The Zoonotic Potential of *Mycobacterium avium* spp. *paratuberculosis*

A Systematic Review

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ABSTRACT

Background: The zoonotic potential of *Mycobacterium avium* ssp. *paratuberculosis* (MAP) has been debated for almost a century because of similarities between Johne's Disease (JD) in cattle and Crohn's disease (CD) in humans. Our objective was to evaluate scientific literature investigating the potential association between these two diseases (MAP and CD) and the presence of MAP in retail milk or dairy products using a qualitative systematic review.

Method: The search strategy included 19 bibliographic databases, 8 conference proceedings, reference lists of 15 articles and contacting 28 topic-related scientists. Two independent reviewers performed relevance screening, quality assessment and data extraction stages of the review.

Results: Seventy-five articles were included. Among 60 case-control studies that investigated the association between MAP and CD, 37 were of acceptable quality. Twenty-three studies reported significant positive associations, 23 reported non-significant associations, and 14 did not detect MAP in any sample. Different laboratory tests, test protocols, types of samples and source populations were used in these studies resulting in large variability among studies. Seven studies investigated the association between CD and JD, two challenge trials reported contradictory results, one cross-sectional study did not support the association, and four descriptive studies suggested that isolated MAP is often closely related to cattle isolates. MAP detection in raw and pasteurized milk was reported in several studies.

Conclusions: Evidence for the zoonotic potential of MAP is not strong, but should not be ignored. Interdisciplinary collaboration among medical, veterinary and other public health officials may contribute to a better understanding of the potential routes of human exposure to MAP.

Key words: Review, systematic [Publication Type]; Crohn's disease; paratuberculosis; zoonoses

La traduction du résumé se trouve à la fin de l'article.

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Mycobacterium avium spp. *paratuberculosis* (MAP) belongs to *Mycobacterium avium* complex that includes 24 species, some of which are pathogenic to humans and animals.¹⁻³ MAP is the causative agent of Johne's disease (JD), a chronic, production-limiting disease of ruminants that occurs more frequently in dairy cattle⁴⁻⁷ than in beef cattle, sheep and goats.⁸⁻¹¹ Subclinically infected cattle will appear healthy for years before the onset of clinical symptoms; sudden weight loss and diarrhea often result in emergency slaughter or death.¹²⁻¹⁴ MAP may persist in the environment for a long time and be transmitted among wild and domestic animal populations by a fecal-oral route.^{1,9,15}

Crohn's disease (CD) is a chronic, debilitating disease that affects the gastrointestinal tract in humans.^{9,12,15} This intestinal bowel disease typically occurs in young adults; major symptoms include frequent episodes of diarrhea and chronic pain.^{1,9,12,13} Approximately 74% of patients require surgery.^{9,12,13} Higher prevalence of CD is reported in Caucasians, and in urban areas.^{12,13,16} For the individual, this disease negatively affects the quality of life and has significant medical costs.¹⁵

The zoonotic potential of MAP has been debated for almost a century due to apparent clinical and pathological similarities between JD and CD.^{1,9,13} The isolation of MAP in 1984¹⁷ from a CD patient's resected bowel tissue captured the interest of the scientific community to investigate this issue.^{1,9,13,18}

Due to the negative impact of JD on cattle production and the potential public health risk through the consumption of milk contaminated with MAP, government agencies are considering control programs and targeted microbial testing of milk at processing.^{4,9-12,14,19-25} Other potential exposure routes, such as water,²⁶⁻²⁸ meat or environment, have not been studied to the same extent.^{22,26,29-32}

Narrative reviews³³⁻³⁷ have addressed the zoonotic potential of MAP. One published meta-analysis³⁸ reported that the evidence for MAP's zoonotic potential was inconclusive. However, the study did not use or report a systematic review process and pertains to literature published prior to 1999. Our broad objective was to investigate the scientific literature associated with the zoonotic potential of MAP by assessing three specific questions: Is there evidence

of an association between MAP and CD? Is there evidence of an association between CD and JD? Is viable MAP present in retail milk or dairy products?

METHODS

Literature search

An electronic search of 19 bibliographic databases (PubMed, etc.) from their inception was conducted in February 2005 and updated in September 2005. All databases were searched using an *a priori* determined and pre-tested search strategy that included three search strings with Boolean combinations of keywords (see Appendix). A hand search included 8 international and North American scientific conference proceedings held from 2001 to 2004 and websites of 12 international advocacy groups. We contacted 28 topic-related scientists to identify new or unpublished studies based on current research grants and recent relevant conference abstracts where a published study was not located. Lists of bibliographic databases, conference proceedings, websites, scientists and search algorithms are available from the first author upon request. To verify the search, reference lists of the five most recent literature reviews^{12,39-42} the five most cited literature reviews³³⁻³⁷ and five most cited primary articles^{17,43-46} investigating the zoonotic potential of MAP were hand searched, and potentially relevant citations were added to our database.

Relevance screening, quality assessment and data extraction

All review steps were conducted by two independent reviewers using *a priori* developed checklists that were pretested among the reviewers with kappa agreement of >0.8. Disagreement between reviewers was resolved by consensus.

Relevant citations were primary research studies of any study design, in English, that investigated ≥ one of the following questions: an association between MAP and CD, between CD and JD, or the presence of MAP in retail milk or dairy products. Relevant conference proceedings were matched to full peer-reviewed articles; where such publications could not be identified, the author was contacted for a full publication or manuscript draft. Conference proceedings were excluded when publications could not be obtained

Figure 1. The movement of 2,683 citations, the exclusion of 2,608 and the inclusion of 75 studies through the systematic review process

* Four genotyping studies were included in the review, but were not assessed for quality due to their descriptive nature.

and the conference abstract did not contain sufficient detail for quality assessment and data extraction.

