The Paratuberculosis Newsletter

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Note from the Editor

I was attending the colloquium at the time this newsletter should have been circulated so unfortunately it is a month late. In this issue, the two exceptional graduate students who were awarded the Richard Merkel award reflect on their experiences at the 14th ICP and there is a commentary on the USDA stewardship of MAP.

Kumi de Silva

IAP business

14th International Colloquium on Paratuberculosis





Emeritus awards were presented to Murray E. Hines (USA) (left) and Douwe Bakker (Netherlands) (right) at the 14th ICP held in Cancun, Mexico from June 4-8 2018. At the meeting we farewelled Ramon Juste who was President of the IAP for the past 11 years and welcomed our new President Vivek Kapur.



Abstracts from the colloquium are now available in the Publications section of the IAP website at https://protect-au.mimecast.com/s/4AoAC2xZYvCxxBqQun2AWy?domain=paratuberculosis.net

Equity Access Policy

A working group has been formed to draft an Equity and Access Policy for the Association. Members of the group are Kumi de Silva, Herman Barkema and Marta Alonso Fernandez. There will be regular updates to inform the membership about progress and we welcome your input.

Financial Report



International Association for Paratuberculosis

112 Barnview Road Kennett Square, PA 19348 USA

Financial Report- May 16, 2018 Checking Money Market PayPal Total Open (1/1/17) \$43,579.17 \$14,075.82 \$ 1,938.95 \$ 59,593.94 May 16, 2018 \$47,114.17 \$14,184.14 \$ 2,216.29 \$ 63,515.00 INCOME 1/1/18 to 5/16/18 5/17/18 to 12/31/18 Annual Total Dues \$ 4,100.00 \$ \$ S \$ Interest s 2.32 Royalties s 11.40 Total \$ 4113.72 \$ \$ EXPENSES 1/1/18 to 5/16/18 5/17/18 to 12/31/18 Annual Total PayPal /Wire fees 192.66 \$ \$ \$ Total \$ s s 192.66

Respectfully Submitted,

Raymond W. Sweeney, VMD Secretary-Treasurer

Retrospective Assessment of USDA Stewardship of *Mycobacterium avium* subspecies *paratuberculosis* Dilemma

Gilles RG Monif

Abstract:

Mycobacterium avium subspecies *paratuberculosis* (MAP) is a significant pathogen for herbivores including cows, goats, and sheep. MAP produces a chronic granulomatous infection of the gastrointestinal tract (Johne's disease) in domesticated herbivores. Once MAP's presence was documented in pasteurized milk and milk-based food products, USDA's primary focus changed from attempting to diminish MAP's effect on producers' bottom line to protection of the quality reputation of milk and milk products. In addressing MAP's potential threat to agribusiness, USDA made a number of administrative decisions that have inflicted substantial long-term damage to the dairy industry.

MAP and Agribusiness

Mycobacterium avium subspecies *paratuberculosis* (MAP) infection of domestic animals has long been a major veterinary challenge. In beef cattle, MAP infection results in lower cow fertility, lower calf weight, and lower weaning calf weight adjusted to 295 days (1). MAP ELISA positive animals have a 10-17% reduction in slaughter weight. If the animal's fecal culture contains MAP, the reduction in slaughter weight can be as high as 31% (2).

MAP infection extracts an added toll from dairy producers. MAP-infected cows exhibit a decrease in milk production ranges from 0.02-1 kg/day. Heavily infected cows decrease their milk production by 4 kg/day (3-5). A large Danish study documented that declines in reproduction, milk production, and fat content attributable to MAP function over such a long period of time that they tend not to be identified by producers (6). With costs of animal maintenance increasing, any decrease in the volume and/or fat content of the milk produced has a negative impact on a producer's bottomline. This "MAP Milk Tax" is directly proportional to the number of infected animals within the herd (7).

