Title

A review of paratuberculosis in dairy herds - Part 1: Epidemiology

Authors

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Abstract

Bovine paratuberculosis is a chronic infectious disease of cattle caused by *Mycobacterium avium* subspecies *paratuberculosis* (MAP). This is the first in a two-part review of the epidemiology and control of paratuberculosis in dairy herds. Paratuberculosis was originally described in 1895 and is now considered endemic among farmed cattle worldwide. MAP has been isolated from a wide range of non-ruminant wildlife as well as humans and non-human primates. In dairy herds, MAP is assumed to be introduced predominantly through the purchase of infected stock with additional factors modulating the risk of persistence or fade-out once an infected animal is introduced. Faecal shedding may vary widely between individuals and recent modelling work has shed some light on the role of super-shedding animals in the transmission of MAP within herds. Recent experimental work has revisited many of the assumptions around age susceptibility, faecal shedding in calves and calf-to-calf transmission. Further efforts to elucidate the relative contributions of different transmission routes to the dissemination of infection in endemic herds will aid in the prioritisation of efforts for control on farm.

Keywords: Dairy; Epidemiology; Johne's disease; Paratuberculosis

Introduction

Bovine paratuberculosis is a chronic infectious disease, first diagnosed in the Oldenburg region of Germany in 1895 (Johne and Frothingham, 1895). The condition was initially believed to be caused by *Mycobacterium avium*, and the authors named the condition pseudotuberculous enteritis. For the next 25 years, the condition was reported across Europe (Lienaux and vand den Eeckhout, 1906; McFadyean, 1906) and the United States (Pearson, 1908); the aetiological agent *Mycobacterium avium* subspecies *paratuberculosis* (MAP) was identified (Holth, H. 1912; Twort and Ingram, 1912); and the term Johne's disease (JD) was introduced (McFadyean, 1906). Over the next 100 years, JD was increasingly recognised globally. The disease is primarily associated with domestic ruminants, however, MAP has also been isolated from a wide range of non-ruminant wildlife including rabbits, foxes, stoats and weasels (Greig et al., 1997; Beard et al., 2001). Of particular interest has been the isolation of the bacterium from humans (Chiodini et al., 1984) and non-human primates (McClure et al., 1987).

MAP is a Gram-positive obligate intracellular pathogen which is dependent on mycobactin, and therefore incapable of environmental replication (Lambrecht and Collins, 1992). MAP's ability to infect through indirect contact is facilitated by a prolonged survival time. Whittington et al. (2004) noted survival times of up to 55 weeks in a shaded, outdoor area in Australia. Of importance regarding pasture-based systems, is that the bacterium was more likely to be isolated from grass than leachates after application to soil (Salgado et al., 2011).

International studies have demonstrated limited strain diversity (Stevenson et al., 2009; Ahlstrom et al., 2016). Phylogenetic analyses have uncovered a biphasic evolution of

MAP strains from a *Mycobacterium avium* subspecies *hominissuis* ancestor: an initial insertion event followed by several deletion events that define the species and two phylogenetic lineages (Turenne et al., 2008; Alexander et al., 2009). Cattle (Type-C) and Sheep (Type-S) are named after the species they were first isolated and characterised from and represent two major groups of strains (Collins et al., 1990). Within these groups, genotyping methods have identified three major substrains: Type-C is synonymous with Type II strains, with Type-S consisting of Type I and Type III strains (Stevenson, 2015).

The pathogenesis of MAP infection has been reviewed recently (Arsenault et al., 2014). Early studies suggested the tonsillar crypts as the primary route of infection (Payne and Rankin, 1961). Later, the small intestine was proposed as the primary portal of entry (Momotani et al., 1988; Sweeney et al., 2006). The site of entry may influence whether infection is cleared or persists in the host (Arsenault et al., 2014). MAP invades sub-epithelial macrophages and persists in phagosomes by interfering with the formation of phagolysosomes (Coussens, 2001). Persistence and proliferation within macrophages are assisted by interference of interferon-gamma (IFN-γ) (Arsenault et al., 2014) and up regulation of interleukin-10 (IL-10) (de Almeida et al., 2008). The later development of a T-helper cell type 2 (Th-2) response, which is generally assumed to be non-protective, is poorly understood (Mortier et al., 2015). However, the presence of extracellular MAP may be a key factor in the development of this response (Magombedze et al., 2014). The disease state matures from preclinical stages to a period of increased bacterial shedding and the development of overt clinical signs (Stabel, 2000).

