ORIGINAL ARTICLE

The potential Public Health Impact of *Mycobacterium avium* ssp. *paratuberculosis:* Global Opinion Survey of Topic Specialists

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Impacts

- The existing research evidence indicates *M. paratuberculosis* may pose a risk to human health although the likelihood and nature of impact on public health remain unknown.
- Humans could be exposed to *M. paratuberculosis* through food, water or direct contact with animals and environment.
- Current agri-food industry mitigation programmes focus on prevention through minimizing human exposure to *M. paratuberculosis* at the farm level, and as such are appropriate precautions given the current scientific evidence.

Keywords:
Paratuberculosis; Crohn's disease; Johne's disease; survey; questionnaire; expert opinion

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Received for publication May 8, 2015

doi: 10.1111/zph.12221

Summary

Global research knowledge has accumulated over the past few decades, and there is reasonable evidence for a positive association between *Mycobacterium avium* spp. *paratuberculosis* and Crohn's disease in humans, although its role as a human pathogen has not been entirely accepted. For this reason, management of public health risk due to *M. paratuberculosis* remains an important policy issue in agri-food public health arenas in many countries. Responsible authorities must decide whether existing mitigation strategies are sufficient to prevent or reduce human exposure to *M. paratuberculosis*. A Web-based questionnaire was administered to topic specialists to elicit empirical knowledge and opinion on the overall public health impact of *M. paratuberculosis*, the importance of various routes of human exposure to the pathogen, existing mitigation strategies and the need for future strategies. The questionnaire had four sections and consisted of 20 closed and five open questions. Topic specialists believed that *M. paratuberculosis* is likely a risk to human health (44.8%) and, given the paucity of available evidence, most frequently ranked it as a moderate public health issue (40.1%). A significant correlation was detected between topic specialists' commitment to *M. paratuberculosis* in terms of the number of years or proportion of work dedicated to this topic, and the likelihood of an extreme answer (high or low) to the above questions. Topic specialists identified contact with ruminants and dairy products as the most likely routes of exposure for humans. There was consensus on exposure routes for ruminants and what commodities to target in mitigation efforts. Described mandatory programmes mainly focused on culling diseased animals and voluntary on-farm prevention programmes. Despite ongoing difficulties in the identification of subclinical infections in animals, the topic specialists largely agreed that further enhancement of on-farm programmes in affected commodities by the agri-food industry (68.4%) and allocation of resources by governments to monitor the issue (92%) are most appropriate given the current state of evidence.

Introduction

Mycobacterium avium ssp. *paratuberculosis* is a slow-growing mycobacterium that has evolved from *Mycobacterium avium* ssp. *hominissuis* and can survive for long periods of time in soil and water (Salgado et al., 2011; Nacy and Buckley, 2008;). It has developed pathogenic qualities similar to *M. tuberculosis*, which enable it to invade and replicate within macrophages of the gastrointestinal tract (Hermon-Taylor, 2009; Naser et al., 2014). Johne's disease caused by *M. paratuberculosis* is common in ruminants worldwide, but has also been reported in other species including non-human primates (McClure et al., 1987; Judge et al., 2006; Stevenson et al., 2009). In domestic ruminants such as cattle, sheep and goats, Johne's disease develops slowly over several years to a fatal wasting condition characterized by diarrhoea, weight loss and declining milk production (Behr and Collins, 2010). *M. paratuberculosis* is important to animal health management and is the target of many voluntary and mandatory on-farm control programmes implemented in collaboration with the main agri-food public health stakeholders, primarily industry (Hermon-Taylor, 2009; Behr and Collins, 2010; Geraghty et al., 2014).

Humans are probably exposed to *M. paratuberculosis* from agri-food sources considering the evidence of low-level contamination of milk, beef and water among other foods (Eltholth et al., 2009; Anon 2010; Mihajlovic et al., 2011). However, the significance and extent of this exposure for food safety and public health is yet to be determined. For almost a century, *M. paratuberculosis* association with human disease has been investigated, mainly for its potential role in Crohn's disease, a human gastrointestinal condition with clinical and pathological characteristics similar to those of Johne's disease (Naser et al., 2014). Crohn's disease is a chronic debilitating disease that significantly affects the quality of life. To date, there is no known cause or cure for the 1–2 million people affected worldwide by this disease (Molodecky et al., 2012; Naser et al., 2014). The causal role, if one exists, of *M. paratuberculosis* in Crohn's disease is not fully understood (Behr and Collins, 2010).

