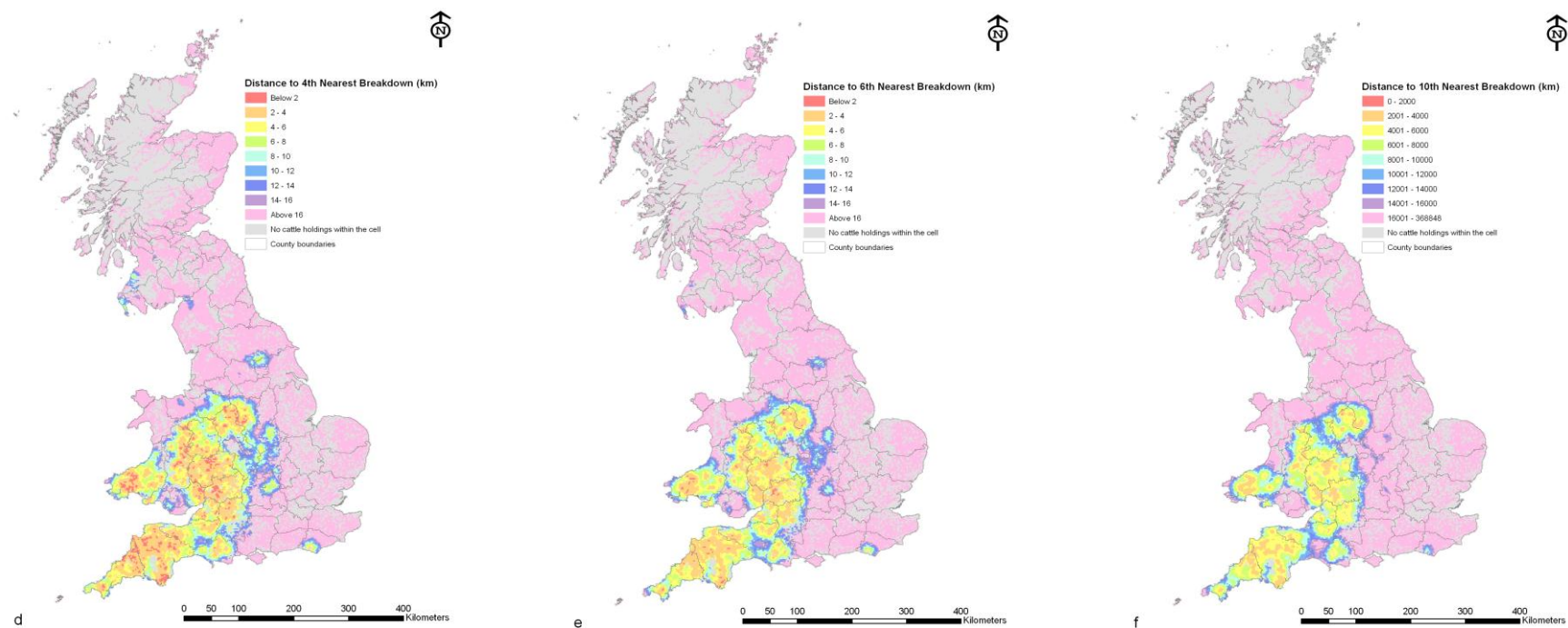
Figure 2a – Average distance from holding to (a) nearest, (b) 2nd nearest, and (c) 3rd nearest OTF-W breakdown in 2005-2007, by 6.25km$^2$ hexagon cell.

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187 Figure 2b – Average distance from holding to (d) 4th nearest, (e) 6th nearest and (f) 10th nearest OTFW breakdown in 2005-2007, by 6.25km$^2$ hexagon
188 cell.

