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The Paratuberculosis Newsletter

The official publication of the International Association for Paratuberculosis

INSIDE THIS ISSUE

Note from the Editor

Dear IAP members,

In your hands or on your screen the second issue of the Paratuberculosis Newsletter in 2025.

In the previous issue we advanced that a Communication Committee within the Board members had been formed for the current term, working on new channels to enhance communication including the publication of newsletters and a redesign of the association's website. In this issue we have expanded on this with a piece from Alejandra Colombatti (see pages 3-4).

In the Upcoming Events section, a small update on our next ICP in Germany (see page 5).

In this issue we are extremely lucky and delighted to have contributions from two long-standing IAP members with a substantial experience in paratuberculosis and an impressive scientific record. This is Dr. William Davis with a review on paratuberculosis and Crohn's Disease research that calls for reflection on where we are now and what we can do such as IAP promoting vaccination (see pages 6-10). And second mentioned, but not least Dr. Richard Whittington with an advance of one of his latest studies on paratuberculosis control by faecal PCR (see pages 11-12). Please don't miss these valuable articles!

Paratuberculosis research is advancing rapidly with over 25 new papers that have seen light since March 2025 so there's plenty of reading to stay informed (see pages 14-16).

As always, we encourage members to connect with the Association's Officers or Board members to share suggestions and feedback to help strengthen our community.

Best wishes,

Natalia Elguezabal

Contribute with your photos

Please consider sharing those photographs you have for publication in the next Newsletter! Let's display the diversity in ruminants, their environments, and where our members are conducting research, science outreach or just having a nice walk.

Cover photograph taken by Fernando Lopitz: Latxa breed sheep grazing in Derio, Bizkaia (Basque Country).

Strengthening Connections, Amplifying Voices: A Note on Communication from the New Board

By Alejandra Colombattii

Effective communication is vital to our Association's growth, with 83 members and a steadily aging membership, the IAP faces a challenge shared by many scientific societies: how to stay vibrant, inclusive, and globally representative in a rapidly changing research environment. Our current offerings—primarily the biannual International Colloquium on Paratuberculosis (ICP), a longstanding website, and a periodic newsletter—are no longer enough to maintain engagement, attract new members, or reflect the diversity and innovation in paratuberculosis research today.

The Communication Committee's mission supported by the entire Board is to enhance member engagement, increase the visibility of IAP, especially among early-career researchers, colleagues from low- and middle-income countries (LMICs), and underrepresented regions, and to create new opportunities for engagement beyond the biennial meeting.

Recognizing the importance of effective communication, the committee focuses on several key initiatives:

- **Revamping the IAP Website:** A new website is currently in development, aiming to include updated resources. This platform will serve as the digital heart of the Association.

- **Enhancing the Newsletter:** We want the newsletter to evolve into a reliable summary of IAP news and the latest developments in paratuberculosis science—shared in a brief, digestible format that respects your time but keeps you connected.

- **New Ideas for Member Engagement Activities:** In years without an ICP, we plan to host at least one virtual meeting or seminar for our members. These gatherings can help foster discussion, strengthen our network, and ensure members are informed and heard.

- **Improving Two-Way Communication:** We recently conducted a survey published in the March newsletter to better understand the interests and needs of our members. While most current members are senior researchers with limited interest in social media, they highlighted a clear need for more value between conferences. Some suggested developing a member-only social media group or discussion forum—ideas we are currently exploring, possibly via the new website or platforms like Slack.

- **Launching a Social Media Presence:** Recognizing the habits of younger scientists, we are discussing starting with Instagram by the end of this year as our primary channel to share highlights from research, committee updates, and key takeaways from the paratuberculosis literature.

Strengthening Connections, Amplifying Voices: A Note on Communication from the New Board (continued)

We are just getting started, and we need your help. To make these goals a reality, we invite all members to help generate content, share ideas, and support the committee's initiatives. Whether it's contributing a short summary of your latest paper, sharing photos from the field, or mentoring a junior member via a virtual event, every action and idea helps us grow.

Please email us at newsletter@paratuberculosis.com if you have ideas, suggestions, or want to get involved with the Communication Committee.

Your participation could make a difference—not just for the IAP but also for the future of paratuberculosis research.

Upcoming Events

In the next months many attractive meetings where we can share our advances in paratuberculosis, learn from others, and raise awareness on this disease will be celebrated. Check out this selection.

