INDEX-TB GUIDELINES

Guidelines on extra-pulmonary tuberculosis for India

Initiative of
Central TB Division
Ministry of Health and Family Welfare, Government of India

Convenors

Department of Medicine, All India Institute of Medical Sciences, New Delhi
WHO Collaborating Centre (WHO-CC) for Training and Research in Tuberculosis
Centre of Excellence for Extra-Pulmonary Tuberculosis, Ministry of Health and Family Welfare, Government of India

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Global Health Advocates, India
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MESSAGE

Tuberculosis has remained a major public health problem since the dawn of civilization and continues to impose a major financial burden on the society. Despite the availability of modern techniques of diagnosis and effective drugs, India continues to host one-fourth of the world's TB disease burden. It is estimated that every two minutes, a person dies from TB in India.

The Revised National Tuberculosis Treatment Programme has been at the forefront of the battle against the scourge in our country. The programme, since its inception in the 1990's, has treated 17.4 million patients and has saved an additional 3.1 million patients.

Challenges such as the HIV epidemic, drug resistance have threatened the success of RNTCP. Another major hindrance has been a lack of uniformity in the management of extra-pulmonary tuberculosis, which contributes a sizeable number of the overall TB cases in our country.

Keeping this in mind, the initiative was taken to carry out an extensive review of the current medical literature on the subject of diagnosis and treatment of various forms of extra-pulmonary tuberculosis. A large number of clinical specialists from different fields and experts from India and abroad have worked tirelessly for the past one and a half years to bring out an evidence based, comprehensive guidelines on the management of all forms of extra-pulmonary tuberculosis.

This document is expected to go a long way in supplementing the efforts of the Ministry of Health and Family Welfare in tackling the enormous burden of TB in India. I would like to take this opportunity to congratulate all the team members involved in the development of these guidelines for the successful completion of this document and look forward for the use of these guidelines by the Revised National TB Control Program and the experts of the country for affective management of Extra Pulmonary TB cases.

(C.K. Mishra)

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दिनांक/Dated 29/07/2016

MESSAGE

Revised National Tuberculosis Control Programme has made a remarkable contribution in reducing the burden of tuberculosis in our country. Prevalence and mortality have been halved as compared to the base year of 1990. This has been the result of administrative commitment which has facilitated several bold decisions and interventions.

More than 13000 Designated Microscopy centres have been set up to enable diagnosis of pulmonary tuberculosis across the country. To address the challenge of drug resistant tuberculosis, a large number of laboratories with facilities for liquid and solid cultures, Line Probe Assay technology and Cartridge Based Nucleic Acid Amplification Test (CBNAAT) have been set up. Diagnosed patients also get free drugs for the entire treatment duration of up to twenty four months.

While significant advance has been made in the above spheres, the management of extra-pulmonary tuberculosis requires additional emphasis. Given the difficulty in diagnosis, the facilities for CBNAAT are being strengthened to enable early detection of EPTB cases. The increased frequency of HIV co infection in these patients is also being adequately addressed.

Universal access will mean increasing the capacity to manage and treat all forms of TB as well as enhanced engagement of the private sector in India which manages nearly half of all TB cases. Universal access has encompassed the private sector through adoption of Standards of TB Care in India. The 12th Five Year Plan and National Strategic Plan to Control TB (2012-2017) have prioritized the engagement of the private sector to enable early diagnosis as well as treatment. The Central TB Division, Ministry of Health and Family Welfare has envisioned provision of free drugs to all patients being treated for TB in the private sector.

Support from all stakeholders will go a long way in achieving our goals concerned with management of TB. It is hoped that the present guidelines will be widely adopted by the public and private sector across the country.

Jprasad

(Dr. Jagdish Prasad)

World Health Organization
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Message from WHO Representative to India

In the last 15 years tuberculosis (TB) control has made good progress globally. However, 9.6 million people developed TB disease in 2014, and 1.5 million died of TB. Worldwide, TB now ranks alongside HIV as a leading cause of death. India with one sixth of the global population has a quarter of the global burden of TB.

In 2014, the World Health Assembly endorsed a new and bold plan called "The End TB Strategy". The strategy aims to end the global TB epidemic by 2035, with the vision "A world free of tuberculosis – zero deaths, disease and suffering due to tuberculosis". This will require a rapid upgrade of care, additional tools and managerial standards to fully address the many different persistent and emerging health issues of this disease. India is committed to achieve the TB targets as per the Sustainable Development Goals.

Pulmonary tuberculosis is the most common presentation and a priority for the public health programme. However, extrapulmonary tuberculosis (EPTB) is an important cause of TB morbidity and death. EPTB can affect virtually all organs and has a wide variety of clinical manifestations. Low level of awareness among clinicians, the difficulty in obtaining samples for diagnosis and lack of right tools make the diagnosis of EPTB a challenge. The recently released WHO guidelines on the use of GeneXpert for extrapulmonary specimens, offers a better chance of early EPTB diagnosis.

WHO has worked closely with the Central TB Division, Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India and All India Institute of Medical Sciences to bridge the gap of early diagnosis and treatment of EPTB. The *INDEX-TB Guidelines* provides evidence-based guidance for suspecting, diagnosing and management of various forms of EPTB. These guidelines offer support to clinicians and programme managers for better diagnosis and management of EPTB. These guidelines will serve as a useful tool to the Revised Technical and Operational Guidelines of the Revised National TB Control Programme.

The *INDEX-TB Guidelines* is a welcome addition to the galaxy of important TB documents in India and will be of immense help for tuberculosis control. It is of vital importance that these guidelines are widely disseminated through various platforms and trainings of public and private doctors.

WHO is committed to providing necessary technical guidance and assistance to the central and state governments to strengthen their health programmes. We will continue to work with all stakeholders on our common resolve of fighting TB. Actions taken today must build on principles of the government stewardship, engagement of civil society, reaching out to private sector, human rights and equity, and adaptation to the unique context of diverse epidemics and settings.

Henk Bekedam
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29/07/2016

MESSAGE

Tuberculosis is an ancient malady that has plagued humanity throughout the ages. Despite remarkable advancements in technology in the diagnosis and treatment of tuberculosis, it continues to remain a massive public health problem and the leading infectious disease responsible for death in the 21st century.

The Revised National Tuberculosis Control Programme was envisioned in 1992 to meet the challenges produced by tuberculosis in the country and it has been energetically implemented throughout the country. It has imbibed the spirit of the millennium development goals, meeting several targets set apart, and on the verge of achieving many more.

However, the journey has not been free of obstacles. One such hurdle remains the rise in prevalence of extra-pulmonary tuberculosis, coincident with the HIV epidemic of the past three decades. Till now, no set guidelines have been established to tackle the protean manifestations of extra-pulmonary tuberculosis and treatment largely remains guided by clinical experience.

This document is the culmination of a herculean effort undertaken by several leading experts from India and abroad, with a multidisciplinary evidence-based approach under the effective leadership of the Department of Medicine, AIIMS, New Delhi. I would like to congratulate the entire team involved in the production of this document and would urge all stakeholders to adopt the guidelines to further the cause of a TB-free India.

(Dr Sunil D Khaparde)

Foreword

It has been observed in the Yajurveda, one of the ancient Hindu scriptures, that Soma, the Moon God himself, suffered from an ailment indistinguishable to the disease we now call "tuberculosis".

Indeed, this scourge has afflicted mankind through the millennia, not sparing anyone; be it the poor or the rich, the common man or the ruler. The global burden of tuberculosis (TB) has been mountainous throughout the past century and continues to remain so even today. It is estimated that a total of 9.6 million people developed the disease and over one and a half million perished to it in 2014 alone.

Most of the focus in the past century has been on the successful diagnosis and treatment of pulmonary TB, and tremendous progress has been made in this regard. While improved living standards and successful anti-TB chemotherapy helped in bringing down the burden to miniscule levels in the developed countries, the disease continued to wreak havoc in developing countries like India. Though the "End TB strategy" aims at TB elimination, with the emergence of multidrug-resistant TB, extensively drug-resistant TB and HIV-TB epidemic, there is a threat to the advances that have been achieved. We persistently stand the risk of a resurgence of a far more virulent TB bacterium.

At the same time, there is a huge amount of uncertainty regarding the management of extra-pulmonary TB (EPTB). The latter accounts for about one-fifth of all TB cases. Although there should be no complacency about pulmonary TB, the world needs to focus on EPTB and latent TB infection as well. Furthermore, with the HIV epidemic, there is a significant increase in the prevalence of EPTB. Till now, there have been no formal guidelines that deal with EPTB as a separate entity with special considerations. The protean manifestations of EPTB, which can involve almost any system of the body, along with the ambiguity regarding management, have made it a formidable enemy in the war against TB. Thus, the need of the hour is to prepare our armamentarium to tackle EPTB effectively.

The lead has been taken by the Department of Medicine, All India Institute of Medical Sciences, which is a WHO Collaborating Centre, and the National Centre of Excellence in Extra-pulmonary Tuberculosis, in collaboration with the Central TB Division, Ministry of Health and Family Welfare, Government of India, to bring forth for the first time an evidence-informed guidelines for the management of various forms of EPTB. This has been a herculean effort, which required the involvement of a large number of experts from different organ system subspecialties as well the guidance of methodology

experts from the Cochrane Collaboration (Cochrane Infectious Disease group, Liverpool, UK and Cochrane South Asia, Vellore, India). Global Health Advocates (for financial management) and various other stakeholders involved in providing TB care in India have been actively involved during every stage of the process. Spanning the past one and a half years, the objectives and scope of the guidelines were charted out, extensive literature review with several new ad hoc systematic reviews were undertaken, and a concise, lucid document which has been extensively peer reviewed has now seen the light of the day. It is hoped that this will be used by the health-care providers at the primary and secondary care levels throughout the country and other high-burden countries for rational and systematic management of EPTB.

The present guidelines assesses the three key areas related to various forms of EPTB: (i) use of Xpert MTB/RIF for diagnosis; (ii) use of corticosteroids; and (iii) duration of treatment.

While there has been a handful of evidence, a large number of lacunae in the present knowledge of the subject were identified. It is hoped that these guidelines will serve as an impetus for further research on the subject and will guide researchers by spelling out the key research questions that could help improve the future editions of this document. The path to conquering EPTB has been taken, but the journey is far from complete.

Professor SK Sharma
Chairman
INDEX-TB Guidelines Group

Acknowledgements

Concept for the guidelines was initiated and mentored by DGHS, Dr Jagdish Prasad; DDG-TB, Dr Sunil D. Khaparde; and Additional DDG-TB, Dr K.S. Sachdeva along with members of Central TB Division, Ministry of Health and Family Welfare, Government of India.

The INDEX-TB Guidelines Core Committee gratefully acknowledges the Group Leaders and Technical Advisory Committee members of each organ system group, the overall support groups and the Methodology Support Team (listed in Annex 1), including Professor S.K. Sharma (AIIMS, New Delhi), under whose leadership this historical document could be prepared.

Professor Paul Garner and Dr Hannah Ryan (Cochrane Infectious Diseases Group, Liverpool, UK), and Professor Prathap Tharyan (Cochrane South Asia, Vellore, India) moderated the guidelines meetings organized to prepare recommendations.

Professor M.C. Misra (Director, AIIMS, New Delhi) supported this endeavour by providing the venue and administrative support for the meetings. Dr Neeraj Nischal (Assistant Professor, AIIMS, New Delhi), Dr Bharati Kalottee (Grant Manager, The Global Fund Grants), and Dr Sapna Naveen (Global Health Advocates, India) coordinated the organization of the meetings of the Guidelines Group.
Dr Bobby John (Principal Advisor, Global Health Advocates, India) provided the financial support for the meetings.

Publication and dissemination of the guidelines was supported in part by a financial contribution from WHO Country Office for India with efforts of Dr Achuthan Nair Sreenivas, National Professional Officer (Tuberculosis) at World Health Organization (WHO).
The Writing Committee was composed of Dr Hannah Ryan and her team (listed in Annex 1).

Useful feedback was obtained from the Peer Review Group (also listed in Annex 1).

Abbreviations

ADA	adenosine deaminase, or adenosine aminohydrolase
AFB	acid-fast bacilli
AIIMS	All India Institute of Medical Sciences
ART	antiretroviral therapy
ATT	anti-tuberculosis therapy
CNS	central nervous system
CoE	Centre of Excellence
CSF	cerebrospinal fluid
CT	computed tomography
CXR	chest X-ray
DGHS	Directorate General of Health Services
ECG	electrocardiogram
ENT	ear, nose and throat
EPTB	extra-pulmonary tuberculosis
ESR	erythrocyte sedimentation rate
FGTB	female genital TB
FNAC	fine-needle aspiration cytology
GHA	Global Health Advocates
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
ICP	intra cranial pressure
IGRA	interferon-gamma release assay
INDEX-TB	Indian extra-pulmonary tuberculosis
IRIS	immune reconstitution inflammatory syndrome
LDH	lactate dehydrogenase
LNTB	lymph node tuberculosis
MRI	magnetic resonance imaging
Mtb	Mycobacterium tuberculosis (referring to the organism causing tuberculosis disease)

PCR	polymerase chain reaction
PET-CT	positron emission tomography–computed tomography
PGIMER	Post Graduate Institute of Medical Education and Research
RNTCP	Revised National Tuberculosis Control Programme
TAC	Technical Advisory Committee
TB	tuberculosis (referring to the disease caused by Mycobacterium tuberculosis)
TBM	tuberculous meningitis
TST	tuberculin skin testing (also referred to as Mantoux test)
VCT	voluntary counselling and testing
WHO	World Health Organization
WHO-CC	World Health Organization Collaborating Centre

Treatment nomenclature

The first-line anti-tuberculosis drugs are referred to by single-letter abbreviations, as follows:

R – rifampicin

H – isoniazid

Z – pyrazinamide

E – ethambutol

S – streptomycin

Regimens are described using shorthand, with numbers to denote the number of months the treatment should be given for. So, 2RHZE/4RHE refers to 2 months' treatment with rifampicin, isoniazid, pyrazinamide and ethambutol, followed by 4 months' treatment with rifampicin, isoniazid and ethambutol.

Clinicians should refer to the current RNTCP guidelines for dosing of ATT drugs in adults and children. At the time of publication, daily dosing regimens are being introduced in five states with a view to all TB patients nationwide receiving daily ATT.

Executive summary

The main objective of these guidelines is to provide guidance on up-to-date, uniform, evidence-informed practices for suspecting, diagnosing and managing various forms of extra-pulmonary tuberculosis (EPTB) at all levels of health-care delivery. They can then contribute to the National Programme to improve detection, care and outcomes in EPTB; to help the programme with initiation of treatment, adherence and completion whilst minimizing drug toxicity and overtreatment; and contribute to practices that minimize the development of drug resistance.

The Core Committee, commissioned by the Central TB Division (CTD) and Directorate of Health Services of the Ministry of Health and Family Welfare, Government of India, with the assistance of 10 Technical Advisory Subcommittees representing the different organ systems affected by EPTB, in partnership with the Methodology Support Team, initiated a process of evidence-informed guidelines development in December 2014 drawing on best international practices. This group produced three outputs:

a) Agreed principles relevant to EPTB care, and complementary to the existing 2014 country standards;

b) Agreed recommendations developed using current international evidence-informed methods on priority areas for EPTB, in Xpert MTB/RIF, use of steroids and length of treatment; and

c) Clinical practice points for each organ system, based on accumulated knowledge in the country and in the working groups.

Principles

In line with the International Standards of TB Care (TB CARE I, 2014), the Guidelines Group as a whole agreed on a set of principles about what every EPTB patient in India needs as a basic standard of care. These principles are a complementary set to the Standards for TB Care in India 2014 (Sreenivas, 2014).

Principle 1	Patients first The provider should adopt a patient-centred approach to managing EPTB, to promote well-being and adherence to treatment and to relieve suffering. Patients have the right to be fully informed about their care at every stage, to be able to make decisions about their treatment and to be treated with dignity and respect.

Principle 2	Promoting early diagnosis Providers should be informed of the clinical features and risk factors for various forms of EPTB and carry out prompt clinical evaluation and appropriate early diagnostic investigation.
Principle 3	Access to a tissue-based diagnosis Where facilities exist, all patients suspected of having EPTB should have appropriate samples taken for microbiological and histological testing, unless diagnostic sampling is deemed to risk undue harm.
Principle 4	Addressing drug resistance All patients with a diagnosis of EPTB should be risk-assessed for drug resistance prior to starting treatment, and drug susceptibility testing should be available for all patients at risk of drug-resistant tuberculosis.
Principle 5	Avoiding unnecessary invasive and costly tests Providers should consider the impact of diagnostic tests on patient management before referring patients for costly or invasive tests, or repeating these tests.
Principle 6	Access to HIV testing As EPTB is particularly associated with HIV, integrated counselling and testing should be made available to all patients suspected of having EPTB.
Principle 7	Identifying patients with concurrent active pulmonary TB All patients suspected of having EPTB should have clinical assessment for pulmonary TB in line with RNTCP guidance for investigating suspected pulmonary TB.
Principle 8	Ensuring effective treatment All patients should receive an appropriate treatment regimen.
Principle 9	Promoting adherence Providers should monitor adherence to treatment and address factors leading to interruption or discontinuation of treatment. Services should promote retention of patients in care.
Principle 10	Record keeping and public health promotion A reliable, well-maintained record of all diagnostic tests, treatments given, treatment monitoring, outcomes and adverse events should be kept for each patient, and data should be collected at the national programme level for the purposes of health-care system planning and development.

Recommendations

The Core Committee and Technical Advisory Subcommittees initially considered the first draft of the clinical guides prepared by each of the organ system subcommittees. This raised many potential points of equipoise that could be subject to formal evidence-informed guideline development using the Grading of Recommendations Assessment Development and Evaluation (GRADE) process. From this process, the Core Committee and Methodology Support Team identified priority topics cutting across several organ systems in EPTB for development of guidelines. These were areas where systematic review of the evidence was feasible given the available study data and time and resource constraints, where there were current important dilemmas in what to recommend and where decisions could improve patient care, patient outcomes, or had important resource implications. For example, agreeing on length of treatment has substantive effects on drugs cost and resource use. The committee viewed this guideline process as an essential step in embedding evidence-based processes in the guidelines development and part of a long-term vision for the country. While the topics appeared clinical, all the decisions had potentially profound public health expenditure and management implications. In addition, the guidelines could have an impact towards improving public health outcomes.

The questions addressed were:

1. Should Xpert MTB/RIF be recommended for use in the diagnosis of: a) lymph node TB; b) TB meningitis; c) pleural TB?
2. Should corticosteroids be recommended for use in the treatment of: a) TB pericarditis; b) TB meningitis; c) pleural TB?
3. How long should ATT be given in the treatment of: a) lymph node TB; b) abdominal TB; c) TB meningitis?

Evidence summaries were then produced by members of the Technical Advisory Subcommittees and the Methodology Support Team, and presented to the Guidelines Panel. The Guidelines Panel considered the evidence in accordance with GRADE criteria and decided on recommendations by consensus.

The guidelines process has adhered to the GRADE criteria (GRADE Working Group, 2008) to produce a set of recommendations that are explicitly linked to the evidence they are based on, with consideration given to the various health-care settings across India. The use of GRADE is in line with the WHO Handbook for Guideline Development (WHO, 2014).

The GRADE criteria require that:

- quality of evidence, as well as the effect estimate, is clearly defined;
- risk of bias of the relevant studies, directness of evidence, consistency of results, precision and other sources of bias in the available evidence are considered and reported for each important outcome;
- evidence summaries are used as the basis for judgements about the quality of the evidence and the strength of recommendations;

- the balance of desirable and undesirable consequences, quality of evidence, values and preferences should be considered and reported when deciding on the strength of a recommendation;
- the strength of recommendations is clearly reported and defined.

Recommendations: Diagnosis of EPTB using the Xpert MTB/RIF test
Lymph node TB Xpert MTB/RIF should be used as an additional test to conventional smear microscopy, culture and cytology in fine-needle aspiration cytology (FNAC) specimens. Strong recommendation, low quality evidence for sensitivity estimate, high quality evidence for specificity estimate.
TB meningitis Xpert MTB/RIF may be used as an adjunctive test for tuberculous meningitis (TBM). A negative Xpert MTB/RIF result on a cerebrospinal fluid (CSF) specimen does not rule out TBM. The decision to give anti-tuberculosis treatment (ATT) should be based on clinical features and CSF profile. Conditional recommendation, low quality evidence for sensitivity estimate, high quality evidence for specificity estimate.
Pleural TB Xpert MTB/RIF should not be routinely used to diagnose pleural TB. Strong recommendation, low quality evidence for sensitivity estimate, high quality evidence for specificity estimate.
Recommendations: Adjunctive steroids in the treatment of EPTB
TB meningitis Steroids are recommended for TB meningitis in HIV-negative people. Duration of steroid treatment should be for at least 4 weeks with tapering as appropriate. Strong recommendation, high quality evidence. Steroids may be used for TB meningitis in HIV-positive people, where other life-threatening opportunistic infections are absent. Conditional recommendation, very low quality evidence.
TB pericarditis Steroids are recommended for HIV-negative patients with TB pericarditis with pericardial effusion. Conditional, low quality evidence. Steroids are recommended for HIV-positive patients with TB pericarditis with pericardial effusion. Conditional, low quality evidence.
Pleural TB Steroids are not routinely recommended in pleural TB. Conditional, low quality evidence.

Recommendations: length of treatment for EPTB
Lymph node TB Six months ATT standard first-line regimen is recommended for peripheral lymph node TB. Strong recommendation, low quality evidence.
Abdominal TB Six months ATT standard first-line regimen is recommended for abdominal TB. Strong recommendation, very low quality evidence.
TB meningitis TB meningitis should be treated with standard first-line ATT for at least 9 months. Conditional recommendation, very low quality evidence.

Clinical practice points

EPTB takes many forms, and evidence regarding best practice for many aspects of case finding, diagnosis and treatment is lacking. In order to reflect the needs of health-care providers and develop a platform for future guidelines and research, the Technical Advisory Subcommittees produced clinical practice points on each aspect of EPTB care. These are summarized in Part 2. These are based on the expert opinion of senior clinicians in medicine and surgery from across India, and provide a basis for further refinement in evidence-informed guideline development in future. This section of the guidelines seeks to address all aspects of diagnosis and treatment of EPTB, and should be used as a reference.

Part 1
Guidelines

1 Introduction

1.1 EPTB and Revised National Tuberculosis Control Programme

The Revised National Tuberculosis Control Programme (RNTCP) has developed comprehensive guidelines for diagnosis and treatment of pulmonary TB. However, management of extra-pulmonary TB (EPTB) under the programme continues to be a challenge.

The burden of EPTB is high, ranging from 15–20% of all TB cases in HIV-negative patients, while in HIV-positive people it accounts for 40–50% of new TB cases (Sharma S.K., 2004).

The programme has identified the need to expand support for diagnosis and treatment of EPTB and has outlined the following issues:

- lack of evidence-based guidelines on diagnosis and treatment of various types of EPTB;
- absence of adequate infrastructure and resources up to the peripheral level of health facilities to identify, diagnose and treat EPTB;
- lack of skilled and trained staff for appropriate sample collection, transportation and diagnosis;
- uncertainty among clinicians about the optimum duration of treatment and treatment end-points;
- lack of data on EPTB, as most of the cases are being treated outside the public sector.

In response, the Department of Medicine at the All India Institute of Medical Sciences (AIIMS), New Delhi, which is the WHO Collaborating Centre (WHO-CC) for Training and Research in Tuberculosis and also the Centre of Excellence (CoE) for Extra-Pulmonary Tuberculosis in collaboration with Central TB Division and Directorate General of Health Services (DGHS) of the Ministry of Health and Family Welfare (MoHFW), Government of India (GoI), with support from Global Health Advocates India (GHA India) has taken an initiative to develop Indian extra-pulmonary TB (INDEX-TB) guidelines.

1.2 National planning for universal access in EPTB

The public health emphasis on infectious pulmonary TB is central to the health of the Indian people. Nevertheless, EPTB remains extremely common and is probably under-recognized and treated. These guidelines aim to help improve awareness, diagnosis and proper treatment of EPTB, thus promoting universal access to appropriate, effective care.

1.3 Objectives

The main objective of these guidelines is to provide guidance on up-to-date, uniform, evidence-based practices for suspecting, diagnosing and managing various forms of EPTB at all levels of delivery.

A subsidiary objective is to help direct further research by identifying knowledge gaps.

These guidelines will contribute to the programme to improve detection, care and

outcomes in EBTP; to provide guidance on initiation of treatment, adherence and completion whilst minimizing drug toxicity and overtreatment; and contribute to practices that minimize the development of drug resistance.

