Zoonotic tuberculosis in human beings caused by *Mycobacterium bovis*—a call for action

Francisco Olea-Popelka, Adrian Muwonge, Alejandro Perera, Anna S Dean, Elizabeth Mumford, Elisabeth Erlacher-Vindel, Simona Forcella, Benjamin J Silk, Lucica Ditiu, Ahmed El Idrissi, Mario Raviglione, Ottorino Cosivi, Philip LoBue, Paula I Fujiwara

Mycobacterium tuberculosis is recognised as the primary cause of human tuberculosis worldwide. However, substantial evidence suggests that the burden of _Mycobacterium bovis_, the cause of bovine tuberculosis, might be underestimated in human beings as the cause of zoonotic tuberculosis. In 2013, results from a systematic review and meta-analysis of global zoonotic tuberculosis showed that the same challenges and concerns expressed 15 years ago remain valid. These challenges faced by people with zoonotic tuberculosis might not be proportional to the scientific attention and resources allocated in recent years to other diseases. The burden of zoonotic tuberculosis in people needs important reassessment, especially in areas where bovine tuberculosis is endemic and where people live in conditions that favour direct contact with infected animals or animal products. As countries move towards detecting the 3 million tuberculosis cases estimated to be missed annually, and in view of WHO's end TB strategy endorsed by the health authorities of WHO Member States in 2014 to achieve a world free of tuberculosis by 2035, we call on all tuberculosis stakeholders to act to accurately diagnose and treat tuberculosis caused by _M bovis_ in human beings.

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Department of Clinical Sciences and Mycobacteria Research Laboratories, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO, USA (F Olea-Popelka PhD); **Genetics and Genomics, Roslin Institute, Royal (Dick) School of Veterinary Studies, University of Edinburgh, Edinburgh, UK** (A Muwonge PhD); **United States Embassy, Mexico City, Mexico** (A Perera DVM); **US Department of Agriculture, Animal and Plant Health Inspection Service, Mexico City, Mexico** (A Perera); **Global TB Programme** (A S Dean PhD, M Raviglione MD) **and Department of Global Capacities, Alert, and Response** (E Mumford DVM), **World Health Organization, Geneva, Switzerland; World Organisation for Animal Health (OIE), Paris, France** (E Erlacher-Vindel DVM, S Forcella DVM); **Centers for Disease Control and Prevention, Atlanta, GA, USA** (B J Silk MD, P LoBue MD); **STOP TB Partnership, Geneva, Switzerland** (L Ditiu MD); **Animal Production and Health Division, Food and Agriculture Organization of the United Nations, Rome, Italy** (A El Idrissi PhD); **Pan American Foot and Mouth Disease Center (PANAFTOSA), Pan American Health Organization/Regional Office for the Americas of the World Health Organization, Duque de Caxias, Brazil** (O Cosivi DVM); **and International Union Against Tuberculosis and Lung Disease, Paris, France** (P I Fujiwara MD)

Correspondence to: Dr Francisco Olea-Popelka, Department of Clinical Sciences and Mycobacteria Research Laboratories, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO 80523, USA **folea@colostate.edu**

Introduction

Mycobacterium tuberculosis is the primary causal agent of human tuberculosis worldwide. However, substantial evidence suggests that the burden of *Mycobacterium bovis*, the causal agent of bovine tuberculosis, might be underestimated in human beings.[1–4] Incorrect extrapolation of data from high-income countries and those with low burden of tuberculosis has probably resulted in the misconception that only a small proportion of people have pulmonary and extrapulmonary tuberculosis caused by *M bovis* globally. This misconception has resulted in a general insufficient awareness[2] among health-care providers and public health officials regarding the importance of *M bovis* as a cause of human tuberculosis (which is hereafter referred to as zoonotic tuberculosis). In this Personal View, we highlight the global human and veterinary public health challenges caused by zoonotic tuberculosis, and outline actions for the short, medium, and long term to improve its prevention, diagnosis, and treatment at the so-called animal–human interface. The proposed actions support the newly aligned policy agendas of both WHO—namely, the end TB strategy,[5] in which every case of tuberculosis should be diagnosed and treated by 2035—and the broad and comprehensive reach of the United Nations Sustainable Development Goals,[6] presenting a key opportunity to improve the health of communities affected by zoonotic tuberculosis.