189

190    The temporal contour maps created using the IDW method for validation of distance

191    threshold by the VOs are presented in Figure 3. Based on the previous distance maps

192    (Figures 2a & 2b), contour maps were produced using the 3$^{rd}$ nearest OTF-W incident with

193    four different distance thresholds of 3km, 5km, 7km and 10km.
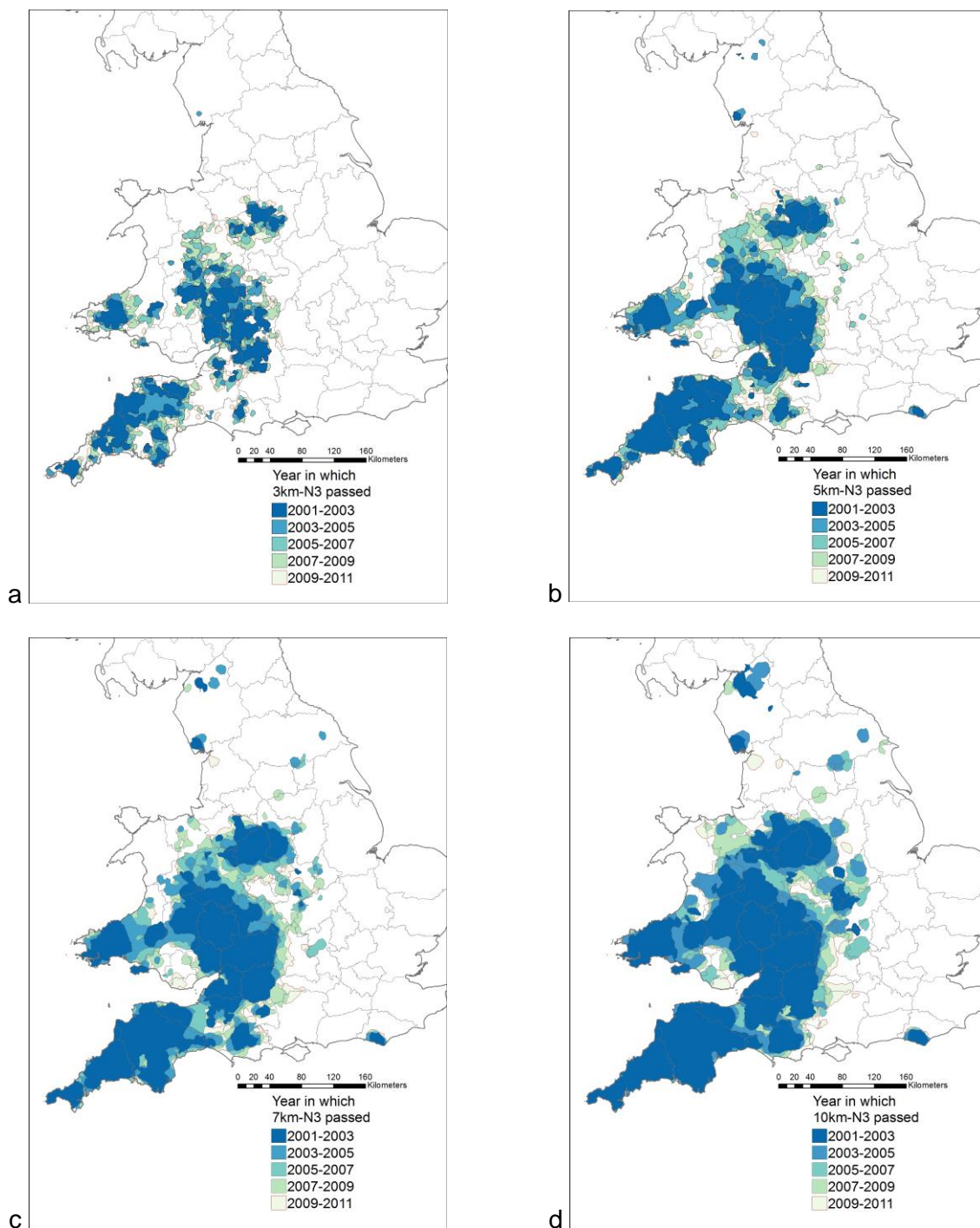


Figure 3 – Contour maps displaying the location of farms for which the 3$^{rd}$ nearest OTF-W breakdown was within a threshold of a) 3km, b) 5km, c) 7km, or d) 10km in each two year time period, as used for validation by VOs.

