

Centenary Review Article

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Tuberculosis: From an incurable scourge to a curable disease - journey over a millennium

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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 multidrug-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.

Key words Clinical manifestations - diagnosis - epidemiology - extensively drug-resistant tuberculosis - human immunodeficiency virus co-infection - multidrug-resistant tuberculosis - treatment - tuberculosis

Introduction

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 *Sanskritam* (*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 literature¹⁻³. 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”)^{4,5}.

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^{2,4,6}. John Jacob Manget gave the description of classical miliary TB in 1700⁷. 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^{1,2}. 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 1882⁸. 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 problem¹.

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 1993⁸. The late 1990s also witnessed the resurgence of drug-resistant TB (DR-TB) with multidrug-resistant TB (MDR-TB) emerging as a major threat⁹⁻¹¹. The first decade of the 21st century has been ravaged by extensively drug-resistant TB (XDR-TB)¹². Recently, concern has been expressed regarding the occurrence of extremely drug-resistant TB (XXDR-TB)^{13,14}, super XDR-TB¹⁵, totally drug-resistant TB (TDR-TB)^{15,16} from some parts of the world. The report on the occurrence of TDR-TB from India¹⁷ has raised concern and consternation¹⁸. Over the millennia, TB never respected anyone and had treated the rich and poor alike with equal disdain.

Definitions

Certain key definitions concerning clinically important forms of TB, drug-resistant TB are listed in Tables IA¹⁹⁻³⁷ and IB^{9-16,31-37} respectively.

Epidemiology

Global burden of TB

The global burden of TB as described in the 16th global report on TB published by WHO in 2012³⁷ is shown in Table IIA; most of the cases occurred in Asia (59%) and Africa (26%).

Indian scenario

The current estimated TB burden in India is listed in Table IIB^{30,37-39}. India has featured among the 22 high TB burden countries; and has accounted for an estimated one quarter (26%) of all TB cases worldwide³⁰

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

Table IA. 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 wk, 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 smear-negative 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 or culture) 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^{29,30}; or, can be categorized clinically to have disseminated TB

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

Source: Refs19-30

Table I B. 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 previously 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^{9,10}

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 (see below)

*MDR-TB suspect*¹¹

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

*MDR-TB*¹¹

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 both²⁰
- (ii) either any fluoroquinolone or at least one second-line anti-TB drug, but not to both²¹

*XDR-TB*¹²

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^{*13,14}

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

TDR-TB (also called super XDR-TB)^{*15,16}

Isolates of *M. tuberculosis* resistant to all first- and second-line licensed anti-TB drugs

***A WHO Consultation held in March 2012³⁶ 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^{13,14}, super XDR-TB¹⁵, and TDR-TB^{15,16}, their usefulness and limitations need further clarification³⁴⁻³⁶ 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.

Source: Refs. 9-16, 20, 21, 34-37

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 regions³⁷. The recent global epidemiological data on M/XDR-TB are shown in Table IIIA, Fig.s 1A and 1B. XDR-TB has been documented from many parts of the world (Fig. 1C)^{40,41}.

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%)⁴²⁻⁴⁵ (Table IIIB). The prevalence of XDR-TB in studies published from India where drug-susceptibility

Table II A. 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 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.

Source: Refs. 37

The World Health Organization (WHO) updates these data annually. The updated information can be accessed from the WHO report of the current year available from: <http://www.who.int/topics/tuberculosis/en/>

Table II B. Provisional estimates of TB burden in India 2010

Variable	Best estimate (low-high)
Incident cases (/100,000 population)*	181 (163-199)
Annual risk of infection†	1.5%
Prevalent cases (/100,000 population)*	249(168-346)
Period Prevalence (2000 GoI estimate)	
AFB-positive	165 (126–204)
Bacillary cases‡§	369 (272–457)
TB mortality (per/100,000 population)	24 (15-35)
HIV prevalence in incident TB cases (%)	4.2 (3.3-5.2)
% TB patients tested that are HIV-seropositive	9.2 (6.1–13)

* Data as on September 25, 2012

†In the nationwide study (2000-2003)³⁸, for the country as a whole, the average annual risk of infection (ARI) computed from estimated prevalence was 1.5%. The ARI showed regional variations and was higher in the northern (1.9%) and western (1.8%) zones compared with the eastern (1.3%) and southern (1%) zones. In a subsequent publication³⁹, observations from two rounds of house-based tuberculin surveys conducted 8-9 year apart among children aged 1–9 years in statistically selected clusters during 2000–2003 and 2009–2010 were reported. It was observed that ARI rates declined by respectively 6 and 11.7% per year in the north and west zones; no change was evident in the south and east zones. At the national level, ARI declined by 4.5% per year between 1998 and 2007³⁹.

‡ Defined as a person with at least one AFB smear positive by sputum microscopy, or at least one sputum culture positive for *M. tuberculosis*

§ Prevalence rate calculated from estimated number of persons with disease in 2000, divided by 2000 population estimate

|| In a recent study (n=98599), the prevalence of bacillary TB, among persons aged 15 years and above, in Faridabad district of Haryana, in northern India was found to be 126 per 100,000 persons (unpublished observations).

TB, tuberculosis; AFB, acid-fast bacilli; GoI, Government of India; HIV, human immunodeficiency virus

Source: Refs. 30,37-39

The Central TB Division updates these data annually. The updated information can be accessed from the Revised National Tuberculosis Control Programme annual report of the current year available at the URL: <http://tbcindia.nic.in/>

Table III A. Global epidemiology of MDR-TB and XDR-TB

Variable	% (95% CI)
Prevalence of MDR-TB among new TB cases	3.7 (2.1–5.2)
Prevalence of MDR-TB among previously treated TB cases	20 (13-16)
Prevalence of XDR-TB among MDR-TB cases	9.0 (6.7–11.2)

CI, confidence intervals; MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis

Source: Refs. 37

The World Health Organization (WHO) updates these data periodically. The updated information can be accessed from: <http://www.who.int/topics/tuberculosis/en/>

testing (DST) was carried out in quality-assured, accredited laboratories is shown in Table IIIC⁴⁶⁻⁵³.

Risk factors

Conventionally several genetic, social, environmental and biological determinants of health have been intuitively recognized by clinicians as risk factors for TB (Table IV)⁵⁴⁻⁷³. Some of these risk factors are discussed below.

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 disease⁵⁸. Several reports have implicated a long list of genes with risk of developing TB (Table IV)⁵⁸⁻⁶¹.

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 decades⁶²⁻⁷³. 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 risk⁶²⁻⁶⁴.

HIV infection and MDR-TB: Even though several institutional outbreaks of MDR-TB among HIV-infected patients drew attention to the problem two decades ago⁷⁴⁻⁷⁸ as per currently available evidence⁷⁹⁻⁸¹, 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 over⁸²⁻⁸⁴. 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 DM⁸⁴ suggesting that DM substantially contributes to the burden of TB, especially sputum smear-positive pulmonary TB in India.

Use of immunomodulator biologicals

Use of immunomodulator drugs (biologicals) has been associated with the development of fatal TB in rheumatoid arthritis^{85,86}.

Table III B. Epidemiology of MDR-TB in India 2011

Variable	Observations (low-high)
Estimated cases with MDR-TB among notified new cases with pulmonary TB	21000 (15000–27000)
Estimated cases with MDR-TB among notified previously treated cases with pulmonary TB	45000 (40000–50000)
% of new TB cases with MDR-TB	2.1 (1.5–2.7)
% of previously treated TB cases with MDR-TB	15 (13–16)

Source: Ref. 37

The World Health Organization (WHO) updates these data periodically. The updated information can be accessed: <http://www.who.int/topics/tuberculosis/en/>

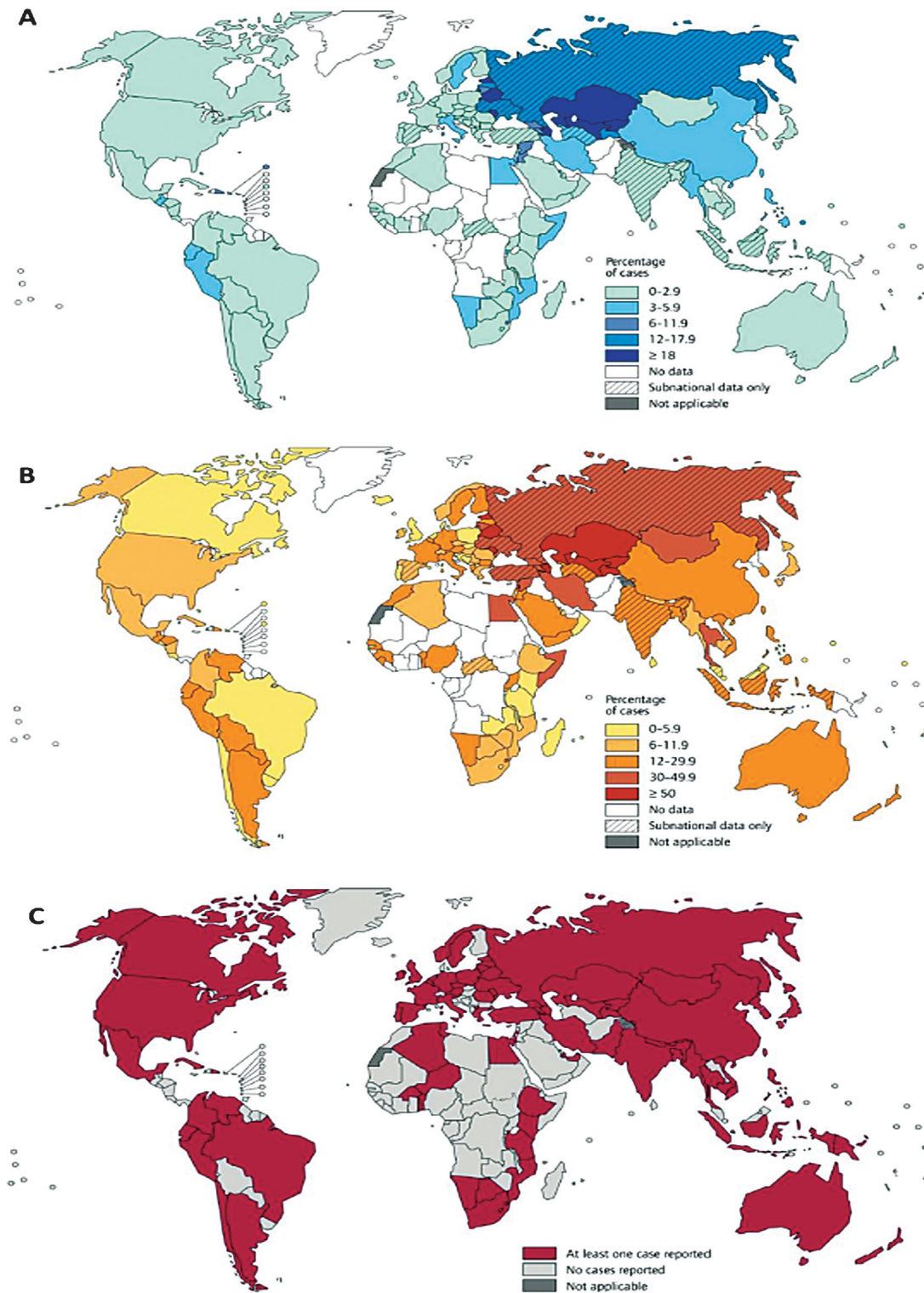


Fig. 1:(A). Distribution of percentage of new tuberculosis cases with MDR-TB 1994-2011. (B). Distribution of percentage of previously treated tuberculosis cases with MDR-TB 1994-2011. (C). Countries that had reported at least one XDR-TB case 1994-2011. MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis. *Reproduced with permission from World Health Organization (reference 41)*

Table III C. Prevalence of XDR-TB in studies published from accredited laboratories for mycobacteriology from India

