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A Brief Overview of Tuberculosis Disease

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ABSTRACT: TB has consistently had a higher yearly mortality rate than HIV or any other infection. This is due to a series of events beginning with the virulence of Mycobacterium tuberculosis, the extremely contagious and persistent bacterium that causes tuberculosis illness. This groundbreaking discovery, combined with the subsequent discoveries of tuberculin in 1890, the Bacillus-Calmette Guérin (BCG) vaccine in 1908, and antituberculosis medications beginning in 1943, gave promise for the eradication of a disease that was more deadly than the plaque. The goal of this review is to highlight recent research on the epidemiology, aetiology, treatment, and control of tuberculosis in order to gain a better understanding of the disease and, perhaps, improved treatment through creative research and public health activities.

INTRODUCTION

TB has consistently had a higher yearly mortality rate than HIV or any other infection. This is due to a series of events beginning with the virulence of Mycobacterium tuberculosis, the extremely contagious and persistent bacterium that causes tuberculosis illness. Another factor is that these bacteria have the ability to develop genetic mutations that confer resistance to a number of previously effective antibiotics. In 2013, the World Health Organization (WHO) estimated that 480,000 cases of multidrug-resistant tuberculosis (MDR-TB) were detected worldwide. Since the discovery of effective antibiotic treatments for tuberculosis, MDR-TB and its more resistant brother, extensively drug resistant (XDR-) TB, have become more widespread. In the next 50 years, some specialists expect that MDR-TB may overtake non-resistant TB as the most frequent type of the disease[1]. Patients infected with tuberculosis (TB), formerly known as consumption [2], an airborne disease that causes severe coughing, fever, and chest pains [3], [4], were advised to "just sleep and eat nourishing meals" in the 1800s. In 1882, German microbiologist Robert Koch announced that Mycobacterium tuberculosis caused tuberculosis, a mystery disease whose Latin-derived name depicts the rod shape of the bacillus[5]. This groundbreaking discovery, combined with the subsequent discoveries of tuberculin in 1890, the Bacillus-Calmette Guérin (BCG) vaccine in 1908, and antituberculosis medications beginning in 1943, gave promise for the eradication of a disease that was more deadly than the plaque. From the early to mid-twentieth century, mortality rates decreased considerably; nevertheless, research funding diminished, and medication and vaccine development stalled between 1970 and 1990 [5], [6]. TB rates increased once more with the start of the AIDS pandemic and resistant strains, as did interest in TB research and prevention [7]. Though the diagnostic and treatment tools needed to combat the disease were largely obsolete by this time, strategies to control and prevent the disease were developed, including the Directly Observed Treatment Short-Course (DOTS) programme in 1993, which was followed by a DOTS-plus programme in 1998 to address multi-drug resistant (MDR) TB[7],[8]. Although recent research has provided great insight into TB transmission, diagnosis, and treatment in the last four years, much more has to be learned in order to effectively reduce the prevalence of TB and finally eradicate it [7], [9]. The disease continues to be a public health concern, coming in second only to HIV/AIDS in terms of high fatality rates [10]. There were around 8.7 million new cases and 1.4 million fatalities due to tuberculosis in 2011 alone [7], [8], [10], with approximately two billion persons latently infected[3]. The goal of this review is to highlight recent research on the epidemiology, aetiology, treatment, and control of tuberculosis in order to gain a better understanding of the disease and, perhaps, improved treatment through creative research and public health activities.

GLOBAL SCENARIO

TB is a global pandemic, according to the WHO. 13 of the 15 nations with the highest

estimated TB incidence rates are in Africa, whereas six Asian countries, namely Bangladesh, China, India, Indonesia, Pakistan, and the Philippines, account for half of all new cases. According to a WHO information sheet on tuberculosis from March 2010[11], one-third of the world's population (nearly 2 billion people) is currently infected with the TB bacillus. According to it, someone in the globe is infected with tuberculosis bacteria every second, and one out of every ten of these newly infected persons will become sick or infectious later in life. Because HIV affects the immune system, those who have HIV and TB co-infection are considerably more likely to develop TB, which is a primary cause of mortality among HIV-positive people. Since 1990, HIV has been the single most important factor leading to the rise in the incidence of tuberculosis in Africa.

DOTS (directly observed treatment-short course) is an internationally acknowledged technique for teaching the fundamentals of tuberculosis case-finding and treatment. It is a management strategy for public health systems that includes political commitment, case identification by quality-assured bacteriology, short-course chemotherapy, assuring patient adherence to treatment, enough drug supply, and effective reporting and recording systems. [12] Between 1995 and 2008, 36 million TB patients were effectively treated in DOTS programmes around the world, averting up to 6 million fatalities. For the first time in 2007, the global treatment success rate (86%) attained in DOTS cohorts exceeded the global target of 85 percent. [12]

The WHO's Southeast Asian Region (SEAR) is vitally significant from a global standpoint. It is home to 25% of the world's human population, and it suffers from high rates of communicable and noncommunicable diseases, despite having a relatively inadequate health infrastructure. Without tangible success in this region, global health advancement will be impossible. Communicable diseases cause six million of the region's 14 million deaths, accounting for 42 percent of all disability-adjusted life years lost[13],[14].

In SEAR, an estimated 3.6 million people are living with HIV/AIDS. The HIV epidemic in this region is complicated and variable at different stages, both within countries and throughout the region. For example, the six states in India's south and northeast account for almost two-thirds of the country's estimated HIV burden despite accounting for only one-third of the country's population. HIV prevalence appears to be gradually declining in four southern Indian states. Three provinces in Indonesia, although overall HIV incidence is low, have been reported to have considerably higher HIV rates. Increased HIV incidence among high-risk groups, such as intravenous drug users (IDUs), has sparked worries in other countries, such as Bangladesh and Nepal, about the likelihood of a generalised HIV epidemic

INDIAN SCENARIO

TB is described in the Vedas and ancient Ayurvedic writings of India. The fight against tuberculosis in India can be divided into three periods: the early period, before the discovery of x-ray and chemotherapy; the post-independence period, when nationwide TB control programmes were established and implemented; and the current period, when a WHO-assisted TB control programme is in place.

