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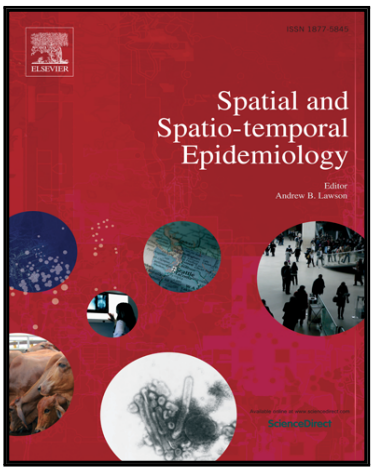

Application of kernel smoothing to estimate the spatio-temporal variation in risk of STEC O157 in England

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Application of kernel smoothing to estimate the spatio-temporal variation in risk of STEC O157 in England

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Introduction

Shiga-toxin producing *E.coli* (STEC) are a group of bacteria associated with human disease and are defined by the presence of one or both phage encoded Shiga toxin genes; *stx*1 and *stx*2 [1]. The main reservoir is ruminant animals, particularly cows and sheep.

First recognised as a human pathogen in 1982 [2], STEC are now globally distributed [3]. There is evidence that a common ancestor of STEC was introduced to countries around the world on a number of occasions in the past, likely due to international transport of animals and/or contaminated animal feed [4]. Following introduction, localised genetic variation has occurred leading to a patchwork of strains that are related at the global level, but show distinct geographical differences.

Infection with STEC is the result of complex set of interactions between distal and proximal risk factors related to the reservoir, the environment, the pathogen, the host and opportunities for transmission [5]. The relative importance of these factors may vary at different spatial scales [6]. For example, the same seasonal distribution of cases is seen in countries separated by large distances and this is thought to reflect the presence of similar agricultural and climatic risk factors [5]. However, these factors alone are unlikely to explain the considerable variation of infection rates between [7-11], and within [12], countries around the world, particularly when considering the comparable levels of carriage by cattle in those countries [13].

Within the United Kingdom, rates of STEC infection in Scotland are more than twice that of England [14]. Within England, rates of infection vary considerably from 0.40 to 1.34 cases per 100,000 person years in London and the North respectively [6, 15] and there is evidence that this relates to living in areas with high densities of farmed animals [6]. However, the strains infecting humans are not always the same as those circulating in the 'local' ruminant reservoir [16, 17]. The reasons for this are unclear but may be due to widespread exposure to a remote source of infection, or localised exposure to a source where the availability of comparative microbiological information is scant [6,

17]. Conversely, evidence from outbreak investigations shows that transmission of highly related strains can occur via multiple routes from geographically restricted sources [18, 19].

Identifying geographical areas with significantly higher or lower rates of infection therefore has the potential to provide important aetiological clues. These can then be used to inform the design of epidemiological studies to generate the evidence base needed for sound public health policies designed to reduce morbidity. Routine integration of spatial information with infectious disease surveillance data is increasingly common and statistical methods that allow precise delineation of high and low risk areas are widely available. These methods include area-based studies; global, local and focused tests for spatial clustering; estimates of spatially varying risk; and spatiotemporal modelling.

Area-based studies compare disease rates or counts between different populations, often combined with other data, to examine the effect of risk factors. Global tests for spatial clustering, such as Moran's I [20] and the Diggle-Chetwynd statistic [21], identify whether there is a general tendency for cases to occur more closely together than would be expected compared to the underlying population at risk. Local and focused tests for clustering, such as Local Indicators of Spatial Association (LISA) [22] and Kuldorff's scan statistic [23], are used to identify specific concentrations of disease that are statistically significant and may require further investigation. Methods to estimate spatial variation in risk are used to describe the change in risk over a given study area and include kernel smoothing, which forms a key component in the estimation of the kernel density-ratio or relative risk function [24-27], and spatial interpolation methods such as inverse distance weighting [28] and kriging [29]. Modelling approaches can either take the form of empirical or mechanistic models that consider the effect of space and time alongside other factors [30-32].

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Smith et al. [33] systematically reviewed the use of spatial methods in infectious disease outbreaks between 1979 and 2013. Most reports were from the United Kingdom and a range of techniques was used, including simple dot maps, cluster analyses and modelling approaches. Spatial methods were used in only 0.4% of the total number of published outbreaks, predominately for environmental or waterborne infections, and were applied in only one foodborne outbreak. Since 2013, spatial methods have been applied specifically to infectious intestinal disease data and have included tests for global [34-38] and local [34, 35, 37, 39-44] clustering, spatial variation in risk [36, 45, 46], modelling and other approaches [31, 35, 36, 39, 41, 42, 45, 47, 48].

The aims of this study were to first estimate the spatial variation in risk of STEC O157 in England; second, to estimate the space-time variation in risk over the study period; and, finally to explore any difference between the residential locations of cases reporting travel and those not reporting travel.