1.4 Scope

The main purpose of the guidelines is to inform national treatment protocols. The major part of the document is concerned with primary and secondary level health care, i.e. at district hospitals and places that have sufficient expertise, clinical capacity and resources to care for EPTB patients. The aim is to standardize practice across the country. The guidelines address diagnosis and treatment in all forms of EPTB, providing recommendations based on systematic reviews of the evidence where possible. The guidelines are intended to be synergistic with existing RNTCP policy.

The guidelines focus on important current areas of debate in EPTB policy and practice. This helps identify priorities and guide resource use and helps policy makers, clinical managers and clinicians implement best practice in these critical areas in the first instance as part of continuous quality improvement in the detection and treatment of EPTB.

1.5 Target audience

The main document is for public and private sector clinicians in primary, secondary and tertiary care, and associated field-level health workers. Suggested points of referral are included to guide general practitioners and field health workers. The guidelines are also intended to inform health-care providers, TB programme managers and policy makers about best practice based on a review of the current evidence.

1.6 Updating the guidelines

The Core Committee and GoI recognized that this guideline represented the start of a process of developing evidence-informed EPTB guidelines in India that would be further developed over time. There was a commitment to updating aspects of these guidelines in the next 3 to 6 years, at which time these topics would be revisited and additional priority topics considered.

2 Methods used to reach recommendations

Representatives from the RNTCP and the Central TB Division of the Ministry of Health and Family Welfare, GoI, worked with representatives from the Department of Medicine at AIIMS New Delhi and other technical advisors to establish a Core Committee for the development of the guidelines (see Annex 1) and a Technical Advisory Committee (TAC), with subcommittees of specialists in each of the organ systems. The Core Committee recruited a Methodology Support Team to provide guidance in the development of the guidelines.

The Core Committee prepared a document that outlined the methods, teams, management of the process and how conflicts of interest would be handled. This was termed the Scoping Document and was approved by representatives from the Central TB Division. The Scoping Document set out the purpose and objectives of the guidelines. This was circulated to members of the TAC along with a suggested framework for identifying key questions for each form of EPTB around diagnosis, treatment and follow-up. During February and March 2015, each TAC subcommittee performed a scoping exercise to identify key questions, and began literature reviews. Each subcommittee carried out a consultation across institutions with experts in every relevant medical specialty to identify topics of interest and key questions relating to the diagnosis and management of all forms of EPTB. Each TAC then prepared a comprehensive state-of-the-art summary of knowledge and opinion about each organ system. This was done using traditional narrative approaches to reviewing. The Methodology Support Team provided advice on taking a systematic approach wherever possible, with training courses organised by Cochrane South Asia.

During the meeting of the guidelines group in March 2015, TAC subcommittees presented their findings for discussion with the Core Committee and Methodology Support Team. This meeting concluded with plans to refine the questions addressed by each subcommittee and outline cross-cutting themes requiring more detailed evidence review. These questions were identified as key policy and clinical questions facing the providers at this point in time.

These questions were around:

- use of tuberculin skin testing
- the role of the Xpert MTB/RIF test in diagnosing EPTB
- the role of other polymerase chain reaction (PCR)-based tests in diagnosing EPTB
- empirical treatment of EPTB in the absence of a laboratory diagnosis, including therapeutic trials and the use of corticosteroids in EPTB
- the duration of anti-tuberculosis treatment (ATT) in EPTB
- the definition of treatment failure in terms of clinical parameters prompting extended treatment, revised diagnosis, or consideration of drug resistance.

The Core Committee and Methodology Support Team selected themes to take forward to systematic evidence review. These were selected on the basis of: a) clinical importance as expressed by the TAC subcommittees; b) current availability of evidence; and c)

feasibility of assembling up-to-date evidence within the time frame required.

2.1 Evidence review

The Methodology Support Team, along with members from TAC subcommittees, prepared the evidence summaries for review by the guidelines panel between March and July 2015. As part of this process, existing systematic reviews were updated; and where no review was available, new systematic reviews were developed and carried out. Given the time, three topic areas were prioritised:

1. The use of Xpert MTB/RIF in diagnosing EPTB
2. The use of corticosteroids in EPTB
3. The duration of treatment in EPTB

We intended to summarize the available evidence for all forms of EPTB within each of these topic areas, but due to time and resource constraints, we limited our systematic reviews to areas where there is substantive evidence available or there is urgent priority for evidence-based clinical policy. Hence, the questions covered in the evidence review were as follows:

1. Should Xpert MTB/RIF be recommended for use in the diagnosis of:
    - lymph node TB
    - TB meningitis
    - pleural TB?
2. Should corticosteroids be recommended for use in the treatment of:
    - TB pericarditis;
    - TB meningitis;
    - pleural TB?
3. How long should ATT be given in the treatment of:
    - lymph node TB;
    - abdominal TB;
    - TB meningitis?

The Core Committee recognised the need to revisit many of the topic areas identified in the scoping process for systematic evidence review to inform the next iteration of these guidelines.

Details of the methods used in the preparation of each review are summarised in Annex 2, which will be made available in the supplementary materials on-line on CTD website as well as ICMR website. The general principles of systematic review followed those set out in the Cochrane Handbook (Higgins, 2011) (Panel 1).

Panel 1. Steps in synthesising the evidence used for the main guidelines

1. Identify the question (or objective) of the review
2. Identify the outcomes that are most important – to patients, to clinicians, to policy makers
3. Write a protocol setting out the inclusion criteria for the review – what studies will help to answer the question?
4. Two researchers then carry out steps 5 and 6 independently, to limit bias in the review process.
5. Perform a structured search of the literature and screen the results using the inclusion criteria set out in the protocol. Only include studies that can address the review question.
6. Perform data extraction from each study using a pre-defined tool – find the data in the included studies that answers the question and describe each of the studies and their populations.
7. Perform a risk of bias assessment of each study using a pre-defined tool – how reliable are the data from each study?
8. Resolve any discrepancies between the two researchers' data collection by discussion.
9. Perform data synthesis that is appropriate – this could include performing a meta-analysis across studies, or simply describing the findings, depending on the level of heterogeneity between the studies and the types of studies included in the review.
10. Summarize the findings in a table, and apply the GRADE criteria to assess the level of certainty and the applicability of the effects estimates.

2.2 Making recommendations

The recommendations were made during a meeting of the INDEX-TB guidelines group in July 2015 at AIIMS, New Delhi. The Methodology Support Team apprised the guidelines panel of the methods used in conducting the systematic reviews, and advised on the interpretation of the evidence in the summaries. Each evidence summary was presented by the author, and the guidelines group had time to consider the methods and results of the review before considering the GRADE assessment of the main effects estimates, guided by the Methodology Support Team.

2.3 Quality of the evidence

GRADE assessments were appraised in detail, and revised where appropriate to reflect applicability to the Indian context.

The quality of the evidence from systematic reviews was assessed for each outcome and rated on a four-point scale, after consideration of the risk for bias (including publication bias) and the consistency, directness and precision of the effect estimates. The terms used in the quality assessments refer to the confidence that the guideline development group had in the estimate and not solely to the scientific quality of the investigations reviewed,

as follows:

Quality of evidence	Interpretation
High	The group is very confident in the estimates of effect and considers that further research is very unlikely to change this confidence.
Moderate	The group has moderate confidence in the estimate of effect but considers that further research is likely to have an important impact on their confidence and may change the estimate.
Low	The group has low confidence in the estimate of effect and considers that further research is very likely to have an important impact on their confidence and is likely to change the estimate.
Very low	The group is very uncertain about the estimate of effect.

2.4 Strength of the recommendation

The group considered the trade-offs between benefits and harms, the implications for primary, secondary and tertiary health-care contexts and values and preferences relevant to the question. A recommendation was then formulated by the group based on consensus decision-making. Each recommendation was qualified as either "strong" or "conditional" based on the level of certainty in the effects and the degree of concordance among the group.

Recommendations were formulated after considering the quality of the evidence, the balance of benefits and harms and the feasibility of the intervention. Although cost is a critical factor in setting national treatment policies, cost was not formally considered. Areas of disagreement were extensively discussed and consensus reached. Voting was not required.

Factor considered	Rationale
Balance of benefits and harm	The more the expected benefits outweigh the expected risks, the more likely it is that a strong recommendation will be made. When the balance of benefits and harm is likely to vary by setting or is a fine balance, a conditional recommendation is more likely.
Values and preferences	If the recommendation is likely to be widely accepted or highly valued, a strong recommendation is more likely.
Feasibility	If an intervention is achievable in the settings in which the greatest impact is expected, a strong recommendation is more likely.

2.5 Strong and conditional recommendations

There was careful discussion about whether recommendations were strong, where very few people would argue against the recommendation; or conditional, where most people would recommend, but it would not be everyone, or that the intervention may be used in some circumstances and not others, or where some may choose a different management option.

	For patients	For clinicians	For programme managers and policy makers
Strong	Most people would want the recommended test or treatment and only a small proportion would not.	Most patients should receive the recommended test or treatment.	The recommendation can be adopted as standard policy and practice in most situations.
Conditional	Most people would want the recommended test or treatment, but many would not.	Clinicians need to be prepared to help patients make a decision that is consistent with their own values, as this test or treatment might not be right for everybody.	There is need for substantial debate and involvement of stakeholders when considering adopting this policy and practice.

2.6 Drafting the guidelines

Following the meeting of the guidelines group in July 2015, the guidelines were drafted under the supervision of the Core Committee and Methodology Support Team.

The recommendations as drafted and agreed by the Guideline Panel are outlined with accompanying summaries of the evidence and decision-making process.

Each TAC subcommittee drafted a report on current best practice in their specialist field, supported by review of the literature. The Methodology Support Team extracted the Clinical Practice Points from the submitted TAC reports, in dialogue with the TAC leads.

The guidelines, supporting evidence summaries and Clinical Practice Points were submitted for peer review by national and international experts. The Core Committee appraised the results of the peer review process, made necessary changes, if any, and submitted the completed document to the CTD for consideration.

The recommendations laid out in this guidelines document are the result of the process of systematic review and critical appraisal described above, and were agreed upon by the entire guidelines panel. The Clinical Practice Points include these recommendations, but also include other information relevant to clinicians and policy makers on each form of EPTB. The Clinical Practice Points were formulated by the expert clinicians who formed each TAC subcommittee, and reflect the consensus

opinions of these experts, rather than the guidelines group as a whole.

In future iterations of these guidelines, it is hoped that time and resources will again be committed to producing transparent, evidence-based recommendations to address more of the many questions that remain in tackling EPTB.

2.7 Panel members and organization

The INDEX-TB Guidelines Core Committee comprises major stakeholders from scientific bodies pertaining to EPTB, and was responsible for recruiting the members of the other committees. The Core Committee prepared the Scoping Document for the guidelines and oversaw the guidelines development process from start to finish.

The Technical Advisory Committee (TAC) is comprised of expert clinicians, public health officials, GoI officials and WHO Regional Office for South-East Asia representatives. Members of the TAC were selected in order to maximize diversity, relevant expertise and representation of both stakeholders and patient groups. TAC subcommittees of expert clinicians generated the key questions to be addressed in the guidelines for each form of EPTB, prepared literature reviews and participated in the appraisal of the evidence summaries and formulation of the main recommendations.

The Methodology Support Team is comprised of staff from the Cochrane South Asia centre at the Christian Medical College in Vellore and from the Cochrane Infectious Diseases Group at the Liverpool School of Tropical Medicine, United Kingdom. The Methodology Support Team was recruited to advise the Core Committee and TAC subcommittees on best practice in terms of the selection of priority questions, production of evidence summaries and systematic reviews, use of evidence summaries to generate recommendations and the drafting of the guidelines document.

The Coordinating Committee organised logistics and periodic meetings as deemed essential by the Central TB Division.

The Peer Review Committee is comprised of national and international experts chosen by the Core Committee and the TACs to appraise the final guidelines document and supply corrections.

2.8 Declaration of interests

Declarations of interest were required from every member of the guidelines group. These were submitted to the CTD. At the commencement of the final guidelines meeting in July 2015, all members of the guideline panel verbally stated any financial or intellectual interests to the rest of the group. The participants and their declarations of interests are published in Annex 1.

2.9 Funding

The preparation of the guidelines was funded exclusively by the National TB Programme through a grant from Global Health Advocates. The WHO Country Office, India, funded the printing of the guidelines. A grant to the Liverpool School of Tropical Medicine from the UK Government Department for International Development for evidence-informed policy development helped support the Methodology Support Team. No external source of funding from industry was solicited or used.

3 Principles

In line with the International Standards of TB Care (TB CARE I, 2014), the guidelines group as a whole agreed on a set of principles about what every EPTB patient in India needs as a basic standard of care. These principles relate to a basic standard of care that all providers should seek to achieve, a complementary set to the Standards for TB Care in India (Central TB Division and WHO Country Office for India, 2014).

Principle 1	Patients first The provider should adopt a patient-centred approach to managing EPTB, to promote well-being and adherence to treatment and to relieve suffering. Patients have the right to be fully informed about their care at every stage, to be able to make decisions about their treatment and to be treated with dignity and respect.
Principle 2	Promoting early diagnosis Providers should be informed of the clinical features and risk factors for various forms of EPTB and carry out prompt clinical evaluation and appropriate early diagnostic investigation.
Principle 3	Access to a tissue-based diagnosis Where facilities exist, all patients suspected of having EPTB should have appropriate samples taken for microbiological and histological testing, unless diagnostic sampling is deemed to risk undue harm.
Principle 4	Addressing drug resistance All patients with a diagnosis of EPTB should be risk-assessed for drug resistance prior to starting treatment, and drug susceptibility testing should be available for all patients at risk of drug-resistant tuberculosis.
Principle 5	Avoiding unnecessary invasive and costly tests Providers should consider the impact of diagnostic tests on patient management before referring patients for costly or invasive tests, or repeating these tests.
Principle 6	Access to HIV testing As EPTB is particularly associated with HIV, integrated counselling and testing should be made available to all patients suspected of having EPTB.

Principle 7	Identifying patients with concurrent active pulmonary TB All patients suspected of having EPTB should have clinical assessment for pulmonary TB in line with RNTCP guidance for investigating suspected pulmonary TB.
Principle 8	Ensuring effective treatment All patients should receive an appropriate treatment regimen.
Principle 9	Promoting adherence Providers should monitor adherence to treatment and address factors leading to interruption or discontinuation of treatment. Services should promote retention of patients in care.
Principle 10	Record keeping and public health promotion A reliable, well-maintained record of all diagnostic tests, treatments given, treatment monitoring, outcomes and adverse events should be kept for each patient, and data should be collected at the national programme level for the purposes of health-care system planning and development.

4 Working definitions of cases and outcomes

4.1 Purpose of defining a TB case

The RNTCP has developed clear definitions for pulmonary TB cases that allow clinicians to categorize patients in terms of their diagnostic status and outcomes of treatment. This provides common terminology that practitioners treating TB patients and policy makers can understand.

Many TB patients never have their diagnosis confirmed by a positive microbiological test due to the limitations of the diagnostic tests currently available, or lack of access to a microbiological test. These patients are often treated based on the clinician's suspicion alone (empirical treatment). Defining EPTB cases by diagnostic status enables clinicians to be clear about treatment decisions, and is essential to facilitate accurate national reporting within the RNTCP.

During the guidelines development process, it became clear that the panels were all using the terms used in pulmonary TB for EPTB. However, because the disease is different for each organ system, individuals were using the terms loosely, and the lack of clarity around treatment end-points and when to classify an EPTB patient as successfully treated or requiring further treatment sometimes caused confusion during discussions.

Creating outcome definitions to guide treatment decisions in EPTB and aid reporting is challenging due to the uncertainty around diagnostic test accuracy, the fact that diagnostic sampling often requires an invasive procedure and the lack of surrogate markers for microbiological cure. However, the Core Committee appreciated that there was a need to agree on a provisional set of definitions for outcomes to assist the panel with decision-making.

A comprehensive classification of EPTB case definitions and outcome definitions has not previously been attempted, and the Core Committee was aware that given the nature of EPTB, these outcomes will not directly map on to pulmonary TB outcomes. Nevertheless, these definitions are required for transparent and clear decision-making. Each TAC subcommittee worked with the Methodology Support Team to formulate these definitions with reference to the RNTCP's definitions for pulmonary TB cases. The committee appreciated that this was a pragmatic approach to help decision-making and used these outcomes in the development of guidelines.

The Core Committee proposed these working definitions be used to help transparent guidance in the clinical guides. The Core Committee discussed that there needed to be refinements in national reporting for EPTB to capture more detailed information about the epidemiology of the disease and patient outcomes. It is proposed to examine the approach and utility of these working definitions with user guidelines users in 2017, and continue dialogue with the RNTCP in relation to improved reporting for EPTB.

Standardized outcome definitions specific to each form of EPTB have not been established internationally. The guidelines group recognized that this creates problems in the treatment of EPTB patients, particularly when a patient still has on-going symptoms after several months of treatment. Recognizing when first-line treatment is failing is not always

straightforward, and uncertainty around what clinical, radiological, biochemical/ haematological markers suggest successful treatment probably leads to some patients receiving excessively long or repeated treatment courses, or being switched to second-line drugs unnecessarily. Conversely, other patients who are likely to have drug-resistant EPTB may not be recognized as early as they could be, and may not receive the optimum treatment. The TAC subcommittees have attempted to produce outcome definitions that they felt were appropriate through consensus in their expert groups, and some of these are included in the Clinical Practice Points. The setting of standardized outcome definitions for each form of EPTB requires an extensive evidence review and consultation process, and is beyond the scope of this guidelines project. However, the guidelines group recognizes the importance of this task, and supports efforts to achieve this internationally.

Working case definitions[1]

Presumptive case: A patient with symptoms and signs of EPTB who needs to be investigated.

Bacteriologically confirmed case: A patient who has a microbiological diagnosis of EPTB, based on positive microscopy, culture or a validated PCR-based test.

Clinically diagnosed case: A patient with negative microbiological tests for TB (microscopy, culture and validated PCR-based tests), but with strong clinical suspicion and other evidence of EPTB, such as compatible imaging findings, histological findings, ancillary diagnostic tests or response to anti-TB treatment.*

A presumptive case started on ATT empirically, without microbiological testing, should also be considered a clinically diagnosed case (empirically treated). A clinically diagnosed case subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Non-EPTB case: A patient who has been investigated for EPTB and has been diagnosed with a different condition, with no microbiological evidence of EPTB found.

Presumptive relapse: A patient who was declared successfully treated at the end of ATT and now presents again with symptoms and signs of any form of TB.

Bacteriologically confirmed relapse: A patient with presumptive relapse who has microbiological evidence of persisting *Mycobacterium tuberculosis (Mtb)* infection on subsequent diagnostic sampling.

Clinically diagnosed relapse: A patient with presumptive relapse who does not have microbiological evidence of persisting *Mtb* infection on repeat diagnostic sampling, and has no evidence of another disease process.

A patient with presumptive relapse who is started on ATT empirically without repeat microbiological tests should also be considered a clinically diagnosed relapse (empirically treated). A clinically diagnosed relapse subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed relapse.

"Ancillary diagnostic tests" refer to organ system-specific tests such as pleural fluid adenosine deaminase activity (ADA) in pleural TB, or CSF biochemistry and differential cell count in TB meningitis.

Working outcome definitions[1]

Successfully treated: A TB patient who has clinical and radiological evidence of resolution of active TB at the end of ATT.

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[1] These definitions from the Core Committee are provisional, working definitions to help people use these guidelines. Appraisal of their usefulness is anticipated in 2017.

* Compatible histological findings include AFB-negative granuloma. If histological examination reveals AFB-positive histological changes, this is consistent with bacteriological confirmation, and the case should be classified as bacteriologically confirmed.

It is recognized that some people have residual tissue damage that causes on-going symptoms or radiological change (sequelae) despite resolution of TB infection.

Completed treatment: A TB patient who completed treatment without clinical evidence of failure but with no record to show complete resolution by radiological or bacteriological evidence of persisting infection by the last month of treatment, either because tests were not done or because results are unavailable.

Presumptive treatment failure: A patient who has no satisfactory clinical or imaging response to treatment after completing 3–6 months ATT.

At what point in the course of treatment clinicians should consider a patient to have presumptive treatment failure is uncertain, and is likely to vary between forms of EPTB. For example, in TB meningitis it may not be acceptable to wait longer than 3 months before taking action for presumptive treatment failure, whereas persisting with first-line treatment for up to 6 months may be more acceptable in lymph node TB. Further research is necessary to help inform clinical judgement on treatment endpoints.

Bacteriologically confirmed treatment failure: A patient with presumptive treatment failure who has microbiological evidence of persisting *Mtb* infection on repeat diagnostic sampling.

Clinically diagnosed treatment failure: A presumptive treatment failure case who does not have microbiological evidence of persisting *Mtb* infection on repeat diagnostic sampling and has no evidence of another disease process, but has strong clinical suspicion of treatment failure and other evidence of active TB, such as imaging findings.

Sequelae of EPTB

Part of the difficulty in defining treatment end-points in EPTB relates to the development of sequelae as a result of the inflammation and subsequent fibrosis produced in different tissues by Mtb infection. Patients with sequelae may have complete microbiological cure following ATT, but continue to have symptoms. In many forms of EPTB, sequelae can mimic the signs and symptoms of active TB infection, making the decision to stop treatment and declare the patient successfully treated difficult. Examples of sequelae include:

- small volume fibrotic lymph nodes following lymph node TB
- neurological deficits following TB meningitis
- intestinal strictures leading to abdominal pain and vomiting following gastrointestinal (GI) TB
- deformity and back pain following spinal TB.

The clinician must balance the risks of possibly terminating treatment prematurely with the risks of continuing treatment with drugs that have well characterised adverse effects. The INDEX-TB Guideline Group acknowledge that this is an area where further research is needed to provide clinicians with better information and tools to guide their decision-making. New diagnostic technologies may be helpful in future, but at present involvement of experienced specialists is suggested in cases where uncertainty exists.

4.2 Paradoxical reactions and IRIS in EPTB

The phenomenon of paradoxical reaction in TB infection has long been observed in both HIV-positive and HIV-negative TB patients. Multiple definitions of paradoxical reaction exist in the literature, but essentially this term refers to the phenomenon of clinical (or radiological) deterioration of TB lesions, or the development of new lesions in a patient with TB who has initially improved on ATT occurring in the early phase of treatment (during the first 3 months). Paradoxical reactions manifest in a wide variety of ways, and can sometimes be life-threatening or lead to increased disability in EPTB survivors. A review of case reports detailing paradoxical reactions in HIV-negative patients found 122 episodes with 17 different clinical and radiological presentations (Cheng, 2002). In this review,

the paradoxical reaction occurred in a different organ system to the initial TB lesion in 25.4% of cases. Pathogenesis of paradoxical reaction is not yet fully understood, and may occur due to a variety of mechanisms. The predominant theory is that it occurs as a result of an excessive immune response to *Mtb* antigens in patients on effective ATT, involving dysregulation in innate and acquired immune pathways (Garg, 2014).

Immune reconstitution inflammatory syndrome (IRIS) refers to a clinical syndrome observed in HIV-positive people after starting antiretroviral therapy (ART) caused by an inflammatory response to an antigen, thought to be due to the reconstitution of the immune response to that antigen. While extensive research has been done and is ongoing, pathogenetic mechanisms and the best strategies to prevent and treat IRIS are not fully understood. IRIS involving TB infection is common, and can manifest in two principal ways: paradoxical TB-IRIS, where an inflammatory exacerbation of TB symptoms occurs after commencing ATT in patients being treated for TB; and unmasking TB-IRIS, where active TB presents in a patient who has commenced ART (Bell, 2015).

Both paradoxical reaction and IRIS pose significant challenges to physicians treating TB patients in India. Worsening of clinical and radiological features of EPTB in both HIV-positive and HIV-negative patients raises several questions:

- Does the patient have treatment failure due to drug-resistant TB?
- Does the patient have drug-sensitive TB that is not responding to ATT for some reason, such as malabsorption or inadequate adherence to treatment?
- Does the patient have another ongoing disease process?
- Does the patient have a drug fever?
- Should the regimen be changed?
- Should the patient be admitted for inpatient care?
- Are adjunctive treatments required to manage the inflammation?

The INDEX-TB guidelines group acknowledge that these are important questions in EPTB, and that detailed evidence review and further research is needed to support recommendations around these issues. Guidance on the initiation of ART in HIV–TB co-infected patients exists elsewhere (see Section 19 Special groups).