Burden of zoonotic tuberculosis

In 2013, Müller and colleagues[1] concluded that the same challenges and concerns of global zoonotic tuberculosis expressed 15 years ago remain valid.[3] The two major issues preventing understanding of the true burden of this disease in human beings are the absence of systematic surveillance for *M bovis* as a cause of tuberculosis in people in all low-income and high tuberculosis burden countries where bovine tuberculosis is endemic, and the inability of laboratory procedures most commonly used to diagnose human tuberculosis to identify and differentiate *M bovis* from *M tuberculosis*,[1–4,7] with the result that all cases can be assumed to be caused by *M tuberculosis*. Hence, the available data for zoonotic tuberculosis do not accurately represent the true incidence of this disease.

Other issues further complicate our understanding. Most published data for zoonotic tuberculosis in people come from studies done within different epidemiological settings (eg, areas in which bovine tuberculosis is or is not endemic) without any standardisation of study design, such as population demographics, patient inclusion criteria, sample size, and laboratory methods used to isolate and differentiate *M bovis*.[1–4,7] Cases of zoonotic tuberculosis are commonly reported as a proportion of the total number of human tuberculosis cases. However, these proportions are usually not based on nationally representative data. Instead, they are often derived from studies involving only specific and selected groups of patients, such as those presenting to tertiary referral hospitals. Additionally, the risk for disease increases in areas where bovine tuberculosis is endemic and where people live in conditions that favour direct contact with infected animals (ie, farmers, veterinarians, and slaughterhouse workers) or animal products (unpasteurised milk and untreated animal products[3,8]). Additionally, areas where bovine tuberculosis is endemic sometimes overlap with areas where HIV prevalence is high (ie, in some African countries). Consequently, it is not surprising that the reported proportions of human tuberculosis cases caused by *M bovis* are highly variable. Without standardisation of study design, the international comparability of such studies is diminished.

Despite the limitations with data quality and representativeness regarding the current zoonotic tuberculosis situation, the proportion of cases reported in some studies is concerning. For example, in the USA, *M bovis* accounts for 1·4% of human tuberculosis cases annually;[9] however, in areas of the USA with large foreign-born populations (mostly Hispanic people and binational residents along the USA and Mexico border region), the prevalence of *M bovis* in people has been steadily increasing.[10–12] In San Diego, CA, USA, *M bovis* accounted for 45% of tuberculosis cases in children and 6% of adult tuberculosis cases.[10,11] One study in California found that the mortality rates during treatment were higher for patients with *M bovis* than for patients with *M tuberculosis*,[10] even after adjustment for HIV infection status. Other studies have found variable proportions of *M bovis* infection among assessed subgroups of tuberculosis patients, such as in Mexico (28%),[13] Nigeria (15%),[14] Tanzania (16%),[15] Ethiopia (17%),[16] India (9%),[17] and Turkey (5%).[18]

We consider that reporting zoonotic tuberculosis cases as a relative proportion of all tuberculosis cases obscures the fact that even a small proportion of the approximately 9 million estimated tuberculosis cases per year globally[19] still represents a substantial absolute number of zoonotic tuberculosis cases. For example, with use of available data,[1] WHO estimated that in 2010 there were 121 268 new cases of zoonotic tuberculosis of which an estimated 10 545 deaths were due to *M bovis* globally.[20] We agree with previous statements[2] indicating that it is not recommended to extrapolate available data for zoonotic tuberculosis from high-income and low tuberculosis burden countries to the global context. In Africa, about 70 000 zoonotic tuberculosis cases have been estimated to occur anually.[1] However, to obtain an accurate picture of the zoonotic tuberculosis burden both nationally and globally, accurate surveillance approaches and laboratory methods should be implemented to report the estimated number of incident zoonotic tuberculosis cases per year.

