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An overview of Zoonotic Tuberculosis

Ishita Gupta[1], Rahul Singh*[2]
[1]PhD Scholar, Division of Veterinary Public Health, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly
[2]PhD Scholar, Department of Veterinary Pathology, Lala Lajpat Rai University of Veterinary & Animal Sciences, Hisar
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Introduction

Tuberculosis (TB) is a chronic infectious zoonotic disease and ranks among the top three global infectious diseases causing fatalities, including AIDS and Malaria. In humans, tuberculosis is considered an occupational hazard for people who have continuous exposure to livestock, like veterinarians and farmers. Consumption of unpasteurized milk and milk products is the main source of infection for humans, and infection rarely occurs by inhalation of infective droplets. According to the World Health Organization's Global Tuberculosis Report (2020), approximately 10.6 million people were infected with TB worldwide in the year 2019, of whom nearly 1.2 million died, including 2,08,000 deaths from the TB-HIV syndemic. The highest number of TB cases were reported in WHO's Southeast Asian region (46%), followed by the African region (23%), and the Western Pacific region (18%).

Global burden of zoonotic tuberculosis

Of the 10 million TB cases reported in 2019, approximately 1.4 per cent (1,40,000) cases were zoonotic TB. However, the estimation of the true burden of the disease still remains a major challenge due to the lack of proper public health surveillance data, insufficient diagnostic facilities, and the high underreporting of cases in most countries.

Although Southeast Asia ranks top in human TB cases worldwide, the reported burden of zoonotic tuberculosis cases is comparatively low. This could be ascertained due to the lack of sufficient diagnostic facilities for confirmatory diagnosis of the disease (Basnyat *et al.,* 2018). In contrast, the proportion of zoonotic tuberculosis cases is lowest in the European region, i.e., < 0.01 per cent (Muller *et al.,* 2013).

A meta-analysis study conducted by Srinivasan *et al.,* (2018) for estimating the prevalence of bovine tuberculosis (bTB) in India, which included 285 publications from the years 1942 to 2016**,** revealed the prevalence of tuberculosis in cattle and buffaloes as 6.3 and 4.4 percent, respectively, and the pooled prevalence was found to be 7.3 percent. They also found prevalence according to the type of production system, in which gaushalas had the highest prevalence (19.1%), followed by organised farms (5.1%) and rural areas (4.4%).

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Etiology and transmission of zoonotic tuberculosis

Mycobacterium bovis is the main cause of zoonotic tuberculosis and is responsible for 10–15 per cent of human tuberculosis cases in developing countries. *M. bovis* is an acid-fast, non-motile, non-spore forming, rod-shaped bacteria that belongs to the *Mycobacterium tuberculosis* complex (MTBC), which includes *M. tuberculosis*, *M. africanum*, *M. bovis*, *M. microti*, *M. caprae,* and *M. pinnipedii.* Recently, a new sub-species of MTBC, *Mycobacterium orygis*, has been reported worldwide, and in the year 2017, it was reported from a cattle farm in Chennai, India. Cattle act as the primary reservoir of *M. bovis,* whereas other species, including humans, goats, pigs, buffaloes, dogs, primates, badgers, deer, possums, and bison, act as susceptible hosts. Infected cattle can transmit the infection to humans either directly through the aerosol route or through the consumption of unpasteurized milk and milk products.

Clinical signs

Animals: Tuberculosis is a chronic, debilitating disease in cattle. The respiratory system is most severely affected. However, when the disease progresses to advanced stages, extrapulmonary involvement is also seen. Common clinical signs include progressive weight loss, weakness, inappetence, low-grade fever, coughing, and enlargement of superficial lymph nodes (commonly retropharyngeal lymph nodes).

Humans: Zoonotic tuberculosis mainly affects the respiratory system, along with extrapulmonary involvement (bones, intestines, and brain). TB has a prolonged course in humans. The most commonly occurring clinical signs include persistent coughing, low-grade fever, night sweats, fatigue, weight loss, and breathlessness, especially during physical activities.

Diagnosis

TB in live animals is diagnosed using the tuberculin skin test, which is an OIE-recommended delayed-type hypersensitivity test that measures an increase in skin fold thickness 72 hours after injecting purified protein derivative (PPD) intradermally. PPD is obtained from the *M. bovis* AN5 strain, and the test can be performed as a single intradermal test (SIT) or a comparative cervical test (CCT). Although isolation is considered as the gold standard for confirmation of TB, it requires more than six weeks and has low diagnostic sensitivity. The interferon-gamma release assay (IGRA) is another way of measuring immune response. It involves the release of interferon gamma from sensitised T-lymphocytes 24 hours after administering the PPD to the infected animals and thus is a measure of cell-mediated immune response.