Methods

In England, isolates of *E. coli* O157 identified locally are sent for confirmation and typing at the Gastrointestinal Bacterial Reference Unit (GBRU). Detection and confirmation of STEC includes biochemical identification and serotyping of bacterial isolates. Since 1989, strains belonging to *E. coli* O157 have been further differentiated using a phage typing (PT) scheme developed in Canada [15]. Retrospective real-time polymerase chain reaction (PCR) targeting *stx*1 or *stx*2 and the intimin (*eae*) gene, associated with intimate attachment of the bacteria to the host gut mucosa, was introduced in 2012 [15]. Since 2015, all isolates have been routinely sequenced allowing identification of genetic lineage/sub-lineage and *stx* subtypes [49, 50].

The National Enhanced Surveillance System for STEC (NESSS) was introduced in England in 2009. The system collects clinical and epidemiological information for each laboratory confirmed case using a standardised questionnaire. This includes details about whether they had travelled abroad or

within the UK prior to their illness onset and the residential postcode of each case (an alphanumeric reference developed by the UK Post Office to facilitate the delivery of mail, each containing around 15 addresses). This information is linked to reference microbiology information including PT, presence of virulence factors and whole genome sequence data [1].

Case selection

We selected primary cases of STEC O157 with valid postcodes reported to the NESSS between 2009 and 2015. Strains of STEC O157 circulating in humans fall into three distinct lineages (I, II and I/II) descended from a common ancestor. Lineage I contains PT 21/28 and PT32; strains encoding *stx*2 only and associated with more severe disease. Lineage II contains PT8 and Lineage I/II PT2 [49]. Cases were categorised into these Lineages and Lineage II was further divided into sub-lineages IIa, IIb and IIc. Because routine whole genome sequencing (WGS) was not introduced until 2015, we extrapolated the phenotypic characteristics of PT and *stx* of strains identified by whole genome sequencing to isolates falling into Lineage II. This was not possible for isolates in Lineage I because sub-lineages are identified using the *stx* subtype which is inferred from the sequence result. The categorisation and numbers of strains are presented in Table 1.

The NESSS categorises cases into primary, co-primary, secondary or unknown. This categorisation is given at the time of the case interview and is quality checked when the data are entered into the system. Primary cases are either those that are not epidemiologically linked to other cases or, in the case of household outbreaks, the case that developed symptoms first. We selected primary cases only and cases linked to known outbreaks were excluded.

Control selection

Controls were randomly sampled from the National Population Database (NPD) [51]. The NPD is a point-based Geographical Information System (GIS) dataset that combines locational information

from providers like the Ordnance Survey with population information about those locations, mainly sourced from UK government statistics. It consists of a number of dataset layers, including population data from the 2011 Census [52]. Data are provided in a 100-metre by 100-metre grid situated on a centroid of the square with the population generalised to this level [51, 53]. Four control locations per case were drawn without replacement. The probability of a location being sampled was weighted by the summed population of each grid square to reflect the spatially varying nature of the underlying population at risk.

Analytical strategy

We chose the kernel smoothing method because our primary interest was to identify large scale variation in risk as opposed to small-scale localised clustering [54]. This method is also well suited to studying the occurrence of cases relative to the heterogeneous nature of the underlying at-risk population present in our data and the tools with which to perform the analyses are free and easily accessible [55].

The data used to estimate a particular relative risk surface are given as two distinct samples of planar points assumed to originate from (unknown, possibly equivalent) density functions f (cases) and g (controls) [55]. A fixed or adaptive [56, 57] bandwidth determines the spread of smoothing kernels centred on each point, producing a nonparametric density estimate that can be evaluated at all locations within the spatial study region. The ratio of case density to control density is calculated to provide a continuous estimate of relative risk which can then be plotted on a map. Where $f > g$ there is a peak in the surface (indicative of heightened risk); where $f \cong g$, the surface is flat (no difference in risk); and where $f < g$, there is a trough in the surface (lower risk). Specialised coordinate-wise hypothesis tests permit detection of statistically significant departures of these peaks and troughs from uniformity, and any such sub-regions can be delineated by drawing associated tolerance contours upon the risk surface in question [26, 27, 56].

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Spatially varying risk

To estimate the spatially varying risk we created case-control datasets for all PTs, Lineages I, II and I/II and Sub-Lineages IIa, IIb and IIc. For all PTs, we included cases that reported travel abroad or within the UK in the seven days prior to the onset of symptoms. For the Lineage and Sub-Lineage analysis, only cases who reported no travel were included. The same control dataset described earlier was used for each analysis.

For all spatial risk surfaces we used adaptive kernel estimation following Abramson's square-root rule [58]. This adaptation reduces the smoothing in areas of high point density (to capture more detail in the final estimate where we have an abundance of data), while increasing the smoothing in areas where the observations are relatively sparse (reflecting our greater uncertainty in areas where we do not have as much information). Such an approach has been shown to work extremely well for applications in geographical epidemiology [56, 57, 59], but the issue of bandwidth selection is more complicated than in the fixed bandwidth case; we require selection of both a "pilot" and a "global" bandwidth value to initialise the estimator for a single density estimate. To simplify the selection problem, recent work has shown constraining these two values to be equal, as well as following an established practice of choosing equal values between both the case and control density estimates [26] offers both theoretical and practical benefits for the resulting risk function estimate.

