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A REVIEW ON TUBERCULOSIS AND ITS PRESENT SCENARIO

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ABSTRACT

Tuberculosis has recently reemerged as a major health concern. Each year, approximately 2 million persons worldwide die of tuberculosis and 9 million become infected. In the United States, approximately 14000 cases of tuberculosis were reported in 2006, a 3.2% decline from the previous year; however, 20 states and the District of Columbia had higher rates. The prevalence of tuberculosis is continuing to increase because of the increased number of patients infected with human immunodeficiency virus, bacterial resistance to medications, increased international travel and immigration from countries with high prevalence, and the growing numbers of the homeless and drug abusers. With 2 billion persons, a third of the world population,1 estimated to be infected with mycobacteria, all nurses, regardless of area of care, need to understand the pathophysiology, clinical features, and procedures for diagnosis of tuberculosis. The vulnerability of hospitalized patients to tuberculosis is often under recognized because the infection is habitually considered a disease of the community. Most hospitalized patients are in a suboptimal immune state, particularly in intensive care units, making exposure to tuberculosis even more serious than in the community. By understanding the causative organism, pathophysiology, transmission, and diagnostics of tuberculosis and the clinical manifestations in patients, critical care nurses will be better prepared to recognize infection, prevent transmission, and treat this increasingly common disease.

KEYWORDS: Tuberculosis, human immunodeficiency virus, vulnerability.

INTRODUCTION

Globally, tuberculosis (TB) still remains a major public health problem. India is a high TB burden country contributing to 26 per cent of global TB burden. During 1944-1980, TB became treatable and short-course chemotherapy emerged as the standard of care. When TB elimination seemed possible in the early 1980s, global human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS) pandemic resulted in a resurgence of TB. Widespread occurrence of multi drug resistant and extensively drug-resistant TB (M/XDR-TB) is threatening to destabilize TB control globally. Atypical clinical presentation still poses a challenge. Disseminated, miliary and cryptic TB are being increasingly recognized. Availability of newer imaging modalities has allowed more efficient localization of lesions and use of image guided procedures has facilitated definitive diagnosis of extrapulmonary TB. Introduction of liquid culture, rapid drug-susceptibility testing (DST), molecular diagnostic methods has helped in rapid detection, speciation and DST profiling of Mycobacterium tuberculosis isolates. While treatment of TB and HIV-TB co-infection has become simpler, efforts are on to shorten the treatment duration. However, drug toxicities and drug-drug interactions still constitute a significant challenge. Recently, there has been better understanding of anti-TB drug-induced hepatotoxicity and its frequent confounding by viral hepatitis, especially, in resource-constrained settings; and immune reconstitution inflammatory syndrome (IRIS) in HIV-TB. Quest for newer biomarkers for predicting a durable cure, relapse, discovery/repurposing of newer anti-TB drugs, development of newer vaccines continues to achieve the goal of eliminating TB altogether by 2050.

The “captain of all these men of death”, tuberculosis (TB) has been a scourge of the humankind from time immemorial. Till date, no other disease in history matches the sheer magnitude of the misery inflicted by TB on the human race in terms of morbidity and mortality. The social and economic consequences of TB have had a profound effect on human existence. Historically, even though several other diseases like smallpox and plague have killed millions of people, their reign has been relatively short-lived; TB has been ever present. The inexorable march of time has witnessed the changing face of TB: from an incurable disease to the hype and hope of being an eminently curable one. However, even today TB remains as a formidable foe threatening to annihilate the human race. This review

attempts to provide an overview of our understanding of TB, availability of rapid diagnostic tests including imaging modalities and anti-TB drugs and to outline the challenges that lie ahead in TB control.

Historical Background

Since ancient times, there have been references to TB or illnesses resembling TB from several parts of the world from many civilizations. The earliest references to TB can be found in the language Samskritam (Sanskrit). In the ancient Indian scriptures, The Vedas, TB was referred to as Yakshma (meaning wasting disease). Description of a TB-like disease has been documented in ancient Chinese and Arabic literature. In English literature, the word "consumption" (derived from the Latin word consumer) has also been used to describe TB. The word "tuberculosis" appears to have been derived from the Latin word tubercula (meaning "a small lump").