Study (year) (reference)	Study period	Design	HIV status	Laboratory	Method of DST testing	Prevalence of XDR-TB among patients with MDR-TB
Thomas <i>et al.</i> (2007) (46)	1999-2003	Field trial involving patients with MDR-TB	ND	WHO-recognized supranational reference laboratory	Culture: LJ medium; DST: MIC and RR method	1/66 (1.5%)*
Sharma <i>et al.</i> (2009) (47)	1997-2003	Retrospective study of case-records of patients with MDR-TB	Negative	WHO-recognized supranational reference laboratory (during the study period)	Culture: LJ medium; DST: proportion method	5/211 (2.4%)
Rajasekharan <i>et al.</i> (2009) (48)	2004-2007	Retrospective study of "treatment failure" pulmonary TB patients	144/1041 (13.9%) patients with MDR-TB were HIV-seropositive	WHO-recognized supranational reference laboratory	Culture: LJ medium; DST: MIC and RR method	48/1041 (4.6%)†
Paramasivan <i>et al.</i> (2010) (49)	2001-2004	Retrospective study of isolates with MDR-TB	ND	WHO-recognized supranational reference laboratory	Culture: LJ medium; DST: absolute concentration method, the RR method	69/1498 (4.6%)
Thomas <i>et al.</i> (2011) (50)	1993-2003, 2006-2007	Retrospective study of case-records of patients admitted for treatment of MDR-TB (n=104)	Negative	WHO-recognized supranational reference laboratory		10/104 (9.6%)‡
Myneedu <i>et al.</i> (2011) (51)	2007-2009	Retrospective study of randomly selected isolates of MDR-TB	ND	Accredited national reference laboratory		45/223 (20.2%)
Joseph <i>et al.</i> (2011) (52)	2006-2007	Prospective feasibility study	Negative§	WHO-recognized supranational reference laboratory	Culture: LJ medium; DST: proportion method	2/38 (5.3%)
Balaji <i>et al.</i> (2011) (53)	2002-2007	Retrospective study of isolates of MDR-TB¶	17/61 (27.9%)	Clinical microbiology laboratory in a medical college accredited by the RNTCP and the CTD, MoH&FW, GoI	Culture: LJ medium; DST: MIC and RR; and proportion method	47/77 (61%)**

* patient had XDR-TB at the time of initial diagnosis

† 3 of the 48 patients (6.25%) with XDR-TB were HIV-seropositive

‡ 1 patient had XDR-TB at the time of initial diagnosis; of the 12 patients with pre-XDR-TB at the time of initial diagnosis (defined as ofloxacin/kanamycin resistance), 5 were cured, 3 died, 1 defaulted and 3 failed to respond to treatment, with emergence of XDR-TB; 6 of 91 patients who had initially ofloxacin and kanamycin susceptible organisms developed XDR-TB; all patients with XDR-TB were HIV-seronegative

§ HIV-seropositive patients were excluded from the study

|| at the baseline, no patient had XDR-TB; 2 treatment failure patients had developed XDR-TB

¶ of the 194 results available for analysis, 77 patients had MDR-TB

** 3 of the 47 patients with XDR-TB were HIV-seropositive

XDR-TB, extensively drug-resistant tuberculosis; HIV, human immunodeficiency virus; MDR-TB, multidrug-resistant tuberculosis; DST, drug susceptibility testing; ND, not described; LJ, Lowenstein-Jensen medium; WHO, World Health Organization; MIC, minimal inhibitory concentration; RR, resistance ratio method; RNTCP, Revised National Tuberculosis Control Programme; CTD, Central TB Division; MoH&FW, Ministry of Health and Family Welfare; GoI, Government of India

Table IV. 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 catheterization

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*

* Published evidence suggests a bi-directional synergistic relationship between HIV infection and TB. Persons infected with HIV are at markedly increased risk for progressive HIV disease following TB infection⁶⁵⁻⁶⁸; reactivation of latent infection and risk of subsequent episodes of TB from exogenous reinfection^{69,70}. Among persons co-infected with HIV and TB, the estimated annual risk of reactivation is 5 to 8 per cent with a cumulative lifetime risk of 30 per cent or more compared to a cumulative lifetime risk of 5 to 10 per cent observed in HIV-seronegative adult patients^{62,71,72}. Furthermore, in persons co-infected with HIV and TB, the course of HIV infection is accelerated subsequent to the development of TB. The sites of active TB infection act as epifoci of HIV replication and evolution independent of systemic HIV disease activity has been postulated to be one of the important reasons for accelerated progression of HIV infection⁷³.

TB, tuberculosis; CMI, cell-mediated immunity; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome

Source: Refs. 56-73

Tobacco smoking

Data from recent systematic reviews on tobacco smoking and TB suggest that tobacco smokers have about three-fold higher risk of TB than non-smokers; even after adjustment for other factors⁸⁷⁻⁹¹.

Changing clinical presentation of TB**Natural history of TB**

The natural history of TB (Fig. 2)^{23,27,62,92-96} is influenced by several factors, the course being determined by the balance between the host

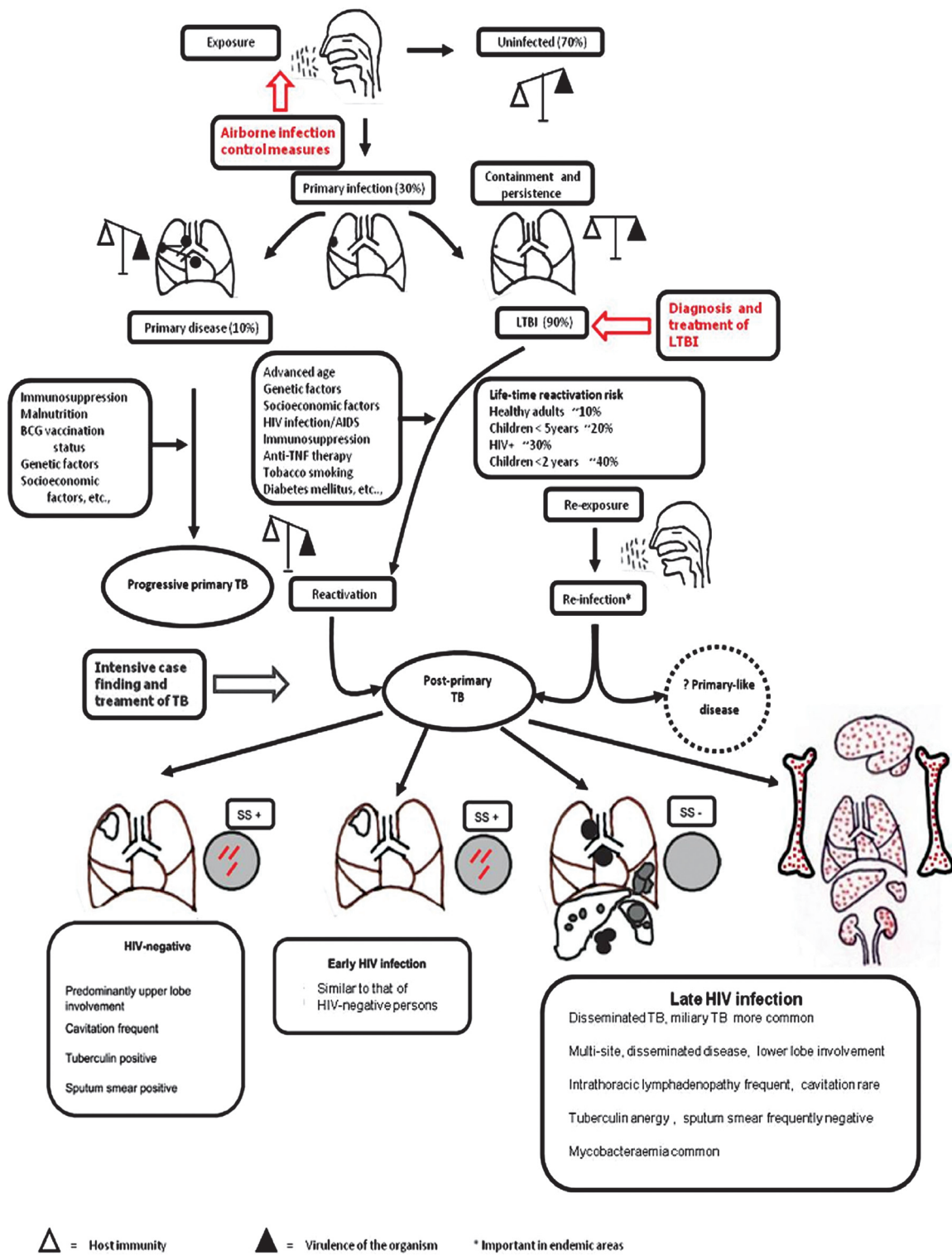


Fig. 2. Natural history of *Mycobacterium tuberculosis* infection and scope for intervention. TB, tuberculosis; BCG, bacille Calmette-Guerin; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; TNF, tumour necrosis factor; LTBI, latent TB infection; SS, sputum smear.

Adapted and updated from references 23, 62, 92.

immunity and the virulence of the TB bacillus. This understanding also facilitates identification of areas where interventional strategies can be identified for control of TB.

Atypical clinical presentations

Cryptic miliary TB: Miliary TB that was earlier seen primarily as a disease of children, is being increasingly encountered in adults since the 1970s^{23,27,28,97}. Apyrexial presentation with progressive wasting strongly mimicking a metastatic carcinoma (cryptic miliary TB) that has been described especially among older people^{23,27,28,98,99} often used to be diagnosed only at autopsy. This entity is being increasingly diagnosed during life in young immunosuppressed persons presently. This has been possible by the advances in imaging studies and increasing use of interventional procedures to procure tissue for confirming the diagnosis.

Acute lung injury and acute respiratory distress syndrome: TB as a primary cause of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) is also being reported in the recent years especially in areas where TB is highly endemic¹⁰⁰⁻¹⁰³. Increased awareness regarding this entity among intensivists, invasivists and internists, has resulted in a focused search for TB as the treatable cause in patients presenting with ARDS of obscure aetiology.

TB in patients receiving immunomodulator biologicals: Data regarding the clinical presentation of TB in patients receiving immunomodulator biological, such as, anti-tumour necrosis factor (anti-TNF) antibodies infliximab, adalimumab, golimumab and certolizumab pegol; and the soluble TNF receptor etanercept are emerging. The rate of TB was three to four-fold higher in patients receiving infliximab and adalimumab than in those receiving etanercept⁸⁶.

Presentation as 'pyrexia of unknown origin': In areas where the disease is endemic, TB tops the list of aetiological causes of pyrexia of unknown origin (PUO)^{104,105}. Till about two decades ago, clinicians either empirically administered anti-TB treatment or had to resort to invasive surgical procedures such as scalene node biopsy, laparotomy to ascertain the diagnosis. Often, the TB was diagnosed only on post-mortem examination. In patients presenting with PUO, miliary TB^{27,28}, intrathoracic (*e.g.*, paratracheal, mediastinal, hilar) and intraabdominal (*e.g.*, retroperitoneal, porta hepatis) lymph node TB^{94,106}, intestinal, omental and mesenteric, hepatic, splenic TB¹⁰⁷, vertebral TB (often

with paraspinal cold abscess)¹⁰⁸, pelvic ascites^{109,110} are important occult locations that are identified as the focus of fever by imaging methods facilitating ante-mortem diagnosis. Many times, bone marrow aspirate and biopsy smear, mycobacterial culture and molecular test evidence could be the only discernible cause of TB in these patients^{62,94}.

Sudden cardiac death: Sudden cardiac death due to TB myocarditis, especially in young persons is increasingly being recognized. This condition is often diagnosed at autopsy and extensive TB infiltration of the myocardium with minimal systemic involvement has been described; occult miliary TB has been implicated as the possible cause of myocarditis^{111,112}. Ante-mortem diagnosis of this condition is now possible with echocardiography, and cardiac magnetic resonance imaging (MRI)^{113,114}.

TB among healthcare workers

Health-care workers (HCWs), who are often in close proximity to patients with TB are at an increased risk of developing TB. It has been estimated that in areas of high TB incidence (>100/100,000 population), the stratified pooled estimates for LTBI and TB incidence rate ratios were 8.4 (95% CI 2.7-14.0%) and 3.7 per cent (95% CI 2.9-4.5), respectively; median estimated population-attributable fraction for TB was as high as 0.4% (115). These figures serve as warning bells, especially with regard to HCWs caring for patients with X/MDR-TB¹¹⁶ and highlight the need for institution of preventive measures. Further, it has been shown that institution of basic administrative and engineering controls and personal protection measures can be effective in reducing the annual tuberculin skin test (TST) conversion rates in HCWs¹¹⁷.

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 condition⁹². The tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) have been used as diagnostic tests for the detection of LTBI (Table VA)¹¹⁸⁻¹²¹.