As such, we follow these guidelines in producing all spatial risk surfaces in this work, calculated as symmetric adaptive risk function estimates using the pooled case/control data set to compute the variable bandwidth factors [57], using equal global and pilot bandwidths chosen simultaneously via the likelihood cross-validation methodology described in [60]. The global bandwidth value was used for the fixed estimate in the sensitivity analyses. The far-right hand column of Table 1 reports the common case/control bandwidth found for each estimate.

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All estimates are edge-corrected to account for kernel weight lost over the boundary of the study region [61, 62] and results are reported as log-relative risk surfaces log f – log g for symmetry around the 'null' log risk value of zero. Finally, corresponding asymptotic p-value surfaces were estimated for each surface [56, 57], and contours were superimposed at the 5% significance level to delineate areas of significantly higher or lower risk.

To estimate the spatial effect of reported travel, we created a dataset containing case data only. Cases were marked with the following travel status categories: 'Foreign travel' (cases reporting travel outside the UK in the seven days prior to onset); 'Any travel' (cases reporting foreign travel and/or travel within the UK in the seven days prior to onset) and; 'No travel' (cases reporting no travel either in the UK or abroad in the seven days prior to onset). We calculated the spatial relative risk for reported foreign travel by comparing cases in the 'Foreign travel' category to those falling into the "Any" and "No" travel categories. To produce the risk surface for 'Any travel', we compared cases falling into the 'Any travel' category with those in the 'No travel category'.

Rural residence is known to be associated with an increased risk of STEC infection in England [6]. To explore the potential confounding effects of this on our analysis, we conducted two sensitivity analyses using both fixed and adaptive bandwidths. The first was restricted to rural areas only and the second used data stratified by urban/rural residence. For both these analyses we compared fixed to adaptive bandwidths to explore whether they produce similar results.

Spatio-temporal risk

Creating a dataset containing all cases marked with the month of disease onset as a temporal event permits exploration of the temporal variation in the spatial risk of STEC O157. However, estimation of spatio-temporal relative risk is somewhat more complicated than purely spatial risk, and the properties of adaptive kernel estimators for such functions have not yet been studied in sufficient detail in the statistical literature. Thus, we approach these estimates using the Fernando-Hazelton

fixed bandwidth kernel estimator [63]. Each spatio-temporal density estimate requires a separate smoothing bandwidth for the spatial and the temporal margins of the data. As in the purely spatial setting, it is recommended to choose the same values of these bandwidths between the case and control estimates. For the sake of comparison, we produced fixed-bandwidth relative risk surfaces [63] using two bandwidth prescriptions. The first used the maximal smoothing principle proposed by Terrell [64] applied separately to the spatial and temporal margins of the data. The second used the fixed bandwidth cross-validated likelihood method [60] to produce a risk surface with less smoothing. Estimates were edge corrected using the same methodology as mentioned earlier and results are reported as raw-risk estimates for ease of interpretation. Asymptotic p-value contours are again superimposed to identify areas of elevated risk only at the 5%, 1% and 0.01% significance levels.

Data preparation was performed using ArcMap v10.2 [65]. All subsequent analyses were performed using the contributed packages sparr [55] and spatstat [66, 67] in the R language [68]. Bandwidth selections were performed using cases and/or controls falling within a simplified polygon of the mainland boundary of England.

Results

The spatial locations of all unmarked cases and controls are shown in Figure 1. A total of 3,592 cases and 14,392 controls were considered for analysis. The majority of cases fell into Lineages I and II (Table 1). Just over half of all cases (1,942; 54%) reported no travel in the seven days preceding the onset of their symptoms, 29% (1,029) reported foreign travel and 17% (621) reported travelling within the UK (Table 1). Over half of the cases (2011;56%) were female and most (2157; 60.1%) were adults aged over 18 years or more. One fifth of cases (735; 20.1%) were children aged five years or less and the remainder (700; 19.5%) were children aged between 6 and 18 years.

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The relative risk surface for all cases (including those reporting travel) is shown in Figure 2. There were three main areas where risk was significantly higher compared to the underlying population at risk. These were in the north/north-west of the country and the south-west. Areas of significantly lower risk were largely confined to the south.

The relative risk surfaces for Lineages I, II and I/II are presented in Figure 3. For Lineage I, the greatest risk was largely seen in the north-west and south-west of the country. Areas of lower risk were confined to the midlands and south as well as a small urban area in the north-west.

Compared to Lineage I, the risk surface for Lineage II was more uniform across the country. Areas of significantly elevated risk for Lineage II were confined to the north and north-west, and two areas in the south-west of the country. Areas of significantly lower risk were largely restricted to the extreme south and south-east of the country.

For Lineage I/II, areas of significantly higher risk were restricted to the north, the east and the far south-west of the country. Areas of significantly lower risk were located in the south-east.

The relative risk surfaces for Sub-Lineages IIa, IIb and IIc are presented in Figure 4. For Sub-Lineage IIc, areas of significantly elevated risk appeared in the north-west and the south-west. Areas of significantly lower risk were located in the south and the far south-east. The risk for IIa appeared highest in the far south-west and for IIb across the north and south-west of the country but these were not statistically significant.

