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In utero infection of cattle with *Mycobacterium avium* subsp. *paratuberculosis*: A critical review and meta-analysis

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Abstract

Mycobacterium avium subsp. *paratuberculosis* (*Mptb*) causes Johne's disease in ruminants. Disease control programmes aim to break the faecal–oral cow–calf transmission cycle through hygienic calf rearing and removal of affected cows from the herd, but these programmes do not take account of the potential for congenital infection. The aims of this study were to critically review research on in utero infection, determine the prevalence of fetal infection in cattle through meta-analysis and estimate the incidence of calves infected via the in utero route. About 9% (95% confidence limits 6–14%) of fetuses from subclinically infected cows and 39% (20–60%) from clinically affected cows were infected with *Mptb* ($P < 0.001$). These are underestimates for methodological reasons. The estimated incidence of calf infection derived via the in utero route depends on within-herd prevalence and the ratio of sub-clinical to clinical cases among infected cows. Assuming 80:20 for the latter, estimates of incidence were in the range 0.44–1.2 infected calves per 100 cows per annum in herds with within-herd prevalence of 5%, and 3.5–9.3 calves in herds with 40% prevalence. These estimates were not markedly sensitive to the value chosen for the proportion of clinical cases. In utero transmission of *Mptb* could retard the success of disease control programmes if the opportunities for post natal transmission via colostrum/milk and environmental contamination were able to be controlled. The consequences of fetal infection for the calves so infected are discussed in the context of diagnosis and vaccination together with recommendations for future research.
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Keywords: Paratuberculosis; Intrauterine; Congenital infection; Transmission; Meta-analysis; Review

Introduction

Johne's disease or paratuberculosis occurs globally in ruminants and in cattle it is associated with economic losses due to culling of clinical cases, reduced milk production and the costs of laboratory testing and control measures (Ott et al., 1999). However, potential impact on consumer demand for milk associated with product safety needs to be considered as the causative organism, *Mycobacterium avium* subsp. *paratuberculosis* (*Mptb*), may also be a cause of Crohn's disease (Stott et al., 2005; Chamberlin and Naser, 2006). Public health authorities internationally acknowledge that a precautionary approach and further research are warranted.

Most authors agree that the faecal-oral route is the primary mechanism for transmission of *Mptb* and this is reflected in disease control recommendations for cattle (Clarke, 1997). These are similar in most countries and based on removal of clinical cases, identification of sub-clinical cases by objective tests, and hygienic calf rearing (Kennedy and Benedictus, 2001; Benedictus and Kalis, 2003). Compliance with calf rearing recommendations is difficult for some farmers (Wraight et al., 2000), but in any case transmission in utero could limit its effectiveness (Lawrence, 1956; McQueen and Russell, 1979). To the authors' knowledge this topic has never been reviewed formally.

The aims of this study were to critically review published data on extra-intestinal and in utero infection, determine the prevalence of fetal infection in cattle through meta-analysis, estimate the incidence of congenital infection in calves and make recommendations for future research.

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Material and methods

The pathogenesis of *Mptb* infection, evidence for extra-intestinal infection and experimental in utero infection trials were summarised following a literature review. An electronic search was conducted using search terms "in utero", "uterus", "fetus", or "placenta" with the term "paratuberculosis". In addition, a collation of early literature from 1895 (Chiodini, 1992) was searched manually.

A meta-analysis of observational studies of the prevalence of fetal infection in naturally infected cows with Johne's disease was undertaken. Data were included only where the infection had been confirmed in the cow, and to avoid opportunistic investigations with likely extreme prevalence estimates, where more than two fetuses had been examined. Data from studies of high rigour were pooled. These were defined as studies where post mortem methods were specified and indicated awareness of the need to minimise cross contamination of maternal and fetal samples, and where microbiological methods for identification of *Mptb* were described. Studies based solely on identification of *Mptb* using nested polymerase chain reaction (PCR) were excluded due to the risk of false positive outcomes. Studies with more than two fetuses that did not meet the other eligibility criteria are summarised in Table 1. Fetal age was ignored in the pooling of data. Animals with clinical signs consistent with paratuberculosis (for example progressive weight loss and diarrhoea) were classified as clinical cases while infected animals without these signs were classified as sub-clinical cases by the original authors.