Quality assessment checklists were adopted for six study designs; case-control, cohort, cross-sectional, randomized control trial (RCT), challenge trial and prevalence studies.⁴⁷ Each checklist contained four to seven questions (depending on study design) representing necessary quality criteria.⁴⁷ Failure to meet one of the following criteria resulted in an “unacceptable” study classification: clearly stated objectives (all studies); level of exposure was representative of target population (cohort); controls from an appropriate source population (case-control/cohort); study population representative of the target population and selected randomly (cross-sectional and prevalence); intervention randomly assigned (RCT/challenge); study protocol clearly described (RCT/challenge); appropriate control group used (RCT/challenge);

adequate time from challenge to outcome assessment (RCT/challenge); adequate description of laboratory protocols (all studies); cases/controls verified by qualified health professional (case-control/cross-sectional/cohort); adequate presentation of estimates, measures of variability and/or raw data (all studies).

Data extraction forms were designed to obtain information on each study: general information, materials and methods, population characteristics, outcome measures, results, statistical analysis and conclusions.

Review management and data analysis

Citations were deduplicated in Procite 5.0⁴⁸ and uploaded into SRS, a web-based interface designed by ©TrialStat Corporation⁴⁹ for electronic review management. The extracted data were exported into MS Excel spreadsheets for descriptive analysis.

Descriptive sensitivity analysis based on a chi-square test for association was used to

TABLE I

Case-control Studies Investigating the Association Between MAP and CD Using Culture, PCR or Other Methods to Isolate MAP

Study Code (Year) ^{ref}	Country	Method	Crohn's Patients (+/n)	Control Group (+/n)	Brief Method Description	Sample/ State	Association Detected OR (95%CI) ^{††}	
Culture Studies								
<i>Acceptable Quality Studies</i>								
CC4 (2005) ⁶⁴	Italy	Culture ^{ll}	19/30	UC nIBD ^{††}	0/2 3/29	MGIT, MJ	biopsy/ fresh	16.12 (3.52, 96.60) p=0.000 ^{††}
CC3 (2003) ⁶⁵	UK	Culture ^{ll}	14/33	nIBD ^{††}	3/33	MGIT, MJ	biopsy/ fresh	7.37 (1.69, 43.89) p=0.002 ^{††}
CC9 (2000) ⁶¹	US	Culture	10/27	UC ^{††} nIBD health	0/14 1/7 1/15	MGIT, MJ	biopsy & resection/ fresh	10 (1.77, 100.01) p=0.002 ^{††}
			0/27	UC nIBD health	0/14 0/7 0/15	BACTEC 12B, MJ		
CC10 (2000) ⁵⁹	US & Denmark*	Culture ^{ll††}	US 0/33 DK0/50	UC nIBD	US 0/35 DK 0/26 US 0/19 DK 0/30	BACTEC 12B, MJ	resection/ fresh	No MAP detected
CC14 (1998) ⁸⁵	US	Culture ^{ll}	0/21	UC health	0/5 0/11	HEYM & Middlebrook 7H10 & 7H11	biopsy/ frozen	No MAP detected
CC37 (1995) ¹⁰³	Germany	Culture ^{ll}	0/23 12/23	nIBD nIBD	0/23 0/23	Lowenstein-Jensen HEYM, MJ	biopsy & resection/ frozen	No MAP detected
