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Zoonotic Tuberculosis – The Changing Landscape

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ABSTRACT

Despite slow reductions in the annual burden of active human tuberculosis (TB) cases, zoonotic TB (zTB) remains a poorly monitored and an important unaddressed global problem. There is a higher incidence in some regions and countries, especially where close association exists between growing numbers of cattle (the major source of *Mycobacterium bovis*) and people, many suffering from poverty, and where dairy products are consumed unpasteurised. More attention needs to be focused on possible increased zTB incidence resulting from growth in dairy production globally and increased demand in low income countries in particular. Evidence of new zoonotic mycobacterial strains in South Asia and Africa (e.g. *M. orygis),* warrants urgent assessment of prevalence, potential drivers and risk in order to develop appropriate interventions. Control of *M. bovis* infection in cattle through detect and cull policies remain the mainstay of reducing zTB risk, whilst in certain circumstances animal vaccination is proving beneficial. New point of care diagnostics will help to detect animal infections and human cases. Given the high burden of human tuberculosis (caused by *M. tuberculosis)* in endemic areas, animals are affected by reverse zoonosis, including multi-drug resistant strains. This, may create drug resistant reservoirs of infection in animals. Like COVID-19, zTB is evolving in an ever-changing global landscape.

Introduction

A zoonosis is an infection directly transmissible from animals to humans naturally (WHO) (WHO, 2020b) and for this to happen regularly, there needs to be a reservoir in an animal population. The majority of zoonoses occur where there is close contact between humans and relatively abundant animal species (Johnson et al., 2020) (i.e. mostly companion animals and those in the animal-based food system with many indirect zoonotic infections occurring through meat and animal product consumption). This

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is also true for zoonotic tuberculosis (zTB). Tuberculosis (TB) causing organisms include *M. tuberculosissensu stricto* and *M. africanum*, causing the majority of human disease. A number of other organisms from the *M. tuberculosis* complex (MTBC), present in animals and the environment, can cause zTB, these include *M. canetti, M. bovis, M. caprae, M. microti, M. pinnipedii, M. mungi,* and *M. orygis.* Here we provide a contemporary view on the status of zTB globally, emerging trends, research gaps as well as recent advances in the agricultural, veterinary and medical sciences which can help to re-focus and promote better policy on this persistent and still poorly documented disease.

Human TB and the zoonotic contribution

TB is consistently the most impactful bacterial disease to affect humanity, with a quarter of all humans infected, and is responsible for the greatest number of infection related deaths, as well as long term disability (WHO, 2020c). The 2020 World Health Organization (WHO) Global Tuberculosis Report (WHO, 2020a) estimates that in 2019, 10 million people (range, 8.9–11.0 million) developed TB disease of which approximately 1.2 million people died, with a further 208,000 deaths attributed to the TB-HIV syndemic (WHO, 2020a). In addition, effects from the coronavirus disease 2019 (COVID-19) pandemic is projected to increase the number of TB cases by 6.3 million in the next five years or an additional 20% deaths in next five years (Cilloni et al., 2020; Hogan et al., 2020; Stop TB partnership, 2020), delaying the WHO End TB Strategy (WHO, 2014). This is mainly due to reduced case finding, the deviation of resources to handle the COVID-19 pandemic in endemic areas, and the interruption of TB treatment programs in many low-income countries.

Although TB remains a global challenge, cases are highly concentrated in very specific parts of the world, affecting areas where poverty and high population density overlap. This is not surprising for an infection that is human density depended linked to poverty, social stigma, poor public awareness, and overwhelmed health systems lacking resources for TB transmission prevention and treatment (Bapat et al., 2017). Nearly 90% of all human TB cases are located in South Asia, East Asia (China), South East Asia (Philippines, Indonesia) and, the most populous countries in Africa (South Africa and Nigeria, where the addition of HIV-derived immunosuppression facilitates the progression of *M. tuberculosis* infection to active TB disease) (WHO, 2020a). A further concern is increasing multi-drug resistant (MDR)-TB, which accounted for 206,030 reported cases (30% of the estimated total) in 2019, associated with an estimated 31,000 deaths (WHO, 2020a).

Animal TB burden

The animal TB burden is highly variable across countries and continents, with main variations according to predominant livestock systems. Although the available data may be biased due to different sampling strategies and diagnostic capacities, the highest animal prevalence is reported from the Americas and Europe (Ramos et al., 2020).

Zoonotic TB burden

Of 10 million people currently with new active TB, 140,000 (range, 69,800–235,000) are estimated to be new cases of zTB (1.4%) of which an approximately 11,400 (8.1%, range 4,470-21,600) died (WHO, 2020a). However, zTB disease is largely underreported and, these wide ranges are indicative of major diagnostic challenges and poor public health surveillance and reporting structures in endemic countries. The highest numbers were reported from Africa (68,900) and South East Asia (43,400) (Ramos et al., 2020) (WHO, 2020a). South-East Asia comprises almost 44% of the global TB burden (WHO, 2020a). This region disproportionately shared TB deaths (38% of global burden) (WHO, 2020a).