Recent research has shifted evidence trends towards a consistently reported association between *M. paratuberculosis* and Crohn's disease, although its role as a human pathogen has not been entirely accepted (Agrawal et al., 2014; Waddell et al., 2015). Despite remaining uncertainties, it is likely that agri-food public health authorities and stakeholders will continue to face policy questions on the overall public health impact of *M. paratuberculosis* including whether the existing mitigation strategies for *M. paratuberculosis* control are sufficient and whether it is justified to allocate public health resources towards preventing or minimizing human exposure to *M. paratuberculosis*. We administered a Web-based questionnaire to gather some answers to these and related over-arching questions from topic specialists in academia, government and industry around the world with a variety of areas of expertise, including animal health, microbiology and human medicine.

The objectives of this study were to gather global topic specialist opinions on the following:

1. Whether *M. paratuberculosis* poses a risk to human health and its importance as a public health issue.
2. The more common human exposure routes to *M. paratuberculosis* and where future research and mitigation strategies should focus.
3. Existing government control and/or surveillance programmes and their perceived adequacy.
4. Whether governments have taken appropriate actions on *M. paratuberculosis* as a public health issue and have allocated adequate resources.

To the best of our knowledge, this is the first survey administered to the global topic specialists with the main aim to assess actual risks posed by *M. paratuberculosis* on human health and to inform the policy and decision-making processes on the suitability of current mitigation strategies and future needs.

Methods

Database of topic specialists

A list of topic specialists working on the *M. paratuberculosis* issue was compiled by identifying authors of published and non-published research papers, reports and conference proceedings dealing with the zoonotic and public health aspects of the *M. paratuberculosis* issue identified from our knowledge synthesis work on this topic (Waddell et al., 2008, 2015). Additional names were acquired from lists of membership in *M. paratuberculosis*-related organizations and recommendations from other *M. paratuberculosis* topic specialists. The initial list of topic specialists included 218 unique names and their corresponding email addresses compiled by the lead author of this article.

Questionnaire description and administration

The questionnaire was designed in collaboration with five individual scientists from Canada and the United States with expertise in survey questionnaire methodology and/or extensive specialized knowledge of the *M. paratuberculosis* issue. The questionnaire draft underwent a multistage pretest for technical aspects, content and comprehension by four professionals with experience in online surveys and three professionals with a range of backgrounds reflective of our target respondents (Dillman, 2000). There were four questionnaire sections: respondent demographics (7 closed/0 open questions), significance of human exposure routes to *M. paratuberculosis* (3/0), overall impact of *M. paratuberculosis* on public health, including relevance of the current and potential mitigation strategies (8/3), and final comments (2/2). The demographics questions addressed areas of expertise and where it was acquired, continent of residence, work setting (e.g. academia), type of work (e.g. clinician), self-indicated level of expertise (low to high, 5-point scale) for specific areas of the *M. paratuberculosis* issue, years of accumulated experience and proportion of current work dedicated to the issue. In the section on various human exposure routes to *M. paratuberculosis,* respondents were asked to rank the significance of various routes of exposure to *M. paratuberculosis* for humans (n = 14 routes) and ruminants (n = 11) through allocating 100 points across the exposure categories listed. Respondents were then asked to indicate on a 5-point scale (no impact to high impact) what commodities should be targeted to reduce human exposure to *M. paratuberculosis*, assuming interventions are available. In the third section, respondents were asked whether *M. paratuberculosis* poses a risk to human health (yes, likely, minor risk, no, don't know) and within the context of agri-food public health in their region, how they would rank *M. paratuberculosis* as a public health issue (high, medium, low, not a priority). Respondents were then asked to share their knowledge of their government's commitment to address *M. paratuberculosis* as a potentially important agri-food public health issue, the current mitigation strategies, monitoring or surveillance programmes and their feasibility, where future efforts should be targeted and what knowledge gaps are impeding animal health and control programmes and investigation into the public health significance of *M. paratuberculosis*. In the final section, respondents were asked whether they have completed a similar questionnaire in the past few years and to identify other topic specialists that should be invited to complete the questionnaire. The questionnaire had 25 questions, 20 closed and 5 open; however, respondents had an opportunity to add additional comments on closed questions.

The questionnaire was administered in English only; all potential respondents received an initial invitation and five weekly reminder email messages between 1 April and 15 May 2012 using LimeSurvey via the University of Guelph (Dillman, 2000; Ornstien, 2011, LimeSurvey Project Team 2012;). No attempt was made to follow-up with non-respondents, as we did not have additional contact information beyond their email address. Most of those who declined participation provided an explanation. Ethical approval was received from the University of Guelph Review Ethics Board (protocol # 12RE016). A copy of the questionnaire is available in the Appendix S1.