Early period of TB control

It was distinguished by the absence of any chemotherapeutic medicines, diagnostic x-ray facilities, and a TB control campaign. This persisted until the middle of the twentieth century. Because no drug or combination of drugs was available/effective against tuberculosis during this time, a sanatorium movement arose in Europe and swiftly expanded throughout the world. Sanatoria was popular because it was thought that a regimen of relaxation, proper nourishment, open fresh air, and high altitude would help the sufferer's immune system "wall off" pockets of pulmonary tuberculosis (TB) infection. Hermann Brehmer founded the world's first sanatorium, the BrehmerschenHeilanstalt für Lungenkranke, in Görbersdorf (Sokoowsko), Silesia, in 1863 for the treatment of tuberculosis (now Poland)[14].

The first open-air sanatorium for the treatment and isolation of tuberculosis patients was established in India in 1906 in Tiluania, near Ajmer, Rajasthan, followed by the first TB facility in Bombay in 1917. [15] Chest radiography began to serve a diagnostic role in detecting deep-seated TB consolidation around 1925. By 1945, the MMR (mass miniature radiography) version of this device had been added to its capabilities. Immunization against tuberculosis was the first true victory against the disease. BCG (bacillus of Calmette and Guerin) was first used on humans in France on July 18, 1921, after being developed from an attenuated bovine strain of tuberculosis by Albert Calmette and Camille Guerin in 1906. A BCG vaccine production centre was established at Guindy, Madras (now Chennai) in 1948, with support from WHO and UNICEF. To combat tuberculosis, India launched a major BCG vaccination campaign in 1951. This was India's first statewide TB campaign,

and for the first time in its history, a message of health and disease prevention was delivered to the country's most remote areas.

This period can be conveniently subdivided into the following two phases:

District tuberculosis programme The Indian government created the District Tuberculosis Program in 1961, and Anantapur district in Andhra Pradesh was the first model district TB centre (DTC). This programme aims to integrate TB control programmes with current government health services in order to minimise the community's TB problem as cost-effectively as possible. [16] Shortly after the Anantapur DTC was established, it became clear that, while case-finding could be done easily anywhere, the main challenge in the fight against tuberculosis was maintaining patients on treatment until they were cured. [17] The Indian government began the National TB Control Program in 1962, based on this district TB centre approach (NTCP).

The short-course chemotherapy era is arrived. Effective anti-TB medications became available around the time India got independence in 1947, in the middle of the twentieth century (Streptomycin: 1944, PAS: 1946, Thiacetazone: 1950, Isoniazid: 1952 and Rifampicin: 1966). [18] The Tuberculosis Research Center (TRC) in Chennai was created in 1956 under the auspices of the Indian Council of Medical Research (ICMR), the government of Chennai state, the WHO, and the British Medical Research Council (BMRC). The era of short-term chemotherapy has arrived. In the middle of the twentieth century, around the time India gained independence in 1947, effective anti-TB drugs became accessible (Streptomycin: 1944, PAS: 1946, Thiacetazone: 1950, Isoniazid: 1952 and Rifampicin: 1966). [18] The Tuberculosis Research Center (TRC) in Chennai was founded in 1956 by the Indian Council of Medical Research (ICMR), the state government of Chennai, the World Health Organization (WHO), and the British Medical Research Council (BMRC).

Due to the availability of two well-tolerated and very efficient medicines, Rifampicin and Pyrazinamide, TB chemotherapy underwent dramatic developments in the 1970s. Short-course chemotherapy (SCC) was made possible by these medications, which simplified and shortened treatment. Rifampicin's discovery in 1967 is regarded as one of the most significant triumphs in the history of anti-TB medication development. Since its discovery, no new medicine has been identified that is as effective against tuberculosis as Rifampicin.

Current WHO-assisted ongoing TB control program

The national programme was reviewed in 1992 by the Government of India, the WHO, and the Swedish International Development Agency (SIDA), and it was concluded that it had managerial flaws, insufficient funding, an over-reliance on x-ray, nonstandard treatment regimens, low rates of treatment compliance and completion, and a lack of systematic information on treatment outcomes. [19] Around the same time, in 1993, WHO proclaimed tuberculosis (TB) to be a worldwide emergency and developed the DOTS plan, which was recommended to all countries. This strategy was founded on five pillars: governmental commitment and continuing funding for TB control programmes, sputum smear exams for diagnosis, continuous supply of high-quality anti-TB medications, drug intake under direct supervision, and precise reporting and recording of all recorded cases.

World Bank acknowledged that the DOTS strategy was the most economical health intervention and agreed to provide credit assistance for the NTCP, initially for the coverage of a population of 271 million persons, which was later revised to cover a population of 730 million persons. Presently, other bilateral and multilateral agencies, Danish International Development Agency (DANIDA), Department for International Development (DFID), US Agency for International Development (USAID), Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria (GFATM), Global Drug Facility (GDF) and WHO are providing invaluable support to the program. The Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria is the single biggest source of external funding for TB control.[20]

The Revised National TB Control Program (RNTCP) was created in 1997 with the help of the above-mentioned international organisations to give the NTCP a new lease on life. [21] It developed and implemented the internationally approved DOTS plan as the most systematic and cost-effective way to revive India's tuberculosis control programme. The importance of political and administrative commitment to ensure the provision of organised and comprehensive tuberculosis control services, as well as reliable and early diagnosis through smear microscopy, an uninterrupted supply of high-quality anti-TB drugs, effective and patient-friendly treatment with short-course chemotherapy (SCC) given under direct observation, and accountability through proper reporting and recording, as well as effective supervision, was emphasised. [22] India's DOTS

programme is now the world's fastest-growing and largest in terms of patients started on treatment, as well as the second largest in terms of population coverage.

Etiology

a causative agent tuberculosis mycobacterium Infection with Mycobacterium tuberculosis has been known throughout human history. It is thought that the bacterium originated in East Africa. Early people travelled out of East Africa, settling in Europe and Asia, and the TB illness followed them, wreaking havoc for ages throughout the known world [23].

