Chapter (refereed)

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Mycobacterium avium subsp. *paratuberculosis*, Johne's disease and Crohn's disease

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Mycobacterium avium* subspecies *paratuberculosis *Mycobacterium avium* subspecies *paratuberculosis* (MAP) is a member of the non-tubercular *M. avium* complex (MAC) [1]. The total genome sequence comprises 4.83 Mbp of GC rich DNA encoding a predicted 4,350 ORFs with >96% of its DNA is virtually identical in sequence and genetic organisation to that of generally non-pathogenic *M. avium*. The remainder of the genome comprising <200 ORFs is either unique to MAP or homologous to genes associated with pathogenicity in other organisms[2]. MAP has diversified into multiple bovine and ovine strains [3] with evidence of the emergence of humanised strains [4]. Some strains are almost impossible to isolate by culture. Others, particularly bovine strains require prolonged incubation [5]. Overall, these are extremely difficult organisms to study experimentally.

Johne's disease in animals Unlike other MAC, MAP has the specific ability to cause Johne's disease in many animal species including primates[1]. Johne's disease is a systemic infection whose principal clinicopathological manifestation is chronic inflammation of the intestine. The disease in animals ranges from pluribacillary to paucimicrobial like Leprosy in humans [6]). Johne's disease was first reported in 1895 in Europe and in 1908 in North America. Currently there is an extensive prevalence of subclinical MAP worldwide [7]. Infected animals secrete MAP in their milk and faeces. MAP is detected in retail pasteurised milk supplies in Britain, the Czech Republic and the USA and long term in the environment (e.g. [8]).

Crohn's disease (CD) in humans Crohn's disease is a systemic disorder whose principal clinico-pathological manifestation is chronic inflammation of the intestine. It is a 'new' disease which first emerged in Europe and North America between 1940 and 1950 with generally increasing incidence and prevalence (New Zealand (2005) $16.5/10^5$ population/year prevalence of $155.2/10^5$; 8). Crohn's disease has also emerged and is rising in former low incidence areas e.g. China. In Europe the incidence of the disease in adults is increasing by about 25% per decade. The Czech Republic and Melbourne show that the rise in the incidence of Crohn's disease in children in recent years has averaged 5 fold per decade (9).

MAP infection in Crohn's disease MAP is strongly associated with CD [9, 10]. MAP in paucimicrobial disease in humans is extremely difficult to detect. Optimised methods showed that 92% of people with Crohn's disease were found to be infected with MAP [11], confirmed independently in Europe and the USA [12, 13]. When appropriate methods are used most people with chronic inflammation of the intestine of the Crohn's disease type are infected with these proven multi-host chronic enteric pathogens .

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