USDA/MAP Interface

In the mid-1990s, scientific studies documented the presence of a bovine pathogen, *Mycobacterium avium* subspecies *paratuberculosis*, in both raw and pasteurized

milk (8,9). Prior to 2001, USDA was focused on addressing the negative economic impact MAP had on herd health (10-11). The presence of a documented bovine pathogen within the nation's food supply altered USDA's primary focus from lessening MAP's negative impact on producers to protection of the quality reputation of milk and milk products.

In 1997, USDA published a controversial paper claiming that U.S. high temperature/short duration pasteurization effectively destroyed MAP (12). The paper's methodology was so constructed as to create a predictable outcome. Despite scientific criticism, USDA never retracted or repudiated this paper.

In 2000, this USDA's publication was introduced into evidence in Congressional hearings that dealt with whether or not a viable bovine pathogen in milk and milk products constituted a potential public health hazard. USDA was chosen over the National Institutes of Health to make this determination.

In 2000, USDA-APHIS had implemented the Uniform Program Standards for the Voluntary Bovine Johne's Disease Control Program.

In 2002, USDA instituted a five year Johne's Disease Prevention Dairy Herd Demonstration Program in order to study the problem. At that time, 20-30% of all U.S. dairy herds had MAP infected animals.

In 2005, 49% of 51 brands of infant formula manufactured by ten different producers in seven different countries were demonstrated to contain MAP DNA (13).

In 2007, the National Health Monitoring System study of 515 dairy farms demonstrated that 31.2% of the participating dairy farms had bulk tank milk that tested positive for MAP. USDA acknowledged that an estimated 70% of U.S. dairy herds then contained MAP infected animals (14).

On October 23, 2008, USDA released its National Johne's Disease Control Program Strategic Plan. Its three specific goals were:

- 1. Reduce the prevalence of MAP/Johne's disease in the national herd;
- Reduce the impact of Johne's disease on individual herds; and
- 3. Reduce the risk of introducing Johne's disease to uninfected herds (15).

Central to the herd monitoring schema proposed by the National Johne's Disease Control Program was identification and removal of infected animals from production. Both of these objectives had already been effectively undermined by prior USDA decisions as they related to MAP diagnostic testing and failure to secure compensation for producers who removed infected animals from production.

In 2012, the World Organization for Animal Health (OIE) proposed having paratuberculosis (diseases in animals caused by MAP) removed as a disease entity from the Terrestrial Animal Health Code. The rationale put forth by OIE to validate this action was that *"because MAP infection is so widespread, continued recognition of MAP as an animal pathogen would only cause economic losses through the restrictions in international animal trade"*.

Today, it is, more probable than not, that every large dairy herd in the U.S. contains infected animals. In some herds, the number of infected animals constitutes a majority of the animals. The greater the number of infectious animals within a dairy herd, the greater is the probability of viable MAP being in bulk milk obtained from these animals.

USDA's MAP Directives

In its stewardship of the MAP dilemma, USDA made a number of administrative decisions that accelerated the dissemination of MAP within milk-producing herds.

USDA decided that MAP was THE cause of Johne's disease and that other mycobacteria within the *Mycobacterium avium* subspecies *avium* branch evolutionary tree were non-pathogens (16-17).

MAP, having evolved from *Mycobacterium avium* subspecies avium (MAA), it was highly probable that, between MAA and MAP, pathogenic polymorphic genomic variants capable of causing Johne's disease existed.

The decision to render irrelevant mycobacteria not possessing the IS900 sequence was in blatant disregard of peer-reviewed scientific publications to the contrary. Despite evidence of heterogeneity among MAP isolates ()and evidence that other mycobacteria on the evolutionary transition from *Mycobacterium avium* subspecies *avium* (MAA) to MAP caused Johne's-like disease in domestic animals (18-35), USDA obligated the diagnostic test manufacturers to construct their tests to specifically identify MAP's IS900 genomic insertion.