IVIS 2025. International Veterinary Immunology Symposium. 11-14 August, 2025. Viena, Austria (https://ivis2025.org/)

76th EAAP. European Association for Animal Production. 25-27 August, 2025. Innsbruck, Austria . (https://eaap2025.org/)

ESVP-ECVP CONGRESS. Joint meeting of the European Society of Veterinary Pathology and European College of Veterinary Pathologists. 27-30 August, 2025. Turin, Italy. (https://www.esvp-ecvp-estp-congress.eu/)

7th ECVM. International Conference of the European College of Veterinary Microbiology. 10-12 September 2025. Berlin, Germany. (https://evis.events/event/524/)

4th International Precision Dairy Farming Conference. 3-5 December 2025. New Zealand. (https://www.precisiondairyfarmingconference.nz/)

33rd WBC. WORLD BUIATRICS CONFERENCE. 6-10 September, 2026. Istanbul, Turkey. (https://www.wbc2026istanbul.com/).

ICP 2026 Germany

ICP 2026 will be hosted in the city of Dresden, Germany. The meeting will take place from June 7th to 11th, 2026 in the German Hygiene Museum. The colloquim will be organized by Heike Kohler, Karsten Donat and Susanne Eisenberg.

The preliminary program, the call for abstracts and further details will be available on the meeting website by end of **September 2025**. https://icp2026.com/.

The deadline for the submission of abstracts will be the **15th of December 2025**.

Commentary to members of the IAP

By William Davis

The IAP has played a central role in advancing knowledge on MAP over the past 45 years. When I joined IAP in ~1990, information on MAP was very limited, with much of the information based on folklore. Information on the composition and function of the immune system was limited, especially for livestock species. I am taking this moment to use the newsletter to reflect on what has been accomplished and future directions of the IAP. I believe we have made major advances in study of the immune response to MAP and other mycobacterial pathogens and development of candidate vaccines. We now know tri-directional signaling between antigen presenting cells (APC), CD4 and CD8 T cells is essential for eliciting development of CD8 cytotoxic T cells able to kill intracellular bacteria [1]. We also know MAP and other mycobacterial pathogens have an Achilles' heel, abrogating their capacity to establish a persistent infection and evade immune clearance [2]. Discovery of the Achilles' heel has led to development of candidate vaccines able to kill intracellular bacteria.

Before describing the latest findings there is a need to review some history to understand what has influenced the approaches taken to study MAP over the past years. The first report describing the appearance of a disease in cattle with similarity to bovine tuberculosis was reported by H. A. Johne in 1895 [3]. The disease had similarities to the intestinal form of tuberculosis that occurs in cattle and humans. The similarity was recognized by Dalziel who reported the first description of a new form of enteritis remarkably similar to enteritis described in cattle [4]. Demonstration that disease was caused by a mycobacterial pathogen proved difficult. This led to a dichotomy in thought on the cause of the disease in cattle and a new form of gastroenteritis in humans referred to as Crohn's disease (CD) (the gastroenterologist who described the clinical features of an emerging new form of enteritis) [5].

Improvement in methods of culture led to identification of a mycobacterial pathogen from patients with CD by Chiodini et al. [6,7]. The difficulty in replicating his studies led to the opinion that the pathogen isolated from patients was not the cause of CD. This thought became entrenched in the minds of gastroenterologists and other members of the medical community leading to the self-perpetuating dichotomy in thought [8,9].

Chiodini contacted me a few years after his first publications on MAP and CD inquiring about whether I would help him with research on the immune response to MAP. He was aware of our ongoing studies to develop monoclonal antibodies to characterized the immune systems of livestock [10]. I was interested in mycobacterial pathogens but not familiar with his research. I agreed to collaborate and assist him in studying the immune response to MAP. I joined IAP and participated in the 3rd International Colloquium on Paratuberculosis reporting on the results of studies with Chiodini [11]. As I mentioned, little was known about MAP, especially anything about the immune response to MAP. Assumptions were made based on folklore. Because of the delay in onset of the immune response, it was thought that there was an age-related difference in susceptibility to MAP. It was also thought exposure did not always lead to infection and clinical disease. It was thought there was 'pass through' where MAP could pass through the intestine without infecting animals.

Commentary to members of the IAP (continued)

Because of evidence showing MAP was emerging as a pathogen impacting the dairy industry, a meeting was convened by the National Academy of Sciences in 2001 to review current knowledge on MAP and its potential role in CD [12]. I served on the committee. Based on findings and recommendations of the committee, funding was provided through the USDA ARS to support research. This provided us and other members of the IAP an opportunity to conduct studies to learn more about the immune response to MAP and pathogenesis [12]. Our first studies were focused on learning whether there were age related differences in susceptibility to infection to MAP and obtaining a profile on the immune response at the cellular level. Our first studies revealed there is no age-related difference in susceptibility [13]. Regardless of age, exposure resulted in infection and establishment of a persistent infection. Subsequent studies with an ileal cannulation model provided information on the initial stages of infection and demonstration that the first isolates of MAP, obtained from humans by Chiodini, retained their capacity to infect cattle [14,15].

