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ZOONOTIC TUBERCULOSIS. A COMPREHENSIVE *ONE HEALTH* APPROACH

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Abstract The objective of this report is to provide information on *Mycobacterium tuberculosis* complex infections in animals and in humans. Included is information on the susceptibility of different species as well as information on etiology, epidemiology, pathogenesis, diagnosis, prevention and control of this disease. The term One Health has been adopted to describe the unified human medical and veterinary interdisciplinary/multidisciplinary collaborative approach to zoonoses and will be critical for future endeavors in the control of the global TB epidemic. This unified paradigm is ideally suited for control of bovine TB and many other international public health and clinical health issues. Sharing resources and increasing interaction between public health and veterinary medical scientists can raise awareness of 'shared risk' of bovine TB between humans and animals and, in resource-limited situations, can maximize use of existing infrastructure and reduce unnecessary duplication of effort in disease control programs.

Key words: *Mycobacterium tuberculosis*, tuberculosis, *M. bovis*, bovine tuberculosis, *One Health* Approach

Resumen ***Tuberculosis zoonótica. El enfoque integral de la iniciativa* Una Salud.** El objetivo de este artículo es proporcionar información sobre las infecciones por el Complejo *Mycobacterium tuberculosis* en animales y en humanos. Se incluye información sobre la susceptibilidad de diferentes especies, así como sobre la etiología, epidemiología, patogenia, diagnóstico, prevención y control de esta enfermedad. La expresión *UNA SALUD* ha sido adoptada para describir el enfoque unificado de la medicina humana y la veterinaria, de colaboración interdisciplinaria/multidisciplinaria en las zoonosis, que puede resultar fundamental para el control de la endemia mundial de tuberculosis. Este paradigma unificado es especialmente relevante para el control de la tuberculosis bovina. Compartir recursos y lograr una mayor interacción entre la investigación en salud pública y en medicina veterinaria puede elevar la conciencia de "riesgo compartido" de la tuberculosis bovina en humanos y animales y, en situaciones de recursos limitados, puede maximizar el uso de la infraestructura existente y reducir la duplicación innecesaria de esfuerzos en los programas de control de la infección y enfermedad.

Palabras clave: *Mycobacterium tuberculosis*, tuberculosis, *M. bovis*, tuberculosis bovina, enfoque *Una Salud*

Tuberculosis (TB) is a reemerging disease and a significant health problem in humans and animals caused by members of the *Mycobacterium tuberculosis* complex which includes: *M. tuberculosis, M. bovis, M. canettii, M. africanum, M. pinnipedii, M. caprae, M. microti* and *M. mungi*[1, 2]. Genomic analyses have challenged the epidemiological hypothesis that *M. tuberculosis* is a human-adapted variety of *M. bovis* that was acquired from cattle[3]. Predisposing factors include close contact between humans and cattle as some of the groups keep their animals indoors and the custom of drinking raw milk and raw meat and other meat products[4, 5]. A study conducted in San Diego from 1994 to 2000 found that 129 of 1931 cases of tuberculosis were caused by *M. bovis*[6]. It is important to emphasize that 68 (52.7%) of the cases were extra-pulmonary, 33 (25.6%) were in children and 29 (22.5%) were in HIV positive individuals.

Pathogenesis

Tubercle bacilli were identified more than130 years ago; however, definitive information on the pathogenesis of the *M. tuberculosis* complex is not available. Tubercle bacilli that are inhaled usually lodge in the alveolar spaces where they are ingested by macrophages. The tubercle bacillus enters the macrophage by binding to cell surface molecules of the phagocyte[6]. Ingestion of the tubercle bacillus by the phagocytes into the phagosome or in-

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tracytoplasmic vacuole protects the organism from the bactericidal components of serum. Following ingestion of the bacillus, lysosomes fuse with the phagosome to form a phagolysosome and it is there that the phagocytes attempt to destroy the bacillus. Virulent bacilli have the ability to escape destruction and survive inside a mononuclear macrophage by inhibiting phagosome fusion with pre-formed lysosomes, thereby limiting acidification of the phagolysosome. It has been suggested that pathogenicity of *M. tuberculosis* complex is a multifactorial phenomenon requiring the participation of the cumulative effect of several glycolipid complexes such as lipoarabinomannan that may interfere with phagosome maturation[7]. Another glycolipid trehalose- 6,6' dimycolate is associated with virulence and cord formation in liquid culture medium. Other glycolipids such as phosphatidyl inositol mannoside are present in the cell walls of the bacilli.