Data analysis

The respondent answers were exported from the LimeSurvey platform (LimeSurvey Project Team 2012) into spreadsheets [Microsoft 2010. Microsoft Excel (computer software). Redmond, WA, USA], cleaned and imported in to STATA 13 (StataCorp 2013. Stata Statistical Software: Release 13. College Station, TX, USA: StataCorp LP) for descriptive statistics and analysis of the categorical and ranking questions.

Two ordinal regression models were developed in STATA 13 to explore the relationships between participant demographic characteristics listed in Table 1 (e.g. area of expertise, location and setting where they acquired expertise, accumulated experience and proportion of work dedicated to *M. paratuberculosis),* and the two outcomes were ranking by topic specialists of *M. paratuberculosis* as a risk to human health (yes, likely, minor risk, no or don't know) and by topic specialists' opinion of its public health priority level (high, medium, low or not a priority). Proportional odds regression, a type of ordinal regression, was selected for use given the ordered nature of the outcomes (e.g. from minor to high risk or low-to-high priority), where we do not make assumptions about the equality of spacing between categories. *A priori* associations with selected explanatory variables (participant demographic characteristics) were tested by univariate analyses, and variables associated with outcomes at P-value <0.10 were offered to the multivariate models and evaluated for significance at P-value <0.05. Two-way interactions were assessed in final models, and variables were assessed for confounding (change >20% in coefficient of another predictor variables). The proportional odds regression family of models includes the proportional odds model, the partial proportional odds model and the heterogeneous choice model; the latter two allow predictor variables to violate the proportional odds assumption. The assumption is that the effect of each variable is the same for each binary comparison within the model; thus, the effect can be averaged across comparisons and a single parameter calculated to represent the effect of the explanatory variable on the response variable and can be evaluated with a Brant test (Dohoo et al., 2012). The partial proportional odds model and the heterogeneous choice model can allow this assumption to be violated, and the explanatory variable may have a different value at different levels of the response variable. We used the Akaike's information criterion (AIC) and Bayesian information criterion (BIC) values to compare between multinomial, proportional odds, partial proportional odds and heterogeneous choice models for the best fit for our data (Dohoo et al., 2012). There are few model diagnostics available for these proportional odds models.

Table 1. Expertise and related characteristics of participating respondents (n = 165) concerning *M. paratuberculosis* as a public health issue

Respondent characteristics	Responses per category n	%
General field(s) of expertise[b]		
Microbiology	74	44.8
Epidemiology	57	34.5
Animal health	81	49.1
Agriculture	10	6.1
Food safety	21	12.7
Public health	16	9.7
Human medicine	13	7.9
Molecular biology/genetics	27	16.4
Risk or economic modelling	4	2.4
Outbreak investigation	8	4.8
Other[a]	24	14.5
Moderate to extensive *M. paratuberculosis* expertise in the following categories[b]		
Animal health		
Beef cattle	97	58.7
Dairy cattle	136	82.4
Developing mitigation strategies	102	61.8
Implementing mitigation strategies	105	63.6
Diagnostic tests		
Routine testing	117	70.9
Development of new tests	109	66.1
M. paratuberculosis sources for humans		
Milk or dairy	117	70.9
Other human food	68	41.2
Water	81	49.1
Environment	97	58.8
Developing mitigation strategies	67	40.6
Implementing mitigation strategies	55	33.3
Zoonotic potential	108	65.5
Predictive or economic modelling	62	37.6
Continent in which *M. paratuberculosis* experience was acquired[b]		
Africa	2	1.2
Asia	8	4.8
Europe	68	41.2
N. America	82	49.7
Oceania	15	9.1
South and Central America	2	1.2
Other (middle east, 2 and unknown, 1)	3	1.8
Setting in which *M. paratuberculosis* experience acquired[b]		
Academia	121	72.7
Government	41	24.8
Industry	13	7.9
Private institute	12	7.3
Accumulated *M. paratuberculosis* experience (n = 163)		
< 3 years	14	8.6
3–10 years	69	42.3
>10 years	80	49.1
% of work with *M. paratuberculosis* focus (n = 163)		
<25%	78	47.9
25–50%	41	25.2
50–75%	16	9.8
>75%	27	16.6

[a]Immunology (7 responses), pathology (7), nutrition (3), internal medicine, food science, international trade, agri-engineering, disease systems.
[b]Some categories sum to more than 100% as respondents selected more than one option.

