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Paratuberculosis: Review of present knowledge

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Introduction

Published literature in the field of paratuberculosis (etiology; *Mycobacterium paratuberculosis*, also known as *Mycobacterium avium* subsp. 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 (*Allworth & 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 (*Beard 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 measured 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-Ifearulundu 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 a 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 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 Johne's disease, are evident. In cattle this includes diarrhea and weight loss (chachexia). However, in other ruminants diarrhea 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 (translating 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 simply 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 (IS900). 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 (*Kalis et al.* 2000). Genetic 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 genetic 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, laboratorians 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 main 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 positive serological 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 Johne's disease the ELISA sensitivity is 85% (*Sweeney et al.* 1995). On *M. paratuberculosis*-infected but clinically normal cattle the ELISA sensitivity is 45% (*Socket et al.* 1992, *Sweeney 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 affecting speed of paratuberculosis control. Test-and-cull programs help accelerate control of paratuberculosis but are not sufficient by themself to control this infection. Vaccination can decrease the rate of clinical paratuberculosis but it does not prevent *M. paratuberculosis* infection (*Kalis et al.* 2001).

Prevention / Biosecurity

Herds become 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), and Australia (*Allworth & Kennedy* 1999, *Kennedy & Allworth* 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 concerns

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 (*Cohavy et al.* 1999, *Collins et al.* 2000, *El Zaatari et al.* 1999, *Hermon-Taylor et al.* 2000, *Naser et al.* 2000, *Olsen et al.* 2001). Whether the infection is 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.* 2001). Hence, dairy products, in particular those made from dairy products not involving pasteurization in their production, are potential modes of human exposure to *M. paratuberculosis*. However, other modes of exposure deserve equal scrutiny as potential transmission routes. *M. paratuberculosis* is a disseminated infection at the end stages. Contamination of beef products can occur both pre- (via the blood stream) and post- (via fecal contamination) slaughter. As with other microbial contaminants, ground beef have 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 thermal 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 (*Falkinham 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 pathogen. A recent cluster of Crohn's disease cases in Mankato, Minnesota, USA was linked to recreational swimming in rivers (*Van Kruiningen & 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 controlling this animal health problem and limiting the risk of human exposure to *M. paratuberculosis* through the food chain or environment. When alternative perspectives on the role that *M. paratuberculosis* may play in Crohn's or any other human disease is debated, as at the NKVet Symposium, critical scientific evaluation of study design, methods of analysis, and data interpretation must be applied to keep the debate on the highest plane of scientific objectivity.

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