194                                                                                                          13

**Validation of thresholds**

195

196 Figure 4 illustrates the specificity and sensitivity of combinations of N-number and distance

197 threshold in describing the endemic or non-endemic status of a 25km$^2$ hexagon correctly. For

198 N1, N2, N3, N4, N6 and N10, the distances where the sensitivity and specificity intersect are

199 similar would be 3.2, 5.6, 7.6, 9.0, 11.0 and 14.0km respectively. The values of sensitivity and

200 specificity at the intersection point increase from 92.0 to 97.6% between N1 and N3, then

201 more slowly to 99.0% at N10. Because a large N-number failed to detect some local endemic

202 areas when the density of bTB incidents was low, N3 was considered most appropriate. The

203 threshold distance for N3 was between 7 and 8km; using 7 km gave near-maximum

204 specificity (98.4%) and slightly reduced sensitivity (96.8%), and was considered to be

205 acceptable, given the poorer suitability of high N-numbers.

206 The results of the mathematical validation were supported by the outcome of the workshop

207 with VOs. Based upon what they considered to be endemic bTB and their experience of

208 where bTB had spread in their local areas, a combination of a 7km threshold with the third-

209 nearest OTF-W incident was found to best represent visually the current edge of the area

210 affected by endemic bTB (Figure 3c).

211 Figure 5 illustrates the two year time period in which a hexagon first became endemic based

212 on our definition. Retraction of endemicity (i.e. reversion to non-endemic status) may have

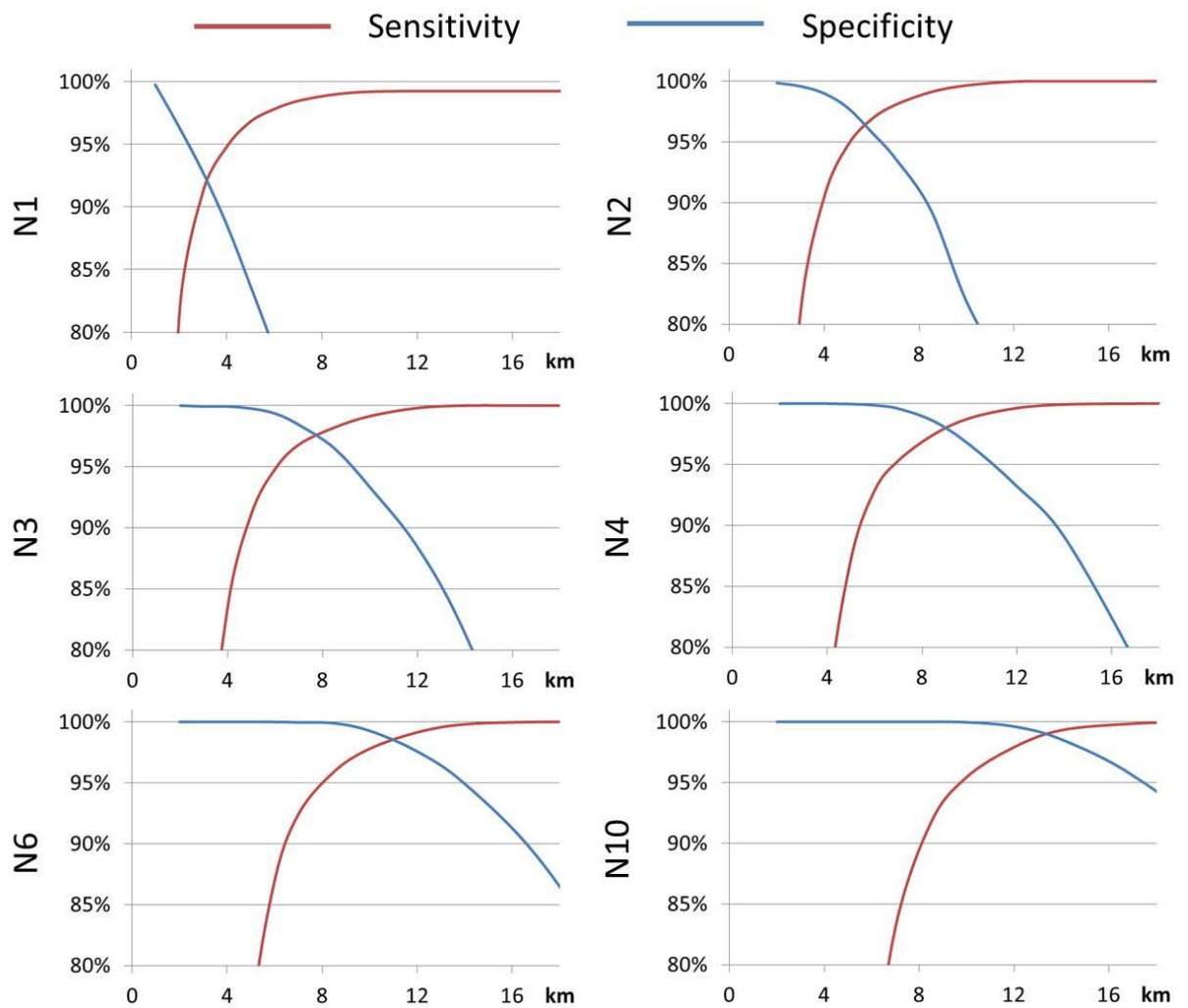213 occurred but was not calculated.