Fracastorius (1443-1553) believed that TB was contagious. Thomas Willis (1621-1675) had documented the clinical presentation of consumption in detail in his treatise Pthisiologica. Richard Morton (1637- 1698) had described several pathological appearances of TB. John Jacob Manget gave the description of classical miliary TB. In 1720, Benjamin Marten conjectured that TB could be caused by "certain species of animalcula or wonderfully minute living creatures". In 1865 Jean Antoine Villemin presented his results suggesting that TB was a contagious disease. However, it was Robert Koch who announced the discovery of the tubercle bacillus during the monthly evening meeting of the Berlin Physiological Society on 24th March 1882.

On this day, after thousands of years, Mycobacterium tuberculosis, the organism causing TB finally revealed itself to humans. Commemorating the centenary of this event, since 1982, 24th March is being celebrated as "World TB Day" world over. Wilhelm Conrad Roentgen's discovery of X-rays, facilitated radiographic visualization of changes caused by TB in a living person. Thus, it was in the early years of 20th century that basic concepts related to aetiological agent of TB, consequent pathological changes in humans and detection of the organism became established.

Discovery of streptomycin, para-amino salicylic acid (PAS) and the availability of isoniazid ushered in modern era of effective treatment of TB in the mid-1940s. With the emergence of 'short-course' treatment cure for TB has become a reality. In the late 1970s, though TB continued to ravage developing countries like India, there was an optimism in the developed world that TB may cease to be a public health problem.

The emergence of the human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) ended this optimism and fuelled the resurgence of TB worldwide. Recognizing the importance of the impact of TB globally, the World Health Organization (WHO) took an unprecedented step and declared TB to be a "global emergency" in April 1993. The late 1990s also witnessed the resurgence of drug-resistant TB (DR-TB) with multidrug-resistant TB (MDR-TB) emerging as a major threat. The first decade of the 21st century has been ravaged by extensively drug-resistant TB (XDR-TB). Recently, concern has been expressed regarding the occurrence of extremely drug-resistant TB (XXDR-TB) super XDR-TB, totally drug-resistant TB (TDRTB) from some parts of the world. The report on the occurrence of TDR-TB from India has raised concern and consternation. Over the millennia, TB never respected anyone and had treated the rich and poor alike with equal disdain.

Epidemiology

Global burden of TB

The global burden of TB as described in the 16th global report on TB published by WHO in 2012; most of the cases occurred in Asia (59%) and Africa (26%).

Indian scenario

India has featured among the 22 high TB burden countries; and has accounted for an estimated one quarter (26%) of all TB cases worldwide.

M/XDR-TB

The results of surveillance data on MDR-TB should be interpreted carefully keeping in mind the fact that globally, less than 4 per cent of new bacteriologically positive cases and 6 per cent of previously treated cases were tested for MDR-TB in 2011 in accredited laboratories, with particularly low levels of testing in the South-East Asia (where India is located) and Western Pacific regions. The recent global epidemiological data on M/XDR-TB. XDR-TB has been documented from many parts of the world.

TB: key clinical definitions

TB Suspect

Any person who presents with symptoms or signs suggestive of TB, such as, productive cough for more than 2 week, which may be accompanied by other respiratory symptoms (e.g., dyspnoea, chest pain, haemoptysis) and/or constitutional symptoms (fever, anorexia, weight loss, fatigue and night sweats).

Case of TB

(i) A "definite case of TB" (vide infra); or
(ii) One in whom a medical practitioner has diagnosed TB and has decided to treat the patient with a "full-course of TB treatment.

Definite case of TB

A patient is categorized as a "definite case of TB", if the diagnosis of TB is based on:

(i) One or more initial sputum smear examinations positive for AFB (applicable in resource-limited settings with a functional external quality assurance system with blind rechecking); or

(ii) Isolation of M. tuberculosis complex from a clinical specimen, either by culture or by a newer method such as molecular line probe assay
(iii) Cytopathological or histopathological evidence of TB in case of extrapulmonary TB.

Pulmonary TB
Active TB disease involving the lung parenchyma.

Smear-positive pulmonary case of TB
A patient with one or more initial sputum smear examinations test positive for AFB on direct smear microscopy; or one sputum examination tests positive for AFB plus radiographic abnormalities consistent with active pulmonary TB as determined by a clinician.