CC22 (1992) ⁸³	US	Culture	1/27	UC nIBD	0/29 0/26	HEYM, MJ	resection	no estimate, p=0.33 ^{††}
CC23 (1989) ⁵²	US	Culture	4/27	UC health	0/29 1/26	HEYM, MJ	biopsy & resection/ fresh	9.56 (0.86, 479.29) p=0.037 ^{††}
CC27 (1987) ⁴³	US	Culture	0/59	UC nIBD	1/19 0/27	HEYM, MJ	biopsy & resection/ frozen	no estimate, p=0.44 ^{††}
			0/59	UC nIBD	0/19 0/27	Lowenstein-Jensen, MJ & Middlebrook 7H10 & 7H11, MJ	biopsy & resection/ frozen	
<i>Unacceptable Quality Studies</i>								
CC26 (2004) ⁹⁴	US*	Culture ^{ll}	14/28	UC nIBD health ^{††}	2/9 0/4 0/11	MGIT, MJ & BACTEC12B, MJ (merged results)	whole blood/ fresh	11 (1.96, 109.07) p=0.001 ^{††}
CC16 (1998) ⁸⁷	Italy	Culture ^{ll}	8/32	UC health	5/27 1/41	Lowenstein-Jensen, MJ	fecal/ frozen	3.44 (0.92, 13.25) p=0.06 ^{††}
PCR								
<i>Acceptable Quality Studies</i>								
CC2 (2005) ⁸²	US	PCR [†]	10/12	UC nIBD ^{††}	2/2 1/6	IS900 [P90/P91] 398bp & [AV1/AV2] 298bp	biopsy/ frozen	8.33 (0.74, 117.24) p=0.05 ^{††}
CC4 (2005) ⁶⁴	Italy	PCR [§]	25/30	UC ^{††} nIBD ^{††}	0/2 3/29	IS900 [89/92], 284bp	biopsy/ fresh	46.67 (8.61, 303.05) p=0.000 ^{††}
CC7 (2005) ⁷⁰	Germany	PCR	52/100	UC ^{††} nIBD ^{††}	2/100 5/100	IS900 [L/AV], 298bp	resection/ frozen	29.87 (12.31, 81.68) p=0.000 ^{††}
CC3 (2003) ⁶⁵	UK	PCR [§]	34/37	nIBD	9/34	IS900 [L/AV] 298bp & IS900 [TJ]1-4] 294bp	not stated	31.48 (6.86, 186.29) p=0.000 ^{††}
CC24 (2003) ⁹²	Canada*	PCR	0/24	UC Rel	1/28 6/28	IS900 [P90/P91] 400bp, IS900 [AV1/AV2]	biopsy/ frozen	no estimate, p=0.096 ^{††}
CC8 (2002) ⁶⁶	Ireland	PCR	6/15	nIBD	0/12	IS900 155bp, APC 435bp, APC 133bp	biopsy/ paraffin embedded	no estimate, p=0.0200 ^{††}
CC28 (2002) ⁹⁵	Japan	PCR	0/16	UC nIBD	0/11 0/18	IS900[MPARA-F/MPARA-R/MPARA-PB] 99bp.	resection/ paraffin embedded	No MAP detected
CC10 (2000) ⁵⁹	US & Denmark*	PCR ^{§††}	US 9/30 DK 6/49	UC nIBD	US12/35 DK 4/26 US 1/8 DK 2/30	IS900 [PBT5/PBT12]	resections/ fresh	0.99 (0.43, 2.23) p=1.0 ^{††}
CC29 (2000) ⁹⁶	Japan	PCR	0/14	UC nIBD	0/5 0/14	16S[RRI/II] [†] 400bp.	biopsy/ fresh and frozen	No MAP detected
CC30 (1999) ⁹⁷	Japan	PCR	0/13	UC nIBD	0/14 0/13	IS900 [P90/P91] 400bp, IS900 [150C/921] 229bp.	resection/ frozen	No MAP detected
CC14 (1998) ⁸⁵	US	PCR [§]	1/21	UC health	0/5 0/11	IS900 [P90/P91], 400bp	biopsy/ frozen	no estimate p=1.0 ^{††}
CC31 (1998) ⁹⁸	France	PCR	0/47	UC nIBD	0/27 0/20	IS900, 262bp	biopsy & resection/ frozen	No MAP detected
CC32 (1998) ⁹⁹	Germany	PCR ^{††}	0/19	UC nIBD	0/13 0/21	IS900[P90/P91] 400bp	resections/ frozen	No MAP detected
CC33 (1997) ⁶⁰	Kuwait	PCR	0/10	UC nIBD	0/6 0/21	IS900[MP] 400bp, MP2[MP] 310bp.	biopsy /frozen	No MAP detected
CC34 (1997) ¹⁰⁰	UK	PCR	0/7	OF health	0/30 0/12	IS900[P90+/P91+] 413bp	oral tissue/ paraffin embedded	No MAP detected
CC35 (1996) ¹⁰¹	US	PCR	0/23	nIBD	0/11	IS900 [P90/P91] 400bp & IS900 [150C/921], 229bp	biopsy & resection/ paraffin embedded	No MAP detected
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TABLE I, continued

