Paratuberculosis: Review of present knowledge

By Michael T. Collins, DVM, PhD

School of Veterinary Medicine University of Wisconsin-Madison, USA

Introduction
Published literature in the field of paratuberculosis (etiology: Mycobacterium paratuberculosis, also known as Mycobacterium avium subspecies paratuberculosis) has grown geometrically in the past decade and comprehensive coverage of the topic is beyond the scope of this paper. Readers who desire more in-depth information on paratuberculosis should obtain recent reviews and proceedings published on this subject (Milworth & Kennedy, Collins 2001, Manning & Collins 1999 a,b). The website: http://johnes.org is another place to obtain current information and references. The goal of this overview is to present some of the major features and recent developments in paratuberculosis.

Prevalence a slow epidemic
Paratuberculosis occurs in virtually every country of the world. While the infection prevalence is high and best documented in dairy cattle, it has been reported in many different ruminant animals (Kennedy & Benedictus 2001). In fact, the range of hosts for this intestinal pathogen appears to be expanding. Scottish investigators found that M. paratuberculosis infections can spread from domestic livestock to rabbits and then on to predators of rabbits (Boord et al. 2001). The prevalence of paratuberculosis is rising globally and will continue to rise unless control measures are instituted. The coming decades may find paratuberculosis to be the single most economically important single etiology infectious disease of dairy cattle.

Economic impact
The economic impact of paratuberculosis has been best reassured in dairy cattle. In such animals it decreases milk production (Jones 1989, Nordlund et al. 1996), decreases lifetime production of cows due to premature culling, decreases fertility (Johnson-Bjarnadottir et al. 2000), and decreases slaughter value of the carcass (Whitlock et al. 1985). An economic impact of potentially greater value is the slowing genetic improvement of herds (or breeds) due to involuntary culling of genetically valuable animals (Kennedy & Benedictus 2001). For herds or flocks, the economic impact of paratuberculosis is not a static parameter, rather it increases as the M. paratuberculosis infection prevalence increases.

Pathogenesis
Younger animals are most susceptible to infection by M. paratuberculosis infection. This is best documented in dairy cattle (Gilmour et al. 1965), but exact measurement of the age-dependent minimal infectious dose has not been reported. Adult cattle can be infected if exposed to large doses of M. paratuberculosis (Rankin 1961). The infection starts in the ileum after ingestion of M. paratuberculosis. After an incubation period of 1 to 10 years in dairy cattle the clinical manifestations of the disease, most often called Johnes' disease, are evident. In cattle this includes diarrhea and weight loss (chacHexia). However, in other ruminant rinderpest is less commonly observed and the incubation period
may be shorter. Dairy cattle typically show signs of paratuberculosis when in their second or third lactation. Observation of clinical signs of paratuberculosis at an earlier age indicates a high infection rate in the herd where the animal was born (transmitting to high infection pressure on young animals). Infected cows excrete M. paratuberculosis in their manure, milk, and colostrum. Fecal contamination of feed and drinking water is a very efficient means of infection spread. In the later stages, the infection disseminates beyond the gastrointestinal tract to all internal organs.

**Diagnosis**

Clinical signs of paratuberculosis resemble those of many other diseases. At the herd level, signs of paratuberculosis are often simple; poor performance or productivity of the herd in spite of good nutrition. Research has provided many new diagnostic tests several of which are available as diagnostic kits helping to provide internationally standardized protocols and reagents for paratuberculosis diagnosis (Collins 1996). Diagnosis of paratuberculosis by detection of the etiologic agent in clinical samples is favored by many because it is easy to interpret: a positive test confirms a diagnosis. Detection of *M. paratuberculosis* can readily be done by culture or by detection of genetic elements unique to this organism (S9000). Methods of culture have improved and it has been shown that pooling of clinical samples can markedly decrease the cost of culture without significantly compromising sensitivity (Kallis et al. 2000). Genomic methods of detection have also improved and techniques to more efficiently extract mycobacterial DNA and or remove PCR inhibitors help to increase assay sensitivity. Both microbiological and genotypic methods of *M. paratuberculosis* detection have the disadvantages of being expensive or slow, or both. Serological methods of paratuberculosis diagnosis have improved. Those based on ELISA technology offers most accuracy per unit cost and can be readily automated for rapid, low-cost herd screening. In order to use serological tests for paratuberculosis most effectively, laboratory and practitioners must learn to deal with diagnostic probabilities rather than certainties and understand the many factors that affect the probability the tested animal has, or does not have an *M. paratuberculosis* infection. Some of the major factors affecting diagnostic probabilities are history of prior cases of paratuberculosis in the herd, clinical status of the animal, and magnitude of the diagnostic test result for those assays that provided quantitative results.

If a herd has never had a case of paratuberculosis, the first step is to confirm a clinical or serological diagnosis of paratuberculosis by culture of *M. paratuberculosis* from feces or tissues. Once the infection is confirmed in a herd or flock, greater reliance can be placed on proper veterinary tests. Diagnostic sensitivity of all tests for paratuberculosis is a function of the stage of infection. For example, when applied to animals with clinical signs of John’s disease the ELISA sensitivity is 85% (Swayne et al. 1995). On a *M. paratuberculosis*-infected but clinically normal cattle the ELISA sensitivity is 45% (Swayne et al. 1992; Swayne et al. 1995). Quantitative interpretation of ELISA results using likelihood ratios is a useful way to guide management of individual animals in a herd and a cost-effective way to selectively cull from the herd those cattle with the highest probability of being infectious.

