Review
J Vet Intern Med 2012;26:32–45

Risk Factors Associated with Transmission of *Mycobacterium avium* subsp. *paratuberculosis* to Calves within Dairy Herd: A Systematic Review

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Background: Paratuberculosis has a worldwide distribution and many countries have implemented control programs to prevent transmission among and within herds. For these programs to be efficient, knowledge of the risk factors involved in transmission is essential.

Objectives: Systematically review the scientific literature concerning risk factors associated with *Mycobacterium avium* subsp. *paratuberculosis* (MAP) transmission to dairy calves.

Study Design: Systematic review.

Methods: An electronic search was done in PubMed and CAB to retrieve references relevant to answer at least 1 of the 5 questions concerning neonatal environment, colostrum, milk, housing of calves, and contact of calves with adult cow feces as risk factors in MAP transmission. A 1st screening was done using titles only, then abstracts, and finally full-length articles were reviewed for relevance. From the articles selected, risk factors and presence of a significant association between these risk factors and MAP transmission were recorded.

Results: Twenty-three articles from 11 different countries and published in 12 different journals were reviewed. The most common study design was cross-sectional (n = 16). The case definition and diagnostic tests used were very variable among studies, but serum ELISA was used in most studies (n = 14). The study unit was the herd in 18 studies.

Conclusions and Clinical Importance: The contact of calves with adult cow feces is the most important risk factor in MAP transmission. The 5 categories of risk factors are linked to one another.

Key words: Control; Johne's disease; Management; Prevention.

Paratuberculosis or Johne's disease is a chronic enteric disease of ruminants caused by *Mycobacterium avium* subsp. *paratuberculosis* (MAP). The bacteria is mostly transmitted by the feco-oral route, but also can be excreted in colostrum[1] and milk from subclinically[1,2] or clinically affected cows.[3] The infection also can be transmitted in utero.[4] Age susceptibility of cattle recently has been studied in a systematic review with meta-analysis using 11 experimental studies published between 1938 and 2006 (n = 140 cattle). It was concluded that 73.7% of calves exposed to MAP before the age of 6 months developed lesions of Johne's disease, whereas only 19.3% of cattle exposed after 12 months of age developed lesions.[5]

Prevention is the key to control paratuberculosis because the long incubation period (2–10 years)[6] and low sensitivity of most diagnostic tests[7] make early detection of infected animals difficult. It has been suggested by simulation models that improving calf management was more efficient to decrease MAP prevalence in a herd than a test and cull strategy.[8,9] These are reasons why control programs should emphasize prevention of MAP transmission, especially to the more susceptible young stock.

The objective of this study was to systematically review the scientific literature concerning risk factors related to MAP transmission to calves.

Abbreviations:

CI	confidence interval
DC	dam colostrum
INF-γ	interferon-gamma
LAM-ELISA	lipoarabinomannan enzyme-immuno-assay
MAP	*Mycobacterium avium* subsp. *paratuberculosis*
MeSH	Medical Subject Heading
OR	odds ratio
PC	pasteurized colostrum

Materials and Methods

The guidelines for conducting a systematic review were based on "A Guide to Conducting Systematic Reviews in Agri-Food Public Health."[10]

Search Strategy

The electronic databases PubMed Medline (1950–2010) and CAB (1973–2010) were searched in January 2011. The systematic search addressed 5 specific questions related to risk factors for transmission of MAP to calves:

1 Is there a relationship between the characteristics of the immediate neonatal environment and the risk of MAP transmission?
2 What is the risk of MAP transmission to neonatal calves through colostrum ingestion?

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Submitted July 8, 2011; Revised October 18, 2011; Accepted November 15, 2011.

10.1111/j.1939-1676.2011.00854.x

3 What is the risk of MAP transmission to neonatal calves through milk ingestion?
4 Does group-housing calves increase the risk of MAP transmission?
5 Is there an increased risk of MAP transmission when calves have contact with adult cow feces?

The following Medical Subject Headings (MeSH) were used for the search in PubMed Medline: "Paratuberculosis/epidemiology" [MeSH] OR "Paratuberculosis/prevention and control" [MeSH] OR "Paratuberculosis/transmission" [MeSH] OR "Paratuberculosis/veterinary" [MeSH] AND "Cattle."

The following key words were used for the search in CAB: Cattle OR Bovine AND Paratuberculosis OR Johne's OR mycobacterium avium paratuberculosis OR mycobacterium avium subsp paratuberculosis OR mycobacterium avium subspecies paratuberculosis AND Transmission OR Control OR Prevention OR Risk Factors OR Strategies OR Management AND Milk OR Colostrum OR Calves OR Calf OR Calving OR Housing OR Environment.

Identification of Relevant Studies

Only studies published in peer-reviewed journals were included. English, French, and Spanish manuscripts were considered. If at least 1 of the 5 questions was potentially answered in the publication, it was deemed relevant. The 1st selection was based only on the title. Citations discarded based on the title concerned diagnostic tests, vaccine, economics, productivity, species other than bovine, Crohn's disease, pharmacology, pathophysiology, genomics, immunology, transmission in utero, by embryo transfer or semen, and in vitro studies. The abstracts then were reviewed and more manuscripts were discarded for similar reasons. Citations concerning prevalence studies or beef cattle were not discarded based on the title, but after reading the abstract if deemed irrelevant. The remaining articles were reviewed in totality by 3 authors (E.D., J.P., G.F.) to ensure they addressed at least 1 of the 5 questions. Articles concerning only theoretical mathematical models were discarded.

Data Extraction

The following information was collected from each article: first author, journal, and year of publication, country (US state or Canadian province if applicable) where the study was done, study design, unit of interest and number of animals or farms, farm or individual case definition, and diagnostic test used when applicable. Relevant risk factors studied for each question and statistical analysis used (univariate or multivariate analysis and significance threshold) were recorded.

For each article, conclusions drawn with regard to the questions of interest were recorded. The possible conclusions were (1) significant association between factor and risk of MAP transmission in the univariate analysis, (2) significant association between factor and risk of MAP transmission in the multivariate analysis (3), no significant association detected. It also was noted when the association was contrary to common knowledge. The level of significance was the threshold used in each manuscript.

