

Guidelines for Tuberculosis Control in New Zealand, 2019

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This publication, which has been prepared for, and is published by, the Ministry of Health, is for the assistance of those involved in providing tuberculosis prevention and treatment services in New Zealand.

While the information and advice included in this publication are believed to be correct, no liability is accepted for any incorrect statement or advice. No person proposing to treat any other person for tuberculosis should rely on the advice given in this publication without first exercising his or her professional judgement as to the appropriateness of that treatment for that person.

Foreword

New Zealand has committed to the World Health Organization (WHO) goal to end tuberculosis (TB) by 2035. There is substantial effort across the health sector in: identifying and treating TB; identifying, investigating and managing case contacts; and preventing the spread of disease. This involves clinicians in primary health care and hospital settings, public health practitioners, occupational health practitioners, infection prevention and control practitioners and many staff from other sectors and agencies.

The Guidelines that follow summarise the state of evidence on best clinical and public health practice internationally as at March 2019. However, clinical judgement and knowledge of local referral procedures will be required when applying the Guidelines to specific situations. The Guidelines will also need to be interpreted in the context of emerging new evidence and technology. They will not cover all situations and expert advice will assist with interpretation.

Providing advice on the clinical management of TB is necessary as inadequate treatment can harm patients and contribute to disease transmission, drug resistance and associated costs. To this end, these Guidelines update earlier advice (TB Guidelines 2010)¹ on TB diagnostics, and recommend use of a standardised daily regimen where appropriate. The wider use of therapeutic drug monitoring and multidisciplinary decision-making are also encouraged. Groups that will benefit from latent TB infection (LTBI) screening and treatment have been better defined. However, the important areas where best practice is still being defined are not covered in these Guidelines – for example, whole genome sequencing, which may enable faster diagnosis of resistance and better definition of clustered cases.

While New Zealand is considered a low TB incidence country, inequities exist; of the 312 new cases notified between 2011 and 2015 and born in New Zealand, half identified as Māori. Providers of TB services need to address this inequity through the delivery of a whānau centred and culturally responsive model of care for Māori.

78 percent of new TB cases (2011-2015) were born outside New Zealand. Actions to reduce importation of TB into New Zealand through immigration screening and management, coupled with increased awareness within primary care, early identification and improved options for treatment that are more acceptable to patients and less stigmatising, such as TeleDOT, will help reduce inequities.

Our efforts to reduce TB could be enhanced by expanding treatment of LTBI. However, implementation across New Zealand would require increased resourcing and funding and needs to be considered alongside other health priorities and the consideration of where, when and how implementation would be best prioritised. There are no immediate plans to implement this approach at a national level. However, individual

¹ Ministry of Health. 2010. *Guidelines for Tuberculosis Control in New Zealand, 2010*. Wellington: Ministry of Health. URL: www.health.govt.nz/publication/guidelines-tuberculosis-control-new-zealand-2010 (accessed 15 May 2019).

district health boards (DHBs) may consider it at a district level, based on their local population priorities and needs.

Considerations of resourcing are not unique to New Zealand and underscore the value of prioritising on the basis of need and cost-effectiveness.

Thanks to the many contributors

That TB is an important focus for many health care workers is underscored by the extensive engagement of many in the discussions and consultation process surrounding this work.

Our thanks go to the authors of the Guidelines and all those who contributed their time, their passion for the prevention and management of TB and their careful consideration of the document.

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Abbreviations

Abbreviation	
24-MIRU	24 loci mycobacterial interspersed repetitive units. This is a molecular typing method used for epidemiological purposes.
ADA	Adenosine deaminase
AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
AIIR	Airborne infection isolation room
ALT	Alanine aminotransferase
ARPHS	Auckland Regional Public Health Service
AS/NZS	Australian/New Zealand Standards
AST	Aspartate transaminase
ATM	Atypical mycobacteria
ATS	American Thoracic Society
BAL	Broncho-alveolar lavage
BCG	Bacille Calmette-Guérin
BID	Twice a day
BSC	Biosafety cabinet
BSC-II	Biosafety cabinet – class II
CARM	Centre for Adverse Reactions Monitoring
CDC	United States Centers for Disease Control and Prevention
CI	Confidence interval
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CSF	Cerebrospinal fluid
CT	Computed tomography
CXR	Chest X-ray
DHB	District health board
DOT	Directly observed therapy
DOTS	Directly observed therapy, short course
DST	Drug susceptibility testing
E	Ethambutol
EBUS	Endobronchial ultrasound-guided
EIA	Enzyme immunoassay
EMU	Early morning urine
EPTB	Extrapulmonary tuberculosis
ESR	Institute of Environmental Science and Research
FDC	Fixed-dose combination
FNA	Fine needle aspirate
G	Gauge
GESA/GENCA	Gastroenterological Society of Australia / Gastroenterological Nurses College of Australia