Mechanisms/pathophysiology

Microbiology

TB illness is caused by ongoing transmission of M. tuberculosis infection30 and LTBI reactivation31. The majority of tuberculosis infections are caused by Mycobacterium tuberculosis (sensustricto) or Mycobacterium africanum, a closely related organism; a small number of cases are caused by zoonotic members of the Mycobacterium tuberculosis complex, such as Mycobacterium bovis or Mycobacterium caprae[24]. There is no known environmental reservoir for M. tuberculosis; the only recognised reservoir is humans[25]. M. tuberculosis is thus a pathogen as well as a symbiont, which has ramifications for our understanding of host–pathogen relationships.

Pathogen–host interactions. Genomic studies have revealed significant genetic variability among isolates from around the world (thousands of single-nucleotide polymorphisms across a genome of 4.4 million base pairs), which could reflect accumulated genetic drift linked to human migration patterns or variable pathogenicity of different lineages[26]. Based on epidemiological investigations, it has been postulated that hypervirulent strains exist. If this is the case, genomic analysis of these strains could reveal lineage-specific virulence factors[27], which could be used to prioritise patient care and infection control decisions. Although certain strains have been associated to numerous characteristics of M. tuberculosis, including greater transmissibility in humans, medication resistance, and mortality in an animal model[26], findings were contradictory among investigations, complicating their quick translation into clinical care. Pathogen–host interactions. Genetic variability has been discovered in genomic investigations. The interactions between the host and M. tuberculosis are also complicated. In the absence of host determinants of susceptibility, investigating M. tuberculosis virulence factors can mask synergistic interactions. For example, a particular host–pathogen interaction could explain why East-Asian lineage strains are highly infective and pathogenic in Asian populations36 but have a normal clinical and epidemiological presentation in Canada[28] and Switzerland[29]. In the right social and epidemiological context, germs that are otherwise unimpressive in terms of genetic and laboratory characterisation can be linked to outbreaks[30].

Virulence. Given that the risk of developing active TB disease from LTBI is many orders of magnitude higher than the risk of developing disease from the live vaccine strain, M. bovis Bacillus Calmette–Guérin (BCG), genomic differences between M. tuberculosis and BCG can be used to look for the source of attenuated virulence[31]. Indeed, genetic comparisons revealed various changes, the most notable of which is the region of difference 1 (RD1)[31-33], which helps to explain why the vaccine may be administered to millions of newborn infants each year with a low risk of illness progression.

The ESX-1 secretion system[34], which is encoded by RD1, is a bacterial secretion system. The ESX-1 secretion system mediates the transfer of bacterial products into the macrophage cytoplasm after the bacteria have been absorbed in phagosomes by the host macrophages[35]. On a practical level, the lack of RD1 in BCG strains allowed the development of immunological assays that could separate the host response to M. tuberculosis infection from the BCG vaccine response (BCG-osis)[36]. Because many non-tuberculous mycobacteria lack RD1, these tests can help identify M. TB infection from infection by common environmental mycobacteria like Mycobacterium avium[37].

LTBI

When M. tuberculosis is exposed, one of two things happens: the pathogen is either eliminated or persists. In the first situation, the pathogen is removed either by innate immune responses (in this case, tuberculin skin tests (TSTs) or interferon- (IFN) release assays (IGRAs) may be negative) or adaptive immune responses (in this case, tuberculin skin tests (TSTs) or interferon-(IFN) release assays ((in which case, TSTs and IGRAs might be positive or negative, depending on whether memory T cell responses have been primed) [6,37]. This person will not benefit from LTBI therapy, regardless of how the infection is eradicated. It has long been known that over half of those who are exposed to TB patients' close

household contacts have negative TST results48. One possible reason for why some people are innately resistant to TB49 is the discovery that there is a genetic propensity to remain TST negative despite extensive exposure.

Immunology. Although our knowledge of the early stages of M. tuberculosis infection in humans is limited, research in small animals (such as mice, guinea pigs, and rabbits) and non-human primates has greatly aided in identifying the significance of early events during primary infection[38]. M. tuberculosis enters the body through the respiratory tract; after inhalation, it travels to the lower respiratory tract, where it encounters alveolar macrophages, the most common cell type infected by M. tuberculosis. The bacteria are internalised by these cells through receptor-mediated phagocytosis, which involves a variety of receptors. This process had been investigated for a long time without taking into account the microenvironment in the alveolus. Surfactants, which are plentiful in the fluid that coats the epithelium, may play a key role in the early host–pathogen interaction[39]. Surfactant protein D, for example, can block alveolar macrophages from phagocytosing M. tuberculosis[40]. In the following days, a few bacteria may be discovered in the cytoplasm of macrophages[42,43]. The benefits of delivering bacterial products into the cytosol are still being researched[43,44]; one theory is that activating the cytosolic surveillance pathway, which results in the induction of a type I IFN response, can promote the growth of intracellular bacterial pathogens like M. tuberculosis[45-49]. Experiments have also revealed that the kind of cell death (apoptosis versus necrosis) experienced by infected macrophages is important not only for the innate response to infection but also for the adaptive immune response that follows[50-52]. Furthermore, investigations show that macrophage ontogeny has a significant impact on their function and fate[53-54]. To assess the role of resident alveolar macrophages vs bone marrow-derived macrophages migrated to the lung in the outcome of M. tuberculosis infection, more research is needed.

M. tuberculosis infects the alveolar macrophages in the airways, gaining access to the lung interstitium, where the infection progresses. However, it is unknown how M. tuberculosis gains access to the parenchyma. One route involves M. tuberculosis directly infecting epithelial cells, while the other involves M. tuberculosis-infected macrophages transmigrating through the epithelium. Regardless of the route, M. tuberculosis infects the parenchyma, causing an increase in the number of cells to flock to the infection site, resulting in a multicellular host reaction known as a granuloma.

Infected dendritic cells[55] or inflammatory monocytes[56] carry M. tuberculosis to pulmonary lymph nodes for T cell priming once the main infection is established. T cell priming and trafficking into the lung have both been demonstrated to be actively delayed by M. tuberculosis[55,57] HIV infection significantly reduces the number of CD4+ T cells, making it a risk factor for M. tuberculosis infection progressing to active TB illness. However, some studies suggest that the risk of active TB disease is increased during the early stages of HIV infection, when the number of CD4+ T cells is normal, implying that other immune responses not dependent on T cells are also compromised[58]. Furthermore, it is unknown if greater T cell responses provide superior protection during vaccination. In example, investigations in an experimental mouse model of tuberculosis showed that increasing total CD4+ T cell responses in a PD1-dependent way resulted in decreased protection and increased mortality[59,60]. Understanding the regulatory systems involved in tuberculosis immunity is crucial for developing a strong host defence that inhibits bacterial growth while maintaining host tolerance.