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Figure 4 - Calculated sensitivity and specificity (vertical axes) with which the 23 Stevenson districts
with the greatest OTF-W incidence per 100 herds can be distinguished from the 40 lowest-incidence
Stevenson districts using the distance to the $N^{th}$ nearest OTF-W incident each year and a distance
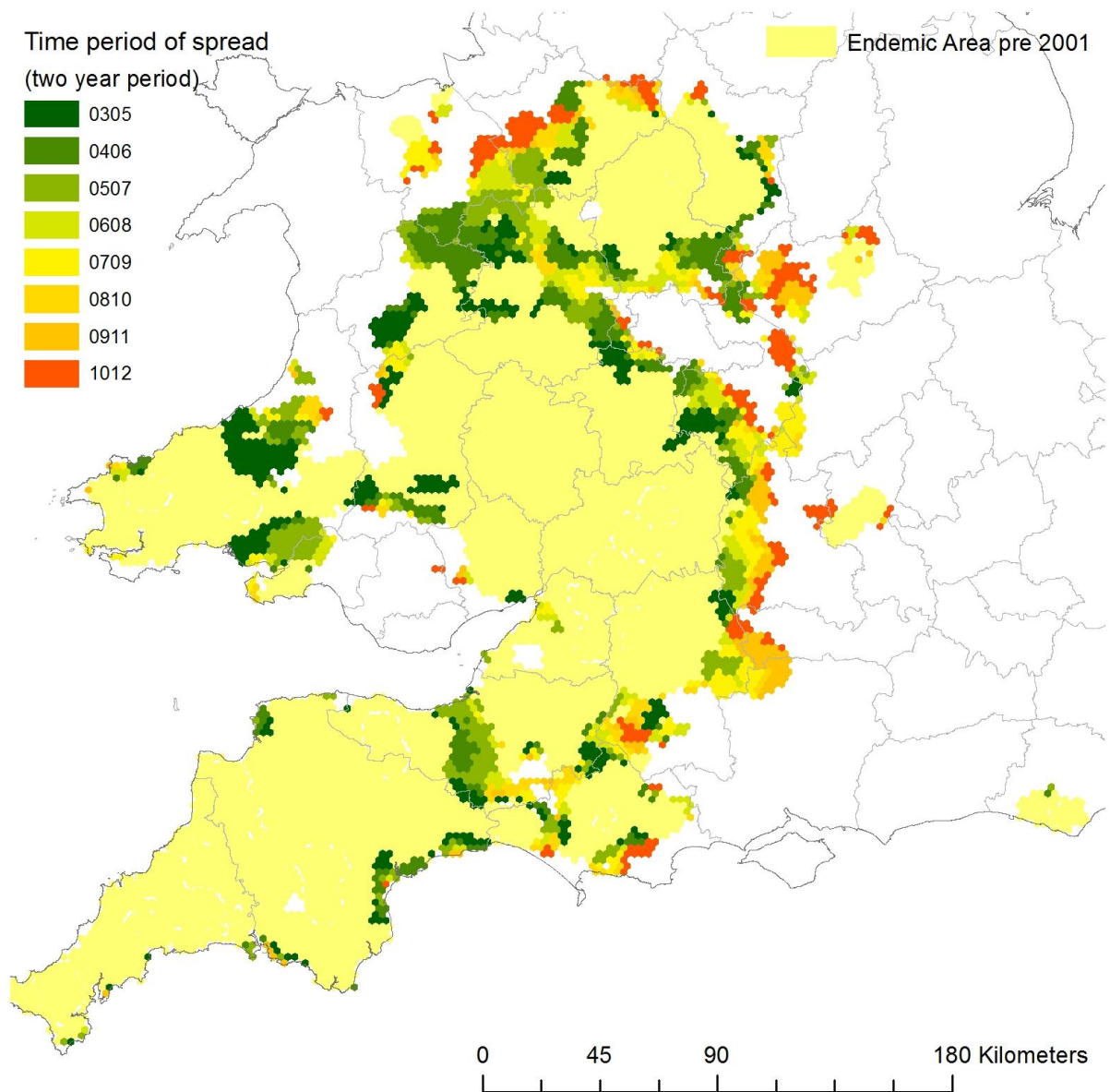threshold (horizontal axes).

