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MINIREVIEW

'One Health' approach to end zoonotic TB

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SUMMARY

Mycobacterium bovis has a wide host range causing TB in animals, both in wildlife and cattle (bovine TB [bTB]), and in humans (zoonotic TB [zTB]). The real burden of bovine and zoonotic TB (b/zTB) remains unknown due to diagnostic challenges. Although progress has been made to reduce the burden of TB, b/zTB has been neglected in low- and middle-income countries (LMICs) with little improvement in prevention, diagnosis or treatment. Using Tanzania as a case study, because of its high TB burden, large wildlife diversity and wide reliance on livestock, we developed an approach to comprehensively estimate the burden and implement multidisciplinary actions against b/zTB. We performed a review of the literature on b/zTB, but there is a lack of available data on the b/zTB burden in Tanzania and, notably, on epidemiological indicators other than incidence. We propose a five-action programme to address b/zTB in Tanzania, and we believe our proposed approach could benefit other LMICs as it operates by implementing and strengthening surveillance and health delivery. The resulting knowledge and system organisation could further prevent and mitigate the effects of such conditions on human and animal health, livestock production, population livelihood and the economy.

KEY WORDS: zoonosis; tuberculosis; epidemiology; one health

TB is caused by bacteria belonging to the *Mycobacterium tuberculosis* complex (MTBC), and is a leading cause of infectious disease deaths globally, especially in sub-Saharan Africa.[1] Among the MTBC, *M. bovis* has the widest host range. It infects humans, causing zoonotic TB (zTB), and domestic animals, including livestock (especially cattle) and wildlife, causing bovine TB (bTB).[2] *M. bovis* can spread via contact with infected lesions or by consumption of contaminated and non-heat-treated dairy products.[3] During the past century, improvements were made to reduce b/zTB and in high-income countries: the adoption of pasteurised milk and public health measures on farms to decrease the prevalence of bTB have contributed to the virtual disappearance of zTB.[3] However, in low- and middle-income countries (LMICs) such approaches have rarely been adopted at scale. Furthermore, both rural and peri-urban communities in LMICs often consume raw milk and unpasteurised dairy products from cattle,[4] which can come into frequent contact with infected cattle and wildlife, increasing the risk of cross-species transmission of pathogens, including *M. bovis*.[3,5]

A key measure to monitor the impact of zTB is the establishment of a robust routine surveillance system to detect and distinguish TB from zTB. *M. bovis* and other MTBC can be differentiated at a molecular level, whereas commonly used microbiological methods (i.e., Xpert® MTB/RIF [Cepheid, Sunnyvale, CA, USA], microscopy and culture) do not allow this.[6] Because of the technical and economic difficulty in implementing molecular tools able to identify *M. bovis*, few countries have specialised and integrated surveillance systems for bTB and TB, including zTB.[7] In 2019, the WHO estimated that 140,000 new zTB cases occurred worldwide, the majority in the WHO's African Region.[8] Even if surveillance systems were strengthened, they would likely have limited reach in pastoral populations most at risk of the disease. Furthermore, *M. bovis* can acquire resistance to TB drugs besides its inherent resistance to pyrazinamide, one of the drugs of the WHO-recommended regimen for drug-susceptible TB.[9] Therefore, there is a risk of

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lower efficacy and unfavourable outcomes, especially when additional resistance to other first-line drugs is frequent, further complicating TB control efforts.

'ONE HEALTH'

'One Health' is an integrated approach aiming to improve human, animal and ecosystem health. In addition to food safety, water and antimicrobial resistance containment, it addresses zoonotic diseases for which sustainable solutions depend upon multi-sectorial, cross-disciplinary interventions. As b/zTB is a model zoonosis, 'One Health' approaches are essential for its control and prevention. Measures such as pasteurisation of milk and the establishment of robust surveillance systems are insufficient to reduce *M. bovis* reservoirs in domesticated animals, wildlife and humans. Hence, the risk of animal-to-human transmission if healthcare is not well coordinated across sectors.[10] A 'One Health' approach is instrumental to bridge existing gaps and implement integrated human–animal surveillance of infectious diseases and effective interventions. The COVID-19 pandemic has increased international interest in the 'One Health' approach, creating an opportunity to address zTB once and for all. By operating in the existing frameworks of the Sustainable Development Goals (SDGs) and the WHO initiatives,[11,12] we propose a set of five actions to tackle b/zTB. We hope these will aid decision makers in designing cost-effective interventions.