The term ‘iceberg phenomenon’ has been used in the context of paratuberculosis. A value of 25 subclinical infections for every single clinical animal born in the herd has been

used as an estimate based on anecdotal observations (Whitlock and Buergelt, 1996). A recent analysis suggested that although the qualitative assumption is likely to hold true, the number of animals in the 'invisible' stages of infection is likely to be somewhat less than this figure (Magombedze et al., 2013).

The consequences of infection on animal and herd-level performance have been widely studied (Garcia and Shalloo, 2015). A reduction in milk yield associated with infection status has been the most consistent finding. A meta-analysis found that the reduction in milk yield associated with faecal culture or PCR positivity was approximately 2 kg of milk/cow/day, or almost 6% (McAloon et al., 2016c). The findings from studies investigating the effect of infection on fertility have been less consistent with several studies documenting improved fertility performance associated with test positivity (Lombard et al., 2005; Gonda et al., 2007; Marcé et al., 2009; Berry et al., 2010; Smith et al., 2010). However, many of these studies suffer from difficulties in quantifying reproductive performance in large numbers of animals and may be hindered by interval-based measurements of fertility performance which are not ideal for conditions where animals are often culled from the population. An increased susceptibility to other diseases has been traditionally attributed to MAP infection; however, apart from a recent article demonstrating an increased incidence of clinical mastitis in infected cows (Rossi et al., 2017), there has been little evidence to support this claim. An earlier study demonstrated an association between the development of displaced abomasum (DA) and milk fever according to shedding levels (Raizman et al., 2007). However, this analysis was conducted with low numbers of animals in each group, five and two for DA and milk fever, respectively.

Perhaps the most significant concern in relation to the importance of paratuberculosis as a disease of dairy cattle is its potential link with Crohn's disease in humans. In a meta-analysis, the odds of a PCR-positive test result in tissues from Crohn's disease patients was seven times that of individuals free from inflammatory bowel disease (Feller et al., 2007). A more recent meta-analysis found a 4.3–8.4 odds of MAP detection through a variety of laboratory methods (Waddell et al., 2015). However, epidemiological evidence for increased risk of Crohn's disease with increased exposure through likely transmission routes is weak and definitive proof of causation remains unavailable (Waddell et al., 2016). Others have concluded that available evidence supports the theory that MAP may cause Crohn's disease in some genetically susceptible human patients (Kuenstner et al., 2017). Based on application of the precautionary principle (Weir et al., 2010), and with the knowledge that many food health 'scares' may not be evidence-driven, reduced exposure of consumers to MAP in animal produce is advocated, not only for the protection of public health, but also for the protection of the dairy industry. Consumer exposure is reduced through pasteurisation. However, it is now well established that commercial pasteurisation does not necessarily eliminate MAP from milk (Grant et al., 2002a; Grant et al., 2002b), nor does combined pasteurisation and desiccation that occurs in the preparation of infant formula for example (Botsaris et al., 2016). Therefore, control must also include reduction of the levels of MAP supplied from dairy farms (Kuenstner et al., 2017). Several challenges exist in the study of farm level control of paratuberculosis and in the implementation of control options and recommendations. The aim of this manuscript is to review the transmission and control of paratuberculosis in dairy herds.

Between-herd transmission

Introduction of MAP to herds most often occurs following the introduction of new stock into the herd. A recent systematic review reported a positive association between animal introductions and herd positivity in 6/14 studies identified (Rangel et al., 2015). In studies published subsequent to this, 3/6 have demonstrated a positive association between animal introductions (Künzler et al., 2014; Wolf et al., 2016; Puerto-Parada et al., 2018) and three have not found an effect (Vilar et al., 2015; Donat et al., 2016; McAloon et al., 2017a). Modelling studies have demonstrated that several factors other than animal purchase modulate the risk of persistence or fade-out of infections once an infected animal has been introduced. In one model, fade-out was predicted following the introduction of a single infected animal in 66% of the iterations (Marcé et al., 2011).

