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Identifying genotype specific elevated-risk areas and associated herd risk factors for bovine tuberculosis spread in British cattle

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ABSTRACT

Bovine tuberculosis (bTB) is a chronic zoonosis with major health and economic impact on the cattle industry. Despite extensive control measures in cattle and culling trials in wildlife, the reasons behind the expansion of areas with high incidence of bTB breakdowns in Great Britain remain unexplained. By balancing the importance of cattle movements and local transmission on the observed pattern of cattle outbreaks, we identify areas at elevated risk of infection from specific *Mycobacterium bovis* genotypes. We show that elevated-risk areas (ERAs) were historically more extensive than previously understood, and that cattle movements alone are insufficient for ERA spread, suggesting the involvement of other factors. For all genotypes, we find that, while the absolute risk of infection is higher in ERAs compared to areas with intermittent risk, the statistically significant risk factors are remarkably similar in both, suggesting that these risk factors can be used to identify incipient ERAs before this is indicated by elevated incidence alone. Our findings identify research priorities for understanding bTB dynamics, improving surveillance and guiding management to prevent further ERA expansion.

1. Introduction

Bovine tuberculosis (bTB) is caused by the pathogen *Mycobacterium bovis (M. bovis)*, and is a disease with important consequences for animal health and production. Historically, bTB has been a major contributor to human TB cases worldwide, and it remains a zoonotic concern in many developed and developing countries (Ayele et al., 2004; Cosivi et al., 1998; Evans et al., 2007). The standard live test used to control bTB in Great Britain (GB) is the Single Intradermal Comparative Cervical Tuberculin (SICCT) skin test, where each animal is checked for an immune response to intradermally injected bTB-derived antigen (de la Rua-Domenech et al., 2006). Control is via a combination of regular test and slaughter using SICCT and abattoir post-mortem testing. Identification of positive test reactors results in a *breakdown*, which places the herd on repeated testing protocols and movement controls until it is deemed clear of infected cattle. In countries that employ a well-developed test and slaughter programme, bTB has either been eradicated (British Veterinary Association, 2009; Radunz, 2006), or has persisted due to the presence of a wildlife reservoir (Nishi et al., 2006; Tweddle and Livingstone, 1994). Both patterns are observed in the British Isles: while Scotland has been declared officially bTB free (British Veterinary Association, 2009), England and Wales have an ongoing bTB epidemic with the Eurasian badger (*Meles meles*) implicated as an important wildlife reservoir for *M. bovis*. This situation is complicated by the protected status of badgers in the UK, and bTB remains a serious and increasing problem in the British cattle industry, with an estimated management cost over £111 m in the 2013/2014 year alone, excluding any Defra policy development costs.[2] Both the incidence of herd breakdowns and the total area deemed at high-risk of breakdowns increased rapidly in the period after 2001, when foot-and-mouth disease (FMD) resulted in both widespread cessation of routine testing for bTB across GB, and subsequent whole herd restocking of cattle was responsible for widespread dissemination of disease.

The epidemiology of bTB in British cattle has been extensively studied, most notably in the context of the large “Randomised Badger

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[2] Response to EIRs request for information about the costs of controlling BTB in 2013. FOI release. Bovine TB control costs in 2013. https://www.gov.uk/government/publications/bovine-tb-control-costs-in-2013.

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Culling Trial" (RBCT; Bourne et al., 2006; Donnelly et al., 2007; Woodroffe et al., 2006), but also in a number of studies of the respective national epidemics (Brooks-Pollock and Keeling, 2009; Brooks-Pollock et al., 2014; Brooks-Pollock and Wood, 2015; Carrique-Mas et al., 2008; Denny and Wilesmith, 1999; Gilbert et al., 2005; Green et al., 2008; Griffin et al., 1996; Johnston et al., 2005; Karolemeas et al., 2010; Woodroffe et al., 2016). Nevertheless, the expansion of areas in GB with a high incidence of herd breakdowns is still not well understood, and there remains considerable debate over the most appropriate approaches for controlling bTB in cattle (Bennett and Willis, 2007; Conlan et al., 2015; White and Whiting, 2000). Despite the controversy, there is overwhelming evidence of an epidemiological link between bTB in badgers and cattle. First, the culling of badgers is known to be associated with changes in the incidence of herd breakdowns (Donnelly et al., 2006; Griffin et al., 2005). Second, the perturbation of the bTB epidemic caused by the interruption of testing and restocking due to the 2001 FMD epidemic in the UK is similarly correlated to changes in incidence of bTB in badgers (Carrique-Mas et al., 2008). Finally, *M. bovis* genotypes in cattle and badgers are strongly associated at a local geographical level (Woodroffe et al., 2009); this is also consistent with the marked spatial clustering of individual genotypes in high incidence areas (Fig. S1 in Supplementary Information).

