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Tip of the iceberg: Zoonotic tuberculosis in humans caused by *Mycobacterium bovis* - A Call to Action

Francisco Olea-Popelka^{1*}, Adrian Muwonge², Alejandro Perera³, Anna S. Dean⁴, Elizabeth Mumford⁵, Elisabeth Erlacher-Vindel⁶, Simona Forcella⁶, Benjamin J. Silk⁷, Lucica Ditiu⁸, Ahmed El Idrissi⁹, Mario Raviglione⁴, Ottorino Cosivi¹⁰, Philip LoBue⁷, Paula I. Fujiwara¹¹.

¹College of Veterinary Medicine and Biomedical Sciences, Department of Clinical Sciences and Mycobacteria Research Laboratories, Colorado State University, Fort Collins, CO, USA; ²Genetics and Genomics, Roslin Institute, Royal (Dick) School of Veterinary Studies, University of Edinburgh, Edinburgh, United Kingdom; ³United States Embassy, Mexico City, U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Mexico City, Mexico; ⁴Global TB Programme, World Health Organization, Geneva, Switzerland; ⁵Department of Global Capacities, Alert, and Response, World Health Organization, Geneva, Switzerland; ⁶World Organisation for Animal Health (OIE), Paris, France; ⁷Centers for Disease Control and Prevention, Atlanta, GA, USA; ⁸STOP TB Partnership, Geneva, Switzerland; ⁹Animal Production and Health Division, Food and Agriculture Organization of the United Nations, Rome, Italy; ¹⁰Pan-American Foot-and-Mouth Disease Center (PANAFTOSA), Pan American Health Organization/Regional Office for the Americas of the World Health Organization, Duque de Caxias, Brasil; ¹¹International Union Against Tuberculosis and Lung Disease, Paris, France.

*Corresponding author: Francisco Olea-Popelka, College of Veterinary Medicine and Biomedical Sciences, Department of Clinical Sciences and Mycobacteria Research Laboratories, Colorado State University, Fort Collins, USA. Phone: + 970 297 5064.
Email: folea@colostate.edu

Abstract

Mycobacterium tuberculosis is recognized as the primary causal agent of human tuberculosis (TB) throughout the world. However, there is substantial evidence that the burden of *Mycobacterium bovis* (*M. bovis*), the causal agent of bovine TB, may be underestimated in humans as the causal agent of zoonotic TB. In 2013, a systematic review and meta-analysis of global zoonotic TB concluded that the same challenges and concerns expressed 15 years ago remain valid. The challenges faced by people with zoonotic TB may not be proportional to the scientific attention and resources allocated in recent years to other diseases. There is a critical need to reassess the burden of zoonotic TB in humans, especially in areas where bovine TB is endemic and people live in conditions that favor direct contact with infected animals or animal products. As countries move towards detecting the 3 million TB cases estimated to be missed annually, and in light of the World Health Organization (WHO) 'END TB' strategy endorsed by the health authorities of WHO Member States in 2014 to achieve a world free of TB by 2035, we call on all TB stakeholders to act to accurately diagnose and treat TB caused by *M. bovis* in humans.

Introduction

Mycobacterium tuberculosis (*M. tb*) is recognized as the primary causal agent of human tuberculosis (TB) throughout the world. However, there is substantial evidence that the burden of *Mycobacterium bovis* (*M. bovis*), the causal agent of bovine TB, may be underestimated in humans¹⁻⁴. Incorrect extrapolation of data from high-income, low TB burden countries has likely resulted in the misconception that only a small number of humans suffer from pulmonary and extra-pulmonary TB caused by *M. bovis* globally. This has resulted in a general lack of awareness² among healthcare providers and public health officials regarding the importance of *M. bovis* as a causal agent of human TB (hereafter referred as zoonotic TB). In this article, we highlight the global human and veterinary public health challenges posed by zoonotic TB and outline short, medium, and long term actions to improve its prevention, diagnosis, and treatment at the 'animal-human' interface. The proposed actions support the newly aligned policy agendas of both the World Health Organization (WHO), namely its 'END TB' strategy⁵, where every case of TB should be diagnosed and treated, and the broad and comprehensive reach of the United Nations Sustainable Development Goals (SDGs)⁶, presenting a key opportunity to improve the health of communities affected by zoonotic TB.