During this time, information obtained by another investigator caught our attention. Dahl and his associates observed the ability of Mtb to establish a persistent infection was dependent on the presence of a single gene, rel, global regulator of the stringent response [16]. They observed, in a mouse model, that a rel deletion mutant in Mtb could only establish a transient infection. Follow up studies with a MAP rel deletion mutant, using cattle, revealed the effect of deleting rel is universal and not restricted to one lineage of mycobacteria. The studies also revealed the loss of ability to establish a persistent infection is attributable to development of CD8 cytotoxic T cells with ability to kill intracellular bacteria [17]. Three important findings were made during these studies. The first was the potential of rel deletion mutants as live vaccines. The second was the finding that the target of the immune response was a major membrane protein, MMP. Stimulation of PBMC from a steer, vaccinated with MAPΔrel, with MMP, elicited a CTL recall response comparable to stimulation with MAPΔrel [17]. The third finding cleared away another self-perpetuating myth, that initiation of the immune response to Map is delayed. This perception was associated with technical difficulties with methods to detect the immune response. Development of an in vitro culture assay revealed an immune response is initiated at the time of Ag presentation to CD4 and CD8 by APC primed with MAP [17].

Further studies revealed the potential of MMP as a peptide-based vaccine for MAP. Vaccination with the MMP expressed in an *E. coli* vector elicited a CD8 CTL response equivalent to the response elicited by the MAP rel deletion mutant. A modified version of the gene placed in a virus vector retained its immunogenic activity and elicited CTL activity equivalent to the response elicited by the rel deletion mutant [18].

Thinking the 'grass was greener on the other side of the fence' we included BCG in our studies, hoping it would be easier to attract funding. It had also become clear that the same impediment was slowing progress in developing a vaccine for tuberculosis, understanding how mycobacterial pathogens evade immune clearance. Studies with rel showed products of genes under the regulation of rel were involved but not how

Commentary to members of the IAP (continued)

they interfered with the immune response. The studies indicated the products mediated their effect in vivo. Historical and more recent studies had shown the mutation in BCG had reduced virulence but did not prevent BCG from establishing a persistent infection. Results from the most recent study, we are trying to get published, have provided evidence that the ability to evade immune clearance is attributed to T cell exhaustion, the loss of functional activity. We vaccinated steers with BCG and BCGΔrel and compared the recall response elicited by BCGΔrel and BCG. We looked for differences in the proliferative response, cytokine production, content of perforin, Granzyme B, and granulysin in CD4 and CD8 T cells, and ability to kill intracellular bacteria. No difference was observed in the proliferative response elicited by BCG or BCGΔrel, expression of cytokines, or content of perforin, granzyme B, or granulysin. A difference in ability to kill intracellular was observed. Stimulation of steers vaccinated with BCGΔrel with BCGΔrel elicited robust killing of intracellular bacteria. Stimulation of steers vaccinated with BCG with BCG elicited CTL with a very limited ability to kill intracellular bacteria. The results support one of the current hypotheses put forth to explain how mycobacterial pathogens evade immune clearance. The reason this difference has not been detected in previous studies has been the lack of an expedient assay to measure intracellular killing of bacteria by CD8 T cells. We developed an assay during studies with MAP [17]. The gene products that modulate development of CTL activity may differ from gene products that elicit efficacious CTL activity. **Expression of MMP is not regulated by rel.** There is no equivalent gene product in Mtb/Mbv.

The second recommendation made by the National Academy of Sciences committee was to review evidence showing MAP is the causative agent of Crohn's disease. Mixed results were being obtained that left the question open as to whether MAP is the causative agent of CD. The finding in some studies that MAP was also detected in patients with other diseases and healthy controls suggested MAP was not the causative agent of CD. The lack of understanding that MAP is zoonotic and similar to Mtb and Mbv, in that infection does not always lead to clinical disease **caused a misinterpretation of results**. As discussed, infection with mycobacterial pathogens elicits development of an immune response that controls but does not clear the infection, leading to a persistent infection. Clinical disease occurs where the immune response is disrupted. Two of the most definitive studies conducted during recent years support MAP being the causative agent of CD. A group of physicians conducted a study involving the use of multiple types of assays to screen for the presence of MAP. The study revealed MAP bacteremia is widespread with infection including patients clinically diagnosed with CD, patients with autoimmune associated diseases and healthy asymptomatic subjects [19]. Studies conducted with Singh et al. provided the most definitive information. Studies of a patient that presented with the clinical symptoms of CD revealed the presence of MAP in the patient's feces [20]. Treatment with antibiotic therapy cleared the infection and the clinical symptoms of CD. The results of studies with this patient show CD and Johne's disease are one and the same [8].