The results of the spatiotemporal analysis are best viewed in the animation provided here (Insert link to MP4). This shows that the spatio-temporal risk was largely confined to the north and south west of the country but was highly dynamic within and between these areas. The over-smoothed surface (left panel in the animation), showed an area of elevated risk largely restricted to the far north-west. In

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late 2010, this area expanded to the east and south and persisted across the north of England for two years before disappearing towards the end of 2013.

In the south-west, risk was similar to the north but lower between 2010 and 2013, after which the highest risk areas were seen in this area. Compared to the north, the areas of high risk were more mobile and appeared in different areas from year to year.

Figure 5 shows the two risk surfaces for cases reporting foreign travel and for those reporting foreign travel or travel within the UK in the seven days preceding onset of symptoms. Cases reporting travel were significantly more likely to live in the south and south east of the country than cases who reported no travel, who were more likely to live in the north or south west.

The results of the sensitivity analysis comparing the main results with those of the rural areas only and the analysis stratified by urban/rural residence are presented in Figures S1 and S2 respectively. Each analysis identified broadly the same areas of higher and lower risk identified by the main analysis. When compared to the adaptive surfaces, those produced using the fixed bandwidths were 'noisier', even though both generally agree on areas of heightened and lowered risk. This is likely the result of simultaneous over- and under-smoothing in different areas of the study region; a common symptom of fixed-bandwidth estimation [59].

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Discussion

Our analysis provides evidence that the distribution of STEC O157 infection in England is non-uniform with respect to the distribution of the at-risk population; that the spatial distribution of the three main genetic lineages infecting humans differs significantly and that the spatio-temporal risk is highly dynamic. We also provide evidence that cases of STEC O157 reporting travel within or outside the UK are more likely to live in the south/south-east of the country, meaning that their residential location may not reflect the location of exposure that led to their infection. We propose

that the observed variation in risk is likely to reflect a differential exposure to a source of STEC O157 that is geographically prescribed.

Comparison with other studies

Contact with the agricultural environment is a known risk factor for STEC infection [6, 69-71]. Within the British Isles, increased risk of STEC O157 infection is associated with rural areas where there are high densities of animals (particularly cattle and sheep) and less likely to be served by mains water supplies [6, 14, 72, 73]. There is evidence that the spatial distribution and relative importance of risk factors differ by pathogen sub-type [6, 45, 73] and similar findings have been produced from Northern European countries [14, 74-79], the United States [45], Canada [74, 80] and New Zealand[12].

Our analysis is exploratory and therefore inference regarding causation cannot be drawn. However, the areas of elevated risk presented here are consistent with findings from other studies in that they are predominately rural areas with sparse populations, high densities of farmed animals and with greater numbers of private water supplies [6]. They also share similar locations to national parks; popular destinations for day trips for local residents and longer holidays, particularly for those living in the south and south east of England [81]. In contrast to most farmland in England, public access to National Parks is largely unrestricted and visitors often camp, walk or cycle in areas where animals and/or their faeces are present [81, 82].

The importance of the pathways through which pathogens are transferred from the environment to humans is subject to debate [82].However, because of their low infectious dose, widespread prevalence in farmed animals and their ability to survive in the environment for extended periods of time STEC are well suited to environmental transmission. Recent studies using boot sock sampling over wide geographical areas demonstrate that *Campylobacter* [82] and STEC [83] can be recovered from boots following recreational walks in the countryside. The rate of recovery for both pathogens was highest in North West England (47% for *Campylobacter* and

25% for STEC) and is likely a reflection of high densities of cattle and sheep in this part of the country [82].

Spatial variation in risk at Lineage and Sub-Lineage level

Strains falling into Lineage I/II were the dominant strain infecting humans in England for many years but are now uncommon [15] and our analysis demonstrates that these strains are also spatially restricted. Lineages I and II have dominated since the late nineties [15] and this is reflected in the geographically widespread areas of elevated risk seen in broadly similar areas of the country. However, at regional level, the spatial distribution of the three lineages differed. Increased risk of infection with STEC in England is generally associated with residential proximity to high densities of farmed animals, however, risk of infection with Lineage I strains is particularly associated with sheep density[6]. This suggests that the presence of particular lineages in the environment is uneven and dependent, at least to some extent, on the underlying distribution of the zoonotic reservoir. This finding is consistent with the distribution of *Campylobacter* sp. in the environment relative to the presence of different animal species in England [82].

Spatio-temporal relative risk

The two versions of the animated spatiotemporal risk surface provide the opportunity to critically appraise the detected sub-regions of significantly elevated risk. For example, a large area that remains significant over a long period of time in the over smoothed estimate (left panel in animation) could to a certain extent be a methodological artefact arising from too generous a bandwidth. However, if certain smaller pockets within such a sub-region persist for noticeable periods in the noisy ("less-smooth") estimate (right panel), this indicates that anomalies in the infection rates are genuine, in turn suggesting these are a result of geographically restricted source. This was indeed the case, particularly in the north and south

west. The appearance, persistence and decline of an area of very high risk in the north of England between 2010 and 2013 appeared distinct to activity elsewhere in the country and corresponds with an unexplained decline in Lineage 1 strains, particularly in rural areas[6].