Protective immunity against mycobacterial infections is dependent on the activation of a cell-mediated immune response. Inflammatory cytokines, i.e. interleukin 1 (IL-1), IL-2 and tumor necrosis factor alpha (TNF-α), produced by mononuclear cells sensitized by mycobacterial antigens recruit natural killer T cells, CD4 T cells, CD8 T cells and gamma delta T cells[6]. These cells produce cytokines that recruit additional cells to the site of infection resulting in the formation of granulomas. Granuloma formation is an attempt of the host to localize the disease process. However, in cases in which the host response is unable to destroy the bacillus due to conditions that compromise immune function such as old age, stress or HIV reactivatio - may occur resulting in the release of bacilli and transmission of infection. Grossly visible lesions in bovidae (Fig. 1) and humans are characterized by a caseous, necrotic center surrounded by a zone of epithelioid cells, multinucleated giant cells, lymphocytes and a fibrous capsule. Mineralization may be present. Tuberculous lesions in cervids appear more abscess-like and are thin walled (Fig. 2).

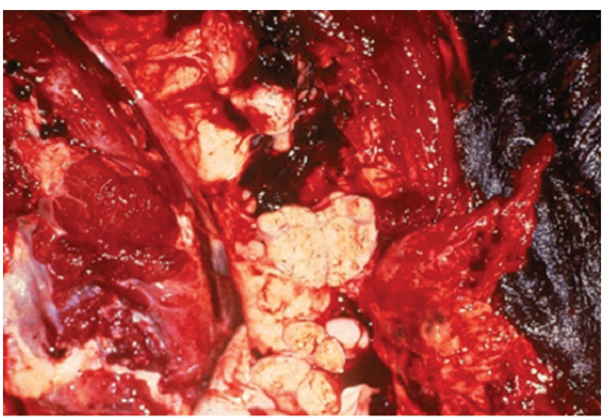

Fig. 1.– Tuberculous lesions in the lung of a American bison (*Bison bison*). *Mycobacterium bovis* was isolated.

Susceptibility of mammals to infection

The susceptibility of different animals to *M. bovis* depends on the route of exposure, virulence of the strain and the dose and duration of exposure[2]. *Mycobacterium bovis* is a pathogen of significant economic importance in wild and domestic animals, especially in countries where little information is available on the incidence of *M. bovis* infection in cattle and humans. Free ranging hoofed stock is generally susceptible to *M. bovis*; but few reports are available on the isolation of *M. tuberculosis*[2]. Swine and dogs are susceptible to both *M. bovis* and *M. tuberculosis.* Cats are quite resistant to *M. tuberculosis.*

Diagnosis

In animals, the diagnosis of tuberculosis is often made at necropsy since clinical signs are of limited value in establishing a presumptive diagnosis. Tuberculin skin testing is referred to as the "Master Key" and considered to be important in control and elimination of tuberculosis in animals and humans[1]. In Fig. 3, a positive response is shown in the eyelid on a non-human primate. Tuberculin

Fig. 2.– Absess- like lesions in the lung of an elk (*Cervus elephus*). *Mycobacterium bovis* was isolated

Fig. 3.– Tuberculin skin test response in a nonhuman primate. *Mycobacterium bovis* purified protein derivative was injected intradermally and the response observed at 48 hours post-injection.

skin testing is quite reliable for detecting active infection in domestic animals; but may lack specificity and sensitivity in some free ranging ruminants. In certain species the tuberculin test may not be positive for several weeks following exposure to virulent tubercle bacilli. Serologic tests for tuberculosis in humans and most animals lack sensitivity and specificity[8]. In USA Bovine Interferon Gamma Test has been approved as supplemental test for use in cattle only. There is a commercial test kit, (Bovigam™) by Prionics®, in which this test is performed in a single tube of blood taken at caudal fold test (CFT) reading. A total of 11 456 tests were conducted in cattle during FY 2013.

Although microscopic lesions compatible with tuberculosis may be present on microscopic examination, it is necessary to isolate the organism and to identify it by biochemical tests or by molecular techniques (i.e. VNTR).

Global rates of human tuberculosis

It has been estimated that one of three people alive today are infected with the tubercle bacillus and tuberculosis kills more people today than at any time in history. The disease is widespread in people around the globe (WHO, Fig. 4). Worldwide, 9.6 million people are estimated to have fallen ill with TB in 2014. Globally, 12% of these new TB cases were HIV positive. That year TB killed 1.5 million people[9]. The reemergence of TB is associated with the increased occurrence of immunocompromised individuals infected with HIV and the widespread occurrence of multiple drug resistant (MDR) strains (WHO, Fig. 5) and extensively drug resistant (XDR) strains of *M. tuberculosis*[9] (WHO, Fig. 6). The traditional picture of human tuberculosis is disease caused by *Mycobacterium tuberculosis*, which often presents as a chronic pulmonary infection that, without treatment, can progress to systemic infection and result in death[9-11].

