Exploring the richness of Mycobacterium bovis strain diversity to decipher the epidemiology of bovine tuberculosis ecology

Reference	BB/N00468X/1
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Institution	University of Cambridge
Department	Veterinary Medicine
Funding Type	Research
Value (£)	530,175
Status	Current
Type	Research Grant
Start Date	01 April 2016
End Date	31 March 2019
Duration	36 months

Abstract

We propose a retrospective study of historical isolates with Whole Genome Sequencing (WGS) to gain specific insights into the mechanisms that drive the patterns of within-herd persistence of bTB in Great Britain. Diversity of M. bovis strains, in common with the whole M. tuberculosis complex, is highly restricted. This lack of diversity has severely hampered the usefulness of traditional genotyping methods to inform detailed epidemiological questions on the directionality of transmission and persistence of bTB strains within herds. Recent applications of WGS by the Wellcome Trust Sanger Institute and others have demonstrated the potential to reconstruct chains of transmission and the inherent difficulties in doing so from poorly sampled populations.

Sampling is a particular concern for the utility of WGS methods for bTB due to the current guidelines that require the isolation and culture of at most one cattle reactor, with no systematic sampling of wildlife populations at the national level. We address this issue by focusing our attention on herds that were part of the Randomised Badger Culling Trial, where attempts were made to sample all test positive cattle in trial herds along with 1980 isolates from badgers. By targeting herds with a history of recurrent bTB incidents we aim to estimate the relative importance of the hidden burden of infection missed by testing and the re-introduction of infection by cattle movements or wildlife populations. We will also focus on more recent recurrent breakdowns from which there are usually multiple isolates.

Our published mathematical within-herd transmission models, carefully estimated from testing data, provided a first estimate that between 25-50% of recurrent bTB incidents could be attributed to infection missed by testing. We seek to benchmark this first estimate, using the new insights from our study to validate or improve the estimation of these disease dynamic models that are already used to advise policy.

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Summary

Bovine tuberculosis (bTB), caused by Mycobacterium bovis, is a multi-species infection that causes a serious burden on the cattle industry in Great Britain (GB), and throughout the world. Despite extensive control measures in cattle, the disease in cattle remains uncontrolled and now costs the UK government around £100 million per year. Control of the disease is governed by a National Strategy, published by Defra.

Control is based around routine surveillance testing of living cattle and all those slaughtered in GB slaughterhouses. Routine surveillance is based around the use of a highly specific but relatively insensitive skin test. When infection is diagnosed, attempts are made to isolate M. bovis from skin test positive cattle, which are all slaughtered. M. bovis can be isolated from around 70% of all infected herds. Herds where infection is diagnosed are placed under movement restriction and all animals are then subjected to repeated skin testing until no further detectable infection is evident. One of the great challenges for control is that half of all farms in high incidence areas of England and Wales that are restricted, tested and released have recurrent disease within 3 years. It is unclear how much of this disease burden is associated with persistence in cattle or with reintroduction from wildlife, specifically badgers, whose infection is closely linked with that in cattle in high incidence areas of GB.

Thus, a key question in bTB control in Britain relates to what the source of the infection is for herd. At the individual level, knowing this allows for specific measures to be put in place to prevent recurrence of infection. At the national level, understanding the sources of constant bTB challenge, allows for more general policy to be developed and targeted at the sources of this reinfection.

Modern genetic methods provide great opportunities for forensic evaluation of outbreaks of diseases. Organisms causing disease can be genetically sequenced todetermine their origins and relationships with other outbreaks and cases. Detailed genetic sequencing of bacteria that cause disease is now becoming common in human medicine to determine what optimal controls should be. New methods mean that this can be done in real time. The bacterium that causes bTB, M. bovis, has been evaluated routinely in in GB using traditional genetic methods over the last 20 years as part of surveillance. These studies have the surprisingly restricted distributions of different genetic types to be mapped in Britain - and hence to determine the likely origins of outbreaks that occur in low incidence areas (often associated with cattle movements); however, the classification is not fine grained enough to allow differentiation of local on-farm persistence of disease from that associated with introduction from relatively short distance cattle movements. Our work will use the amazing library of M. bovis isolates held by Defra's laboratory agency and will apply modern whole genome sequencing methods to 2000 carefully selected retrospective samples. We will use samples from recent routine surveillance from over GB, particularly focussing on farms where disease has been persistent, to evaluate the different drivers of persistence that so hamper our control efforts. We will also use samples from the randomised badger control trial where there is unparalleled availability of badger isolates and far more intensively parallel sampled cattle to reveal more details of the complex transmission dynamic between the two species, in order to allow more precise targeting of measures to prevent cattle becoming infected in the future.