The partial proportional odds model was used to evaluate whether the topic specialist's ranking of the risk to human health was predicted by their demographic characteristics listed in Table 1. In the final model 'animal health expertise', those 'working in academia' and 'the proportion of work dedicated to *M. paratuberculosis*' were all significant explanatory variables. Of these explanatory variables, the proportional odds assumption was violated by 'academia' and 'proportion of work', so the model was chosen and structured to allow these variables not to follow the assumption.

The heterogeneous choice model using STATA's 'oglm' function was used to evaluate whether participant characteristics predicted the *M. paratuberculosis* public health priority ranking. The only significant explanatory variable was 'years of experience working on *M. paratuberculosis*', which violated the proportional odds assumption. This model allowed 'years of experience' to be heteroscedastic or vary at different outcome categories (Williams, 2010).

Chronbach's alpha was used to assess the internal consistency between responses for *M. paratuberculosis* as a risk to human health and the ranking of the public health priority level for *M. paratuberculosis*. Values >0.7 were considered to indicate high reliability or low response variance (Ritter, 2010). Open-ended questions were summarized descriptively, grouping respondents' answers into themes.

Results

Response frequency and evaluation of non-responders

From a total of 318 potential respondents (218 identified from publications and 100 suggested by respondents) to whom five reminders were sent, we received 156 fully completed, 9 partially completed and six questionnaires without responses, yielding a response rate of 53.7% (171/318). The average/median reported times to complete the questionnaire were 28 and 20 min, respectively. Ninety-five per cent of the respondents indicated they had not participated in a similar survey in the past few years. We had no response from 93 potential respondents, and 54 withdrew from participation for several reasons; for example, they did not feel they represented the targeted respondents, they no longer studied *M. paratuberculosis*, they did not have permission to participate in the survey, or they indicated another person in their group had already participated.

Respondent demographics and expertise

M. paratuberculosis expertise of participants and where it was acquired is summarized in Table 1. Expertise was mainly acquired in N. America (48.0%), Europe (39.8%) and Oceania (8.8%). Most respondents considered themselves to work in a research capacity (74.3%), mainly in academia (70.2%) and government (24.0%). Among respondents, 87% had three or more years' experience spanning many disciplines and topics including animal health (47.4%), microbiology (43.3%), dairy cattle (79.5%) and/or dairy products (68.4%). Fewer professionals had expertise related to human health (7.6%) or public health (9.4%); thus, most respondents with expertise in the zoonotic potential of *M. paratuberculosis* (63.2%) declared a background in animal health or related disciplines.

Estimation of significance of human exposure routes to *M. paratuberculosis*

Among potential human exposure routes for *M. paratuberculosis*, 144 respondents indicated direct contact with ruminants and consumption of dairy products (pasteurized and unpasteurized) as the most likely routes (Table 2). This was followed in ranking by living on a farm, consumption of beef, and water (municipal, well and recreational water use) as likely sources/routes. There were several comments on the lack of data to support a ranking, particularly for less studied food categories (e.g. produce and seafood). The majority of the topic specialists indicated that targeting mitigation strategies towards the dairy industry followed by beef, sheep and goats would likely have the most impact on reducing human exposure to *M. paratuberculosis* assuming that effective interventions are available (Fig. 1). Targeting drinking water and recreational water was considered to

Table 2. Results of topic specialist respondents' ranking[a] (median, 25th and 75th quartiles and maximum) of human and ruminant exposures to *M. paratuberculosis*

Variable	Median[a]	25th quartile	75th quartile	Maximum
Human exposure to *M. paratuberculosis* (n = 144)				
Direct contact with ruminants	10	3	20	98
Working/living on a farm	10	3	18	60
Human to human	0	0	1	45
Municipal treated water	2	0	5	80
Well water	2	0	6	80
Recreational water	5	0	10	80
Environment	5	0	10	50
Pasteurized dairy	10	3	25	90
Unpasteurized dairy	14	5	25	80
Beef	5	2	10	50
Pork	0	0	0	10
Chicken	0	0	0	5
Seafood	0	0	0	6
Produce	0	0	5	50
Ruminant exposure to *M. paratuberculosis* (n = 145)				
Contact with other ruminants	10	5	20	50
Young ruminant contact with mother	25	15	34	80
Unpasteurised milk	10	5	18	75
Trade/introduction of *M. Paratuberculosis*-positive animals into a herd	13	6	20	85
Farm environment	10	5	20	90
Drinking water	4	0	5	40
Recreational water	0	0	2	20
Environment outside the barn area	2	0	5	20
Feed	1	0	5	25
Wildlife	1	0	5	20

[a]Topic specialists allocated 100 points across exposure categories for each question to provide the relative weight of each exposure for humans and ruminants, respectively.

have moderate potential impact on human exposure to *M. paratuberculosis* if effective control was possible.