The granuloma is a benign tumour. Decoding the underlying mechanisms that are involved in the formation and maintenance of granulomas is a top research focus, as they are implicated in both infection control and, in certain cases, pathogen persistence[61]. From the host's perspective, the granuloma is a bacterial 'prison,' with the capacity to 'shut off' infection from the rest of the body; but, from the bacterial perspective, it is a growing collection of phagocytic cells to infect and proliferate inside. For example, the M. tuberculosis ESX-1 secretion system can trigger a type I IFN response, which has been associated to the recruitment of a distinct myeloid population (CD11b+F4/80+Gr1int) to the nascent granuloma that is extremely permissive to M. tuberculosis infection[62]. Surprisingly, a study found that immune responses are spatially divided around the granuloma, with pro-inflammatory components in the centre and anti-inflammatory components in the surrounding tissue[63]. It's also been suggested that the granuloma has a maximum bacterial burden (or carrying capacity) beyond which the infection would progress[61]. If the infection is contained by the granuloma without causing significant tissue

pathology, the person has LTBI and may be a candidate for preventive treatment.

Progression to active TB disease

In most people with LTBI, a mix of macrophages, dendritic cells, and T cells is enough to keep the infection under control and asymptomatic. However, for unknown reasons, the infection can develop to clinical illness in a subset of hosts in as little as weeks or as long as decades. Certain natural trials in human immunology shed light on why some people with LTBI are unable to control the infection and develop active TB illness.

From a bacteriological standpoint, intact antigenic proteins appear to be a key factor to illness progression. M. tuberculosis genes anticipated to be involved in the generation of immunodominant CD4+ T cell antigens do not differ between strains and lineages, suggesting that M. tuberculosis could benefit from antigen-specific CD4+ T cell activation in humans[64]. Although HIV is obviously a risk factor for development from LTBI to active TB illness in a person, HIV/AIDS is adversely associated with contagion[65], which lends indirect support to this notion. Immunodominant antigens are important for a variety of reasons, including understanding disease pathophysiology and developing a vaccination strategy. Identifying immunodominant M. TB antigens in order to generate a repertoire of M. tuberculosis-specific T cells was once thought to provide the cornerstone for T cell-mediated protective immunity and, thus, a viable vaccine-based strategy. A vaccine developed employing an immunodominant M. tuberculosis antigen, however, failed to improve protection in a human trial[66], while eliciting a moderate degree of improved T cell-mediated responses. We still don't know the exact basis for BCG protection, or how much of it is mediated by CD4+ T cells or innate immune pathways81, after over a century of BCG vaccination.

Mechanisms of drug resistance

The concept of medication resistance was originally described in the infectious disease tuberculosis (TB) in 1948, during the first human trial of TB therapy[67]. The widespread establishment of resistant strains has been described as each new anti-TB medicine has been introduced into clinical practise, usually within a decade.

Drug resistance develops in M. tuberculosis due to genetic changes (there are no reports of resistance developed by the acquisition of new DNA). Despite the fact that there is an ever-growing list of genes connected to drug resistance, allelic exchange tests have only proved the causality between mutation and drug resistance for a minority of altered genes[68]. Target modification (for example, a mutant bacterial RNA polymerase that evades the action of rifampicin) or a faulty enzyme that transforms a pro-drug into an active drug are the two basic mechanisms of drug resistance in these genes (for example, a mutant bacterial catalase that fails to activate isoniazid).

Drug susceptibility studies, both phenotypic and genotypic, have shortcomings that make it difficult to understand resistance mechanisms[69]. Phenotypic tests produce a binary outcome (the M. tuberculosis strain is either sensitive or resistant to a given treatment dose), and they are best standardised for a limited number of medicines (for example, isoniazid, rifampicin and ethambutol). Furthermore, drug susceptibility studies based on genotype may miss a mutation in a phenotypically resistant isolate. Finally, detecting a mutation in a phenotypically resistant isolate via gene (or genome) sequencing does not always imply discovering the resistance's underlying mutation. Any of the following mutations could be present: causative, stepping-stone, compensating, or companion mutations (that is, merely a marker of the strain circulating in that particular setting). In other words, the discovered mutation might not be enough to create medication resistance. Only causative mutation should be used in diagnostic assays to detect drug resistance. As a result, knowing the sort of mutation found is critical.

Several groups have begun performing whole-genome sequencing on clinical isolates with the short-term goal of identifying novel resistance-associated mutations and the long-term goal of developing a test that could detect resistance faster than culture-based drug susceptibility tests and eventually replace them[70,71]. Studies demonstrate that this strategy is feasible; nevertheless, because of its low sensitivity (there are still phenotypically resistant isolates for which the underlying mutation cannot be identified[72]) and high cost, culture-based assays are still used in clinical care[73].

Diagnosis, screening and prevention

Diagnosis

The type of TB diagnostic tool to use is determined by the testing goal (detecting LTBI, active TB disease or drug resistance).

LTBI. The TST and the IGRA are two tests that can be used to detect LTBI. The IGRA can also distinguish between positive TST

responses caused by BCG and those induced by M. tuberculosis infection[74].

The TST involves injecting 5 tuberculin units (5 TU) of pure protein derivative (PPD) S or 2 TU of PPD RT23 into the skin using the Mantoux technique. A delayed-type hypersensitivity reaction will emerge within 48–72 hours in someone who has cell-mediated immunity to these antigens. The magnitude of the induration, the pre-test probability of M. tuberculosis infection, and the risk of developing active TB disease if the person was genuinely infected are all factors in interpreting the TST. All of these criteria are incorporated into the Online TST/IGRA Interpreter (www.tstin3d.com), which also calculates the probability of significant adverse events due to LTBI treatment[75].