Fisher's exact test was used to compare the proportions of infected fetuses from clinically and sub-clinically infected cows, and the odds ratio and its confidence limits were calculated using Prism GraphPad. Exact 95% confidence limits for proportions were calculated using Minitab Statistical Software.

The incidence of calf infection derived via the in utero route was estimated using the upper and lower confidence limits for the prevalence of in utero infection of fetuses in cows with both clinical and sub-clinical infection, estimates of the proportion of infected cows that were clinical cases, and estimates of within-herd prevalence among cows (assuming that each cow produces a live calf each year).

Results

An appraisal of natural in utero transmission of *Mptb* in cattle was informed by review of the pathogenesis of paratuberculosis, extra-intestinal spread of the organism and experimental infections of the bovine reproductive tract. Studies in other species were considered.

Pathogenesis of Mptb infection

Following oral exposure, *Mptb* is taken up by M cells overlying Peyer's patches in the ileum and organisms then move to macrophages in the lamina propria (Momotani et al., 1988). The intestinal lymph nodes become involved and *Mptb* may be found in both locations but not for some weeks after infection (Perez et al., 1996). Chronic, granulomatous enteritis develops where epithelioid cells containing numerous *Mptb* accumulate in the lamina propria and submucosa (multibacillary or lepromatous lesions). However, in some animals *Mptb* may not be numerous in lesions (paucibacillary or tuberculoid lesions).

Cell mediated immune responses initially restrict the organism but later wane, allowing development of the multibacillary form (Clarke, 1997). Serum antibodies are detectable in the later stages of the disease. Cattle may begin to shed *Mptb* in faeces from about 1 year of age and clinical signs of weight loss and diarrhoea occur usually after 2–4 years (Whittington and Sergeant, 2001). Young animals are believed to be most susceptible to infection with an age-based resistance developing. This forms the basis for the hygienic calf rearing techniques that are recommended to control paratuberculosis.

Extra-intestinal spread of Mptb within infected animals

There is a large amount of evidence for extra-intestinal spread of *Mptb* and this occurs most commonly in advanced sub-clinically or clinically affected animals. *Mptb* has been found in extra-intestinal lymph nodes, milk, liver, spleen, semen, testes, epididymis, seminal vesicle and other parenchymous organs of cattle (Pavlik et al., 2000; Barrington et al., 2003; Ayele et al., 2004). There is an extensive literature on the presence of *Mptb* in bovine milk (see, for example, Ellingson et al., 2005). Haematogenous or lymphatic spread are possible routes for movement of the organism to extra-intestinal sites. Indeed, the organism has been found in peripheral blood (Koenig et al., 1993; Barrington et al., 2003; Buergelt et al., 2004; Buergelt and Williams, 2004). There have been similar findings in tissues, blood and milk of sheep, goats, wild ruminants and primates (Morin, 1982; Williams et al., 1983a,b; Reddy et al., 1984; McClure et al., 1987; Gwęzdz et al., 1997; Gwozdz et al., 2000; Naser et al., 2000; Eppleston and Whittington, 2001; Djonne et al., 2003; Lambeth et al., 2004; Juste et al., 2005). As Johne's disease has a systemic component the developing fetus is at risk of infection.

Experimental infection of the bovine reproductive tract

The fate of *Mptb* (5×10^8 colony forming units, cfu, in 5 mL saline) inoculated into the uterus of thirteen 3–4-year-old cows 24 h after service by bull or artificial insemination (AI) was followed at intervals to 28 days after inoculation (Merkal et al., 1982). *Mptb* was isolated from the uterine body and horns 1, 2, 3, 7 and 14 days post inoculation, with one colony also being found in a pelvic lymph node harvested from one cow. The findings indicate the potential for *Mptb* to survive in the uterus and to move to adjacent lymph nodes. Similarly, the intrauterine route was investigated as a means of infection by inoculating three cows with massive doses of the organism (200–400 mg wet weight) at the time of AI (Owen and Thoen, 1983). One cow shed *Mptb* in faeces from 5 months post exposure. This cow was the only one to conceive but aborted at 8 months gestation and *Mptb* was recovered from liver, spleen, mesenteric lymph node and intestine of the fetus. The study was not well designed as the cows may not have been free of Johne's disease when purchased for the trial and the animals cohabitated with three cows given oral doses of *Mptb*.

Mptb may form a close association with the early bovine conceptus. Following the seeding of bovine ova with sus-

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