Smear-negative pulmonary case of TB
A patient with pulmonary TB in whom: sputum smear examination was negative for AFB on atleast two occasions; radiographic abnormalities are consistent with active pulmonary TB; there is no response to a course of broad-spectrum antibiotics (except in a patient for whom there is laboratory confirmation or strong clinical evidence of HIV infection); and a decision by a clinician to treat with a full course of anti-TB treatment. A patient with positive mycobacterial culture but negative AFB sputum smears is also a smearnegative case of pulmonary TB.

New case of TB
A patient who has never had treatment for TB or who has taken anti-TB drugs for less than one month.

Retreatment case of TB
Retreatment case of TB includes:
(i) A patient previously treated for TB who is started on a retreatment regimen after previous treatment has failed (treatment after failure);
(ii) A patient previously treated for TB who returns to treatment having previously defaulted; and
(iii) A patient who was previously declared cured or treatment completed and is diagnosed with bacteriologically-positive (sputum smear orculture) TB (relapse).

Extrapulmonary TB
Active TB disease involving one or more extrapulmonary focus without pulmonary parenchymal involvement.

Disseminated TB
Active TB disease characterized by concurrent involvement of at least two non-contiguous organ sites; or demonstration of M. tuberculosis in the blood, or, bone marrow.

Miliary TB
Miliary is a form of disseminated TB that results from a massive haematogenous dissemination of tubercle bacilli which results in tiny discrete foci usually the size of millet seeds (1 to 2 mm) more or less uniformly distributed in the lungs and the other viscera.

HIV-TB
A HIV seropositive individual is co-infected with active TB disease.

Intrathoracic mediastinal and/or hilar lymph node TB or TB pleural effusion, without radiographic abnormalities in the lungs is categorized as extrapulmonary TB. If a patient with extrapulmonary TB also has involvement of lung parenchyma, the patient gets categorized as pulmonary TB (e.g., miliary TB) as per case definitions used in National Programmes for TB Control; or, can be categorized clinically to have disseminated TB.

TB, tuberculosis; AFB, acid-fast bacilli, HIV, human immunodeficiency virus.

Drug-resistant TB: key definitions
Resistance among new cases
Resistance to anti-TB drugs observed in isolates from new patients with TB.

Resistance among previously treated cases
Resistance to anti-TB drugs observed in isolates from prevsiouly treated patients with TB.

Susceptible strains
Strains that respond to first-line anti-TB drugs in a uniform manner are termed “susceptible strains”.

Resistant strains
Resistant strains differ from the sensitive strains in their capacity to grow in the presence of a higher concentration of anti-TB drugs.

DR-TB
Isolates of M. tuberculosis resistant to any one anti-TB drug (SDR-TB); or two or more anti-TB drugs; but not amounting to MDR-TB.

MDR-TB suspect
A patient suspected of drug-resistant tuberculosis, based on RNTCP criteria for submission of specimens for drug-susceptibility testing.

MDR-TB
Isolates of M. tuberculosis resistant to rifampicin and isoniazid with or without resistance to other anti-TB drugs.

Pre-XDR-TB
Isolates of Mycobacterium tuberculosis resistant to isoniazid and rifampicin (i.e., MDR-TB tuberculosis) plus
(i) Either any fluoroquinolone or an injectable agent, but not both.
(ii) Either any fluoroquinolone or at least one second-line anti-TB drug, but not to both.

XDR-TB
Isolates of Mycobacterium tuberculosis resistant to isoniazid and rifampicin (i.e., MDR-TB tuberculosis) plus any fluoroquinolone and at least 1 of 3 injectable second-line anti-TB drugs, namely, capreomycin, kanamycin, or amikacin.

XXDR-TB
Isolates of M. tuberculosis resistant to all first-line and second-line anti-TB drugs available (fluoroquinolones, ethionamide, amikacin, para-aminosalycilic acid, capreomycin, kanamycin, cycloserine) and to additional drugs (rifabutin, clofazimine, dapsone, claritromycin, thiacetazone).

TDR-TB (also called super XDR-TB)
Isolates of M. Tuberculosis resistant to all first- and second-line licensed anti-TB drugs.