Overall public health impact of *M. paratuberculosis*

Among 154 respondents, 33.8% indicated that *M. paratuberculosis* poses a public health risk, 44.8% responded there is likely a risk, but the evidence is not sufficient or consistent enough to be sure, or the risk is low (14.9%) and a few respondents indicated there is no risk (3.9%) or don't know (2.6%). Univariate analyses using a partial proportional odds model of *a priori* selected variables indicated that having 'animal health expertise', 'working in academia' and the 'proportion of work dedicated to *M. paratuberculosis*' were all significant (positive) predictors of the respondent's answer to the risk to human health question. All remained significant in the multivariate partial proportional odds model (Table 3). Controlling for 'animal health expertise' and 'working in academia' which both further increased the odds of answering yes, the model predicted a significant increase in the probability of answering yes to this question with increasing proportion of work dedicated to *M. paratuberculosis* (Fig. 2).

When respondents were asked to consider various agri-food public health priorities in their region and then rank the importance of *M. paratuberculosis*, 24.2% of 157 responders ranked this issue as high priority, medium (40.1%), low (23.6%) or not a priority (12.1%). Using a heterogeneous choice model to evaluate associations between *a priori* selected respondent characteristics and rating of priority level, only the respondent's years of experience working on the *M. paratuberculosis* issue was a significant ($P < 0.05$) predictor and it violated the proportional odds assumption (Brant test $P < 0.05$) (Williams, 2010). The heterogeneous choice model that allows for select variables to violate the proportional odds assumption

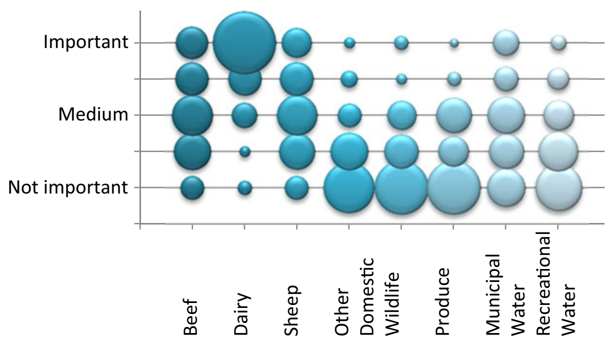

Fig. 1. Bubble plot showing topic specialist opinion on the importance of applying intervention efforts for controlling human exposure to *M. paratuberculosis* in various animal and environmental sectors, assuming availability of interventions.

Table 3. Partial proportional odds model, allowing proportion of work on *M. paratuberculosis* and animal health expertise to violate the proportional odds assumption (omodel test $P = 0.000$), while working in academia followed the proportional odds assumption

Variable	Coefficient	Standard error	*P* value (*z*)
% work 25–50	−0.988	0.403	0.014
% work 50–75	−1.683	0.575	0.003
% work >75	−0.949	0.456	0.038
Work in academia	−0.958	0.387	0.013
Risk to human health? (proportional odds)			
Yes			
Animal health expertise	−1.144	0.400	0.004
Constant	2.177	0.409	0.000
Likely			
Animal health expertise	−0.779	0.446	0.081
Constant	−0.312	0.356	0.382
Minor risk			
Animal health expertise	−1.101	0.894	0.218
Constant	−2.004	0.555	0.000

The models' Wald χ^2 with 148 observations was *P*-value = 0.004. The constant in this model is a non-academic, with no animal health expertise working on *M. paratuberculosis* <25% of the time.

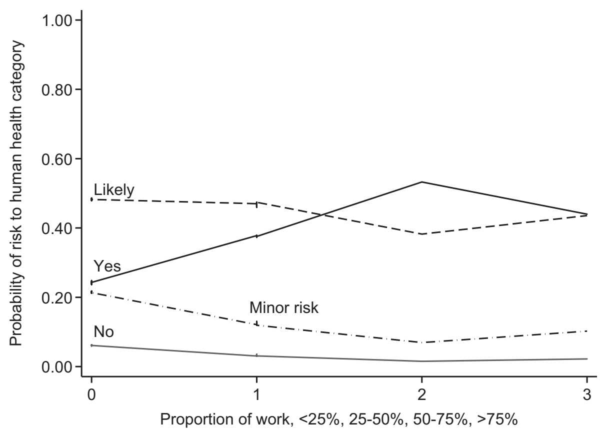

Fig. 2. Graphical depiction of the relationship between the proportions of participating topic specialist's work dedicated to *M. paratuberculosis* (<25%, 25–50%, 50–75% and >75%) and the probability of answering one of four options for whether there is a risk to human health (high, likely, minor risk, no), modelled using a partial proportional odds model also controlling for working in academia and expertise in animal health.