Figure 5 – A map illustrating the two year time period in which a hexagon became endemic for the first time (defined by the presence of three OTF-W incidents within 7 km). Once a hexagon became endemic, it stayed endemic in this map. Reversion to non-endemic status may have occurred but was not calculated.

## 226 Rate of spread

227 The rate of spread for each hexagon where spread occurred between September 2001 and

228 August 2012 is presented in Figure 6. Rate of spread was obtained for ~2,300 cells and

229 varied between 0.04km / year and 15.9km / year, with a mean of 3.7km / year (SD = 2.2km /

230 year), and a median of 3.3km / year. The upper 95th percentile was 7.9km per year.
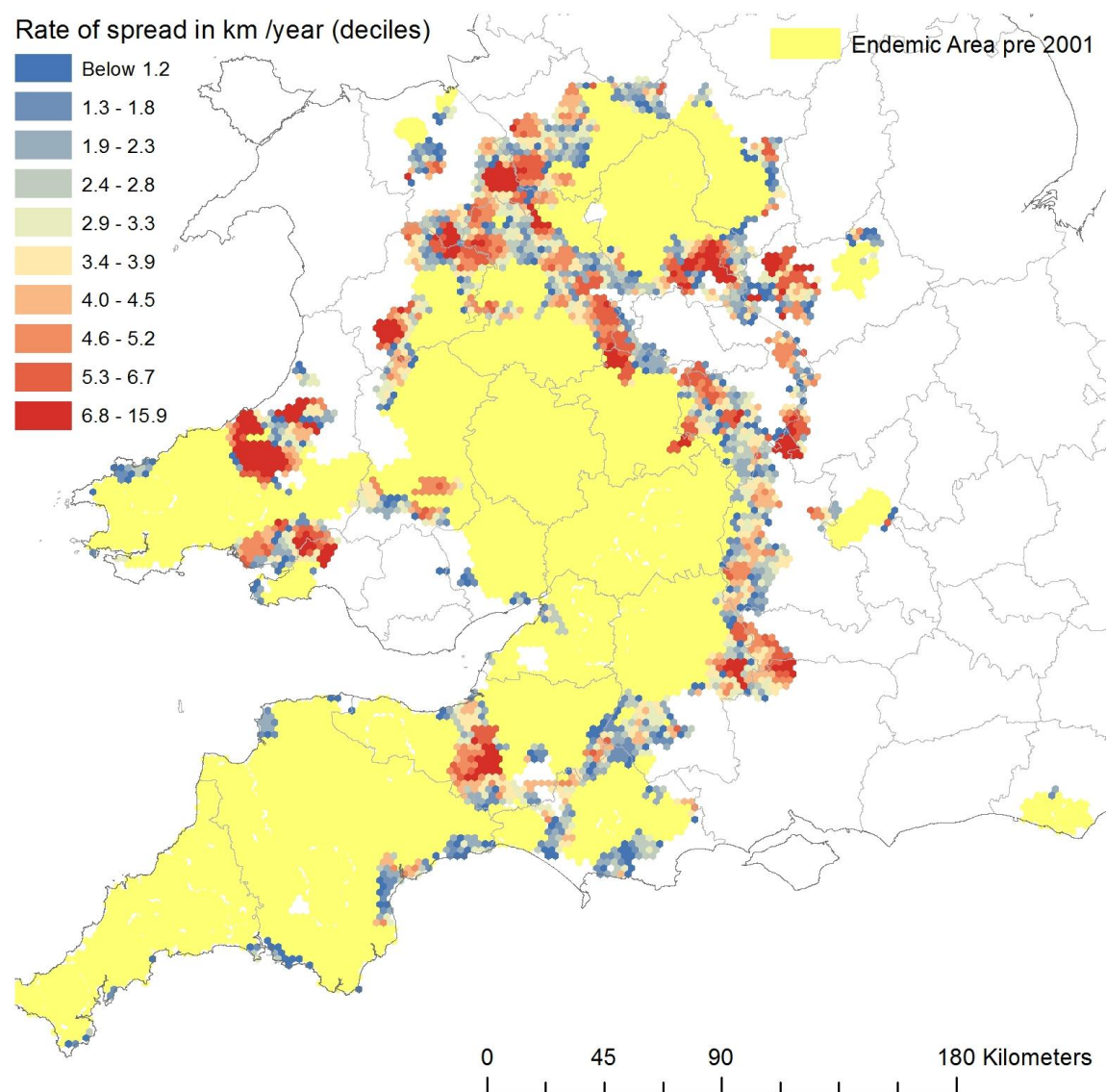