Herd size has been identified as a risk factor for herd positivity (Vilar et al., 2015; Donat et al., 2016; McAloon et al., 2017a). This finding is not unique to paratuberculosis and is of interest given that increasing herd size is a trend in dairy production globally (Barkema et al., 2015). The reasons for this observation are not clear. In some instances, larger herds may have been amalgamated from smaller herds, and therefore the effect of herd size on MAP prevalence is confounded by purchasing behaviour. Larger herd sizes may also facilitate more effective contacts between individuals and may have associated management practices which facilitate establishment of infection once MAP has been introduced. Another explanation in serological studies, could be related to the imperfect specificity of the diagnostic test. Cut-point number of reactors are used to try to account for imperfect specificity (e.g. defining the herd as positive based on two reactors rather than one). However, as herd size increases, the probability of observing two or more false positive reactors increases, irrespective of the infection status of the herd.

Within-herd transmission

Studying the transmission of MAP within infected farms is hindered by the considerable difficulty in conducting field studies of natural transmission. Paratuberculosis is characterised by a prolonged latency and poor sensitivity of currently available diagnostic tests (Nielsen and Toft, 2008), caused by the biology of MAP infection. Many findings are extrapolated to the field from experimental infection studies, which may not be representative of the conditions on a commercial farm. An alternative, more economical method for studying paratuberculosis transmission has been the use of mathematical infectious disease models. However, such models differ according to the modelling approach used, the assumptions made, and the degree of simplification of biological processes relevant to transmission (Marcé et al., 2010). An example of the disparity between these models and the 'real-life' situation is that the predicted within-herd prevalence in MAP-infected herds may be higher than the observations made from the field. For example, using a French model, it was estimated that 15 years following the introduction of infection into a 140-cow dairy herd, and in the absence of on-farm MAP control, approximately 214 (95% Confidence Interval, 28-274) animals out of 278 animals (including youngstock) would be infected (including infected, infectious and affected animals) (More et al., 2015), whereas estimated mean within-herd true prevalence from prevalence studies is generally less than 15% (Verdugo et al., 2015; McAloon et al., 2016b). It should, however, be pointed out that these estimates are from a Bayesian latent class analysis which are in themselves problematic when applied to paratuberculosis (McAloon et al., 2019).

Infection susceptibility

An age-dependent susceptibility to paratuberculosis has been long established and forms the basis of on-farm control programmes. A meta-analysis concluded that there was a

184 considerable difference in age susceptibility to infection between adults and calves less than 6
185 months of age and between adults and calves aged between 6-12 months of age (Windsor and
186 Whittington, 2010). In a recent experimental infection study calves could be infected with
187 both high and low doses of MAP up to 12 months of age (Mortier et al., 2013). However, the
188 low dose used in this study, 5×10^7 given over two consecutive days, was higher than the
189 minimal doses of 1.5×10^6 used in other studies, (Sweeney et al., 2006). Nevertheless, this
190 observation could have considerable consequences for control programmes: a recent French
191 modelling study reported that the rate of decay in susceptibility with age had a dramatic
192 effect on within-herd transmission (Ben Romdhane et al., 2017).
193
194 Interest in the role of genetics in disease resistance in cattle has developed recently
195 (Berry et al., 2011). Several different loci are likely involved in resistance to MAP, however
196 findings between studies are often inconsistent. A meta-analysis reported eleven loci on nine
197 different chromosomes associated with MAP infection (Minozzi et al., 2012). However, out
198 of eight recently published studies investigating genetic susceptibility, only three quantitative
199 trait loci were consistently found in more than one study (Kiser et al., 2017). Response to
200 disease in general is influenced by the ability to accurately classify phenotypic traits in the
201 population (Bishop and Woolliams, 2014). For MAP infection, phenotypes have been defined
202 according to antibody response in either milk or serum; faecal detection using either PCR or
203 culture; or demonstration of the organism in tissues. This variation in phenotypes has been
204 shown to have an important impact on the outcome of genome-wide association studies
205 (Küpper et al., 2014).
206
207 Early studies demonstrated heritability estimates of less than 0.10 (Koets et al., 2000),
208 whereas more recent studies have found higher heritability estimates of up to 0.28 (Küpper et