In humans, sputum smear microscopy is used for mass screening, and it has a sensitivity of 60–65 per cent. Further, the Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) is a real-time PCR cartridge-based assay that can directly detect *M. tuberculosis* from clinical samples by amplifying DNA/RNA segments and can also detect rifampicin resistance within 2 hours. The mostly used LJ medium for *M. tuberculosis* inhibits the growth of *M. bovis,* and thus the majority of cases remain undetected. Novel techniques like whole genome sequencing and spoligotyping require laboratory infrastructure and trained personnel and therefore cannot be used for routine purposes.

Vaccination and treatment

Bacillus Calmette-Guérin (BCG) vaccine is primarily used for the prevention of tuberculosis in humans. BCG vaccine is produced from a live attenuated *M. bovis* strain that is sub cultured in Middlebrook

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7H9 culture medium over a period of 13 years. Danish 1331, a WHO-recommended TB vaccine strain, is commonly used. In cattle, there is a limitation associated with BCG vaccine use because vaccinated animals can react positively to the tuberculin test, therefore leading to the culling of false positive animals.

Treatment

Treatment of bovine tuberculosis is not recommended due to the highly infectious nature of the disease and cost effectiveness in animals. Therefore, for effective control, a test and slaughter policy should be implemented. However, in humans, the internationally recommended (Directly Observed Treatment Short course) therapy by the WHO is used as a TB control strategy. It is the best curative method available for human TB treatment. The course of DOTS therapy is six months, consisting of an initial intensive phase of two months followed by a continuous phase from the 3^{rd} to the 6^{th} month.

Key challenges associated with zoonotic TB

Clinical differentiation between infections caused by *M. bovis* and *M. tuberculosis* is not possible. Furthermore, *M. bovis* TB infection in humans causes extrapulmonary lesions in addition to pulmonary lesions, and conventionally used diagnostic tests cannot differentiate between *M. bovis* and *M. tuberculosis* infections, thereby leading to underreporting of the diseases. Treatment of zoonotic tuberculosis poses a major challenge due to the emerging resistance of tuberculosis microbe against conventionally used anti-tuberculosis drugs in humans. *M. bovis* is naturally resistant to Pyrazinamide, which is one of the four currently used standard first-line anti-TB drugs. Resistance to additional drugs has also been detected in some *M. bovis* isolates, including rifampicin and isoniazid. As most healthcare providers start the treatment without proper drug susceptibility testing, patients with zoonotic TB receive inadequate treatment, which further increases the chances of multidrug-resistant (MDR-TB) and extensively drug-resistant TB (XDR-TB).

Ten priority areas for tackling zoonotic TB

The World Health Organisation (WHO), the World Organisation for Animal Health (OIE), the Food and Agriculture Organisation of the UN (FAO), and the International Union Against Tuberculosis and Lung Disease (The Union) launched the roadmap for tackling zoonotic TB in October 2017. The roadmap is based on a One Health approach, recognising the need for interdependence between human and animal health sectors to address the major health and economic impacts associated with the disease, and is based mainly on three core themes:

1. **Improving the scientific evidence base**
    - Systematically survey, collect, analyse and report better-quality data.
    - Expanding the availability of appropriate diagnostic tools.
    - Identifying and addressing research gaps in zoonotic and bovine TB.
2. **Reducing transmission between animals and humans**
    - Ensuring food safety.
    - Improving animal health.
    - Reducing the risk of transmission of zoonotic TB to humans.
3. **Strengthening intersectoral collaborative approaches**
    - Increasing awareness and establishing effective intersectoral collaboration.
    - Developing and implementing policies and guidelines.

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- Implementing joint interventions.
- Advocate for investments.

Conclusion

The UN Sustainable Development Goals (SDGs) highlight the importance of multidisciplinary approaches to combating TB and improving human health. WHO's End TB Strategy, in the context of the SDGs, calls for the diagnosis and treatment of every TB case, including zoonotic TB cases. Tuberculosis in humans cannot be fully addressed without controlling bovine TB in animals. Therefore, the need of the hour is to have good molecular diagnostic tests for a more accurate diagnosis of cases and to improve food safety by implementing adequate interventions.

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