Mammalian tuberculosis
Summary

Introduction

1. This note provides a summary of an analysis undertaken by a DISCONTOOLS group of experts on mammalian tuberculosis. They reviewed the current knowledge on the disease, considered the existing disease control tools, identified current gaps in their availability and quality and finally determined the research necessary to develop new or improved tools. Full details can be downloaded from the web site at http://www.discontools.eu/

Disease profile

2. Mammalian tuberculosis (TB) is a chronic bacterial disease caused by animal-adapted members of the *Mycobacterium tuberculosis* complex (MTBC). TB in animals (livestock and wildlife) is caused mostly by *M. bovis*, but important variants, including *M. caprae*, *M. pinnipedii*, *M. orygis* are also reported. Mammalian TB presents as a spectrum of disease states which makes diagnosis challenging. While *M. bovis* causes zoonotic TB (zTB) in humans, most human TB cases are caused by *M. tuberculosis.*
3. Cattle are the primary host for *M. bovis*, although other livestock and some wildlife are susceptible and can maintain infection. Wildlife can act as spillover, maintenance, or reservoir hosts and represent a well-documented and serious problem in several territories. Among wildlife species that act as reservoir hosts are brush–tailed possums in New Zealand, badgers in the UK and Ireland, and kudu and African buffalo in southern Africa.
4. The main routes of *M. bovis* transmission vary between host species. In cattle, *M. bovis* is believed to be transmitted between animals mostly by the airborne respiratory route. In infected cattle, bacteria can be shed intermittently in respiratory secretions, faeces and milk and to a lesser extent in urine, vaginal secretions or semen. Ingestion appears to be the primary route of transmission for scavenging carnivores. There is evidence of some level of transient environmental risk, which may contribute to indirect transmissions within and between host species. *M. bovi*s can infect humans, primarily via ingestion of raw dairy products, but also via the airborne route and through breaks in the skin.
5. Disease progression and mortality rates vary in different host species and are likely influenced by genetic and non-genetic factors, including dose and route of exposure. In cattle, TB is usually a slowly progressive condition with no obvious signs of disease in the early stages. In the later stages, now rarely seen because of active surveillance, symptoms include emaciation, fever, weakness, lack of appetite and respiratory distress. Infections can persist for years. In countries with eradication programmes, most infected cattle are identified early and removed: overt clinical symptoms are uncommon.
6. Recent whole-genome sequencing (phylodynamics) studies in livestock: wildlife systems suggest that interspecies and intraspecies mammalian TB transmission dynamics are likely to be context dependent. In most studies transmission was primarily detectable in the intraspecies compartments, particularly the cattle-cattle compartment; low level, bidirectional, interspecies transmission was detected in these studies.

Risk

7. Mammalian TB is a barrier to trade, particularly in live animals. Controls on livestock movements, including pre-movement testing where appropriate, may have impact on transboundary trade. Outbreaks are extremely disruptive, costly, and often devastating, presenting serious challenges to the management and sustainability of farm businesses. Human disease caused by *M. bovis* is rare in countries with successful mammalian TB control and eradication programmes, established meat inspection procedures and milk pasteurisation. Where mammalian TB is less well controlled in livestock and consumption of raw dairy products is frequent, the disease may represent a human health risk. Control

and eradication programs are based on test-and-slaughter procedures in cattle. These measures can be very expensive and consequently are seldom used in developing countries. Reservoirs of infection in wildlife contribute to the challenge of complete eradication in several countries.

8. In countries without disease control, cattle-to-cattle transmission rates can be high, particularly when in the context of intensive cattle husbandry. There is a high risk of farm-to-farm and transboundary spread of infection through the unwitting movement of infected animals. Pre-movement testing reduces this risk, but testing may not detect all infected animals.