Establishing a programme in Tanzania

Tanzania is one of the sub-Saharan countries with the highest burdens of both TB and HIV-TB: in 2020, there were 133,000 and 28,000 estimated incident cases, respectively.[1] About 70,000 incident zTB cases are estimated to occur annually in Africa.[13] Although several research studies on zTB have been conducted, Tanzania, like most countries in sub-Saharan Africa, has no routine system to detect and report cases.[14] Of note, technologies largely used for drug-resistant TB surveillance (e.g., Xpert MTB/RIF) do not identify *M. bovis*, although the Mycobacteria Growth Indicator Tube can distinguish *M. bovis* if a special supplement is used, but this is not available in LMICs. Tanzania is renowned for wildlife diversity and abundance, with the majority of land use being dominated by livestock systems, including pastoral systems.[14] There is widespread consumption of unpasteurised milk, soup mixed with raw blood, or raw meat, and extremely close human–livestock–wildlife contact in many rural communities (e.g., in the northern Regions). However, there is currently limited information on the role of wildlife as a reservoir or the importance of different sources of infection and the modes of transmission of *M. bovis*.[5,14]

Few data are available on the true burden of zTB in Tanzania (Figure and Supplementary Table S1).[2,5,14–26] The prevalence of TB in both cattle and wildlife has been assessed using a wide range of tests (e.g., intradermal skin test and molecular assays) to be 0.2–8.0%. Among humans, zTB was identified in specific population subsets in 0–10.8% of subjects.[14] The zTB burden has been analysed in different populations, from patients with TB lymphadenitis to those with pulmonary TB and selected subpopulations, such as livestock keepers.[14] In addition, there is a lack of data on burden metrics other than incidence, as well as on disease duration, complications, disability weights and the case fatality ratio. The true burden of *M. bovis* in Tanzania is far from being completely and sufficiently described, as shown by the wide uncertainty intervals around the observed estimates, which could be the result of true differences in populations surveyed or lack of standardisation of methods. This limits the opportunity to produce evidence-based policies for better zTB control in the country, especially in rural areas. To overcome these challenges, we focused on Tanzania as an example to apply the proposed approach.[5,14,15]

Action 1: Estimating the burden

Estimating the burden of b/zTB in animals and people is crucial for public health decision-making, especially in high-risk areas. The Ngorongoro Conservation Area (NCA), located in northern Tanzania, is an area of over 8,000 km^2 designated for pastoral activities of the local Maasai community. Livestock keeping is common among the Maasai, with cattle, sheep and goats as the predominant livestock species, typically managed extensively in mixed herds.[27] Similarly, high-risk dietary habits, including the consumption of raw milk, are common in this area.[17,27] Because of these factors and the presence of an established research facility in the NCA at Endulen Hospital, Endulen is an ideal study site to estimate the burden of b/zTB in animals and humans. Estimating the incidence of bTB in animals and zTB in humans requires extensive sampling of respiratory and non-respiratory specimens, including raw milk. Specifically, the incidence of bTB infection among animals should be evaluated by a dedicated interferon-gamma release assay on animal blood samples and by assessing production measures (e.g., milk yield).[27] An active, population-based surveillance system in the Endulen community with household visits performed to screen household members for TB-like symptoms and signs should be used to estimate the burden of zTB. Participants with signs of TB should be referred to a sentinel site where specimens can be collected and analysed. Patients diagnosed with zTB should be treated with follow-up to evaluate complications and treatment outcomes.