231
232 Figure 6 – A map illustrating the hexagons where endemic bTB (defined by the presence of three OTF-
233 W incidents within 7 km) spread between 2001 and 2012. Rate of spread in km per year is calculated
234 for the two year time period during which endemic bTB first passed through the hexagon. Reversion to
235 non-endemic status may have occurred but was not calculated. Hexagons which were classed as
236 endemic prior to 2001 are coloured yellow and are considered to be the 'core' endemic area.

237

## Discussion

239 We have developed a novel, and generally applicable method for assessing the spread of

240 endemic bTB in England and Wales. This information can be used to investigate the factors

241 associated with spread, and to identify areas for targeted interventions to stop and reverse

242 endemic spread.

243 The most frequently used numerator to measure bTB is the number of incidents, usually

244 attributed to the time period in which the incident was detected.  If only those bTB incidents

245 that had OTF status withdrawn (OTF-W) are counted, there is more certainty that the incident

246 represents true bTB infection, although the number of incidents decreases. There may,

247 however, be advantages in taking into account the number of OTF status suspended (OTF-S)

248 incidents and inconclusive reactors in assessing the development of endemicity, since these

249 events may represent the early stages of infection (Clegg et al. 2011), thus allowing better

250 estimates of the timing of recently-arrived endemic bTB.

251 The simplest individual animal numerator is the number of reactors to the SICCT skin test. An

252 advantage of counting reactors rather than incidents is that in long incidents, repeated

253 detection of reactors may contribute data in more than one time period.  Another is that the

254 number of reactors tends to increase with size of herd and OTF status (Conlan et al. 2012),

255 information that is not contained in a simple count of incidents.  During developmental work

256 attempts were made to filter the number of reactors to select those that were probably

257 infected locally, those which were "recurrent" reactors (those in herds in which a previous

258 incident was closed in the previous 24 months) and those that had visible lesions or yielded

259 *M. bovis* in culture. All three filters reduced the numerator considerably, but can be valuable

260 in discriminating for animals that have proven endemic bTB infection.

261 All measures of detection of bTB using classical incidence measures were too variable;

262 causing the annual pattern of bTB detected in 6.25km² hexagonal cells to be too haphazard

263 for the creation of distinct annual fronts. Two smoothing methods, one using data from the six

264 surrounding cells and the other using kernel smoothing, were used to improve the continuity

265 of each year's boundary of the endemic area, but inevitably they allowed artefactual regularity

266 to creep in.

