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

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

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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 humans[1–4]. 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 awareness[2] 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' strategy[5], 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.

Burden

In 2013, a systematic review and meta-analysis[1] of global zoonotic TB concluded that the same challenges and concerns expressed 15 years[3] 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 annually[9], 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 increasing[10–12]. 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 Mexico[13] (28%), Nigeria[14] (15·4%), Tanzania[15] (16%), Ethiopia[16] (17%), India[17] (8·7%), and Turkey[18] (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 globally[19] 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 data[1], 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 statements[2] 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 Africa[1], 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:

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

2) Several clinical features of zoonotic TB 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-TB treatment regimen. Given that most patients in the world begin TB treatment without identification of the causative *Mycobacterium* species, this increases the risk of inadequate treatment of patients with undiagnosed *M. bovis* who do not have drug susceptibility testing (globally in 2014, only 12% of the 2.7 million new bacteriologically-confirmed TB cases were tested for drug resistance [23]). In the US, the recommendation for nine-months of antimicrobial therapy for *M. bovis* instead of the standard six months of therapy for *M. tb*[24,25] presents additional challenges due to decreased patient adherence and increased costs associated with prolonged therapy. Hence, it is important to quantify and evaluate the impact of *M. bovis*' inherent pyrazinamide-resistance on treatment outcomes among zoonotic TB patients.

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

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

Controlling bovine TB

The prevention and control of zoonotic TB requires 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 organizations[37,38] to comprehensively address the challenges posed at the 'animal-human' interface. For example the World Organisation for Animal Health (OIE) recognizes bovine TB as an important animal disease and zoonosis[39]. In the years 2014-2015, using its World Animal Health Information System (WAHIS)[40],of 180 member countries, 90 reported the occurrence of bovine TB, 6 reported suspecting the presence of bovine TB, and 7 reported having no information on bovine TB in their cattle population. The Food and Agriculture Organization (FAO) has prioritized bovine TB as an important infectious disease that should be controlled at the animal-human interface through national and regional efforts[41]. Today, bovine TB 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 has an important impact on livelihoods, particularly in poor and marginalized communities because bovine TB negatively impacts on the economy of farmers (and countries) by losses due to livestock deaths, losses in productivity 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 animals ('in contact') in the same herd as well as movement control on infected herds. It is important to note that measures to control bovine TB at the source have proven to be efficient and successful in several countries[43,44]. In the United States, the annual federal appropriation for the bovine TB program has leveled off at approximately 15 million dollars annually since 2005[45] and more than 200 million dollars in emergency funding was infused into the bovine TB program between 2000 and 2008[45] to fund disease investigation, control and eradication activities when cost exceeded the annual allocations. In The Republic of Ireland, the cost of the national bovine TB control program is €60 million (~67·3 million US dollars as May 2015) per year[46], and in the United Kingdom (UK), the bovine TB control program cost is estimated to be more than £1 billion (~1·54 billion US dollars as May 2015) over a 10 years period (2014-2024)[47]. Estimates of the economic burden of bovine TB are not available in most low-income countries where bovine TB is endemic.

Given the subsistence nature and reliance on animals as a source of livelihood in low- income countries, it is expected that the economic impact to the individual farmer will be important. Implementing measures for controlling bovine TB, based on international standards[48,49] are necessary to reduce risk and prevent *M. bovis* zoonotic transmission to humans. We consider it imperative to demonstrate the added economic value as well the public health benefits when implementing a One Health approach[50] to prevent and control bovine and zoonotic TB.

Actions needed to address the challenges posed by zoonotic TB

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

These four specific actions should be complemented in the medium and long term by greater 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 with regards to prevention, diagnosis, and control of both zoonotic TB in people and bovine TB. Strengthening the link between scientists and regulators will allow a expedited and efficient sharing of scientific information and data that can be used to guide an evidence-based policy making process as well 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 behaviors and access to health care should be considered. Finally, investing in research on new technologies for diagnosis and prevention of both bovine and zoonotic TB should be prioritized.

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

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

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