USDA further distorted the possibility of identifying MAP infection within milk producing herds by allowing MAP diagnostic tests to be a statement of probability of developing Johne's disease and not a statement of the presence or absence of anti-MAP antibodies. USDA approved methodology that tests positive only when a high level of anti-MAP antibodies is present. A negative MAP ELISA test designation does not address the issue of whether or not a given animal is or ever has been infected by MAP. Monif and Williams demonstrated a 7.3% - 13.5% positive correlation between a positive commercial MAP ELISA test and the presence of MAP in the animal's feces (36). McKenna et al. showed that the commercial MAP ELISA tests identified only 6.8% to 8.8% of tissue positive cattle (37). Pinedo et al. demonstrated that MAP ELISA tests had a poor correlation with the documented presence of MAP in the corresponding milk. Cows whose milk tested positive for MAP had negative or inconclusive MAP titers in 23.5% and 11.8% of the cases respectfully (38). The ability to attribute such findings to post-milking fecal contamination is undermined by necropsy documented cases of Johne's disease with positive agar immunodiffusion (AGID) tests that serologically tested negative in MAP ELISA tests (39).

By certifying MAP ELISA tests to be but a statement of probability of developing Johne's disease rather than a valid measurement of the presence or absence of MAP antibody, the USDA certified MAP ELISA tests grossly underestimated the number of MAP infected animals. Once a MAP infected animal is introduced, the organism becomes difficult to eradicate from the production area.

A major error of omission has been USDA's long standing failure to make an animal's MAP serological status part of an animal's certificate of health (40-41). USDA is responsible for the U.S. national standards for animal product warranty. Quality of merchandise is primarily addressed through the animal's health certificate. The Code's language in 9 CFR chapter 1 sub-chapter C restricts the inter-state movement of infected livestock (42). Revisions to part 71 and 80 of the Code of Federal Regulations (CFR) were intended to specifically restrict the interstate movement of MAP-infected animals except to recognized slaughter establishments. By not requiring a statement on the health certificate as to whether an animal is or is not infected by MAP, USDA enhanced the ability of MAP infected animals to be shipped across state and, more importantly, national borders.

The United States has been a leading global exporter of MAP infected breeding animals. Fifty-four percent of MAP diseased animals detected by the Japanese Animal Quarantine Service came from the United States (43).

Discussion

USDA's decision to allow its certified MAP serum tests to identify but a limited segment of MAP infected animals coupled with the failure to indicate an animal's MAP status on its certificate of health has resulted in, not only the introduction of infected animals into previously uninfected herds, but a massive increase in the prevalence of MAP infection within the U.S. herds that then translates into a progressive increase in the occult Milk Tax paid by producers.

Ironically, USDA succeeded in answering the 2001 Congressional mandate determination of whether or not viable MAP isolates in milk constituted a public health hazard. USDA's administrative decisions facilitated MAP being able to theoretically infect a sizeable part of the U.S. population.

MAP receptor sites line the entire small bowel (44). The probability of an individual having been infected by MAP is a function of diet and time. What the resultant experiment in nature demonstrated is that for individuals with intact immunity, human MAP infection is of apparent little to no significance. For individuals with advanced immunodeficiency syndromes, MAP can function as an opportunistic, pathogenic mycobacterium. For neonates with little to no established acquired immunity, MAP infection puts in place the immune mechanism for the future development of Crohn's disease (45-47).

Conclusion

By its actions, USDA has put the dairy industry in the United States at increasing risk. Confronted with constricted profit margins and rising costs, most small dairies that can implement quality control are rapidly disappearing. Larger dairies have had to resort to volume expansion for survival. Increasing cow density per acre adds to the occult MAP Milk Tax paid only by producers.

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Delegates at the 14th ICP in Cancun, Mexico



Reflections of the 14th ICP by the Richard S. Merkel awardees

Caroline Corbett

(University of Calgary, Canada)



Travelling to the beautiful Riviera Maya for the 14th ICP this year was an incredible experience made possible to me by the

Richard S. Merkal award. From the very moment that I arrived at the hotel, I was overcome with the excitement of my fellow research colleagues to discuss the progress that has been made in paratuberculosis research. Although this progress can be slow at times, the commitment and eagerness to share ideas, push boundaries and ask tough questions to formulate new solutions to the challenges facing the production animal industries around the world, is infectious.