Study Appraisal

The study appraisal process was done by 2 authors independently (E.D., J.P.). We used a qualitative checklist derived from Sanderson et al.[11] The internal and external validities of the studies were evaluated to determine support for causal association between risk factor and paratuberculosis infection. The validities were described separately, but with the same scale: low, moderate, or high. The following stepwise criteria were used to evaluate internal validity: (1) study design and (2) quality of the study (specifically case definition and diagnostic test reliability). Study designs for which time of exposure could not be ascertained (case-control, cross-sectional) could not be classified as high. A qualitative score was given as follow: + for case-control and cross-sectional studies, ++ for longitudinal, follow-up prevalence and retrospective cohort studies, and +++ for experimental and randomized-controlled clinical trial. The case definition had to be stated and clear. Diagnostic tests and threshold used also were important considerations. Fecal culture to identify MAP has a stronger diagnostic value than a serologic test (ELISA) to detect the immune response.[7] More specifically, requiring 2 positive ELISA results to call a herd infected is a more reliable criterion than requiring 1 positive ELISA result to call an individual cow infected. A qualitative score was given as follows according to the diagnostic method used: 0 for identification of a case with clinical signs by owners or veterinarians, 1 if detection of humoral response on an individual animal was used, 2 for more than 1 individual animal with positive humoral response to consider a herd positive, and 3 if the test used was aimed at detecting MAP directly.

The internal validity was high for study design ++ or +++, with a clear case definition and diagnosis based on MAP isolation. The support for causal association was judged moderate if the study design was +, and isolation of MAP was used for diagnosis or with a study design ++ with detection of antibody response for diagnosis. All other study designs were considered to provide low support for causal association.

The criteria used to determine external validity were sample size and how sampling was done. Studies with <40 herds or cows enrolled in a voluntary control program were judged to have a low-external validity. If the sample size was $\geq$40 and the sampling was done randomly, the external validity was judged high. Moderate external validity was used to describe studies with $\geq$40 enrolled cows in a control program, or studies with fewer herds for which the sampling was done randomly.

Also, how the herds were selected, the time lag between evaluation of risk factors by a questionnaire, and testing of the herd for MAP and type of possible biases were recorded.

Results

The PubMed Medline search yielded 441 citations. Thirty-four citations were not in English, French, or Spanish. The remaining citations (n = 407) were screened using the title only, and 268 were considered irrelevant. After reading the abstract (n = 139), 84 more were discarded. Fifty-five articles were read completely and reviewed, and 20 were kept for data extraction.

The CAB search yielded 346 citations that were screened using their titles, and 257 were discarded. After review of 89 abstracts, 36 were discarded because they did not address any of the questions, 11 because they were not in English, French, or Spanish, and 33 were duplicates from the PubMed search. Nine articles were reviewed, and 3 were kept for data extraction.

Twenty-three articles were included in the study. The year of publication varied from 1992 to 2010 and articles originated from 12 different journals. The work was done in 11 different countries. The most common

study design was cross-sectional (n = 16). The study unit was the herd (n = 18) or the cows (n = 5). The number of farms studied varied from 1 to 2,953. The definition of a positive animal or a positive herd was variable. The most common diagnostic test used was serum ELISA (n = 14). Details of the data extracted for the 23 articles are presented in Table 1. Study appraisal is presented in Table 2.

The characteristics of the immediate neonatal environment and the risk of MAP transmission (question 1) were addressed in 18[12–29] of 23 manuscripts (Table 3). Eleven articles reported a significant association between the immediate neonatal environment and MAP infection. Contamination of udders with manure,[12] group-housing of periparturient cows,[29] and presence of more than 1 cow in the maternity pen[28] were 3 factors that increased the risk of being a MAP-infected herd. Benedictus et al[13] found a relationship between lifelong infection status of calves born from negative dams and calving pen contamination. Calves exposed to a contaminated calving pen by infected cattle or shedding cattle between 3 and 10 days of life were more likely to become infected by MAP, and to have a positive fecal culture compared with calves not exposed. Odds ratio varied from 2.2 to 3.9, if infected cattle contaminated the calving pen and varied from 3.6 to 6.6, if shedding cattle were in the calving pen. Ridge et al in 2005[25] found an increased risk of infection when calving occurred in a shed or a calving pad compared with a paddock. Ridge et al in 2010[26] found that calving in a paddock or in a shed compared with a calving pad increased the risk of MAP transmission.

Çetinkaya et al[15] demonstrated a protective effect of calving in an individual pen when the cows are at grass. Goodger et al[19] identified that scores in the newborn calf care category, which includes time of removal from the dam, were significantly correlated with the apparent prevalence of MAP in dairy herds. Nielsen and Toft[23] found that proper management of the calving area (proper hygiene of the feeding area, more straw) reduced the odds of MAP infection at the herd level. Cashman et al[14] found that the probability of having a MAP-positive culture was significantly decreased as the percentage of the calvings that were attended increased.

A case-control study by Johnson-Ifearulundu and Kaneene[20] reported an association that was contrary to common thinking. In this study, washing cows' udders before parturition was associated with an increased risk of infection with MAP.

The risk of MAP transmission through colostrum ingestion (question 2) was addressed in 11[12,14,18,19,21,22,27,28,30–32] of 23 manuscripts (Table 4). A significant association between the type of colostrum fed to calves and MAP transmission was detected in 4 manuscripts. Dieguez et al[18] found that feeding colostrum from ELISA-positive cows increased the risk of being an infected herd by MAP. Nielsen's study[31] was specifically designed to study colostrum as a risk factor for MAP infection in dairy cattle. The risk of a cow having a positive ELISA is greater for cows that, when they were calves, had been fed pooled colostrum from multiple cows than it was for cows that had been fed colostrum from their own dams. Calves fed pooled colostrum from multiple cows were at greater risk of testing positive, once adult to an in-house milk ELISA compared with calves fed colostrum only from their own dam. In Stabel's[30] randomized-control trial, 6 calves were fed colostrum from their dam (DC) and 5 calves received pasteurized colostrum (PC). The DC calves were allowed to nurse their dam for 8 hours after birth, received milk from their dam for 3 weeks, and milk replacer for the next 3 weeks. The PC calves were separated from their dam immediately after birth before they could nurse and were fed milk replacer for 6 weeks. After weaning, the 11 calves were housed together until 1 year of age. There was no significant difference among serum ELISA results, fecal shedding of MAP, and positive culture of MAP from postmortem tissues of the 2 groups. The only significant difference noted was that IFN-γ secretion was higher in DC calves compared with PC calves at 5 months of age. In Goodger's study,[19] newborn care was significantly associated with the prevalence of MAP in dairy herds. Newborn calf care included colostrum management factors: cleanliness of udder and bottles, and if the colostrum was pooled.