5 Recommendations for the use of Xpert MTB/RIF in EPTB diagnosis

What is Xpert MTB/RIF?

Xpert MTB/RIF is a commercially available diagnostic test for Mycobacterium tuberculosis complex, which uses polymerase chain reaction (PCR) to test specimens for genetic material specific to Mtb, and simultaneously detects a gene which confers resistance to rifampicin, rpoB (Blakemore, 2010). It is manufactured by Cepheid, Sunnyvale, California, USA. Unlike other commercial PCR-based tests, it is a fully automated test using the GeneXpert® platform. The specimen is loaded into a cartridge and all the steps in the assay are then fully automated and contained within the unit. One of the reagents is powerfully tuberculocidal, making the used test cartridges safe to handle outside of a specialist laboratory environment. This allows the test to be brought closer to the clinical setting.

Xpert MTB/RIF was originally designed to test sputum samples from patients with active pulmonary TB, and has been shown to have high accuracy for diagnosing TB in these patients (Steingart, 2014).

What makes the use of Xpert MTB/RIF in EPTB different?

Since its introduction to research settings in 2010, several investigators have tested the accuracy of this test in non-respiratory samples for the diagnosis of various forms of EPTB. There are several a priori reasons why the Xpert MTB/RIF may perform differently with non-sputum samples: Xpert MTB/RIF has a specimen treatment step which is designed to liquefy sputum but this may not be an optimum pre-test processing for non-sputum samples; although the test has a limit of detection of 131 colony forming units per mL, it has been shown to perform less well in paucibacillary disease; as many forms of EPTB require invasive sampling methods, the size and quality of the specimens may affect the sensitivity of the test. In 2016, a new version of Xpert MTB/RIF, Xpert MTB/RIF Ultra, will be introduced with a lower limit of detection. We anticipate that roll-out and accumulation of efficacy data will take time, and so we have summarized the available evidence for the current version of the test.

Why is this a priority question for these guidelines?

MoHFW has engaged with international partners to roll out Xpert MTB/RIF for the diagnosis of pulmonary TB as part of the RNTCP. Members of the INDEX-TB TAC subcommittees recognized the need for evidence-informed guidance on the use of Xpert MTB/RIF for the diagnosis of EPTB in India, because as this test becomes more widely available, clinicians will need to know when to use and how to interpret this test in different forms of EPTB. The advantages of having a rapid test for EPTB must be weighed against the accuracy of the test and the possible harms from misdiagnosis when considering the use of this test.

The evidence considered by the guideline group in making these recommendations was based on a systematic review carried out by Denkinger et al. In this review, diagnostic test accuracy studies using Xpert MTB/RIF and culture for the diagnosis of M. tuberculosis infection in three forms of EPTB were summarized, with pooled estimates of sensitivity and specificity (Denkinger, 2014). As there was little data on sensitivity and specificity of Xpert MTB/RIF for the diagnosis of rifampicin resistance, this was not addressed

in this review, and hence has not been addressed within these recommendations. To ensure the guideline group was able to make recommendations based on the most up-to-date information, a summary of studies published since this review was undertaken in 2013 was also presented to the guidelines group (See Annex 2, online supplementary materials).

WHO has endorsed standard operating procedures for the use of Xpert MTB/RIF for non-respiratory specimens (https://www.ghdonline.org/uploads/GeneXpert_SOP_Xpert_processing_EPTB_specimens_DRAFT.pdf).

5.1 Lymph node TB

Recommendation	Xpert MTB/RIF should be used as an additional test to conventional smear microscopy, culture and cytology in FNAC specimens.
Strength of recommendation	Strong
Evidence	Pooled sensitivity against culture 83.1% (95% CI 71.4–90.7%) (13 studies, 955 specimens with 362 culture positive, low quality evidence) Pooled specificity against culture 93.6% (05% CI 87.9–96.8%) (13 studies, 955 specimens with 362 culture positive, high quality evidence) In a population of 1000 patients with presumptive lymph node tuberculosis (LNTB) where 200 truly have the disease, if treatment was determined only by Xpert MTB/RIF: • 166 (142 to 182) would be correctly treated for TB (low quality evidence) • 34 (58 to 18) with TB would be missed (low quality evidence) • 48 (96 to 24) without TB would be treated (high quality evidence)
Panel's view on advantages of using the test	Quicker diagnosis May lead to fewer patients being treated with ATT when they do not have LNTB (no direct evidence available) Reduced stigma from reduction in overtreatment May identify rifampicin resistance (evidence not formally reviewed)
Panel's view on disadvantages of using the test	Patients with false negative Xpert results may have ATT withheld or stopped inappropriately False negatives may go on to develop disseminated disease False positives exposed to ATT unnecessarily May falsely diagnose rifampicin resistance – harm to patient from side effects of second line drugs, and high cost Cost implications of managing missed cases (repeat diagnostic sampling, repeat hospital/clinic visits) Stigma for patients given a false positive diagnosis Litigation for misdiagnosis

Explanatory notes

The guidelines group considered the evidence for the diagnostic accuracy of Xpert MTB/RIF in lymph node specimens obtained by fine needle aspiration and biopsy. In making the recommendation, the group considered the context of a district level health-care centre, acknowledging that the current basis for diagnosis of lymph node TB under the RNTCP is cytological examination and smear microscopy for acid-fast bacilli of fine needle aspirate from an affected lymph node (FNAC). The group considered whether there was sufficient evidence to recommend that Xpert MTB/RIF replace FNAC as the principal diagnostic test, and concluded that this would be inappropriate given the fact that one in five patients are missed by Xpert MTB/RIF. The group agreed that Xpert MTB/RIF can be useful in confirming a diagnosis in patients suspected of LNTB when considered alongside the results of FNAC, noting that a negative Xpert MTB/RIF test does not rule out LNTB.

Diagnostic investigations should be carried out in the context of quality of care that can assure patient safety, in line with the Guideline's Principles 3 and 4. Xpert MTB/RIF is of use where clinicians have appropriate expertise in carrying out diagnostic sampling from lymph nodes safely and accurately, and where there is access to Xpert MTB/RIF testing in a laboratory with adequate quality assurance.

5.2 TB meningitis

Recommendation	Xpert may be used as an adjunctive test for tuberculous meningitis (TBM). A negative Xpert result does not rule out TBM. Decision to give ATT should be based on clinical features and CSF profile.
Strength of recommendation	Conditional
Evidence	Pooled sensitivity against culture 80.5% (95% CI 59.0–92.2%) (13 studies, 839 specimens with 159 culture positive, low quality evidence) Pooled specificity against culture 97.8% (05% CI 95.2–99.0%) (13 studies, 839 specimens with 159 culture positive, high quality evidence) In a population of 1000 patients with presumptive TB meningitis where 100 truly have the disease, if treatment was determined only by Xpert MTB/RIF result: • 81 (59 to 92) would be correctly treated for TB (low quality evidence) • 19 (41 to 8) with TB would be missed (low quality evidence) • 18 (45 to 9) without TB would be treated (high quality evidence)
Panel's view on advantages of using the test	If Xpert MTB/RIF is positive it is highly likely to be TBM – this could increase access to a reliable diagnosis Quick result Already widely available

Panel's view on disadvantages of using the test	High number of false negatives – significant concern that this could lead to missed or delayed diagnosis, although direct evidence of the impact of Xpert MTB/RIF test results on patient outcomes in TBM is lacking Delayed diagnosis leads to worse outcomes (death) Additional costs

Explanatory notes

The group noted that the stakes are high in the diagnosis of TBM due to the high mortality associated with this disease, particularly when the diagnosis is delayed. Although the sensitivity of smear microscopy of CSF specimens is extremely low and Xpert MTB/RIF has a higher sensitivity than this test, the fact that one in five patients with TBM are missed by Xpert MTB/RIF raised concerns that patients could be harmed by delayed treatment if clinicians relied on a negative result. The guidelines panel concluded that as Xpert MTB/RIF is not sufficiently sensitive for TB meningitis, the decision to give or withhold ATT should not be based on a negative Xpert result alone. A positive Xpert MTB/RIF result may be reassuring due to the high specificity of the test, but it should only be used as an adjunct to other diagnostic methods.

A concentration step in the processing of CSF before using Xpert MTB/RIF appears to increase the sensitivity of the test. In a subgroup analysis, a concentration step involving centrifugation and resuspension of the sample appeared to enhance the sensitivity of Xpert (84.2% (95% CI 78.3–90.1%) versus 51.3% (95% CI 35.5–67.1%) for unconcentrated samples; specificity 98.0% (95% CI 96.7–99.2%) versus 94.6% (95% CI 90.9–98.2%) for unconcentrated samples (Denkinger, 2014).

5.3 Pleural TB

Recommendation	Xpert MTB/RIF should not be used to diagnose pleural TB
Strength of recommendation	Strong
Evidence	Pooled sensitivity against culture 46.4% (95% CI 26.3–67.8%) (14 studies, 841 specimens with 92 culture positive, low quality evidence) Pooled specificity against culture 99.1% (95% CI 95.2–99.8%) (14 studies, 841 specimens with 92 culture positive, high quality evidence) In a population of 1000 patients with presumptive pleural TB where 200 truly have the disease, if treatment was determined only by Xpert MTB/RIF results: • 92 (52 to 136) would be correctly treated for TB (low quality evidence) • 108 (148 to 64) with TB would be missed (low quality evidence) • 8 (40 to 0) without TB would be treated (high quality evidence)

Panel's view on advantages of using the test	• If Xpert is positive it is highly likely to be pleural TB – this could increase access to a reliable diagnosis, although direct evidence of the impact of Xpert MTB/RIF test results on patient outcomes in pleural TB is lacking • May help in avoiding invasive procedures like pleural biopsy (closed and thoracoscopic) • Quick result • Already widely available
Panel's view on disadvantages of using the test	• High number of false negatives – significant concern that this could lead to missed or delayed diagnosis, although direct evidence of the impact of Xpert MTB/RIF test results on patient outcomes in pleural TB is lacking • Delayed diagnosis leads to worse outcomes (pleural thickening, impaired lung function, active pulmonary TB) • Additional costs
Explanatory notes Although the pooled estimate of specificity was high, the sensitivity of Xpert MTB/RIF in pleural fluid specimens was very low, with more than half of all pleural TB patients being missed by this test. The guidelines panel felt that although a positive Xpert result might help if the diagnosis was unclear, there were concerns regarding possible harm to patients associated with reliance on this test, whether the result is positive or negative. Anecdotally, some group members described patients they had treated who had positive Xpert results and were started on ATT, but also had malignancy, diagnosis of which was delayed as the positive Xpert test had led to a diagnosis of pleural TB	

6 Recommendations for use of corticosteroids in EPTB

6.1 In treating tuberculous meningitis in HIV-negative people

Tuberculous meningitis (TBM) is a life-threatening condition affecting adults and children, which can leave survivors with a range of neurological disabilities. The causes of death and disability in TBM are multifactorial. The main pathological mechanisms are persistent or progressive raised intracranial pressure with or without hydrocephalus, arachnoiditis and involvement of optic nerves or optic chiasma leading to visual deficit, cranial neuropathies and vasculitis of the cerebral blood vessels, leading to stroke.

Steroids are thought to reduce inflammation, improve blood flow and reduce cerebral oedema and intracranial pressure. However, the risks associated with steroids include immunosuppression, which is a major concern in the context of an infectious disease, GI bleeding, hyperglycaemia and hypertension, among others. Several randomized controlled trials have been conducted on the effect of corticosteroids in managing TBM. The conclusions from these trials, seen individually, appear inconsistent. One trial (Thwaites G.E., 2004) showed that dexamethasone increases survival rate, but it also raised two questions; do patients who survive because of dexamethasone therapy tend to be left with severe disability, and are there differential effects among subgroups of patients with different degrees of disease severity?

The guideline group reviewed evidence from the updated Cochrane review "Corticosteroids for managing tuberculous meningitis" (Prasad, 2016).

Recommendation	Steroids are recommended for TBM in HIV-negative people. Duration of steroid treatment should be for at least 4 weeks, with tapering as appropriate.
Strength of recommendation	Strong
Evidence	Corticosteroids reduce death from TBM from 41 per 100 people to 31 (27 to 36) per 100 people (nine studies, 1318 participants, high quality evidence). These studies were conducted in a variety of settings, and only one included HIV-positive people (n = 98). Disabling neurological deficit is not common in survivors, and steroids may have little or no effect on this outcome (RR 0.92, 95% CI 0.71 to 1.20; eight trials, 1295 participants, low quality evidence).
Panel's view on advantages of using steroids	Reduced mortality from TBM

Panel's view on disadvantages of using steroids	Adverse effects of steroids such as GI bleeding, bacterial infection, high blood pressure, high blood sugar Increased numbers of survivors with severe disability, although the evidence from the review does not support this
Explanatory notes The panel considered the evidence in the systematic review relevant and applicable to the Indian context, noting that three of the eight studies included were carried out in India, while three others were carried out in South-East Asia. The group noted that the effects may be greater for patients with British Medical Research Council (MRC) Stage I and II, which indicate mild and moderate severity in TBM, but the recommendation should stand for all TBM patients (MRC, 1948). MRC staging is explained in the Clinical Practice Points, Section 2 - CNS TB. Duration of corticosteroids was discussed. The group agreed that there is no clear evidence for any one regimen of steroids and debated what the best option would be. The expert group agreed that steroids should be given for at least 4 weeks and then tapered. Some patients may need longer treatment with steroids, of up to 6–8 weeks, and decision to extend the course of steroids should be made based on disease severity and complications of TBM.	

6.2 In treating tuberculous meningitis in HIV-positive people

The guideline group considered the evidence separately for HIV-negative and HIV-positive people because HIV co-infection is associated with particular complications of TBM disease, and particular adverse events associated with steroid use.

Recommendation	Steroids may be used for TB meningitis in HIV-positive people, where other life-threatening opportunistic infections are absent.
Strength of recommendation	Conditional
Evidence	Corticosteroids reduce death from TB meningitis from 41 per 100 people to 31 (27 to 36) per 100 people (nine studies, 1318 participants, high quality evidence). Eight out of the nine studies either excluded HIV-positive people or did not report HIV status. One study included 98 HIV-positive people out of 545 participants (Thwaites G.E., 2004). A subgroup analysis showed that corticosteroids had no effect on mortality in this group (RR 0.90, 95% CI 0.67 to 1.20), although this result should be interpreted with caution as the authors did not stratify the randomization by HIV status, and the number of HIV-positive participants was small. The very small numbers of events reported in this single study for the outcome disabling neurological deficit mean that we do not know what the effect of corticosteroids is in HIV-positive people for this outcome.

Panel's view on advantages of using steroids	Reduced mortality from TBM
Panel's view on disadvantages of using steroids	• Adverse effects of steroids such as GI bleeding, bacterial infection, high blood pressure, high blood sugar • Increased numbers of survivors with severe disability • Increased morbidity and mortality from opportunistic infections and HIV-associated cancers • Increased adverse drug reactions and interactions with ARVs
Explanatory notes	The group was concerned about the lack of evidence for the use of steroids in people with HIV and TBM. The group noted that there are circumstances where steroids are clearly indicated, for example in cases of raised intracranial pressure/mass effect from a tuberculoma. Steroids are associated with increased risk of serious, life-threatening opportunistic infections in patients with advanced HIV disease. The criteria to be taken into account are stage of TBM disease, evidence of raised intracranial pressure or mass effect, CD4 cell count and presence or absence of other opportunistic infections. Giving long courses of steroids in patients with HIV may be undesirable, especially in patients with advanced HIV disease. Specialist advice in managing such cases is warranted. Important opportunistic infections to rule out include cryptococcal meningitis and cerebral toxoplasmosis. There is evidence that steroids are associated with increased adverse events and disability in patients with HIV-associated cryptococcal meningitis (Beardsley J, 2016).

6.3 In treating TB pericarditis in HIV-negative people

TB pericarditis is a potentially life-threatening form of EPTB, which can also lead to disability in survivors. TB pericarditis is generally characterized by pericardial effusion, which can be immediately life-threatening. Some patients go on to develop constrictive pericardial disease which causes cardiac disability and may be life-threatening, despite the resolution of TB infection. Corticosteroids have long been used to relieve the inflammation that causes the pericardial effusion, although their effect on reducing mortality and rates of long-term constrictive pericardial disease have been controversial. Corticosteroids are associated with certain risks, including immunosuppression, which is a major concern in the context of an infectious disease like TB and in HIV coinfection, as well as gastrointestinal bleeding, hyperglycaemia and hypertension, among others.

The guideline group reviewed evidence summarised from the draft updated Cochrane review "Corticosteroids and other interventions for treating tuberculous pericarditis" (Wiysonge, 2016).

Recommendation	Steroids are recommended for HIV-negative patients with TB pericarditis with pericardial effusion.
Strength of recommendation	Conditional
Evidence	The review included six studies, all from sub-Saharan Africa. The majority of the participants in these trials were HIV-positive; these estimates are based on disaggregated data for HIV-negative participants where possible. Corticosteroids may have no effect on all-cause mortality (RR 0.85, 95% CI 0.64 to 1.11, 810 participants, three studies, low quality evidence), but probably reduce death from pericarditis (RR 0.55, 95% CI 0.31 to 0.98, 810 participants, three studies, moderate quality evidence). Corticosteroids may have no effect on progression to constrictive pericarditis (RR 0.62, 95% CI 0.35 to 1.1, 431 participants, 1 study, low quality evidence). The guideline group further downgraded the quality of the evidence by 1 for indirectness as all the studies took place in sub-Saharan Africa, and because the HIV status of some participants was uncertain. Most of the data comes from one large trial in mainly HIV-positive patients. Steroids were associated with more people developing cancer, mainly HIV-related cancers. The authors note this some of these patients also received immunotherapy with M. indicus pranii. The review team is currently clarifying whether there is an interaction between M. indicus pranii and corticosteroids in relation to cancer with the trial authors.
Panel's view on advantages of using steroids	• Increased survival, although the results of the systematic review do not support this • Reduced incidence of constrictive pericarditis • Reduced need for pericardectomy, although the review did not find clear evidence of this • Reduction of ATT-associated adverse effects, although the results of the systematic review do not support this
Panel's view on disadvantages of using steroids	• Adverse effects of steroids such as GI bleeding, bacterial infection, high blood pressure, high blood sugar • Increased numbers of survivors with severe disability due to constrictive pericarditis

Explanatory notes

The group noted that the effects estimates in the review suggest that steroids have little or no effect on all-cause mortality, but probably do reduce mortality from TB pericarditis. The largest study (which had one-third HIV-negative participants) showed a reduction in the number of participants with constrictive pericarditis at the end of treatment in the analysis of all patients. The GRADE tables are based on data disaggregated into people that are HIV-positive and HIV-negative. Both these analyses give point estimates that show reduced risk of constrictive pericarditis with corticosteroids, although disaggregation means that in the smaller group of participants who were HIV-negative the result is not statistically significant. The group felt that it was likely that the result for HIV-negative participants did not reach statistical significance due to the meta-analysis being underpowered, rather than because corticosteroids had no effect on progression to constrictive pericarditis. The group felt that risk of constrictive pericarditis and associated morbidity was the most important outcome for consideration in making this recommendation. The recommendation therefore only relates to steroid use in patients who present with pericardial effusion caused by TB pericarditis; the group did not recommend steroids for patients presenting with constrictive TB pericarditis.

6.4 In treating TB pericarditis in HIV-positive people

The group considered the evidence for HIV-positive people with TB pericarditis separately, principally because there is a concern about corticosteroids leading to increased risk of HIV-associated adverse events.

Recommen dation	Steroids are recommended for HIV-positive patients with TB pericarditis with pericardial effusion.
Strength of recommendation	Conditional
Evidence	The review included four studies, all from sub-Saharan Africa. The majority of the participants in these trials were HIV-positive; these estimates are based on disaggregated data for HIV-positive participants where possible. Corticosteroids may have no effect on all-cause mortality (RR 1.14, 95% CI 0.88 to 1.49, 997 participants, two studies, low quality evidence), or on death from pericarditis (RR 1.33, 95% CI 0.68 to 2.62, 939 participants, 1 study, low quality evidence). Corticosteroids probably reduce progression to constrictive pericarditis (RR 0.51, 95% CI 0.28 to 0.94, 997 participants, two studies, moderate quality evidence). Corticosteroids may have no effect on HIV-associated opportunistic infections over 2 years' follow-up (RR 1.12, 95% CI 0.82 to 1.53, 939 participants, 1 study, low quality evidence). There may increase the risk of HIV-associated cancer over two years follow-up, but this was from one trial and participants also received M. indicus pranii which may have confounded the result.

Panel's view on advantages of using steroids	• Increased survival, although the results of the systematic review do not support this • Reduced incidence of constrictive pericarditis • Reduced need for pericardectomy, although the review did not find clear evidence of this • Reduction of ATT-associated adverse effects, although the review did not find clear evidence of this
Panel's view on disadvantages of using steroids	• Adverse effects of steroids such as GI bleeding, bacterial infection, high blood pressure, high blood sugar • Increased adverse events associated with HIV such as opportunistic infections and cancer • Increased numbers of survivors with severe disability

Explanatory notes

As for HIV-negative people, the group considered the outcome of greatest clinical significance to be the risk of constrictive pericardial disease following TB pericarditis. Again, the group recognized that there was a lack of evidence of effect on mortality. The evidence for steroids increasing the risk of HIV-associated cancers was also considered. The group felt that this may be of less concern in India as the epidemiology of HIV-associated diseases is different compared with Africa, notably, the prevalence of Kaposi's sarcoma is low. The group concluded that the priority was to reduce rates of constrictive pericardial disease, as this is associated with long-term morbidity and the need for invasive surgery (pericardectomy) for patients, and high cost and resource use for the health-care system. Therefore they made a conditional recommendation to use steroids in HIV-positive people with TB pericarditis with pericardial effusion. Steroids may be even more risky in patients with advanced HIV disease with low CD4 cell counts, and may increase the risk of opportunistic infections and HIV-associated cancers. This risk needs to be balanced with the risk of constrictive pericarditis in HIV-positive people with TB pericarditis.

6.5 In treating pleural TB (irrespective of HIV status)

Pleural TB is one of the most common forms of EPTB. Characterized by pleural effusion, it usually resolves without treatment of any kind, but untreated patients may experience longer duration of the acute symptoms and risk recurrence of active TB at a later point in time (Light, 2010). Pleural TB can be complicated by massive effusion leading to respiratory compromise in the short term; pleural thickening, fibrosis and pleural adhesions causing impaired respiratory function in the medium to long term.

It is though that pleural TB is caused by a delayed-type (type IV) hypersensitivity reaction following mycobacterial infection of the pleura (Rossi, 1987). This explains the tendency towards resolution of the effusion and associated symptoms with or without treatment of the TB infection. There appears to be a spectrum of disease in pleural TB in terms of the extent of the underlying lung infection, which could be important in terms of patient outcomes and the potential for corticosteroids to be effective. The extent of underlying lung infection seems to be an important determinant of outcome (Shu, 2011).

The guideline panel considered evidence based on a rapid update of an existing Cochrane review "Corticosteroids for tuberculous pleurisy" (Engel, 2007). This review was conducted because there

was uncertainty about the efficacy of corticosteroids in reducing the short-term and long-term effects on the acute symptoms of pleural TB and the long-term sequelae. Steroids are associated with several adverse effects, especially in people with HIV, and administering them in the absence of evidence of efficacy may be exposing patients to unnecessary risk.

Recommendation	Steroids are not routinely recommended in pleural TB.
Strength of recommendation	Conditional
Evidence	The review included four studies, all from sub-Saharan Africa. The majority of the participants in these trials were HIV-positive. Corticosteroids may reduce pleural effusions at 4 weeks (RR 0.76, 95% CI 0.62 to 0.94, 394 participants, three studies, low quality evidence), but we don't know whether corticosteroids have an effect on resolution of pleural effusion at 8 weeks (RR 0.72, 95% CI 0.46 to 1.12, 399 participants, four studies, very low quality evidence).
Evidence	Corticosteroids may reduce pleural thickening at the end of follow up (RR 0.69, 95% CI 0.51 to 0.94, 309 participants, four studies, low quality evidence). Corticosteroids may increase the risk of adverse events (RR 2.80, 95% CI 1.12 to 6.98, 586 participants, six studies, low quality evidence). This review found insufficient data to estimate the effect of corticosteroids on respiratory function. The reviewers deemed it inappropriate in this case to attempt to generate separate estimates for HIV-positive and HIV-negative people due to a lack of disaggregated data.
Panel's view on advantages of using steroids	• Faster recovery • Reduced chest X-ray changes at the end of treatment • Return to baseline lung function • Reduced long-term pulmonary disability
Panel's view on disadvantages of using steroids	• Adverse effects of steroids such as GI bleeding, bacterial infection, high blood pressure, high blood sugar • Risk of adverse events, such as HIV-related cancer due to further immunosuppression in HIV-positive people
Explanatory notes Pleural TB is not associated with high mortality; therefore the group felt that the most important outcome to consider was respiratory function. The review found insufficient data addressing this outcome, and the panel felt that the outcomes reported in the review were not appropriate proxy measures for this outcome. The panel noted that chest X-ray appearance at the end of treatment may be important to some patients for social or financial reasons, but otherwise pleural thickening causing chest X-ray changes was not a clinically relevant outcome. Given the lack of evidence of effect on respiratory function, and the risks associated with steroid use, the group made a conditional recommendation against the use of steroids for pleural TB.	