The days were filled with oral presentations that stimulated conversations at the coffee and meal breaks, that would continue into the evening at dinners around the various restaurants of the Hard Rock Hotel. Stepping from the cool air conditioning of the conference center out to the warm tropical air didn't stop colleagues from discussion the various poster presentations, and future plans for improving control programs around the world.

I started my research in paratuberculosis over 4 years ago under the supervision of Drs. Herman Barkema and Jeroen de Buck at the University of Calgary. For the first 3 years of my PhD, the primary focus of my research was on calf-to-calf transmission, currently overlooked in the industry control programs. However, I picked up some orphan projects regarding environmental sampling and prevalence estimates in Canada, and I could not be more excited at the direction these chapters of my thesis took me. I hope that control programs can evolve as new research comes to light, and new collaborations can be formed to answer the difficult research questions.

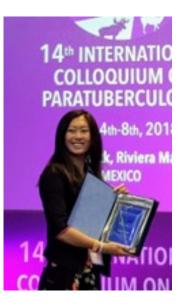
Now that I have completed my PhD, I hope to find myself in a position where I can continue to help translate and interpret scientific results to guide decision makers, industry and stake holders, and researchers towards making informed decisions regarding infectious diseases and control.

Lucy Luo (University of Calgary, Canada)

Ever since I started my MSc project creating a marked vaccine strain for paratuberculosis in September 2015 with Dr. Jeroen De Buck, I had envisioned myself presenting at the biggest international conference in this field. I feel so fortunate to have fulfilled this dream at the 14th International Colloquium on Paratuberculosis, which was made possible by the Richard Merkal Memorial Fellowship. It was such an incredible honour to share my research with the very people that inspired me throughout my graduate journey, and it was extremely rewarding to see how supportive and engaged everyone was in my work. I met so many remarkable people in the field of paratuberculosis research throughout the conference. This made me equally nervous and excited; I had been following everyone's work for 2.5 years, so to finally meet them in person and share my work with them was an absolute privilege. It was interesting speaking with students and professors from other countries who were all taking different approaches to the same issues in the field. I also thoroughly enjoyed learning about the emerging research in other aspects of the field that I had not been exposed to enough prior. Everyone was so friendly and excited about their work, which made the conference an extremely positive experience for me. The fact that the conference was held in an all-inclusive resort in Mexico added to the positive experiences shared and relationships formed, not only in the convention center but also at fancy dinners and the beach!

As part of my research project, I performed a calf infection trial and worked closely with producers, veterinarians. and industry representatives. Throughout this experience, I became increasingly interested in pursuing a career in veterinary medicine, so I applied to the DVM program at the University of Calgary as I was completing my MSc degree. Immediately following my presentation at ICP, I had received news that I was accepted into the program! This week was certainly unforgettable; I graduated with my MSc degree on the opening day of ICP, then had the honour to present in front of an incredible group of researchers, followed by my acceptance into the DVM program. Thanks to paratuberculosis research, I finally found my passion in life. I had an incredible time meeting students and professors at the conference, many of whom were veterinarians as well, so attending and presenting at ICP was the perfect transition from my MSc to my DVM studies. A major theme I found at ICP was the importance of collaboration; this experience has undoubtedly shaped me into a better scientist and will help me approach veterinary school with a collaborative mind set.

Overall, my attendance at this conference was an excellent finale to my MSc degree. I had the privilege to share my work with the top researchers in the field, meet the professors who inspired me along the way, and make strong connections for the future. My outlook on the research in this field was broadened and I have a better understanding of the control programs in other countries. I am so grateful to the Richard Merkal Memorial Fellowship, without which all of this would not have been possible.