The risk of MAP transmission through milk ingestion (question 3) was addressed in 13[12,14,15,17,21,22,24–28,30,31] of 23 manuscripts (Table 5). A significant association between the type of milk fed to calves and MAP transmission was detected in 4 manuscripts. Nielsen's study[31] was specifically designed to study colostrum and milk as risk factors for MAP transmission in dairy cattle. Calves suckling with foster cows had an odds ratio of 2.012 (95% CI: 1.370–2.956) to be ELISA positive compared with calves fed milk replacer. In-house milk ELISA was repeated up to 4 times a year on all lactating cows. Ridge et al[25] demonstrated that feeding waste milk to calves was significantly associated with increased occurrence of MAP infection based on serum ELISA and clinical cases. In a subsequent study, Ridge et al[26] found that feeding waste milk to calves decreased the risk of MAP transmission. In McNab's case-control study,[21] being a high-risk herd, based on the herd mean LAM-ELISA optical density and the distribution of individual LAM-ELISA results among the herds, was positively associated with the proportion of newborn calves fed no raw milk.

Group-housing calves as a risk of MAP transmission (question 4) was addressed in 11[13–16,20,21,23,24,28,29,33] of 23 manuscripts (Table 6). Four studies found a significant association between group-housing of preweaned calves and MAP transmission. Tiwari et al[28] found that group-housing preweaned calves in winter was associated with the number of ELISA-positive cows in a herd. Benedictus et al[13] confirmed in a 20-year longitudinal study the risk of transmission of MAP to calves raised with a future high shedder (>100 colony forming units of MAP/gram of feces on culture). Calves born within 90 days after the birth of a future high shedder were 19.1 times more likely to become

Table 1. Data extracted from the 23 articles included in the systematic review.

Authors	Year	Country	Study Design[a]	Number Animals/Herds (Study Unit in Bold)	Case Definition	Diagnostic Tests
Correia-Gomes et al[17]	2010	Portugal	Cross-sectional	5,294 cows/**122 herds**	Milk ELISA+ = cow+ One cow+ = herd+	Milk ELISA[b]
Ridge et al[26]	2010	Australia	Retrospective cohort	**137 herds**	ELISA+ or clinical case of JD after 2nd whole herd test = herd+	ELISA (not specified)
Ansari-Lari et al[12]	2009	Iran	Cross-sectional	**110 herds**	PCR+ on bulk-tank milk = herd+	IS900-PCR
Norton et al[24]	2009	New Zealand	Cross-sectional	**427 herds**	Perception of clinical case by veterinarians, farmers' records	Not done
Pithua et al[32]	2009	United States	Randomized-control clinical trial	**497 calves**/12 JD endemic herds	ELISA, FC or both + at 30, 42 or 54 months of age	ELISA IDEXX[c] HEYM
Tiwari et al[28]	2009	Canada	Cross-sectional	7,689 cows/**257 herds**	ELISA+ = cow+ Count ELISA+ cows/farm	ELISA IDEXX[c]/ BIOCOR[d]
Benedictus et al[13]	2008	United States	Longitudinal	≈**400 cows** from 1 herd over 20 years	FC+ (twice/year all ≥ 2 year old and some young stock) = cow+	HEYM
Cashman et al[14]	2008	Ireland	Cross-sectional	**59 herds**	PCR or culture+ of milk sock filters = herd+; 6 times over 24 months	PCR, culture
Dieguez et al[18]	2008	Spain	Cross-sectional	5,528 cows >1 year old/**101 herds**	Herd−: no ELISA+ cows or only one ELISA+ but no cows with CS Herd+: 2–4 ELISA+ cows or 1 ELISA+ and at least 1 with CS Highly + herd: ≥5 ELISA+ cows or 2–4 ELISA+ and at least 2 cows with CS	ELISA IDEXX[c]
Nielsen et al[31]	2008	Denmark	Cross-sectional	**93,994 cows**/799 herds	ELISA+ = cow+	In-house ELISA[e]
Stabel[30]	2008	United States	Randomized-controlled clinical trial	**6 DC calves** **5 PC calves**	FC+, ELISA+ or ↑ INF-γ Monthly Culture or PCR+ on necropsy tissues at 12 months of age	HEYM, ELISA,[f] INF-γ,[g] IS900 PCR
Tavornpanich et al[27]	2008	United States	Cross-sectional	60 lactating cows per herd/**21 herds**	Low to zero seroprevalence herd: ≤2 ELISA+ cows; high seroprevalence: ≥3 ELISA+ cows	ELISA IDEXX[c]
Nielsen and Toft[23]	2007	Denmark	Follow-up prevalence	All lactating cows/**97 herds**	Continuous OD milk ELISA	In-house ELISA[e]
van Roermund et al[33]	2007	The Netherlands	Experimental	(A) 2 × 5 calves 1w old + 2 × 6 cows (B) **2 × 5 donor calves + 2 × 5 receiver calves**	Culture+ (feces or necropsy tissues), ELISA+ or ↑ INF-γ Animals kept until 43–48 months of age	Culture,[h] ELISA Pourquier,[b] INF-γ[i]
Ridge et al[25]	2005	Australia	Cross-sectional	All cows over 2 years tested annually/**54 herds**	ELISA+ or clinical case of JD after 2nd whole herd test	ELISA[j]
Muskens et al[22]	2003	The Netherlands	Cross-sectional	All cows ≥3 year old/ **370 herds**	≥1 cow ELISA+ in herd < 34 cows and ≥2 cows ELISA+ in herd ≥34 cows = herd+	ELISA IDEXX[k]
Wells and Wagner[29]	2000	United States	Cross-sectional	31,745 cows/**967 herds**	≥2 ELISA+ cows per herd or 1 ELISA+ cow with ≥5% culled with CS of JD = herd+	ELISA IDEXX[c]

(Continued)

Table 1. (Continued).

