

Paratuberculosis Summary

Introduction

1. This note provides a brief summary of analysis prepared by a DISCONTTOOLS group of experts on Paratuberculosis (ParaTB). They reviewed the current knowledge on the disease, considered the existing disease control tools, identified current gaps in the availability and quality of the control tools and finally determined the research necessary to develop new or improved tools. Full details are available on the web site at <http://www.discontools.eu/> and can be downloaded by selecting Disease Database, then the specific disease and highlighting the variables of interest.

Disease profile

2. Paratuberculosis (or Johne's disease) is caused by *Mycobacterium avium* subsp *paratuberculosis* (MAP). The disease associated with MAP is primarily apparent in the adult cattle, sheep, goats and deer. Cattle and sheep are usually infected with strains adapted to those species although most strains appear to be able to infect a number of different species to some extent. The type of clinical disease varies significantly between species and the course of infection can vary greatly within species. Paratuberculosis is an untreatable, intestinal disease of ruminants characterised by a slow progressive wasting of the animal with increasingly severe diarrhoea. MAP can affect camelids and wildlife, including deer and rabbits. Animals in zoological collections are also frequently infected. The range of animals which can serve as carriers of MAP, with and without becoming clinically affected, has not been fully described.

3. In cattle there are 3 stages. Calves are particularly susceptible and often ingest MAP during the first month of life. Some calves may be infectious in the first months of life. This is followed by a long latent period during which the animals are neither clinically affected nor infectious. During the latent period, animals remain clinically normal but then become infectious by intermittently excreting MAP in low numbers in their faeces. These asymptomatic carrier animals may be important sources of transmission. Finally, clinical disease may occur. In cattle, this may be characterised by a profuse and persistent diarrhoea and weight loss, but often the clinical stage includes a slowly progressing drop in milk production. In sheep and goats the only clinical signs may be weight loss.

Risk

4. Paratuberculosis has been recognised as a widespread problem throughout the world. Prevalence in most regions is currently unknown, and prevalence studies have low design uniformity, making comparisons among regions unreliable due to different sampling strategies and case definitions. Additionally, in most studies, the true herd-level prevalence and animal-level prevalence have not been estimated.

5. Meta-analyses have demonstrated that the association of MAP with Crohn's disease in humans is specific and cannot be denied, although a causal role has not yet been demonstrated. Furthermore, transmission from cattle to humans has never been proven. However, addressing JD worldwide should be considered a proactive step in ensuring consumer confidence if a link was to be established between JD and Crohn's disease.

6. Some infected animals may excrete large numbers of organisms in their faeces which contaminate food, water and the environment. MAP can also be excreted in milk and colostrum. Transmission is mainly via the ingestion of contaminated material, but MAP can also be transferred *in utero*. With the long latent period the speed of spread is difficult to assess but high numbers of calves can be infected at any one point in time if hygiene and husbandry are unsatisfactory. Generally infection is introduced into a herd by the purchase of infected animals.

Diagnostics

7. There are commercial kits available for ELISAs to detect antibody, interferon-gamma kits to detect cellular immune response and culture and PCR kits to detect the organism and bacterial DNA. Tests based on presence of MAP in faeces may be false-positive regarding infection because they may just detect transient passive digestive carriers. Tests can be divided in early-stage diagnostics (detecting pro-inflammatory immune responses, e.g. interferon-gamma assays), late-stage diagnostics (detecting anti-inflammatory immune responses, e.g. IgG1 ELISA) and herd-level diagnostics (based on environmental sampling or bulk-tank milk analysis).

8. None of the existing tests are apt to reliably detect latent infections, and all tests may result in low rates of false-positive reactions under field conditions. The chronic nature of infection makes test interpretation a challenge.

9. Quantitative or digital PCR are promising techniques to assess the number of MAP bacteria in faeces. Other promising routes potentially leading to improved MAP diagnosis include metabolomic profiling, microRNA detection and changes in faecal microbiota.

Vaccines

10. A killed vaccine has been widely applied in Australian sheep herds, where it has become the dominant JD control practice. Using this killed vaccine reduced the prevalence of MAP infection and faecal shedding, and mortality in Australian sheep herds considerably. This vaccine does not prevent MAP infection and can therefore not be used on its own to eradicate MAP infection.

In cattle no effective vaccine is available, and the lack of an efficacious vaccine that protects against infection with MAP is hampering control programmes. Existing ParaTB cattle vaccines can reduce clinical impacts of infection, including sometimes reduced shedding, but they do not prevent infection. Additional obstacles are interference with tests to identify animals infected with other mycobacterial species (e.g., *M. bovis*) and that they can cause severe reactions at the injection site. Therefore, the development of a ParaTB vaccine with accompanying diagnostic tests that prevents infection and shedding and does not impair tuberculosis diagnostics remains 1 of the most pressing gaps for the livestock industry.

Pharmaceuticals

11. Therapy to treat MAP infections could have a potential but it is currently unlikely that any therapy could eliminate the organisms once infection has occurred. Such a strategy is unlikely to be cost-effective as an intervention in production animals.

Knowledge

12. There are major gaps in understanding the protective immune responses. The assumption that cell mediated immunity is protective and antibodies are not may not be valid and should be studied in much more detail with relevant antigens in relevant host tissues besides blood. Most research has focused on assessing immune changes via the peripheral blood, but understanding the local immune changes in the infected gut will be important in understanding the disease further.

13. The range of animals which can serve as carriers of MAP, with and without becoming clinically affected, has not been fully described. For extensively managed animals on pasture, there is a need for research into the rate of faecal-oral transmission under various stocking densities and in various ages of animals.

14. Work on genetic resistance and disease susceptibility may aid the understanding of pathogenesis and host response. Identification of host genetic factors contributing to resistance or selection markers to identify highly susceptible animals may aid control strategies

Conclusion

15. Despite decades of JD control programmes being implemented, JD continues to cause considerable losses to the livestock industry. This can be ascribed to important knowledge gaps about this disease.

16. New and improved tools to control MAP infections are required and should be a priority. There is a need to increase the sensitivity of the diagnostic and screening tools, especially when applied to early infected animals. An important requirement is for cost-effective and specific immuno-diagnostics that can discriminate between “non-infected”, “exposed”, “MAP infected” and “infectious” animals.

17. Improved vaccines which prevent excretion of the organism and ideally protect young animals from infection, do not result in interference with diagnostic tests and do not cause cross reactions with the TB test are required.