Upcoming events

- The <u>30th World Buiatrics Congress</u> will be held in Sapporo, Japan from 28 Aug 1 Sept 2018. The Scientific program will cover issues on cattle health and reproduction. Topics will include a wide range of production diseases, major infectious diseases, calves and new-born diseases, tropical epidemiology, public health and food security and other animal health and management problems.
- The <u>6th European Veterinary Immunology Workshop</u> (EVIW) will be held from 5-7 September 2018 in Utrecht, the Netherlands. Plenary and concurrent session topics include: Innate immunity, Adaptive immunity, Infection and immunity, Vaccination, Clinical immunology, Allergy, Mucosal immunology and the microbiome in relation to immune responses
- The 15th ICP will be held Dublin, Ireland in 2020
- The 16th ICP will be held in Jaipur, India in 2022

Paratuberculosis News

The University of Sydney is seeking a Professor (Level E) in Production Animal Health at the for the Faculty of Science, Sydney School of Veterinary Science. Further information can be found <u>here</u>.

Closing date: 11.30pm (AEST) Sunday 5 August 2018

Recent publications (March-June 2018)

Abdellrazeq GS, Elnaggar MM, Bannantine JP, Park KT, Souza CD, Backer B, Hulubei V, Fry LM, Khaliel SA, Torky HA, Schneider DA, Davis WC. 2018. <u>A Mycobacterium avium subsp. paratuberculosis relA</u> <u>deletion mutant and a 35 kDa major membrane protein elicit development of cytotoxic T lymphocytes</u> with ability to kill intracellular bacteria. Vet Res 49:53.

Aboagye G, Rowe MT. 2018. Optimisation of decontamination method and influence of culture media on the recovery of Mycobacterium avium subspecies paratuberculosis from spiked water sediments. J Microbiol Methods 150:24-28.

Albarrak SM, Waters WR, Stabel JR, Hostetter JM. 2018. Evaluating the cytokine profile of the WC1(+) gammadelta T cell subset in the ileum of cattle with the subclinical and clinical forms of MAP infection. Vet Immunol Immunopathol 201:26-31. Azimi T, Nasiri MJ, Chirani AS, Pouriran R, Dabiri H. 2018. <u>The role of bacteria in the inflammatory bowel</u> disease development: a narrative review. Apmis 126:275-283.

Bach E, Raizman EA, Vanderwal R, Soto P, Chaffer M, Keefe G, Pogranichniy R, Bach H. 2018. <u>Immunogenicity of PtpA secreted during Mycobacterium avium ssp. paratuberculosis infection in cattle</u>. Vet Immunol Immunopathol 198:1-5.

Bach H, Richard-Greenblatt M, Bach E, Chaffer M, Lai W, Keefe G, Begg DJ. 2018. <u>Protein Kinase G</u> Induces an Immune Response in Cows Exposed to Mycobacterium avium Subsp. paratuberculosis. Biomed Res Int 2018:1450828.

Barratt AS, Arnoult MH, Ahmadi BV, Rich KM, Gunn GJ, Stott AW. 2018. <u>A framework for estimating</u> society's economic welfare following the introduction of an animal disease: The case of Johne's disease. PLoS One 13:e0198436.

Bates A, O'Brien R, Liggett S, Griffin F. 2018. <u>The effect of sub-clinical infection with Mycobacterium</u> avium subsp. paratuberculosis on milk production in a New Zealand dairy herd. BMC Vet Res 14:93.

Begg DJ, Plain KM, de Silva K, Gurung R, Gunn A, Purdie AC, Whittington RJ. 2018. <u>Immunopathological</u> changes and apparent recovery from infection revealed in cattle in an experimental model of Johne's disease using a lyophilised culture of Mycobacterium avium subspecies paratuberculosis. Vet Microbiol 219:53-62.

Bo M, Niegowska M, Arru G, Sechi E, Mariotto S, Mancinelli C, Farinazzo A, Alberti D, Gajofatto A, Ferrari S, Capra R, Monaco S, Sechi G, Sechi LA. 2018. <u>Mycobacterium avium subspecies paratuberculosis and</u> <u>myelin basic protein specific epitopes are highly recognized by sera from patients with Neuromyelitis</u> optica spectrum disorder. J Neuroimmunol 318:97-102.

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