7 Recommendations for duration of treatment in EPTB

There are variations in existing guidelines and in clinical practice around the world about the optimum duration of ATT in the various forms of EPTB. While the 6-month regimen using the first-line drugs rifampicin, isoniazid, pyrazinamide and ethambutol has long been in use for pulmonary TB, there has been considerable uncertainty about duration of treatment for some forms of EPTB. The guidelines group considered the evidence for the optimum length of treatment for three forms of EPTB – lymph node TB, abdominal TB and TB meningitis.

7.1 In peripheral lymph node TB

Lymph node tuberculosis (LNTB) can present with involvement of peripheral, mediastinal and/or abdominal lymph nodes. As well as enlarged lymph nodes perceivable clinically or visualized on chest X-ray, abdominal ultrasound scan or computed tomography (CT) scan, clinical features sometimes include weight loss, fever and night sweats. The problem of persistently enlarged lymph nodes at the end of treatment has vexed clinicians and some practitioners extend treatment duration in such patients, fearing relapse of active TB disease in this group.

Recommendation	Six months ATT standard first-line regimen (2RHZE/4RHE) is recommended for peripheral lymph node TB.
Strength of recommendation	Strong
Evidence	The review included two randomised controlled trials, one from multiple secondary care hospitals in the United Kingdom and another from a single tertiary care hospital in Hong Kong, China. Participants were adults and adolescents with newly diagnosed peripheral and mediastinal LNTB, and HIV status was not reported in either study.
Evidence	There may be no difference between 6-month and 9-month ATT regimens in terms of relapse rates (RR 0.89, 95% CI 0.37 to 2.16, 253 participants, two studies, low quality evidence). There is probably no difference between 6-month and 9-month ATT regimens in terms of successful treatment at the end of follow up (21–55 months) (RR 1.11, 95% CI 0.97 to 1.26, 312 participants, two studies, moderate quality evidence). A review of five prospective cohort studies (706 participants) where patients with residual lymphadenopathy at the end of ATT were followed up demonstrated that relapse in this subgroup of patients was uncommon – 6 cases of relapse were reported across all studies.

Committee's view on advantages of 6-month treatment	• Cure rates and relapse rates are similar in the data collected for 6 months and 9 months (low quality evidence) • Patients more likely to complete shorter regimens • Less exposure to adverse effects of ATT
Committee's view on disadvantages of 6-month treatment	Theoretically, risk of relapse is higher with shorter regimens, but existing evidence is unclear

Explanatory notes

The guidelines group considered evidence from randomized controlled trials comparing 6 months' with 9 months' ATT in terms of outcomes such as relapse after completion of ATT, treatment completion and default. The group noted that the rates of relapse in the 6-month and 9-month groups were similarly very low, although there were concerns that the pooled data was still not sufficiently powered to detect a difference in this uncommon event.

The group noted that all the evidence pertained to peripheral LNTB, and that other factors needed to be taken into consideration for patients with mediastinal or abdominal LNTB, or disseminated TB. No recommendation was made regarding treatment duration in these patients.

A subgroup of patients, dubbed partial responders, have persisting small volume lymphadenopathy (<1 cm) at the end of treatment. The group agreed that the available evidence suggests that few partial responders appear to relapse, and that these patients generally do not require extension of ATT and can be managed by observation only. Further evidence is required to make firm recommendations for this particular group.

While this recommendation applied to adults and children with LNTB, the group noted that the evidence only relates to adults and adolescents, and so providers treating children should bear in mind that this recommendation is based on indirect evidence for children.

7.2 In abdominal TB

Abdominal TB can present with isolated involvement of any of the following sites: peritoneal, intestinal, upper GI (oesophageal, gastroduodenal), hepatobiliary, pancreatic and perianal. The clinical features as well as diagnostic modalities depend on the site of involvement. Internationally, most guidelines recommend treating all types of abdominal TB with the same regimen as for pulmonary TB – a 2-month intensive phase with four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) followed by a 4-month continuation phase with isoniazid and rifampicin. However, the evidence base for this practice is extrapolated from studies of pulmonary TB cases, and direct evidence for the optimum duration of treatment in abdominal TB has been lacking.

Shorter duration of treatment may increase compliance, leading to reduced numbers of relapses as well as the emergence of drug-resistance strains. Furthermore, shorter regimens decrease the risk of anti-TB drug toxicity. Whether a 6-month regimen achieves successful treatment rates as good as with a 9-month regimen without significantly increasing the number of relapses is the key concern for accepting a shorter ATT regimen. The present review aims to evaluate the effects of treatment with the 6-month regimen compared to the 9-month regimen for abdominal TB.

Recommendation	Six months ATT standard first-line regimen is recommended for abdominal TB.
Strength of recommendation	Strong
Evidence	The review included three randomised controlled trials, two from India and one from South Korea, with 328 participants. One trial included both GI TB and peritoneal TB patients, and the other two included GI TB patients only. None of the studies included children, or HIV-positive people. We do not know whether there is a difference in relapse rates in patients treated for 6 months and those treated for 9 months (RD 0.01, 95% CI -0.01 to 0.04, 328 participants, three studies, very low quality evidence).
Committee's view on advantages of 6-month treatment	• Patients more likely to complete shorter regimens • Less exposure to adverse effects of ATT
Committee's view on disadvantages of 6-month treatment	• Theoretically, risk of relapse is higher with shorter regimens, but existing evidence does not support this

Explanatory notes

The guidelines group reviewed the evidence and felt that for new patients with abdominal TB and with low risk of drug resistance, 6 months ATT followed by a period of observation was appropriate. The group recognized the paucity of data to answer this question, but noted particularly that there were very few relapses in both arms across all studies. The group noted that the available evidence came from patients with GI and peritoneal TB, and were concerned that other forms of abdominal TB, while comparatively rare, may require different management. The group agreed that some patients may require extension of ATT and the need for this should be assessed by the treating clinician, with particular regard to the patient's total ATT dosing.

The gastroenterologists in the group pointed out that some patients have lasting sequelae which may cause symptoms mimicking relapse of abdominal TB or failed treatment. It is important to differentiate these patients, who have peritoneal adhesions or luminal strictures from patients with active TB disease. Giving continued ATT in these patients is not required and could be harmful.

7.3 Duration of treatment in TB meningitis

Tuberculous meningitis (TBM) constitutes a medical emergency, and it is essential to start ATT as soon as it is suspected, in order to reduce rapidly progressing, life-threatening outcomes. In contrast to pulmonary TB, there is a lack of standardized international recommendations for treating TBM. This is partly due to the limited existing evidence regarding the optimal choice and dose of anti-TB drugs, as well as the most appropriate duration of treatment for this form of extra-pulmonary TB.

Two main arguments have led to the perception that longer treatment (than for pulmonary TB) is needed for TBM to bring about microbiological cure and prevent relapse. The first one is that the blood-brain barrier hinders the penetration of anti-TB drugs to reach adequate drug concentration in the infected site. The second one concerns relapse rates. When assessing pulmonary TB regimens, relapse rates of 5% are generally considered acceptable (Donald, 2010). However, relapse of TBM is fearsome as it is a life-threatening condition and can lead to severe neurodisability. Thus, whether any risk of relapse is tolerable for TBM is to be considered when establishing TBM regimens. However, longer anti-TB treatments reduce compliance and increase drug toxicity and costs (Van Loenhout-Rooyackers, 2001).

The standard first-line regimen for drug sensitive TBM, according to WHO guidelines, is a 2-month intensive phase with isoniazid, rifampicin, pyrazinamide and ethambutol or streptomycin followed by a 10-month continuation phase with isoniazid and rifampicin – 2 HRZE or S/10 HR (WHO, 2014). Several different regimens are used in current practice, with variations regarding doses, selection of the fourth drug and duration of treatment from 6 to more than 24 months. There are variations in practice regarding the number of drugs used in both the intensive and continuation phases. As an example, the South African regimen consists of a 6-month intensive course with four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) with no continuation phase. A study reviewing the duration of treatment for TBM by comparing case series of both adults and children showed similar completion and relapse rates for 6-month treatment regimens including at least isoniazid, rifampicin and pyrazinamide and longer treatment (van Loenhout-Rooyackers et al., 2001).

Given the potentially devastating outcomes of relapse on the one hand, and the disadvantages of long therapy on the other hand, we performed a systematic review of the literature in an attempt to establish the most appropriate duration of treatment for TBM.

Recommendation	TB meningitis should be treated with standard first-line ATT for at least 9 months.
Strength of recommendation	Conditional
Evidence	The review included six observational (cohort) studies, with two reporting a comparison between short (6 to 9 month regimens) and long (12 months or more) regimens. The studies were from a variety of settings: Turkey, Ecuador, Papua New Guinea, South Africa and two from Thailand. None reported the HIV status of the participants, who were a mix of adults and children. As the data were from a highly heterogeneous set of observational studies, a meta-analysis was not performed. The data were presented to the group in a table demonstrating the absolute numbers of relapsed cases, defaulters, all-cause deaths and deaths after 6 months' treatment across all studies. The evidence was graded as very low quality.

Committee's view on advantages of shorter treatment	• Patients are more likely to complete shorter regimens • Less exposure to adverse effects of ATT • Low numbers of relapses • Good cure rates
Committee's view on disadvantages of shorter treatment	• Longer ATT regimens are associated with poor compliance • Longer regimens expose patients to increased risk of adverse effects of ATT • Concern that shorter regimens may increase the risk of relapse, leading to death or disability
Explanatory notes	The group recognized that there is very low quality evidence for the use of 6 to 9 months versus 12 months or longer ATT in TB meningitis. There is considerable variation in existing guidelines, with the WHO currently recommending 12 months and the RNTCP recommending 9 months for adults and 12 months for children. There is also considerable variation in current clinical practice, with some clinicians present reporting that they are happy to treat for 9 months while others are treating for 12 or 18 months as a minimum. The neurologists in the group were particularly concerned about this question, highlighting that this is an area of clinical equipoise. The paediatricians present were also concerned, as TBM disproportionately affects children and is an important cause of childhood mortality and disability.
	The key factors dictating mortality in TB meningitis may be early treatment and the use of corticosteroids, and the role of treatment duration remains unclear. Extension of ATT may sometimes be indicated, and this should be assessed by the treating clinician on a case-by-case basis. There was disagreement about the optimum duration of treatment, with some group members arguing that 12 months should be the minimum duration recommended; however, the final recommendation was the consensus view of the group. All group members recognized that there is a need for high-quality, large scale randomized trials to answer this question.

8 Research priorities

Relative to pulmonary TB, there is much less research into EPTB. There are several reasons for this, most notably that PTB is transmissible and accounts for four-fifths of all TB disease. However, EPTB remains an important public health problem in India and around the world, and is likely to remain so in the future, especially given the association with HIV co-infection and other forms of immunosuppression.

Several research gaps have been identified during the INDEX-TB guidelines process. Here, we summarize:

a) Some aspects of research priorities related to the specific areas of EBTP addressed by formal GRADE assessment and recommendations in these guidelines;

b) Topics raised during the scoping stage that have not been subject to formal evidence review in this iteration of the guidelines, but may be a priority in subsequent editions.

We also reflect on the type of evidence that would help to answer these questions.

8.1 Key questions from Index-TB 2015 recommendations

The duration of ATT in EPTB

Research into the optimum duration of treatment for all forms of EPTB is lacking. Randomized trials comparing 6-month and 9-month regimens have been carried out for lymph node TB and abdominal TB, but no randomized comparative studies have been conducted directly comparing regimens of different durations containing rifampicin, isoniazid and pyrazinamide (RHZ) for most forms of EPTB. In settings such as India where there are variations in practice, it might be possible to answer these questions using well-conducted prospective cohort studies rather than randomized controlled trials. Life-threatening forms of EPTB, particularly TB meningitis, require particular attention. As the most important concern when determining the length of ATT is the risk of relapse of TB infection, future cohort studies need to recruit large numbers and have follow-up periods lasting several years to determine relapse rates.

Treatment end-points

A crucial area for further research, closely related to duration of treatment, is establishing clear treatment end-points in EPTB. Each TAC subcommittee identified a group of patients in every form of EPTB who have an equivocal response to treatment, and the clinicians in each group described the uncertainty on how to proceed with these patients—whether to continue ATT for longer or to observe. Newer diagnostic modalities such as PCR-based tests and positron emission tomography–computed tomography (PET-CT) are potentially useful in such cases, but further research is needed to establish their role.

Again, long-term follow-up data from cohort studies would help to address some of these questions. With the widespread use of mobile phones and increasing numbers of Indians having access to the Internet, new ways of keeping track of participants in large cohort studies need to be investigated.

The role of the Xpert MTB/RIF test in diagnosing EPTB

As Xpert MTB/RIF is rolled out across high TB burden countries, further diagnostic test

accuracy studies in EPTB are required to better inform the use of this test. The data used to inform the recommendations made in this guideline are based on diagnostic test accuracy studies from a variety of settings using a variety of diagnostic samples and sample processing techniques.

Changes to the test, and the introduction of diagnostic sample processing standard operating procedures endorsed by WHO (WHO, 2014), mean that the accuracy of Xpert MTB/RIF is likely to improve. However, this may not be true for all specimen types and all settings. Future studies are needed to:

- provide estimates of sensitivity and specificity in moderate and high TB burden settings for the latest version of Xpert MTB/RIF;
- provide estimates of sensitivity and specificity in HIV-positive and HIV-negative people with EPTB;
- provide estimates of sensitivity and specificity in forms of EPTB where study data are currently lacking—bone and joint TB, TB pericarditis, urogenital TB, abdominal TB, ENT TB and ocular TB.

There is also an emerging research agenda on how use of Xpert MTB/RIF may improve patient outcomes. Operational and evaluation studies related to its deployment and use in general health services are needed.

The use of corticosteroids in EPTB

In people with TB pericarditis

The updated Cochrane review which informed the recommendation for steroids in TB pericarditis attempted to disaggregate all data by HIV status, because HIV-positive people may be more at risk of adverse events due to pre-existing immunosuppression. The guideline group agreed that rather than reduced mortality during the acute illness with pericardial effusion, the principal goal of giving steroids was to reduce progression to constrictive pericardial disease. Further studies powered to detect an effect of steroids on risk of developing constrictive pericardial disease due to TB pericarditis, with HIV-positive and negative participants, would be useful to inform future recommendations. The largest trial in the systematic review supporting the recommendations included another intervention. M. indicus pranii, an immunotherapy used in the treatment of leprosy, was tested alongside prednisolone in a 2x2 factorial design. In this trial, the number of people developing cancer was higher in the group receiving both prednisolone and M. indicus pranii. These findings are still being discussed with the authors of the review and the investigator of the trial as it seems uncertain whether this effect is attributable to prednisolone, M. indicus pranii, or a synergy between the two.

In people with pleural TB

The studies included in the Cochrane review informing the recommendation against the routine use of steroids in people with pleural TB looked at a variety of short-term outcomes (such as resolution of pleural effusion) as well as some proxy outcomes for lasting lung damage (pleural thickening, pleural adhesions). Future studies investigating the effects of steroids on long-term lung function and disability, as well as adverse events related to steroids and to HIV, are needed to inform future recommendations.

In people with TB meningitis

The Cochrane review update that informed the recommendation in this guideline concluded that there was high quality evidence of reduced mortality in HIV-negative TBM patients who received corticosteroids, and that there was low quality evidence of no effect on disability among survivors. Given this clear benefit in terms of reduced mortality, further placebo-controlled studies of corticosteroid use in TBM would not be ethical. However, further research would be beneficial to address the following:

- Effects of corticosteroids in HIV-positive people with TBM, with long-term follow up of survivors to identify HIV-related adverse events;
- Optimum choice of corticosteroid and dosing regimen. As some corticosteroid

related adverse effects are dose-dependent, it would be helpful to know the optimum regimen for effectiveness and reduced adverse events.

8.2 Key questions identified during INDEX-TB scoping

Several topics were identified during the scoping phase for this guideline that we did not have the time to address with formal evidence review. These include the following:

- Empirical treatment of EPTB
- Tuberculin skin testing in EPTB
- PCR-based diagnostics for EPTB
- Radiological imaging for diagnosis in EPTB (including USS, CT, MR and PET)
- Interventions to improve diagnosis in children with suspected EPTB
- Duration of treatment in EPTB (TBM, abdominal TB and LNTB in progress)
- Diagnostic algorithms in EPTB – impact on patient-important outcomes
- Diagnosis of EPTB in people living with HIV, including EPTB immune reconstitution
- Diagnosis and management of drug-resistant EPTB
- Interventions to improve adherence to treatment in EPTB
- Diagnosis and management of paradoxical reactions in EPTB
- Treatment end-points in EPTB
- Radiological imaging for assessing treatment success in EPTB
- Markers of treatment failure in EPTB
- Surgical management in EPBT (particularly in bone and joint, pericardial and urogenital TB)
- Treatment of EBPT in people with chronic kidney and liver disease
- Operational interventions to improve pharmacovigilance and promote safe prescribing in EPTB.

The TAC subcommittees also identified research topics that were specific to particular forms of EPTB.

Several of these topics could be addressed through collaborative efforts between the RNTCP, the medical colleges and specialist centres and international partners such as the Union and the WHO. The RNTCP is well placed to initiate collaborative projects across India to further this research agenda in a coordinated fashion. The guideline group recognized that enhanced operational data collection through the RNTCP could provide evidence to assist with some of these questions, and establishing large-scale cohort studies in collaboration with providers across India could prove fruitful, but would require significant systems strengthening and planning to be successful. One important factor in addressing the burden of EPTB in India is establishing reliable baseline data collection for all forms of EPTB, so that priorities can be set in accordance with accurate prevalence data.

Working case and outcome definitions in EPTB

Throughout the guidelines process, all members of the guidelines group noted the difficulties arising from a lack of standardized case definitions and outcome definitions in EPTB (see Section 4). This is a challenging task, given the difficulties with diagnosis and determining treatment end-points in each form of EPTB; however, inconsistencies in definitions compound the problems in carrying out research and interpreting research findings, reporting cases to the national programme and treating patients. In Section 4 of this document, generic case and outcome definitions for EPTB were laid out in order to standardize the language in the guidelines.

Further evidence review and consultation work is required internationally to establish definitions that clinicians, researchers, policy makers and patients can recognize and use.

An evaluation of the experiences of the working definitions with clinicians is anticipated in 2017.

Part 1 References

Beardsley J, Wolbers M, Kibengo FM, Ggayi AM, Kamali A, Cuc NTK, et al. for the CryptoDex Investigators (2016). Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis. N Engl J Med. 374:542–54.

Bell LCK, Breen R, Miller RF, Noursadeghi M, Lipman M (2015). Paradoxical reactions and immune reconstitution inflammatory syndrome in tuberculosis. Intl J Infect Dis. 32:39 –45.

Blakemore R, Story E, Helb D, Kop J, Banada P, Owens MR, et al.(2010). Evaluation of the analytical performance of the Xpert MTB/RIF assay. J Clin Microbiol. 48(7):2495–501.

Cheng VC (2002). Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients. Eur J Clin Microbiol Infect Dis. 21(11):803–9.

Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M, Steingart KR, et al. (2014). Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. Eur Respir J. 44(2):435–46.

Donald P (2010). The chemotherapy of tuberculous meningitis in children and adults. Tuberculosis (Edinburgh), 90(6):375–92.

Garg RK, Malhotra HS, Kumar N (2014). Paradoxical reaction in HIV-negative tuberculous meningitis. J Neurol Sci. 340 (1–2):26–36.

Guyatt Gordon H, O. A.-Y. (2008). Going from evidence to recommendations. British Medical Journal, 336, 1049. http://www.gradeworkinggroup.org/publications/. Retrieved July 2015

Higgins JPT, Altman DG, Sternen JAC (2011). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration.

Light R (2010). Update on tuberculous pleural effusion. Respirology. 15(3):451–8.

MRC. (1948). Medical Research Council Report. Streptomycin treatment of tuberculous meningitis. Lancet. 1:582–96.

Prasad K, Singh MB, Ryan H. (2016). Corticosteroids for managing tuberculous meningitis. Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD002244. DOI: 10.1002/14651858.CD002244.pub4.

Rossi GA, Balbi B, Manca F (1987). Tuberculous pleural effusions. Evidence for selective presence of PPD-specific T-lymphocytes at site of inflammation in the early phase of the infection. American Review of Respiratory Disease. 136(3):575–9.

Sharma SK, Mohan A (2004). Extrapulmonary tuberculosis. Ind J Med Res. 120(4):316–53.

Shu CC, Wang JT, Wang JY, Lee L, Yu C (2011). In-hospital outcome of patients with culture-confirmed tuberculous pleurisy: clinical impact of pulmonary involvement . BMC Infectious Diseases. 11:46.

Sreenivas A, Rade K, Sachdeva KS, Ghedia M, Parmar M, Ramachandran R, et al. (2014). Standards for TB Care in India. New Delhi: World Health Organization Country Office for India.

Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N (2014). Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Systematic Rev. (1):CD009593. doi: 10.1002/14651858.CD009593.pub3.

TB CARE I (2014). International Standards for Tuberculosis Care, third edition. The Hague: TB CARE I.

The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) (2015). 2015 ESC Guidelines for the diagnosis and management of pericardial diseases. European Heart Journal. 36:2921–64.

Thwaites GE, Nguyen Duc Bang ND, Nguyen Huy Dung NH, Hoang Thi Quy HT, Do Thi Tuong Oanh DTT, Nguyen Thi Cam Thoa NTC, et al. (2004). Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med. 351(17):1741–51.

Van Loenhout-Rooyackers JH, Keyser A, Laheij RJ, Verbeek AL, van der Meer JW (2001). Tuberculous meningitis: is a 6-month treatment regimen sufficient? Int J Tuberc Lung Dis. 5(11):1028–35.

WHO (2010). Treatment of Tuberculosis: Guidelines, fourth edition. Geneva: World Health Organization.

WHO (2014). Guidance for national tuberculosis programmes on the management of tuberculosis in children, second edition. Geneva: World Health Organization.

WHO (2014). WHO Handbook for Guideline Development, second edition. Geneva: World Health Organization.

Wiysonge, C. N. (2016). Corticosteroids and other interventions for treating tuberculous pericarditis. Cochrane Database of Systematic Reviews , publication pending

Part 2

Clinical practice points

9 Ocular TB

Ocular infection with M. tuberculosis is uncommon, but the difficulty of diagnosing it means that prevalence estimates may not be reliable. Incidence of TB as a cause among patients presenting with uveitis has been reported at 10.1% in north India (Singh, 2004), but much lower in south India at 0.6% (Biswas, 1996-1997). This discrepancy may be due to several factors, including access to ophthalmology services, evolution of diagnostic criteria, description of new diagnostic entities and improvement in diagnostic tools.

Ocular TB can cause moderate to severe visual impairment in up to 40% of affected eyes (Basu, 2014). Delay in diagnosis and treatment can result in chronic inflammation and loss of vision. Improving access to a diagnosis is therefore a high priority.

9.1 Patients who should be referred for assessment by an ophthalmologist

Patients with symptoms consistent with anterior, intermediate, posterior or pan-uveitis, including the following:

- Red eye
- Blurred vision
- Photophobia
- Irregular pupil
- Eye pain
- Floaters
- Flashing lights (photopsia).

9.2 Patients who should be investigated for ocular TB

Presumptive ocular TB	A patient with one of the following clinical presentations: • Granulomatous anterior uveitis • Non-granulomatous anterior uveitis, not associated with any other known clinical entity, e.g. HLA-B27 • Intermediate uveitis, with/without healed/active focal lesions • Posterior uveitis, including subretinal abscess, choroidal/disc granuloma, multifocal choroiditis, retinal periphlebitis and multifocal serpiginous choroiditis • Panuveitis • Rarely, scleritis (anterior and posterior), interstitial and disciform keratitis *Note:* Extraocular TB disease is often absent in ocular TB patients, and patients do not usually have systemic symptoms of fever and weight loss.