Diagnostics

9. The predominant method for diagnosis of mammalian TB in live cattle is some WOAH approved variant of the tuberculin skin test, consisting of an intradermal injection of a purified protein derivative from a culture of *M. bovis (bovine PPD),* or to increase specificity, the comparison of reactions induced after injection of bovine and avian PPDs (the latter produced from a culture of *M. avium).* Test performance is context-dependent; comparative tuberculin testing has high specificity (>99%) and variable sensitivity (55-94%). IFN-γ release assays (IGRAs), which tend to be more sensitive, but less specific, than tuberculin tests are increasingly being applied to augment tuberculin testing, particularly in chronically infected herds.
10. Tuberculins are manufactured to quality and potency standards but are challenging to standardise (e.g. BCL3 facilities are required, including animal facilities to perform guinea pig potency assays). Therefore, more defined skin test reagents, based on specific *M. bovis* antigens have been developed and are being trialled.
11. Serology tests are available and under development but generally lack sensitivity compared to the IGRA and skin tests but have been usefully applied in some wildlife and domestic animal species (e.g. deer or South American Camelids). More comprehensive evaluation and validation is required.
12. Specialist mycobacterial culture is used by reference laboratories to confirm field-based diagnosis. There is no gold standard for laboratory confirmation; culture is the reference standard and is increasingly being replaced by PCR-based tests with improvements in turnaround and costs. A toolbox of molecular biology and genomic tests is available to characterise the pathogen isolated from submitted samples; this facilitates phylogenetic analyses and test-and-trace functionality.
13. Rigorous (i.e., quality controlled), rational, and informed application of existing tests should be reinforced. Tuberculin based testing was sufficient to significantly reduce herd prevalence in the UK in the mid-20th century, although the context may have changed since due to intensification, increased host numbers, density, movements etc. Tests with improved performance characteristics, especially sensitivity are still required; by definition, apparent prevalence will underestimate true prevalence in all hosts tested. Tests that are rapid, sensitive, specific, cost-effective, and simple are needed for live animals, including for cattle in developing countries, and for wildlife species.

Vaccines

14. The lead candidate vaccine for animals remains BCG, a live attenuated variant of *M. bovis* used safely to vaccinate millions of humans since the 1920s. BCG vaccination in cattle is not permitted currently in the EU or UK. Earlier studies with BCG showed variable efficacy in cattle at population and animal levels. A more recent cattle study suggested 39% end-point BCG “vaccine efficacy.”
15. While not providing complete or sterile immunity, consensus from several studies is that BCG vaccination can reduce susceptibility and substantially reduce *M. bovis*-induced pathology, with an assumed reduction in transmissibility in several host species.

16. BCG in cattle will compromise specificity of tuberculin-based diagnostics; DIVA tests for cattle have been developed and are undergoing field trials currently in the UK.
17. Recent “non-inferiority” field trial data from Ireland showed BCG reduced susceptibility in badgers, but without impacting onward transmission in infected badgers. The impact of this intervention on TB in cattle is being evaluated and modelled.
18. Improved vaccines for cattle are under active development based on genetically modified BCG or *M. bovis*, DNA, protein or virally vectored subunits, used stand-alone or in conjunction with BCG. Non-sensitising vaccines would overcome the problem of skin test sensitisation associated with BCG.
19. BCG vaccines may reduce *M. bovis* in wildlife reservoirs and an injectable vaccine has been licensed and deployed in badgers in the UK and Ireland. The further development of delivery systems for the application of vaccines in wildlife is needed.

Pharmaceuticals

20. Antimicrobials are not permitted for mammalian TB control in livestock.

Knowledge

21. Further investigations into the host/pathogen interactions and immune responses would provide valuable information for the development of new vaccines, better diagnostics, and intervention options. A better understanding of the epidemiology of *M. bovis* infections in cattle herds and populations would enable strategies to be developed for the use of new vaccines when available. The role of environmental persistence of *M. bovis* in the epidemiology and transmission of mammalian TB to cattle needs further investigation.
22. Industry-led genetic and genomic selection has emerged as an additional tool to reduce host susceptibility, initially in dairy cattle, but increasingly in non-dairy cattle. Herd keepers are encouraged to select lower risk sires or avoid higher risk sires. No significant “antagonisms” with other breeding goals are evident, but this is being kept under review.
23. Knowledge is lacking concerning the occurrence and epidemiology of mammalian TB in developing countries. Even though the prevalence of mammalian TB in cattle is widely known in most European countries, information is lacking on infection by *M. bovis*, *M. caprae*, *M. pinnipedii* and even *M. tuberculosis* in other animal species. Similarly, the pathogenesis, morbidity and clinical signs associated with disease in other animal species are not well described. Further studies on different wildlife species are needed in developed and developing countries to develop effective diagnostic tests and intervention options.
24. Social (behavioural) science has an important role to play in knowledge transfer in several territories and in translating epidemiological investigation and risk analysis into improved outcomes.

Conclusions

25. Control programmes have eliminated, or nearly eliminated, mammalian TB from domesticated animals in many developed countries although complete eradication has proven elusive particularly where a wildlife reservoir(s) contributes; additional cattle-based interventions have been needed, including risk-based trading, regionalisation etc. Mammalian TB represents an important human health risk particularly in developing countries where control is absent or poor.
26. Aspects of the epidemiology, pathogenesis, immunology, host pathogen interactions, genetics require further integrated study to develop improved diagnostic tests, vaccines and other interventions.

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