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

Table V A. Diagnostic methods for latent TB infection

Diagnostic test	Comments
Tuberculin skin test (TST)	The tuberculin skin test quantifies the delayed-type hypersensitivity reaction to a protein derivative of <i>Mycobacterium tuberculosis</i> . Cut-off levels ranging from greater than or equal to 5 mm induration (in immunosuppressed persons) to greater than equal to 15 mm induration (in individuals with no risk factors) have been advocated in various clinical settings for interpreting the TST results. Universal BCG vaccination coverage practiced in developing countries and the presence of environmental nontubercular mycobacteria affect the TST results
Interferon-gamma release assays (IGRAs)	The IGRAs are a new class of <i>in vitro</i> assays that measure interferon- γ released by effector T-cells following stimulation with certain antigens of <i>M. tuberculosis</i> , namely early secreted antigen-6 (ESAT-6), culture filtrate protein-10 (CFP-10), and TB7.7. Commercial IGRAs, such as, the QuantiFERON-TB Gold In-Tube (Cellestis, Valencia, CA, USA); and the T-SPOT.TB (Oxford Immunotec, Oxfordshire, UK) tests are now widely being used for the diagnosis of latent TB infection

BCG, bacille Calmette-Guerin

cent being reported for both¹²²⁻¹²⁵. In this connection, a recent policy statement issued by the WHO¹²⁵ and the European Centre for Disease Prevention and Control guidelines¹²⁴ discourage the use of IGRAs in preference to TST, in areas where TB is highly endemic.

Diagnosis of active TB disease

The current diagnostic and genotyping methods for TB are listed in Table VB¹²⁵⁻¹⁴¹. Innovations such as use of fluorescent staining, light-emitting diode (LED) based microscopes have helped optimizing the yield of sputum smear examination¹²⁶. Sputum mycobacterial culture is considered to be the 'gold standard' for the diagnosis of TB and it also facilitates DST. However, reliable, periodically accredited facilities for mycobacterial culture and DST are not widely available in TB high burden countries limiting their usefulness. Conventional sputum mycobacterial culture takes 6-8 weeks time and valuable time is lost in establishing the definitive diagnosis. In the 1980s, new semi-automated and automated culture systems based on liquid culture medium became available, such as the BACTEC-TB460 radiometric system (Becton Dickinson, Sparks, MD, USA) and facilitated rapid culture and detection of *M. tuberculosis* with a turn-around time of about 10 days^{127,129}. For nearly a two decades, this was used for rapid culture and DST. The non-radiometric rapid liquid culture methods like Mycobacteria Growth Indicator Tube (MGIT) and BacT/ALERT (BioMe'rieux) then emerged. In 2007 the WHO endorsed the use of liquid

culture assays, DST¹²⁹ and rapid speciation (strip speciation) tests that detect a TB-specific antigen from positive liquid or solid cultures to confirm the presence of TB bacillus [Capilia TB; Tauns Laboratories Inc., Shizuoka, Japan]¹³⁰ for faster diagnosis of TB and MDR-TB³⁷.

The nucleic acid amplification based TB diagnostic tests (NAAT) are based on the amplification of short specific sequences of DNA or RNA of *M. tuberculosis* complex by PCR and the amplified products are then detected by agarose/acrylamide gel electrophoresis, or by various hybridization methods¹⁴². Several in-house PCR assays and commercial kits have been used for rapid diagnosis of TB.

Integrated automated NAAT, the GeneXpert (Cepheid Inc., Sunnyvale, CA, USA) platform combines automated sample preparation, real-time PCR amplification, identification of *M. tuberculosis* and detection of rifampicin resistance in less than 120 minutes¹⁴². GeneXpert has the advantage of being simple to use even in field conditions and appears promising technology for rapid diagnosis of TB. However, this test requires uninterrupted electric power supply and is expensive. This test is being evaluated by Revised National Tuberculosis Control Programme (RNTCP) in field conditions.

Promising results from studies carried out in low-resource countries suggest that loop mediated

Table V B. Some of the current diagnostic, genotypic methods for TB¹²⁵⁻¹⁴¹

Diagnostic method	Time for results		Comments
	For isolation of <i>M. tuberculosis</i>	Detection of drug resistance from isolates	
<i>Conventional methods</i>			
Ziehl -Neelsen stain	30 minutes	-	For over a century, sputum smear examination for the detection of AFB in clinical specimens by Ziehl-Neelsen method and Lowerstein-Jensen culture have been used as diagnostic tools for TB. Sputum smear examination is a reliable, reproducible and cost-effective tool for diagnosing patients with TB and monitoring the response to anti-TB treatment. Therefore, sputum smear examination has been extensively used as a diagnostic method in national programmes for TB control progress of treatment especially in developing countries.
LED microscopy			Light-emitting diode (LED) microscopy is a low cost method that offers the benefit of fluorescence microscopy without the associated operational requirement of including a dark room and special microscope; may be battery operated
Lowenstein-Jensen culture	6-8 weeks	8-12 weeks	Gold standard for the diagnosis of TB and it also facilitates DST
Liquid culture, DST (e.g., BACTEC-TB460, MGIT 960, BacT/ALERT); rapid speciation (Capilia TB)	5-12 days	5-10 days	BACTEC-TB460 radiometric system measures radioactive CO ₂ liberated during decarboxylation of ¹⁴ C labelled substrates. When the inoculum contains live TB bacilli, they utilize the ¹⁴ C labelled substrate (palmitic acid) and release ¹⁴ CO ₂ . The BACTEC instrument quantitatively measures the radioactivity and daily increase in the growth index is directly proportional to the rate and amount of growth in the medium. By adding inhibitory substances to the medium, DST can also be done. The MGIT was introduced initially as a manual system and subsequently as an automated BACTEC MGIT-960 system (Becton Dickinson, Sparks, MD, USA). This system employs tubes containing enriched Middlebrook 7H9 broth with an oxygen sensitive fluorescent sensor embedded in silicone on the bottom of the tube which, upon consumption of the oxygen by the mycobacteria in the culture medium, fluoresces orange when probed with an UV light
<i>Non-commercial culture methods</i>			
MODS	Median time 7 days	7-14 days	The MODS assay utilizes a liquid medium which facilitates faster growth of the TB bacillus and thereby aids in the early microscopic visualization of characteristic cord formation using an inverted light microscope. Comparison of growth in drug-containing and drug-free wells, susceptible or resistant strains allows anti-TB DST
<i>Newer solid cultures</i>			
Nitrate reductase assay	14-18 days	10 days	The nitrate reductase assay is based on the principle of detection of nitrites by the action of nitrate reductase (the Griess method). The accuracy of these methods have been evaluated in systematic reviews and meta-analyses that confirmed their high sensitivity and specificity for detecting DR-TB.
Thin layer agar culture	14-18 days	10 days	The thin layer agar culture uses a solid medium and is based on the detection of early mycobacterial growth based on colony morphology. The sample is inoculated on plates containing Middlebrook 7H11 and Middlebrook 7H11 enriched with para-nitrobenzoic acid (PNB). <i>M. tuberculosis</i> complex is expected to grow on plate containing Middlebrook 7H11, but not on Middlebrook 7H11 enriched with PNB where its growth will be inhibited.

Contd...

Diagnostic method	Time for results		Comments
	For isolation of <i>M. tuberculosis</i>	Detection of drug resistance from isolates	
Colorimetric redox indicator assay	-	8 days	Colorimetric detection methods, instead of looking for mycobacterial growth as colonies, detect the metabolic activity of the TB bacillus measured in a coloured reaction, using redox indicators, such as resazurin; and tetrazolium salts like 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
<i>NAAT</i>			
Line probe assays (INNO-LiPA Rif TB Assay, MTBDRs ₁)	Within 24 h	Within 24 h	The LPAs are deoxyribonucleic acid strip-based tests that utilize nucleic acid amplification methods like PCR and reverse hybridization methods and facilitate rapid detection of mutations associated with DR-TB. INNO-LiPA Rif TB assay detects the presence of <i>M. tuberculosis</i> and mutations in the <i>rpoB</i> gene, which confer resistance to rifampicin. This test has lower sensitivity when used directly on clinical specimens. The “GenoTypeMTBDRPlus” test performs well both on isolates from culture as well as clinical specimens. It can identify mutations in the <i>rpoB</i> gene (rifampicin resistance) as well as mutations in the <i>katG</i> and <i>inhA</i> genes (isoniazid resistance) and can detect at least 90 per cent of MDR-TB cases in a few hours. Initial results using GenoType MTBDR _{s1} (Hain Life Sciences, Germany) that facilitates detection of resistance to the second-line anti-TB drugs, such as, fluoroquinolones, amikacin/capreomycin and also to ethambutol appears promising
GenExpert/Cepheid	2 h	2 h	The Xpert MTB/RIF system (Cepheid Inc., USA), a fully automated, cartridge-based system, uses a heminested real-time PCR assay to amplify <i>Mycobacterium tuberculosis</i> specific sequence of the <i>rpoB</i> gene, which is probed with molecular beacons for mutations within the rifampicin-resistance determining region. This technique has been shown to detect <i>M. tuberculosis</i> and rifampicin resistance directly from untreated sputum in less than 2 h time.
<i>Other isothermal NAAT</i> TMA/NASBA, SMART, RPA, HAD, RCA, RAM, LAMP, CPA, SMART-AMP, SDA, NEAR, NEMA, ICA, EXPAR			Under validation at several sites for their ability to generate same-day results at point-of-care (POC)
<i>Genotyping methodologies</i>			Techniques, such as, IS6110 RFLP and MIRU-VNTR have been used for genotyping <i>M. tuberculosis</i>
<p>AFB, acid-fast bacilli; DST, drug-susceptibility testing; UV, ultraviolet; MGIT, Mycobacteria Growth Indicator Tube; LPA, line probe assay; PCR, polymerase chain reaction; DR-TB, MDR-TB, multidrug-resistant tuberculosis; MODS, microscopic observation drug susceptibility; NAAT, nucleic acid amplification tests; TMA, transcription-mediated amplification; NASBA, nucleic acid sequence based amplification; SMART, signal mediated amplification of RNA technology; RPA, recombinase polymerase amplification; HAD, helicase-dependent amplification; RCA, rolling circle amplification; RAM, ramification amplification; LAMP, loop mediated amplification; CPA, cross priming amplification; SMART-AMP, smart amplification; SDA, strand displacement amplification; NEAR, nicking enzyme amplification reaction; NEMA, nicking enzyme mediated amplification; ICA, isothermal chain amplification; EXPAR, exponential amplification reaction; RFLP, restriction fragment length polymorphisms; MIRU-VNTR, mycobacterial interspersed repetitive units – variable number tandem repeats</p>			

isothermal amplification (LAMP) has the potential to be a candidate as a molecular test for the rapid diagnosis of TB in clinical samples^{143,144}. *M. tuberculosis* produces volatile organic compound (VOC) metabolites *in-vitro*, and their presence in the breath has been considered to be apparent biomarkers of infection^{145,146}.

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 TB¹⁴⁷. This view has been endorsed by the RNTCP of Government of India also¹⁴⁸.

Diagnosis of extrapulmonary TB (EPTB)

The yield of conventional AFB smear and mycobacterial culture and some commonly used non-conventional tests in the diagnosis of EPTB is shown in Table VI¹⁴⁹⁻¹⁶³. A focused diagnostic approach, procurement of appropriate body fluid and tissue specimens and subjecting these to a battery of diagnostic tests including culture (and DST where feasible) will enhance the diagnostic yield in EPTB. There is a need to systematically evaluate and establish the utility of recently available newer tests such as GeneXpert to

facilitate an early diagnosis and increase the diagnostic yield.

Development of accreditation system, quality assured laboratory network expansion

The eventual goal of controlling and probably eliminating TB hinges on rapidly and correctly identifying all TB cases and ensure that all diagnosed patients receive individualized treatment with anti-TB drugs tailored to the DST profile of the isolates obtained¹⁶⁴. The ongoing struggle to meet the global target for case detection of diagnosing at least 70 per cent of new smear-positive cases, reflects the yawning gap between the need and the availability of quality assured laboratory infrastructure, especially in developing countries like India. Strengthening the capacity of public-sector laboratory networks, ensuring their accreditation initially and periodically thereafter so that a network of reliable quality assured accredited laboratories is eventually available to take TB control forwards are initial steps in this direction. The Expanding Access to New Diagnostics for TB (EXPAND-TB) project¹⁶⁵, a collaboration among WHO, the Global Laboratory Initiative (GLI), Foundation for Innovative New Diagnostics (FIND) and the Global Drug Facility (GDF), and funded by UNITAID and other partners aims to improve capacity to diagnose MDR-TB in upgraded laboratory services in 27 countries.