Public health implications

We consider that acting to address the challenges caused by zoonotic tuberculosis is essential in view of the following facts. First, the true incidence of zoonotic tuberculosis remains uncertain because of the absence of routine surveillance data from most countries. Hence, the number of people contracting zoonotic tuberculosis annually, and thus suffering the health challenges caused by *M bovis* infection might be higher than is currently estimated. On the basis of low available estimates and likely geographical distribution associated with zoonotic tuberculosis risk factors, the number of people with zoonotic tuberculosis largely exceeds the number of people affected by other diseases that have received greater attention, funding, and resources.[21,22]

Second, several clinical features of zoonotic tuberculosis present special challenges for patient treatment and recovery. *M bovis* is naturally resistant to pyrazinamide, one of the four medications used in the standard first-line anti-tuberculosis treatment regimen. Because most patients worldwide begin tuberculosis treatment without identification of the causative mycobacterium species, the risk of inadequate treatment of patients with undiagnosed *M bovis* who do not have drug susceptibility testing is increased (globally in 2014, only 12% of 2·7 million new bacteriologically confirmed tuberculosis cases were tested for drug resistance[23]). In the USA, the recommendation for 9 months of antimicrobial therapy for *M bovis* instead of the standard 6 months of therapy for *M tuberculosis* presents additional challenges due to decreased patient adherence and increased costs associated with prolonged therapy.[24,25] Hence, quantification and assessment of the effect of *M bovis* inherent pyrazinamide resistance on treatment outcomes among zoonotic tuberculosis patients is important.

Third, *M bovis* infection and zoonotic tuberculosis in human beings is often associated with extrapulmonary tuberculosis[26] that might be misdiagnosed or undiagnosed,[27] and therefore initiation of treatment can be delayed because of the complexities of obtaining a sample (eg, lymph nodes aspirates) for culture.

Lastly, zoonotic tuberculosis is mostly a foodborne disease. Therefore, the epidemiology and transmission dynamics differ substantially from that of the airborne disease caused by *M tuberculosis*. However, in view of recent data describing pulmonary tuberculosis caused by *M bovis*,[28–34] *M bovis* airborne transmission among people seems possible and deserves further investigation as a source of secondary transmission.

Control of bovine tuberculosis

The prevention and control of zoonotic tuberculosis needs a cross-sectorial and multidisciplinary approach, linking animal, human, and environmental health. The One Health approach[35,36] is increasingly being endorsed by many prominent organisations[37,38] to comprehensively address the challenges at the animal–human interface. For example, the World Organisation for Animal Health (OIE) recognises bovine tuberculosis as an important animal disease and zoonosis.[39] In 2014–15, using their World Animal Health Information System[40] of 180 member countries, 90 reported the occurrence of bovine tuberculosis, six reported suspecting the presence of bovine tuberculosis, and seven reported having no information about bovine tuberculosis in their cattle population. The Food and Agriculture Organization has prioritised bovine tuberculosis as an important infectious disease that should be controlled at the animal–human interface through national and regional efforts.[41] However, bovine tuberculosis continues to cause important economic losses due to the reduced production of affected animals and the elimination of affected (or all) parts of animal carcasses at slaughter. This economic loss has an important effect on livelihoods, particularly in poor and marginalised communities because bovine tuberculosis negatively affects the economy of farmers (and countries) by losses due to livestock deaths, losses in productivity