Genotyping of *M. bovis* in GB is based on a combination of spoligotyping and variable number tandem repeat (VNTR) typing (Smith and Upton, 2011). *M. bovis* is a member of the *Mycobacterium tuberculosis* complex, which is clonal (Smith et al., 2006), allowing the overall bTB epidemic to be split into multiple discrete genotype-specific epidemics, and therefore one can consider herd breakdowns due to the same genotype as belonging to the same epidemic. Thus, the close association of badger- and cattle-derived genotypes is a strong indicator of transmission between the two species, which can be transmission from badger to cattle or transmission from cattle to badger. All these data are indicative of a single, linked "episystem" with complex interactions at various spatial scales. Identifying the relative roles of the two host species in maintaining and establishing high incidence areas of herd breakdowns is fundamental to improve control in these areas. While we do not know the relative contribution of badgers and cattle to the epidemic, the bidirectional spread between the two species would suggest that the interaction between them is an important part of a disease maintenance system, broadly speaking contained within SW England and Wales, but also responsible for onward transmission of bTB to other areas such as Scotland that would otherwise be without incidents.

In GB, bTB testing was historically managed at the parish level, with herds that were located in high risk parishes of the country tested annually, while those located in low risk parishes tested every two, three or four years according to perceived risk in accordance with criteria listed in European Union directive 64/432/EEC; in recent years, more geographically streamlined designations of High Risk Areas (HRAs) and Low Risk Areas (LRAs) have been introduced. In 2010, all herds in Wales were officially placed on annual routine herd test (The Tuberculosis (Wales) Order, 2010). In England, a new bTB surveillance regime has been in place since 2013, whereby herds in designated LRAs are tested once every four years, herds in HRAs of the west of England are tested annually (DEFRA, 2013), and herds located in a 'transitional zone' of intermediate bTB incidence known as the Edge Area (EA) are tested annually. Herds that are located in increasing bTB incidence parts of the EA are tested every 6 months since January 2015. However, as of late 2017, the testing regime in EA has been under review (Animal and Plant Health Agency, 2017).

Breakdowns can potentially be seeded a considerable time prior to detection. As test intervals have historically been at least in part determined by the local breakdown incidence, in a spatially expanding epidemic, testing could lag behind the establishment of new areas where cattle herds are at a higher risk of a breakdown. In this case, this could also be associated with interaction with reservoir hosts. A critical component to understanding how areas with elevated risk of bTB spread, and therefore how to best control them, is the development of epidemiologically driven definitions of these areas. In this analysis, we propose a novel approach to identifying areas with elevated risk for three geographically discrete bTB genotypes, utilising the predicted impact of recorded cattle movements to estimate the role of unobserved transmission in a likelihood based-setting, in conjunction with the recorded spatial distribution of *M. bovis* genotypes. To avoid confusion with the already established formal term High Risk Areas (HRAs), we will designate our estimated high-risk areas as elevated-risk areas (ERAs). We then determine the total probability of infection due to three factors: (i) livestock movements, (ii) local-based spread, and (iii) a background, country-wide rate. Finally, we test for any significant differences in risk factors between the identified ERAs and the transitional areas (TAs) (areas with intermittent elevated risk during the study period), as well as assess any general trends of spatial spread of bTB in England and Wales. In this analysis, we concentrate on the years 2002–2008, a period when the rapid expansion of bTB meant that the signature of transition is likely to be most marked.

2. Materials and methods

Breakdowns are often detected only after harbouring infection for a considerable time (Karolemeas et al., 2011). This is exacerbated by the differences in testing regimes across GB. To identify areas likely to harbour hidden infections, we examine the "shadow" of breakdowns caused by outward cattle movements from herds at higher risk of having undetected infected animals. A previously published model (Green et al., 2008) used this concept to estimate the relative proportion of transmission due to movement-based spread, using the explicit dynamic social network that is defined by recorded cattle movements. Green and colleagues (Green et al., 2008) used parishes under one- or two-year testing as a proxy for ERAs or, alternatively, ERAs were defined by 6 km circles centred around breakdowns from the previous year. Here, we adapt this approach to explicitly identify putative ERAs for specific genotypes utilising a novel grid-square approach.

2.1. Source data

Cattle movements were extracted from the Cattle Tracing System (CTS) of GB (provided by RADAR), and bTB breakdown details were extracted from the animal health database VetNet (provided by Defra). The model considered 136,302 premises identified by the CTS that have had at least one recorded movement, where the data had been cleaned and premises coordinates were available. The model utilises the movement of all cattle, which are represented as daily links between pairs of premises. Movements to slaughter were removed. As markets involve transient contact at best between cattle, stays at markets were not considered as infectious (Skuce et al., 2011), and were removed from the dataset such that movements $A \rightarrow B \rightarrow C$, where B is a market, were replaced by a single movement $A \rightarrow C$ set to occur on the recorded date of arrival at C. Individual movements with equal dates, start, and end points were grouped into batches. For 2002–2008, there were 6,625,056 resulting batch movements with a mean batch size of 3 animals.

Here, we consider only breakdowns confirmed by successful culture of *M. bovis*, as this is also a requirement for obtaining bacterial genotypes. For 2002–2008, there were 15,939 such confirmed breakdowns. Of these, 99.4% were matchable to unique county/parish/holding (CPH) codes present in the CTS data, across 10,838 different premises.

Genotype data consisting of spoligotypes and VNTR types were obtained from the Animal and Plant Health Agency (APHA). Three genotypes were chosen for investigation on the basis of their geographical predominance in expanding regions of high incidence, at the edge of annual testing areas. As defined by the international naming convention (Smith and Upton, 2011), these were genotype 25:a