al., 2012). Simulation models using these estimates have determined that the effect of selection is likely to be small. A Dutch simulation demonstrated that dam selection in isolation was likely to take over 379 years to eliminate infection. The effect with sire selection was greater, but still took more than 147 years (van Hulzen et al., 2014).

An increased susceptibility has been shown in Channel Island breeds of cattle (Cetinkaya et al., 1997; Jakobsen et al., 2000; Sorge et al., 2011). However, such findings should be interpreted with some caution as in many cases there is potential for breed to be confounded by herd.

Infectious dose

Infection with MAP primarily occurs via the faecal-oral route. Doses used in experimental studies have not been consistent (Begg and Whittington, 2008), and may be inflated to reliably cause infection. Inoculation with 10^3 colony forming units (cfu) was enough to cause infection in sheep (Brotherston et al., 1961), whereas higher doses of greater than 10^8 have been used in calf studies (Gilmour et al., 1965). A US study demonstrated that a dose of 1.5×10^6 was enough to reliably establish infection, whereas 2×10^5 was not (Sweeney et al., 2006). Recently, an inoculation of 5×10^7 given over two consecutive days was used as the low dose in a Canadian study and was successful in establishing infection (Mortier et al., 2013).

MAP-shedding & exposure

Faecal shedding levels in MAP-positive cows vary widely (Crossley et al., 2005). MAP culture is commonly conducted using 1-3 g aliquots of faeces in Herrold egg yolk medium (HEYM) culture tubes. Interestingly, it has been shown that if multiple tubes are

cultured from a single sample, a considerable proportion (24%) may only have colonies present in one tube, demonstrating considerable within sample variation (Crossley et al. 2005). This is important given that most animals are low shedders. For example, a US study found that 71% of cows were low shedders (<10 cfu/tube, i.e. <5 cfu/g), 10% were medium (10-50 cfu/tube) with 19% classified as high shedders (>50 cfu/tube) (Whitlock, 2000).

The shedding distribution of faecal-orally transmitted organisms is often positively skewed (Chen et al., 2013), and recently there has been increasing interest in the role of super-shedders. Super-shedding animals were originally defined as those animals shedding more than 10^7 cfu MAP/g faeces (Whitlock, 2005). The overall cow-level prevalence of super-shedders in a 3577-cow Californian dairy herd was 0.5% but accounted for 10% of PCR-positive cows and 14% of ELISA-positive cows (Aly et al., 2012). Modelling work conducted at Cornell University demonstrated that super-shedders are not necessarily 'super-spreaders' (Slater et al., 2016). This work demonstrated that the association between shedding levels and infectiousness is not linear; in fact, a 1000-fold increase in bacterial shedding results in only a 2-3 fold increase in infectiousness (Slater et al., 2016). However, other research groups have found that the level of MAP shedding from individual animals is one of the most important control phenotypic traits that can impact on the spread of infection (Ben Romdhane et al., 2017). In addition, field and research observations do support clusters of infection occurring in time and space (Zare et al., 2013). It is possible that many of these clusters are caused by the presence of a super-shedder at that time point.