Bandwidth selection for kernel estimation

Choosing an optimal bandwidth is important for making reliable inference from relative risk surfaces. Even with tailored bandwidth selection methods [84], classical fixed bandwidth estimators can be unstable and do not cope well with the smoothing requirements of highly heterogeneous patterns [55, 56, 85]. However, choosing appropriate smoothing parameters for the more sophisticated adaptive estimator is far more difficult, and this is an active area of research [59, 85] .

We used a recently developed likelihood-based selection strategy for the purely spatial analyses [60], and while theoretically valid, further research into how well this type of simultaneous global/pilot bandwidth selection might perform in practice is warranted. This bandwidth selection method did not identify an optimal bandwidth within a scale-appropriate range for the risk surfaces of Sub-lineages IIa and IIb, erring toward excessive smoothing. Such a result is suggestive of spatial uniformity of risk, though the relatively low numbers of cases falling into these sub-lineages may, at least in part, be to blame in these instances. Of note is that Sub-lineage IIb (an unusual clone of PT8 encoding *stx*2), only emerged in significant numbers following an outbreak towards the end of 2015 [19, 86] and so fell outside the scope of our analysis. Further work on the recent spatio-temporal nature of this event is recommended.

Cases reporting foreign travel or travel within the UK

To provide the best estimate of indigenous risk, our study design at Lineage and Sub-lineage level did not consider cases reporting travel and did not therefore capture the possible location of exposure related to foreign or UK travel. Notwithstanding this, the inclusion of cases reporting travel made little difference to the overall results suggesting that the distribution of

these cases is broadly similar to the underlying population at risk. However, when considering spatial relative risk *between* cases, those who did report travel were significantly more likely to live in the south and south-east of the country. This is consistent with previous findings that for these cases, exposure to risk factors not present in their residential environment are important when considering the source of their infections [6].

Data quality and potential limitations

One potential limitation to our study is that for every STEC O157 infection reported to national surveillance systems in England, there are an estimated 7.4 in the community [87]. The reasons for this are likely to be related to severity of disease, health seeking behaviours and whether a clinician takes a sample and requests a microbiological examination from a laboratory. It is unknown whether these reporting biases vary geographically and hence would affect the spatial patterns presented in this paper.

There were no changes to laboratory methods or surveillance systems during the study period [15]. However, a large petting farm outbreak in 2009 [88] attracted media attention and prompted a review of national guidelines for the public health management of STEC which had the potential to improve case ascertainment and follow-up from 2010 onwards.

In addition, the Health Protection (Notification) Regulations 2010 [89] came into force during the study period. This legislation introduced the mandatory reporting of STEC as a causative agent, and haemolytic uraeamic syndrome (HUS) as a notifiable disease. Our results do not suggest that these events created a reporting differential based on severity of disease because risk is elevated in similar geographical areas for Sub-lineage IIc strains that tend to be associated with less severe symptoms than those falling into Lineage I.

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We also considered the effect of rural versus urban residence in our sensitivity analysis, the results of which suggest that the observed spatial variation is unlikely to be explained by rural residence alone and that, and that the adaptive bandwidths used in this paper do not produce different results to fixed bandwidths.

Conclusion

To conclude, the risk of sporadic infection with STEC O157 varies significantly across England. We suggest that this is due to differential exposure of the population to geographically restricted risk factors. The appearance, expansion and decline of an area of significantly elevated risk in the north of England between 2010 and 2013 corresponds with an overall reduction of STEC O157 in England, seen most acutely in PT21/28 reported in rural areas [6]. Cases reporting travel prior to onset of illness were more likely to live in south of England.

These differences could be related to a combination of changes in the strains circulating in the ruminant reservoir, animal movements (livestock, birds or wildlife), contaminated animal feed or the behavior of individuals prior to infection. Further work to identify the importance of behaviours and exposures reported by cases relative to residential location is needed. Statistically speaking, designing a semi-parametric, generalised additive style of model (see for example [90, 91]) is one way we could build in extraneous predictors and estimate any associated effects on infection risk in such an analysis. We anticipate the findings in this work will help guide such future research endeavours.

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Richard Elson is based at Public Health England. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of Health or Public Health England.

Biographical sketch

Richard Elson is an epidemiologist employed by Public Health England with a particular interest in the spatial and spatio-temporal distribution of gastrointestinal infections.

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Table 1. Case selection criteria and associated common case-control bandwidths.

Case details		**PTs**	***stx***	**n**	**Common smoothing bandwidth (km)**
All cases		-	-	3,592	9.39
Reporting foreign travel		-	-	1,029	31.84
Reporting any travel		-	-	1,650	31.84
Lineage I*		21/28, 32	2	752	12.37
Lineage II*		4,8,34,54	-	778	18.10
	Sublineage IIa	34,54	2	134	92.79
	Sublineage IIb	4,8	2	140	60.15
	Sublineage IIc	8,54	1&2	493	20.31
Lineage I/II*		2	2	120	21.69
Others		1,14,31,33,46,51,8 (*stx*1),4(*stx*1&2)	-	652	-

* Cases reporting no travel.