Authors	Year	Country	Study Design[a]	Number Animals/Herds (Study Unit in Bold)	Case Definition	Diagnostic Tests
Johnson-Ifearulundu and Kaneene[20]	1998	United States	Case-control Cross-sectional	**46 case herds-37 control herds**	≥2 ELISA+ cows = herd+	ELISA IDEXX[l]
Çetinkaya et al[15]	1997	England	Cross-sectional	**2,953 herds**	Reporting a case in 1993 or in 1994	Not done
Obasanjo et al[34]	1997	United States	Cross-sectional	**33 herds**	One FC+ = herd+ Whole herd testing from 6 months to 2 years	HEYM
Goodger et al[19]	1996	United States	Cross-sectional	All cows from **24 herds**	Herds already known to have MAP: 1 clinical case/year or ≥2 + FC in past year MAP apparent prevalence from ELISA+ cows	ELISA IDEXX[c]
Collins et al[16]	1994	United States	Cross-sectional	4,990 cows/**158 herds**	ELISA+ = cow+ One cow = herd+ Random sample of adult milking cows, on herd size basis	ELISA[m]
McNab et al[21]	1992	Canada	Case-control	**56 case herds-58 control herds**	Herd mean LAM-ELISA OD and distribution of individual LAM-ELISA	LAM-ELISA

CS, clinical signs; DC, dam colostrum; FC, fecal culture; HEYM, Herrold's egg yolk medium; INF-γ, interferon-gamma; JD, Johne's disease; LAM-ELISA, lipoarabinomannan enzyme-immuno-assay; OD, optical density; PC, pasteurized colostrum; PCR, polymerase chain reaction.

[a]Study design in accordance with description of the study in materials and methods not always according to author definition.

[b]Institut Pourquier, Montpellier, France.

[c]IDEXX Herdchek ELISA; IDEXX Laboratories, Westbrook, ME.

[d]BIOCOR Paracheck ELISA; BIOCOR Animal Health Inc, Omaha, NE.

[e]Nielsen SS. Variance components of an enzyme-linked immunosorbent assay for detection of IgG antibodies in milk samples to Mycobacterium avium subspecies paratuberculosis in dairy cattle. J Vet Med B Infect Dis Vet Public Health 2002;49:384–387.

[f]Parachek, PRIONICS AG, Schlieren-Zurich, Switzerland.

[g]Bovigam, Prionics, Lincoln, NE.

[h]Jorgensen JB. An improved medium for culture of Mycobacterium paratuberculosis from bovine faces. Acta Vet Scand 1982;23:325–335.

[i]Bovigram, CSL Ltd, Parkville, Australia.

[j]Johne's Absorbed EIA Kit; CSL Ltd.

[k]Herdcheck Mpt Ab, Idexx Skandinavia AB, Sweden.

[l]IDEXX Laboratories, Portland, ME.

[m]Yokomizo Y, Merkal RS, Lyle PA. Enzyme-linked immunosorbent assay for detection of bovine immunoglobulin G1 antibody to a protoplasmic antigen of Mycobacterium paratuberculosis. Am J Vet Res 1983;44:2205–2207.

Table 2. Data extracted from the 23 articles for support to causal association and results of the study appraisal.

Authors	Year	Herds Selection	Time Lag between Questionnaire and Testing	Potential Bias	Internal Validity	External Validity
Correia-Gomes et al[17]	2010	Random sample from program, stratified by municipalities	6 months for visits (Nov 2003–Apr 2004) Testing + questionnaire at same time	Misclassification	Low	Moderate
Ridge et al[26]	2010	Random selection, from program	6 months for visits; testing over 18 years (May 1990–Mar 2008)	Misclassification	Moderate	Moderate
Ansari-Lari et al[12]	2009	From 3 districts with more than 80% of dairies in the region	Mar–Aug 2006	Misclassification	Moderate	Moderate
Norton et al[24]	2009	Farmers nominated by veterinarians	1999 No testing	Misclassification	Low	Moderate
Pithua et al[32]	2009	Endemic herds But randomization for calves	N/A	N/A	High	Moderate
Tiwari et al[28]	2009	Stratified 2-stages random sampling	Questionnaire during visits	Misclassification	Low	High
Benedictus et al[13]	2008	N/A	N/A	N/A	High	Low
Cashman et al[14]	2008	Not random, apparently free of endemic MAP	Testing Sep 2001–Aug 2003 Data from current (2003) and historic (1994–2002) practices	Recall	Moderate	Moderate
Dieguez et al[18]	2008	Random, stratified by areas	First half of 2004	Misclassification	Low	High
Nielsen et al[31]	2008	From program	Mailed Mar 2007–reminder 1 month later (data from Jan 1999 to Dec 2006)	Misclassification (try to minimize) Recall	Low	Moderate
Stabel[30]	2008	N/A Randomization of calves	N/A	N/A	High	Low
Tavornpanich et al[27]	2008	From clientele of a practice Typical of region (size, management)	Questionnaire Aug–Nov 2001 Testing Jan–Jun 2004 (2.5 years later)	Misclassification (but minimized by testing later)	Low	Low
Nielsen and Toft[23]	2007	Not random, part of a project Higher in size	Questionnaire from Aug 1999 to Dec 1999 Testing 26 months later	Misclassification (but minimized by testing later)	Moderate	Moderate
van Roermund et al[33]	2007	N/A	N/A	N/A	High	Low
Ridge et al[25]	2005	From program	Visits Jun–Nov 2002 Testing since 1996 or 1997 in most herds	Misclassification	Low	Moderate
Muskens et al[22]	2003	Random	Questionnaire + testing Jul–Oct 1998	Misclassification	Low	High
Wells and Wagner[29]	2000	Stratified random sample	Questionnaire Jan–May 1996 (practices currently used and 3 years prior)	Misclassification (try to minimize) Recall	Low	High
Johnson-Ifearulundu and Kaneene[20]	1998	Stratified, multistage sampling	Questionnaire (data from 1993) + testing Jun–Dec 1996	Misclassification (try to minimize) Recall	Low	High
Çetinkaya et al[15]	1997	Random, stratified in 3 regions	Questionnaires mailed Mar–Sep 1995; no testing	Misclassification	Low	High
Obasanjo et al[34]	1997	From program	Phone interviews Jul–Oct 1993 Last herd testing Sep 1989–Apr 1993	Misclassification	Low	Low

(Continued)

Table 2. (Continued).