Disease caused by *M. bovis*

Mycobacterial infections outside the respiratory system, or extra pulmonary TB, are documented but often underreported[10, 11]. In addition to *M. tuberculosis*, *M. bovis* is the agent most commonly associated with non-pulmonary TB. Disease caused by *M.bovis* (BTB) is a recognized public health problem in many non-industrialized countries, where direct contact with livestock reservoir hosts and consumption of unpasteurized dairy products and improperly cooked meat are important routes for the zoonotic transmission of *M. bovis* from animals to humans[4, 5]. The primary reservoir host for *M. bovis* is domestic cattle; however, BTB has been reported in most mammalian species[12]. It is important to emphasize that other domestic and wild animals have been recognized as potential reservoirs of *M. bovis* for cattle and human infection.

Human TB by *M. bovis*

M. bovis in humans continues to be reported in industrialized countries and in immigrants from regions of the world

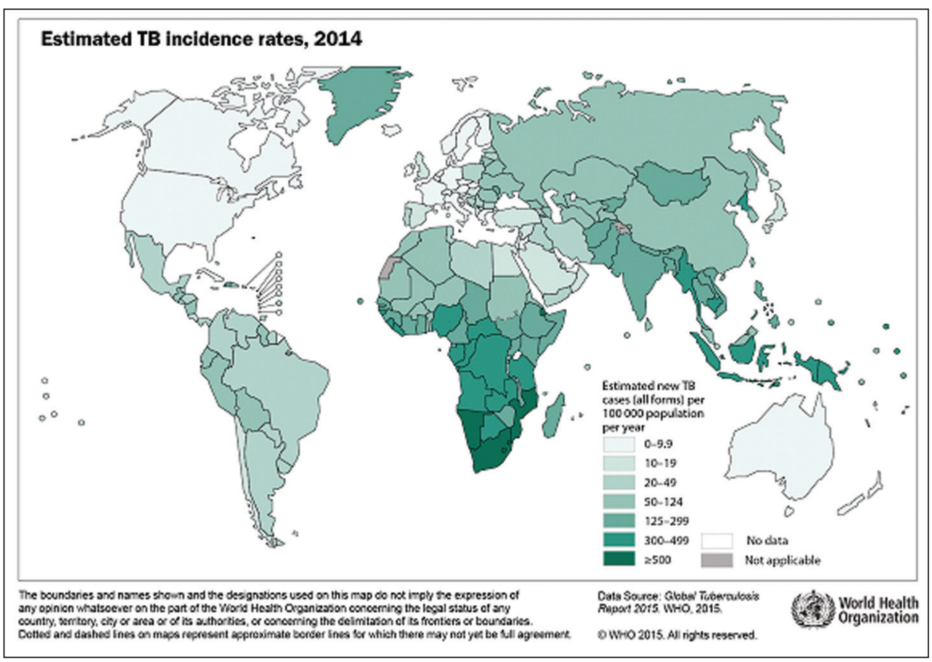

Fig. 4

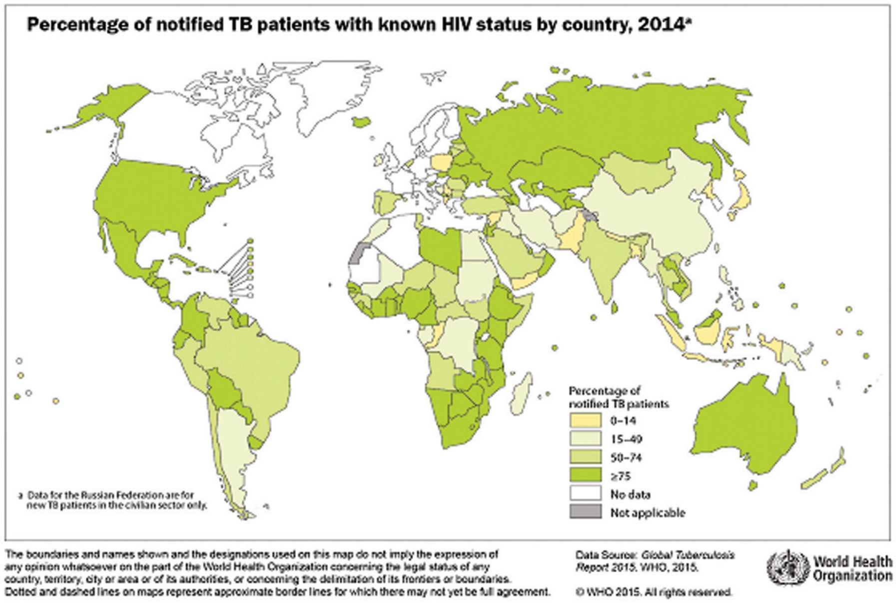

Fig. 5

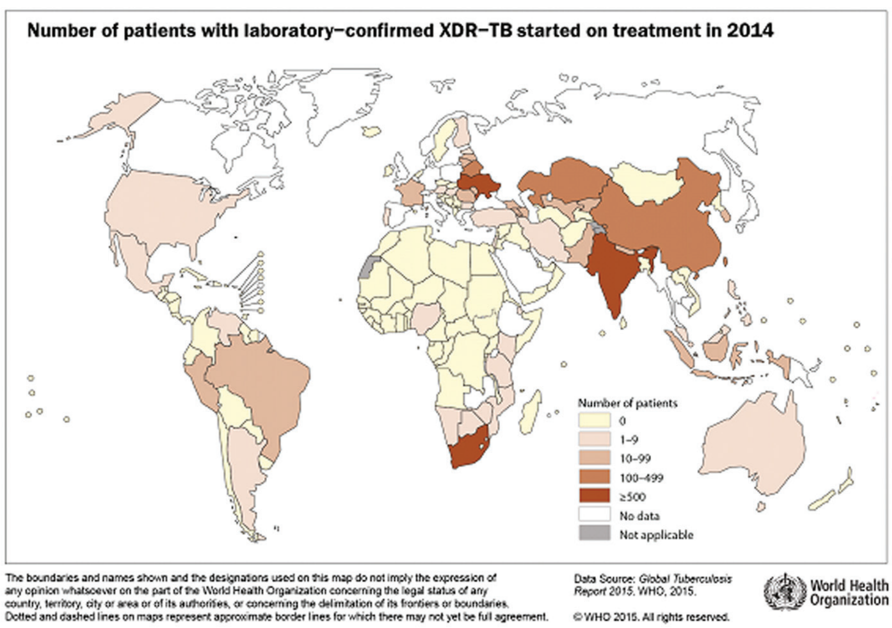

Fig. 6

where TB in cattle is endemic[1, 2, 4]. The real incidence of *M. bovis* in humans in developing countries continues to be roughly underestimated, due to the scarcity of appropriate laboratory facilities to isolate and to differentiate *M. bovis* strains. In Latin America, less than 1% of TB cases are reported as due to *M. bovis*[4]. However, the economic relevance that meat and dairy industries play in these countries stimulates the promotion of bovine TB eradication programs. Indeed, control measures based on surveillance in abattoirs, test-and-slaughter policy and disease notification have been intensified in the last decades in several South American countries[13]. Human-to-human transmission