Table VI . Diagnostic yield of commonly used tests in the diagnosis of certain forms of extrapulmonary TB

Test	Pleural fluid ¹⁴⁹⁻¹⁵³			Ascitic fluid ^{111,154-156}			Pericardial fluid ^{157,158}			Cerebrospinal fluid ¹⁵⁹⁻¹⁶³		
	% positive (range)			% positive (range)			% positive (range)			% positive (range)		
AFB smear	<10			<3			<1			<5 (4-40)		
L-J culture	~25 (10-70)			~20 (10-83)			~ 30 (25-60)			~ 20 (20-70)		
Biopsy histopathology	~60 (50-97)			75			Not routinely used			Not applicable		
Histopathology + culture	95			>90			Not routinely used			Not applicable		
	Cut-off ≥	Sen	Spec	Cut-off ≥	Sen	Spec	Cut-off ≥	Sen	Spec	Cut-off ≥	Sen	Spec
ADA (IU/l)	37	0.97	0.94	32	0.95	0.98	40	0.87	0.89	*	*	*
IFN-γ (pg/ml)	134	0.89	0.97	112	0.97	0.97	50	0.92	100			

* Various studies and meta-analyses have yielded conflicting results. For example, in one recent meta-analysis¹⁶² reported sensitivity <59% and specificity >96% for a cut-off value of 8 U/L; in another recent meta-analysis¹⁶³ using cut-offs ranging from 5-15.5 IU/l, sensitivity of 0.79 (95% CI 0.75-0.83), and specificity 0.91 (95%CI 0.89-0.93) has been reported. It appears that even though CSF-ADA cannot distinguish between bacterial meningitis and TB meningitis, ADA values could be important to improve TBM diagnosis, if bacterial meningitis has been ruled out with certainty; may be useful in countries with low incidence of TB

AFB, acid-fast bacilli; L-J, Lowenstein-Jensen; ADA, adenosine deaminase; IFN-γ, interferon-γ; Sen, Sensitivity; Spec, Specificity; CI, confidence intervals

In India, The RNTCP has also adopted a rigorous procedure for granting accreditation to culture and DST laboratories both in public and private sectors and medical colleges to provide accurate and reliable services for MDR-TB diagnosis and treatment follow-up. By 2015, it is expected that universal access to MDR-TB diagnosis and treatment will be made available for all smear positive TB cases under the RNTCP³⁰.

Imaging Studies

Imaging modalities such as conventional radiography, ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography CT (PET-CT) have been used to localize the disease, assess the extent of organ involvement and evaluate response to treatment. The chest radiograph is the mainstay of imaging pulmonary TB (Fig. 3A-3E). However, the chest radiograph can be normal in HIV-infected patients with late HIV disease

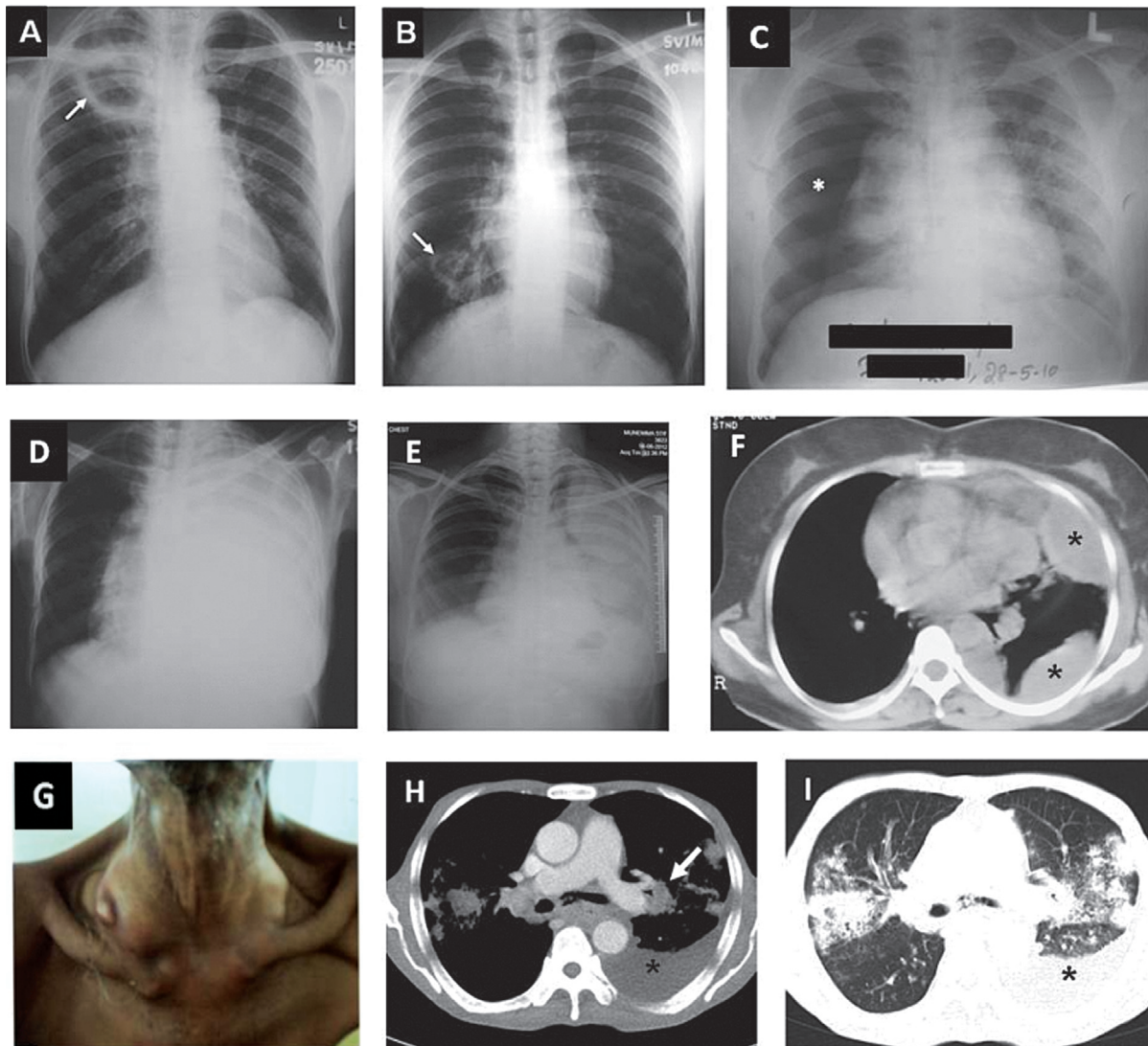


Fig.3 (A) Chest radiograph (postero-anterior view) showing a cavity in the right upper zone (arrow), and (B) lower zone (arrow). (C). Chest radiograph (postero-anterior view) in a patient presenting to the emergency room with severe breathlessness showing right-sided pneumothorax (asterisk). Sputum smear was positive for acid-fast bacilli. (D). Chest radiograph (poster-anterior view) showing left-sided massive pleural effusion. (E). Chest radiograph (poster-anterior view) in another patient showing left-sided loculated pleural effusion. (F). CECT (chest) of the same patient showing left-sided loculated pleural effusion (asterisks). (G) Clinical photograph of a patient with disseminated TB showing right-sided cervical lymphadenopathy with cold abscess. (H) CECT chest of the same patient showing left-sided pleural effusion (asterisk), left hilar lymphadenopathy [arrow (mediastinal window)]; and (I) and bilateral parenchymal infiltrates and left sided pleural effusion (asterisk) (lung window).

with active TB disease and in some patients with miliary TB^{166,167}. Ultrasonography helps in detecting pleural effusion and ascites (which may sometimes be loculated), focal lesions in the liver and spleen, cold abscesses, intra-abdominal lymphadenopathy, involvement of other abdominal organs. High resolution CT (HRCT), thin-section multidetector row CT (MDCT) have been helpful in identifying pulmonary and miliary lesions, even in those in whom the chest radiograph is normal and has facilitated more frequent antemortem diagnosis of 'cryptic miliary TB' that was earlier diagnosed only at autopsy. CT of the thorax also allows detection of intrathoracic lymphadenopathy, calcification, pleural, pericardial and vascular lesions (Figs. 3F-3I, 4). CT and MRI of the brain and CT of the abdomen have also been extensively used to study CNS TB and abdominal TB, respectively (Fig. 5). Magnetic resonance spectroscopy (MRS) has been found to be useful in patients with intracranial tuberculomas where a characteristic large lipid peak with reduced n-acetyl aspartate peak can be seen. PET-CT using ¹⁸F labelled 2-deoxy-D-glucose (FDG) is helpful in locating, defining the extent of activity of TB at various organ sites (that may sometimes not be clinically discernible) (Fig. 6) especially in patients with disseminated TB and assessing the activity of lesions that might persist following anti-TB treatment on follow-up. ¹¹C-choline PET scans can help differentiate between lung cancer and tuberculoma. The standard uptake value of tuberculoma is low in ¹¹C-choline PET scans¹⁶⁸.

In patients presenting with PUO with no focal localizing clue, nuclear medicine techniques using gallium-67 citrate, technetium-99m methylene diphosphonate (Fig. 7), radiolabelled white blood cells, and human immune globulin imaging have been used to identify occult foci of infection especially in the bones. However, these techniques have been relatively non-specific and have not been able to distinguish bacterial mediated infection from non-bacterial inflammation due to other causes¹⁶⁹. Recently, the radiopharmaceutical technetium-99m labelled ciprofloxacin (^{99m}Tc-CPF) has been developed and shown to localize in high concentrations in bacterial abscesses, and not in areas of sterile inflammation^{170,171}. Though not specific for TB, this technique has been used to localize foci of TB osteomyelitis as well¹⁷² and also assess the adequacy of short-course treatment of TB osteomyelitis¹⁷³.

Procurement of body fluids/tissues for diagnostic testing

Radiographic image guided interventional procedures, biopsy of peripherally accessible lesions

(e.g., lymph nodes), endoscopic procedures like laparoscopy, colonoscopy, thoracoscopy, can be used in appropriate settings to procure material for diagnostic testing for TB. Endoscopic interventions, such as, endobronchial ultrasound bronchoscopy (EBUS) and endoscopic oesophageal ultrasound, FNACs, biopsies are useful in situations where patients are sputum smear-negative, are unable to produce sputum, present with intrathoracic (e.g., mediastinal, sub-carinal, hilar) lymphadenopathy to procure tissue. Material thus obtained should be subjected to cytopathological, histopathological, microbiological (including DST) and molecular methods for confirmation of TB diagnosis.

Treatment

Evolution of modern 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 (Fig. 8)¹⁷⁴⁻¹⁹⁴. The first controlled clinical trial in the history of medicine conducted by the British Medical Research Council (BMRC)¹⁷⁹ demonstrated the activity of streptomycin. The BMRC assessed the addition of PAS to streptomycin in a controlled clinical trial¹⁸¹ 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 1951¹⁸². Subsequent studies by BMRC^{183,184} 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 BMRC¹⁸⁵ 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 drugs¹⁸⁶ 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", a fact that is often neglected even