Although the TST offers some advantages, particularly in low-resource settings, such as inexpensive reagent and equipment costs and low expertise and laboratory requirements, it also has two significant drawbacks. First, late (that is, post-infancy) or repeated BCG immunisation (booster vaccines) and, to a lesser extent, exposure to non-tuberculous mycobacteria94 impair its specificity. Second, its predictive value is limited[74]. The majority of people who get a positive TST result do not develop active TB illness. Efforts are currently being made to develop or verify novel skin tests that can replace PPD with more specific RD1 antigens95.

Active tuberculosis. Imaging techniques (chest X-rays and PET-CT), microscopy (sputum smears), culture-based procedures, and molecular analyses are all utilised to detect active TB disease. While imaging tests are useful for screening, a microbiological diagnosis is required for active TB disease. The many diagnostic technologies that have been assessed and endorsed by the WHO.

Chest radiography is a well-established triage or screening test, and digital radiology and computer-aided diagnostic software are significant recent developments[76]. Abnormal chest X-rays must be followed up with microbiological investigations since X-rays lack specificity. Although advanced imaging methods are too expensive and not suggested for normal use[77], they are bringing fresh insights into the diversity of lung pathologies.

Despite its limitations, sputum smear microscopy remains the most extensively used active TB disease test in low- and middle-income countries[78]. However, the ongoing roll-out of Xpert MTB/RIF (Cepheid Inc., Sunnyvale, California, USA), a molecular assay based on Cepheid Inc.'s automated GeneXpert technology, is significantly altering the TB diagnostics landscape, with >17 million cartridges procured via subsidised pricing programmes since its introduction in 2010. (Refs [79.80]). The WHO currently conditionally recommends Xpert MTB/RIF as the first-line diagnostic test in all adults and children suspected of having active TB disease[81] due to its superior accuracy over sputum smear microscopy[82-85].

Furthermore, sputum smear microscopy detects only 22–43 percent of active TB illness in HIV-positive people[86]. As a result, the WHO strongly advises using Xpert MTB/RIF as a first-line diagnostic test in these patients[81]. Furthermore, the detection of lipoarabinomannan (LAM) antigen in urine has emerged as a possible point-of-care test for detecting HIV-associated active TB illness, with a modest reduction in mortality in a small cohort of hospitalised HIV-positive patients[87].The WHO now recommends a LAM rapid test to assist and expedite the diagnosis of active tuberculosis disease in two specific populations: HIV-positive adult in-patients with signs and symptoms of pulmonary and/or extrapulmonary TB and a CD4+ T cell count of 100 cells per l, and HIV-positive patients who are seriously ill regardless of their CD4+ T cell count or with an unknown CD4+ T cell count[88].

Collecting respiratory specimens is difficult (small children are unable to produce sputum) and the disease may be extrapulmonary[89], making diagnosis and monitoring therapy response complicated. Because nonspecific symptoms (such as failure to thrive) are common in children with active TB disease, a history of interaction with an adult with active TB disease should be considered. There is no gold-standard test for childhood tuberculosis, thus diagnosis is based on an algorithm. Because of the low quantity of bacilli in children with TB, sputum smear microscopy is frequently negative. Signs, symptoms, evidence of M. tuberculosis infection (a positive TST or IGRA), history of contact with active TB disease, and results of chest X-ray (for example, revealing hilar adenopathy), liquid culture, and molecular tests (Xpert MTB/RIF) are all used in the diagnostic algorithm. At least two specimens must be submitted for microscopic examination, Xpert MTB/RIF testing, and culture if sputum can be collected (from older children and adolescents). Two to three fasting stomach aspirates can also be collected in young children (7–8 years old).

Resistance to drugs. There are phenotypic, culture-based (testing the capacity of bacteria to proliferate in the presence of anti-TB medications) and molecular-based (based on the detection of drug-resistant genetic alterations in M.

tuberculosis) approaches for detecting drug resistance. The use of Xpert MTB/RIF as a diagnostic tool for active TB disease has considerably boosted the early diagnosis of MDR-TB[90-92] in several situations. The introduction of the Xpert MTB/RIF has cleared the door for universal drug susceptibility testing and attracted new product developers to the TB field[80,93]. However, clinical trials of Xpert MTB/RIF have revealed that the therapeutic impact of this novel technology may be hampered in health systems with gaps in the TB care cascade[80,94,95]. Aside from Xpert MTB/RIF, the WHO recommends loop-mediated isothermal amplification for pulmonary TB diagnosis[96] and molecular line probe assays for rapid drug susceptibility testing of first-line drugs (such as isoniazid and rifampicin) and selected second-line drugs (such as fluoroquinolones and injectable second-line drugs)[97,98].

New diagnostic techniques. The development of novel diagnostic techniques is a priority, given the limits of existing diagnostics. A number of diagnostic tools are in the works[93,99]. Although the pipeline appears to be solid at first sight, the majority of the products are intended for use in laboratories and rely on the single validated TB biomarker: bacterial nucleic acid sequences. Such molecular diagnostics might not be affordable or simple enough to be included into primary care. Short-, medium-, and long-term measures are necessary to address these needs.

Aside from their diagnostic value, new molecular methods can assist discover drug resistance mutations and contribute to the goal of a universal drug susceptibility test for all people with active tuberculosis at the time of diagnosis by 2015. To ensure that the 'test and treat' method is completed quickly, new upcoming drug regimens will require adequate companion diagnostics[100]. Next-generation sequencing technologies are showing significant promise in this regard. [70,71] However, they will require translational effort to make them inexpensive and deployable in low-income, high-burden nations. The objective in the medium term is to develop a non-sputum-based, quick, low-cost test for use in primary care, where the majority of individuals seek treatment[93]. A relevant biomarker signature must be identified for such a test (primarily antigens, antibodies, volatile organic compounds or enzymatic markers). Despite the fact that multiple interesting biomarkers have been identified[101-103], validation is still underway, and no tests are likely to be submitted for policy approval until 2019. (Ref. [104]).

In the long run, the key goal is to find a biomarker that can accurately predict which LTBI patients are most likely to develop active TB disease, so that these patients can receive preventative treatment and the enormous LTBI 'pool' can be successfully reduced[93,105]. Another goal is to create a biomarker-based test to assess therapy efficacy, as current molecular diagnostics are insufficient. The present pipeline for such tests is inadequate. Biomarker discovery, validation, and translation into therapeutic tools will require more funding[105].

