The genetic and spatial epidemiology of bovine tuberculosis in the UK: from molecular typing to bacterial whole genome sequencing

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Abstract

Bovine tuberculosis (bTB) is a disease of cattle and other animals caused by the bacterium Mycobacterium bovis. In the UK, control of the disease presents significant difficulties, with bTB currently one of the most important diseases affecting the livestock industry in this region. The involvement of infection in a wildlife reservoir, the Eurasian badger Meles meles, is a key challenge to the eradication of bTB in the UK and causes much public controversy. In such a situation it is essential to use all available tools to control the spread of the disease. For many years, molecular typing of the M. bovis population has been routinely employed to understand the epidemiology of bTB in Britain and Northern Ireland (NI), providing broad scale information on the M. bovis population. More recently, high-resolution bacterial whole genome sequencing (WGS) of M. bovis has become feasible, although its use had yet to be explored in depth for the epidemiology of bTB. In this thesis, I describe various approaches to the use of pathogen genetic and spatial information to explore the epidemiology of bTB in the UK. I start at the broad scale, analysing the molecular types of M. bovis across the whole of NI, and go on to evaluate the use of WGS for M. bovis in targeted subpopulations of cattle and badgers. Following a general overview (Chapter 1), I explore the processes underlying the pattern of relative abundances of M. bovis molecular types in NI, showing that simple neutral processes are not capable of generating the distribution observed, and using simulation models to demonstrate that historical increases in bTB prevalence and/or transmission heterogeneity may be responsible (Chapter 2). In Chapter 3, I examine the spatial structure of the NI M. bovis population, demonstrating significant spatial clustering of M. bovis molecular types and correlations between the types present in cattle and badgers. I go on to develop a landscape genetics analysis which provides preliminary indications that transmission in badgers might be responsible for the spatial structure observed in M. bovis infections in cattle. In Chapter 4, I evaluate the use of high density bacterial WGS in M. bovis isolates belonging to a single molecular type. I use these data to demonstrate some of the potential of WGS, while also highlighting limitations inherent in using these approaches in such a slowly evolving pathogen. In Chapter 5, I take methods developed in the preceding chapters and apply them to the study of bTB in a well studied badger population, characterising the genetic diversity of M. bovis present in these badgers and their links to local cattle infections. As a whole, this body of work shows that there is much to be gained in our understanding of the epidemiology of bTB from genetic and genomic data, both from examining the large historical datasets that already exist on molecular types of M. bovis in the UK, as well as from the

application of high resolution bacterial WGS in this system.

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