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due to chronic disease, and restrictions for trading animals both at the local and international level.[42] Furthermore, extra expenses arise linked to surveillance and regular testing of cattle, removal of infected animals and other in-contact animals in the same herd, and movement control on infected herds. It is important to note that measures to control bovine tuberculosis at the source have proven to be efficient and successful in several countries.[43,44] In the USA, the annual federal appropriation for the bovine tuberculosis programme has levelled off at approximately US$15 million per year since 2005,[45] and more than $200 million in emergency funding was infused into the programme between 2000 and 2008 to fund disease investigation,[45] as well as control and eradication activities when cost exceeded the annual allocations. In Ireland, the cost of the national bovine tuberculosis control programme is €60 million (approximately $67·3 million as of May, 2015) per year,[46] and in the UK the cost is estimated to be more than £1 billion (approximately $1·54 billion as of May, 2015) in 2014–24.[47] Estimates of the economic burden are not available in most low-income countries in which bovine tuberculosis is endemic. In view of the subsistence nature and reliance on animals as a source of livelihood in low-income countries, it is expected that the economic effect to the individual farmer will be important. Implementation of strategies to control bovine tuberculosis based on international standards are necessary to reduce risk and prevent *M bovis* zoonotic transmission to human beings.[48,49] We consider it imperative to show the added economic value and the public health benefits when implementing a One Health approach[50] to prevent and control bovine and zoonotic tuberculosis.

Future actions to address the challenges

The need to reassess and reprioritise formally the burden of zoonotic tuberculosis in people is important. The challenges faced by people with zoonotic tuberculosis might not be proportional to the scientific attention and resources allocated in recent years to other diseases. The most important and concrete actions to be implemented in the short term to overcome the major challenges caused by zoonotic tuberculosis are: to develop and implement official policy and guidelines clearly outlining priority activities; to implement effective and comprehensive strategies to routinely survey for zoonotic tuberculosis cases; to expand the use of appropriate diagnostic tools to obtain accurate and representative data for the incidence of *M bovis* infections in people, especially in countries where *M bovis* is endemic; and through the successful implementation of these three specific actions, to use the resulting scientific evidence to further inform and advance future policy. Additionally, a public health campaign needs to be implemented to educate policy makers, health-care providers, and the general public to better prevent, diagnose, and treat zoonotic tuberculosis in communities at highest risk. Because of epidemiological and economic differences across regions, these actions should be adapted to the prevailing conditions in different parts of the world.

These specific actions should be complemented in the medium and long term by increasing collaborations between clinicians, researchers, and public health practitioners in the medical, veterinary, social science, economic fields, and authorities under the umbrella of One Health. Combining expertise and efforts from different fields and institutions will broaden the scope of options to address the challenges we still face today at the animal–human interface. Strengthening the link between scientists and regulators will allow an expedited and efficient sharing of scientific information and data that can be used to guide an evidence-based policy making process, and the development of community-tailored prevention and control strategies at the animal–human interface. When designing these prevention and control strategies, people and communities' attitudes and practices towards cattle and their products, as well as health-seeking behaviours and access to health care, should be considered. Finally, investment in research into new technologies for diagnosis and prevention of both bovine and zoonotic tuberculosis should be prioritised.

We believe that priority should be given to the prevention, diagnosis, and treatment challenges that zoonotic tuberculosis still presents today, particularly for the most vulnerable and marginalised communities; and to apply measures to control bovine tuberculosis because this zoonotic disease continues to negatively affect both the health and economy of a considerable number of people, and the health and welfare of animals.

As countries move towards detecting the 3 million tuberculosis cases estimated to be missed annually, and in view of WHO's end TB strategy endorsed by the health authorities of WHO Member States in 2014 to achieve a world free of tuberculosis by 2035,[5] we call on all tuberculosis stakeholders to act to accurately diagnose and treat tuberculosis caused by *M bovis* in human beings. Ultimately, its control at the animal source and the prevention of its transmission to people will be necessary to achieve the ambitious goal of zero tuberculosis deaths, disease, and suffering. Finding and treating every case of tuberculosis, whether caused by *M tuberculosis* or *M bovis*, will count towards the achievement of this ambitious goal.

Contributors
FO-P and PIF wrote the first draft of this Personal View. All authors contributed to the conception of this paper, contributed equally to drafting and revising it critically for important content, provided final approval of the version to be published, agreed to be accountable for all aspects of it, and ensured that questions related to the accuracy of any part of this Personal View were appropriately investigated and addressed.

Conflict of interests
We declare no competing interests.

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