BCG vaccine

BCG, the only currently licenced vaccination to prevent the development of active TB illness, is given to almost 90% of babies worldwide every year[106,107]. The BCG World Atlas (http://www.bcgatlas.org) contains information on BCG policies and practises around the world[107]. The BCG vaccination was initially used in humans in 1921, and it has since been tested in a number of interventional trials and observational studies looking at less-common indications of active tuberculosis. The BCG vaccine's efficacy against pulmonary tuberculosis in adults has been found to be 0–80 percent in clinical trials [108,109]. The causes of the observed variation in BCG vaccine efficacy are unknown. It has been reported that BCG vaccine efficiency changes with latitude[108], but it is unclear whether this is due to the force of exposure to certain non-tuberculous mycobacteria, all non-tuberculous mycobacteria, M. tuberculosis itself, or other, as yet undefined causal factors. The BCG vaccine protects between 50 and 80 percent of newborns and children under the age of five from severe, extrapulmonary types of active TB illness, according to case–control studies [108]. The BCG vaccine has also been linked to protection against M. tuberculosis infection in children[107].

Because TB morbidity and mortality in children under the age of five can be substantial, the BCG vaccine is critical in avoiding active TB disease in this age range. The majority of occurrences of transmissible, pulmonary active TB illness, however, occur in teenagers and adults, for whom the BCG vaccine's efficacy is unknown[110,111]. Furthermore, a meta-analysis of paediatric BCG vaccine efficacy found that protection lasts up to 10 years on average, with vaccine efficacy diminishing over time[112]. As a result, current BCG regimens are unlikely to contribute much to the control of the global TB pandemic, because in most countries, the BCG vaccine is only given once, at birth, and its protection is unlikely to last throughout adolescence[107].

New vaccines

Despite its variable efficiency, the BCG vaccine has demonstrated that a vaccine can elicit protective immunity against tuberculosis, even if the protective mechanism is not well understood. Indeed, the primary goal of current vaccination research is to help avoid active TB disease in the 10% of infected people who are unable to control their infection as LTBI. In an ideal world, a vaccine would completely prevent M. tuberculosis infection (for example, as measured by prevention of conversion of an IGRA). Novel trial designs can be used to evaluate a vaccine's ability to meet these objectives[113]. Transmissible active TB illness must be prevented in the people most at risk to maximise the impact of vaccine on morbidity and mortality. Because M. tuberculosis infection is mostly transmitted by teenagers and adults with active pulmonary tuberculosis, much of the recent vaccine development focuses on vaccinations for these age groups. However, because the BCG vaccine is only partially effective in neonates and is not recommended for HIV-infected infants, a better vaccine for newborns is also desired.

According to simulations, a 60 percent effective vaccine administered to 20 percent of adolescents and adults may prevent 30 million instances of active tuberculosis in the first 20 years (a total of 35 million cases could be prevented if 90 percent of neonates were also vaccinated)[114].

Another modelling study found that vaccines aimed at adolescents and adults could have a substantially bigger impact on global TB burdens than vaccines aimed at newborns during the 2024–2050 time horizon, and that such medicines could be reasonably cost-effective[115].

TB vaccine development is fraught with difficulties (Box 1). Despite these limitations, at least 13 vaccine candidates are currently being investigated in clinical trials (Table 2), with three platform types: whole-cell or mycobacteria lysates, viral vector vaccines, and adjuvanted recombinant protein vaccines. The antigenic make-up of M. tuberculosis vaccines ranges from thousands of antigens in mycobacterial vaccines to four or fewer antigens in viral vector and recombinant protein vaccines.

Drug-resistant tuberculosis (DRTB) has emerged and spread in many countries with a high tuberculosis (TB) burden. Because vaccine targets are anticipated to be fully independent of drug targets, an effective vaccination should operate equally effectively against drug-sensitive and drug-resistant strains of Mycobacterium tuberculosis. As a result, a novel tuberculosis vaccination could help to preserve the therapeutic efficiency of TB drugs while also addressing the critical drug resistance issue. Due to scientific and economic hurdles, private sector biopharmaceutical companies are only partially supporting the development of TB vaccines.

Despite the fact that tuberculosis is the largest cause of death worldwide owing to a single infection, the market for TB vaccines is limited[114]. Even in high-income countries, the poor with limited financial resources account for the majority of active tuberculosis cases. This reality has an impact on the market projection for a new vaccine, limiting for-profit investment in TB vaccine research and development.

Management

According to the WHO, 80 percent of all active TB patients are infected with M. tuberculosis strains that are fully susceptible to all current antibiotics, whereas the remaining 20% are infected with drug-resistant strains (13.3 percent isoniazid mono-resistant and 5.3 percent MDR)[5,11]. Based on these figures, roughly 1.9 million persons had active drug-resistant tuberculosis illness in 2014, a significant burden. For patients, drug resistance necessitates lengthier and more hazardous treatment regimens.

LTBI

Only HIV-positive individuals, adults and children who had contact with patients with active pulmonary TB disease, and patients starting anti-TNF treatment, on dialysis with end-stage renal disease, preparing for organ or haematological transplantation, or with silicosis should undergo LTBI screening[117], according to the WHO's first comprehensive guideline on LTBI management[117]. The justification for prioritising these populations is that they are at a very high risk of advancing from LTBI to active TB disease, which might be avoided with LTBI therapy. The treatment of LTBI in those who have come into touch with active MDR-TB patients remains debatable. The WHO recommends that these people be closely monitored for at least two years. When the advantages outweighed the risks, clinicians could explore individually customised treatment regimens (based on the medication susceptibility profile of the patient with active MDR-TB disease to which the individual had been exposed) for children under the age of 5 years[117].

The WHO recommends 6–9 months of isoniazid, 3 months of rifapentine plus isoniazid, 3–4 months of isoniazid plus rifampicin, or 3–4 months of rifampicin alone[117] for LTBI treatment. All regimens are known to be effective[86,117], however patient compliance with lengthier regimens can be poor[118]. Rifampicin-containing regimens are shorter and may be more appropriate in populations where isoniazid mono-resistant strains are prevalent. Regardless of the regimen, it is critical to guarantee adherence and give proper counselling to patients.