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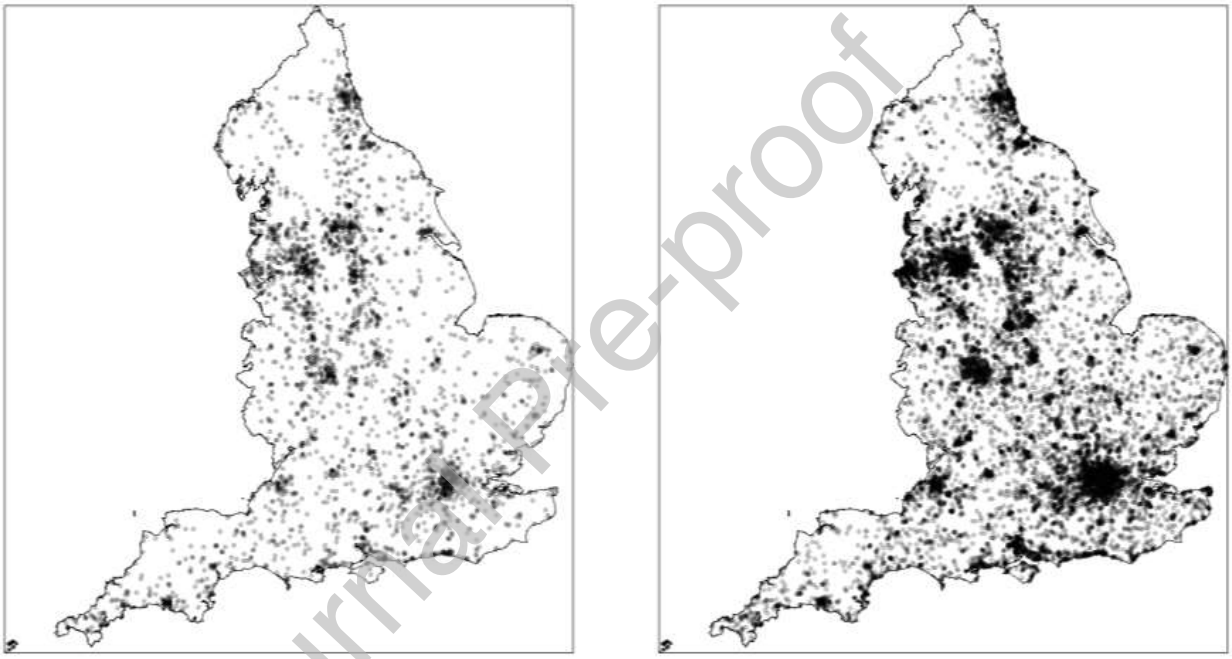

Figure 1 Spatial location of 3,592 STEC O157 cases (left panel) and 14,392 randomly selected controls (right panel).

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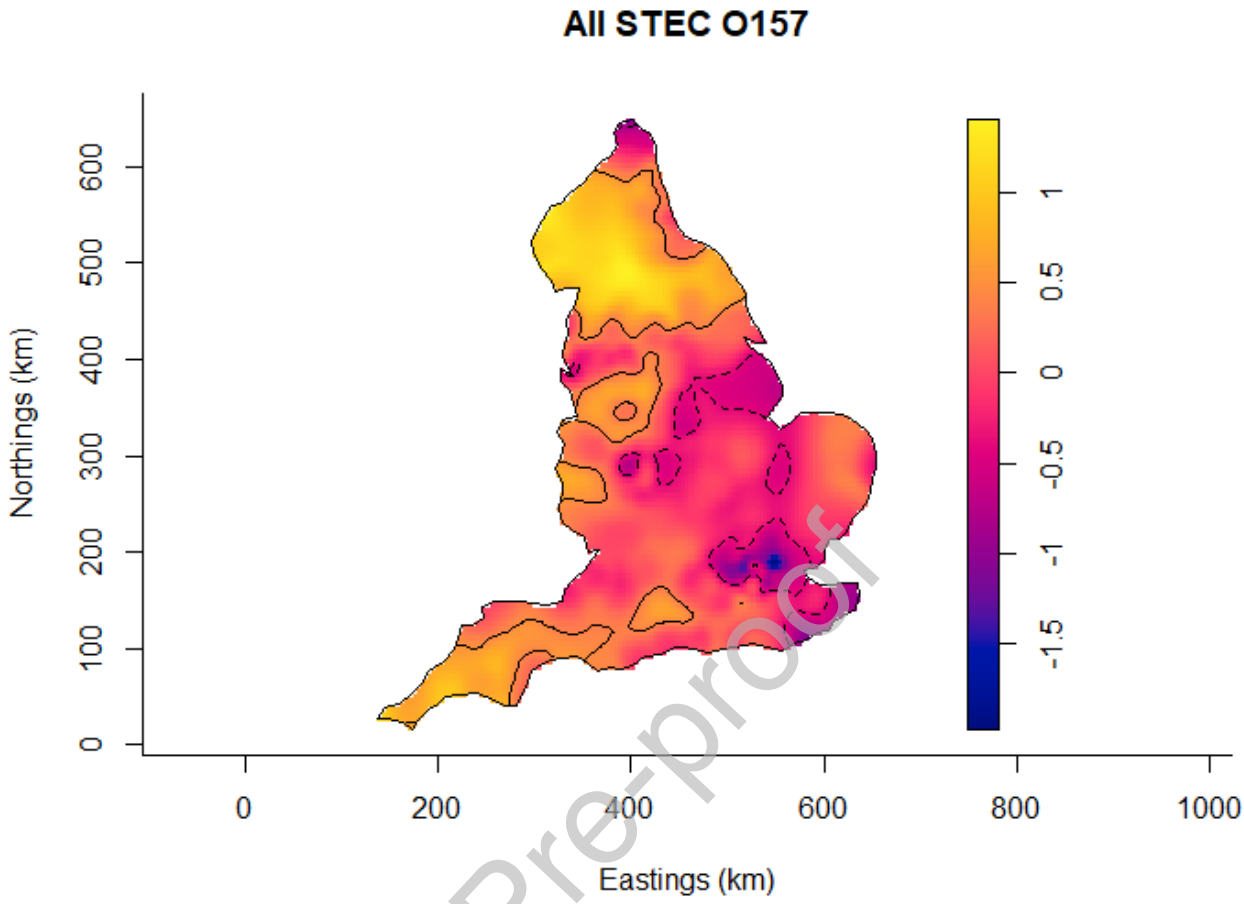