Authors	Year	Herds Selection	Time Lag between Questionnaire and Testing	Potential Bias	Internal Validity	External Validity
Goodger et al[19]	1996	Inclusion criteria, known to have MAP	Visits for testing Nov 1992–Mar 1993 Visits for questionnaire 6–12 months later	Misclassification	Low	Low
Collins et al[16]	1994	Random, stratified by herd size	Testing Oct 1989–Jun 1990; Questionnaires mailed (date unknown)	Misclassification	Low	High
McNab et al[21]	1992	Stratified random	Not mentioned, questionnaire on-farm	Misclassification try to be reduced by asking changes in practices within the past 5 years, but create a recall	Low	High

infected with MAP. Wells and Wagner[29] found that group-housing of calves before weaning increased the risk of being a herd infected with MAP. Cashman et al[14] found that herds raising calves in individual pens had decreased odds of a positive culture for MAP on the milk sock filter residue.

The contact between calves and adult cow feces and the risk of MAP transmission (question 5) was addressed in 14[14,17–20,22–25,27–29,33,34] of 23 manuscripts (Table 7). A significant association between MAP transmission and contact between calves and adult cow feces was detected in 5 manuscripts. Norton et al[24] found an almost dose-response relationship between the frequency of grazing calves in a hospital paddock and the odds of being a high incidence herd. Herds where calves were housed with adults before 6 months of age were more likely to be infected by MAP.[18] Obasanjo et al[34] found a similar association in herds for which calves between 0 and 6 weeks of age were exposed to adult feces. An experimental study[33] demonstrated that calves in contact with adult fecal shedders are at higher risk of becoming infected. In Goodger's study,[19] a regression analysis identified that newborn care was significantly associated with the prevalence of MAP in dairy herds. Herds having high score for management practices were less likely to be infected with MAP. Questions relevant to evaluate the contact between calves and adult cow feces were included in the manure-handling category and were manure equipment not used for feeding, young stock not near adult manure, and barn cleaner not near calves.

Discussion

Based on the present systematic review, contact with adult cow feces appears to be the most important risk factor for MAP transmission. Contact of calves with feces from adult cows was a risk factor for MAP transmission with high odds ratio (range, 4.59–30.5). Contact with adult cow feces represented a specific question, but appeared to be addressed by a surrogate variable in other questions. Calving environment, colostrum, milk, or housing might be a surrogate measure of fecal contamination. For example, it was found that suckling of foster cows (question 3: milk) increased the risk of being MAP infected. In this situation, the exact role of MAP (milk or feces on the teats) cannot be determined with certainty. Another example is question 1, concerning the neonatal environment. Most of the risk factors were closely related to fecal contamination (hygiene), for example, cleanliness of the calving area and udder washed before collection of colostrum.

The source of colostrum or milk as a risk factor for MAP transmission appeared to be of less relevance because most of the studies with moderate or high support for a causal association did not find an association between these risk factors and MAP transmission. There were 3 studies designed specifically to examine the impact of colostrum source. Of the 2 studies classified as high in the study appraisal, 1 did not find

Table 3. Manuscripts that studied risk factors concerning neonatal environment (question 1): results from univariate and multivariate analyses.

Authors	Risk Factors Examined	Univariate Analysis	Multivariate Analysis
Correia-Gomes[17]	(1) CA: yes or no; (2) hours to separate dam-calf: ≤ 6, 7–12, >12 hours	NS	Not included in final model
Ridge[26]	CA: calving pad versus shed versus paddock	CA: $P = .259$	Calving in a paddock HR 2.94 (CI1.289–6.708) or in a shed HR 6.61 (CI 1.693–25.786) increased risk of MAP transmission $P < .01$
Ansari-Lari[12]	(1) Calves with dam >3 hours; (2) separate CA; (3) contaminated udders of periparturient cows with manure	Udder contaminated with manure (3) $P < .2$	Contamination of udders of periparturient cows with manure (3) OR 6.38 (CI 1.29–31.49) $P = .02$
Norton[24]	(1) Calf-dam contact after birth; (2) CA: main herd or separated	NS	CA included in model for biologic importance but NS
Tiwari[28]	CA/management: (1) time with dam; (2) cleanliness of teat area; (3) use for sick cows; (4) location; (5) number of cows[a]	More than 1 cow in maternity pen (5) CR 1.5 (SE 0.26)	More than 1 cow in maternity pen (5) CR 1.7 (CI 1.2–2.2) $P < .01$
Benedictus[13]	CA contamination for calves born from MAP negative dam (shedding/infected animals versus negative and unknown)	Calves between 3 and 13 days of age in a contaminated CA $P < .05$	ND
Cashman[14]	(1) Calf-dam separation; (2) calving attendance; (3) time allowed to suckle their dam; (4) precalving udder clipping	Probability of positive culture significantly reduced as % calving attended increased (2) $P < .05$	ND too small data set
Dieguez[18]	(1) Separate CA; (2) time of separation calf-dam; (3) udder/teat washed before collection or calf suckling	NS	Not included in model
Tavornpanich[27]	(1) Time separation calf-dam; CA: (2) separated from sick cows/lactating; (3) frequency of bedding changes; (4) group versus separate pen	NS	Not included in model
Nielsen[23]	CA: (1) used for sick cows; (2) no specific CA; (3) 7 aspect of CA hygiene	ND	Hygiene in feeding area (3) OR 2.70 (CI 1.04–6.8) for 3rd best versus best Amount of straw in bedding (3) OR 3.0 (CI 1.21–8.1) for worst versus best
Ridge[25]	(1) CA: calving pad versus shed versus paddock; (2) time before calf removed from dam	ND	Calving in paddock decreased risk of MAP transmission (1) $P = .047$
Muskens[22]	(1) Separate CA; (2) $\geq 90\%$ cows calved in CA; (3) $\geq 90\%$ cows calved in clean CA; (4) noncalving cattle in CA; (5) calf removed from dam immediately	Separate calving area (1) $P = .06$; $\geq 90\%$ cows calved in CA (2) $P = .08$; Noncalving cattle in CA (4) $P = .05$	NS
Wells[29]	(1) With dam >24 hours; (2) CA for sick cows; (3) bedding for CA; (4) group-housing periparturient; (5) teats and udder washed before colostrum collected or calves suckle	Group-housing periparturient (4) $P = .01$	Group-housing periparturient (4) OR 1.5 (CI 1.0–2.3) $P = .06$
Johnson-Ifearulundu[20]	(1) Separation (in hours) calf-dam; (2) washing cows' teats and udder before parturition; Maternity pen: (3) used for calving; (4) used for sick cows; (5) frequency of cleaning	(2) Washing teats and udder; (3) Maternity pen for parturition	Washing udders before parturition (2) OR 8.66 (CI 1.87–40.08) $P = .006$