Active drug-sensitive TB disease

For active drug-sensitive TB disease, the current preferred regimen (Table 3) is a minimum of 6 months of treatment with rifampicin, isoniazid, pyrazinamide, and ethambutol for the first two months (the intensive phase of treatment), followed by isoniazid and rifampicin for four months (the continuation phase)[119,120]. Repeat sputum smears, cultures, and chest X-rays are routinely used to track treatment efficacy and progress.

Despite its high success rate (about 86 percent under normal, programmed field conditions1; the regimen itself is more efficacious), the typical 6-month regimen has numerous drawbacks. A certain proportion of individuals will experience toxicity[121], which is due in part to the treatment's long duration. Mild elevations in liver enzymes, skin rash, gastrointestinal intolerance, neuropathy, and arthralgia are common adverse effects that can be handled symptomatically

without stopping the offending medicines. Severe hepatitis, immunological thrombocytopenia, agranulocytosis, haemolysis, renal failure, optic neuritis, and ototoxicity are all serious side effects. Furthermore, long-term treatment reduces patient compliance. As a result, supportive measures are required to guarantee optimal adherence, as treatment failure, relapse, and the establishment of drug resistance are all linked to incomplete treatment.

Direct observed therapy (DOT), in which every dose of treatment is personally watched by a health practitioner, is the most prevalent adherence monitoring method, while its effectiveness is debatable[122]. Although DOT is still useful in many situations, new approaches to improving adherence are being tested, including mobile phone reminders, smart pill boxes, video DOT, and the use of call centres to follow up with patients. It is critical to utilise a team-based, patient-centric strategy that includes education, counselling, and patient empowerment[123], regardless of the modality.

Active drug-resistant TB disease

For optimising treatment outcomes, avoiding disease transmission, and reducing future drug resistance, early and prompt identification and commencement of an effective regimen against active drug-resistant TB illness are critical. [124,125]. Designing an adequate regimen is a difficult process because it is dependent on the patient's characteristics as well as the organism's individual drug susceptibility profile[124-126].

Treatments for active drug-resistant tuberculosis currently have a low evidence base, are lengthy, employ medications with unknown efficacy, and are associated with substantial toxicity. In TB-endemic nations, adherence rates and outcomes are both poor (about 50% treatment success for active MDR-TB disease in most TB-endemic countries)1. Furthermore, in addition to regular medical examinations, various toxicity-related measures require close monitoring during therapy[127], putting additional strain on health-care institutions. The WHO modified its treatment guidelines for active drug-resistant TB illness in May 2016 based on promising outcomes of a seven-drug regimen that is being implemented in many countries. This shorter regimen should only be used in specific circumstances, according to the recommendation[128]. Although the regimen is intended to assist the majority of patients with active MDR-TB disease, if it is given incorrectly or without proper drug sensitivity testing, resistance may grow.

The possibility of completely drug-resistant bacteria has raised two major concerns. [125,128]. First, new drug research and introduction has lagged behind the growth of drug-resistant strains. This failure reflects a lack of public and corporate investment since the 1970s, when the incidence of tuberculosis (TB) declined in most high-income nations and the need for new treatments was viewed as less urgent. Second, introducing new drugs in settings with a high prevalence of drug-resistant strains without addressing one of the fundamental causes of the emergence of such strains (for example, weak health-care systems with poor TB patient management) increases the risk of amplifying anti-TB drug resistance.

Surgery can help with drug-resistant TB care in addition to pharmacological therapy. Surgical surgery to remove the entire afflicted portion of the lung can be successful in individuals with unilateral disease (or apical bilateral disease in certain circumstances) who have sufficient lung function and have failed to respond to medicinal treatment. Elective partial lung resection (lobectomy or wedge resection) is related with increased treatment outcome in individuals with rifampicin-resistant TB or MDR-TB[126].

Principles of managing MDR-TB

In chosen patients, in appropriate contexts, a 9–12-month regimen (conditional WHO guideline with very low-quality data) could be employed, taking into account past therapy and local resistance profiles.

A longer treatment plan is utilised if patients are not qualified for the shorter treatment regimen. For a period of 20 months, the regimen contains pyrazinamide as well as at least four second-line medications to which the organism is predicted or proved to be susceptible.

A later-generation fluoroquinolone (such as moxifloxacin, levofloxacin, or gatifloxacin), an injectable agent (such as amikacin, kanamycin, or capreomycin*), and two or more core second-line agents should be included in the second-line drugs (such as ethionamide, prothionamide, cycloserine, terizidone, clofazimine or linezolid)

To strengthen the regimen, first-line medicines (such as isoniazid or ethambutol) could be added.

When toxicity or resistance develops, additional medicines such as bedaquiline and delamanid might be added, bringing the total number of medications used to four.

A failing regimen should not be supplemented with a single new medicine.

Adherence and emotional support, as well as, if necessary, drug misuse counselling, are critical.
Adverse medication reactions, which are prevalent, should be monitored in patients.
Multidrug-resistant tuberculosis, or MDR-TB. Capreomycin cross-resistance with aminoglycosides is not complete, and it may be a therapeutic choice in select and appropriate circumstances, as well as in the face of aminoglycoside resistance when no other safe or effective options are available.

Multidrug-resistant tuberculosis (MDR-TB) regimens should be created using similar ideas (Box 2)

Drugs like linezolid, bedaquiline, and delamanid (if available) are frequently required, requiring the use of at least four drugs that are likely to be efficacious at the same time.

Patients often only receive one or two effective treatments due to a lack of access to newer and repurposed drugs, resulting in poor treatment outcomes.

Meropenem and clavulanate are two more medicines utilised, but their role and effectiveness are unknown.

Moxifloxacin can still be utilised in the context of fluoroquinolone (for example, ofloxacin) resistance since cross-resistance between fluoroquinolones is not complete.

Optimising existing medications Because new regimens are urgently needed and new drug development is time-consuming, expensive, and uncertain, interim solutions have included highly intermittent regimens, existing anti-TB drugs that were never widely prescribed, higher doses of currently used anti-TB drugs[130,131], and're-purposed' drugs (drugs that were originally designed for other diseases that could prove effective against drug-resistant TB). Rifapentine, for example, has similar anti-mycobacterial activity in vitro as rifampicin but a fivefold longer half-life. It has been demonstrated to be effective as a rifampicin substitute when administered once or twice a week[131].