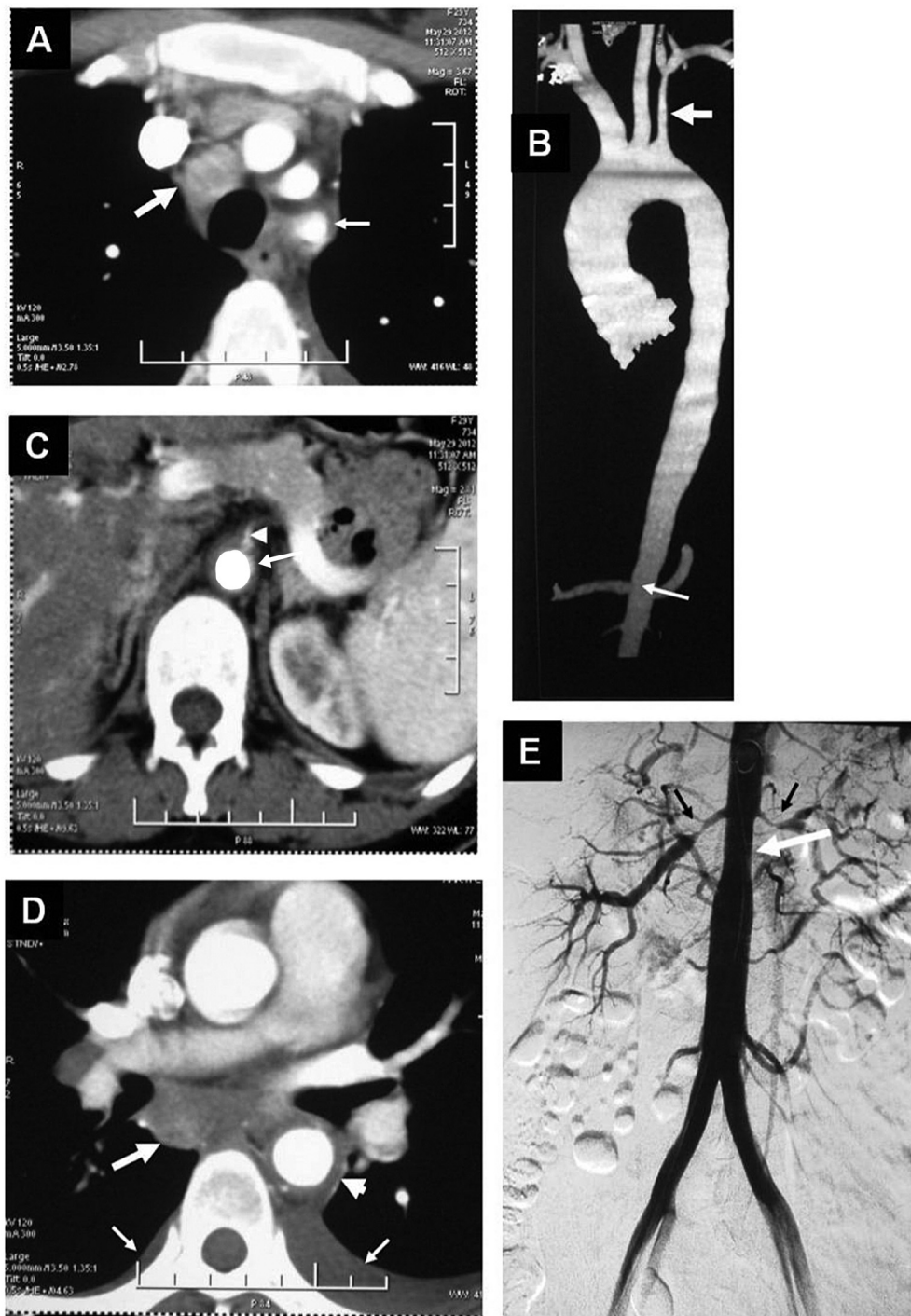


Fig. 4. Nonspecific aortoarteritis. (A) Axial contrast enhanced CT showing an enlarged mediastinal lymph node (thick arrow) and diffuse wall thickening of left subclavian artery (Thin arrow) (B). Volume rendered CT angiography image showing diffuse long segment narrowing of left subclavian artery (thick arrow) and abdominal aorta at the renal artery origin level as well as infrarenal segment (thin arrow) (C). Axial contrast enhanced CT showing diffuse wall thickening of abdominal aorta (long arrow) with luminal narrowing of the origin of superior mesenteric artery (arrow head) (D). Axial contrast enhanced CT showing an enlarged subcarinal mediastinal lymph node (thick arrow) and diffuse wall thickening of descending thoracic aorta (arrow head). Bilateral pleural effusions [left more than right (thin arrows)] can also be seen (E). Digital subtraction angiography (DSA) showing diffuse long segment narrowing of abdominal aorta at the renal artery origin level and infrarenal segment (white arrow). There is a marked narrowing of the bilateral renal arteries (black arrows)

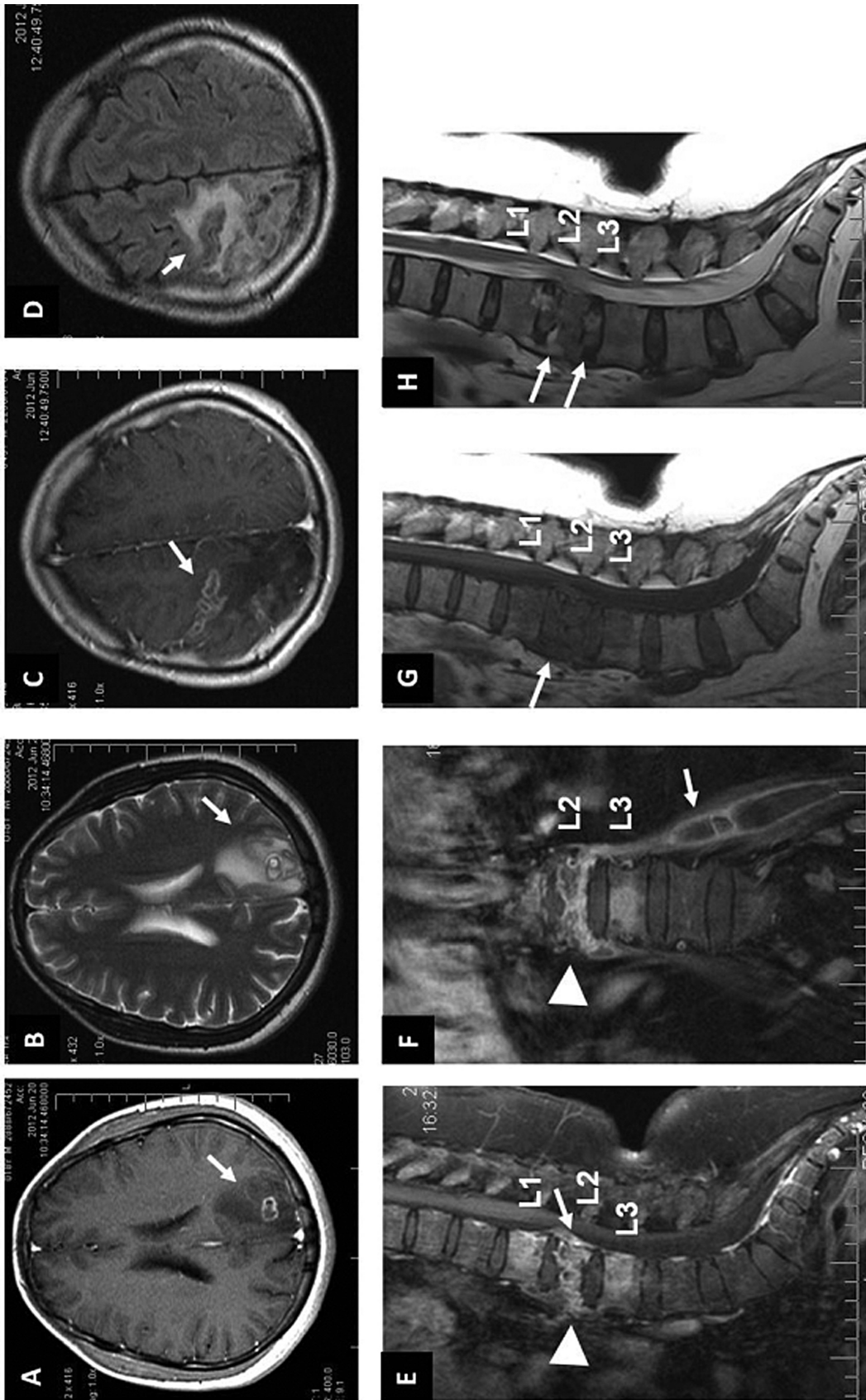


Fig. 5 (A) T1-weighted pre-contrast and (B) contrast-enhanced MRI images showing ring enhancing lesion with perilesional oedema in the left parietal lobe (arrows). (C) T1-weighted axial MRI image showing conglomerate ring enhancing lesions in the right frontoparietal regions (arrow) (D) FLAIR sequence showing hypointense lesions with perilesional oedema (arrow) (E). T1-weighted contrast enhanced MRI showing collapse of L2 vertebral body with abnormal enhancement in L1-L3 vertebrae, prevertebral regions (arrow-head) and epidural abscess (arrow) at L2 (F). Coronal image of the same patient showing collapse of L2 vertebral body (arrow-head) and left-sided psoas abscess (arrow). (G) Pre-Contrast T1-weighted sagittal MRI showing hypointense signal in L1-L3 vertebral bodies (arrow). T2-weighted sagittal image showing hyperintensities in the end-plates of L1-L2 and L2-L3 vertebral bodies and intervening discs (arrows).

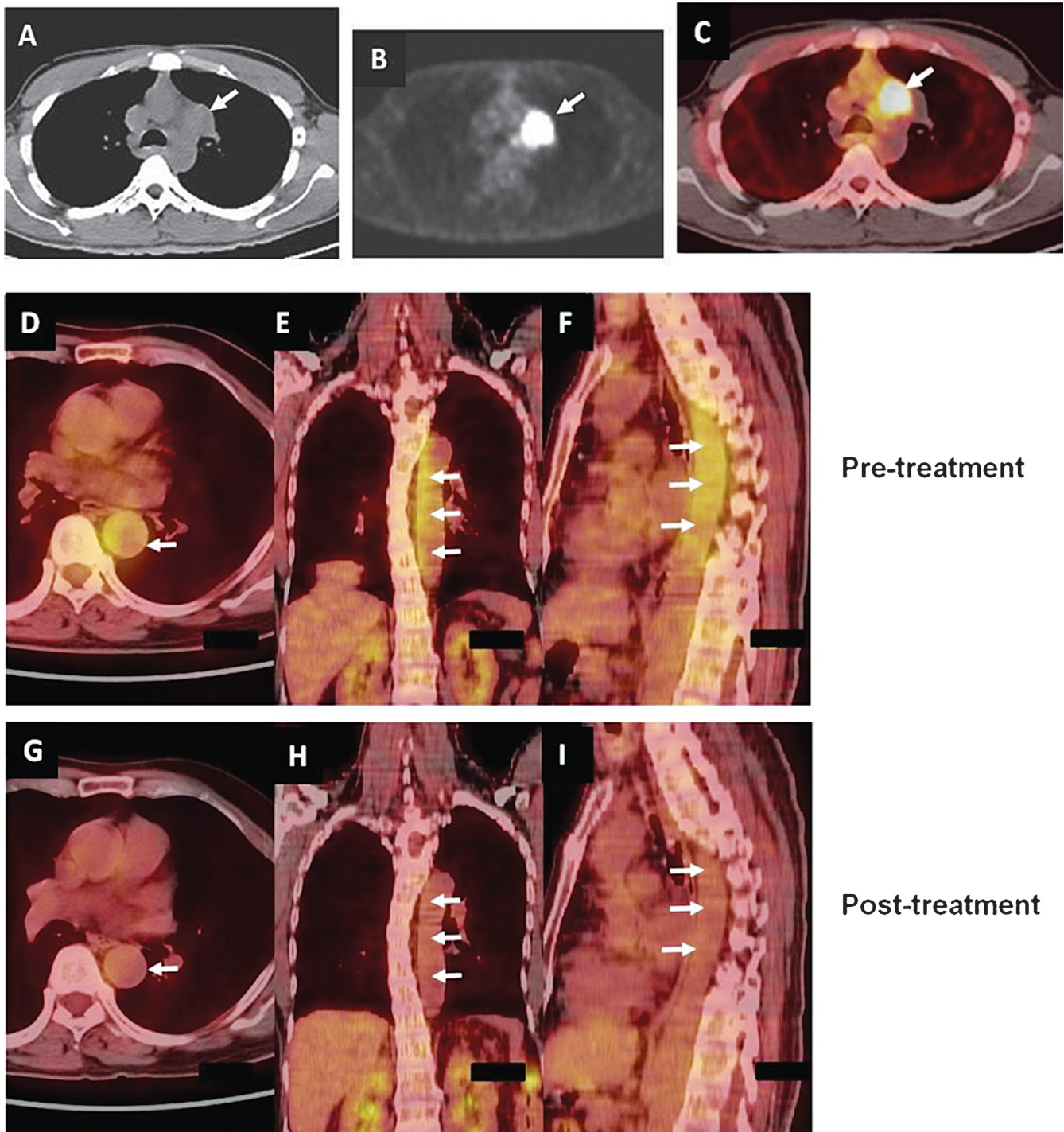


Fig. 6. Intrathoracic lymph node TB. (A) CT of the chest (mediastinal window), FDG-PET (B) showing left-sided hilar lymphadenopathy (arrow). (C) PET-CT image of the same patient showing increased uptake in the lesion (arrow). (D,E,F, upper panel). Nonspecific aortoarteritis. PET-CT images showing increased uptake (arrows) at the time of initial presentation. (G,H,I lower panel) The post-treatment images of the same patient shows significant decrease in the uptake suggestive of resolution of lesions with treatment.