Case-control Studies Investigating the Association Between MAP and CD Using Culture, PCR or Other Methods to Isolate MAP

Study Code (Year) ^{ref}	Country	Method	Crohn's Patients (+/n)	Control Group (+/n)	Brief Method Description	Sample/ State	Association Detected OR (95%CI) ^{††}
CC36 (1996) ¹⁰²	Belgium	PCR	0/36	UC 0/13 nIBD 0/23	IS900 [P90/P91], 400bp & IS900 [TDB3/TDB4]	biopsy & resection/ frozen	No MAP detected
CC11 (1995) ⁶³	New Zealand	PCR	2/9	UC 2/15 nIBD 0/11	IS900 [TDB3/TDB4]	biopsy/ frozen	3.43 (0.20, 53.25) p=0.27 ^{‡‡}
CC25 (1995) ⁹³	UK	PCR	0/68	UC 0/49 nIBD 1/26	IS900, 400bp	biopsy & resection/ frozen	no estimate p=1.0 ^{‡‡}
CC37 (1995) ¹⁰³	Germany	PCR [§]	0/4	nIBD 0/1	16S [264/283] [†] , 283bp.	biopsy & resection/ frozen	No MAP detected
CC1 (1995) ⁸¹	Japan	PCR	10/10	UC 11/18 ^{††} nIBD 14/16 UC 9/10 nIBD 11/12	IS900 [IS1/IS2], 400bp groEL[TB1/TB2] [†] , 626bp & IS900 [IS1/IS2] 400bp	biopsy/ fresh	no estimate p=0.09 ^{‡‡} no estimate p=1 ^{‡‡}
CC6 (1994) ⁸⁴	France	PCR	13/18	UC ^{††} 1/5 nIBD ^{††} 2/6 gutD ^{††} 6/24	IS900 [150C/921] 229bp.	biopsy and resections/ frozen	7.5 (1.79, 33.72) p=0.001 ^{‡‡}
CC12 (1994) ⁶⁸	UK	PCR	4/31	UC ^{††} 0/10 nIBD ^{††} 0/20	IS900 [1/2] 354bp.	biopsy & resection/ paraffin embedded	no estimate p=0.11 ^{‡‡}
CC13 (1994) ⁶⁷	Denmark	PCR	15/82	UC ^{††} 2/65 nIBD 3/45	IS900 [PTB1/PTB2], 434bp & [PTB5/PTB12], 317bp	resection/ frozen & paraffin embedded	4.70(1.52, 17.18) p=0.002 ^{‡‡}
CC5 (1992) ⁹¹	UK	PCR	26/40	UC 1/23 nIBD 5/40	IS900 [P90/P91], 400bp.	resection/ frozen	17.64 (5.54, 60.77) p=0.000 ^{‡‡}
<i>Unacceptable Quality Studies</i>							
CC20 (2004) ⁹⁰	Italy	PCR ^{**}	11/82	UC 0/20 health 0/20	IS900[P89/P92], 284bp	biopsy & resection/ paraffin embedded	no estimate p=0.016 ^{‡‡}
CC26 (2004) ⁹⁴	US*	PCR [§]	13/28	UC 4/9 nIBD 3/4 health 0/11	IS900[P90/P91], 398bp	whole blood/ fresh	2.1 (0.58, 7.92) p=0.20 ^{‡‡}
CC38 (2003) ¹⁰⁴	US	PCR	0/35	UC 0/36 nIBD 0/21	IS900, 229bp	tissue/ paraffin embedded	No MAP detected
CC18 (2001) ⁸⁹	US & Finland	PCR ^{**}	9/37	UC 3/21 nIBD ^{††} 0/22	IS900 [P90/P91], 400bp	biopsy & resection/ paraffin embedded	4.29 (0.94, 26.32) p=0.056 ^{‡‡}
CC21 (2000) ⁷¹	Greece	PCR	7/20	Tb & Sd nIBD 0/100 4/50	16SrRNA [M16SD2/M16SU], 504bp [†] & hybridization to PRAVMPAR probe	biopsy & resection/ paraffin embedded	19.65 (4.19, 100.42) p=0.000 ^{‡‡}
CC39 (2000) ¹⁰⁵	Ireland & UK	PCR	0/3	OF 0/21	IS900 [P90/P91], 413bp	oral biopsy/ paraffin embedded	No MAP detected
CC16 (1998) ⁸⁷	Italy	PCR [§]	15/32	UC health ^{††} 9/27 nIBD 1/41	IS900[150C/921], 229bp	fecal/ frozen	5.12 (1.75, 15.10) p=0.0005 ^{‡‡}
CC40 (1998) ¹⁰⁶	Japan	PCR	0/14	UC 0/5 nIBD 0/14	PCR 16S[RR/II]	biopsy & resection/ frozen	No MAP detected
CC15 (1996) ⁸⁶	US	PCR	8/8	UC 2/2 nIBD 0/2	IS900 [P90/P91], 400bp.	resection/ frozen	no estimate, p=0.09 ^{‡‡}
CC42 (1993) ¹⁰⁸	US	PCR	6/17	UC 0/2 health 0/3	IS900[IS900-1/IS900-2], 354bp	biopsy & resection	no estimate, p=0.27 ^{‡‡}
CC19 (1992) ⁴⁵	US	PCR	6/18	UC 0/5 health 1/6	IS900[P90, P91], 400bp	biopsy & resection	5 (0.45, 252.53) p=0.20 ^{‡‡}
<i>Other Methods</i>							
<i>Acceptable Quality Studies</i>							
CC2 (2005) ⁸²	US	FISH	8/12	UC 0/2 nIBD ^{††} 0/6	20-mer MAP IS900 specific oligo-nucleotide probe	biopsy/ frozen	no estimate p=0.005 ^{‡‡}
CC41 (1988) ¹⁰⁷	UK	DNA hybridization	0/17	nIBD 0/4	MAP strain Ben probes: pMB22/21/19	tissue/ frozen	No MAP detected
CC17 (1987) ⁸⁸	US	DNA hybridization	10/19	UC 2/6 nIBD 1/6	Non-specific mycobacterial DNA probes [†]	biopsy & resection/ frozen	3.33 (0.56, 24.32) p=0.16 ^{‡‡}
<i>Unacceptable Quality Studies</i>							
CC20 (2004) ⁹⁰	Italy	In situ hybridization	73/82	UC ^{††} 0/20 nIBD ^{††} 0/20	In situ hybridization	biopsy & resection/ paraffin embedded	no estimate p=0.000 ^{‡‡}
CC18 (2001) ⁸⁹	US & Finland	In situ hybridization	7/37	UC 2/21 nIBD ^{††} 0/22	In situ hybridization	biopsy & resection/ paraffin embedded	no estimate p=0.039 ^{‡‡}

* Population-based sample, † primers/probes used were not specific to MAP, ‡ case study
Other methods used on the same samples: § Culture, || PCR, ¶ FISH, ** In situ hybridization, ¶¶ ELISA

†† Significant difference between CD & control group if more than one control group (p>0.05)

‡‡ ad hoc chi-square (or Fisher's exact) calculation of odds ratio (OR) and confidence intervals (95% CI) using raw data. (CD vs. summary of controls)

UC = Ulcerative colitis, nIBD = non-Inflammatory Bowel Disease, Health = Healthy controls, Tb = tuberculosis, Sd = Sarcoidosis, Rel = relative,

OF = Oral Facial Granulomas

MGIT = Mycobacterial Growth Indicator Tube, HEYM Herrold's Egg Yolk Medium, MJ = supplemented with mycobactin J

FISH = fluorescence in situ hybridization

US = United States, UK = United Kingdom

TABLE II

Case-control Studies Investigating the Association Between MAP and CD Using Immuno-assays