Additionally, fluoroquinolones are an antibiotic family that is commonly used to treat infections in the lower respiratory tract. They exhibit great in vitro activity against M. tuberculosis, are as effective as isoniazid in the initial phase of drug-sensitive TB treatment[132], and are critical medications in the treatment of drug-resistant TB[133]. However, three large trials have shown that short (4-month) fluoroquinolone-based regimens for drug-sensitive TB cannot reach cure rates comparable to the usual 6-month regimen[131,134,135].

Another potential repurposed medicine is linezolid, which has been used successfully in patients with isoniazid, rifampicin, or fluoroquinolone-resistant strains[136]. Linezolid, on the other hand, has little experience because to its high cost and toxicity. Similarly, carbapenems have been useful in patients with extremely resistant strains[137], but they are expensive and need parenteral administration with some exceptions (such as faropenem). The most promising techniques to improving the treatment of TB (all forms) are the discovery of novel drugs and the creation of new regimens.

The current pipeline and newly authorised medications The US FDA authorised bedaquiline (a diarylquinoline) at the end of 2012, the first truly novel anti-TB medicine in almost 40 years[138]. Bedaquiline and another novel medication, delamanid (a nitroimidazo-oxazole derivative), were approved by the European Commission in 2014 for the treatment of individuals with pulmonary MDR-TB[139]. Many more countries have now approved bedaquiline. Both bedaquiline and delamanid act by inhibiting ATP synthase and inhibiting mycolic acid synthesis, respectively, and there is no known cross-resistance with other approved anti-TB medications. Furthermore, both drugs appear to have very good'sterilizing' properties in preclinical models, which measure their ability to kill tuberculous organisms when there are very few left in the body or when they are growing or reproducing very slowly; this ability could translate into a shorter TB therapy duration[140,141].

These new medications, on the other hand, were approved based on very little proof. To evaluate if these two medications can be delivered simultaneously, the ideal treatment length, their real capacity to contribute to treatment shortening, and the optimal companion therapies, well-designed and well-executed randomised trials will be required. The ultimate goals are to shorten and simplify TB treatment while also enhancing cure rates and producing regimens with fewer side effects, particularly in the treatment of drug-resistant TB[142].

The TB drug pipeline is presently the broadest it has ever been[143], with many early TB drug discovery programmes, the majority of which are incorporated into the TB Drug Accelerator, a collaborative TB drug discovery programme financed by the Bill & Melinda Gates Foundation[144].

The majority of the chemicals under 'Discovery' come from whole-cell screening, and genuine target identification and validation are still

continuing. Ten substances (new or repurposed) are now being examined in phase I studies or as part of anti-tuberculosis (TB) medication regimens among products under clinical development. The majority of these chemicals are classified as oxazolidinones, nitroimidazoles, or fluoroquinolones. Many phase II and phase III trials aim to combine new or repurposed medicines in therapy regimes that are considerably shorter and simpler than current standard of care, have greater or equal efficacy, and have decreased or similar associated toxicity. The majority of TB treatment-shortening trials are aimed at people who have TB that is resistant to traditional first-line therapy, while some trials aim to find universal regimens that are equally effective against drug-sensitive and drug-resistant TB, obviating the necessity for drug sensitivity testing.

Childhood TB

Models reveal that active TB disease in children is more common than official records suggest, and that MDR-TB cases are significantly more common than previous estimates[145,146]. In adults, active tuberculosis causes pulmonary disease, but in children, the disease spectrum varies, ranging from paucibacillary lymphadenitis to severe disseminated (miliary) disease[23,147].

Children who have had contact with adult patients with active TB disease are at a higher risk of contracting M. tuberculosis and developing active TB disease, hence LTBI testing and treatment are prioritised for them[148]. The same concepts that apply to adult LTBI treatment apply to youngsters. Anti-TB medications are generally well tolerated by youngsters, with little danger of harm. Drug dosages in children must be adjusted for body weight and age due to developmental changes in pharmacokinetics and pharmacodynamics. Drug resistance in adult patients with active TB disease who have had contact with children may be useful in deciding on a regimen.

The essential principles and conventional regimens for treating active tuberculosis in children are identical to those used in adults[150]. Treatment should be given daily at least throughout the intensive period, and in extreme cases of active disease, it may be continued up to 9–12 months[150]. The WHO guidelines [149,150] address how to manage HIV infection in children with active TB illness. MDR-TB in HIV-positive children is treated using the same principles as MDR-TB in HIV-negative children.

Quality of life

Several studies have found that patients with active TB disease[151] had a poorer self-reported health-related quality of life than healthy people or people with LTBI. Lung impairment with chronic pulmonary disability, bronchiectasis, aspergillomas, and chronic pulmonary aspergillosis are known sequelae that are more common in drug-resistant TB patients than in drug-sensitive TB patients[152]. Long-term pulmonary rehabilitation and chest physiotherapy may be required for patients with decreased lung function.

Patients with drug-resistant tuberculosis have a prognosis comparable to those with drug-sensitive tuberculosis if they are not treated (10-year case fatality rates of approximately 70 percent) 16. The current WHO-recommended MDR-TB regimen has a cure rate of about 50%, whereas the cure rate for extensively drug-resistant TB in endemic areas in the absence of medications like bedaquiline, delamanid, and linezolid is about 20% [149,153]. As a result, tuberculosis (particularly drug-resistant tuberculosis) poses a serious danger to human health and quality of life. To promote favourable outcomes and maintain quality of life, high-quality patient care, compatible with the International Standards for TB Care201, is critical.

Unfortunately, many low-income, high-burden countries fail to meet international norms, especially

in the private health sector, which is a key supplier of health care in many countries with high TB prevalence[154-158]. Poor quality of care is thus a primary driver of tuberculosis mortality in high-burden nations, and it may explain why TB incidence remains high in some places. While national programmes are accountable to national and international agencies for implementing proper standards of care, involving and regulating the private sector[158] remains one of the most difficult difficulties in TB management. To tackle this difficulty, innovative public–private mix options are needed, such as social franchising, insurance-based initiatives, intermediate agencies, and provider consolidation, with a strong emphasis on the use of information and communication technologies.

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