*A WHO Consultation held in March 2012 suggested that "a new definition of resistance beyond XDR-TB is not recommended, given technical difficulties with DST of many anti-TB medicines, the lack of standardized DST methods for several anti-TB drugs (including new investigational drugs) and insufficient evidence to link such DST results to treatment outcomes of patients."

While the clinical and operational value of the definitions of MDR-TB and XDR-TB have been fairly evident, standardization of technical requirements for the application of terms, such as, XXDR-TB, super XDR-TB, and TDR-TB, their usefulness and limitations need further clarification and these terms need to be interpreted in the proper perspective. TB, tuberculosis; SDR-TB, single drug-resistant tuberculosis; DR-TB, drug-resistant tuberculosis; MDR-TB, multi-drug-resistant tuberculosis; RNTCP, Revised National Tuberculosis Control Programme; HIV, human immunodeficiency virus; XDR-TB, extensively drug-resistant tuberculosis; XXDR-TB, extremely drug-resistant tuberculosis; TDR-TB, totally drug-resistant tuberculosis.

Indian scenario
Observations from reliable accredited mycobacteriology laboratories from India suggest that the prevalence of MDR-TB is quite low in new TB cases (<3%) compared with previously treated patients (15-30%). The prevalence of XDR-TB in studies published from India where drug-susceptibility testing (DST) was carried out in quality-assured, accredited laboratories.

Risk factors
Conventionally several genetic, social, environmental and biological determinants of health have been intuitively recognized by clinicians as risk factors for TB.

Genetic factors
Certain key issues should be considered while evaluating genetic susceptibility to TB disease. Susceptibility to TB does not follow a Mendelian pattern and is polygenic and multifactorial. Presence of two different genomes, (of the TB bacillus and the host) and their interaction can have influence on the disease. Several reports have implicated a long list of genes with risk of developing TB.

Table 1.1: Estimates of global burden of TB 2011.

Variable	Best estimate (low-high)
Incident cases (/100,000 population)	125 (120-130)
Prevalent cases (/100,000 population)	170 (150-192)
TB mortality (/100,000 population)	15 (13-18)
HIV prevalence in incident TB cases (%)	13 (12-14)

In 2010, there were 8.8 million (range, 8.5-9.2 million) incident cases of TB. Of these, 13% were among people living with HIV. The proportion of TB cases co-infected with HIV was highest in countries in the African Region which had accounted for 82% of TB cases among people living with HIV. Women accounted for an estimated to 3.2 million incident cases.

Among HIV-seronegative persons, there were an estimated 1.1 million (range, 0.1-1.2) deaths; among HIV-seropositive persons, the corresponding number was 0.35 million (0.32-0.39). In 2010, there were 5.7 million notifications of new and recurrent cases of TB, equivalent to 65% of the estimated number of incident cases; India and China together accounted for 40% of the world wide incident cases of TB. At a global level, a fall in the absolute number of TB cases has been observed since 2006; TB incidence rates have also been falling by 1.3% per year since 2002.

HIV infection
HIV infection and AIDS stand out as the most significant among all the risk-factors for TB and has consistently and significantly altered the incidence rate of TB over the last three decades. The impact of HIV/AIDS has been most profound in HIV prevalence sub-Saharan Africa where a dramatic increase in TB notification rates have been documented concurrent with increasing HIV prevalence. Among persons living with HIV (PLWH) TB can develop at any stage of HIV infection and there is a strong evidence suggesting that a declining CD4+ T-lymphocyte count and high viral load are risk factors for disease, while treatment with highly active antiretroviral therapy (HAART) reduces risk. HIV infection and MDR-TB: Even though several institutional outbreaks of

MDR-TB among HIV infected patients drew attention to the problem two decades age as per currently available evidence, HIV infection per se does not appear to be a risk-factor for MDR-TB.

Diabetes mellitus

The lethal interaction between diabetes mellitus (DM) and TB is being increasingly recognized world over. Epidemiological modelling data suggest that in India, 14.8 per cent of all pulmonary TB cases and 20 per cent of sputum smear-positive cases have DM suggesting that DM substantially contributes to the burden of TB, especially sputum smear-positive pulmonary TB in India.

Use of Immunomodulator biological

Use of immunomodulator drugs (biologicals) has been associated with the development of fatal TB in rheumatoid arthritis.