**Control**

Paratuberculosis control programs should be designed to suit the needs and abilities of the business and producer. The more effort expended in changing herd management methods to limit *M. paratuberculosis* infection transmission and the more money spent on diagnostics,\[ ...\]
the faster paratuberculosis control can be achieved. Of all control methods, changing herd management, in particular heifer rearing methods, is the single most important factor affording speed of paratuberculosis control. Test-and-cull programs help accelerate control of paratuberculosis but are not sufficient by them- selves to control this infection. Vaccination can decrease the rate of clinical paratuberculosis but it does not prevent M. paratuberculosis infection (Kallio et al. 2001).

Prevention / Biosecurity

Herd becomes infected by buying M. paratuberculosis-infected cattle. Pre-purchase testing for Johne's disease is today's standard of veterinary practice. Regardless of method, testing the herd of origin for replacement cattle is much more reliable than testing only the individual purchased cattle. Herd certification programs have started in the U.S. (Ann. 1997), The Netherlands (Benedictus et al. 1999. Kennedy & Alfswain 1999), and Australia (Albrook & Kennedy 1999. Kennedy & Alfswain 1999). These "certification" programs are formalized efforts to classify herds based on the likelihood of their being M. paratuberculosis-infected. Such programs help to limit spread of paratuberculosis by creating a system for cattle buyers, purchase animals that have a very low likelihood of having this infection.

Zoonotic concern:

Crohn's disease and Johne's disease are similar in clinical signs and pathology. New tests for M. paratuberculosis find evidence of that this agent infects people with Crohn's disease (Chaves et al. 1999. Collins et al. 2000. El Zaouari et al. 1999. Hermon-Taylor et al. 2000. Venter et al. 2000. Olsen et al. 2001). Whether the infection in primary (causal) or secondary (incidental or secondary) remains to be determined. Opportunities for human exposure to M. paratuberculosis are several. Most attention has been paid to the idea that dairy products constitute a vehicle for human exposure to M. paratuberculosis. Evidence indicates that M. paratuberculosis is excreted in raw milk and may resist killing by pasteurization (Stabel et al. 2000). To date, only a few dairy products reported to involve pasteurization in their production, are potential modes of human exposure to M. paratuberculosis. However, other routes of exposure deserve careful scrutiny as potential transmission routes.

M. paratuberculosis is a disseminated infection at the end stages. Contamination of beef products can occur both pre- and post- via the blood stream. With other microbial contaminants, ground beef has the highest risk of being a vehicle for M. paratuberculosis exposure of humans. No published reports quantify the M. paratuberculosis numbers in ground beef nor the statistical death rate of M. paratuberculosis suspended ground beef. Hence, estimation of the risk of humans' exposure to M. paratuberculosis via beef products is nearly impossible. Water contaminated with manure from domestic animals is another potential route of human exposure that has not been examined. Given that M. avium is commonly found in domestic (city) water supplies due to its inherent resistance to chlorine (Follinian et al. 2001. Ann. 1997), it is rational to believe that M. paratuberculosis too could contaminate surface waters that end up in domestic water supplies and thus expose humans this potential pathway. A recent cluster of Crohn's disease cases in Mankato, Minnesota, USA was linked to recreational swimming in rivers (van Kraningen & Freda 2001).

The debate on the zoonotic potential of M. paratuberculosis will continue and likely become more heated in the coming months and years. It is vital that this debate be conducted in an open, public and objective manner. Veteri-
nary medicine must face its dual responsibility to animal agriculture and to the public in con-
trolling this animal health problem and limiting the risk of human exposure to M. paratuber-
culos is through the food chain or environment. When alternative perspectives on the role of M. paratuberculosis may play in Crohn's or any other human disease is debated, as at the IVK Vet Symposium, critical scientific evaluation of study design, methods of analysis, and data in-
terpretation must be applied to keep the debate on the highest plane of scientific objectivity.

References
Alldworth MB, Kennedy DJ. Progress in national con-
Anonymous. USDA APHIS VS, CNHAHMS, Johnes' disease in U.S. dairy operations, 52 pages. Na-
berculosis infection in Notarimas wildlife in Scotland. J Clin Microbiol. 2001, 39, 1517-
1521.
cedings of the Sixth International Colloquium on Paratuberculosis. International Association for Paratuberculosis. Madison, WI.
Cobey D, Hamel J, Horvitz M, Espino M, Lander C, Sautin C, Taragon SR, Brusilova J Identification of a novel mycobacterial homologue (HpgH) as an antigentic target of pANCA mon-
oclonal antibody and serum immunoglobulin A from patients with Crohn's disease. Infect. Im-
Collins MT. Diagnosis of paratuberculosis. Veteri-
Collins MT. Task Force on Mycobacterium paratu-
Collins MT, Lofy G, Mover C, Cichow D, Christensen S, Reichenberger M, Hatly, S, Hanson B, Thom-
El Cassar F, Hasek SL, Holten K, Burch P, Graham H. Characterisation of Mycobacterium parame-
19.
Falkland TR, Norton CL, LeChevallier MR. Fac-
tor influencing numbers of Mycobacterium avium. Mycobacterium intracellular, and other mycobacteria in drinking water distribution system.
Appl. Env. Microbiol. 2001, 67, 1225-
1231.
Gilmour JL, Nicoll DL, Brooker AG. Experi-
mental oral infection of calves with Mycobac-
Kalu CH, Hessekeck JR, Barkema HR, Collins MT. Culture of strategically pooled bovine fecal sam-
Kalu CH, Hessekeck JR, Barkema HR, Collins MT. Use of long-term vacination with a killed vac-
Kennedy DJ, Alldworth MB. Progress in national con-

Acts vet. scand. vol. 44 no. 3-4. 2005