of *M. bovis* has been reported[14-17] and may be important where HIV infectionin humans is prevalent, *M. bovis* infection in cattle is enzootic, and pasteurization of dairy products is not routinely practiced[4]. Eradication of *M. bovis* in cattle and pasteurization of dairy products are the cornerstones of human disease prevention[4]. Measures should be developed for identifying and controlling *M. bovis* infection in wild animals as they may be important reservoirs of infection for domesticated food producing animals.

The World Health Organization (WHO) lists BTB as one of seven neglected zoonoses that pose serious threats to public health and the World Organization for Animal Health (Organization International for Epizootics, OIE) has called for the control and eradication of BTB. Global awareness of the importance of BTB in humans has increased with the spread of HIV-AIDS: rates of BTB in HIV-AIDS patients are higher than those in the general population and BTB/HIV-AIDS co-infections now constitute the majority of BTB cases in several countries[10, 11].

Animal TB in the USA

Bovine tuberculosis continues to cause disease in bovidae and free-ranging and captive wild and farmed cervidae in industrialized and non-industrialized countries around the globe[2]. In the United States BTB has been reported in beef and dairy cattle in widespread areas. Since 1998, United States Department of Agriculture (USDA) online monthly reports show 106 BTB-affected cattle herds have been detected in 9 States and 10 cervid herds in 9 States within the United States. From fiscal year 2001 to 2014, USDA reports reveal there have been 437 cases of *M. bovis* positive cattle detected in the US from Slaughter Surveillance; including 52 in adult cattle and 385 in fed-cattle. Of these latter, 302 (78%) were traced to Mexican origin cattle fed in the US.