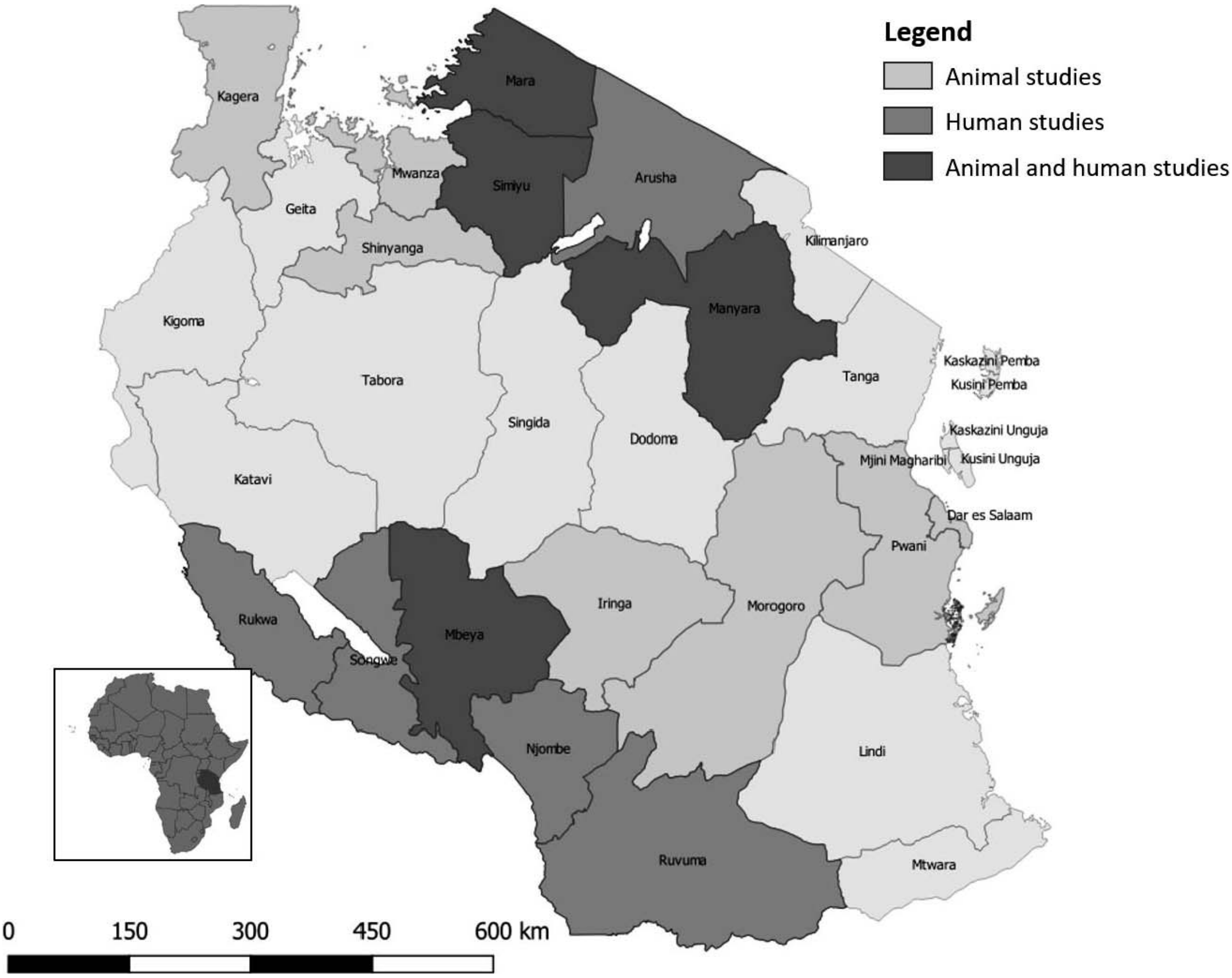

Figure Regions of Tanzania with at least one study describing the detection of *M. bovis* among animals, humans or both from 1997–2017.[2,5,14–26] Figure was produced using QGIS (version 3.16.16).

Action 2: Employing comprehensive epidemiological indicators

Disease incidence provides only a partial view of the human burden of disease. Policy formulation and implementation cannot rely solely on a pure epidemiological metric but should be based on a wide spectrum of indicators encompassing disease duration, occurrence of complications and the case fatality ratio in different subsets. The information should be disaggregated by age and sex to compute a broader epidemiological measure such as the disability-adjusted life-years (DALYs) lost.[28] However, this metric might also still underestimate the real consequences of this zoonosis on human health. This is because of the direct impacts of disease arising from the zoonotic transmission of *M. bovis*, as well as the indirect impacts from production losses that affect people's nutritional health and wellbeing because of the high dependency on livestock for food security and livelihood. Therefore, a broader, composite indicator, from a 'One Health' perspective, ought to be adopted to account for these societal impacts. The zoonotic DALY, where the economic costs of livestock infection are converted to animal loss equivalents through a time-trade-off approach is one example of a combined metric.[29,30]

Action 3: Identifying risk factors and animal sources of zoonotic TB

The identification of risk factors associated with the spread of *M. bovis* from animals to humans and the detection of animal sources is key for public health decision-making in a high TB burden setting, such as Endulen. Previous studies, although limited by the small number of zTB covered, helped improve case detection of zTB. Now, conducting a combined case-control and molecular source attribution study,[14] with risk factor analysis based on the identification of zTB cases can address our knowledge gaps. Both groups in the study should be queried for potential risk factors for zTB, with a particular focus on the consumption of food items. A multivariable logistic regression analysis can then be used to identify possible risk factors associated with zTB occurrence, severity and outcome. Implementing a Bayesian inference on an asymmetric island model, whole-genome sequencing of strains isolated could also be used for source attribution of each human isolate with time-matched animal and food isolates. This analysis will estimate relative posterior probabilities for each human isolate to originate from the different putative sources. An accurate understanding of zTB transmission dynamics is needed to develop effective containment strategies.