267 Presence of bTB was indicated by detection via targeted surveillance testing in England and

268 Wales. As such, it is dependent on the frequency and efficacy of both the testing strategy and

269 the diagnostic test. Prior to 2013, the frequency of bTB testing of a herd was determined at a

270 local level, based on the level of bTB within their parish in the previous six years. In 2011,

271 47% of herds in England had an annual parish testing interval (PTI), 11% had a PTI of two

272 years, 0.8% had a PTI of three years, and 42% had a PTI of four years, while all herds in

273 Wales have been tested annually since October 2008 (AHVLA 2012). In areas of three or four

274 yearly testing, not all herds will be tested within the defined two-year period assessed in this

275 study, which will have reduced the estimated number of herds or animals infected (the

276 numerator). Long testing intervals can also lead to an underestimation of incidence due to

277 loss of undetected infected animals through sale and routine slaughter. If unaccounted for,

278 testing interval introduces an element of bias to any approach to assess temporal trends in

279 incidence, whereby earlier years (where fewer herds were tested annually) will be more

280 affected by underestimation of incidence. One way to address the influence of testing interval

281 is to use the testing history of herds to estimate the probability of a herd being infected at

282 different time points prior to the test which resulted in an incident.

283 The distance approach used here allowed for the calculation of the rate of spread of the

284 endemic front using a boundary displacement approach. Boundary displacement is less

285 widely used compared to trend surface analysis (TSA) and other models involving distance

286 regression from a point of origin, which have been used to obtain rate of spread for infectious

287 diseases, including bluetongue in cattle (Pioz et al. 2011), rabies (Moore 1999) and plague

288 (Adjemian et al. 2007), and invading populations of non-indigenous species (Evans &

289 Gregoire 2007; Tobin et al. 2007). However, boundary displacement has been evaluated to

290 be in broad agreement to distance regression, particularly where sample sizes are large

291 (Tobin et al. 2007; Gilbert & Liebhold 2010).

292 Because of their reliance on a fixed point of origin, distance regression approaches are

293 perhaps better suited to epidemic spread than to the spread of endemic disease. Core bTB-

294 endemic areas were established prior to the time series included in this study, resulting in

295 uncertainty relating to the location of the origin, which has been shown to lead to large

296 margins for error in rate of spread (Gilbert and Liebhold 2010). Potential issues associated

297 with boundary displacement were minimised by the selection of a definition of endemicity that

298 does not require aggregation, and for which a large sample of data is available. Holding-level

299 data provides a spatially dense sampling frame, even in areas of low herd density.

300 The rates of spread of endemic bTB observed were extremely variable and displayed little

301 spatial homogeneity. Possible explanations for the most rapid rates of spread might include

302 delays in the detection of disease due to the 2001 FMD outbreak and the influence of

303 restocking post-FMD rather than local spread (Gopal et al. 2006, Carrique Mas et al. 2008).

304 Converging spread of different genotypes in different directions might also result in unusually

305 high rates of spread. Retraction of spread (i.e. where endemic hexagons revert to a non-

306 endemic status) has not been calculated here, but would be of interest, particularly for

307 reviewing the impact of interventions at the edge of the endemic area.

## 308 **Conclusions**

309 A novel method for defining endemic bTB has been developed using a distance-based

310 mapping approach. The definition based upon having three OTF-W incidents within 7km of a

311 holding was found to maximise sensitivity and specificity for discriminating between endemic

312 and non-endemic areas, and defined endemic areas which were in agreement with the
313 experience of bTB field veterinarians. These thresholds have been found to be most
314 appropriate when using data for England and Wales between 2001 and 2011. However, it
315 would be prudent to bear in mind that changes in the epidemiology of bTB over time as well
316 as changes to surveillance regimes, may affect the suitability of these thresholds. The
317 definition developed here has allowed the expansion of the endemic fronts of bTB in England
318 and Wales to be mapped, which in turn enables further analysis of the factors associated with
319 this expansion.