Work has been conducted evaluating the longitudinal pattern of faecal shedding. Two distinct shedding patterns among infected cows have been observed; so-called 'progressors', characterised by continuous and progressive shedders, and 'non-progressors', characterised

by intermittent and low shedding of MAP bacteria and a virtual absence of a humoral immune response (Schukken et al., 2015). In naturally infected animals, less than 10% of cows became high shedders (>100 cfu/g), of which more than 95% were culled or died within 12 months of sampling (Mitchel et al., 2015). Furthermore, in the same study, naturally infected animals generally only shifted from non-shedding to shedding states once, whereas experimentally infected animals often shifted state up to ten times, suggesting that only a small subset of animals follow the 'expected' pathway from non-shedding to low-shedding to higher shedding, with the majority of naturally infected animals being predominantly low and intermittent shedders (Mitchell et al., 2015).

Observational studies are hindered by difficulty in identifying and quantifying faecal exposure on commercial farms. For example, in a systematic review of transmission routes, contact between calves and adults was highlighted as the most important factor influencing transmission; however, this finding was only observed in 5/14 studies that investigated this factor (Doré et al., 2011). Since then, a number of studies have demonstrated associations between herd positivity and indicators of hygiene or cleanliness (Künzler et al., 2014; Donat et al., 2016; Wolf et al., 2016; McAloon et al., 2017a) or issues around calving management such as individual use (Pithua et al., 2013), segregated calving for positive animals (Donat et al., 2016), use of the calving pen to house sick animals (McAloon et al., 2017a) and not using calving pens (Vilar et al., 2015).

Early investigations found that MAP was shed in low numbers (2-4/50 mL milk) in colostrum and milk from both clinically and subclinically infected animals (Sweeney et al., 1992; Streeter et al., 1995). More recently, MAP shedding to the order of 250 cfu/mL colostrum was found in clinical animals, with lower levels (24 cfu/mL) in subclinical

284 animals. The same study reported that the level shed in milk was also influenced by the stage
285 of lactation, with the highest levels present in the first 60 days-in-milk and negligible
286 shedding in mid and late lactation (Stabel et al., 2014). In another longitudinal study, only a
287 small proportion of subclinically infected cows were found to shed MAP in milk (Khol et al.,
288 2013). On a commercial farm, colostrum is frequently contaminated with faecal material
289 (McAloon et al., 2016a). Consequently, much of the MAP present in colostrum and milk is
290 thought to occur through environmental contamination rather than direct shedding. For
291 example, in an endemically infected herd, 80% of PCR-positive colostrum had a source other
292 than the dam (Pithua et al., 2011), and more recently, an association between poor udder
293 hygiene and MAP positivity in milk has been demonstrated (Beaver et al., 2017).
294
295 Observational studies have not consistently pointed to an important role of colostrum
296 in the transmission of MAP. In a Danish study, calves fed colostrum from multiple sources
297 were 1.2 times more likely to be positive than those fed dam-only colostrum (Nielsen et al.,
298 2008). Similarly, Irish herds where calves were fed non-dam colostrum were 2.1 times more
299 likely of having 2 or more reactors as those where calves were fed dam-only colostrum
300 (McAloon et al., 2017a). However, in a longitudinal study, calves fed PCR-positive
301 colostrum were not at a significantly greater risk of testing positive as adults compared to
302 those fed PCR-negative colostrum (Pithua et al., 2011). Similarly, although colostrum
303 pasteurisation reduced the incidence of MAP-infection in calves as detected by interferon
304 gamma (Stabel et al., 2008), in the long-term, risk of infection for this cohort as adults was
305 not different (Godden et al., 2015). Based on qualitative interviews, it has been recently
306 suggested that farmers may overemphasise the role of colostrum and milk in the transmission
307 of paratuberculosis indicating that the message of MAP being predominantly faecal-orally
308 transmitted should be strengthened (McAloon et al. 2017b).

In utero transmission

A meta-analysis found that up to 9% of calves born to subclinically infected animals and 39% of calves born to dams with clinical JD may be infected in utero (Whittington and Windsor, 2009). However, field reports of the importance of in utero transmission are conflicting. Whereas earlier studies reported that calves born to seropositive dams were 6.6 times more likely to be positive than those born to seronegative dams (Aly and Thurmond, 2005), more recently, the shedding status of the dam was found to have no effect on the 2-year old shedding status of the calf when reared in an endemic environment (Eisenberg et al. 2015). The within-herd apparent prevalence of these eight farms ranged from 0-16%. It is therefore possible that in high prevalence herds, the relative contribution of vertical transmission to horizontal transmission may be reduced. Furthermore, heifers were only 2 years old at testing in this trial.