Commentary to members of the IAP (continued)

I believe IAP is now in a position to take center stage in leadership in establishing a program to control diseases caused by mycobacterial pathogens. Studies with MAP have led to the discovery that mycobacterial pathogens have an Achilles' heel. Ability of mycobacterial pathogens to establish a persistent infection is associated with the presence of products encoded by genes regulated by a single gene, rel. T cell exhaustion is induced when the gene products are expressed in vivo, leading to a loss in the ability of CD8 T cells to kill intracellular bacteria. Silencing the genes by deleting rel prevents induction of T cell exhaustion with consequent development of functional CD8 CTL. The rel mutants developed to conduct the studies are vaccine candidates with known functional activity. The target of the immune response to the MAP rel mutant is known, MMP. A virus vectored form of the gene encoding MMP is a peptide-based candidate vaccine that elicits CTL.

The first step in the program is to have multiple laboratories document our results followed by a vaccination program to clear MAP from dairies and the food stream. While implementing a program to clear MAP from dairies, a program should be initiated to demonstrate deletion of rel from BCG increases its efficacy as a vaccine. Bovine tuberculosis is also a problem, especially in developing countries. Clearance of both pathogens from livestock would reduce exposure. Of importance, demonstration of the improved efficacy of a rel deletion mutant in BCG in livestock would provide data showing a mutant would also improve vaccine efficacy for humans.

The newsletter could be used as a forum for further discussions and a way to organize a committee to move a vaccination program forward.

William (Bill) C. Davis, Prof., Vet. Micro/Path
Director, WSU Monoclonal Antibody Center
College of Veterinary Medicine
Washington State Univ.
Pullman WA, USA 99164-7040

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Commentary to members of the IAP (continued)

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Test and cull using faecal PCR

By Richard Whittington

Dear newsletter readers, I would usually not advertise a scientific paper, instead relying on the old fashioned method of people stumbling across it, and perhaps even reading it in their spare time. However, I thought I would try to get a little attention this time, because we have been frustrated by the abandonment of government-led JD control programs in Australia, and by the idea that JD is just another disease that farmers can chose to manage. **But how can they do this by themselves?** We need to be aware of options and we may need to provide advice as individuals, if there is no organized control program. Some farmers may read more than we do on the internet.

One dairy farmer approached our research group about 10 years ago because she was very distressed about clinical JD cases appearing in her dairy herd. She did not like to see them, it was as simple as that. They had occurred for many years, despite the herd participating in an official (but now defunct) serum ELISA-based test-and-cull program. She wanted to try something new. She had found out about the faecal PCR test developed in our university lab. It had just been adopted nationally by government labs for herd-level JD diagnosis. She wanted to try using it in individual cattle for test-and-cull. The sensitivity of the test had been properly benchmarked against faecal culture in liquid medium, so it was quite sensitive, but unlike culture, it could deliver results relatively quickly. The paper reports a 9 year observational study, the first to use a fecal qPCR test in a test-and-cull strategy for BJD in an Australian dairy herd. It might be one of the first examples anywhere. The results were interesting. Clinical BJD cases ceased immediately, and prevalence declined over time. Is eradication possible with this approach? Not so far – the reasons are provided in the paper. However, the farmer was very happy and continues to use the approach in her herd. This illustrates what is possible for dairy farmers in the real world. They face many practical management constraints in their daily decision making, but many are willing to take action to control JD. Farmers in New Zealand have recently been in touch hoping to do something similar.

Before rushing for the exits to buy faecal PCR test kits, I would urge caution and seek out a test that has been properly validated. Ensure that liquid faecal culture was the gold standard (not solid medium culture which is far less sensitive and could make an average PCR protocol look good). Testing is costly, so you do not want to miss too many infected cows.

Here is the abstract. The paper will appear in the Journal of Dairy Science in 2025. We had the privilege of hosting the senior author, Anabel Garcia, in our research team; apart from dealing with huge JD data sets, she endured bushfires, covid lockdowns and even one or two “normal” years. She has just returned to Panama with a PhD, and a strong interest in the control of mycobacterial diseases in her country and beyond.

