Zoonotic Tuberculosis

Chapter 1

Tuberculosis in animals and humans

An introduction

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Tuberculosis is an important disease in animals and humans worldwide. It causes substantial morbidity, mortality, and economic loss. There is significant variation in terms of how different organisms of the *M. tuberculosis* complex affect specific animals, including humans. However, there are also important intersections between animals and humans with regard to TB. The best example is the occurrence of *M. bovis* disease in humans and domesticated and wild animals.

The tubercle bacillus infects an estimated 2 billion persons or approximately one third of the world's population, and it is estimated that 1.5 to 2 million people die from TB each year. Ninety-five percent of cases occur in people in developing countries. TB is one of the leading causes of infectious disease-related deaths worldwide [1]. The genus *Mycobacterium* includes several species that cause TB disease in humans and other animals. The *Mycobacterium tuberculosis* complex includes *M. tuberculosis*, *M. cannettii*, *M. africanum*, *M. bovis*, *M. pinnipedii*, *M. mungi*, *M. caprae*, and *M. microti*.

Significant progress has been made toward the elimination of TB caused by *M. tuberculosis* complex from humans in industrialized countries [2]. However, in many countries where TB programs have only recently been established, there has been only limited progress toward control of the disease. The development of drug-resistant (multidrug-resistant and extensively drug-resistant) strains has compromised the efficacy of TB treatment in humans and has markedly increased the cost associated with the use of multiple drug therapies [3]. Moreover, the susceptibility of human immunodeficiency virus (HIV)–infected individuals to *M. tuberculosis* complex is of major concern to public health officials in developing countries where the acquired immune-deficiency syndrome is rampant [4].

M. bovis accounts for only a small percentage of the reported cases of TB in humans; however, it is a pathogen of significant economic importance in wild and domestic animals

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around the globe, especially in countries where little information is available on the incidence of *M. bovis* infection in humans [5–7].

Tubercle bacilli were identified more than 130 years ago. However, a definitive understanding of the pathogenesis of the disease caused by the *M. tuberculosis* complex is deficient [8,9]. The tubercle bacillus enters the macrophage by binding to cell surface molecules of the phagocyte. Ingestion of the tubercle bacillus by phagocytes into the phagosome or intracytoplasmic vacuole protects the organism from the natural defenses in the serum. Following ingestion of the bacillus, lysosomes fuse with the phagosome to form phagolysosomes, and it is there that the phagocytes attempt to destroy the bacillus [10]. However, virulent bacilli have the ability to escape killing. Virulent mycobacteria survive inside a mononuclear phagocyte by inhibiting phagosome fusion with preformed lysosomes, thereby limiting acidification. It has been suggested that the pathogenicity of *M. tuberculosis* complex is a multifactorial phenomenon. However, in cases in which the host response is unable to destroy the bacillus due to conditions that compromise immune function, resulting in low CD4+ T-cell counts, such as immune suppression due to chemotherapy, stress, or HIV, reactivation may occur, resulting in the release of bacilli and transmission of infection.

The susceptibility of different host species varies for the *M. tuberculosis* complex, depending on the route of exposure, the dose of organisms, and the virulence of the strain [11]. Humans, nonhuman primates, and guinea pigs are very susceptible to *M. tuberculosis*. Cattle, rabbits, and cats are susceptible to *M. bovis* and are quite resistant to *M. tuberculosis*. Wild hoofed stock is generally susceptible to *M. bovis*, but few reports are available on the isolation of *M. tuberculosis* [12–14]. Swine and dogs are susceptible to both *M. bovis* and *M. tuberculosis* [15].

In humans, TB is a pulmonary and systemic disease caused by *M. tuberculosis* complex species, predominantly *M. tuberculosis*. TB infections occur when susceptible individuals inhale droplet nuclei containing tubercle bacilli and the droplet nuclei reach the alveoli of the lungs. The tubercle bacilli that reach the alveoli are ingested by alveolar macrophages and the majority of these bacilli are destroyed or inhibited. A small number multiply intracellularly and are released when the macrophages die. If alive, these bacilli may spread through the lymph or bloodstream to more distant tissues and organs, including areas in which TB disease is most likely to develop: the apices of the lungs, the kidneys, the brain, the bones, and through the lymphatic system to regional lymph nodes. This process of dissemination primes the immune system for systemic responses.