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Burden

In 2013, a systematic review and meta-analysis¹ of global zoonotic TB concluded that the same challenges and concerns expressed 15 years³ ago remain valid. The two major issues preventing us from understanding the true burden of this disease in humans are: 1) the lack of systematic surveillance for *M. bovis* as a causal agent of TB in people in all low-income, high TB burden countries where bovine TB is endemic, and 2) the inability of laboratory procedures most commonly used to diagnose human TB to identify and differentiate *M. bovis* from *M. tb*^{1-4, 7}, with the result that all cases of TB may be assumed to be caused by *M. tb*. Hence, the available data on zoonotic TB do not accurately represent the true incidence of this disease.

Other issues further complicate our understanding. Most published data on zoonotic TB in humans come from studies conducted within different epidemiological settings (e.g., some studies have come from areas where bovine TB is or is not endemic), without any standardization 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}. Zoonotic TB cases are commonly reported as a proportion of the total number of human TB 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 zoonotic TB disease increases in areas where bovine TB is endemic and people live in conditions that favor direct contact with infected animals (i.e. farmers, veterinarians, and slaughterhouse workers) or animal products (unpasteurized milk and untreated animal products^{3,8}). Additionally, areas where bovine TB is endemic sometimes overlap with areas where HIV prevalence is high (i.e. in some African countries). Consequently, it is not surprising that the reported proportions of human TB cases caused by *M. bovis* are highly variable. Without standardization of study design, the international comparability of such studies is diminished.

Despite the limitations with data quality and representativeness regarding the current zoonotic TB situation, the proportion of zoonotic TB cases reported in some studies is concerning. For example, in the United States (U.S.), *M. bovis* accounts for 1.4% of human TB cases annually⁹, however, in areas of the U.S. with large foreign-born populations (mostly Hispanics and binational residents along the U.S.-Mexico border region), the prevalence of *M. bovis* in people has been steadily increasing¹⁰⁻¹². In San Diego California, *M. bovis* accounted for 45% of TB cases in children and 6% of adult TB cases^{10,11}. Importantly, one study in California found that mortality rates during treatment were higher for *M. bovis* patients when compared to patients infected with *M. tb*¹⁰, even after adjustment for HIV infection status. Other studies have found variable proportions of *M. bovis* infection among evaluated subgroups of TB patients, such as in Mexico¹³ (28%), Nigeria¹⁴ (15.4%), Tanzania¹⁵ (16%), Ethiopia¹⁶ (17%), India¹⁷ (8.7%), and Turkey¹⁸ (5.3%).

We consider that reporting zoonotic TB cases as a relative proportion of all TB cases obscures the fact that even a relatively small proportion of the approximately 9 million estimated TB cases per year globally¹⁹ still represents a considerable absolute number of zoonotic TB cases. It is worth noting that even a 'small' percentage of zoonotic TB patients represent a considerable number of TB patients worldwide. For example, using available data¹, the World Health Organization (WHO) estimated that in 2010, there were 121,268 new cases of zoonotic TB with an estimated 10,545 deaths due to *M. bovis*²⁰, globally. We agree with previous statements² indicating that is indeed not recommended to extrapolate available figures on zoonotic TB from high income, low TB burden countries to the global context. In Africa¹, it has been estimated that 70,000 zoonotic TB cases occur per year. However, in order to obtain an accurate picture of the zoonotic TB burden both at national and global levels, proper surveillance approaches and laboratory methods should be implemented to report the estimated number of incident zoonotic TB cases per year.