Although South Asia has the highest burden of TB potentially related to high rates of poverty, rapid urbanization, high population density, higher prevalence of diabetes and high air pollution (Basnyat et al., 2018), the reported burden of zTB is relatively low. However, this may be partially explained by insufficient laboratory facilities and lack of accurate identification of the causative agent of zTB (*M. orygis* seems to be the major pathogen in Indian cattle, *Bos indicus*) (Brites et al., 2018). The region possesses multiple risk factors for zTB including high human-animal density, close and frequent physical contact with infected animals, inadequate disease control measures, as well as consumption of unpasteurized milk and milk products (Bapat et al., 2017; Mukherjee et al., 2018). For example India has an estimated 21.8 million (95% CI: 16.6, 28.4) infected cattle in a rapidly growing dairy sector (Srinivasan et al., 2018)

In contrast, the TB incidence in the European region (WHO Regional Office for Europe, 2021) is among the lowest in the world with a consistent decline since 2015 with currently being reported 10 cases per 100,000 population, unevenly distributed across the European Union/European Economic Area. zTB cases in this region as a proportion of TB cases is <0.01% (Müller et al., 2013) and most cases are caused by *M. bovis* and *M. caprae*.

Given the limited point of care (POC) diagnostics and poor reporting there is no reliable data to determine if zTB incidence and prevalence is going up or down in many regions. Rapid testing could assist veterinarians and farmers to quickly diagnose TB, so infected animals can be separated from the rest of the herd. Current zTB burden and mortality estimates are all based on *M. bovis*, the most commonly diagnosed cause of zTB globally, but essentially ignoring the contribution of other MTBC species. Emerging evidence suggests that several other mycobacterial species such as *M. orygis* are also contributing to zTB (Duffy et al., 2020), but laboratory services for accurate identification and speciation are not universally available, thus the true global burden of zTB is without a doubt much higher.

Past experience directs attention to areas where living conditions favour direct contact with infected cattle, that may facilitate aerosol spread, or ingestion of unpasteurised milk products (e.g. queso fresco). There are rare transmission events from sheep and goats caused by *M.caprae* and from non-milk-producing species such as rodents (*M. microti)*, banded mongooses (*M. mungi*), as well as seals and sea lions (*M. pinnipedii*) with increasing reports of *M. orygis* from Indian cattle (Jagielski et al., 2016; Brites et al., 2018; Duffy et al., 2020).

The detrimental impact of different MTBC species goes beyond human health, since they also affect the health of cattle and other animal species with consequential impact on livelihoods, animal-based industrial food systems, and conservation of wildlife species, including many iconic species such as bison, rhino's, lions and even highly threatened African wild dogs (De Garine-Wichatitsky et al., 2013; Sichewo et al., 2019; Marais et al., 2019; Luciano and Roess, 2020). The existence of zTB animal carriers adds to the problem with e.g. deer, buffalo, European badgers, wild boar, brushtail possums, bison, goats, camelids (including alpaca, llama, camels), pigs, antelopes, dogs and cats, a number of species implicated in cases in Europe in addition to the primary reservoir cattle. However, incidence and/or risk of transmission of MTBC species from free-living wildlife species to humans, even among those with high prevalence such as African buffalo and European badgers, to-date remains very low (Biet et al., 2005).

Some risk factor surveys have explored the association between cattle TB prevalence and mixing with wildlife, and prevalence of

cattle with TB is estimated by some (Sichewo et al., 2019) to be high in situations of intense co-grazing and sharing water resources in Africa and USA. However, the force of infection in these studies and other examples cited is not conclusive and uncertainties remain on this question. For example, there are questions on directionality and rate of transmission between badgers and cattle in TB studies in the UK (Sandoval Barron et al., 2018). A rare study of this interface in a mixed system in Uganda showed infection prevalence rates that were ten times higher in wild buffalo than in co-grazing cattle (Meunier et al., 2017), suggesting a low transmission rate from wildlife to cattle.

Reverse zoonoses

Reverse zoonoses or zooanthroponoses have been recorded in studies from Africa and India (Duffy et al., 2020). Studies in Nigeria (Adesokan et al., 2019) identified *M. bovis* in humans and a reverse zTB transmission from an emerging Uganda I *M. tuberculosis* strain between pastoralists and cattle evidenced by MIRU-VNTR. In this study, 59.2% Uganda I/SIT46 (pastoralists =28; cattle =1), 16.3% Latin American Mediterranean/SIT61 (pastoralists =8), 2.0% T/SIT53 (pastoralists =1) had strains of *M. tuberculosis* and new strains of *M. bovis* and *M. africanum* (Adesokan et al., 2019). Furthermore, *M. tuberculosis* has been isolated in a slaughtered goat in Nigeria and this was attributed to close human-animal contact in most settings in the country (Cadmus et al., 2009; Adesokan et al., 2019).