and instead vary for different outcome categories was the best fit to the data (Table 4). The relationship between ranking of *M. paratuberculosis* as a public health issue compared to other agri-food public health issues within the respondents region and years of experience working in this area is shown graphically in Fig. 3. There was a significant and opposite correlation between the extreme answers: 'high' and 'low' priority and years' experience. There was a small probability that respondents chose 'not a priority'

Table 4. A heterogeneous choice model (heteroscedastic ordered logistic regression), allowing years of experience with *M. paratuberculosis to* be heteroscedastic (Brant test $P < 0.05$)

Variable	Coefficient	Standard error	*P* value (*z*)
Public health ranking			
Years of experience	−1.220	0.415	0.003
lnsigma			
Years of experience	0.343	0.143	0.017
/ <3 years	−3.591	0.892	0.000
/ 3–10 years	−0.519	0.446	0.244
/ >10 years	1.755	0.596	0.003

The models' Wald χ^2 with 154 observations was *P*-value = 0.0002. The constant in this model is <3 years of experience.

and a high probability that they selected 'medium priority', and both of these latter choices were unrelated to years' experience on this issue.

Respondent answers to ranking *M. paratuberculosis* risk to human health compared to the overall importance of *M. paratuberculosis* as a public health issue had a high Cronbach's alpha (0.763), an indicator of internal consistency. No other questions were considered appropriate for the evaluation of internal consistency.

Mitigation strategies

Among 139 respondents, 92.1% responded that agri-food public health authorities should be allocating resources to keep abreast of new evidence related to *M. paratuberculosis,* in terms of both zoonotic potential and mitigation options. However, only 50% of respondents (n = 149) thought that government should be involved in implementing new interventions based on minimizing human exposure to *M. paratuberculosis.* The currently available programmes (summarized in the next paragraph) were considered appropriate by 68.4% of respondents (n = 114).

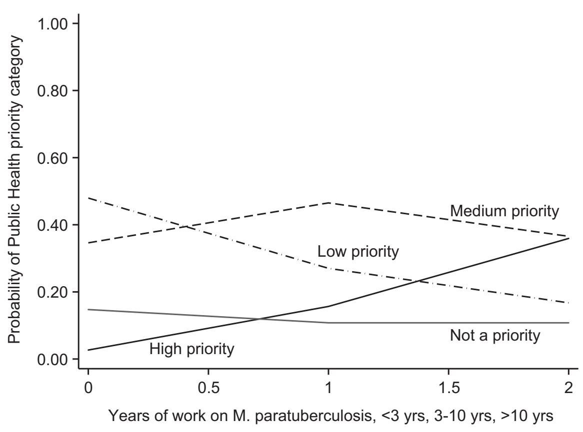

Fig. 3. Graphical depiction of the relationship between the years of experience among participating topic specialists working on *M. paratuberculosis* (<3, 3–10, >10 years) and the probability of each ranking option for *M. paratuberculosis* as a public health issue (high, medium, low and not a priority), modelled using a heterogeneous choice model controlling.

In an open-ended question, respondents described various forms of agri-food government and/or industry control programmes or regulations targeting the control of *M. paratuberculosis* along the food chain (n = 111). Respondents were asked to list mandatory and voluntary programmes they were aware of including commodity, country and a brief programme description. Mandatory programmes (42 responses) were reported in Denmark, the Netherlands, Austria, N. Ireland, Sweden, Australia and Japan. With the exception of the Netherlands, these programmes focused on test and cull of *animals testing positive for M. paratuberculosis infection*, movement restrictions and mandatory notification of Johne's disease cases. The Netherlands was mentioned by several respondents as having the only true *M. paratuberculosis* control programme. The Dutch Paratuberculosis Milk Assurance Programme for dairy cattle tests bulk milk regularly (Weber et al., 2008), and a positive test triggers herd level control actions. There were many voluntary *M. paratuberculosis* control programmes mentioned (69 responses), which largely focus on on-farm prevention and control for dairy cattle with the exception of a caprine programme for Spain and ruminant programmes for the UK, Australia and New Zealand. For most of these programmes, respondents indicated that uptake and implementation were spotty in their region and the main drivers were potential economic benefits of improved animal health and production. Countries mentioned as having these programmes included Australia, Belgium, Canada, Denmark, France, Iran, Ireland, Japan, the Netherlands, New Zealand, Norway, Scotland, Spain, Sweden, United Kingdom and United States. Most of these programmes were relatively new and 'rolled out' between 2009 and 2012.