Kind courtesy: Dr TC Kalawat, Department of Nuclear Medicine, Sri Venkateswara Institute of Medical Sciences, Tirupati (Figures 6 A-C and Drs. Arun Malhotra, Rakesh Kumar, Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi (Figures 6D-I)

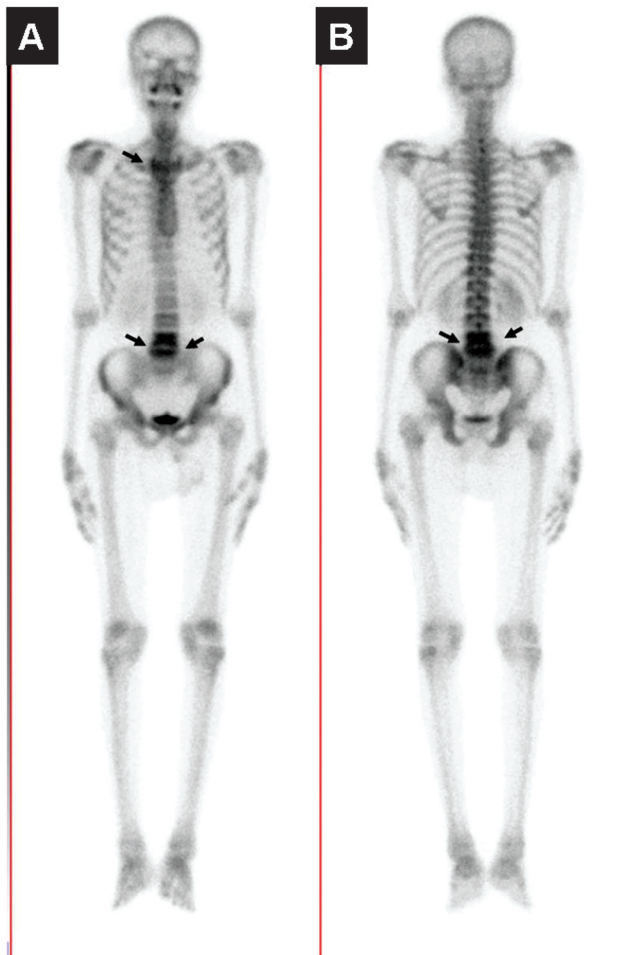


Fig. 7 (A) ^{99m}Tc -methylene diphosphonate (MDP) whole body anterior and (B) posterior sweep views in a patient presenting with backache and low-grade fever showing diffuse increased radiotracer localization in the body of L4 and 5 vertebrae (arrows) suggestive of spinal TB.

(Kind courtesy: Dr TC Kalawat, Department of Nuclear Medicine, Sri Venkateswara Institute of Medical Sciences, Tirupati)

today¹⁸⁷. The classic NIRT studies^{187,188} also established the efficacy of intermittent administration of anti-TB medications. These fundamental principles have since then remained the pillars on which modern treatment of TB is based.

Subsequently, with the introduction of rifampicin¹⁸⁹ based on the data from studies conducted in the 1970s¹⁹⁰ the standard treatment duration of anti-TB treatment could be shortened to 9 months. By then the 9-month rifampicin containing regimens replaced the then prevailing standard treatment of 18-months. In 1972, the therapeutic role of pyrazinamide used in a reduced dosage was rediscovered in the studies conducted by East Africa Medical Council and BMRC¹⁹³. Combining

pyrazinamide to rifampicin containing regimens then ensued. The 6-month regimens containing rifampicin and pyrazinamide were as effective as either rifampicin or pyrazinamide containing regimens in the clinical trials by the British Thoracic Society¹⁹⁴ heralding the modern 6-month short-course chemotherapy endorsed by the WHO that has become the standard of care worldwide. Since then, most countries have been using the WHO endorsed standardized daily or thrice-weekly intermittent treatment regimens in National TB Control Programmes.

National Tuberculosis Programme (NTP)

In 1962, the NTP was started in India, the first time ever a 'national programme' was conceived to tackle the menace of TB in the world. Short-course chemotherapy was introduced in the NTP by 1985.

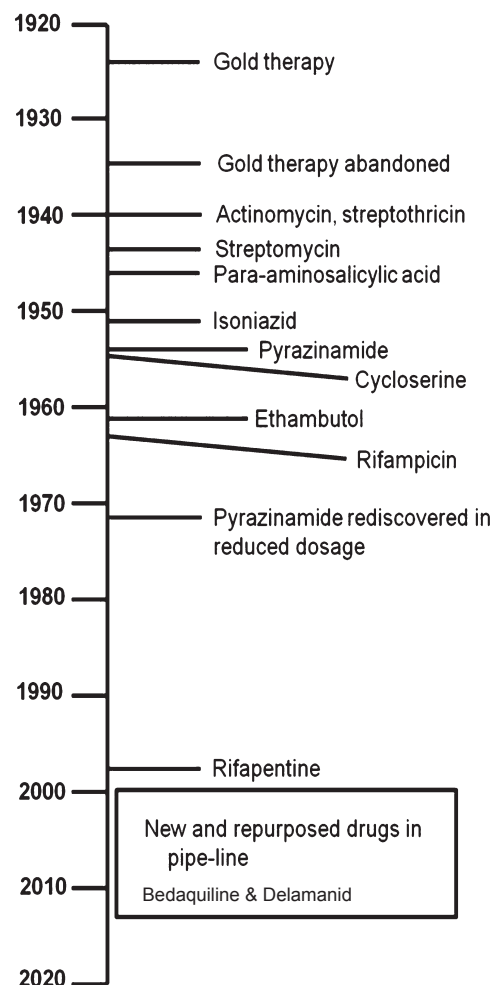


Fig. 8. A brief history of development of antituberculosis drugs.

However, uninterrupted drug supply and treatment adherence continued to plague the NTP and the programme did not make a significant epidemiological impact on the prevalence of TB in the country¹⁹⁵. This led to introspection and a comprehensive joint review of the TB programme in India by members of several organizations including the Government of India, WHO and Swedish International Development Agency (SIDA) in 1992 identified many issues that were affecting the programme performance¹⁹⁶.

Revised National Tuberculosis Control Programme

To revamp TB control in India, in 1993, the RNTCP, based on the WHO-recommended DOTS strategy, began operations in five pilot sites. Following pilot testing, large scale expansion of RNTCP in India began in 1997 in a phased manner and by March 24, 2006, the whole country was covered by the RNTCP. The Programme aims at achieving and maintaining a cure rate of at least 85 per cent among new sputum positive (NSP) patients, and to achieve and maintain case detection of at least 70 per cent of the estimated NSP cases in the community^{196,197}.

Treatment of active TB disease: issues concerning dosing frequency and duration of treatment

The current treatment regimens listed in the recent WHO guidelines for national programmes²⁹ and the RNTCP of Government of India³⁰ are shown in Tables

VIIA, VIIB and VIIC. The WHO guidelines²⁹ suggest that HIV patients co-infected with TB should be treated with daily regimens. This recommendation has been based on evidence from meta-analyses^{198,199} that showed that HIV co-infected patients with pulmonary TB were at a higher risk of acquired rifampicin resistance, when failing a three times weekly short-course intermittent regimen. In the meta-analysis¹⁹⁹ of treatment of active TB in HIV co-infected patients, data from six randomized trials and 21 cohort studies showed that compared with daily therapy in the initial phase (n=3352 patients from 35 study arms), thrice-weekly therapy (n=211 patients from 5 study arms) was associated with higher rates of treatment failure (adjusted risk ratio, 4.0; 95% CI 1.5-10.4) and relapse (adjusted risk ratio 4.8; 95% CI 1.8-12.8) and a trend toward higher relapse rates if rifamycins were used for only 6 months, compared with 8 months or more, or if antiretroviral therapy was not used. In a study from India²⁰⁰ the outcome of fully intermittent thrice-weekly antituberculosis treatment regimens of 6-month isoniazid, rifampicin, pyrazinamide and ethambutol, followed by 4 months of isoniazid and rifampicin; and a 9-month regimen where the intensive phase was same but continuation phase was 7 months, were assessed in HIV-TB co-infected patients. In the 'intent-to-treat analysis', among patients who had a favourable outcome at the end of treatment, bacteriologically confirmed recurrence rate was significantly higher

Table VII A. WHO standard treatment regimens for new TB patients

Patient category	Intensive phase	Continuation phase
New patients	2HRZE*†	4HR*†
	2HRZE‡	2H ₃ R ₃ ‡
	2H ₃ R ₃ Z ₃ E ₃ §	2H ₃ R ₃ §
		2HRE

Numbers preceding the regimen indicate duration in months; numbers in subscript indicate the number of times the drug is administered per week

* new TB patients are defined as those who have no history of prior TB treatment or who received less than 1 month of anti-TB drugs (regardless of whether their smear or culture results are positive or not)

† optimal dosing frequency

‡ acceptable alternative for any new TB patient receiving directly observed therapy. Daily (rather than three times weekly) intensive-phase dosing may help to prevent acquired drug resistance in TB patients starting treatment with isoniazid resistance

§ acceptable alternative provided that the patient is receiving directly observed therapy and is not living with HIV or living in an HIV-prevalent setting

|| in settings where the level of isoniazid resistance among new TB cases is high and isoniazid susceptibility testing is not done (or results are not available) before the continuation phase begins

The guidelines also suggest that patients who remain sputum smear-positive at the end of the intensive phase should submit another specimen for smear microscopy the following month. If that specimen is also smear-positive, culture and DST should be undertaken so that a result will be available earlier than the fifth month of treatment

H isoniazid; R rifampicin; E ethambutol; Z pyrazinamide, DST, drug-susceptibility testing

Source: Refs. 29

Table VII B. WHO standard treatment regimens for previously treated TB patients

DST	MDR prevalence	
	High (treatment failure)*	Medium or low (relapse, default)*
Routinely available†		
Rapid molecular-based methods	DST results available in 1–2 days; confirm or exclude MDR to guide the choice of regimen	
Conventional methods	Empirical MDR regimen‡ while awaiting DST results. <i>Regimen should be modified once DST results are available</i>	2HRZES/HRZE/5HRE <i>Regimen should be modified once DST results are available</i>
Not available§	Empirical MDR regimen while awaiting DST results. <i>Regimen should be modified once DST results are available</i>	2HRZES/HRZE/5HRE for full course of treatment. <i>Regimen should be modified once DST results or DRS data are available</i>

* the NTP needs to review country-specific data to verify, or modify, the assignment of treatment failure patients to high likelihood of MDR and patients returning after relapse or default to medium or low likelihood of MDR

† ideally DST is done for all patients at the start of treatment so that the most appropriate therapy for each individual can be determined. The guidelines also advocate that patients who remain sputum smear-positive at the end of the intensive phase should submit another specimen for smear microscopy the following month. If that specimen is also smear-positive, culture and DST should be undertaken so that a result will be available earlier than the fifth month of treatment

‡ a country's standard MDR regimen is based on country-specific DST data from similar groups of patients

§ a temporary measure that can be implemented only if culture and DST can be arranged in the first few months of MDR treatment in each enrolled patient

MDR, multidrug-resistance; DST, drug susceptibility testing; DRS, drug-resistance surveillance

Source: Ref. 29

Table VII C. Categorization and treatment regimens under RNTCP

Treatment category	Type of patient	Regimen*
New (Category I)	New sputum smear-positive	2H ₃ R ₃ Z ₃ E ₃ + 4H ₃ R ₃
	New sputum smear-negative	
	New extrapulmonary	
	New others	
Previously treated (Category II)	Smear-positive relapse	2H ₃ R ₃ Z ₃ E ₃ S ₃ + 1H ₃ R ₃ Z ₃ E ₃ + 5H ₃ R ₃ E ₃
	Smear-positive treatment failure	
	Smear-positive treatment after default	
	Others†	

* The number before the letters refers to the number of months of treatment. The subscript after the letters refers to the number of doses per week. The dosage strengths are as follows: H = isoniazid (600 mg), R = rifampicin (450 mg), Z = pyrazinamide (1500 mg), E = ethambutol (1200 mg), S = streptomycin (750 mg). Patients who weigh 60 kg or more receive additional rifampicin (150 mg). Patients who are more than 50 years old receive streptomycin (500 mg). Patients who weigh less than 30 kg receive drugs as per body weight. Patients in Categories I and II who have a positive sputum smear at the end of the initial intensive phase receive an additional month of intensive phase treatment

Seriously ill also includes any patient, pulmonary or extrapulmonary who is HIV-positive and declares his/her sero-status to the categorizing/treating MO.

† In rare and exceptional cases, patients who are sputum smear-negative or who have extra-pulmonary disease can have relapse or failure. This diagnosis in all such cases should always be made by a medical officer and should be supported by culture or histopathological evidence of current, active TB. In these cases, the patient should be categorized as 'Others' and given previously treated (Category II) treatment

Source: Ref. 29

with the 6-month regimen compared with the 9-month regimen.