9.3 Diagnosis

Test	Patients	Comments
X-ray of chest	All	All patients presenting with symptoms consistent with TB should have a chest X-ray. CT of the chest may also be useful as this test is more sensitive for evidence of current or previous pulmonary TB infection. Evaluation by a TB specialist or general physician as well as the ophthalmology team is advised.
HIV test	All	EPTB is associated with HIV infection. All patients should be offered integrated counselling and testing.
Ocular imaging	All	Depending on the presentation, imaging is required to assess extent or complications of disease, and to monitor response to treatment. Fundus photography, fluorescein angiography, optical coherence tomography, or multimodal imaging may be required.
Tuberculin skin testing (Mantoux test)	All	Although usually not recommended in active TB disease, tuberculin skin testing (TST) may be useful in establishing supporting evidence of TB infection. While a positive result may support the diagnosis of TB, a negative test cannot rule out TB. Clinical evaluation by a TB specialist or general physician as well as the ophthalmology team is advised.

Test	Patients	Comments
PCR testing of vitreous or aqueous specimens	Selected	Various PCR-based tests exist for TB, but evidence of diagnostic test accuracy for the diagnosis of ocular TB is highly variable. Whilst the accuracy of these tests seems to vary significantly, they are often the only specific test that may identify ocular TB. Further evidence is needed to determine which tests are the most accurate, and when they are best used. Vitreous/aqueous humour sampling must only be carried out by a trained practitioner.
Biopsy	Highly selected	Biopsy of the structures of the eye is highly invasive and carries the risk of exacerbating visual loss. However, in rare cases such as scleral or iris granuloma, it may be the only way to make a diagnosis and ensure effective treatment. Specimens should be sent for histopathology with staining for acid-fast bacilli (AFB) and culture.

9.4 Diagnostic categories

Possible ocular TB: Patients with the following (1, 2 and 3 together or 1 and 4) are diagnosed as having possible ocular TB:

1. At least one clinical sign suggestive of ocular TB (see Presumptive ocular TB), and other aetiology excluded
2. X-ray/CT chest not consistent with TB infection and no clinical evidence of extraocular TB
3. At least one of the following:
    - Documented exposure to TB
    - Immunological evidence of TB infection
4. Molecular evidence of Mtb infection.

Clinically diagnosed ocular TB: Patients with all the following (1, 2 and 3 together) are diagnosed as having probable ocular TB:

1. At least one clinical sign suggestive of ocular TB (see presumptive ocular TB), and other aetiologies excluded
2. Evidence of chest X-ray consistent with TB infection or clinical evidence of extraocular TB or microbiological confirmation from sputum or extraocular sites
3. Documented exposure to TB and/or immunological evidence of TB infection.

Bacteriologically confirmed ocular TB: A patient with at least one clinical sign of ocular TB, along with microbiological (smear/culture) or histopathological confirmation of Mtb from ocular fluids/tissues.

9.5 Treatment

Treatment of ocular TB

All patients with possible ocular TB, clinically diagnosed ocular TB or bacteriologically confirmed ocular TB need treatment with ATT with or without other adjuvant therapy.

Aims

1. Protect visual function
2. Control ocular inflammation
3. Prevent recurrence of inflammation.

First line treatment for adults and children with ocular TB	Drugs	RHZE/4RHE Corticosteroids (local or systemic) and other immunosuppressants are often used as adjunctive treatments. There is insufficient evidence currently to make specific recommendations regarding their use.
	Duration	Total treatment duration: 6 to 9 months
	Referral	All patients with presumptive ocular TB must be referred to an ophthalmologist for assessment and treatment.
	Follow up	Regular review during and after treatment. Suggested methods for monitoring treatment: • Clinical evaluation (slit-lamp biomicroscopy and indirect ophthalmoscopy) • Fundus photography • Fundus autofluorescence • Optical coherence tomography
	Response to treatment	Treatment outcomes in ocular TB need to be defined differently, as microbiological confirmation of TB is rarely possible in ocular tissues. Thus, treatment success or failure is primarily guided by the level of inflammation seen inside the eye. • **Remission:** Inactive disease for at least 3 months after discontinuing all therapy based on the Standardization of Uveitis Nomenclature recommendations (Jabs, 2005). • **Treatment failure:** No decrease in inflammation, or less than a two-step decrease in level of inflammation after 3 months of ATT (inflammatory scores of fundus lesions such as retinal perivasculitis or multifocal serpiginous choroiditis are not yet defined and are left to the judgment of treating physicians). • **Relapse:** An increase in the level of inflammation after complete remission (at least two-step increase).

	Approach to treatment failure	1. Rule out non-TB aetiology: detailed ocular and systemic evaluation, ancillary tests 2. Rule out paradoxical reaction: usually occurs within 2 months of starting ATT; responds to continuation or escalation of corticosteroid therapy 3. Rule out drug resistance: once previous two points have been ruled out, check contact with MDR TB patient; if facilities exist, consider ocular fluid sampling for molecular diagnosis of drug resistance
	Surgery	The main indications for surgery in ocular TB are as follows: • Complications of retinal vasculitis—retinal neovascularization, vitreous haemorrhage, tractional or combined retinal detachment, epiretinal membrane • Diagnostic vitrectomy when conventional methods fail to establish diagnosis • Non-resolving vitreous inflammation • Visually significant vitreous floaters after completion of medical therapy • Management of complications of uveitis such as cataract and glaucoma

10 Central nervous system TB

10.1 Background

TB can cause meningitis (TBM), cerebral and spinal tuberculoma, myelitis and arachnoiditis. These are all severe forms of TB associated with high incidence of death or disability.

Exact prevalence of CNS TB in India is not known, but it accounts for an estimated 1% of all cases of TB, which equates to around 17 000 cases in India in 2014 (WHO, 2015). Case fatality rates for the most common form of CNS TB, i.e. TB meningitis, are high. All forms of CNS TB can leave survivors with long-term disabilities.

10.2 Patients who should be investigated for TBM

TBM is a medical emergency. Early diagnosis and prompt treatment with ATT saves lives.

TBM classically presents as subacute or chronic meningitis with symptoms developing over days or weeks. Evidence suggests that patients presenting with less than 5 days of symptoms are more likely to have bacterial or viral meningitis than TBM (Thwaites, 2009). However, it should be noted that TBM can present acutely with a short duration of illness, and this acute presentation is not uncommon.

Presumptive TBM	Any patient with clinical features of meningitis in the form of fever, headache, neck rigidity and vomiting, with or without altered sensorium and associated focal neurological deficits for a period of 5 days or more

Common symptoms	Less frequent symptoms	Uncommon symptoms
Headache	Confusion	Photophobia
Fever	Cranial nerve palsy	Paraparesis
Vomiting	Hemiparesis	Seizures
Neck stiffness	Coma	
Weight loss		

10.3 Diagnosis

The most important aspect of TBM diagnosis is to suspect TBM and act quickly to refer the patient to a centre where they will receive:

- rapid access to CSF examination
- rapid access to neuroimaging
- prompt treatment with ATT and supportive care.

Diagnostic workup

Test	Patients	Comments
Lumbar puncture for CSF	All (unless absolutely contraindicated)	CSF findings typical of TBM: lymphocytic (more rarely neutrophilic) pleocytosis with low serum:CSF glucose ratio and high protein. Additional tests on CSF are summarized in the table below.
HIV testing	All	HIV infection predisposes people to CNS infections, including TBM. All patients should be offered integrated counselling and testing.
Chest X-ray	All	Chest X-ray may assist the diagnosis with evidence of current or previous pulmonary TB infection.
CT brain with contrast	All	High priority for comatose or deteriorating patients helps to diagnose hydrocephalus, which may require neurosurgical intervention.
MRI brain with contrast	Selected	Magnetic resonance imaging (MRI) provides more detailed information than CT. May be of assistance where diagnosis is uncertain, in complex cases, and in HIV-positive patients.

CSF sampling and testing

Lumbar puncture should be performed in every patient (unless there are contraindications to the procedure) and CSF should be analysed with the following tests given in the table below. Other tests may also be indicated in some circumstances.

At least 6 mL of CSF should be collected for adults, 2–3 mL for children.

Results available	Tests
Hours to days	- Cell count and differentiation - Protein - CSF:serum glucose ratio (serum samples need to be taken alongside the CSF) - Gram stain for bacterial meningitis (e.g. N. meningitidis, S. pneumonia) - AFB stain for TB - India ink and cryptococcal antigen testing for cryptococcal meningitis - Xpert MTB/RIF can be used as an adjunctive test in the diagnosis of TBM, but a negative test does not rule out a diagnosis of TBM. If it is safe to obtain, 1 mL of CSF is optimal for this test (Nhu, 2014). - Other PCR-based tests for Mtb are available, but diagnostic accuracy is highly variable. - PCR-based tests for viral pathogens, as appropriate
Days	- Bacterial culture, speciation and drug susceptibility testing - Cytological examination for malignant cells
Days to weeks	- Fungal culture, speciation and drug susceptibility testing - Mycobacterial culture, speciation and drug susceptibility testing

Recommendation

Xpert may be used as an adjunctive test for TBM. A negative Xpert result does not rule out TBM. The decision to give ATT should be based on clinical features and CSF profile.

(Conditional recommendation, high quality evidence for specificity estimate, low quality evidence for sensitivity estimate).

Other tests

Interferon-gamma release assays such as ELISPOT and Quantiferon Gold are designed for the diagnosis of latent TB, and are not indicated in the diagnosis of TBM. Currently, the use of these tests is restricted in India.

Adenosine deaminase (ADA) is not useful in the diagnosis of TBM.

MRC staging

The British Medical Research Council (MRC) staging is a widely recognized system for classifying disease severity in TBM (MRC, 1948).

Stage I Mild cases, for those without altered consciousness or focal neurological signs

Stage II Moderate cases, for those with altered consciousness who are not comatose and those with moderate neurological signs, e.g. single cranial nerve palsies, paraparesis, and hemiparesis

Stage III Severe cases, for comatose patients and those with multiple cranial nerve palsies, hemiplegia or paraplegia, or both.

10.4 Treatment

Aims:

- Microbiological cure
- Prevention of complications, morbidity and mortality
- Management of treatment complications

First line treatment for adults and children with TB meningitis	Drugs	Intensive phase: 2 months RHZE The was the recommendation made by the INDEX-TB Guidelines Panel at the INDEX-TB meeting in 2015, based on the evidence summarized in Annex 2 in the online supplementary materials, as follows: Continuation phase: at least 7 months RHE The Technical Advisory Sub-committee for CNS TB, who drafted these clinical practice points, expressed a preference for an alternative approach to the continuation phase that differs from the INDEX TB recommendation in two ways: a) recommend the use of pyrazinamide instead of ethambutol; and b) treatment to be continued in all patients for a total of at least 12 months. The current RNTCP guidance is to use ethambutol in the continuation phase because of the risk of isoniazid mono-resistance. The variations in expert opinion reflect the uncertainty regarding the optimum choice of regimen, and further research is required. If vision is impaired or cannot be assessed, use streptomycin instead of ethambutol in the intensive phase. Use of streptomycin in pregnant women, and patients with kidney impairment or hearing loss should be avoided.
	Duration	Recommendation: TB meningitis should be treated with standard first-line ATT for at least 9 months (conditional recommendation, very low quality evidence) Note: see Drugs section above.

	Referral	ATT should be started as early as possible in all cases of TBM. Presumptive TBM patients should be referred to a secondary/tertiary care centre immediately. If referral and transfer is likely to take more than 24 h, or if the patient is critically ill, treatment with ATT may be started prior to transfer. Where possible, CSF sampling prior to initiation of treatment is preferred, as ATT reduces the accuracy of the diagnostic tests for TB, but this should not unduly delay initiation of ATT.
	Follow up	Patients should be assessed for clinical response at the end of the treatment period and at intervals for 2 years. Sustained resolution of clinical features including headache and fever should guide stopping of ATT. Residual neurological deficits may be permanent and should not be used to assess for active TB infection.
Drug-resistant cases		Drug-resistant TBM should be suspected in patients with poor response to standard ATT and history of exposure to MDR-TB.
Steroids	HIV-negative patients	Recommendation: Steroids are recommended for TB meningitis in HIV-negative people. Duration of steroid treatment should be for at least 4 weeks, with tapering as appropriate (strong recommendation, high quality evidence)
	HIV-positive patients	Recommendation: Steroids may be used for TB meningitis in HIV-positive people, where other life-threatening opportunistic infections are absent (conditional recommendation, low quality evidence) Important opportunistic infections to consider include cryptococcal meningitis and cerebral toxoplasmosis. There is evidence that steroids are associated with increased adverse events and disability in patients with HIV-associated cryptococcal meningitis (Beardsley J, 2016).
	Suggested regimen	In hospital: intravenous dexamethasone 0.4 mg/kg/24 h in 3–4 divided doses may be preferred with a slow switch to oral therapy and taper. Currently, there is insufficient evidence to recommend one formulation/ regimen of steroids over any other.
Surgery		Patients who develop hydrocephalus with raised intracranial pressure may require CSF diversion by ventriculo-peritoneal shunt insertion. Such patients should be managed in settings with neurosurgical services.

10.5 Complications

Complication	Clinical features	Management
Hydrocephalus	Symptoms and signs of raised intracranial pressure (ICP) such as worsening headache, vomiting, ocular palsies, decreasing conscious level, papilloedema Urgent neuroimaging is needed to assess cause of raised ICP if patient is deteriorating	Ventriculo-peritoneal shunt insertion is indicated for patients at all stages of severity with hydrocephalus or raised ICP not responding to ATT and steroids. Early shunt insertion may be beneficial. Treatment with diuretics such as mannitol should be limited to emergency management, aimed at decreasing ICP until shunt insertion can be performed. External ventricular drainage is not usually recommended, unless surgery is contraindicated or urgent CSF diversion is indicated to buy time before a shunt can be inserted.
Stroke	Focal neurological deficit consistent with a stroke syndrome. Stroke in TBM may not be clinically apparent and may be diagnosed on neuroimaging. Stroke is a significant contributor to disability following TBM.	Most effective treatment strategy is uncertain and evidence is lacking. Acute stroke or evidence of on-going vasculopathy may warrant continuation of steroids, usually intravenously. There is some evidence that aspirin may prevent stroke in TBM in adults. Further trials in adults and children are on-going.
Optico-chiasmatic arachnoiditis	Visual loss, which may arise during treatment with ATT, or on the withdrawal of corticosteroids Characteristic CT and MRI findings	Most effective treatment strategy uncertain Steroid therapy is the first-line treatment, using intravenous dexamethasone. Pulsed methylprednisolone or oral thalidomide has been used in some case series for patients not responding to steroids. Microsurgical intervention and intrathecal hyaluronidase are controversial and not currently recommended.

Complication	Clinical features	Management
Seizures	Generalized seizures secondary to encephalopathy Tuberculoma or infarction may cause secondary generalized seizure	Acute management with anti-epileptic drugs as per local protocol for seizure The use of anti-epileptic drugs alongside ATT must be carefully managed due to the potential for drug interactions and increased risk of liver dysfunction with multiple hepatotoxic agents. Prophylactic anti-epileptic drugs are not required in TBM patients who have not had seizures during their clinical course. Continued treatment with anti-epileptic drugs may be necessary in patients with recurrent seizure and decisions about duration and withdrawal should be individualized to the patient by the treating specialist.

10.6 CNS tuberculoma

Tuberculoma of the central nervous system (CNS) is less common than TBM and has lower morbidity and mortality, but remains an important cause of intracranial space-occupying lesions. Tuberculoma can arise anywhere in the brain or spinal cord, and may present as a mass lesion causing focal neurological deficits depending on anatomical location and/or seizure, or may be found in concurrence with TBM.

Presumptive CNS tuberculoma	Any patient presenting with seizures, headache, fever or focal neurological deficits with neuroimaging features consistent with a mass lesion of inflammatory nature.

Patients with presumptive CNS tuberculoma should be referred for investigation and treatment by a specialist. Neuroimaging, particularly multimodal MRI, with interpretation by a specialist is indicated to characterize the lesion(s).

Diagnosis

Diagnosis is based on the following:

- Patient history – previous TB disease and contact with a pulmonary TB patient make tuberculoma more likely.
- Clinical findings – active TB elsewhere in the body makes tuberculoma more likely. Chest X-ray should be performed. Other imaging such as CT chest should be considered to look for TB, identify other lesions amenable to biopsy, and look for features suggestive of other pathology such as malignancy.
- HIV status – HIV testing is important as HIV-positive people are at increased risk, not only of tuberculoma, but also other diagnoses such as

coccidiomycosis and toxoplasmosis. Other causes of immunosuppression are also important.

- MRI/CT scan findings consistent with tuberculoma
- CSF findings – CSF can be normal, or show features similar to TBM. The sensitivity of culture for Mtb is low, and PCR-based tests require further investigation in tuberculoma.

Stereotactic or open biopsy is rarely performed as this is a highly invasive procedure, but it may be indicated in patients where the diagnosis remains very uncertain after non-invasive tests, or there is no response to ATT.

The differential diagnosis for tuberculoma includes, but is not limited to:

- neurocysticercosis
- pyogenic abscess
- metastatic lesions from a primary malignancy elsewhere in the body, e.g. lung cancer
- glioma
- demyelinating lesion.

Treatment

The aims of treatment are:

- Resolution of neurological and constitutional symptoms
- Resolution of the lesion on neuroimaging.

There is a lack of evidence as to the optimum duration of treatment in CNS tuberculoma. The expert group suggested that ATT should be given for 9 to 12 months initially, with repeat neuroimaging at 3 months and 9–12 months to monitor response to treatment. Treatment should then be tailored to the clinical and radiological response of the patient.

Paradoxical reaction with increase in the size and number of lesions can occur, usually in the first 3 months of treatment, and requires treatment with steroids as well as continued ATT.

Treatment failure should be suspected when lesions either increase in size or fail to reduce in size after 3 to 6 months ATT despite appropriate dosing and good adherence. The treating clinician needs to weigh the benefits and risks of biopsy against those of commencing second-line treatment empirically for suspected MDR-TB, or persisting with first-line treatment for suspected paradoxical reaction. If a biopsy is performed due to strong consideration of an alternative diagnosis, the specimens should be sent for: a) histopathology with staining for AFB; b) Mtb culture and drug susceptibility testing; c) other microbiological tests as indicated by the case history.

11 Ear, nose and throat TB

Head and neck TB constitutes 10–15% of all EPTB cases, with the majority of these cases being cervical lymph node TB, and <1% extra-nodal head and neck TB cases. Malignancy is the most important differential diagnosis in ear, nose and throat (ENT) TB and diagnostic approaches must take this into account.

11.1 Presentation

Laryngeal TB

Presents with hoarse voice and pain on swallowing, mimicking non-specific laryngitis or laryngeal carcinoma. Can be infectious, unlike other forms of EPTB.

Ear TB

Usually presents with chronic suppurative otitis media – painless discharging ear not responding to antibiotics, with hearing loss disproportionate to the clinical appearance. Can be complicated by facial paralysis, promontorial fistulae and inner ear involvement, which may also occur in TB meningitis.

Oral TB

Multiple presentations as TB can affect any part of the mouth. Lesions are usually ulcerative and painless, sometimes with a necrotic base and discharge.

Oropharyngeal TB

TB of the tonsils presents with asymmetrical enlargement with ulceration, mimicking carcinoma. TB of the cervical spine can extend to cause retropharyngeal abscess presenting with pain on swallowing, and complicated by airway compromise which requires emergency intervention.

Sinonasal TB

Very rare, usually presents with nasal obstruction, bleeding and runny nose and lymphadenopathy

Salivary gland TB

Very rare; usually associated with immunosuppression. Presents with swelling

Thyroid gland TB

Very rare; multiple presentations from isolated nodules to thyrotoxicosis.

11.2 Diagnosis

Test	Patients	Comments
X-ray of chest	All	All patients presenting with symptoms consistent with TB should have a chest X-ray.
HIV test	All	EPTB is associated with HIV infection. All patients should be offered integrated counselling and testing.
Incisional or punch biopsy from the affected site	All	Incisional or punch biopsy from the affected site, carried out by a trained specialist practitioner is the preferred method of diagnostic sampling for ENT lesions, and should be sent for: • histopathology • staining for acid-fast bacilli (fluorochrome or ZN staining) • culture for *Mtb*
Fine needle aspiration cytology (FNAC)	Selected	FNAC may also be used, particularly where there is lymph node involvement or an abscess, with aspirate sent for: • microscopy for AFB • Xpert MTB/RIF • cytology • culture for *Mtb*
CT or MR imaging of the head and neck	Selected	May be required to further characterize the disease, look for involvement of bone/deep structures, and aid in diagnosis. This should be requested and interpreted by a specialist.

11.3 Treatment

First line treatment for adults and children with ENT TB	Drugs	2RHZE/4–7RHE Steroids have no role in the treatment of ENT TB, and should be avoided as they may do harm.
	Duration	Total treatment duration: 6 to 9 months All cases involving bone, including all TB otitis media cases, should receive 9 months treatment.
	Referral	All patients with ENT TB, except those who have accessible cervical lymph nodes which are amenable to FNAC, will need referral to ENT specialists for diagnosis.
	Follow up	Monthly follow-up for patients with sinonasal and ear/temporal bone TB is suggested during treatment to assess response and monitor adherence, and after treatment to assess resolution and detect recurrence.
	Surgery	May be indicated in some circumstances to treat complications or for reconstruction of the ear or nose. Where facial nerve palsy complicates tuberculous otitis media, surgical decompression should be considered if there is no improvement after 3 to 4 weeks of ATT (good practice statement). Surgical drainage of retropharyngeal abscess complicating TB of the cervical spine may be considered, but requires specialist judgement. Surgery should be avoided in TB of the salivary glands or thyroid; medical treatment is usually sufficient.

There is little evidence to guide recommendations about the duration of treatment in ENT TB, and so this outline is based on the consensus of the ENT expert group.

11.4 Sequelae

Sequelae are related to tissue destruction. Serious complications result from resorption of facial bone. Airway compromise resulting from ankylosis is a life-threatening complication, which requires emergency surgical treatment.

TB of the ear can lead to permanent hearing loss, facial nerve palsy and balance problems (vestibulopathy). It can be complicated by infection of the underlying bone and meningitis from spread into the central nervous system.

Sinonasal TB can lead to deformity of the nose, and can be complicated by involvement of the eye socket.

12 Lymph node TB

Lymph node TB (LNTB, also called TB lymphadenitis) refers to Mtb infection of the lymph nodes, and may occur as the sole manifestation of TB infection, or alongside pulmonary or miliary TB. LNTB is the most common form of EPTB in India, accounting for around 35% of EPTB cases (Sharma S.K., 2004). Total estimated incidence of LNTB was 30.8 per 100 000 population in India in 2013 (RNTCP, 2014).

Care should be taken to identify patients who need to be investigated for LNTB, as there are multiple differential diagnoses for chronic lymphadenopathy.

TB of the deep lymph nodes in the chest (mediastinal TB) may present with cough or shortness of breath. Abdominal LNTB patients may have abdominal pain or distension.

12.1 Patients who should be investigated for LNTB

Presumptive peripheral LNTB	Patients with enlarged lymph nodes (over 1 cm across) in the neck, armpit or groin. Patients may also present with symptoms of fever, weight loss, night sweats and cough
Presumptive mediastinal LNTB	Patients with cough, fever, shortness of breath, weight loss or night sweats who have hilar widening on chest X-ray and/or mediastinal lymphadenopathy on chest CT in the absence of evidence of active pulmonary TB
Presumptive abdominal LNTB	Patients with dull or colicky abdominal pain, abdominal distension, weight loss, night sweats or fever, and evidence of abdominal lymphadenopathy on abdominal ultrasound scan, CT or MR

12.2 Diagnosis

Test	Patients	Comments
X-ray of chest	All	All patients presenting with symptoms consistent with LNTB, to seek for active or previous pulmonary TB
HIV test	All	EPTB is associated with HIV infection. All patients should be offered integrated counselling and testing.