Study Code (Year) ^{ref}	Country	Crohn's Patients, +/n or %	Control Groups, +/n or %	Lab Assay/Antigen	Association Detected (odds ratio ^{††})
Acceptable Quality Studies					
CC51 (2004) ³¹	Canada*	107/283	UC health rel 135/402 UC ^{††} 47/138	ELISA / solid-phase MAP antigens (commercial kit)	1.18 (0.87, 1.59) p=0.25 ^{‡‡}
CC46 (2001) ¹¹²	Norway	10	UC ^{††} 10	ELISA/ MAP 14kDa, AhpC & AhpD	CD vs. UC 14kDa antibody level, no estimate, p<0.05
CC10 (2000) ⁵⁹	US & Denmark*	30/261	UC nIBD health ^{††} 2/49 UC ^{††} 9/274	ELISA/ solid-phase MAP antigens (commercial kit) [§]	3.32 (1.66-6.63) p=0.0006
CC44 (2000) ¹¹⁰	US	p35 40/53 p36 79/89 p35&36[†] 39/53	p35 1/10 p36 4/27 p35&36[†] 1/10 health ^{††} 5/35 p35 7/50 p35&36[†] 0/35 UC 0/13 nIBD 0/21	SDS immunoblot/ p35&p36 ^R	p35&p36[†] 114.4 (15.63, 4732.92) p=0.000 ^{‡‡}
CC32 (1998) ⁹⁹	Germany	0/19	UC nIBD 0/13	Immunoblot/ mycobacterial heat-shock protein 65	No MAP detected
CC43 (1992) ¹⁰⁹	Italy	p38 57% p18 & p24 53%	UC: p18 10% p24 0%	ELISA/ p18 & p24, Western Blot/ p38, (MAP strain 203)	p18 only, 10.15 (4.54, 24.18) p=0.000 ^{‡‡}
CC45 (1988) ¹¹¹	US	ACD 40 ICD 32	AUC 10 IUC 18 NIBD 29 health rel 40/20 UC ^{††} 0/34 nIBD ^{††} 0/55	ELISA/ Map strain Linda protoplasmic antigen, LAM & anti-lipid A antiserum	no estimate, IgA levels higher p<0.0001
CC60 (1984) ¹⁸	US	13/56	UC ^{††} 0/34 nIBD ^{††} 0/55	ELISA/MAP protoplasmic antigen, MAP strain Linda	no estimate, p<0.0003
Unacceptable Quality Studies					
CC47 (1999) ¹¹³	US	77/89	UC ^{††} 4/27 nIBD ^{††} 1/15 health(50), Tb(8), Leprosy(8) ^{††} 30/68	Immunoblot/ MAP p36 ^R	8.25 (3.69, 19.09) p=0.000 ^{‡‡}
CC48 (1999) ¹¹⁴	Japan	5/13	UC nIBD health ^{††} 4/20 nIBD 2/4 health ^{††} 0/20	ELISA/ protoplasmic extract MAP (commercial kit)	3.96 (0.74, 19.89) p=0.10 ^{‡‡}
CC49 (1999) ¹¹⁵	US	9/10	UC ^{††} 0/10 health ^{††} 0/10	ELISA/ GST fusion protein ^R	no estimate, p<0.0001
CC52 (1996) ¹¹⁷	UK	?/40	UC ?/15 nIBD ?/20 health ?/21	ELISA/ p18	No estimate, no p-value
CC50 (1994) ¹¹⁶	Belgium	?/73	health ^{††} ?/50	ELISA/ MAP a362 (34kDa) protein ^R	No estimate, IgG p<0.05, IgA p<0.00
CC53 (1993) ¹¹⁸	UK	6/91	UC ?/15 nIBD 2/10 health ?/30	ELISA/ MAP protein ^R	CD vs nIBD, 0.28 (0.04, 3.37) p=0.18 ^{‡‡}
CC54 (1991) ¹¹⁹	US	32/35	UC 13/15 nIBD 12/12	Immunoblot/ Map st. Linda 70kDa protein	0.85 (0.07, 8.07) p=1.0 ^{‡‡}
CC55 (1988) ¹²⁰	UK & France	1/20	nIBD ?/12 health ?/20	Indirect ELISA/ MAP A60 protein	No estimate, no p-value
CC56 (1980) ¹²¹	US & UK	19/24	UC 17/24 health 19/24	Antigen antibody agglutination tests/ antigen: MAP (M28) & antibody patient sample serum	1.27 (0.35, 5.27) p=0.78 ^{‡‡}

* Population-based sample

Other methods used on the same samples: § Culture, || PCR

†† Significant difference between CD and control group p>0.05

‡‡ ad hoc chi-square (or Fisher's exact) calculation of odds ratio (OR) and confidence intervals (95% CI) using raw data (CD vs. summary of controls), unless otherwise specified.

UC = Ulcerative colitis, nIBD = non-Inflammatory Bowel Disease, Health = Healthy controls, Tb = tuberculosis, Rel = relative, ACD = active Crohn's disease, ICD = inactive Crohn's disease, AUC = Active ulcerative colitis, IUC = inactive ulcerative colitis

PBMC = peripheral blood mononuclear cells, LAM = lipoarabinomannan, 18kDa = bacterioferin, p24 is shared between M. avium and MAP, ^R = recombinant protein, † = MAP recombinant clone expressing 35 and 36K antigen, GST = glutathione S-transferase

US = United States, UK = United Kingdom, ? = results not reported

evaluate whether the assigned quality status (acceptable vs. unacceptable quality studies) or year of publication impacted the review findings and conclusions. For studies that did not report a statistical analysis, the primary author performed a chi-square test of association or Fisher's exact test (one or more cells was <5) from available

unadjusted case-control study results with binomial outcomes in Tables I and II.⁵⁰

RESULTS

From 2,683 de-duplicated citations, 75 studies were relevant primary papers published in English that were suitable for

quality assessment, data extraction and descriptive data summarization. This included four genotyping studies not assessed for quality due to their descriptive nature (Figure 1).