The prevalence of BTB in the US has been below 0.0002% since 2001[12]. The official National Bovine Tuberculosis Eradication Program requirements stipulate that slaughter surveillance of adult cattle and bison in each State or zone detect a 0.05 percent prevalence level. At slaughter, veterinarians conduct ante-mortem and post-mortem inspections on the slaughter cattle for grossly visible tuberculous lesions. When lesions (or PPD-test positive animals) are detected, the animals are traced to the source origin and follow-up PPD (Tb) skin tests are conducted on the animals in the herd of origin and in cattle in contact herds[18]. The key elements of the US BTB eradication efforts are; 1) animal identification; 2) surveillance/testing; 3) quarantine; 4) test-and immediate slaughter protocol (removal of reactors from the herd); 5) indemnity; 6) whole herd depopulation - when necessary; 7) Accredited-free herds/ areas and States; 8) Industry/State/Federal Cooperation and 9) International importation restrictions[19].

Economic losses

The economic costs of BTB, from losses in livestock productivity (e.g., milk, meat, animal mortality) to losses in human productivity due to illness are greater in non-industrialized countries where BTB control programs are absent or ineffective. It has been estimated that The National Bovine Tuberculosis Eradication Program saves cattle producers more than $150 million dollars per year in the USA[12].

BCG vaccination

Mycobacterium bovis Bacille Calmette Guerin (BCG) vaccine has been widely used in humans in high burden countries. Although it does not protect against the adult form of TB, BCG vaccination can provide protection against primary TB in children (disseminated TB and TB meningitis); therefore, it is included in vaccination programs for newborns and infants in developing countries[4]. BCG vaccines are not utilized in animals since they fail to protect against infection, they fail to prevent progression of disease and they interfere with interpretation of PPD tuberculin skin test results[20]. It is important to note that symptomatic TB patients, usually consult for treatment, and the effective TB treatment can cut the chain of infection; however, animals with clinical disease that are contagious remain in the population and are reservoirs of infection for other animals. Therefore, vaccines for animals must be highly efficacious to be of practical value in control of bovine tuberculosis[2, 20].

Drug resistant TB

The widespread occurrence of extensively drug resistant (XDR) strains of *M. tuberculosis* is of concern to public health workers around the globe[9]. The average cost of treatment for a multi-drug resistant (MDR) patient was $134 000 and the average cost of treatment of an XDR patient was $334 000; therefore the financial resources for treatment may not be available in many non-industrialized countries[21]. Treatment duration is at least 20 months. In addition, cure rates are significantly lower than those obtained in non-drug resistant cases. Consequently, it may be necessary to quarantine and isolate patients with advanced disease in sanatoriums to minimize the spread of drug resistant strains as was practiced for limiting the spread of *M. tuberculosis* before the discovery of anti-tuberculosis drugs[2, 22].

One Health

In order to address challenges associated with BTB in the global strategy to control TB, both human and animal health professionals must work together for effective prevention and control of zoonotic TB[23, 24]. The term One Health has been adopted to describe the unified human medical and veterinary medical interdisciplinary/multidisciplinary collaborative approach to zoonoses and will be critical for future endeavors in the control of the global TB epidemic[25]. This unified paradigm is ideally suited for control of BTB. Sharing resources and increasing interactions between public health and veterinary medical scientists can raise awareness of 'shared risk' of BTB between humans and animals, and in resource-limited situations, can maximize use of existing infrastructure and reduce unnecessary duplication of effort in disease control programs.

Shared research in human and animal health can efficaciously speed the development of new diagnostic tests for humans and livestock, and improve TB surveillance, control, and eradication programs. Utilization of One Health principles for interdisciplinary/multidisciplinary collaborations offers a valuable approach for all global regions. This modernized informational approach is and will be of significant value to public health officials, research workers, allied health scientists, state and federal regulatory veterinarians, medical (physicians), veterinary medical practitioners, and professionals interested in the health care of domestic and wild animals.

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Conflict of Interest: None to declare

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It is the practice of many readers to note, in the margin of their books, the most important passages, the strongest arguments, or the brightest sentiments. Thus they load their minds with superfluous attention, repress the vehemence of curiosity by useless deliberation, and by frequent interruption break the current of narration or the chain of reason, and at last close the volume, and forget the passages and marks together.

Es la práctica de muchos lectores anotar, en los márgenes de sus libros, los pasajes más importantes, los argumentos más fuertes, los sentimientos más brillantes. Así cargan su mente con atención superflua, reprimen la vehemente curiosidad con deliberación inútil y por la frecuente interrupción rompen la corriente narrativa o la cadena de razonamiento, por último, cierran el volumen y olvidan tanto los pasajes como las notas.

Samuel Johnson (1709-1784)

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