(Continued)

Table 3. (Continued).

Authors	Risk Factors Examined	Univariate Analysis	Multivariate Analysis
Çetinkaya[15]	(1) CA (when cows at grass and when housed): outside, inside (group or individual); (2) time calf with dam	(1) CA (grassed and housed) $P \leq .25$; (2) NS	(1) Calving: individual pen when cows at grass OR 0.21 (CI 0–0.93) $P = .04$ (2) Included in model for biologic importance but NS
Goodger[19]	(1) Newborn calf care: (a) colostrum management: clean udder, clean bottles; (b) removal from dam. (2) CA: (a) individual, (b) bedding, (c) cleaning	Descriptive	Newborn calf care significantly associated with MAP apparent prevalence (1) $P = .001$ and interaction terms $P < .002$ $R^2 = 0.90$
Collins[16]	(1) Calving location; (2) Separation dam-calf	(1) Calving location: summer $P = .11$; winter $P = .35$ (2) Calf-dam separation $P = .25$	NS
Mc Nab[21]	(1) CA: calving pen, tie stall, free stall or lot, pasture; (2) contact newborn: only dam, cows close to calving, adults not closed to calving	Descriptive	NS

CA, calving area; CI, 95% confidence interval; CR, count ratio; HR, hazard ratio; ND, not done; NS, not significant; OR, odds ratio; SE, standard error.

[a]Details of questionnaire obtained from the author, not in the manuscript.

Table 4. Manuscripts that studied risk factors concerning colostrum (question 2): results from univariate and multivariate analyses.

Authors	Risk Factors Examined	Univariate Analysis	Multivariate Analysis
Ansari-Lari[12]	Pooled	NS	Not included in model
Pithua[32]	Raw maternal (MC) versus plasma-derived commercial replacer (CC)	At all ages (ELISA+ or FC+): CC 7.6% (18/236) versus MC 11.9% (31/261) OR 0.523 (CI 0.272–1.003) $P = .051$	Logistic regression both test all ages: OR 0.523 ($P = .051$) Weibull model both tests: HR: 0.559 ($P = .056$) Less likely to be MAP ELISA and culture + if pasteurized; NS
Tiwari[28]	(1) Pooled all cows; (2) pooled MAP neg. cows; (3) 4 types: fresh, frozen, fermented, heat treated[a]	NS	Not included in final model
Cashman[14]	(1) Pooled; (2) multiple suckling	NS	ND to small data set
Dieguez[18]	From MAP+ cows	$P < .001$	OR 87.3 (CI 15.7–483.9) $P < .001$
Nielsen[31]	From multiple cows	Descriptive	From multiple cows OR 1.243 (CI 1.089–1.418); $P = .0012$
Stable[30]	Dam colostrum (DC) versus pasteurized colostrum (PC)	ND	INF lower for PC versus DC at 5 months $P < .005$
Tavornpanich[27]	Pooled (never, sometimes, always)	NS	Not included in final model
Muskens[22]	Not from dam	NS	Not included in final model
Goodger[19]	Newborn calf care: colostrum management: not pooled	Descriptive	High score for newborn calf care significantly associated with MAP apparent prevalence ($P = .001$) + significant interactions
Mc Nab[21]	(1) Pooled; (2) nurse dam	Descriptive	NS

CC, commercial colostrum; CI, 95% confidence interval; FC, fecal culture; HR, hazard ratio; MC, maternal colostrum; ND, not done; NS, not significant; OR, odds ratio.

[a]Details of questionnaire obtained from the author, not in the manuscript.

a significant association between ingestion of maternal colostrum and risk of MAP transmission[32] and the other one found only an increase in INF-γ in DC calves.[30] The 3rd study, classified as low in the study appraisal, found an increased risk of MAP transmission when colostrum from multiple cows was fed but with a small OR of 1.243 (95% CI: 1.089–1.418).[31]

Table 5. Manuscripts that studied risk factors concerning milk (question 3): results from univariate and multivariate analyses.