Table 1.2: Social, environmental and biological determinants of health considered to be risk factors for TB.

Genetic susceptibility:
Genes associated with risk of TB:
Natural resistance-associated macrophage protein 1
Interferon γ
Nitric oxide synthase 2A
Mannan binding lectin
Vitamin D receptor
Some Toll-like receptors
Physiological conditions
Pregnancy, postpartum, Ageing
Undernutrition
Urbanization, overcrowding, housing conditions, migration, economic trends, poverty, homelessness
Immunodeficiency disorders affecting CMI including HIV infection and AIDS.
Organ transplantation
Malignant neoplasms
Carcinomas of the head and neck, stomach, intestines and lungs
Hodgkin's disease, non-Hodgkin's lymphoma
Acute lymphocytic and myelogenous leukaemia.
Silicosis
Intravenous drug abuse, heroin addiction
Alcohol use
Chronic liver disease
Chronic kidney disease, haemodialysis
Post-surgery (e.g., gastrectomy)
Iatrogenic
Ureteral catherization
Extracorporeal shockwave lithotripsy
Laser lithotripsy
Cardiac valve homograft replacement
Intravesical BCG therapy for urinary bladder carcinoma.
Drugs
High dose, long-term corticosteroid treatment
Immunosuppressive therapy
Immunomodulator biologicals (anti-tumour necrosis factor agents)
Connective tissue disorders:
Diabetes mellitus
Indoor air-pollution
Tobacco smoking

Diagnosis

Latent TB infection Diagnosis of LTBI has been considered important as a tool for assessing the burden of TB for epidemiological purposes. Because LTBI contributes significantly to the pool of active TB cases later on, its recognition is assuming importance in high-risk groups where there is a potential for instituting treatment for this condition. The tuberculin skin test

(TST) and interferon-gamma release assays (IGRAs) have been used as diagnostic tests for the detection of LTBI. In high burden TB countries, neither IGRAs nor TST have been found to be adequate in accurately identifying persons who will benefit from treatment of LTBI with false positivity rates greater than 50 per cent being reported for both. In this connection, a recent policy statement issued by the WHO and the European Centre for Disease Prevention and Control guidelines discourage the use of IGRAs in preference to TST, in areas where TB is highly endemic.

Serodiagnostic Tests

A broad range of serodiagnostic tests with a varying degree of reliability, repeatability and concordance have been used for the diagnosis of TB. Since no commercial serological assay could consistently result in an improved outcome, the WHO recently recommended that commercial serological tests should not be used for the diagnosis of pulmonary and extrapulmonary TB. This view has been endorsed by the RNTCP of Government of India also.

Conventionl treatment of Tuberculosis

Evolution of multiple drug treatment

The humankind had to wait for more than 60 years following Robert Koch's momentous announcement of the discovery Mycobacterium tuberculosis for drug(s) that could cure TB to become available. The first controlled clinical trial in the history of medicine conducted by the British Medical Research Council (BMRC) demonstrated the activity of streptomycin. The BMRC assessed the addition of PAS to streptomycin in a controlled clinical trial which showed a lower rate of clinical deterioration, higher rate of culture conversion, and a lower rate of streptomycin resistance in patients receiving streptomycin plus PAS, suggesting that combination treatment with PAS was helpful in preventing the emergence of drug resistance to streptomycin. The first clinical trial with isoniazid was initiated in 1951. Subsequent studies by BMRC183, 184 further assessed the utility of using two of the three drugs, namely, streptomycin, isoniazid and PAS in various combinations to treat TB. A later clinical trial by BMRC established the duration of anti-TB treatment that would effectively prevent relapse, to be 18-24 months. Ethambutol, discovered in 1961 got added to the armamentarium of anti-TB drugs and soon replaced PAS in the standard regimens. In the 1960s seminal research conducted by Wallace Fox and co-workers at the National Institute for Research in Tuberculosis (NIRT), Chennai [then called as Tuberculosis Chemotherapy Centre, Madras; later renamed as Tuberculosis Research Centre (TRC), Madras in 1978] showed that home or ambulatory treatment was almost as effective as sanatorium treatment "provided the regular use of anti-TB medication was well organized and supervised".

