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Title: **Zoonotic TB - call for an open ONE-HEALTH debate**

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Tuberculosis is caused by bacteria of the *Mycobacterium tuberculosis* complex (MTBC) and impacts on both human and animal populations. Animal-adapted MTBC threatens the well-being of humans, animals and their livelihoods. The WHO annual TB Report estimated there were 143,000 new human cases of zoonotic tuberculosis (zTB) with 12,300 deaths caused by *Mycobacterium bovis* globally (1). Prevalence estimates of zTB are inaccurate since routine laboratory tests cannot differentiate between infections caused by the human and animal-adapted species of the MTBC, including newer members such as *Mycobacterium orygis* (2). Thus, the true effect of zTB on the human TB epidemic remains unclear. Accurate disease differentiation is also important since *M. bovis* is universally resistant to pyrazinamide, a key first line TB drug.

zTB is acquired through consuming unpasteurized milk products, or unusually from direct contact with infected livestock or offal (3). A true wildlife source of zTB remains unknown (4). MTBC strains are able to transmit between domestic cattle and other reservoir species, specifically maintaining *M. bovis*. Bovine TB is usually associated with intensively managed farmed livestock, captive and semi-captive or fenced wild animals, or those adapted to human domesticated agricultural landscapes (5). Whilst efforts to eradicate bovine TB from livestock are ongoing, other reservoirs remain a threat to control programs. These include European badgers, brushtail possums, ferrets, feral pigs, buffalo, wild boars, elks and white-tailed deer (6). Bovine TB inflicts economic losses through lost production and control costs, creating barriers to livestock trade, and impedes conservation efforts. The *M. bovis* debate in Africa is currently influenced by regional importance in countries such as South Africa and Ethiopia where intensification of cattle industry is more advanced. Imported cattle like Holstein Friesian bring European strains of *M. bovis* into their national herds. This argues against intensification. Intensifying without biosecurity and neglecting the highly resilient pastoral sector remain shortsighted approaches to livestock systems, and retards bovine TB control programs.

Contacts rates and population densities are the major drivers for evolution of the animal-adapted MTBC. *M. bovis* infection and wildlife TB are rarely expressed in natural ecosystems and experience of low disease prevalence in indigenous cattle in mixed systems suggests this is not necessarily a problem, although risks are reported (7). For example, in Queen Elizabeth National Park, Uganda, *M. bovis* has been detected by serology in around 20% of African buffalo for over 60 years, with occasional open cases, it is without any apparent ecological significance. Conversely, the surrounding Ankole cattle, which share pasture, have cryptic *M. bovis* infection (~2% prevalence) with no perceived issues in the stock or regarding zTB (8). This *African* 'resilience' is fast changing consequential to increasing pressure being put on land use and increasing demand for milk and meat. Cases of zTB are uncommon in countries where bovine TB in cattle is controlled. The focus should be on better detection and reporting of cases and improving standards of food safety and hygiene.

Whilst Zooanthroponosis appears rare, deaths amongst elephants due to *M. tuberculosis* acquired from humans have been reported from Asia (9) and Africa (10). Some elephants are inveterate rubbish pit raiders and the Asian's report close association with *M. tuberculosis*-infected animal handlers. Reverse zTB transmission from human pastoralists to cattle from an emerging Uganda-I *Mtb* strain been also been reported (11). These cases highlight the importance of extending the "One Health" debate to addressing the zoo-anthroponotic threat.

The time is now right to call for an open debate to address the impact of zTB and MTBC framed within a 'One-Animal-Environmental-Human-Health' (One Health) approach, focusing on the wellbeing of animal handlers, animals and environment into consideration. This should include the relative importance of direct and indirect routes of transmission, the roles of the environment, management, genetics and agricultural practice on disease expression. It should include an intersectoral approach from the ministerial level to the community level, with engagement of both public and private stakeholders. Multi-sectoral and multidisciplinary research efforts are needed to: a).improve understanding of the disease ecology of animal-adapted MTBC in different geographical areas; b).understand the role of livestock and wild-life in environmental contamination; c).determine the role of wildlife in the dynamics of MTBC infection; d).develop sustainable prevention and control strategies in human and agricultural landscapes through a systems approach. Greater awareness and expertise among health care providers, laboratory capacity, and access to point-of-care triage diagnostics, followed by accurate, rapid confirmatory molecular diagnosis. This should include molecular-guided cooperation for better detection and integrated, reliable recording and reporting of cases of MTBC, bovine TB and zTB between human and veterinary health services.

Animal TB is driven by agricultural intensification and production, intensification of wildlife management, contact between cattle and wildlife, poverty and the disturbance of ecological systems. zTB cannot be adequately addressed by national TB programs alone, collaborative relationships must be fostered among different disciplines. Internationally agreed standards for surveillance and diagnostic methods for bovine TB should be used to ensure safe trade and minimize risks to human and animal health and must be complemented by national frameworks for improving food safety (14). Inadequate attention to zoonotic TB is constraint on reaching ambitious End TB targets and the United Nations Sustainable Development Goal 3.

Political acceptance of vaccination as a pillar to affordable and effective bovine TB and zTB control in Africa is needed now to protect livestock, wildlife and humans (12) especially where the prevalence of *Mtb* infection in cattle is high, and test-and-slaughter strategies used in Europe are not feasible for economic or cultural reasons. Meanwhile, pasteurization of milk remains an effective control measure to prevent most *M. bovis* transmission to humans. Inspection of carcasses at abattoirs must be applied

routinely, leading to removal of contaminated animal products from the food chain and the traceback of animals to potentially infected origins and in pastoral settings, new means to improve awareness and control are needed (13). Importantly, reducing the risk of exposure and transmission at the human-animal interface requires awareness of the threat, beyond the known cattle reservoirs, and engagement and collaboration with local communities (14).

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