Daily vs thrice-weekly treatment: Under the RNTCP, in India, 15,852,745 patients have been treated with thrice-weekly intermittent treatment and 2,853,494 lives have been saved²⁰¹ reflecting the huge success achieved by the RNTCP programme over the last 15 years. While thrice-weekly intermittent treatment seems adequate in HIV-seronegative patients, use of daily therapy is an important issue to contend with in HIV-seropositive persons. The prospect of considering the implementation of a daily treatment regimen and the logistics of direct observation of treatment are being actively considered and a clear-cut government policy on the same is expected to be available soon. However, head-on comparisons of adequately powered, fully daily, partial daily (daily intensive phase and thrice-weekly intermittent continuation phase) and fully thrice-weekly intermittent regimens are not available in the literature and studies of this nature will help in arriving at optimal dosing frequency issue so that policy can be modified.

There is also a lack of consensus regarding the optimal duration of therapy in patients with EPTB, especially bone and joint TB, neurological TB; disseminated and miliary TB. While 6-months of treatment may be adequate in HIV-seronegative new patients with pulmonary TB and focal extrapulmonary TB, individual patients may require 9 to 12 months of treatment when TB meningitis is present given the serious risk of disability and mortality; and 9 months of treatment when bone and joint TB is also present. The efficacy and safety of erstwhile Category III (intermittent thrice-weekly rifampicin, isoniazid and pyrazinamide for 2 months, followed by rifampicin and isoniazid for 4 months) DOTS has been documented in the patients with uncomplicated small (<1500 ml) unilateral pleural effusion²⁰², and peripheral lymph node TB²⁰³.

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 (Fig. 9)^{204,205}. 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-TB²⁰⁶. 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 covered³⁰.

Key issues in TB treatment monitoring

Drug-drug interactions

Clinically significant interactions during anti-TB treatment should be carefully monitored as these may sometimes result in therapeutic failure or drug toxicity^{207,208}. This is particularly important in HIV-co-infected persons, the elderly and those with significant co-morbidities receiving treatment for the same (Box I)²⁰⁷⁻²²⁸.

Drug induced hepatotoxicity (DIH)

Principles underlying evaluation of patients with DIH are listed in Box I²⁰⁷⁻²²⁸.

Immune reconstitution inflammatory syndrome (IRIS)

Paradoxical deterioration of lesions of TB in patients receiving anti-TB treatment has been known for a long time (218). Key developments in the understanding of IRIS are listed in Box I²¹⁹⁻²²⁸. Minor manifestations of IRIS can be managed with non-steroidal anti-inflammatory drugs (NSAIDs). Moderate-to-high dose corticosteroid treatment, sometimes for prolonged periods may be required for the treatment of paradoxical TB-IRIS and may be beneficial in TB-IRIS with CNS manifestations, tracheal compression due to lymphadenopathy, acute kidney injury and acute respiratory distress syndrome (ARDS)^{218,219}.

Treatment of LTBI

The WHO has stressed on the importance of interventions like ART provision and the three *I*s for HIV-TB coinfection, namely intensified TB case finding, infection control, and isoniazid preventive therapy (IPT), as part of prevention, care and treatment services²²⁹. The diagnosis and treatment of LTBI have been extensively reviewed recently⁹². It is necessary to rule out active TB disease before initiating treatment for LTBI. Important issues concerning LTBI and its treatment^{92,230-234} are listed in Box 2.

Control of TB

Global measures: India conceived the NTP and set an example to the world in the programmatic approach to TB control in 1962¹⁹⁷. Since then several efforts have been undertaken globally to achieve control of TB and

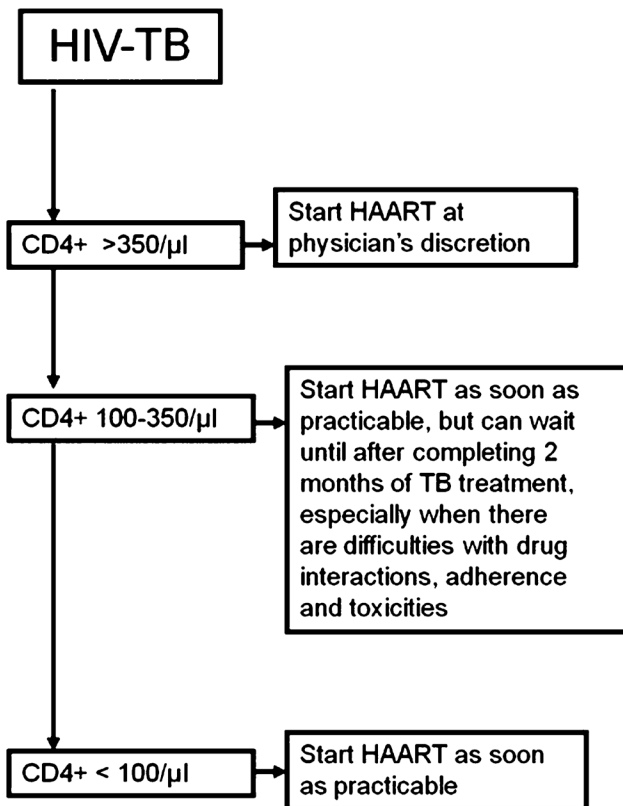
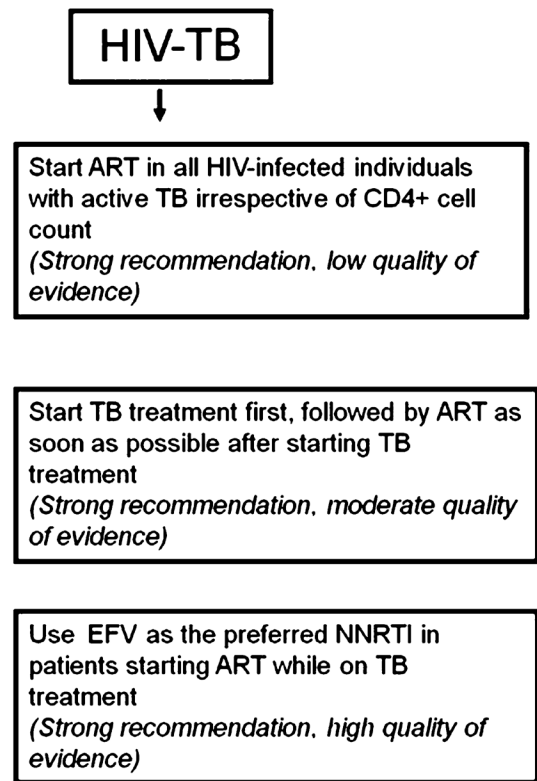
BHIVA guidelines**WHO guidelines**

Fig. 9. Guidelines on timing of antiretroviral treatment in patients with HIV-TB co-infection

ART, antiretroviral treatment; BHIVA, British HIV Association; EFV, efavirenz; HAART, highly active antiretroviral treatment; HIV, human immunodeficiency virus; NNRTI, non-nucleoside reverse transcriptase inhibitors;

Source: References 204,205

are summarized in Box III²³⁵⁻²³⁸. These developments reflect the efforts towards achieving universal access to preventive, diagnostic and treatment services for all forms of TB.

As a result of the implementation of RNTCP, prevalence of all forms of TB has been brought down (from 338/100,000 population in 1990 to 249/100,000 population in 2009); TB mortality has also reduced (from >42/100,000 population in 1990 to 23/100,000 population in 2009) in India. The Phase II (2006-2012) of the RNTCP has achieved the set goals, the country is coursing towards achieving “universal access” for control of TB¹⁹⁷ and appears to be on track to achieve the TB related United Nations Millenium development Goals (UNMDG). Jointly with National AIDS Control Programme (NACP), RNTCP has developed “National framework of joint TB/HIV collaborative activities” that are being implemented in the country¹⁹⁷.

Involvement of Medical Colleges in TB control

For the first time in the global history of TB control, Indian Medical Colleges were involved in the RNTCP. This unique experiment in the history of TB control has resulted in medical colleges providing diagnostic services (Designated Microscopy Centres), treatment (DOT Centres), referral for treatment, recording and reporting data, carrying out advocacy for RNTCP and conducting operational research on the RNTCP²³⁸.

Prevention

Even though the declining trends observed in the global burden of TB currently^{37,239-242}, this trend seems insufficient to achieve the global target of elimination of TB in 2050¹⁶⁴. Therefore, the need for other measures including infection control measures, newer or repurposed anti-TB drugs, newer and better vaccines for TB is pressing.

Box 1. Key issues in monitoring treatment of TB*Drug-drug interactions*

- Drug-drug interactions usually involve rifampicin^{207,208} isoniazid and the fluoroquinolones and the CYP450 isoform enzymes are responsible for many drug-drug interactions. The CYP3A4 isoform metabolizes many drugs, including PIs and NNRTIs. Rifampicin acts as a powerful inducer of CYP3A4, and also CYP2C19 and CYPD6; rifapentine is a less potent inducer; and rifabutin much less so. Isoniazid acts an inhibitor of CYP3A4. The CYP3A4 inhibitors have no effect on rifampicin metabolism, but increase the concentration of rifabutin²⁰⁵.
- Several drugs, such as, anticoagulants, anticonvulsants, antiinfectives, cardiovascular therapeutics, oral contraceptives, glucocorticoids, immunosuppressants, psychotropics, sulphonylureas, and theophylline among others interact with rifampicin. Drug-drug interactions with isoniazid and anticonvulsants, benzodiazepines, theophylline, paracetamol etc., are known.

Anti-TB drug-induced hepatotoxicity

- In endemic areas, acute viral hepatitis may be a confounding factor in up to 15 per cent of patients suspected to have DIH due to anti-TB drugs and should be ruled out as a cause of hepatic dysfunction^{213,214}. In comparison to patients with anti-TB DIH, patients with co-existent viral hepatitis have a later onset of acute hepatitis, large elevations in AST and ALT and a longer time for normalization of deranged liver functions²¹⁴.

In patients with DIH, the potentially hepatotoxic drugs, rifampicin, isoniazid and pyrazinamide should be stopped²¹¹. These patients should be treated with non-hepatotoxic drugs like ethambutol, streptomycin and a fluoroquinolone, till the liver functions normalize. In a recent randomized controlled trial from India²¹⁵, 175 patients with a diagnosis of anti-TB DIH were randomized to receive one of three different pre-defined reintroduction regimens of anti-TB drugs and were evaluated prospectively. The recurrence rate of DIH was not significantly different between the groups receiving isoniazid, rifampicin, and pyrazinamide administered simultaneously at full dosage from day 1; and the groups receiving reintroduction regimens based on the ATS²¹⁶ and BTS guidelines²¹⁷.

Immune reconstitution inflammatory syndrome

- Paradoxical deterioration of lesions of TB in patients receiving anti-TB treatment has been known for a long time²¹⁸. IRIS has been recognized since the time of zidovudine monotherapy in the early 1990s and has described been in relation to infection, inflammatory disorders, autoimmune diseases and malignancy²¹⁹. IRIS is characterized by paradoxical worsening of an existing infection or disease process or appearance of a new infection/disease process soon after initiation of therapy²²⁰⁻²²².

TB-IRIS

- A higher incidence of TB-IRIS has been reported in studies from West²²³⁻²²⁵ compared to studies from developing countries²²⁶⁻²²⁸.
- Early initiation of antiretroviral treatment before the onset of severe immunodeficiency and after the treatment of opportunistic infections can help in preventing the development of IRIS. A low baseline CD4+ T-cell count; rapid recovery in CD4+ T-cell numbers; rapid decline in HIV viral load; presence of disseminated TB (may be attributable to high burden of bacilli); highly active antiretroviral therapy being started within first 2 months of TB treatment have all been associated with an increased risk of developing IRIS²⁰⁵.

CYP450, cytochrome P450; PIs, protease inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; DIH, drug induced hepatotoxicity; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ATS, American Thoracic Society; BTS, British Thoracic Society; TB, tuberculosis; HIV, human immunodeficiency virus; IRIS, immune reconstitution inflammatory syndrome

Source: Ref. 207-228

Airborne infection control measures

Recognizing the importance of airborne infection control and in view of the association of TB with HIV and the emergence of X/MDR-TB, guidelines have been issued for implementing the same by the WHO²³⁹ and the RNTCP²⁴⁰ as well. However, there is a wide gap between the needs and the actual implementation of these guidelines presently especially in the overcrowded government hospitals in India and other developing countries.

TB Vaccine

Till date the bacille Calmette-Guerin (BCG) vaccine is the only vaccine available for TB²⁴¹⁻²⁴⁴. Though BCG

confers consistent protection against severe forms of TB, such as TB meningitis, disseminated and miliary TB in children in areas where TB is endemic its ability to protect against pulmonary TB has been found to be variable^{245,246}. New candidate vaccines for TB are in various stages of development and are listed in Table VIII^{241,242,247}.