Importantly, an even more troubling possibility in some settings (particularly where there are poor animal management and meat inspection coupled with high burden of MDR-TB) is the prospect of animals serving as a vehicle of transmission for drug resistant *M. tuberculosis* as a result of reverse zoonosis at the human-animal interface (Botelho et al., 2014; Cadmus et al., 2019). In India, *M tuberculosis* (MANU strain) was found to be more prevalent in cattle than *M. bovis* (Sweetline Anne et al., 2017). *M. tuberculosis* MANU1 strain infection in cattle is likely due to spillover from humans in TB endemic areas (Sweetline Anne et al., 2017; Mukherjee et al., 2018) and demonstrates the potential for MDR-TB strains to acquire an animal reservoir that could then pose a future risk to human TB control. Reverse zoonoses with *M. tuberculosis* has also been reported in zoo animals especially in elephants, primates and felines (Montali et al., 2001). *M. orygis* infection has also been recorded in primates in zoo environments, suggesting shedding from humans or other infected animals.

Molecular studies and diagnostics

M. orygis was first reported as a causative agent of TB in an oryx (*Oryx gazella, Family: Bovidae*) (van Ingen et al., 2012), but has since been identified in many other species as well. These include African buffalo (Gey van Pittius et al., 2012), in a dairy cow and its caretaker from New Zealand (Dawson et al., 2012), in free-ranging rhinoceros (*Rhinoceros unicornis*) from Nepal (Thapa et al., 2016) and in 18 cattle from a dairy farm and several rhesus macaque (*Macaca mulatta*) in a zoo which died of TB from Bangladesh (Rahim et al., 2017). In addition, a single case of lymphadenitis caused by *M. orygis* was reported from a person in New York, USA (Marcos et al., 2017).

M. orygis is probably a previously unidentified pathogen of Indian cattle (Brites et al., 2018), but it seems increasingly important as a global pathogen. Isolation of *M. orygis* from humans and its apparent prevalence in cattle in South Asia raises a question as to whether this newly recognized pathogen could be included as additional causative agent of zTB. In this context, Duffy et al. (2020) characterized 940 cultures of *M. tuberculosis* complex from hospitalized TB patients in India by modified PCR, deletion analysis and whole genome sequencing (WGS) for adequate identification of all MTBC species. Results showed that 97.1% were MTBC, *M. orygis* 0.7% and *M. bovis* BCG 0.5%, none were from wild strains of *M. bovis* and only 1.6% nontuberculous Mycobacteria. Twenty-five isolates were assigned subspecies by WGS as compared with 715 MTBC sequences obtained from the database. The seven *M. orygis* isolates from human samples have descended from cattle. This study presents a convincing case that zTB case definitions should include human TB caused by *M. orygis*.

TB in live animals is mainly diagnosed using the intradermal tuberculin skin test (TST) to detect delayed hypersensitivity response to tuberculin. Culture or molecular techniques (PCR and WGS) are used for microbiological confirmation of the TB-causing agent. Blood tests based on host immune responses (e.g. IFN-ɣ release assay, ELISA, ELISpot, Differentiating Infected from Vaccinated Animal [DIVA] test) (Waters et al., 2006; Vordermeier et al., 2011) are also used for identification of infection with *M. bovis*, but its accuracy for diagnosing infection with other zTB agents has not been established. For all these tests, the identification of the zTB agent depends on proper collection of quality specimen. However, these tests are not routinely done in high burden countries, due to lack of resources and adequately trained personnel. This is particularly the case for molecular diagnostics, meaning that TB data often lack the resolution required for epidemiological studies.

To tackle the diagnosis challenge, we need to learn from current efforts towards the improvement of human TB diagnosis in the field. There are efforts to adapt current POC tests used for human TB to detect potentially zTB organisms in cattle (Kelley et al., 2020) by investigating the presence of specific and unique MTBC antigens (biomarkers) in urine, milk and meat juice to quickly identify if an animal has TB (e.g. Alere Determine^{TM} Lipoarabinomannan (LAM) Ag test, SILVAMP TB-LAM (FujiLAM) test). Other tests are based on detecting the presence of specific antibodies in serum against unique cell wall components of the MTBC cell wall (e.g. Lionex test, P22 ELISA). Much work needs to be done to increase the sensitivity of these tests to detect zTB organisms in animals.