Our work will translate directly into Defra's plans for more intensive investigation and intervention on farms that repeatedly become infected in high incidence areas. The approaches that we develop will become, as in human medicine, part of the routine approaches taken when investigating disease.

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Impact Summary

Bovine tuberculosis (bTB) is the most significant endemic disease of farmed animals in GB and costs the taxpayer around £100M each year. bTB has been spreading in cattle since the 1980s. Control in cattle is the responsibility of Defra and is affected by a range of different measures, including statutory testing of live cattle, movement restrictions on suspected infected animals and slaughterhouse surveillance. The intensity of the programme varies significantly between different GB regions. The disease in cattle in areas where the incidence is high, especially the South West, cannot be fully controlled without some measures that will reduce transmission from wildlife, specifically badgers. However, even here, the relative importance of infection from badgers is hotly contested, despite strong evidence for a critical role. A key feature of the disease in high incidence areas is that persistence of disease on farms is very common; at least half of all farms that have been released from control after outbreaks will have the infection diagnosed again within 3 years and, further, a quarter of farms across GB will have breakdowns that last more than 240 days. These patterns of intensive persistence in some parts of the High Risk areas of England are responsible for large amounts of the cost of the disease.

APHA has started to use Illumina MiSeq technology, which allows the real time whole genome sequencing of M. bovis isolates from cattle during breakdowns. This capability, combined with the background analysis of the geographically restricted phylogenies that this programme will deliver, will come on stream at a time, as discussed in the Defra bovine TB strategy document published in 2014, that detailed consideration of the epidemiology in persistently infected farms in high incidence areas of England will be used to address the major challenge of these units. Thus, the approaches developed during this programme should be utilised within disease control elements of AHA even before the end of the grant.

The lack of diversity of isolates currently resolved has limited insights into the dynamics of transmission within cattle, in particular the roles of persistence, cattle-movements and transmission to and from the wildlife reservoir. Whole genome sequencing offers the opportunity to examine these dynamics at a higher resolution (cluster and farm outbreak level) than has been possible before. A detailed phylogenetic analysis of the available samples, over time and space, as proposed here, should also shed light onto the epidemiological and ecological mechanisms that underlie the apparent series of mini local epidemics that are such a clear feature of the disease in high risk areas in GB.

Whole genome sequencing has been proposed as a routine part of ongoing bTB surveillance to improve breakdown management and is part of the action plan for delivering Defra's strategy for achieving 'Officially Bovine-Tuberculosis-Free Status' for England. A retrospective analysis of historical samples offers an opportunity to reveal new insights into the within-herd persistence and hidden transmission dynamics of bovine tuberculosis and enable new and more efficient uses of epidemiological tracing and evidence based control in the future.

Taken overall, this work will a) develop methods and approaches that directly feed into Defra's disease control teams on the ground and b) provide critical information that will allow appropriate emphasis to be placed on the relative importance of different routes of introduction of disease onto cattle farms so that appropriately weighted policies can be developed to address these challenges. We will work carefully with all key stakeholders from the outset to ensure maximal impact of our work, both through gaining from their insight and identification of specific questions and also through communication of outputs.

Committee	Research Committee A (Animal disease, health and welfare)
Research Topics	Animal Health, Microbiology
Research Priority	X – Research Priority information not available
Research Initiative	Eradication of bovine tuberculosis through basic research and discovery (ERADbTB) [2015]
Funding Scheme	X – not Funded via a specific Funding Scheme

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