The summary of important changes in TB during the last 130 years since the time of Robert Koch in 1882 are listed in Table IX.

The Future

The search for newer and more efficient biomarkers for predicating a durable (non-relapsing) cure, indication of reactivation risk, prediction

Box 2. Latent TB infection: key issues

- Most of the widely used regimens to treat LTBI include IPT and short-course rifamycin-containing regimens of varying duration ranging from 2 to 12 months⁹². Presently, the WHO recommends IPT for LTBI treatment at a daily dose of 5 mg/kg (maximum 300 mg) for at least 6 months and ideally for 9 months²³⁰. However, longer duration of IPT is associated with lesser compliance and it has been observed that if proper adherence is ensured, 12-month isoniazid therapy is more beneficial than 6-month isoniazid therapy²³⁰.
- In the PREVENT TB clinical trial²³², a open-label, randomized non-inferiority trial comparing 3 months of directly observed once-weekly therapy with rifapentine (900 mg) plus isoniazid (900 mg) with 9 months of self-administered daily isoniazid (300 mg) alone in subjects at high risk for developing TB, use of rifapentine plus isoniazid for 3 months was as effective as 9 months of isoniazid alone in preventing TB and had a higher treatment-completion rate.
- Evidence-based guidelines for the treatment of LTBI in contacts of patients with MDR-TB are not available. An international survey²³⁴ evaluated TB programme practices, for managing MDR-TB contacts in countries with an MDR-TB prevalence of > 2% in new patients; 25 of the 35 countries meeting the survey criteria had responded. Of these, 19 countries usually or always evaluated contacts and treated LTBI; 10 reported having a guideline for managing MDR-TB contacts, 11 usually or always evaluated MDR-TB contacts, 9 treated LTBI. Some of the newer or repurposed anti-TB drugs are being tested for treating LTBI in MDR-TB contacts²³⁵, but it might take considerable time for the evidence thus generated to be translated into practice guidelines.
- As of now, administering a combination regimen basing on the profile of the suspected isolate of *M. tuberculosis* for 6-12 months seems to be a treatment option.

LTBI, latent tuberculosis infection; IPT, isoniazid preventive therapy; MDR-TB, multidrug-resistant tuberculosis

Source: Refs 92, 230-235

of eradication of LTBI; and prediction of vaccine efficacy^{248,249}, discovery of newer anti-TB drugs²⁵⁰⁻²⁵³ and development of newer additional candidate vaccines²⁵⁴⁻²⁵⁷ is required to achieve the WHO and UNMDG goal of halting the incidence, prevalence and death rates associated with TB by 2015 and eliminating the disease altogether by 2050¹⁹⁷. Translation of newer innovative diagnostics for TB, such as, use of a 'hand-held' nuclear magnetic resonance (NMR) apparatus capable of offering a 30-minute diagnosis of TB²⁵⁸, applications of nanotechnology^{259,260} to point-of-care diagnostic tests needs to be pursued.

Newer, repurposed drugs in pipeline

Presently, several newer or repurposed drugs are in pipeline in various stages of development as anti-TB drugs^{252,261}. Among the newer drugs, delamanid (OPC67683), bedaquiline (TMC207) and the nitroimidazole-oxazine PA-824 have been found to be active against both drug-sensitive and drug-resistant strains. Bedaquiline (TMC207) has been approved for use by the United States-Food and Drug Administration (US-FDA). Their efficacy and safety have been demonstrated in MDR-TB patients in double-blind, placebo controlled phase II clinical trials²⁶²⁻²⁶⁴. The Government of India is planning to regulate the introduction of these newer drugs in a systematic fashion by streamlining the conduct of clinical trials in India. Evidence is available that isoniazid-resistant clinical

isolates of *M. tuberculosis* remain fully susceptible to the drug pyridomycin, a compound produced by *Dactylosporangium fulvum* with specific bactericidal activity against mycobacteria²⁶⁵. Pyridomycin merits further evaluation as an anti-TB drug.

Initiatives like the Critical Path to New TB Regimens (CPTR) involving several pharmaceutical companies and non-governmental organizations have been attempting to develop the newer drugs concomitantly in combination trials so that the best regimen and the shortest duration of time can be evolved²⁶⁶. Additional vaccine candidates are likely to enter clinical trials in future²⁵⁴⁻²⁵⁷.

The last 70 years have witnessed an initial euphoria of emergence of drug treatment of TB that raised hopes and even signalled a likely 'elimination' of TB. In spite of political commitment, global and national programmatic strategy to contain and control TB, eventual elimination of TB in near future appears to be a mirage as of now. The widespread occurrence of X/MDR-TB threatens to take us back to the era of untreatable TB. TB has come a long way, from despair and the status of an incurable malady, through a brief interlude of a curable disease to a scourge that is menacingly threatening the return to dark ages. The fall in the absolute number of TB cases globally observed since 2006 is heartening. With newer and repurposed anti-TB drugs emerging and becoming available for

Box 3. Global efforts at TB control (1991-2013): a journey

Year	Important developments
1991	TB is recognized by WHO as a global public health problem The 44 th World Health Assembly resolution (WHA 44.8) (i) urged member States to intensify TB control as an integral part of primary care using the new WHO strategy elaborated on the basis of the IUATLD approach; (ii) encouraged international partners to continue to help control TB by collaborating with National programmes; and (iii) requested the establishment of global targets
1993	WHO declares TB as a “global emergency”
1994	First global anti-TB drug resistance surveillance launched
1995	DOTS strategy launched
1997	First WHO Global Tuberculosis Report: epidemiology and surveillance published
1998	Stop TB Initiative launched UNAIDS and WHO policy on isoniazid preventive therapy First WHO ad-hoc committee on the TB epidemic in London, United Kingdom
2000	Creation of the Global Alliance for TB Drug Development Establishment of the Green Light Committee Ministerial meeting on TB, Amsterdam, The Netherlands Guidelines for establishing DOTS-Plus projects published
2001	Global DOTS Expansion Plan launched Global Drug Facility launched Formalization of the Stop TB Partnership governance Global Plan to Stop TB 2001–2005
2002	Establishment of the Global Fund to fight AIDS, Tuberculosis and Malaria Financing and strategy for 22 high-burden countries included in WHO Global Tuberculosis Report An Expanded DOTS Framework for Effective TB Control issued
2003	Third edition of the “Guidelines for National Programmes” published Financing and strategy (all countries) included in the in WHO Global Tuberculosis Report
2005	Creation of FIND WHO TB-HIV policy launched
2006	Global Plan to Stop TB 2006–2015 Establishment of UNITAID Launch of the WHO Stop TB Strategy Emergence of XDR-TB
2008	Creation of the TB Vaccine Initiative
2009	WHO policy on TB infection control in health-care facilities, congregate settings and households published Online data collection introduced in the in WHO Global Tuberculosis Report
2010	Updated Global Plan to Stop TB 2011–2015 Fourth edition of the “Guidelines for National Programmes” published
2012	ENGAGE-TB initiative developed by WHO. This initiative aims at integrating community-based activities to control TB in the ongoing work of such NGOs, aligned with national strategies and plans and supported by new operational guidance
2013	Post-2015 TB Strategy In February 2013, participants in a workshop convened by the WHO and the Stop TB Partnership have proposed a set of goals and targets to guide the global fight against TB after 2015. The overall aim was to achieve “zero TB deaths, zero TB disease and zero suffering”. The following interim targets, namely, to reduce TB deaths and TB incidence rate by 75 and 40%, respectively by 2025 compared with 2015; and to attain a target of zero catastrophic expenditures for families affected by TB by 2025 were agreed upon

TB, tuberculosis, IUATLD, International Union Against Tuberculosis and Lung Disease; UNAIDS, the Joint United Nations Programme on HIV/AIDS; FIND, Foundation for Innovative New Diagnostics; UNITAID, an international drug purchase facility initiative financed with resources that would be both sustainable and predictable formed in 2006 by Brazil, Chile, France, Norway and the United Kingdom; AIDS, acquired immunodeficiency syndrome

Source: Refs. 37, 236, 237

Table VIII. Some of the potential TB vaccines in various stages of development

Vaccine category	Candidates	Stage of development
Recombinant BCG for pre-exposure prime vaccination	VPM 1002 rBCG30	Phase IIa ongoing Phase I completed/on hold
Viral-vector for pre-exposure booster vaccination	Oxford MVA85A/Aeras-485	In a double-blind, randomized, placebo-controlled phase 2b trial ²⁴⁷ MVA85A was unable to protect against tuberculosis disease or <i>Mycobacterium tuberculosis</i> infection in infants
	Crucell Ad35/Aeras-402 AdAg85A	Phase IIb ongoing Phase I
Fusion protein in adjuvant for pre-exposure booster vaccination	M72+AS01 or AS02 Hybrid 1+IC31 Hybrid 56+IC31 Hybrid 1+CAF01 Aeras-404: HyVac4+IC31	Phase IIa ongoing Phase I, soon entering IIa Phase I ongoing Phase I ongoing Phase I
Whole bacterial vaccine for therapeutic vaccination	RUTI <i>Mycobacterium vaccae</i> <i>Mycobacterium w (Mycobacterium indicus pranii)</i>	Phase IIa ongoing Phase III completed Phase III

Source: Refs. 241,242,247

use, the march of the humankind towards the goal of TB elimination, *i.e.*, reducing the annual incidence to less than 1 case/1,000,000 population by 2050²⁶⁷ appears to be on course in the right direction.

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Table IX. Summary of important changes in TB

Robert Koch's discovery of the TB bacillus (1882) enabled specific diagnosis of TB

Wilhelm Roentgen's discovery of X-rays (1895) facilitated ante-mortem visualization of TB lesions

Developed by Calmette and Guerin between 1908 and 1921, BCG vaccine became available for human use. In 1974, WHO included BCG vaccine in the expanded immunization programme and is still the only available vaccine for TB. Despite its doubtful efficacy it is recommended as it attenuates the severity of miliary and meningeal TB in children

Evolution of modern multiple drug treatment of TB occurred during 1944-1980 that led to eventual establishment of short-course chemotherapy that is the standard of care today. TB considered curable; TB elimination contemplated in developed countries.

Emergence of HIV/AIDS epidemic (1981); the cursed duet of HIV and TB coinfection results in a global resurgence of TB. Outbreaks of MDR-TB emerge in the USA. TB is recognized as a global emergency in 1993 by the WHO.

Epidemiological data

Systematization of global TB data collection has resulted in more reliable epidemiological data (including drug-resistant surveillance data) becoming available.

For the first time in the history of humankind, a fall in the absolute number of TB cases has been observed since 2006. But the march towards the eventual elimination of TB by 2050 appears to be still difficult to achieve.

Newer risk factors

Newer risk factors, such as, tobacco smoking, use of immunomodulator biologicals, diabetes mellitus being recognized.

Changing clinical picture of TB

HIV/AIDS epidemic, increased use of immunosuppressant medications result in more frequent occurrence of disseminated, miliary TB; cryptic, occult TB and atypical clinical presentations have resulted in diagnostic delays.

Imaging modalities

Availability of newer imaging modalities, such as, ultrasonography, CT, MRI, bone scan, PET-CT has facilitated more efficient clinical localization of lesions. Increasing use of image guided procurement of body fluids and tissues aids establishment of definitive diagnosis of TB.

Diagnostic methods

Advances in diagnostic modalities from the conventional smear and culture methods like liquid culture, rapid DST testing, molecular diagnostic methods being refined to arrive at a rapid diagnosis including DST profile. Global accredited diagnostic laboratory facility capacity building taken up.

The rise and fall of serodiagnostic tests and more clarity on the diagnostic use of IGRAs emerges

Treatment

Global implementation of DOTS begins (1995); programmatic management of X/MDR-TB shapes up.

Vaccine

TB vaccine scenario that appeared bleak in the 1990s has seen the emergence of several newer TB vaccines that are in various phases of clinical trials.

The future

Newer/repurposed anti-TB drugs and vaccines are being tested. Bedaquiline (TMC207) has been approved for use by the USFDA. The Government of India is planning to regulate the introduction of these newer drugs in a systematic fashion after conducting phase 3 clinical trials at select sites in India.

CT, computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography computed tomography; DST, drug-susceptibility testing; IGRAs, interferon-gamma release assays; X/MDR-TB, extensively drug-resistant and multidrug-resistant tuberculosis; BCG, bacille Calmette Guerin; USFDA, United States-Food and Drug Administration

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