Analysis of *M. bovis* genotypes in GB and the implications for BTB control.

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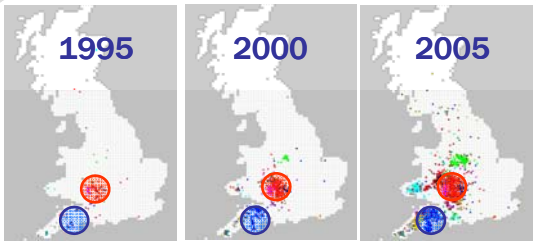
Introduction

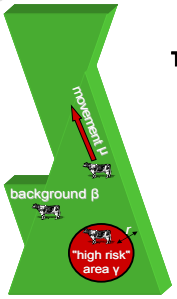
Bovine tuberculosis (BTB) control in Great Britain cost nearly £80 million in 2006/7[1]. Spread is due to both cattle movements and other factors, most controversially transmission from infected badgers. Genotyping of *Mycobacterium bovis* isolates provide a valuable tool for analysing differences in the transmission of BTB amongst different segments of the British cattle population.[2] Genotypes show remarkable spatial localisation over at least ten years (Figure 1, red and blue circles), despite the known role of cattle movements in spreading disease.[3] Considering each genotype as responsible for a separate epidemic, we identify the relative proportions of transmission attributable to cattle movements for each genotype, and determine whether or not there are any observable phenotypic differences at this level.

Figure 1: Spatial Distribution of Genotypes



Genotype distributions 1995-2005 (by colour)

Figure 2: Model construction



Three transmission routes:

Movement (μ)
Background (β)
high-risk area (γ)

Genotyping

Spoligotype and VNTR type are used to identify sub-populations in this analysis.[2] **Spoligotyping** identifies polymorphisms in the spacer units in the direct repeat (DR) region of the chromosome. This region comprises multiple, virtually identical, 36-base pair regions interspersed with DNA spacer sequences. The position of a spacer sequence in the DR region is conserved relative to the other spacer sequences. Polymorphisms are generated by the loss of hybridization signal from spacers. For clonal bacteria such as *M. bovis*, the spoligotype pattern can be used as a proxy for the complete genotype of the cell. Variable number tandem repeat (**VNTR**) typing measures variation in the number of repeats at a series of loci dispersed throughout the genome. The loci used in typing of mycobacterial isolates have been named as exact tandem repeat or ETR loci and mycobacterial interspersed repetitive units (MIRU) loci. In Great Britain most isolates have been typed using six ETR loci.

Simulation model

We use a previously developed model[3] to determine the proportion of BTB breakdowns that can be explained by cattle movements (figure 2).

Movements are organised into groups of animals moving between two locations on a given day. For 2002-5, there were nearly three million such batches. We model individual premises. Each maintains a simulated probability of infection, updated each model day. This model assumes that:

- **Movements** from infected premises are infectious at rate μ per animal and occur with only low within-herd transmission, i.e. only cattle previously passed through high-risk areas are infectious.
- Farms in areas of endemic BTB or **'high-risk' areas** may have higher cattle-cattle transmission and/or spread from wildlife reservoirs. These farms are infected at rate γ (normalised by total premises in area). We model high risk areas as being all premises within a radius r of an index case.
- **Background** infection through other causes occurs at rate β per premises.
- There is **no cross-immunity** at the herd level

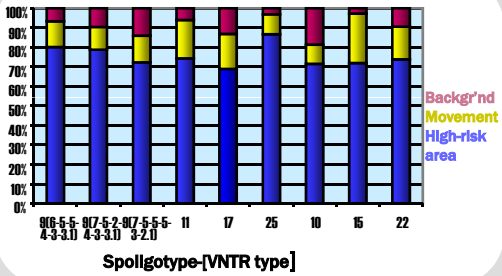
Data and Parameterisation

Cattle Tracing System (CTS) data were provided by RADAR, BTB breakdowns (cases) were as reported to VetNet courtesy of VLA and locations from the June Agricultural Survey for 2003, also from RADAR. Genotype data were provided by the VLA. Until 2005, genotypes were usually only recorded for three isolates per herd breakdown. Models were seeded with simulations in 2003 to predict forwards into 2004, using 2004 data to calculate model likelihood. Maximum likelihood models were obtained by fitting the four parameters using downhill simplex and Markov Chain Monte Carlo methods.

Results

The best fit model (fig. 3) shows little difference in the parameter estimates amongst the most prevalent genotypes, with overlapping C.I.s (not shown). Types 25 and 15 are unusual, however represent a small proportion of all isolates.

Figure 3: Genotype Specific Parameters



Implications for BTB control

A critical question is whether or not BTB is adapted to different areas, either for reasons of differing management practices or because of genotype related adaptations. Evidence here suggests that, differences in the effective epidemiological parameters, are not resolved on this spatial scale. Critically, should more of one genotype be found outside of core areas than is expected due to movements, this is unlikely to be due to phenotypic differences. Thus ongoing work is to compare patterns of movements from genotype-specific risk areas to breakdowns associated with the relevant genotypes, to identify areas of incipient high risk, possibly due to newly established, endemic infection in badgers.

References: [1]http://www.defra.gov.uk/animalh/tb/stats/expenditure.htm; [2]N.Smith et al. Nat. Rev. Micro. (2006) 4: 670–681; [3]D.M. Green, A.P. Mitchell, I.Z. Kiss & R.R. Kao Proc. Roy. Soc. B. (2008) **275**: 1001–1005.

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