Ultrasound or CT scans of chest and abdomen	Selected	Indicated when diagnosis is not clear, and in HIV-positive people Finding abdominal lymphadenopathy should prompt biopsy to rule out lymphoma as a differential diagnosis.
Fine needle aspiration cytology (FNAC)	All	Send specimen for: a) Xpert MTB/RIF test; b) microscopy and culture for Mtb with drug susceptibility testing; c) Cytology
Excision biopsy	Selected	IF FNAC has been inconclusive, or where malignancy is suspected. Send specimen for: a) Xpert MTB/RIF test; b) microscopy and culture for Mtb with drug susceptibility testing; c) histopathology
Specimens should be taken from the affected lymph nodes prior to commencing ATT. A non-dependent aspiration with Z-technique for manipulating overlying skin by an appropriately trained operator is suggested for superficial lymph nodes. Deep lymph nodes require radiologically-guided sampling. In abdominal LNTB, ultrasound/CT-guided percutaneous FNAC or biopsy is required. In mediastinal LNTB, endobronchial ultrasound-guided FNAC is preferred where facilities exist.		

Recommendation:

Xpert MTB/RIF may be used as additional test to cytology for LNTB (strong recommendation, high quality evidence for specificity, low quality evidence for sensitivity).

Diagnostic definitions

Bacteriologically Confirmed LNTB case	A patient with symptoms and signs of LNTB and has at least one of the following: • positive microscopy for AFB on examination of lymph node fluid or tissue • positive culture of Mtb from lymph node fluid or tissue • positive validated PCR-based test (such as Xpert MTB/RIF)
Clinically diagnosed LNTB case	A presumptive LNTB patient who undergoes diagnostic testing and has all of: • negative microscopy, negative culture and negative PCR-based tests • no other diagnosis made to explain signs and symptoms • strongly suggestive evidence on other tests, such as radiological findings, histopathological findings, clinical course

12.3 Treatment

First line treatment for adults and children with LNTB	Drugs	2RHZE/4RHE
	Duration	Recommendation Six months ATT standard first-line regimen is recommended for peripheral lymph node TB (strong recommendation, low quality evidence).
	Referral	Generally, LNTB patients can be managed at primary care level. Referral to secondary care for specialist diagnostic sampling may be required.
	Follow up	Assess response to treatment at 4 months. Consider possible treatment failure in patients who have worsened or deteriorated after initial improvement – this requires diagnostic investigation and possibly a change of treatment. Deterioration in the first 3 months may be due to paradoxical reaction – this does not require repeat diagnostic tests or change of treatment. Some patients with LNTB have residual lymphadenopathy at the end of treatment. This is not usually due to continued active TB infection where the largest node is less than 1 cm in size. Some patients have residual nodes more than 1 cm in size, and these patients are classified as partial responders. There is uncertainty about whether continued ATT in these patients is beneficial. The expert group suggested these patients should receive an additional 3 months of RHE, followed by a biopsy sent for histology and TB culture in patients who fail to respond to that. While some evidence suggests that these patients may not require further ATT, the data is insufficient at this stage. For mediastinal TB, progress on ATT can be monitored with chest X-ray, but CT scan may be indicated if lymph nodes do not reduce in size after 4 months. In patients who fail to improve on ATT, the alternative diagnoses of lung cancer, lymphoma, sarcoidosis and fungal infection should be considered. Current expert opinion on when to stop ATT in patients with persistently enlarged mediastinal lymph nodes is to stop when there is documentation of absence of interval change in CT/MRI of mediastinal lymph nodes for more than 4 months, with resolution of all other signs and symptoms.

13 Pleural TB

The second most common form of EPTB, pleural TB is a common cause of pleural effusion in India. Pleural TB usually presents with pleural effusion caused by the immune system's response to the presence of mycobacterial antigens in the pleural space, generating inflammation and causing fluid to accumulate. The effusion will usually resolve spontaneously even without ATT, but patients who are not treated are at risk of recurrent active TB infection.

13.1 Patients who should be investigated for Pleural TB

Presumptive pleural TB	A patient with cough, chest pain or shortness of breath, with or without fever and weight loss, with evidence of a pleural effusion on examination or CXR

13.2 Diagnosis

Test	Patients	Comments
X-ray of chest	All	To confirm presence of a pleural effusion and look for underlying pulmonary disease. Progress may be monitored using CXR.
HIV test	All	EPTB is associated with HIV infection. All patients should be offered integrated counselling and testing.
CT scans of chest and abdomen	Selected	Useful when diagnosis is not clear, particularly if malignancy is suspected; or in in HIV-positive patients who are at higher risk of disseminated TB More sensitive than CXR for identifying underlying pulmonary disease
Ultrasound of chest	Selected	Alternative to CXR to identify pleural effusion, and is more sensitive in picking up pleural effusion than CXR
Pleural aspiration/ thoracocentesis	All	Most patients do not require complete therapeutic drainage of their pleural effusion, unless it is causing respiratory compromise; in which case, specialist monitoring is required during and following drainage. All patients should have a diagnostic sample of pleural fluid taken.

Test	Patients	Comments
Pleural aspiration/ thoracocentesis	All	Send specimen for: a) glucose, protein, ADA and lactate dehydrogenase (LDH) levels (send concurrent blood sample for serum protein and LDH); b) differential cell count; c) microscopy and culture for Mtb; and d) cytology Pleural TB usually causes an exudative effusion, defined on the basis of Light's criteria (pleural fluid/ serum protein >0.5; pleural fluid/serum LDH >0.6; pleural fluid LDH > two-thirds the upper limit of serum LDH) (Light R.W., 1972) Test for adenosine deaminase activity (ADA) level performed on pleural fluid can help support a diagnosis of pleural TB (Greco, 2003) (Liang, 2008). It should be noted that other causes of pleural effusion such as empyema, rheumatoid serositis and lymphoma can occasionally also lead to elevated ADA (Porcel, 2010). > 70 U/L – highly likely to be pleural TB 40–70 U/L – indeterminate level, other risk factors need to be considered <40 U/L – low likelihood of pleural TB, investigate for other causes Because the most common differential diagnosis in children is partially treated parapneumonic effusion, ADA may yield a higher proportion of false positives in this group. Further investigation is required as to the utility of ADA in the diagnosis of pleural TB in children.
Sputum samples	Selected	Send sputum for Xpert MTB/RIF, microscopy and culture as per pulmonary TB guidelines whenever concurrent pulmonary and pleural TB is suspected.
Pleural biopsy (closed or thorascopic)	Selected	Much higher yield than pleural fluid when subjected to microscopy and culture for Mtb; also, histopathological examination can be performed Thoracoscopically-obtained specimens have a higher diagnostic yield than closed pleural biopsy. Indicated where diagnosis is uncertain despite other tests, or where pleural malignancy is a significant differential diagnosis.

Recommendation:

Xpert MTB/RIF should not be used to diagnose pleural TB (strong recommendation, high quality evidence for specificity, low quality evidence for sensitivity).

13.3 Treatment

First line treatment for adults and children with pleural TB	Drugs	2RHZE/4RHE Recommendation: Corticosteroids are not routinely recommended in pleural TB (conditional recommendation, low quality evidence).
	Duration	Total duration of treatment: 6 months
	Referral	Uncomplicated cases do not require referral to specialist centres.
	Follow up	Most patients who respond to treatment will have improvement in their general condition by 2 weeks, and significant improvement in pleural effusion by 6–8 weeks. A follow up CXR at 8 weeks after starting ATT is useful to assess progress. Increasing size of effusion despite treatment may be due to paradoxical reaction, or an alternative diagnosis requiring further investigation.

14 TB of the heart

TB infection of the heart most commonly manifests as TB pericarditis. TB myocarditis is a recognized form of EPTB, but is very rare. In this summary, the main practice points for the diagnosis and management of TB pericarditis are covered.

While it has a low prevalence overall, TB pericarditis accounts for 60–80% of cases of acute pericarditis in high TB burden countries, and 75% of cases of constrictive pericarditis (Fowler, 1991). TB pericarditis has a high mortality if untreated in the acute phase of illness, and survivors can develop constrictive pericardial disease as the acute inflammation resolves, which can cause disability and death later on. ATT greatly reduces both death in the acute phase of illness and the development of constrictive pericardial disease.

14.1 Patients who should be investigated for TB pericarditis

Presumptive TB pericarditis	A patient with chest pain, shortness of breath, with or without fever and weight loss or haemodynamic abnormalities, who has evidence of pericardial effusion or constriction on chest X-ray (CXR) electrocardiogram (ECG) or echocardiogram

14.2 Diagnosis

Test	Patients	Comments
X-ray of chest	All	All patients presenting with symptoms consistent with TB should have a chest X-ray. Features suggestive of pericardial disease include hilar widening, and a globular or "water bottle" heart shadow, although the cardiac shadow may appear normal. Evidence of pulmonary TB or pleural effusions may be noted.
HIV test	All	EPTB is associated with HIV infection. All patients should be offered integrated counselling and testing.
ECG	All	May reveal evidence of pericardial effusion (low voltage trace, T wave flattering or inversion). Patients are at risk of atrial arrhythmia.

Test	Patients	Comments
Echocardiogram (transthoracic)	All	Reveals or confirms pericardial effusion and/or constriction, and can detect signs of impending tamponade which requires urgent intervention.
CT of the chest	Selected	Useful for demonstrating pericardial thickening or calcification, or associated lung/mediastinal abnormalities. Not routinely required.
Cardiac MRI	Highly selected	Only required in patients where a diagnosis of restrictive cardiomyopathy is being considered as a significant differential diagnosis.

Cardiac tamponade

Cardiac tamponade occurs when fluid accumulating in the pericardial sac impedes ventricular filling, causing cardiovascular compromise, which can progress to cardiac arrest. Pericardiocentesis is urgently required to relieve the pressure in the pericardial sac and allow normal ventricular filling.

Pericardiocentesis

The European Society of Cardiology guidelines give recommendations about pericardiocentesis (The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC), 2015). If the patient does not have signs of cardiac tamponade, pericardiocentesis can be considered for diagnostic purposes, but should only be carried out by trained personnel using ultrasound guidance.

Microbiological tests

Microscopy and culture of pericardial fluid for Mtb have very low sensitivity, meaning that few cases have a microbiologically confirmed diagnosis. In patients with concurrent pulmonary disease, smear and culture of serial sputum samples may yield a diagnosis.

Very few studies have assessed the diagnostic accuracy of Xpert MTB/RIF in pericardial fluid, and so the INDEX-TB guidelines panel did not make a recommendation regarding the use of Xpert MTB/RIF on pericardial specimens.

If pericardial fluid is obtained, it should be sent for culture for Mtb, despite low sensitivity of this test. A differential cell count and raised ADA level may support the diagnosis.

14.3 Treatment

First line treatment for adults and children with TB pericarditis	Drugs	2RHZE/4RHE Recommendation: Corticosteroids are recommended for all patients with TB pericarditis who have pericardial effusion (conditional recommendation, low quality evidence for HIV-positive people, very low quality evidence for HIV-negative people).
	Duration	Total treatment duration: 6 months
	Referral	Patients who develop cardiovascular compromise require urgent management in a specialist setting. Patients who develop constrictive pericardial disease as a late complication may benefit from assessment by a cardiologist.
	Follow up	Assess response to treatment at 4 months. Consider possible treatment failure in patients who have worsened or deteriorated after initial improvement – this requires diagnostic investigation and possibly a change of treatment. Deterioration in the first 3 months may be due to paradoxical reaction; this does not require repeat diagnostic tests or change of treatment.
	Surgery	Pericardiocentesis is indicated as an urgent intervention in cardiac tamponade resulting from pericardial effusion. Pericardectomy is sometimes indicated in patients who develop constrictive pericardial disease as a late complication. Some of these patients will improve without surgery, but others may require pericardectomy too for progressive cardiac failure.

15 Abdominal TB

Abdominal TB refers to TB infection of any organ in the abdominal cavity, including the gut and peritoneum. Abdominal TB cases make up about 3% of all EPTB cases in India (Sharma S.K., 2004).

Abdominal TB causes a variety of presentations relating to the site of disease within the abdomen, stage of disease and complications. When treated with appropriate ATT, mortality is low, but some patients experience ongoing complications which can affect their long-term health, such as strictures in the bowel and adhesions. The most commonly affected sites in the abdomen are the GI tract distal to the duodenum (the ileum, jejunum and colon) and the peritoneum. The other organs are more rarely affected.

15.1 Patients who should be investigated for abdominal TB

Site	Typical presentation
Peritoneal	Abdominal distension, abdominal pain, fever
Intestinal	Recurrent intestinal colic, partial or complete intestinal obstruction, chronic diarrhoea, unexplained weight loss, palpable mass in lower abdomen, lower GI bleeding
Oesophageal*	Dysphagia, odynophagia, hematemesis, constitutional symptoms
Gastroduodenal*	Gastric outlet obstruction, upper GI bleeding
Hepatobiliary*	Fever of unknown origin, hepatomegaly with or without space occupying lesions, abnormal LFTs (especially elevated alkaline phosphatase), abnormal imaging (abscess, space occupying lesions), jaundice
Pancreatic*	Abdominal pain, and/or obstructive jaundice, and/or dilated pancreatic and/or bile ducts with evidence of (peri)-pancreatic mass or cyst with or without constitutional symptoms
Perianal	Complex perianal fistulae, persistent discharge from the fistula, fistulae which recur after multiple surgical excisions

* Sites where other differential diagnoses like malignancy are more common than TB infection

Presumptive abdominal TB	A patient with abdominal pain, distension, fever, unexplained weight loss, chronic diarrhoea or an abdominal mass.

15.2 Diagnosis

All patients with presumptive abdominal TB

Test	Patients	Comments
X-ray of chest	All	All patients presenting with symptoms consistent with TB should have a chest X-ray.
HIV test	All	EPTB is associated with HIV infection. All patients should be offered integrated counselling and testing.

Patients with presumptive peritoneal TB

Ascitic fluid sampling	All	Simple percutaneous sampling of ascitic fluid can aid in the diagnosis of peritoneal TB. Specimens should be sent for: a) cytology; b) albumin and protein; c) adenosine deaminase (ADA); d) microscopy for AFB; e) culture for Mtb and other organisms A serum albumin:ascitic fluid albumin ratio (SAAG) of <1.1 with a high protein (>2.5 g/mL) is suggestive of an exudative process, in keeping with abdominal TB (although several other conditions also cause this). ADA >39 IU/mL in ascitic fluid is suggestive of abdominal TB (Riquelme A, 2006). Sensitivity of smear microscopy and culture for Mtb on ascitic fluid samples is low; however, culture is required to confirm the diagnosis and test for drug susceptibility. PCR-based methods for identifying Mtb in ascitic fluid samples are highly variable in terms of diagnostic accuracy, and so no recommendation on the use of these tests has been made.
Ultrasound of abdomen	All	Many abnormal features may be noted, including intra-abdominal fluid (free or loculated), inter-loop ascites, mesenteric lymphadenopathy, bowel wall thickening, enlarged lymph nodes with central necrosis and peripheral enhancement and peritoneal and omental thickening.
US-guided FNAC or core biopsy of mesenteric or retroperitoneal lymph nodes, omentum or peritoneum	Selected	Microscopy and culture of FNAC/biopsy specimens of affected structures is more sensitive than ascitic fluid testing alone. Requires a trained practitioner. Specimens should be sent for: a) histology; b) microscopy for AFB; c) culture for Mtb and other organisms.
CT or MR scan of abdomen	Selected	Many abnormal features may be noted, but as with ultrasound, none are diagnostic for peritoneal TB. These tests may be useful when other differential diagnoses are being considered. Not routinely suggested. Radiation exposure should be considered when deciding to perform a CT.

Laparoscopy	Selected	Visual appearance on laparoscopy can be highly suggestive of peritoneal TB. Typical appearances include: • Thickened peritoneum with tubercles: multiple, yellowish white, uniform sized (about 4–5mm) tubercles diffusely distributed on the parietal peritoneum. The peritoneum is thickened, hyperaemic and lacks its usual shiny lustre. The omentum, liver and spleen can also be studded with tubercles. • Thickened peritoneum without tubercles. • Fibro-adhesive peritonitis with markedly thickened peritoneum and multiple thick adhesions fixing the viscera. Targeted diagnostic sampling at laparoscopy may improve the yield from biopsy specimens sent for microscopy and culture for Mtb and histopathology. Laparoscopy is not routinely recommended due to the high cost and invasive nature of the procedure, and is usually reserved for cases where the diagnosis remains unclear after other tests.

Patients with presumptive GI TB

Ileocolonoscopy	All	Unless contraindicated, all patients suspected of TB affecting the lower GI tract should be offered endoscopic examination with appropriate biopsy sampling. Examination of the ileum by retrograde ileoscopy is important, as this is the commonest site of involvement in GI TB. Appearances vary considerably, and differentiating GI TB from other bowel diseases such as Crohn's disease is often challenging. Biopsy specimens should be sent for: a) histology and staining for AFBs; b) culture for Mtb PCR-based methods for identifying Mtb in biopsy specimens from the GI tract are highly variable in terms of diagnostic accuracy, and so no recommendation on the use of these tests has been made.
CT/MR enterography/ enteroclysis	Selected	Assessment of the small intestine may require specialist imaging to identify and characterise lesions. Selecting the appropriate test depends on what pathology is suspected, and should be at the discretion of a specialist clinician and/or radiologist. Common findings include short segment strictures and ileocecal wall thickening with enlarged necrotic lymph nodes.
Upper GI endoscopy	Selected	If symptoms suggest involvement of the upper GI tract, endoscopy with biopsy is indicated.
Barium studies	Selected	Barium studies of the upper GI tract and small bowel may be indicated where endoscopy is not available or not possible, or where small bowel stricture is suspected.

Diagnosis of other forms of abdominal TB

The principal differential diagnosis in biliary and pancreatic TB patients is usually malignancy, and some patients are diagnosed post-operatively after surgery to resect a suspected tumour. Specialist imaging and image-guided diagnostic sampling techniques are required in cases of suspected biliary and pancreatic TB, and patients should be referred to centres providing these services.

Perianal TB is relatively uncommon, and the differential diagnosis includes a variety of conditions such as Crohn's disease, foreign body reactions, malignancy and sexually transmitted diseases. Careful assessment by specialists is advised.

15.3 Treatment

First line treatment for adults and children with abdominal TB	Drugs	2RHZE/4RHE Recommendation: 6 months ATT standard first-line regimen is recommended for abdominal TB. Strong recommendation, very low quality evidence
	Duration	Total treatment duration: 6 months, extended at the discretion of the treating clinician
	Referral	Patients with presumptive GI, hepatobiliary, pancreatic or perianal TB will require referral to a gastroenterologist for clinical assessment and diagnosis. Patients with presumptive peritoneal TB where the diagnosis is uncertain also require referral.
	Follow up	Assess response to treatment at 3 months and 6 months. Consider possible treatment failure in patients who have worsened or deteriorated after initial improvement – this requires diagnostic investigation and possibly a change of treatment. Deterioration in the first 3 months may be due to paradoxical reaction – this does not require repeat diagnostic tests or change of treatment.
	Surgery	Complications of GI TB include strictures that can cause acute and recurrent partial obstruction, and perforation in some cases. Strictures can be managed with endoscopic dilatation, but some cases require resection of the stricture or hemicolectomy. Oesophageal and gastroduodenal TB patients rarely require surgery; ATT alone is usually adequate. Duodenal strictures may be treated with balloon dilatation. Bypass surgery may be required if this is not successful. Hepatobiliary or pancreatic TB patients who develop biliary obstruction may require endoscopic or percutaneous biliary stenting. Liver abscess which fails to respond to treatment, or ruptured abscesses may require surgical intervention. Perianal TB cases with complex fistula may require surgical intervention.

16 Urogenital TB

Urogenital TB refers to TB of the female and male genital tract and the urinary tract. It is usually an insidious disease, and can lead to a variety of presentations depending on the affected site and stage of disease. Serious adverse outcomes include infertility in both women and men, chronic pelvic pain, dysmenorrhoea, bladder dysfunction, renal failure and death. Some (particularly female) patients may experience no symptoms at all other than infertility, meaning that a high index of suspicion and careful clinical evaluation are needed to make the diagnosis.

Urogenital TB makes up approximately 4% of all EPTB cases annually in India. This may be an underestimate of the true number of cases, as the difficulty of diagnosing the condition and lack of clear case definitions may be hampering reporting of cases.

In this summary of the key practice points, forms of urogenital TB are divided into three broad categories:

- Urinary TB – referring to TB of the kidney, ureters and/or bladder
- Female genital TB – referring to TB of the uterus, fallopian tubes and/or ovaries
- Male genital TB – referring to TB of the epididymis and/or testes

16.1 Urinary TB

Patients who should be investigated for urinary TB

Presumptive urinary TB	A patient with lower urinary tract symptoms (frequency, urgency and nocturia) associated with dysuria and/or haematuria for at least 2 weeks, which has not responded to a 3–7 day course of antibiotics. Some patients have systemic symptoms of fever, weight loss and night sweats. *Note:* The use of fluoroquinolones in the treatment of UTI can reduce the sensitivity of subsequent tests for Mtb in the urinary tract, and should therefore be avoided, unless an organism is identified in urine cultures and antibiotic susceptibility test results support fluoroquinolone use.

Diagnosis

Test	Patients	Comments
X-ray of chest	All	All patients presenting with symptoms consistent with TB should have a chest X-ray to look for evidence of previous or active pulmonary TB.
HIV test	All	EPTB is associated with HIV infection. All patients should be offered integrated counselling and testing.
Renal function tests	All	An important complication of urinary TB is renal impairment. All patients should have blood tests and calculation of estimated glomerular filtration rate (eGFR) to detect this. Renal impairment should prompt rapid assessment of the urinary tract using ultrasound to look for outflow tract obstruction as a cause. This requires urgent intervention with urinary catheterisation; or in the instance of hydronephrosis, percutaneous nephrostomy or double J stent insertion to decompress the affected kidney.
Urine microscopy and culture for non-mycobacterial organisms	All	To identify sterile pyuria, which may suggest urinary TB To diagnose active infection with other bacteria. The patient should be reassessed after appropriate antibiotic treatment for symptom resolution. Superadded bacterial infection can occur with urinary TB.
Early morning urine sampling	All	Three to five early morning urine samples collected for staining and microscopy for AFBs and culture for Mtb. While the sensitivity of these tests is low, culture remains the most reliable way to confirm a diagnosis of urinary TB and allows drug susceptibility testing to be carried out.
Ultrasound of the kidneys, ureters and bladder (US KUB)	All	This scan may be normal in early disease. It can help identify structural abnormalities such as hydronephrosis which can either suggest a diagnosis or guide further tests. It is non-invasive and well-tolerated.
Intravenous urography (using plain X-ray)	Selected	This test also helps identify lesions in the urinary tract and has the advantage of being widely available and cheap; however, it has low sensitivity for early lesions. Risks include contrast nephropathy (patients with renal impairment are at particular risk), and contrast reaction (asthmatic patients and patients with cardiac failure may be at higher risk).

Test	Patients	Comments
Contrast-enhanced CT urography	Selected	This test is more sensitive than IV urography using plain X-rays for identifying and characterising TB lesions in the urinary tract. Risks include contrast nephropathy and contrast reaction. The relatively high dose of ionizing radiation involved must be taken into account when considering this test, particularly for children and women of childbearing age. It is contraindicated in pregnant women.
MR urography without contrast	Selected	This test is also gives structural information about the urinary tract, and is sensitive for identifying and characterising TB lesions. It is more expensive and less accessible than plain X-ray and CT urography, but has the advantage of not requiring intravenous contrast and not necessitating a dose of radiation. Pregnant women, children and patients with pre-existing renal function may benefit from this test.
FNAC	Selected	Where accessible mass lesions or fluid collections are identified on imaging, radiologically guided aspiration with specimens subjected to staining and microscopy for AFBs, culture and cytology may confirm the diagnosis of TB.
Urethrocystoscopy with/without bladder biopsy	Selected	Indicated when - other less invasive tests are inconclusive - bladder malignancy is also suspected Although this is an invasive test, risk to the patient is low when carried out by an experienced practitioner. Has the advantage of allowing visualisation of lesions and targeted biopsy
Biopsy	Most	Biopsy of lesions in the urinary tract is required when - other less invasive tests are inconclusive - malignancy is also suspected Specimens should be subject to: a) staining and microscopy for AFBs; b) culture and drug susceptibility testing; c) histopathology

Treatment

Aims of treatment are:

- to achieve TB cure
- to prevent the long term sequelae
- to restore normal anatomy if it has been distorted.