Zoonotic TB Public Health Implications

We consider that acting to address the challenges posed by zoonotic TB is essential in view of the following facts:

07 1) The true incidence of zoonotic TB remains uncertain due to the absence of routine surveillance data from most
08 countries. Hence, the number of people contracting zoonotic TB annually, and thus suffering the health
09 challenges posed by *M. bovis* infection may indeed be higher than currently estimated. Based on even low
10 available estimates and likely geographical distribution associated with zoonotic TB risk factors, the number of
11 people suffering from zoonotic TB largely exceeds the number of people affected by other diseases that have
12 received greater attention, funding, and resources^{21,22}

13
14 2) Several clinical features of zoonotic TB present special challenges for patient treatment and recovery. *M. bovis*
15 is naturally resistant to pyrazinamide, one of the four medications used in the standard first-line anti-TB
16 treatment regimen. Given that most patients in the world begin TB treatment without identification of the
17 causative *Mycobacterium* species, this increases the risk of inadequate treatment of patients with undiagnosed *M.*
18 *bovis* who do not have drug susceptibility testing (globally in 2014, only 12% of the 2.7 million new
19 bacteriologically-confirmed TB cases were tested for drug resistance²³). In the US, the recommendation for nine-
20 months of antimicrobial therapy for *M. bovis* instead of the standard six months of therapy for *M. tb*^{24,25} presents
21 additional challenges due to decreased patient adherence and increased costs associated with prolonged therapy.
22 Hence, it is important to quantify and evaluate the impact of *M. bovis*' inherent pyrazinamide-resistance on
23 treatment outcomes among zoonotic TB patients.

24
25 3) *M. bovis* infection and zoonotic TB in humans is often associated with extra-pulmonary TB²⁶, which may be
26 mis- or undiagnosed²⁷ and therefore initiation of treatment can be delayed due to the complexities of obtaining a
27 sample (e.g. lymph nodes aspirates) for culture.

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29 4) Zoonotic TB is mostly a foodborne disease. Therefore, the epidemiology and transmission dynamics differ
30 significantly from that of the airborne disease caused by *M. tb*. However, it is worth noting that in light of recent
31 data describing pulmonary TB caused by *M. bovis*²⁸⁻³⁴, *M. bovis* airborne transmission among people appears
32 possible and deserves further investigation as a source of secondary transmission.

33 34 **Controlling bovine TB**

35
36 The prevention and control of zoonotic TB requires a cross-sectorial and multidisciplinary approach linking
37 animal, human, and environmental health. The One Health approach^{35,36} is increasingly being endorsed by many
38 prominent organizations^{37,38} to comprehensively address the challenges posed at the 'animal-human' interface.
39 For example the World Organisation for Animal Health (OIE) recognizes bovine TB as an important animal
40 disease and zoonosis³⁹. In the years 2014-2015, using its World Animal Health Information System (WAHIS)⁴⁰, of
41 180 member countries, 90 reported the occurrence of bovine TB, 6 reported suspecting the presence of bovine
42 TB, and 7 reported having no information on bovine TB in their cattle population. The Food and Agriculture
43 Organization (FAO) has prioritized bovine TB as an important infectious disease that should be controlled at the
44 animal-human interface through national and regional efforts⁴¹. Today, bovine TB continues to cause important
45 economic losses due to the reduced production of affected animals and the elimination of affected (or all) parts of
46 animal carcasses at slaughter. This has an important impact on livelihoods, particularly in poor and marginalized
47 communities because bovine TB negatively impacts on the economy of farmers (and countries) by losses due to
48 livestock deaths, losses in productivity due to chronic disease, and restrictions for trading animals both at the
49 local and international level⁴². Furthermore, extra expenses arise linked to surveillance and regular testing of
50 cattle, removal of infected animals and other animals ('in contact') in the same herd as well as movement control
51 on infected herds. It is important to note that measures to control bovine TB at the source have proven to be
52 efficient and successful in several countries^{43,44}. In the United States, the annual federal appropriation for the
53 bovine TB program has leveled off at approximately 15 million dollars annually since 2005⁴⁵ and more than 200
54 million dollars in emergency funding was infused into the bovine TB program between 2000 and 2008⁴⁵ to fund
55 disease investigation, control and eradication activities when cost exceeded the annual allocations. In The
56 Republic of Ireland, the cost of the national bovine TB control program is €60 million (~67.3 million US dollars as
57 May 2015) per year⁴⁶, and in the United Kingdom (UK), the bovine TB control program cost is estimated to be
58 more than £1 billion (~1.54 billion US dollars as May 2015) over a 10 years period (2014-2024)⁴⁷. Estimates of
59 the economic burden of bovine TB are not available in most low-income countries where bovine TB is endemic.

