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A bloody evidence: is *Mycobacterium bovis* bacteraemia frequent in cattle?!

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Bovine tuberculosis (bTB), a chronic disease caused by *Mycobacterium bovis*, constitutes a major economic and health problem affecting cattle. Furthermore, there is the concern of transmission to humans, as well as between cattle and wildlife reservoirs. Costs associated with the disease include reduced productivity in affected animals, testing, culling of affected animals, movement and trade restrictions. Bovine TB is listed in the top 14 principal diseases that affect livestock production in Africa and South Asia, and the direct impact of this disease in these countries is estimated to be US$300 million annually\(^1\) while globally the disease costs US$3 billion annually.\(^2\)

An important component in the prevention and control of bTB is the early and definitive diagnosis of subclinical infections. The majority of currently employed bTB eradication programs mostly rely on two main diagnostic tools: tuberculin intradermal tests and interferon-gamma release assays (IGRA). These tests detect immune responses by infected animals to the bacteria. Such responses may be influenced by previous exposure to other mycobacterial agents, as a high level of homology exists among mycobacterial species.\(^3\) The current testing limitations and the significant economic losses that ensue, as well as the risk of transmission among livestock, human and wildlife emphasize the desperate need for rapid and inexpensive diagnostic methods able to detect and distinguish *M. bovis* infection from other pathogenic and environmental mycobacteria.\(^1^4\)

More specific diagnostic tests, relying on the identification of the pathogen or its antigens, have proven to be challenging. Due to the slow growth of *Mycobacterium tuberculosis* complex (MTC), culture is not suitable as a timely diagnostic test. Molecular-based methods (which are independent of viable bacteria) have not been promising in providing faster results from a variety of samples, including blood, due to low sensitivity even with high volume extraction.\(^5\) In humans, the isolation of *Mycobacterium tuberculosis* from blood samples of tuberculosis (TB) patients has been documented since the 20th century.\(^6\) Guinea pigs inoculated with blood from patients with disseminated TB had detectable but transient *M. tuberculosis* bacteraemia, with re-appearance of circulating bacilli in the bloodstream up to 6 weeks thereafter. Nevertheless, *M. tuberculosis* blood culture was seldom used as a diagnostic tool for TB. With the advent of the human immunodeficiency virus (HIV) mycobacterial blood cultures became an important test to detect disseminated *Mycobacterium avium-intracellulare* complex disease, a serious and life-threatening condition especially common in immune-compromised individuals. At this time, it was observed that *M. tuberculosis* was frequently isolated from these samples. HIV-related immunosuppression is associated with poor containment of *M. tuberculosis* in the lungs,
resulting in an increased risk of systemic dissemination, and consequently increased detection by blood culture.\(^7\)\(^-\)\(^8\) Especially for this cohort, mycobacterial blood culture may be a useful diagnostic accessory, as immunosuppression is often associated with decreased reactivity in IGRA assays and skin test.\(^8\) In fact, predictors of \textit{M. tuberculosis} bacteraemia in humans include: advanced immunosuppression (i.e., low CD4 count), HIV infection, prolonged cough and fever, weight loss and lymphadenopathy.\(^9\) The overall mortality associated with \textit{M. tuberculosis} bacteraemia for a human is elevated (50%), and \textit{M. tuberculosis} bacteraemia is associated with severe clinical disease and poor infection outcome.\(^8\)\(^-\)\(^9\)

\textit{M. bovis} bacteremia in infected cattle has been assumed to be rare. Intriguingly, extra-pulmonary TB is more frequent in \textit{M. bovis} infection (as compared to \textit{M. tuberculosis} infection), which suggests hematogenous dissemination of the pathogen. However, despite the high risk of disseminated infection, bacteraemia has only rarely been reported in cattle.\(^10\)\(^-\)\(^12\) The success level of culture can be determined by the growth rates, the inability of potential isolates to adapt to in-vitro culture conditions, especially in situations where the number of bacilli are limiting, which could result in false-negative results by culture.\(^3\)\(^,\)\(^5\)\(^,\)\(^9\) Also, for bTB in cattle, culture of tissues collected \textit{post-mortem} is often used to confirm infection. Mycobacteremia occurrence in infected animals by itself is not sufficient to make blood culture a valuable diagnostic test for bTB, as the long period needed for culture would still hinder its use as a screening test.

In this issue of \textit{Virulence}, Swift \textit{et al.}\(^13\) use a new method to detect MTC in blood samples from bTB infected cattle. The authors have developed a sensitive and rapid method for detection of MTC in bovine peripheral blood mononuclear cells (PMBC). The manuscript provides proof of concept for this assay, which has the potential to profoundly impact bTB control measures and effectiveness. First, the authors tested a bacteriophage-based method combined with an isothermal DNA amplification protocol using recombinase polymerase amplification (Phage-RPA) to detected mycobacteria in blood samples spiked with \textit{M. bovis} BCG. The authors were able to confirm the detection within 48 h, with a limit of detection of approximately 10 \textit{M. bovis} BCG bacilli/ml for blood samples artificially inoculated. When blood samples from single comparative cervical intradermal tuberculin (SCCIT) - positive animals were tested, viable MTC bacteria were detected in 66 % (27/41) of samples. Of the 41 animals sampled, only 13 had visible lesions. Alarmingly, over 50 % of the animals with no visible lesions had detectable mycobacteremia. Importantly, no MTC DNA was detected in the blood samples from TB negative herds. The alarming frequency of viable MTC detection in the peripheral blood of SCCIT - positive animals changes the paradigm of this disease. Mycobacteremia has only rarely been reported in \textit{M. bovis} infected cattle, and its occurrence was expected to be associated with disseminated and advanced clinical disease, as it appears to be the case in humans. In addition to its diagnostic applications, the high frequency of \textit{M. bovis} detection in bTB-infected animals
provides useful insights into bTB pathogenicity and, undoubtedly, challenges the current dogma that (i) \textit{M. bovis} bacteremia is rare in cattle and (ii) that its occurrence is a hallmark of poor mycobacterial containment and advanced clinical disease.

Bovine TB remains as one of the most damaging diseases to livestock, in spite of long and extensive control efforts. The dire situation of bTB worldwide, in both developed and in developing countries illustrates the great need for better control strategies. Even though additional and more extensive studies are needed to confirm their surprising results, Swift \textit{et al.}\textsuperscript{13} findings are a useful reminder that dogmas can lead to scientific advancements but, maybe just as frequently, dogmas can prevent advancements and breakthrough discoveries. Perhaps, revisiting dogmas will be the key to halt bTB.


10. Lepper AWD, Corner LA, Pearson CW. Serological Responses in Experimental Bovine