Calf-to-calf transmission

Over the last few years, important work has been carried out examining calf-to-calf transmission. A Canadian study has demonstrated that calves that were orally inoculated with MAP were able to infect their penmates (Corbett et al., 2017). The basic reproductive ratio (R_0) of MAP transmission among group-housed dairy calves was estimated at 0.9 - 3.2 depending on the infection definition and modelling method used (Corbett, 2018). This finding was in line with earlier work demonstrating an R_0 of 0.1-3.2 for calf to calf transmission (van Roermund et al., 2007). Internationally, control programmes have recognised the potential risk of calf-to-calf transmission. Risk Assessment and Management Plans (RAMP) which form the basis of many of these control programmes often contain a question on the housing of dairy calves with lowest risk attributed to individually housed calves. The potential benefits in disease transmission are not unique to paratuberculosis and

are likely to be of particular benefit in the control of infectious diarrhoea for example. However, the individual housing of calves is problematic. A growing body of research has shown beneficial effects of group and pair housing of calves in terms of improved starter intake, weight gain, cognitive ability and reduced fear responses (De Paula Viera et al., 2012; Gaillard et al., 2014; Costa et al., 2015). Furthermore, EU Council Directive 2008/119/EC[1] recommends that calves are reared in groups and dictates as a minimum that a calf must have visual and tactile contact with another calf. Further work to determine the attributable fractions of calf-to-calf transmission is required; however, in the meantime, the role of early shedding in calves and the potential for calf-to-calf transmission must be considered when implementing controls on specific farms.

Other transmission routes

Environmental dust samples have been confirmed to contain viable MAP (Eisenberg et al., 2010) raising the possibility of a 'spore-forming' ability (Lamont et al., 2012). Corner et al. (2004) argued that the respiratory tract could be a potential infection route in cattle and the potential of intestinal infection in calves following aerosol administration to the respiratory tract has been confirmed in experimental studies (Eisenberg et al., 2011). Later work found that the presence of MAP-positive dust samples increased as within-herd prevalence increases (Eisenberg et al., 2013).

MAP has also been isolated from the semen of infected bulls (Larsen et al., 1981; Khol et al., 2010) and saliva of infected cows (Sorge et al., 2013), although these are not believed to be important transmission routes.

[1] European Union Council Directive 2008/119/EC. 2008. Laying down minimum standards for the protection of calves. http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32008L0119&from=EN (Accessed 4 July 2018)

Cross-species transmission

The importance of cross-species transmission from sheep to cattle is unclear. In a prospective Australian study, only two occurrences of sheep to cattle transmission occurred in 1774 calves reared on farms with histories of ovine JD (Moloney and Whittington, 2008). However, recent advances in molecular epidemiology have demonstrated greater evidence for sheep to cattle transmission. Type I strains were more commonly isolated from New Zealand beef cattle than Type II strains, consistent with transmission between sheep and cattle (Verdugo et al., 2014).

The role of wildlife has also gained interest recently. A recent review found that although MAP has been isolated from a variety of domestic and wild animals, only five are considered potential reservoirs, four of which are species of deer (Carta et al., 2013). In Scotland, several studies have shown that rabbits may act as reservoirs of infection. Mean faecal shedding from infected rabbits was found to be 7.6×10^5 cfu/g (Daniels et al., 2003). Increased prevalence of MAP in rabbits was found in herds with difficulty controlling JD in cattle (Shaughnessy et al., 2013). More recently, a counterintuitive increase in rabbit prevalence was found in cattle herds that had decreased the prevalence of infection through test-and-culling (Fox et al., 2018).

Conclusions

Much has been learned about the epidemiology of paratuberculosis in dairy herds. Further efforts to elucidate the relative contributions of different transmission routes to the dissemination of infection in endemic herds will aid in the prioritisation of efforts for control on farm.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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