Figure 2. Estimated log relative risk for all cases of STEC O157 (including cases reporting travel). Tolerance contours are superimposed as solid lines at the 95% confidence level. Solid lines indicate areas of significantly higher risk and dashed lines indicate areas of lower risk.

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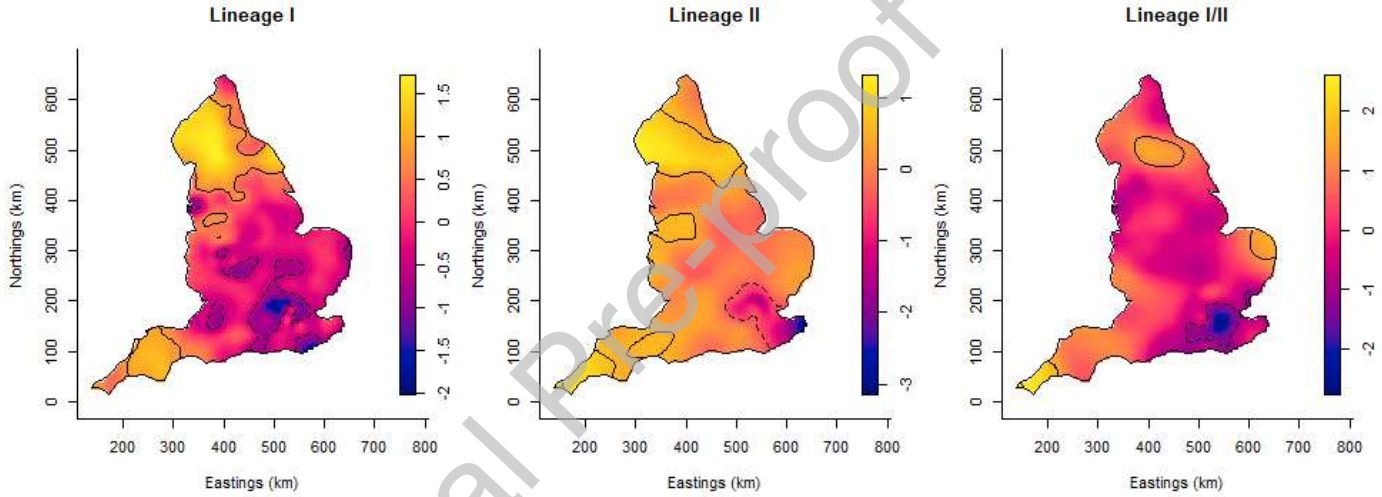

Figure 3. Estimated log relative risk for STEC O157 Lineages I, II and I/II in cases reporting no travel. Darker areas indicate areas of lower risk. Tolerance contours are superimposed as solid lines at the 95% confidence level. Solid lines indicate areas of significantly higher risk and dashed lines indicate areas of lower risk.