While the research for new and improved tests continues, the value of the comparative intradermal tuberculin test (CITT) in the herd diagnosis of TB should not be ignored in settings where the test is logistically practical to perform. The diagnostic performance offers a sensitivity and specificity comparable to current blood-based tests if conducted by well-trained animal health professionals. The use of the CITT in developing countries has been largely discontinued because of an erosion of technical expertise in performing and interpreting the test. The institution of a harmonised training programme across an endemic region, based on validated test and interpretation parameters could form a valuable foundation for the monitoring of the TB status of cattle populations and would facilitate the validation of new and improved tests.

Vaccine development

Outcomes of clinical efficacy trials for preventing the development of active TB disease in people infected with *M. tuberculosis* using the adjuvanted protein subunit vaccine M72/AS01E give some hope at least for this form of the disease (Schrager et al., 2020). Historically, eradication of bovine TB from cattle herds by test-and-slaughter or test-and-cull of infected animals was preferred over control by vaccination of cattle. Eradication efforts, have, however, proven unsuccessful possibly because a wildlife reservoir is present or where eradication is not affordable or culling is culturally unacceptable. Oral BCG administration has demonstrated significant protection against human (Colditz et al., 1995) and animal TB (Buddle et al., 2018).

Oral BCG vaccine administered to wildlife reservoirs including European badgers, brushtail possums, wild boar, and deer has shown to induce protection against TB and could prove to be a practical means to vaccinate these species at large scale (Buddle et al., 2018). This offers a potential solution in settings where "test and cull" is not an option and especially in wildlife species threatened by extinction. A major constraint of using BCG vaccination in cattle is the fact that trading blocs like the European Union prohibit the use of TB vaccines in cattle, since vaccination compromises the interpretation of traditional TB diagnostic tests. However, these concerns have been addressed with the development of more specific tests that differentiate infected from vaccinated animals (DIVA®) (Vordermeier et al., 2011) and of a diagnostic compatible BCG vaccine strain not eliciting an immune response in the compatible skin test (Chandran et al., 2019). Although BCG should offer some protection against multiple MTBC species, including *M. orygis*, it should be recognized that protection will not be complete and should be used to complement, rather than replace, more traditional control measures.

Focusing attention on zTB emergence

As currently documented, zTB only accounts for around 1.4% of total TB (Luciano and Roess, 2020) disease burden in humans, which partially explains why it remains a neglected and 'low priority' problem globally, though it may account for about 3% of all TB in Africa. However, the failure of even advanced economies and health systems such as the UK and USA, to eliminate animal TB or reduce risk of zTB to zero in consequence, is concerning. Growing incidence of TB and zTB in certain low and middle income countries, with risks to their population health and migration to other countries, is a stark warning, that failure to control it now, poses a major risk of future emergence, especially in settings where disease rates were traditionally low - as the consumption of milk and meat rises.

The developing challenge is rooted in demographic drivers and risks from growing animal-based food systems and the introduction of so-called 'improved breeds' of cattle for dairy into many settings, particularly Africa, which are highly susceptible to *M. bovis* (Ohlan, 2014). Equally important is the lack of veterinary control measures and the consumption of unpasteurised milk products. This warrants a review of development and design of animal industry and zTB risk factors in these settings. Whilst new challenges are emerging and concerns over zTB aired over two decades ago, they remain valid today (Olea-Popelka et al., 2017; Zumla et al., 2020).

The changing landscape of zTB must be given more political and scientific attention. This is crucial due to the inherent resistance of the pathogen to first line medication. zTB is preventable in humans by effectively controlling the disease in cattle. However, control measures against the risk of zTB are not universally suitable for different cattle farming systems or affordable to developing nations. It should be the responsibility of a multi-disciplinary task team taking a One Health approach to identify and evaluate control measures, which are culturally acceptable as well as practical and affordable for veterinary services to implement.

Conclusion

Although some progress has been made towards achieving the UN goals on reducing human TB disease, animal TB persists and zTB remains a risk with a poorly defined incidence. COVID-19 will likely make TB eradication targets more difficult to attain, while zTB is proving difficult to address with many diagnostic and management challenges. Wildlife pose a low risk for zTB transmission to humans, but iconic species may be threatened by increased disease rates. Food safety interventions, such as milk pasteurisation, are the best tool currently to prevent zTB. However, as the use of unpasteurised dairy products grows globally the incidence of zTB is predicted to increase, as argued for India.

Better molecular diagnostic tools are enabling more precise determination of zTB causes, driven by a variety of MTBC species, the most notable of which is *M orygis* in South Asia. Given this changing landscape, there is an urgent need to review the gaps in the Road Map for Zoonotic TB (WHO, 2017) in order to enhance the implementation of the 10 priority areas identified by WHO in earlier statements for tackling zTB in the world.

Ethical approval

Ethical approval was not required.

Conflict of interest

All authors have a specialist interest in ONE-HEALTH and zoonotic diseases. All authors declare no conflicts of interest.

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