## Acknowledgements

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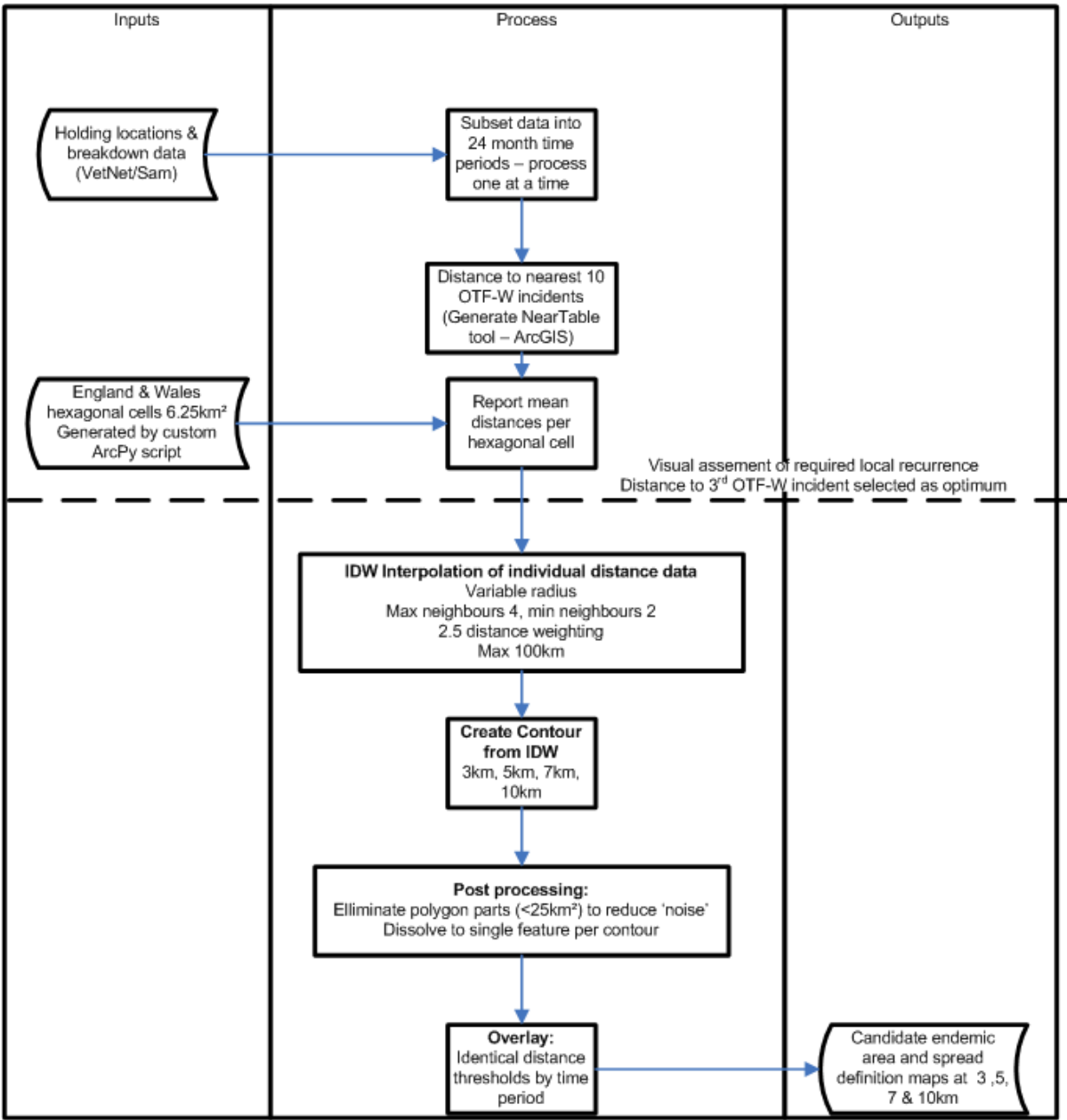
**Supplementary Information**

381 Figure SI1 – Geoprocessing workflow diagram for defining endemicity of bovine tuberculosis
382 in England and Wales.