Action 4: Assessing the field applicability of new diagnostic tools for zoonotic TB

The frequent extrapulmonary manifestations of zTB make its diagnosis challenging and, therefore, an assessment of field applicability of novel diagnostic methods and their comparison with extensive conventional standards is required. Among novel diagnostic methods, special consideration should be given to the use of culture methods promoting *M. bovis* growth (e.g., pyruvate-containing media). More invasive sampling might be useful to avoid missing some non-pulmonary forms of the disease. Finally, one should evaluate the diagnostic performance of focused assessment with sonography for HIV-TB abdominal ultrasound at study healthcare facilities.[31]

Action 5: Designing 'One Health' interventions to reduce transmission

The design of integrated 'One Health' interventions is key to reducing the transmission of TB at the human–animal interface, especially among vulnerable and marginalised communities. Such broader scope should rely on evidence accrued from the first four objectives, especially from the analysis of risk factors for zTB.[32] The integration of human and veterinary research, as exemplified by the longstanding collaboration between the Endulen Hospital and the Institute of Biodiversity, Animal Health and Comparative Medicine at the University of Glasgow, Glasgow, UK, is an example of a key 'One Health' approach. In addition, the interaction and collaboration of different sectors of society including high-risk communities, educators, media and private companies, have the potential to increase awareness about b/zTB and foster preventive strategies. Finally, the involvement of local, national and international stakeholders is crucial to fund and support research efforts on b/zTB and the implementation of effective measures to reduce b/zTB transmission. The collaborative interventions emerging from different sectors will be crucial in reducing the burden of TB locally and, potentially globally, in line with the SDGs and the End TB Strategy.

A CALL TO ACTION

An increased awareness of the value of 'One Health' approaches and the advent of powerful analytic and molecular diagnostic tools provides an opportunity to tackle the challenges of b/zTB.

Our proposed approach, which we conceptually applied to Tanzania, could serve as a model for high TB burden countries, especially for LMICs, to strengthen their surveillance and health delivery systems. Governments and donors should further commit to investing in operational and epidemiological research to investigate the burden and the impact of this health problem. The resulting knowledge and logistical organisation from the implementation of programmes and interventions based on this approach can, eventually, empower governments to better prevent b/zTB and mitigate their impact on human and animal health, livestock production, and the livelihoods and economy of affected countries and vulnerable populations.[33] The same knowledge and capacity could be further applied to similar health issues (such as other zoonoses, epidemics, and pandemics) that are likely to become more frequent because of increasing loss of biodiversity and climate change.[34,35]

Conflicts of interest: None declared.

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RÉSUMÉ

Mycobacterium bovis a un large éventail d'hôtes et provoque la TB chez les animaux, tant chez les animaux sauvages et le bétail (TB bovine [bTB]) que chez l'homme (TB zoonotique [zTB]). Le fardeau réel de la TB bovine et zoonotique (b/zTB) reste inconnu en raison des difficultés de diagnostic. Bien que des progrès aient été accomplis pour réduire le fardeau de la TB, la b/zTB a été négligée dans les pays à revenu faible et intermédiaire (LMICs), avec peu d'améliorations en matière de prévention, de diagnostic ou de traitement. En utilisant la Tanzanie comme étude de cas, nous avons développé une approche pour estimer de manière exhaustive ce fardeau et mettre en œuvre des actions multidisciplinaires contre la b/zTB. Nous avons effectué une revue de la littérature disponible sur la b/zTB en Tanzanie en raison de l'important fardeau de la TB dans ce pays, de la grande diversité de sa faune sauvage et de sa grande dépendance vis-à-vis du bétail. Les données relatives au fardeau de la b/zTB en Tanzanie sont limitées ; il existe notamment un manque d'indicateurs épidémiologiques autres que l'incidence. Nous proposons un programme en cinq actions pour lutter contre la b/zTB en Tanzanie, que nous pensons pertinent pour d'autres pays. D'autres LMICs pourraient profiter de cette approche, car elle permet de mettre en œuvre et de renforcer la surveillance et les services de santé dédiés à la b/zTB. Les connaissances et l'organisation du système qui en résulteront pourraient permettre de prévenir et d'atténuer les effets de ces conditions sur la santé humaine et animale, la production animale, les moyens de subsistance de la population et l'économie.