Sixty case-control studies investigated the association between MAP and CD, 37 were of acceptable quality. The association

TABLE III

Case-control Studies Investigating the Association Between MAP and CD Using Lymphocyte/cytokine Assays

Study Code (Year) ^{ref}	Crohn's Patients (n)	Control Patients (n)	Lymphocyte Population	Antigens	Mitogens	Cytokine	Association Detected
Antigen/mitogen-induced proliferation of lymphocytes							
CC46 (2001) ¹¹²	10	10 UC	PBMC	AhpC, AhpD, 14 kDa Ag, PPD-T, PPD-J, rota virus	ConA, PHA	—	No significant association¶¶
CC58 (1995) ^{†123}	13	17 UC 17 health	PBL‡	M. tuberculosis PPD, MAP PPD	PHA	—	No significant association
CC57 (1991) ¹²²	33	18 UC†† 9 nIBD†† 5 AI†† 23 health††	PBL	MAP lysate, M. tuberculosis lysate, M. leprae lysate, 1/100 Candida lysate	ConA	—	Positive association, p<0.01
Suppression of mitogen-induced proliferation of lymphocytes							
CC59 (1992) ^{†124}	10	9 UC	PBMC	MAP PPD, M. tuberculosis PPD, Kunin Ag, M. avium lysate, M. kansasii lysate, M. fortuitum lysate	ConA	—	No significant association
	5	6 UC	LPL	MAP PPD, M. tuberculosis PPD, Kunin Ag	ConA	—	
CC57 (1991) ¹²²	33	6 health 18 UC 9 nIBD 5 AI 23 health††	PBL	MAP lysate	ConA	—	Positive association, p<0.01
Antigen/mitogen-induced Cytokine Production from Lymphocytes							
CC46 (2001) ¹¹²	9	10 UC	whole blood	AhpC, AhpD, 14 kDa Ag, PPD-T, PPD-J, rota virus	—	IFN-gamma, IL-5	No significant association¶¶
CC10 (2000) ^{*59}	101	31 UC†† 169 health††	whole blood	M. avium PPD, M. bovis PPD	PHA	IFN-gamma	Positive association p<0.05§ ¶¶
	56	64 UC 63 health††	PBMC	M. avium PPD, M. bovis PPD	PHA	IFN-gamma, IL-5	

† Study was of unacceptable quality assessment, * population-based sample

‡ Measured cell proliferation and evaluated the lymphocyte cell surface markers to determine the nature of the cell response

†† Significant difference between CD and control group p>0.05

Other methods used on the same samples: § Culture, || PCR, ¶¶ ELISA

UC = Ulcerative colitis, nIBD = non-Inflammatory Bowel Disease, Health = Healthy controls, AI = Auto Immune Disorders,

PBL = peripheral blood lymphocytes, PBMC = Peripheral blood macrophage cells, IL = Interleukin, LPL = lamina propria lymphocytes, SI = Stimulation index

between CD and JD was investigated in two challenge trials (one of acceptable quality), one acceptable-quality cross-sectional study, and four genotyping studies. One randomized control trial and seven prevalence studies investigated MAP detection in raw and pasteurized milk, all of acceptable quality. Among 24 studies assessed as unacceptable, 13 did not meet one criterion and 11 did not meet two or more criteria, most frequently due to an inappropriate selection of controls.

A summary of case-control studies investigating the association between MAP and CD by laboratory test and assigned quality status is shown in Tables I to III. Polymerase chain reaction (PCR), culture or both were used in 36 (60%), 11 (18.3%) or 7 (11.7%) studies; 25, 9 and 5 were of acceptable quality, respectively (Table I). In situ hybridization was used in 5 (8.3%) studies and in conjunction with PCR in 3 (5%) studies; 3 and 2 were of acceptable quality, respectively (Table I). Different immunological (antigen-antibody) tests were applied in 17 (28%) studies; enzyme-

linked immunosorbent assay (ELISA) in 12 (20%), immunoblot in 5 (9%) and antigen-antibody agglutination tests 1 (2%) studies; 6, 1, 2 and 0 were of acceptable quality, respectively (Table II). Five studies (8.3%) used induced proliferation or suppression of lymphocytes with immunohistochemistry (1 study), flow cytometry (1), lymphocyte proliferation (2) and T-cell activation assay (1); three were of acceptable quality (Table III).

The source population in 60 case-control studies were hospitals 41 (68%), clinic settings 7 (12%), regional registries 3 (5%) and tissue libraries 9 (15%). Only three studies selected their samples from a population base. Controls included ulcerative colitis patients (UC) (52 studies), non-inflammatory bowel disease patients (nIBD) (39), apparently healthy controls (24), CD patient relatives (3) and patients with other diseases (8).

A significant positive association between MAP and CD was detected in 23 of 60 case-control studies, the association was non-significant in 23 studies and no MAP

was detected in 14 studies; 14, 13 and 10 were of acceptable quality, respectively. The mean, median and range of MAP isolation or antibody/antigen detection was 19.1%, 2.2% and 0-100% for PCR, 8.5%, 0.0% and 0-63.3% for culture, and 27.4%, 14.0% and 0-100% for immunology/other methods. The assigned quality of the study had no impact on whether there was a significant positive association, no association or no MAP detected. There were significantly fewer (p=0.02) non-significant studies published after the year 2000 (3/19) compared to before (19/41).