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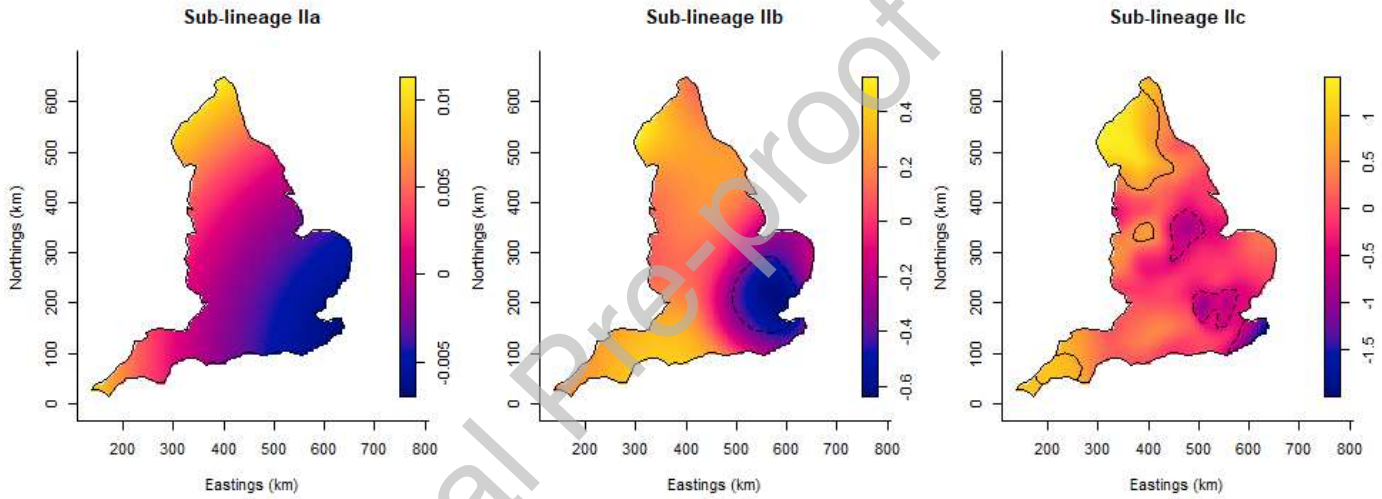

Figure 4. Estimated log relative risk for STEC O157 sub-lineages of Lineage II in cases reporting no travel. Darker areas indicate areas of lower risk. Tolerance contours are superimposed as solid lines at the 95% confidence level. Solid lines indicate areas of significantly

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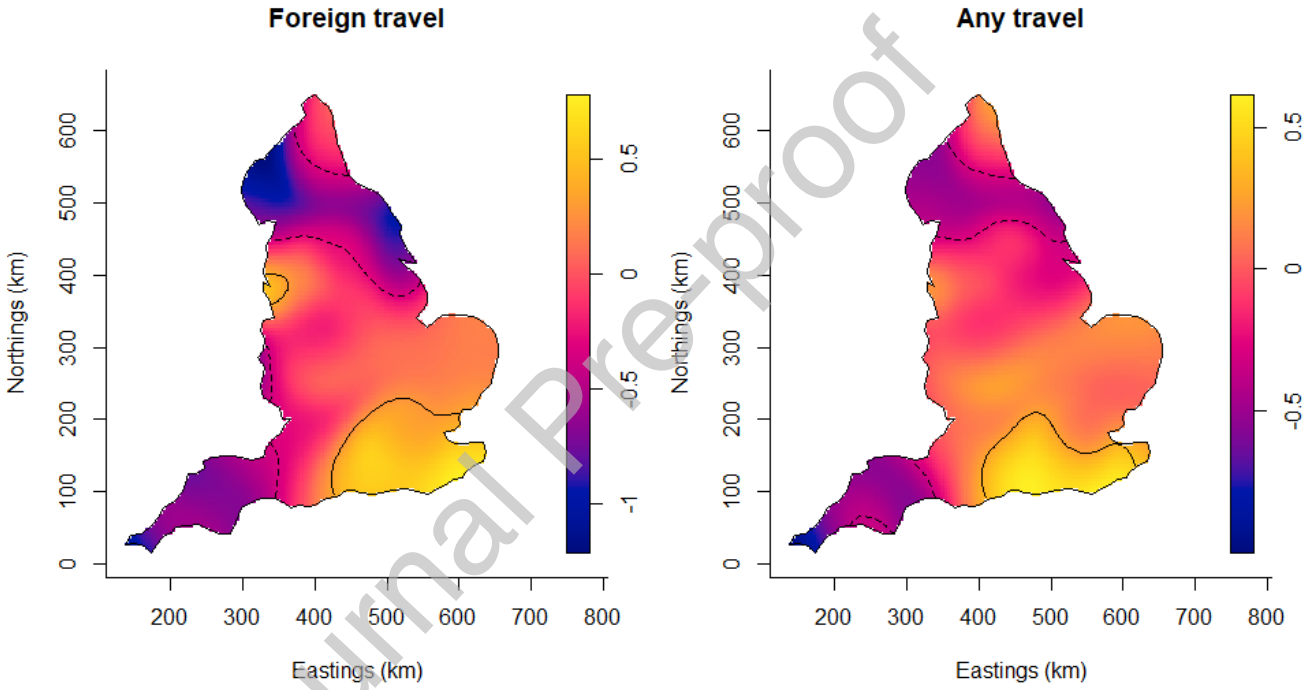

Figure 5. Estimated log relative risk for cases of STEC O157 reporting foreign travel (left panel) and those reporting any travel. Tolerance contours are superimposed at the 95% confidence level. Solid lines indicate areas of significantly higher risk and dashed lines indicate areas of lower risk higher risk and dashed lines indicate areas of lower risk.

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