The routes of ruminant exposure to *M. paratuberculosis* ranked most highly by respondents were dam–calf transmission, contact with other ruminants and introduction of a *M. paratuberculosis*-infected cow to the herd (Table 2). Respondents indicated that more work on intervention programmes is warranted (n = 75) and suggested targeting the dairy industry (98.7%), meat industry (80.0%) and environmental contamination mainly from agricultural run-off (54.7%).

Open-ended questions requesting information on programmes for monitoring and surveillance of *M. paratuberculosis* or Johne's disease along the food chain received 95 responses; however, most described the same voluntary control programmes described in the previous question. Respondents reported surveillance programmes in Norway and Sweden for small ruminants and in Denmark for bovine milk. For many countries, respondents reported that Johne's disease is notifiable, but not an infection for which they routinely screen animals. One respondent noted that Japan has a policy where they may require proof of freedom from *M. paratuberculosis* among imported and domestic animals (Momotani, 2012).

Knowledge gaps

Respondents identified the most important knowledge gaps, which should be addressed to better position *M. paratuberculosis* within the public health agenda. The most frequently cited gap was uncertainty in the role of *M. paratuberculosis* in human disease (62 responses) including better understanding of the pathogenesis (37), epidemiology (10), infectious dose (2), transmission (4), genetic susceptibility (6) and public health impact (3). The lack of 'good' (sensitive and specific) and affordable diagnostic tests for monitoring *M. paratuberculosis* in ruminants, other animals, humans and the environment (13 responses) was frequently stated as an important barrier for developing effective prevention and control programmes in ruminant populations. Other important knowledge gaps mentioned include the development of efficient and cost-effective on-farm mitigation strategies (11) and the need for further research into various agri-food sources of *M. paratuberculosis* exposure for humans including dairy (4), shell fish (1), produce (1) and environment–water (7). Identified research gaps for Johne's disease (8) included a better understanding of genetic susceptibility and immunopathogenesis, development of vaccines to *M. paratuberculosis* for ruminants that do not interfere with skin testing for bovine *M. tuberculosis* (three responses), and an improved understanding of the transmission cycle (2) for *M. paratuberculosis*.

Discussion

Researchers have extensively investigated the roles of *M. paratuberculosis* as a cause of Johne's disease, a microbial hazard of potential risk to public health and as an environmental contaminant. Within the context of public health, most research has focused on *M. paratuberculosis* as a foodborne hazard that could pose a risk to humans via exposure from raw and inadequately pasteurized milk and dairy products, and more recently via other foods (e.g. meat, produce) and drinking water. This questionnaire targeted and received responses from topic specialists from all regions of the world working on various aspects of the *M. paratuberculosis* issue to reveal their insights and views on various zoonotic and public health aspects of this topic. The results demonstrated the variability in topic specialist's opinions on the overall public health impact of *M. paratuberculosis* and highlighted many knowledge gaps pertaining to the role of *M. paratuberculosis*' role in human disease and controlling the infection in ruminants worldwide. Some of the critical barriers to consensus on the pathogen's *zoonotic* potential include a lack of evidence for a dose–response gradient and temporal relationship with exposure (Behr and Collins, 2010). Many knowledge gaps likely remain due to well-known challenges involved with studying chronic illnesses that arise following lifelong exposure and long latency periods between exposure and disease development, similar to what has been observed in ruminants that develop Johne's disease. These gaps in our understanding continue to be a driver for research in this area, but they also contribute to the reason *M. paratuberculosis* is not a highly ranked public health issue.

The majority of topic specialists agreed that *M. paratuberculosis* is likely a risk to human health and that *M. paratuberculosis* is a high- or medium-priority agri-food public health issue. Responses to the two questions eliciting this information had a high Cronbach's alpha, suggesting that they were likely measuring the same construct (Ritter, 2010). However, many topic specialists also indicated there is incomplete evidence on which to base this conclusion and the effect of decreasing human exposure to *M. paratuberculosis* is unknown. This ranking did not vary significantly by geographical location, but we did find a significant correlation between the commitment of the topic specialists to the *M. paratuberculosis* issue determined by years spent working on this issue or by the proportion of their work dedicated to the issue, and their ranking of the risk to public health. This is an indication that survey respondents with extensive experience in *M. paratuberculosis* may be biased in their views or that their greater knowledge of the pathogen provides a more informed opinions.