Only seven relevant studies investigated an association between CD and JD. In two challenge trials, MAP strains isolated from human CD tissue were used to challenge young goats, and only one study found some JD-like pathological lesions at necropsy.^{51,52} A cross-sectional survey did not find an association between the prevalence of CD among individuals who lived on a farm reporting JD in the last 15 years compared to those who lived on JD-negative farms.²¹ Four genotyping studies

TABLE IV

Prevalence Studies Investigating the Presence of MAP in Milk Samples

Study Code (Year) ^{ref}	Country	Brief Method Description Culture media/ time PCR/ primer	Sample Source	Raw Milk Culture (+/n)	Milk PCR (+/n)	Pasteurized Milk Culture (+/n)	Milk PCR (+/n)
PREV6 (2005) ¹⁹	US	Dubos Resuscitation Media to solid HEYM slants, (8-16 wks) & liquid TDS and ESP II (4-8 wks) IS900, 229 bp & hspX, 211 bp	Pasteurized milk samples from retail			20/702	452/702
PREV7 (2005) ⁴	Czech Republic	HEYM, (12m) & subcultures with and without MJ (3 m), Culture confirmed by IS900 [P3N P4N], 257bp PCR IMS, 400 bp.	Paired raw and pasteurized milk from 3 JD positive farms, fecal results A=3.7%, B=37.7%, C=0% and retail milk samples	raw milk A 10% B 19.7% C 0%		Retail 4/244 Small scale 2/200	
PREV2 (2004) ¹²⁵	Ireland	PCR IMS, 400 bp.	Paired bulk tank & pasteurized milk samples from 27 Irish dairies	1/389	50/389	0/357	35/357
PREV1 (2002) ⁶	Ireland	Bactec B12B (14 wks) & HEYM (16 wks)	Raw & pasteurized milk from commercial bulk tanks & retail outlets	0/310		0/86	
PREV3 (2002) ⁵	Canada	Middlebrook 7H9 broth and 7H11 slants, (22-27m) IS900 [P90 P91] 413bp & [P25 P26] 213 bp +bead-beater	Pasteurized milk from dairies and retail			0/244	110/710
PREV5 (2002) ¹²⁶	UK	HEYM & BACTEC 12B, MJ (IMS)-PCR, IS900, 400bp	Bulk tank and pasteurized milk samples	4/221	19/230	10/544	67/547
RCT1 (2002) ¹²⁷	N. Ireland	BACTEC 12B, HEYM 18wk IS900[P90/P91]	Paired bulk tank & pasteurized milk samples from positive JD dairy farms	4/60	4/60	10/144	30/144
PREV4 (1996) ⁴⁴	UK	Dubos broth (13 - 40 m), hybridization [p25/p26], 229bp IS900 [p90/p91]413bp	Pasteurized milk from retail outlets			15/54	22/312

IMS = immunomagnetic separation, MGIT = Mycobacterial Growth Indicator Tube, HEYM = Herrold's Egg Yolk Medium, MJ = supplemented with mycobactin J, TDS = Trek Diagnostic Systems
UK = United Kingdom, US = United States

investigated clusters of MAP alleles from cattle, sheep, other animals and humans and reported that bovine and ovine MAP strains were mutually exclusive, highly conserved and many human MAP isolates were related to bovine strains.^{7,10,53,54}

A summary of studies reporting MAP detection in raw and pasteurized milk is shown in Table IV.

DISCUSSION

We developed and applied a structured and replicable protocol based on a comprehensive and verified literature search that included contacting topic-related scientists, however it is possible that some unpublished studies were not located and their addition might affect the interpretation of the results. In addition to this inherent limitation of systematic review methodology, a weakness is that non-English studies were excluded due to logistic limitations.

Our results indicate the evidence for the association between MAP and CD is not

strong; however, its zoonotic potential must not be ignored. The isolation of MAP from CD patients, patients with similar or different diseases and apparently healthy individuals indicate that MAP might pose a risk in some CD patients or is an opportunistic organism sporadically detected in the general population.

All of the studies investigating the association between MAP and CD were retrospective case-control studies, representing a lower level of evidence on the hierarchy of evidence, that are subject to selection bias and could not establish a temporal link between exposure and disease due to the case selection procedure, long incubation period of CD and the lack of appropriate data on human exposure to MAP.^{47,55-58}

There was considerable variability among laboratory tests, test protocols, sampling protocols, sample storage and source of population among case-control studies. The lack of agreement among researchers on how to study this potential association might be one reason for reporting different

results.^{2,59,60} The observed trend of fewer non-significant studies published after the year 2000 compared to before, may be related to publication bias or improvement of laboratory tests for MAP detection. Culture protocols have changed over time; the development of the Mycobacteria Growth Indicator Tube (MGITTM) culture system improved the isolation of MAP from tissue, but not the length of time for culture growth (three months to two years).^{61,62} Most of the studies were PCR-based; these techniques have changed over time to optimize detection of MAP's IS900 multi-insertion sequence through use of mechanical disruption and smaller primers.⁶²⁻⁶⁵ However, PCR cannot differentiate between live or dead MAP cells and thus, results using only this method should be interpreted with caution.⁶⁰ It has been reported that freezing or paraffin embedding tissue samples for storage may fragment DNA, resulting in false negative results.^{66,67} Tissue samples obtained through biopsies result in smaller amounts

of tissue compared to resection tissue samples and may also affect MAP recovery.^{59,66,68-70} Sensitivity and specificity of laboratory tests was rarely stated, thereby limiting the estimation of possible false-positive or false-negative results.¹⁸ Future research should focus on improving sensitivity and specificity of laboratory tests, standardization of sampling, and appropriate meta-analysis of case-control studies to better understand the sources of heterogeneity among them.⁷¹⁻⁷⁴