First line treatment for adults and children with urinary TB	Drugs	2RHZE/4RHE
	Duration	Six months
	Referral	Requires assessment by a urology team to perform specialist diagnostic tests and treat structural urinary tract complications. Urgent referral is required for patients presenting with renal failure secondary to bilateral hydronephrosis.
	Follow up	Assess response to treatment at 8 weeks – resolution of systemic symptoms, improvement in urinary symptoms, check renal function. Repeat imaging may be indicated, especially if partial or impending ureteric stricture was identified at diagnosis. Obstruction can occur as a late complication as the healing of the lesion results in fibrotic stricture. If early morning urine culture is positive at diagnosis, this may be repeated at 8 weeks, and at the end of ATT.
	Surgery	Urgent surgical intervention is required when ureteric obstruction prevents drainage of urine from the kidney, to prevent renal damage. Reconstructive procedures are required when there are ureteric strictures or small capacity bladder complicates urinary TB. Nephrectomy is rarely indicated, except where chronic pain, hypertension, nephrocutaneous fistula or stone formation complicates a poorly- or non-functioning kidney.

16.2 Female genital TB

Presentation is varied and a high index of clinical suspicion is required to make the diagnosis. Most cases of female genital TB (FGTB) are found in premenopausal women, theoretically because an atrophic endometrium provides a poor milieu for mycobacterial growth. Around 11% of patients present with no symptoms other than infertility, and these patients require a diagnostic workup to look for all common causes of infertility. In patients with pelvic symptoms or vaginal bleeding post menopause, malignancy is an important differential diagnosis to consider.

Patients who should be investigated for female genital TB

Presumptive FGTB	A premenopausal woman presenting with infertility, menstrual problems, unexplained abdominal pain or pelvic mass. Rarely, patients have systemic symptoms of fever, weight loss and night sweats. Ectopic pregnancy and cervical/vulval lesions are rare presenting features. A postmenopausal woman presenting with vaginal bleeding

Diagnosis

Test	Patients	Comments
X-ray of chest	All	All patients presenting with symptoms consistent with TB should have a chest X-ray to look for evidence of previous or active pulmonary TB.
HIV test	All	EPTB is associated with HIV infection. All patients should be offered integrated counseling and testing.
Pregnancy test	All of child-bearing age	To rule out pregnancy as possible cause of symptoms, and to ensure further testing is safe and appropriate
Pelvic ultrasound	All	Part of the initial assessment of most patients presenting with gynaecological symptoms
Hysterosalpingogram	Selected	May be done as part of the investigation of infertility, but many women with FGTB will have a normal HSG
CT pelvis or MRI pelvis	Selected	To further characterize lesions and plan surgical intervention in selected patients. Disadvantage of CT is exposure to ionising radiation, which is particularly a concern in women of childbearing age
FDG-PET CT	Selected	Although not widely available, PET scans may give more information about the presence and activity of tubercular tubo-ovarian mass lesions. Further evidence about the diagnostic accuracy of PET CT for detecting and monitoring the progression of FGTB is needed.
Endometrial aspirate	Selected	Where facilities exist, endometrial aspirate can be obtained and sent for: a) staining and microscopy for AFB; b) culture and drug susceptibility testing. Sensitivity is low, and negative results cannot rule out FGTB.
Laparoscopy	Selected	Laparoscopy with biopsy of lesions is required when - other less invasive tests are inconclusive - malignancy is also suspected - as part of infertility investigations when less invasive tests are inconclusive Laparoscopy offers the dual advantage of pelvic organ visualization and specimen collection from otherwise inaccessible sites. Specimens should be subject to: a) staining and microscopy for AFBs; b) culture and drug susceptibility testing; and c) histopathology.

Making a diagnosis

The group concluded that the diagnosis of FGTB should be made based on any one of:

- laparoscopic appearance typical for FGTB
- any gynaecological specimen positive for AFBs on microscopy or positive for Mtb on culture
- any gynaecological specimen with findings consistent with FGTB on histopathological examination.

Treatment

Aims of treatment:

- To achieve TB cure
- To prevent the long term sequelae
- To restore normal anatomy if has been distorted

First-line treatment for adults and children with urinary TB	Drugs	2RHZE/4RHE
	Duration	Six months
	Referral	Requires assessment by a gynaecologist to make the diagnosis and treat complications. Empirical ATT in women presenting with infertility alone should only be started following assessment by a specialist.
	Follow up	Assess response to treatment at completion of 6 months' ATT
	Surgery	Surgery is not part of primary treatment in FGTB; however, it is sometimes needed for large, residual tubo-ovarian abscesses. Surgery in FGTB is associated with higher complication rates as there are a lot of adhesions as well as the possibility of infection recurrence. Tubal anatomy can sometimes be restored surgically in infertile women following a course of ATT. However, infertility may be an irreversible long-term consequence of FGTB. Giving repeated courses of ATT to women who remain infertile following completed ATT for FGTB is not necessary.

16.3 Male genital TB

Patients who should be investigated for male genital TB (MGTB)

Presumptive MGTB	A patient with scrotal pain or swelling for 2 weeks or more not responding to a 7–14 day course of antibiotics, or with discharging sinuses in the scrotum. Rarely, patients have systemic symptoms of fever, weight loss and night sweats.

Diagnosis

Test	Patients	Comments
X-ray of chest	All	All patients presenting with symptoms consistent with TB should have a chest X-ray to look for evidence of previous or active pulmonary TB.
HIV test	All	EPTB is associated with HIV infection. All patients should be offered integrated counselling and testing.
Renal function tests	All	All patients with suspected MGTB must be evaluated for co-existent urinary TB (see above).
Urine microscopy and culture for non-mycobacterial organisms		
Early morning urine sampling		
Ultrasound of the kidneys, ureters and bladder (US KUB)		
Ultrasound scan of the scrotum	All	To evaluate swelling/mass lesions and guide FNAC
FNAC epididymal mass	All	Specimens should be subject to: a) staining and microscopy for AFB; b) culture and drug susceptibility testing; and c) cytology There is a risk of damaging the epididymis and causing infertility.
Biopsy	Selected	If FNAC does not confirm the diagnosis or malignancy is suspected, biopsy of the lesion is indicated. Specimens should be subject to: a) staining and microscopy for AFBs; b) culture and drug susceptibility testing; c) histopathology

Treatment

First-line treatment for adults and children with MGTB	Drugs	2RHZE/4RHE
	Duration	Six months
	Referral	All cases need evaluation by an urologist to make the diagnosis.
	Follow up	Assess at 8 weeks to assess for response to treatment. Repeat FNAC/biopsy may be required for mass lesions which continue to grow despite treatment (specialist assessment required).
	Surgery	Surgery is not usually required, and is not a routine part of treatment. Epididymectomy may be required if there is a caseating abscess which persists despite completing a course of ATT.
	Sequelae	Infertility is a possible long-term complication of MGTB. Infertility following completed treatment for MGTB should not be interpreted as indicative of treatment failure or recurrence of infection.

PCR-based tests in urogenital TB

Confirming the diagnosis in urogenital TB is very difficult. Often, invasive procedures must be done to obtain specimens. Conventional diagnostic methods (microscopy and culture) have low sensitivity.

PCR-based tests (either commercially available or in-house assays) are increasingly used to diagnose FGTB. A literature review prepared for this guideline found that estimates of sensitivity and specificity varied widely across reports in the literature, and the Technical Advisory Subcommittee for FGTB raised concerns about their experience of high rates of false positives when these tests are applied to peritoneal/gynaecological specimens. There were no data at the time of publication looking at the use of Xpert MTB/RIF for the diagnosis of FGTB. The guideline group decided that a recommendation was not possible at this time regarding the use of PCR-based tests in FGTB, and noted that high quality diagnostic test accuracy studies are needed to address this question.

Similarly, further evidence is needed on the diagnostic test accuracy of Xpert MTB/RIF and other PCR-based tests on urine, FNA aspirates and biopsy specimens for the diagnosis of urinary TB or MGTB. Again, the expert group acknowledged that while these tests are in current use, the guideline group could not make a recommendation about their use at the present time.

17 Spinal TB and other forms of bone and joint TB

TB infection of the bones and joints causes chronic pain, deformity and disability, and TB of the cervical spine can be life threatening. Bone and joint TB makes up around 10% of all EPTB cases, with spinal TB being the most common form (Sharma S.K., 2004). Around 1–2% of all TB cases worldwide are spinal TB cases (Watts, 1996). Both adults and children can be affected.

Since it is the most common and most disabling form, spinal TB is covered in detail here, with key practice points at the end about TB affecting other parts of the skeletal system.

17.1 TB of the spine

Presumptive spinal TB	A patient with localized back pain for more than 6 weeks with tenderness on examination of the spinous processes, fever and weight loss, with or without signs of spinal cord compression. Patients with advanced disease may have severe pain, spinal deformity, paraspinal muscle wasting and neurological deficit. In addition in children, failure to thrive, night cries, inability to walk/ cautious gait, and use of hands to support the head or trunk are important signs.

Diagnosis

Test	Patients	Comments
X-ray of chest	All	All patients presenting with symptoms consistent with TB should have a chest X-ray.
HIV test	All	EPTB is associated with HIV infection. All patients should be offered VCT.
X-ray of spine	Limited use	Spinal lesions take 3 to 6 months to appear on plain X-ray, so this test is of limited use in the early stages of the disease. However, X-rays are useful to evaluate treatment response on follow up.
MRI spine	All	All patients with suspected TB spine require an MRI to assess the extent of disease and the degree of bony destruction, and confirm spinal cord involvement in patients with neurological signs. MRI is useful in making a diagnosis in the early stages of disease while some MRI appearances are highly suggestive of a diagnosis of spinal TB (Jain, 2012).

CT spine	Selected	Some patients may require CT of the spine in addition to MRI, although CT cannot be used to detect early spinal cord involvement.
Biopsy of the lesion	All	The INDEX-TB guidelines TAC subcommittee for bone and joint TB assert that in TB endemic areas, it is reasonable to start ATT in patients with strong clinical and radiological/ MRI evidence of TB of the spine and monitor their progress.Where possible, all patients should have a biopsy of the lesion to provide a specimen for culture to confirm the diagnosis and perform drug susceptibility testing, and to rule out other diagnoses. Percutaneous CT-guided biopsy is preferred, but some patients may require open biopsy. The risks and benefits of obtaining a biopsy must be considered. Specimens should be sent for: a) Microscopy and culture for pyogenic bacteria; b) Microscopy and culture for Mtb; and c) histopathology/cytology. There is currently insufficient evidence surrounding the use of PCR-based tests such as Xpert MTB/RIF in the diagnosis of TB of the bones and joints.

Treatment

There is uncertainty surrounding the optimum duration of treatment for TB of the bones and joints. Some older trials suggested that 6 months treatment may be sufficient, but more advanced diagnostic imaging has led to uncertainty whether these patients are cured for spinal TB at the end of that time. The TAC subcommittee performed a brief review of the literature to inform their decision regarding duration of treatment in bone and joint TB; a systematic review was not performed. The group found that there is a lack of consensus about what constitutes healed status in the literature.

The expert group agreed that all cases of bone and joint TB should be treated with extended courses of ATT with a 2-month intensive phase consisting of four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol), followed by a continuation phase lasting 10–16 months, depending on the site of disease and the patient's clinical course.

Drugs	2RHZE/10RHE All patients require close monitoring for development or progression of neurological deficit in the first 4 weeks of treatment. Some patients require surgical intervention.
Duration	Total treatment duration: 12 months (extendable to 18 months on a case-by-case basis)
Referral	Optimum management of spinal TB requires the involvement of multiple specialists including a spinal orthopaedic surgeon, microbiologist/infectious diseases specialist and spinal radiologist, as well as physiotherapists and orthotists. All presumptive spinal TB cases should be referred and managed in specialist centres.

Follow up	Patients without neurological deficit should be advised to return to the clinic immediately if new symptoms develop, and all ambulant patients should be assessed weekly for neurological signs. Patients with neurological deficit require staging and grading of their deficit. These patients should be assessed weekly with neural charting to detect neural recovery or deterioration. Repeat X-rays of the spine are suggested every 3 months following initiation of treatment to assess for radiological healing. Repeat MRI scans are suggested at 6, 9, 12 and 18 months following initiation of treatment to assess healing. At the end of treatment, all patients require follow up every 6 months for at least 2 years, and should be told to return to the clinic promptly if they develop new symptoms in the interim.
Surgery	While some require early surgical intervention, most patients can be managed with ATT alone in the initial phase of treatment. Surgery may be required for two principal purposes in spinal TB-to establish diagnosis, or to treat spinal deformity, instability and neurological deficit. Where available, percutaneous biopsy under CT guidance reduces the need for open biopsy, but this may still be required in some cases, particularly where imaging results are atypical for spinal TB and the diagnosis is uncertain. Patients with large, fluctuant cold abscesses may require therapeutic aspiration to relieve symptoms and promote healing. Indications for surgery in TB spine with neurological deficit: • Neural complications developing or getting worse or remaining stationary during the course of non-operative treatment (3–4 weeks) • Paraplegia of rapid onset • Spinal tumour syndrome • Neural arch disease • Severe paraplegia – flaccid paraplegia, paraplegia in flexion, complete sensory loss and complete loss of motor power for more than 6 months • Painful paraplegia in elderly patients. Indications for surgery in spinal TB without neurological deficit: • When diagnosis is uncertain and open biopsy is indicated • Mechanical instability – panvertebral disease, where bony involvement of both the vertebral body and posterior complex is seen on imaging, or disease affects facet joints bilaterally • Suspected drug resistance – where patients show inadequate clinical improvement or deterioration on ATT • Spinal deformity – severe kyphotic deformity at presentation, or in children at high risk of progression of kyphosis with growth after healing of disease.

Surgery	• Indications for instrumented stabilization: • Panvertebral disease • Long segment disease where a > 4–5 cm long graft is required to bridge the gap after surgical decompression in dorsal spine • In lumbar and cervical spine • When kyphosis correction surgery is contemplated • Lesion in a junctional area.
Sequelae	Early onset paraplegia: Some patients have paraplegia secondary to acute inflammation in and around the cord in early disease. This generally carries a good prognosis with prompt treatment with ATT. MRI and intraoperative findings suggestive of extradural fluid compressing the cord, cord oedema or myelitis generally correlate with neural recovery. Late onset paraplegia: This is defined as the reappearance of neural deficit after a disease-free period of at least 2 years in patients who completed ATT and achieved healed status with a residual kyphotic deformity. This can occur as a result of progression of deformity in healed patients, or as a result of relapse of active TB infection. These two scenarios necessitate different treatment and carry different prognoses. Expert management is required. Deformity: Bony destruction and subsequent healing leads to deformity, which will depend on the site and extent of infection. Some deformity requires surgical correction to prevent further progression or restore function. There is debate over the optimum timing of surgery to correct deformity, but the group agreed that surgery should preferably take place during treatment with ATT for active TB infection.

17.2 TB of the appendicular skeleton

TB of the bones and joints can affect people of any age, but some forms are seen more frequently in children.

Risk factors include previous TB infection, immunosuppression caused by conditions such as HIV, diabetes mellitus and chronic liver or kidney failure, among others; or by immunosuppressive drugs such as long-term corticosteroids.

Key principles of diagnosing TB of the bones and joints are:

- Suspect TB as a possible cause in people with signs of joint infection with an insidious onset
- Refer to an orthopaedic team who can assess the joint and perform a biopsy for culture (for *M. tuberculosis* as well as other organisms) and histopathology

- All patients should have specimens taken for microscopy and culture where possible

Invasive diagnostic procedures are not always practicable, and in such circumstances the treating clinician must use his judgement as to whether treatment with ATT should be started without a microbiological/histopathological diagnosis, or whether a period of observation is appropriate. The INDEX-TB guidelines TAC subcommittee for bone and joint TB assert that in TB-endemic areas, it is reasonable to start ATT in patients with strong clinical and radiological evidence of TB of the bones and joints and monitor their progress. Where the diagnosis is uncertain, tissue specimens are required before giving ATT.

Where possible and safe for the patient, getting specimens for microscopy, culture and histopathology prior to starting ATT is beneficial because:

- positive culture confirms the diagnosis
- drug susceptibility testing can be carried out to guide ATT
- false negative culture results are more likely if specimens are taken after ATT has been started
- alternative diagnoses can be picked up.

When taking specimens for microbiological testing and histopathology, the following principles are important:

- Early in the course of TB joint infection, aspiration of fluid from the joint will not usually yield a diagnosis, and so tissue biopsy of the affected structures is preferred. This may be done under radiological guidance, using arthroscopy, or via open surgical biopsy. Arthroscopy with biopsy offers the advantage of visualization of the lesion with excision of affected tissue for diagnostic testing, and simultaneous therapeutic intervention if required.
- Fluid or pus from joint aspirates, and pus from collections/cold abscesses should also be sent for microscopy and culture.
- Enlarged lymph nodes regional to the infected site may also be considered for biopsy/FNAC.
- Sinus tract curettage/edge biopsy may also be sent for culture and histopathology, but microbiological results should be interpreted with caution as contamination/colonization/secondary infection with skin commensals or coliforms is common.
- As a general principle, specimens for culture should be collected whenever a therapeutic invasive procedure is carried out, e.g. when a joint is debrided following unsuccessful non-operative management.
- Specimens should be sent for
    - microscopy and culture for non-mycobacterial pathogens (pyogenic bacteria, *Brucella*, fungal species)
    - microscopy and culture for TB
    - histopathology.

This table lists the presenting features of TB of the joints, with basic information about diagnosis and treatment. This section is based on the expert opinion of the INDEX-TB TAC subcommittee for bone and joint TB.

Hand and wrist Hand and wrist	*Identify:* More common in children under 5 years, but can affect any age group Patients present with a variety of features depending on the site of infection. The hand or wrist gradually becomes painful and/or swollen with joint effusions and synovial thickening, causing boggy swelling with restricted range of motion. Systemic symptoms such as fever, weight loss, anorexia and regional lymphadenopathy may be present. In advanced disease, wasting of the muscles of the hand and forearm, deformity, enlargement of digits/metacarpals (sausage finger/spina ventosa), discharging sinuses, cold abscess and compound palmar ganglia may be present. Rarely, patients have carpal tunnel syndrome, or nail involvement. *Diagnose:* Early X-ray changes are subtle and easily missed, but later in the disease sequential X-ray changes are seen which can be used to classify the disease (Martini M, 1986). USS, CT and MRI features are non-specific but these modalities may be used to assess extent of disease or identify biopsy sites or drainable collections. *Treat:* 2RHZE/10–16RHE with rest to the joint provided by immobilisation in plaster/brace for 4 to 6 weeks followed by gradual mobilisation as tolerated (specialist management by upper limb orthopaedic surgeon required). Surgery is rarely needed, but may be indicated for nerve compression, impending bone collapse, joint debridement, drainage of large abscesses and correction of deformity in healed disease.
Elbow	*Identify:* Can affect any age group Patients present with a variety of features depending on the site of infection. The elbow gradually becomes painful and/or swollen with joint effusions and synovial thickening, causing boggy swelling with restricted range of motion. Systemic symptoms such as fever, weight loss, anorexia and regional lymphadenopathy may be present. Rarely, ulnar nerve or posterior interosseous nerve palsies may be the presenting feature. In advanced disease, wasting of the arm and forearm muscles, deformity on flexion/extension, pathological dislocation, discharging sinuses and cold abscesses may develop. *Diagnose:* See Hand and wrist TB *Treat:* See Hand and wrist TB

Shoulder	*Identify:* Can affect all ages, but is more common in adults than children. Relatively rare, it usually presents in the advanced stage with disabling symptoms that may mimic more common pathologies such as neuropathic shoulder, rheumatoid arthritis, and adhesive capsulitis. A high index of suspicion and careful clinical evaluation are required to make the diagnosis. Patients present with pain in the shoulder and restricted range of motion (particularly limited external rotation and abduction), with muscle wasting (particularly deltoid and supraspinatus). Systemic symptoms such as fever, weight loss, anorexia and lymphadenopathy are uncommon, as is swelling of the joint. In advanced disease, there may be marked destruction of the humeral head and glenoid with muscle atrophy, or deformity (particularly, fibrous ankylosis with humeral head pulled up against the glenoid and the arm fixed in adduction and internal rotation). Discharging sinuses around shoulder, arm and scapula and cold abscess are uncommon. "Caries sicca" is the most common form – which is a dry arthropathy (rather than exudative). *Diagnose:* See Hand and wrist TB. In early disease, arthroscopic biopsy offers the advantage of direct visualization of joint, allowing excision of tubercular synovium, granulation tissue, rice bodies and pannus over cartilage. However, in advanced disease where arthroscopy is not feasible, an open debridement and biopsy is indicated. *Treat:* 2RHZE/10-16RHE with rest in sling or brace and gentle mobilization as tolerated. Prolonged immobilisation with spica is no longer widely advocated. Surgery is rarely needed, but may be indicated for drainage of large abscess, excision of persistent sinuses, joint debridement to remove loose bodies and pannus, arthrodesis to relieve a painful fibrous ankylosis, or joint replacement in healed disease with severe joint destruction. Resection arthroplasty has not been shown to improve outcomes, and should be avoided in favour of nonoperative treatment even in cases with severe bony destruction at diagnosis.

Hip	*Identify:* Can affect any age, but most common in children and young adults There are three stages in the course of the disease: 1. **Synovitis.** Characterized by gradual onset of hip pain and limping (antalgic gait) with fullness around the hip caused by joint effusion, restricted range of movement and deformity (the affected limb is flexed, abducted and externally rotated with apparent lengthening of the extremity). 2. **Early arthritis.** Characterized by progression of bony destruction leading to deformity with the limb flexed, adducted and internally rotated with apparent limb shortening. There is pain with every hip movement, with muscle spasm and atrophy. 3. **Advanced arthritis.** Characterized by very painful joint movements and grossly restricted range of movement with shortening of the limb. Pathological dislocation or subluxation may occur due to bony destruction at the acetabulum/femoral head. The attitude of the limb and deformity does not always correlate with the stage of arthritis.
Hip	*Diagnose:* 1. **Synovitis stage**. X-ray changes and US appearance, with aspiration of the joint effusion for microscopy, AFB smear and culture may provide sufficient information in high TB burden areas to start treatment. MRI scan can give more information about the extent of the disease. Biopsy should be carried out if there is uncertainty about diagnosis. 2. **Early arthritis**. Radiographic changes with biopsy 3. **Advanced arthritis**. Radiographic changes with biopsy *Treat:* 1. **Synovitis**. 2RHZE/10–16RHE with appropriate analgesia and rest to the joint in above-knee skin traction or skeletal traction for around 4 weeks. Active assisted exercises to mobilize thereafter. Surgery is rarely required. 2. **Early arthritis**. 2RHZE/10–16RHE with appropriate analgesia and rest to the joint in above-knee skin traction or skeletal traction until spasm is relieved, and non-weight bearing exercises as tolerated. Synovectomy and joint debridement are sometimes indicated if the response to nonoperative treatment is inadequate at 6 to 8 weeks. Drainage of large joint effusions or abscesses may be required. Send specimens for culture. 3. **Advanced arthritis**. 2RHZE/10-16RHE with appropriate analgesia and rest to the joint in traction. Arthrolysis with joint debridement is usually indicated, followed by a period of skeletal traction, with early supervised mobilization of the hip as tolerated. 4. **Advanced arthritis with subluxation/dislocation**. 2RHZE/10–16RHE with appropriate analgesia and rest to the joint in traction. Gross bony destruction at this stage requires surgical management with excision arthroplasty, arthrodesis or total hip replacement.

Knee	*Identify:* Can affect any age group Patients present with a painful, swollen, tender knee which may be warm to touch, with limping and reduced range of motion. Systemic symptoms of fever, weight loss and anorexia may be present, with regional lymphadenopathy on examination. In advanced disease, the joint may feel boggy due to synovial thickening, with joint effusion and wasting of the thigh muscles. Discharging sinuses or cold abscess may be seen. Deformity ranging from a mild flexion deformity to severe triple deformity consisting of flexion, posterior subluxation, external rotation and valgus may be present. *Diagnose:* X-ray changes are non-specific in early disease, with progressive changes in late disease, which can be used to classify the stage of disease. MRI changes can be highly suggestive of TB of the knee. Diagnosis is confirmed with microscopy, culture and histopathological examination of US-guided/arthroscopic/open surgical biopsy of the synovium. *Treat:* 1. **Synovitis stage**. 2RHZE/10–16RHE with rest to the joint in traction to prevent flexion deformity with gentle mobilization for 6 weeks, and then reassess. Arthroscopic or open joint debridement may be necessary in some cases if there is little improvement with non-operative treatment. 2. **Early arthritis stage**. 2RHZE/10–16RHE with rest to the joint in double traction to prevent triple deformity. Joint debridement is usually necessary, with corrective plaster/bracing following surgery if joint is unstable. 3. **Advanced arthritis stage**. In children, 2RHZE/10– 16RHE with rest to the joint in double traction, followed by corrective plaster, with arthrodesis deferred until growth is complete. In adults, with painful arthritic knee or fibrous ankylosis, arthrodesis by compression is often necessary. 4. **Healed tubercular knee with deformity**. Corrective osteotomy or total knee replacement may be necessary to restore normal alignment and improve function.