Because of the primed immune system, extracellular bacilli attract macrophages and other immunologically active cells. The immune response kills most of the bacilli, and the remaining bacilli are confined through the formation of granulomas. At this point, latent TB infection (LTBI) has been established, which may be detected using the Mantoux tuberculin skin test or interferon-gamma release assays. Within weeks after infection, the immune system is usually able to halt the multiplication of the tubercle bacilli, preventing further progression.

In some people, the tubercle bacilli overcome the defenses of the immune system and begin to multiply, resulting in the progression from LTBI to TB disease. This process may occur soon after or many years after infection. Unless treated, approximately 3%–5% of persons who have been infected with *M. tuberculosis* will develop TB disease in the first

2 years after infection, and another 2%–5% will develop disease at some time later in life. Thus, approximately 5%–10% of persons with normal immune systems who are infected with *M. tuberculosis* will develop TB disease at some point in their lives. Immunocompromised persons have a much higher risk of progression from infection to disease. For example, HIV-infected persons not receiving antiretroviral therapy have an 8% annual risk of progression [16].

TB continues to be an important disease both in humans and animals. It causes substantial morbidity, mortality, and economic loss worldwide. There is significant variation in terms of how different organisms of the *M. tuberculosis* complex affect specific animals, including humans. However, there are also important intersections between animals and humans with regard to TB. Perhaps the best example is the occurrence of *M. bovis* disease in humans and domesticated and wild animals.

M. bovis persists in humans, causing pulmonary and extrapulmonary disease. Unlike transmission of *M. bovis* from cattle to humans, the role of human-to-human airborne transmission in the spread of *M. bovis* has been somewhat controversial [17]; the predominant view has been that human-to-human transmission is a rare event and that it is only likely to occur in populations that are particularly susceptible to TB (e.g., HIV-infected persons). However, reports of clusters of cases with social and molecular epidemiologic links with patients with pulmonary *M. bovis* have suggested that human-to-human transmission does occur, even in nonimmunosuppressed persons [18].

Investigations are needed to elucidate the relative importance of *M. bovis* as regards TB incidence in humans, especially in developing countries [1]. Efforts should be concentrated in countries where HIV infection is widespread, as HIV-infected individuals are more susceptible to mycobacterial disease. Eradication of *M. bovis* in cattle and pasteurization of dairy products are the cornerstones of the prevention of human disease [19]. Standard public health measures used to manage patients with contagious *M. tuberculosis* should be applied to contagious patients with *M. bovis* to stop person-to-person spread. Finally, measures should be developed to identify and control *M. bovis* infection in wild animals, as these animals may be important reservoirs of infection for domesticated food-producing animals.

It is important to emphasize that pathogenic tubercle bacilli have a wide host range; several species of the genus *Mycobacterium* infect humans as well as wild and domestic animals. There is therefore a need for medical and veterinary medical professionals to cooperate in disease outbreaks [20]. This concept has been promoted previously [21]. However, this is of increasing importance in TB control in the twenty-first century because of the occurrence of drug-resistant *M. tuberculosis* complex strains and the immunosuppression of host responses from multiple causes, resulting in increased susceptibility to tubercle bacilli.

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Note

This chapter was originally printed in part as the first of an educational series on *Mycobacterium bovis* as a zoonotic disease and its implications for tuberculosis control in human populations. This series was offered as a reminder that tuberculosis is a disease with an animal reservoir and that therefore ultimate eradication must recognize this animal reservoir and incorporate strategies to deal with it in the global strategy for the control and elimination of tuberculosis in humans. We believe that this has been neglected in the current strategy and needs to be acknowledged and incorporated, however minimally, in future revisions of the global strategy.

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