The use of different control groups might be another reason for contradictory results among case-control studies. Differential diagnosis between CD, UC and other inflammatory bowel diseases is difficult, particularly at early stages of disease, resulting in potential misclassification bias.⁷⁵⁻⁷⁷ Future studies should have larger sample sizes and increased rigour in selecting controls from the appropriate source population.⁷⁶

Evidence for the association between JD and CD was also not strong because the research evidence came from seven studies representing lower level of evidence on the hierarchy of evidence^{47,78} and these studies reported contradictory or inconclusive findings. Four genotyping studies that suggested strain sharing between humans and cattle were based on a small number of MAP isolates, a limitation recognized by their authors.⁷⁹ There was a lack of longitudinal prospective cohort or case-control studies that might be suitable for studying the zoonotic potential of MAP in 'high exposure' or 'low disease' populations, respectively. This might be explained by the large costs and logistical difficulties associated with the implementation of such studies. Although properly designed and analyzed ecological studies might provide useful insights in the zoonotic potential of MAP, globally longitudinal and spatial exposure data in animal and human populations are not available or are insufficient.⁸⁰ Integrated surveillance systems and interdisciplinary research based on molecular biology and epidemiology tools are needed to better understand the association between JD and CD.

Low, but fairly consistent detection of MAP in raw and pasteurised milk confirmed that potential human exposure to MAP through milk consumption is possible. The importance of the public health risk associated with this route of exposure

Appendix

Lists of search algorithms (A), bibliographic databases (B), conference proceedings (C), websites (D) and topic-related scientists (E) are available from the first author upon request

A: Search algorithms

- Search Terms 1 "Crohn's Disease and John's Disease"
(Articles under refined questions 1&2):
((john disease) OR (john's disease) OR (john* disease) OR (paratuberculosis))

AND

((crohn* disease) OR (crohn disease) OR (crohn's disease) OR (krohn disease) OR (krohn* disease) OR (inflammatory bowel disease) OR (inflammatory bowel diseases))
- Search Terms 2 "Crohn's Disease and milk products"
(Articles under refined question 3):
((crohn* disease) OR (crohn disease) OR (crohn's disease) OR (krohn disease) OR (krohn* disease) OR (inflammatory bowel disease) OR (inflammatory bowel diseases))

AND

((milk) OR (dairy))
- Search Terms 3 "John's Disease and milk products"
(Articles under refined question 3):
((john disease) OR (john's disease) OR (john* disease) OR (paratuberculosis))

AND

((milk) OR (dairy))

relative to exposure by other means remains unclear.²² Regardless, some countries initiated or are considering targeted surveillance programs for JD at the farm level or for MAP in milk and dairy products at processing.²² It is likely that such programs will be costly and will take concerted efforts by all stakeholders in the dairy production chain.²²

In summary, this systematic review did not identify strong evidence for the zoonotic potential of MAP; however, detection of MAP in milk suggests the potential public health risks associated with this organism. Other potential exposure routes (water, meat, environment) need to be further investigated. The risks and preventive measures associated with different exposure routes should be evaluated and communicated with the public.

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RÉSUMÉ

Contexte : Le potentiel zoonotique de la paratuberculose aviaire (*Mycobacterium avium* ssp *paratuberculosis* – MAP) fait l'objet de débats depuis près d'un siècle en raison des similitudes entre la maladie de Johne (MJ) chez les bovins et la maladie de Crohn (MC) chez les humains. À l'aide d'un examen qualitatif systématique, nous avons évalué la documentation scientifique sur les liens éventuels entre ces deux maladies (le MAP et la MC) et la présence du MAP dans le lait ou les produits laitiers vendus au détail.

Méthode : Nous avons consulté 19 bases de données bibliographiques, les actes de 8 conférences et 15 articles cités en référence, et contacté 28 scientifiques spécialistes du sujet. Deux évaluateurs indépendants ont effectué un tri des documents selon leur pertinence, en ont évalué la qualité et ont extrait les données.

Résultats : Soixante-quinze articles ont été analysés. Sur les 60 études cas-témoins portant sur l'association entre le MAP et la MC, 37 étaient de qualité acceptable. Vingt-trois études faisaient état d'associations significativement positives, 23 faisaient état d'associations non significatives, et 14 n'ont détecté le MAP dans aucun échantillon. Les études utilisaient différents essais de laboratoire, protocoles d'essai, types d'échantillons et populations sources, ce qui explique la très grande variabilité d'une étude à l'autre. Sept études portaient sur l'association entre la MC et la MJ, deux tests de provocation ont produit des résultats contradictoires, une étude transversale n'a pas confirmé d'association, et quatre études descriptives donnaient à penser que le MAP isolé est souvent étroitement lié aux isolats du bétail. Plusieurs études ont détecté le MAP dans du lait cru et pasteurisé.

Conclusion : Bien qu'elles ne soient pas concluantes, les preuves du potentiel zoonotique du MAP ne sont pas négligeables. Une collaboration interdisciplinaire entre les autorités de santé publique (médicales, vétérinaires et autres) pourrait contribuer à améliorer les connaissances des voies possibles d'exposition humaine au MAP.

Mots clés : examen systématique [type de publication]; maladie de Crohn; paratuberculose; zoonoses