Ankle	*Identify:* More common in children and young adults, but can affect any age group Patients present with a slow-onset painful, swollen ankle with pain on weight bearing causing a limp, and a history of weight loss, anorexia and fever. On examination, the joint may be warm, red and tender, boggy to palpate due to synovial thickening, with regional lymphadenopathy and restricted range of motion. In advanced disease, calf muscle wasting, effusion, deformity and discharging sinuses may be seen. Differential diagnoses: non-mycobacterial septic joint, neoplastic lesion, e.g. chondroblastoma in children. *Diagnose:* X-ray features are non-specific, and are subtle in early disease. MRI and CT scan may demonstrate changes, but these are not specific to TB. *Treat:* 2RHZE/10–16RHE with rest to the joint in a functional position (in plaster/ ankle-foot orthoses) for 4–6 weeks followed by gentle non weight-bearing mobilization as tolerated. Surgery is rarely required, but is indicated for impending bone collapse, large abscess, or correction of deformity in healed patients.
Foot	*Identify:* More common in children and young adults, but can affect any age group Patients present with slow-onset pain, swelling of the foot and a limp. Specific features depend on which bones are involved, e.g. TB of the calcaneus causing heel-up limp and tenderness over heel. Systemic features such as fever, weight loss and lymphadenopathy are uncommon. In advanced disease, there may be effusion, synovial thickening, deformity (caused by collapse of tarsal bone), discharging sinuses or a cold abscess. *Diagnose:* As for Ankle TB *Treat:* As for Ankle TB

Outcomes

Healed status

For patients with a diagnosis of confirmed/probable bone TB, healed status is determined by:

- completion of ATT and no relapse of disease at 2 years' follow up
- resolution of fever, night sweats, weight loss (if initially present)
- resolution of sinuses/ulcers (if initially present)
- radiological signs of bone healing, including remineralisation of affected bone, sharpening of joint/vertebral margins. On MRI, resolution of marrow oedema, fatty replacement in marrow and no contrast enhancement

Presumptive treatment failure

For patients with a diagnosis of bacteriologically confirmed or clinically diagnosed bone TB, treatment failure should be suspected when they have any of the following after completing at least 5 months' ATT:

- Persisting or worsening local and systemic symptoms and signs
- No improvement, or deterioration of the lesion on repeat imaging
- Appearance of new lesion(s)
- Non-healing ulcer/sinus
- New abscesses/lymphadenopathy
- Wound dehiscence post-operatively.

Possible causes of deterioration on treatment or failure to improve on treatment:

- Poor adherence to ATT – inadequately treated skeletal TB
- Drug resistance
- Paradoxical reaction
- Immune reconstitution syndrome associated with HIV
- Alternative diagnosis – patient does not have TB or has two diagnoses.

Suggested investigations in patients with presumptive treatment failure:

- Complete blood count and inflammatory markers such as ESR, liver enzymes, urea and electrolytes, fasting blood glucose/HbA1c and HIV test
- Repeat imaging and repeat diagnostic sampling, for example CT-guided biopsy of the lesion
- Send tissue for: a) staining for AFB and culture for Mtb with drug susceptibility testing; b) Gram's stain and bacterial and fungal culture; c) histopathology. PCR-based diagnostic tests are of variable sensitivity in bone TB, and there is uncertainty about specificity in previously treated TB patients.

The expert group suggests that patients with bacteriologically confirmed or clinically diagnosed treatment failure be treated with second-line drugs. For patients with bacteriologically confirmed treatment failure, treatment should be guided by drug susceptibility testing. For clinically diagnosed treatment failure, the specialist team should carefully monitor empirical treatment with second-line drugs.

Paradoxical reaction

A patient with confirmed or probable skeletal TB on ATT who initially improves and then subsequently has worsening constitutional symptoms or signs of TB in the absence of another diagnosis or drug resistance. Features include increased size of lesion, appearance of new lesions, recurrent fever and night sweats, or development of another form of TB.

In drug-resistant cases, the patient will usually fail to improve from the start of ATT, or deteriorate from the start of ATT. There will be no improvement until an effective second-line ATT regimen is started.

In paradoxical reaction, there is usually an initial improvement, followed by deterioration. The patient will usually begin to improve again without changes to the ATT regimen; ATT should not be stopped or altered. NSAIDS and other supportive treatment are usually sufficient.

18 Cutaneous TB

Cutaneous TB is caused by M. tuberculosis, *M. bovis*, and, rarely, Bacille Calmette-Guérin (BCG). TB of the skin is uncommon, accounting for around 1.5% of EPTB cases. Cutaneous TB often coexists with other forms of TB, especially pulmonary TB and lymph node TB.

Scrofuloderma and lupus vulgaris are the most common manifestations of cutaneous TB, and are particularly prevalent in children. The manifestations of cutaneous TB are summarized in the table below (Tappeiner, 2008).

Although it is not life threatening, cutaneous TB can cause profound distress to the patient due discomfort and disfigurement if not adequately treated. As some manifestations mimic other skin diseases, it can be difficult to diagnose, and patients may have received unnecessary or inappropriate treatment from several practitioners before the correct diagnosis is made. Evaluation by an experienced dermatologist is crucial if the diagnosis is not clear.

Clinical disease	Aetiology	Host immune status
Lupus vulgaris Scrofuloderma	Haematogenous spread	Can affect immunocompetent or immunocompromised people
Acute miliary TB Orificial TB Metastatic tuberculous abscess (tuberculous gumma)	Haematogenous spread	Usually seen in immunocompromised people
Primary Inoculation TB	Inoculation of the skin with Mtb, e.g. by needle stick injury, or at site of trauma	No previous TB infection, immunocompetent
Tuberculosis verrucosa cutis	Inoculation of the skin with Mtb, e.g. by needle stick injury, or at site of trauma	Previous TB infection, immunocompetent
Normal primary complex-like reaction Post-vaccination lupus vulgaris Perforating regional adenitis	BCG innoculation	No previous TB infection
Lichen scrofulosorum Papulonecrotic tuberculid	True tuberculids – thought to represent hypersensitivity reactions, rather than local TB infection of the skin	Not clear; likely some immunity due to previous exposure

Clinical disease	Aetiology	Host immune status
Nodular vasculitis (erythema induratum of Bazin) Erythema nodosum	Facultative tuberculids – Mtb may be one of several aetiological agents causing this pathology	Not clear; likely some immunity due to previous exposure

18.1 Patients who should be investigated for cutaneous TB

Presumptive cutaneous TB	Patients with the following clinical presentations: • Ulcers or discharging sinuses over the sites of lymph nodes, bones and joints • Persistent, asymptomatic raised reddish/reddish brown skin lesion of more than 6 months' duration, which may show scarring at one end • Persistent warty skin lesion of more than 6 months' duration

18.2 Diagnosis

Test	Patients	Comments
X-ray of chest	All	All patients presenting with symptoms consistent with TB should have a chest X-ray to look for previous or active pulmonary TB.
HIV test	All	EPTB is associated with HIV infection. All patients should be offered integrated counselling and testing.
Further radiological tests	Selected	All patients require clinical assessment for TB affecting other organ systems such as the chest, abdomen, lymph nodes, bones and joints and CNS. Radiological evaluation should be focused according to the history and examination findings.
Skin biopsy	All	Skin biopsy is required to determine the aetiology of the lesion. Histopathological examination by an experienced specialist remains the most reliable way of making the diagnosis. Staining and microscopy for AFB has very low sensitivity. Culture has low sensitivity; but if positive, confirms the diagnosis of cutaneous TB and facilitates drug susceptibility testing PCR-based tests are in use with variable diagnostic accuracy, but a lack of evidence from high quality studies means they cannot be recommended for routine use currently.

Test	Patients	Comments
Mantoux test (tuberculin skin testing)	Selected	The Mantoux test is not usually part of the diagnosis of active TB infection. However, the Cutaneous TB Group agreed that in selected cases where diagnosis was equivocal, it might be used as an ancillary test. However, only a strongly positive result (with a diameter of 22 mm or more at reading) supports a diagnosis of cutaneous TB (Ramam, 2011). A negative or weakly positive result does not rule out TB. Sensitivity and specificity estimates for this test vary widely across case series, and the result must be interpreted in the context of the other clinical findings.

18.3 Treatment

All patients with the following results should be treated for cutaneous TB:

- Patients with histology diagnostic of cutaneous TB
- Patients with positive culture of Mtb or microscopy for AFBs from skin biopsy
- Patients with equivocal histology findings and negative microscopy and culture, but strongly positive Mantoux test

First line treatment for adults and children with TB pericarditis	Drugs	2RHZE/4RHE
	Duration	6 months
	Referral	Referral to a dermatologist for diagnosis and management is encouraged. Physicians in primary or secondary care can used teledermatology services to guide referral decisions. Complex cases where the diagnosis is uncertain or the response to ATT is inadequate may require referral to a specialist centre.
	Follow up	Assess response to treatment at 4–6 weeks. Most patients will show significant improvement by this time. Failure to improve or deterioration may be due to misdiagnosis or drug resistance. Specialist referral is advised for such patients. Subsequent follow up of patients responding to treatment can continue at 8 weekly intervals until treatment is completed.
	Sequelae	Scarring caused by the initial infection and then healing of the skin can cause disfigurement. There is an increased risk of squamous cell carcinoma in patients with long-standing untreated disease.

19 Special groups

Pregnant and breast-feeding women may be treated with RHZE with pyridoxine 10 mg daily, as for other patients. There is no need to cease breast feeding. Some drugs used in secondary regimens such as streptomycin, prothionamide, ethionamide and the quinolones are contraindicated due to teratogenicity.

Women who need contraception should be counselled on the use of oral contraceptives while receiving rifampicin. Women should be offered an oral contraceptive pill containing a higher dose of oestrogen (50 µg) after consultation with a clinician, or a non-hormonal method of contraception while taking rifampicin and for 1 month after the end of treatment.

Patients with kidney impairment may need dose titration of some ATT drugs, and may not tolerate certain drugs at all. Specialist guidance is recommended. There are specialist guidelines for patients with chronic kidney disease elsewhere, such as the British Thoracic Society Guidelines for the Prevention and Management of TB infection in Adult Patients with Chronic Kidney Disease (British Thoracic Society Standards of Care Committee and Joint TB Committee, 2010).

Patients with previous liver disease such as history of acute hepatitis or current alcoholic or non-alcoholic fatty liver disease do not require changes to standard first-line treatment. Patients with acute hepatitis and a non-life-threatening form of EPTB should have treatment with ATT deferred until liver function tests normalize. If EPTB is life threatening, e.g. TB meningitis, specialist advice to select an ATT regimen, which contains the least hepatotoxic drugs, is required.

There is uncertainty around the safety of the standard first-line regimen in patients with liver cirrhosis. People with more advanced liver cirrhosis (Child's B and C liver disease) may be at increased risk of drug-induced hepatoxicity (Sharma, 2015).

The WHO guidelines recommend that the number of hepatotoxic drugs used in this setting should depend on the severity of liver disease (WHO, 2010). The following possible regimens are suggested, after consultation with expert clinicians. The choice of regimen depends on the balance of risks and harms relating to effective treatment of TB and prevention of liver injury.

Regimens containing two hepatotoxic drugs (rather than the three in the standard regimen):

- Nine months of isoniazid and rifampicin, plus ethambutol (until or unless isoniazid susceptibility is documented)

- Two months of isoniazid, rifampicin, streptomycin and ethambutol, followed by 6 months of isoniazid and rifampicin
- Six to nine months of rifampicin, pyrazinamide and ethambutol

Regimens containing one hepatotoxic drug:

- Two months of isoniazid, ethambutol and streptomycin, followed by 10 months of isoniazid and ethambutol.

Regimens containing no hepatotoxic drugs:

- Eighteen to twenty-four months of streptomycin, ethambutol and a fluoroquinolone

People with HIV

TB and HIV disease are linked, and identifying people who have both conditions is important to improve outcomes. All EPTB patients should be offered an HIV test as part of their diagnostic process. People with HIV require specialist advice and support pertaining to their diagnosis and treatment options.

HIV-positive people are more likely to have disseminated TB infection at presentation. More detailed diagnostic tests to look for other opportunistic infections and to assess the extent of disease may be useful.

There is increasing evidence that newer diagnostic tests for TB, including Xpert MTB/RIF, have different diagnostic test accuracy in people with advanced HIV and low CD4 counts. These guidelines have not addressed this issue in detail, but information about this can be found elsewhere in the literature.

HIV-positive people are at higher risk of paradoxical reactions, or immune reconstitution inflammatory syndrome (IRIS), and these reactions may be life-threatening. The decision to commence ART must also be considered in patients who are not already receiving it. Guidance on initiation of ART can be found elsewhere at: BHIVA guidelines 2011 (Pozniak, 2011); Rapid Advice on ART for HIV infection in adolescents and adults (WHO, 2009); Guideline on when to start ART and on pre-exposure prophylaxis for HIV (WHO, 2015).

Part 2 References

Basu, S. M. (2014). Degree, duration and causes of visual impairment in eyes affected with ocular tuberculosis. *J Ophthalmic Inflamm Infect. , 4* (1), 10.

Beardsley J, W. M. (2016). Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis. *New England Journal of Medicine , 374* (6), 542-54.

Bell, L. B. (2015). Paradoxical reactions and immune reconstitution inflammatory syndrome in tuberculosis. *International Journal of Infectious Diseases , 32*, 39-45.

Biswas, J. N. (1996-1997). Pattern of uveitis in a referral uveitis clinic in India. *International Ophthalmology , 20* (4), 223-8.

Blakemore, R. S. (2010). Evaluation of the analytical performance of the Xpert MTB/RIF assay. *Journal of Clinical Microbiology , 48* (7), 2495-2501.

British Thoracic Society Standards of Care Committee and Joint TB Committee. (2010). Guidelines for the prevention and management of Mycobacterium tuberculosis infection and disease in adult patients with chronic kidney disease. *Thorax , 65*, 559-570.

Cheng, V. H. (2002). Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients. *European Journal of Clinical Microbiology and Infectious Diseases , 21* (11), 803-9.

Denkinger, C. S. (2014). Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *European Respiratory Journal , 44* (2), 435-46.

Donald, P. (2010). The chemotherapy of tuberculous meningitis in children and adults. *Tuberculosis (Edinburgh) , 90* (6), 375-392.

Fowler, N. (1991). Tuberculous pericarditis. *Journal of the American Medical Association , 266*, 99-103.

Garg, R. M. (2014). Paradoxical reaction in HIV negative tuberculous meningitis. *Journal of the Neurological Sciences , 340* (1-2), 26-36.

GRADE Working Group. (2008). *http://www.gradeworkinggroup.org/publications/*. Retrieved July 2015

Greco, S. G. (2003). Adenosine deaminase and interferon gamma measurements for the diagnosis of tuberculous pleurisy: a meta-analysis. *Int. J. Tuberc. Lung Dis. , 7* (8), 777-786.

Guyatt Gordon H, O. A.-Y. (2008). Going from evidence to recommendations. *British Medical Journal , 336*, 1049.

Higgins, J. A. (2011). Chapter 8: Assessing risk of bias in included studies. In G. S. Higgins JPT, *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.* The Cochrane Collaboration.

Jabs, D. N. (2005). Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *American Journal of Ophthalmology , 140*, 509-161.

Jain, A. S. (2012). Magnetic resonance evaluation of tubercular lesion in spine. *International Orthopaedics , 36* (2), 261-9.

Liang, Q. S. (2008). Diagnostic accuracy of adenosine deaminase in tuberculous pleurisy: a meta-analysis. *Respiratory Medicine , 102* (5), 744-754.

Light R.W., M. M. (1972). Pleural effusions: the diagnostic separation of transudates and exudates. *Annals of Internal Medicine , 77* (4), 507-513.

Light, R. (2010). Update on tuberculous pleural effusion. *Respirology , 15* (3), 451-458.

MRC. (1948). Medical Research Council Report. Streptomycin treatment of tuberculous meningitis. *Lancet , 1*, 582-96.

Nhu, N. H. (2014). Evaluation of GeneXpert MTB/RIF for diagnosis of tuberculous meningitis. *Journal of Clinical Microbiology , 52* (1), 226-33.

Porcel, J. E. (2010). Diagnostic performance of adenosine deaminase activity in pleural fluid: a single-center experience with over 2100 consecutive patients. *European Journal of Internal Medicine , 21* (5), 419-423.

Pozniak, A. C. (2011). British HIV Association guidelines for the treatment of TB/HIV coninfection. *HIV Medicine , 12*, 517-524.

Prasad, K. S. (2016). Corticosteroids for managing tuberculous meningitis. *The Cochrane Library* (4), 1-64.

Ramam, M. M. (2011). How useful is the Mantoux test in the diagnosis of doubtful cases of cutaneous tuberculosis? *International Journal of Dermatology , 50* (11), 1379-82.

RNTCP. (2014). *TB India 2014 Revised National TB Control Programme Annual Status Report.* Ministry of Health and Family Welfare, Central TB Division, Directorate General of Health Services. New Delhi: Central TB Division.

Rossi, G. B. (1987). Tuberculous pleural effusions. Evidence for selective presence of PPD-specific T-lymphocytes at site of inflammation in the early phase of the infection. *American Review of Respiratory Disease , 136* (3), 575-579.

Sharma S.K., M. A. (2004). Extrapulmonary tuberculosis. *Indian Journal of Medical Research , 120* (4), 316-353.

Sharma, P. T. (2015). Clinical and biochemical profile of tuberculosis in patients with liver cirrhosis. *Journal of Clinical and Experimental Hepatology , 5*, 8-13.

Shu, C. W.-T.-Y.-N.-J. (2011). In-hospital outcome of patients with culture-confirmed tuberculous pleurisy: clinical impact of pulmonary involvement. *BMC Infectious Diseases , 11*, 46.

Singh, R. G. (2004). Pattern of uveitis in a referral eye clinic in north India. *Indian Journal of Ophthalmology , 52*, 121-5.

Sreenivas, A. R. (2014). *Standards for TB Care in India.* New Delhi: World Health Organisation Country Office for India.

Steingart K.R., H. M. (2006). Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. *Lancet Infectious Diseases , 6* (9), 570-81.

Steingart, K. S. (2014). Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *The Cochrane Database of Systematic Reviews , 1*, 1-66.

Tappeiner. (2008). Tuberculosis and Infections with atypical mycobacteria. In G. L. Wolff K, *Fitzpatrick's Dermatology in General Medicine, 7th ed.* (p. 1768). New York: McGraw Hill Medical.

TB CARE I. (2014). *International Standards for Tuberculosis Care* (3rd ed.). The Hague: TB CARE I.

The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC). (2015). 2015 ESC Guidelines for the diagnosis and management of pericardial diseases. *European Heart Journal , 36*, 2921–2964.

Thwaites G.E., N. D. (2004). Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *New England Journal of Medicine , 351* (17), 1741-1751.

Thwaites, G. F. (2009). British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. *Journal of Infection , 59*, 167-187.

Van Loenhout-Rooyackers, J. K. (2001). Tuberculous meningitis: is a 6-month treatment regimen sufficient? *International Journal of Tuberculosis and Lung Disease , 5* (11), 1028–35.

Watts, H. L. (1996). Current concepts review: tuberculosis of bone and joints. *The Journal of Bone and Joint Surgery [Am] , 78* (A), 288-98.

WHO. (2015). *Global Tuberculosis Report* (20th ed.). Geneva: World Health Organisation.

WHO. (2014). *Guidance for national tuberculosis programmes on the management of tuberculosis in children* (2nd ed.). Geneva: World Health Organisation.

WHO. (2015). *Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV.* Geneva: World Health Organisation.

WHO. (2009). *Rapid Advice: Antiretroviral therapy for HIV infection in adults and adolescents.* Geneva: WHO.

WHO. (2010). *Treatment of tuberculosis: Guidelines Fourth Edition.* Geneva: WHO.

WHO. (2014). *WHO Handbook for Guideline Development.* Geneva: World Health Organisation.

Wiysonge, C. N. (2016). Corticosteroids and other interventions for treating tuberculous pericarditis. *Cochrane Database of Systematic Reviews*, publication pending.

Annexures

Annex 1 – Participants

Written Declaration of Interest forms were received from the following members marked with asterisk (*) in the list of Core Committee, Methodology Support Group and Technical Advisory Groups

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Dr V.K. Vijayan*	Chest Physician, VP Chest Institute, New Delhi; Advisor to Director General, Indian Council of Medical Research, New Delhi

Annex 2 – Declaration of conflicts of interest

All members of the Core Committee, the Technical Advisory Committees and the Methodology Group completed a declaration of potential conflicts of interest. Although none of the declared interests were considered to have direct relevance to warrant exclusion from the Group, the most significant ones, in accordance with good practice, are noted in the summary here. Members other than those listed below expressed no significant conflicts of interest in their declaration forms.

All committees	Declared potential conflicts of interest
Dr S.K. Sharma	Holds Government research grants in EPTB; Director of WHO-TB Collaborating Centre
Dr Rohit Sarin	Holds Government research grants in EPTB
Dr C.N. Paramasivan	Receives grants and aid money for research on feasibility of new TB diagnostic tests
Dr M.S. Jawahar	Employed in NIRT, Chennai as Scientist in TB Research till 2013
Dr C. Narasimhan	Work on Cardiac sarcoid and TB
Dr Alka Kriplani	Guided two Government funded projects on GU-TB
Dr J. Harikrishnan	Currently participating in two RCTs involving Vitamin D supplementation in HIV patients and smoking cessation in PTB
Dr J.B. Sharma	Completed a Government funded project in female genitor-urinary TB
Dr Alladi Mohan	Holds government research grants in PTB and EPTP
Dr Varinder Singh	Involved in a NUFU, University of Norway funded project evaluating role of micronutrients in pulmonary TB
Dr B. Vengamma	Declared having conducted Government funded primary research in EPTB in the past
Dr Kusum Sharma	Involved in DBT funded projects investigating utility of Xpert MTB/Rif in ocular TB patients during guidelines development
Dr Govind K. Makharia	Received funds from CTD, GoI for conducting an RCT on duration of ATT in abdominal TB till May 2014
Dr D. Ramachandra Reddy	Worked as Deputy Director of Medical Education, Tamil Nadu and as an Educator at TANSACS (Tamil Nadu State AIDS control Society)

All committees	Declared potential conflicts of interest
Dr D. Behera	Chaired the National Task Force, RNTCP, India and National OR Committee, India during guidelines development
Dr Mathew Varghese	Member of the MoHFW, GoI, Task Force on Standard Treatment Guidelines for India
Dr Vidushi Kulshrestha	Had received funds from ICMR, India through her institution AIIMS, New Delhi before April 2011 on two research projects related to roles of PCR and empirical ATT in infertile women
Dr Bobby John	Involved in organizations potentially interested in EPTB guidelines. He was working as Managing Director of Aequitas Consulting Pvt. Ltd. where he received funds for policy review/research and other contracts during the formulation of the guidelines. He was employed by the Bill and Malinda Gates Foundation up to December 2011.
Dr Aparna Mukharjee	Worked as Senior Research Officer in a project titled "Micronutrient supplementation in conjunction with standard anti-TB therapy in newly diagnosed paediatrics pulmonary patients". Project ended in 2012.
Dr Hannah Ryan	Received a grant from Department for International Development, UK that aims to increase the number of evidence-based decisions in middle- and low-income countries, through her organization - Cochrane Infectious Diseases Group
Dr Paul Garner	Received a grant from Department for International Development, UK that aims to increase the number of evidence based decisions in middle- and low-income countries
Dr Prathap Tharyan	As Director of Cochrane South Asia, received funds from the Department for International Development, UK, via the Effective Health Care Research Consortium
Dr S.K. Kabra	Involved in a NUFU, University of Norway-funded project evaluating role of micro-nutrients in pulmonary TB and in study entitled "Role of GeneXpert MTB/RIF assay in the diagnosis of pulmonary tuberculosis in children", funded by Indian Council of Medical Research
Dr Dileep Babasaheb Kadam	Involved in research in TB relating to management, TB in association with hypertension and diabetes, and the development of a reporting protocol for TB. Projects funded by NIH and DBT
Dr Kadhiravan	Wrote narrative reviews on use of steroids in TB and treatment of genitourinary TB. Current research in adjuvant treatment for TBM
Dr Jamhoith Tonsing	Global fund, USAID and DFID-funded operational research through clinical trials for shortening MDR TB regimen