60 Given the subsistence nature and reliance on animals as a source of livelihood in low- income countries, it is
61 expected that the economic impact to the individual farmer will be important. Implementing measures for
62 controlling bovine TB, based on international standards^{48,49} are necessary to reduce risk and prevent *M. bovis*
63 zoonotic transmission to humans. We consider it imperative to demonstrate the added economic value as well
64 the public health benefits when implementing a One Health approach⁵⁰ to prevent and control bovine and
65 zoonotic TB.

67 **Actions needed to address the challenges posed by zoonotic TB**

69 There is critical need to reassess and reprioritize formally the burden of zoonotic TB in humans. Indeed, the
70 challenges faced by persons with zoonotic TB may not be proportional to the scientific attention and resources
71 allocated in recent years to other diseases. The four most important and concrete actions to be implemented in
72 the short term to be able to overcome the major challenges posed by zoonotic TB are: first, to develop and
73 implement official policy and guidelines clearly outlining priority activities; second, implement effective and
74 comprehensive strategies to routinely survey for zoonotic TB cases; and third, expand the use of appropriate
75 diagnostic tools to obtain accurate and representative data regarding the incidence of *M. bovis* infection in people
76 especially in countries where *M. bovis* is endemic. Finally, through the successful implementation of these three
77 specific actions, the resulting scientific evidence will be used to better inform and advance future policy.
78 Additionally, a public health campaign needs to be implemented to educate policy makers, health care providers,
79 as well as the general public to better prevent, diagnose, and treat zoonotic TB in those communities at highest
80 risk. Due to epidemiologic and economic differences across regions, these actions should be adapted to the
81 prevailing conditions in different parts of the world.

83 These four specific actions should be complemented in the medium and long term by greater collaborations
84 between clinicians, researchers and public health practitioners in the medical, veterinary, social science,
85 economic fields, and authorities under the umbrella of One Health. Combining expertise and efforts from different
86 fields and institutions will broaden the scope of options to address the challenges we still face today at the
87 animal-human interface with regards to prevention, diagnosis, and control of both zoonotic TB in people and
88 bovine TB. Strengthening the link between scientists and regulators will allow a expedited and efficient sharing of
89 scientific information and data that can be used to guide an evidence-based policy making process as well the
90 development of community-tailored prevention and control strategies at the animal-human interface. When
91 designing these prevention and control strategies, people and communities' attitudes and practices towards
92 cattle and their products, as well as health-seeking behaviors and access to health care should be considered.
93 Finally, investing in research on new technologies for diagnosis and prevention of both bovine and zoonotic TB
94 should be prioritized.

96 We believe greater priority should be given to the prevention, diagnosis, and treatment challenges that zoonotic
97 TB still poses today, particularly for the most vulnerable and marginalized communities, and to apply measures
98 to control bovine TB due to the fact this zoonotic disease continues to negatively impact both the health and
99 economy of a considerable number of people, as well the health and welfare of animals.

01 As countries move towards detecting the 3 million TB cases estimated to be missed annually, and in light of the
02 WHO 'END TB' strategy endorsed by the health authorities of WHO Member States in 2014 to achieve a world
03 free of TB by 2035⁵, we call on all TB stakeholders to act to accurately diagnose and treat TB caused by *M. bovis* in
04 humans. Ultimately, its control at the animal source and the prevention of its transmission to humans will be
05 necessary to achieve the ambitious goal of zero TB deaths, disease, and suffering. Finding and treating every case
06 of TB, whether caused by *M. tb* or *M. bovis*, will count towards the achievement of this ambitious goal.

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76 **Contributors:**

- 77 • Francisco Olea-Popelka and Paula I. Fujiwara wrote the first draft of this 'Personal View'.
- 78 • Francisco Olea-Popelka, Adrian Muwonge, Alejandro Perera, Anna S. Dean, Elizabeth Mumford, Elisabeth
79 Erlacher-Vindel, Simona Forcella, Benjamin J. Silk, Lucica Ditiu, Ahmed El Idrissi, Mario Raviglione,
80 Ottorino Cosivi, Philip LoBue, and Paula I. Fujiwara contributed substantially to its conception.
- 81 • All of the authors equally contributed to drafting and revising it critically for important content;
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