Treatment of HIV-TB co-infection and X/MDR-TB

Treatment of active TB in patients co-infected with HIV requires careful consideration of drug-drug interactions between anti-TB and anti-retroviral drugs. Treatment of X/MDR-TB is expensive and time-consuming, and requires special facilities with adequate infrastructure, reliable, access to periodically accredited mycobacterial culture and sensitivity laboratories, medical, nursing and paramedical personnel trained in the management of X/MDR-TB. In India, the RNTCP started treatment of X/MDR-TB through the DOTS-Plus services in 2007 in a phased manner and at present all Indian states have been covered.

Prevention

Even though the declining trends observed in the global burden of TB currently, this trend seems insufficient to achieve the global target of elimination of TB in 2050. Therefore, the need for other measures including infection control measures, newer or repurposed anti-TB drugs, newer and better vaccines for TB is pressing.

Novel approaches in the treatment of Tuberculosis and current research in the area

Targeted drug delivery: Targeted drug delivery, sometimes called **smart drug delivery**, is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. The goal of a targeted drug delivery system is to prolong, localize, target and have a protected drug interaction with the diseased tissue. The conventional drug delivery system is the absorption of the drug across a biological membrane, whereas the *targeted release system* releases the drug in a dosage form. The advantages to the targeted release system is the reduction in the frequency of the dosages taken by the patient, having a more uniform effect of the drug, reduction of drug side-effects, and reduced fluctuation in circulating drug levels. The disadvantage of the system is high cost, which makes productivity more difficult and the reduced ability to adjust the dosages. Targeted drug delivery systems have been developed to optimize regenerative techniques. The system is based on a method that delivers a certain amount of a therapeutic agent for a prolonged period of time to a targeted diseased area within the body. This helps maintain the required plasma and tissue drug levels in the body, thereby preventing any damage to the healthy tissue via the drug. The drug delivery system is highly integrated and requires various disciplines, such as chemists, biologists, and engineers, to join forces to optimize this system.

Sustained drug delivery: Sustained release dosage forms are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects. This can be achieved through a variety of formulations, including liposomes and drug-polymer conjugates (an example being hydrogels). Sustained release's definition

is more akin to a "controlled release" rather than "sustained". Sustained release products provide advantage over conventional dosage form by optimizing biopharmaceutics, pharmacokinetics and pharmacokinetics properties of drug. Thus sustained release formulation provides important way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. Availability of wide variety of polymer and frequent dosing interval helps the scientist to develop sustained release product. These dosage forms are available in extended release, targeted release, delayed release, prolonged action dosage form. Some factors like molecular size, diffusivity, pKa-ionization constant, release rate, dose and stability, duration of action, absorption window, therapeutic index, protein binding, and metabolism affect the design of sustained release formulation. These formulations are evaluated for weight variation, friability, hardness, thickness, in vitro release rate etc. The future of sustained release products is promising in some area like chronopharmacokinetic system, targeted drug delivery system, muco-adhesive system, particulate system that provide high promise and acceptability. This article contains various types, evaluation and factors affecting the design of sustained release formulation.

CONCLUSION

Tuberculosis or **TB** (*tubercles bacillus*) is a common and often deadly infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis* in humans. It is spreaded through the air when people who have the disease cough, sneeze, or spit. Most infections in humans result in an asymptomatic, latent infection, and about one in ten latent infections eventually progresses to active disease, which, if left untreated, kills more than 50% of its victims. The classic symptoms are a chronic cough with blood-tinged sputum, fever, night sweats, and weight loss. Infection of other organs causes a wide range of symptoms. Diagnosis relies on radiology(commonly chest X-rays), a tuberculin skin test, blood tests, as well as microscopic examination and microbiological culture of bodily fluids. Treatment is difficult and requires long courses of multiple antibiotics. Contacts are also screened and treated if necessary. Antibiotic resistance is a growing problem in (extensively) multi-drug-resistant tuberculosis. Prevention relies on screening programs and vaccination, usually with Bacillus Calmette Guérin vaccine. One third of the world's population is thought to be infected with *M. tuberculosis*, and new infections occur at a rate of about one per second. The proportion of people who become sick with tuberculosis each year is stable or falling worldwide but, because of population growth, the absolute number of new cases is still increasing.

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