Authors	Risk Factors Examined	Univariate Analysis	Multivariate Analysis
Correia-Gomes[17]	Exclusively dam milk: yes or no	NS	Not included in final model
Ridge[26]	Antibiotic and waste milk	$P = .132$	Protective effect of feeding antibiotic/waste milk HR 0.42 (CI 0.247–0.720) $P < .001$
Ansari-Lari[12]	Unpasteurized milk	ND (all calves fed unpasteurized milk)	ND (all calves fed unpasteurized milk)
Norton[24]	(1) Penicillin milk; (2) nurse cows	NS	NS
Tiwari[28]	(1) Pooled all cows; (2) pooled MAP neg. cows; (3) mastitic (clinic or high SCC) or antibiotic residue[a]	NS	Not in final model
Cashman[14]	(1) Milk mixed with colostrum; (2) pooled milk	NS	ND too small data set
Nielsen[31]	(1) Different sources milk: (a) replacer, (b) bulk tank, (c) pooled high SCC, (d) bulk tank if insufficient milk high SCC; (2) foster cows	Descriptive	Suckling foster cows (2) OR 2.012 (CI 1.37–2.956) $P = .0004$
Stabel[30]	Milk from infected dam	ND	Not discussed
Tavornpanich[27]	Unsalable milk	$P = .34$ (NS if $P \geq .2$) but in final model for biologic importance	Caudal probability for risk factor = 0.712 NS but ASSOCIATION
Ridge[25]	Replacer, whole, whole + colostrum, whole + antibiotic residues	Descriptive	Feeding "antibiotic milk" $P < .001$ increased risk of MAP infection
Muskens[22]	Only fed milk replacer	$P = .04$ sero + 25.2% versus sero− 15.7%	NS
Çetinkaya[15]	Pooled, milk replacer	NS	Included in model for biologic importance but NS
Mc Nab[21]	Raw milk	Descriptive	Newborn calves to weaning fed no raw milk more in high-risk (case) herds $P = .02$

CI, 95% confidence interval; ND, not done; NS, not significant; OR, odds ratio; SCC, somatic cell count.
[a]Details of questionnaire obtained from the author, not in the manuscript.

The most common study design used was cross-sectional study. This type of observational study provides little evidence of causality and is considered moderately relevant to "real-world" situations.[35] When a management practice is identified to be more prevalent in MAP-infected herds, it does not provide any evidence that it is a risk factor involved in MAP transmission. Also there is no certainty that the risk factor was present before the exposure to MAP in cross-sectional studies. The same applies to case-control studies. Wells and Wagner[29] studied not only associations between risk factors and herd status for Johne's disease but also associations with the herd manager's familiarity with Johne's disease and the prior diagnosis of Johne's disease in a herd. In herds where managers were familiar with Johne's disease, the cows were 1.5 times more likely to have their teats and udder washed before colostrum was collected or the calf was allowed to suckle, compared with herds where managers were not familiar with the disease. Also, in herds with a previous diagnosis of Johne's disease, newborn calves were 3.4 times more likely to be separated from the dam less than 1 hour after birth compared with herds where the disease was not previously diagnosed. This may explain why some studies found associations that seemed opposite to what might be expected according to common knowledge. In cohort studies, where the risk factor or exposure is recorded before disease occurs, an inverse association can be found if the cohort is not followed long enough, because Johne's disease has a very long incubation period.[6] This can be especially true for retrospective or historic cohort studies in which recalling historical management practices can be very subjective and a source of recall bias.

Ridge published 2 different studies on herd management practices and transmission of Johne's disease in dairy herds in Victoria, Australia.[25,26] The relation between some management practices and Johne's disease transmission in the herds differed between the 2 studies. For example, in the 2005 study, feeding waste milk to calves was a significant risk factor for Johne's transmission, but, surprisingly, was found to be a protective factor in the 2010 study. The 1st survey to assess calf rearing practices was done in 2002, and the 2nd one between July 2005 and January 2006. The herd status for MAP (clinical cases or ELISA-positive cow) was updated in March 2008. The author stated that between the 2 surveys, several changes had been made concerning calf management practices. Once again, because of the long incubation period of Johne's disease, a herd that was being fed waste milk in the past could find infected cows several years after the

Table 6. Manuscripts that studied risk factors concerning group-housing of calves (question 4), results from univariate and multivariate analyses.

Authors	Risk Factors Examined	Univariate Analysis	Multivariate Analysis
Norton[24]	Individual versus group	NS	Not included in final model
Tiwari[28]	For preweaned: group/individual pens, hutches (summer versus winter)	Group-housing in winter $P = .15$	Group-housing in winter CR 2.0 (CI 1.3–2.8) $P < .01$
Benedictus[13]	Calf-to-calf transmission (exposure to future high shedder) calves from test-neg dam and no contamination in calving area	4/14 infected were born within 90 days after birth of future high shedder ($\chi^2 = 12.7$; $P = .0004$; Fisher 2-sided: $P = .0064$; OR 19.1) 3/4 born 30–90 days after ($\chi^2 = 6.91$; $P < .0086$; Fisher 2-sided: $P = .036$; OR 9.7)	ND
Cashman[14]	Individual calf pens	Individual pens → odds milk sock filter culture + significantly lower $P < .05$ (OR 0.21; CI 0.04–1.0)	ND (too small data set)
Nielsen[23]	Calves <2 months: single pen or other	ND	NS
van Roermund[33]	Infection calf-to-calf	R (3 months) = 0.9 (CI 0.1–3.2); 1-sided test H0: $R \leq 1 \rightarrow P = .64$; H0: $R \geq 1 \rightarrow P = .61$ (NS, but transmission possible)	ND
Wells[29]	Group-housing for calves before weaning during preceding year	$P = .05$	$P = .04$ if grouped OR 1.5 (CI 1.0–2.3)
Johnson-Ifearulundu[20]	Individual calves hutches or not	NS	Not included in final model
Çetinkaya[15]	Individual pens (never, first 30 days, more 30 days)	$P \leq .25$	NS
Collins[16]	Calves housing before weaning (calf barn, hutches, pens in cow barn, other)	Calf housing before weaning $P = .33$	Not included in final model
McNab[21]	Housing newborn calves to weaning: individual tied, indoor pens, outdoor hutch or pen	Descriptive	Heifer calves, weaning to 8 months, individually tied in summer $P = .02$ (not neonatal calves)

ND, not done; NS, not significant; CR, count ratio; OR, odds ratio; CI, 95% confidence interval.

management practice was discontinued because a cow may develop the disease several years later. In this case, a selection bias is possible in terms of the survey constructs with regard to the farmers' knowledge of the status of the herd and adjusting their behaviors according to their status.