There were many knowledge gaps highlighted by topic specialists, many of which will require further research. The most highly ranked sources of *M. paratuberculosis* for humans were considered to be dairy products and ruminants, and in recent years, increasing research has demonstrated that meat, produce and water may also be contributing sources, highlighting a shift in opinion and research focus since 2005 (Waddell et al., 2008; Eltholth et al., 2009; Elliott et al., 2014). Further evaluation of sources of *M. paratuberculosis* for humans and verifying effectiveness of food safety interventions (e.g. pasteurization of dairy products) were identified knowledge gaps that should be recommended research priorities (Grant et al., 2005). Respondents indicated that control of Johne's disease on-farm (dairy and meat, small and large ruminants) will have the greatest impact by decreasing contamination of animal-derived food products as well as the local environment and water (recreational and drinking) that is subject to animal faecal contamination, thus decreasing human exposure from many possible sources. For humans, there are few effective interventions not already in use to limit exposure; therefore, it is hard to justify allocating resources to *M. paratuberculosis* programmes when many other known foodborne pathogens such as *Salmonella* and *Campylobacter* are also competing for the same resources and their causal association with human illness and burdens of illness is much more definitive than in the case of *M. paratuberculosis.* Thus, our precautionary recommendation is that concerted research efforts should continue to address the critical knowledge gaps noted throughout this study and industry is encouraged to continue efforts to develop cost-effective disease control programmes for affected ruminants, which will decrease *M. paratuberculosis* exposure for many species (Nacy and Buckley, 2008).

Johne's disease knowledge gaps proposed by topic specialists include genetic susceptibility of animals, immunopathogenesis, understanding the *M. paratuberculosis* transmission cycle and how some cattle seem to clear themselves of the infection. Some topic specialists indicated that the development of an effective vaccine that does not cross-react with tests for tuberculosis and reduces faecal shedding of *M. paratuberculosis* in addition to preventing clinical disease would be an effective intervention and should be a priority (Bannantine et al., 2014).

Knowledge of the global burden of Johne's disease in ruminant populations is also sparse and in some cases conflicting information exists. This paucity of evidence has previously been cited as a reason countries chose to develop or not develop control programmes for Johne's disease (Nielsen, 2009). Topic specialists provided details of a few mandatory and voluntary Johne's disease control programmes from various countries. This list is likely not exhaustive, perhaps due to a lack of representation from certain countries, or as Nielsen noted, a lack of knowledge and available literature on these programmes (Nielsen, 2009). The main drivers for adoption of these mostly voluntary on-farm programmes are potential direct and indirect economic benefits to the agricultural from improved animal health and productivity and perceived enhanced product quality from *M. paratuberculosis*-free sources (Sorge et al., 2010a,b; Bhattarai et al., 2013). Many of these on-farm programmes focus on management recommendations to reduce the spread of infection among ruminants (e.g. biosecurity) rather than enhancing immunity (e.g. vaccination). Respondents reported that test and cull components of the on-farm control programmes have moved towards integrated risk-based approaches to testing in an effort to make the control programmes affordable for producers; however, poor diagnostic test sensitivity and specificity, particularly with respect to detection of subclinically affected animals, limits programme effectiveness (Behr and Collins, 2010; Whist et al., 2014). Thus, it is critically important to improve diagnostic tests for *M. paratuberculosis* that are capable of detecting subclinically infected ruminants, as well as infection in other animals and humans and contamination in the environment (Schukken et al., 2009; Gardner et al., 2011; Geraghty et al., 2014). To improve widespread adoption of Johne's disease control programmes, programme evaluations are needed to demonstrate their cost-effectiveness (Bhattarai et al., 2013; Wolf et al., 2014).

Conclusion

This survey of the professional community of *M. paratuberculosis* topic specialists indicates a general consensus that humans are exposed to *M. paratuberculosis* via direct contact with ruminants and consumption of dairy products, but also through consumption of drinking water (treated and untreated) and other foods (beef). The topic specialists indicated that the relative importance of these vehicles still requires investigation and there is still uncertainty about the role of *M. paratuberculosis* in human disease. Thus, monitoring scientific advancements on this issue and effective interventions, as well as encouraging industry to develop cost-effective control programmes in the interest of animal health management, while simultaneously being proactive on a potential public health issue was considered appropriate by the topic specialists and is similar to the recommendations from previous expert colloquia (Anon 2000; Nacy and Buckley, 2008,Weir et al., 2010).

Acknowledgements

The authors would like to thank Dr. Ian Young and Dr. Ulrike Sorge, Judy Greig, Mariola Mascarenhas and Mai Pham for their expertise in the development and pretesting of this survey. We are especially grateful to all the topic specialists who took the time to complete our questionnaire and provide insight into the *M. paratuberculosis* issue and its potential impact on public health.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Public health impact of *Mycobacterium avium* ssp. Paratuberculosis: A survey of expert opinion