Test and cull using faecal PCR (continued)

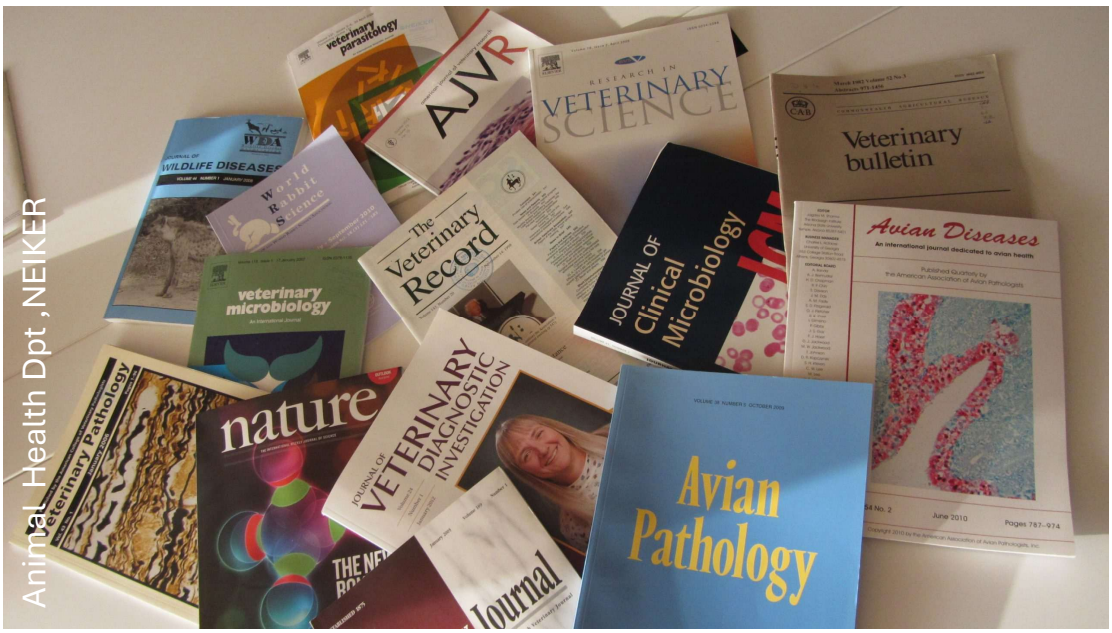
By Richard Whittington

Garcia et al 2025. Evaluation of a test-and-cull strategy to control bovine paratuberculosis based on the detection of Mycobacterium avium subsp. paratuberculosis DNA using the HT-J fecal PCR test. J Dairy Sci.

Abstract

Bovine Johne's Disease (BJD) is a chronic, debilitating enteritis caused by Mycobacterium avium subsp. paratuberculosis (MAP) with both animal welfare and economic consequences. The detection of MAP in feces is an important measure of transmission from infectious animals through environmental contamination. Therefore, control programs focused on early removal of infectious animals from a herd, combined with management approaches to reduce exposure of susceptible young animals, have a high likelihood of reducing the disease burden. Quantitative PCR (qPCR) tests to detect MAP in feces enable rapid and sensitive detection of infectious animals. The aim of this study was to evaluate the use of the high-throughput Johne's (HT-J) direct fecal qPCR in a test-and-cull approach to control BJD. Testing was performed annually from 2015 – 2023 on a dairy farm in Victoria, Australia. A total of 7,153 fecal tests were conducted on 1,955 individual Jersey cows. A pooled screening approach was used (5 or 10 animals/pool) with follow-up testing of individual cows. Significant reductions in both the prevalence of fecal shedders (from 9.6% in 2015 to 1.2% in 2023) and mycobacterial shedding levels were achieved, together with elimination of clinical cases. Factors that may improve outcomes using this approach were also identified. This was the first application of this test in a BJD control program in a dairy herd in Australia and demonstrated the potential of the approach to effectively control BJD.

Here is a link to the online ahead of print article.



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Contribute to the Next Newsletter

The next newsletter will be published in September 2025.

We invite all members to contribute by sharing opinion pieces, news about recent publications or project updates, regional control programs, job opportunities, or any relevant information on paratuberculosis research and communications.

Please submit your article to:

newsletter@paratuberculosis.com; nelguezabal@neiker.eus

Submission deadline for the upcoming issue is July 31st, 2025.

We welcome all submissions!

Some of the images included in this issue have been generated with Leonardo AI (LAI).

Recent Literature on MAP

Research papers focused on *Mycobacterium avium* subsp. *paratuberculosis* published during the past three months have been included in the following list.

Links to the open access versions of the papers have been included in the titles when possible.

Enjoy reading!

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Remember to have a nice break from work! See you back in September.