Systematic review is the study design that gives the strongest level of evidence.[36] The search method and criteria for inclusion are transparent and repeatable. In this study, gathering information from good primary studies allows summarizing knowledge to answer questions on a specific topic. We searched a major medical database and an additional agricultural database that only added 3 different articles to the review. Some studies never get published, and the language of publication can be a barrier for accessing the results. We searched for studies written in 3 different languages and only found relevant studies written in English. Studies that found significant results are more likely to get published and may be published in peer-reviewed journals. So, we might have created a bias toward studies that found significant results. Also, because of the timelines of a systematic review, we did not search nonpeer-reviewed journals and proceedings from conferences.[37]

Most systematic reviews focus on only 1 research question. We decided to study 5 different questions concerning risk factors for MAP infection of dairy calves to cover all the different possibilities of MAP transmission. It might have been less laborious to review the literature with only 1 specific question, but we may not have identified the close relationship among risk factors. Moreover, we would have minimized the importance of contact with adult cow feces in MAP transmission because that risk factor was identified by many questions as discussed previously.

Information concerning the different risk factors of MAP transmission to calves was summarized qualitatively. With this systematic review, it was not possible to compile quantitative data of the different studies

Table 7. Manuscripts that studied risk factors concerning contact with adult cow feces (question 5): results from univariate and multivariate analyses.

Authors	Risk Factors Examined	Univariate Analysis	Multivariate Analysis
Correia-Gomes[17]	Pasture share with cows	$P < .25$	NS
Norton[24]	(1) Age at 1st contact with adult (2) Calves in hospital paddock	Sometimes = low incidence (OR 1.98; CI 1.25–3.15); frequently = high incidence (OR 4.53; CI 1.62–2.69) (2)	Paddock frequently = high incidence (2) OR 5.92 (CI 1.37–25.48)
Tiwari[28]	Equipment for manure and heifer feed	NS	Not in final model
Cashman[14]	Slurry spread on calf pasture, calves grazed adult pasture (animal waste and hygiene management)	NS	ND too small data set
Dieguez[18]	(1) <6 months housed with adults (2) Fed pasture or herbage treated with manure	Housing with adult <6 months (1) ($P < .001$); herbage with manure (2) ($P < .001$)	Replacement animals housed with adult cattle <6 months (1) ($P = .026$; OR 4.59 (CI 1.20–17.6)
Tavornpanich[27]	(1) Heifers $\leq$6 months exposed to adult manure (2) Manure-handling equipment to feed (3) Lagoon	Manure-calves (1) $P = .09$ Manure-feed (2) $P = .19$ Lagoon (3) $P = .13$	NS caudal probability: Manure-calves (1) 0.68; Manure-feed (2) 0.662; Lagoon (3) 0.680
Nielsen[23]	Calves <2 months separated from cows (Y versus N)	ND	NS
van Roermund[33]	Cow-calves transmission	MLE estimator for R (3 months) is 2.7 with CI 1.1–6.6; 1-sided test H0: $R \leq 1 \rightarrow P = .019$ (H0 rejected), H0: $R \geq 1 \rightarrow P = .99$	ND
Ridge[25]	Unweaned calves housing: adequately separated from adult cattle and their effluent		NS suggestive association between adequate separation of the calf shed from adult cattle, feces of adults or effluent and reduced BJD incidence $P = .07$
Muskens[22]	Age in months when calves no longer housed separately from adults	Average: sero− = 8.6 ± 8.7; sero+ = 10.2 ± 8.4 $P = .11$	NS
Wells[29]	Heifers <12 months: (1) Common feed or water sources with adult (2) Equipment to handle manure and their feed	Heifers <12 months sharing feed/water with adults was associated with JD status (1) but inverse direction…spurious association	Not included in model
Johnson-Ifearulundu[20]	Common equipment for feed and manure; common feed and water source between calves and adults; feed for calves on fields manure spread	$P \leq .95$ and 70 or more observations for 3 factors so offered to multiple regression	NS
Obasanjo[34]	(1) Exposure calves 0–6 weeks to adults feces (2) Young stock contact adult feces from same equipment used for clean (3) Feces spread on forage fed to any age group	(1) OR 8.3 (CI 1.4–47.5); (2) OR 6.4 (CI 1.0–38.8); (3) OR 10.3 (CI 1.8–60)	Any practice leading to exposure of calves 0–6 weeks to feces of adult cows (1) OR 30.5 (1.2–808.7)
Goodger[19]	(1) Milk-fed calf care = pens void of adult manure (2)Manure handling = young stock not near adult manure, barn cleaner not near calves, manure equip. for feeding	Descriptive	$R^2 = 0.90$; high score for manure handling significantly associated with MAP apparent prevalence (2) (main effect $P < .001$ and interactions terms significant)

CI, 95% confidence interval; ND, not done; NS, not significant; OR, odds ratio.

and conduct a meta-analysis. Different study designs were used, the case definition for a MAP-positive cow or MAP-positive herd was variable, the diagnostic tests to detect a MAP infection differ, and finally, the statistical analysis of the data varied. For all of these reasons, a meta-analysis was not realistically feasible. Instead, we decided to classify qualitatively the studies according to the strength of the causal association between risk factor and MAP using a checklist of 3 different criteria. Although we attempted to make this appraisal repeatable, such classification remains subjective and can be viewed as a potential bias because systematic reviews are meant to be objective studies. On the other hand, it enables us to weigh the results, significant or not, in the different studies.

Paratuberculosis was first diagnosed in 1885 in Germany, and the first report in North America was in 1908 in Pennsylvania.[38] For almost a hundred years, studies were focused on understanding the pathophysiology of the disease. Interestingly, studies relevant to any of the 5 questions were published only in the past 20 years. Epidemiology and risk factor studies are relatively recent science. Although multiple studies have been done to find risk factors involved in MAP transmission, to our knowledge, this is the 1st systematic review on risk factors associated with transmission of MAP to calves.

From this study, we can conclude that the contact of calves with adult cow feces is the most important risk factor for MAP transmission, because all 5 questions studied were addressing the fecal-oral route of transmission.

Acknowledgments

The study was supported by the Programme de Soutien à l'Innovation en Agroalimentaire du ministère de l'Agriculture, des Pêcheries et de l'Alimentation du Québec.

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