Abbreviation	
GFR	Glomerular filtration rate
GLI	Global Laboratory Initiative
GP	General practitioner
H	Isoniazid
HHS	United States Department of Health and Human Services
HBeAg	Hepatitis Be antigen
HCU	Heater-cooler unit
HCW	Health care worker
HEPA	High-efficiency particulate air
HIV	Human immunodeficiency virus
HSWA	Health and Safety at Work Act 2015
IBW	Ideal body weight
ICT	Immunochromatographic test
IDSA	Infectious Diseases Society of America
IFN-gamma	Interferon-gamma
IGRA	Interferon gamma release assay
INZ	Immigration New Zealand
IPC	Infection prevention and control
IRHWG	Immigration and Refugee Health Working Group
IU	International unit
IUATLD	International Union against Tuberculosis and Lung Disease
LFT	Liver function test
LPA	Line probe assay
LTBI	Latent tuberculosis infection
M	Moxifloxacin
MALDI-TOF	Matrix-assisted laser desorption ionization – time of flight
MDR	Multidrug resistance
MDR-TB	Multidrug-resistant tuberculosis
MELAA	Middle Eastern, Latin American and African
MGIT	Mycobacteria growth indicator tube
MIC	Minimal inhibitory concentration
MIRU	Mycobacterial interspersed repetitive units
MIRU-VNTR	Mycobacterial interspersed repetitive units – variable number tandem repeat
MTB	<i>Mycobacterium tuberculosis</i>
MOTT	Mycobacteria other than tuberculosis
MRI	Magnetic resonance imaging
MTBC	<i>Mycobacterium tuberculosis</i> complex
NAAT	Nucleic acid amplification test
NALC	N acetyl-L-cysteine
NICE	National Institute for Health and Care Excellence (United Kingdom)
NNT	Number needed to treat
NPA	Nasopharyngeal aspirates
NTAC	National Tuberculosis Advisory Committee (Australia)

Abbreviation	
NTM	Non-tuberculous mycobacteria
OR	Odds ratio
PAS	Para-amino-salicylic acid
PC	Physical containment level
PCBU	Person conducting a business or undertaking
PCR	Polymerase chain reaction
PNB	p-nitrobenzoic acid
PPD	Purified protein derivative
PPE	Personal protective equipment
QAP	Quality assurance programme
QFT-GIT	QuantiFERON®-TB Gold In-Tube assay
QFT-Gold	QuantiFERON®-TB Gold assay
R	Rifampicin
RCPA	The Royal College of Pathologists of Australasia
RCPA MSIG EQA	The Royal College of Pathologists of Australasia Mycobacterium Special Interest Group External Quality Assurance
RCT	Randomised controlled trial
RD1	Region of difference 1
RHSS	Refugee Health Screening Service
RPT	Rifapentine
RR	Relative risk
S	Streptomycin
SDG	Sustainable Development Goals (United Nations)
TAT	Turnaround times
TB	Tuberculosis
TBCN	Tuberculosis clinical network
TBNA	Transbronchial needle aspirate
TNF- α	Tumour necrosis factor alpha
TSH	Thyroid stimulating hormone
TST	Tuberculin skin test
TU	Tuberculin unit
UNHCR	United Nations High Commissioner for Refugees
WGS	Whole genome sequencing
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis
Xpert MTB/RIF	GeneXpert MTB/RIF assay; a cartridge-based rapid diagnostic nucleic acid amplification test that can identify <i>M. tuberculosis</i> DNA and resistance to rifampicin
Z	Pyrazinamide
ZN	Ziehl-Neelsen

Chapter 1: Introduction

Executive summary

Through the World Health Organization (WHO), New Zealand has adopted the global community's ambitious End TB Strategy (WHO 2014). New Zealand is a low tuberculosis (TB) incidence country, but TB is still a public health threat. Increasing rates of multidrug-resistant TB (MDR-TB) and increasing international connectedness mean TB control will remain a priority for the foreseeable future. Ongoing review of clinical and public health practices are required to address this threat.

This chapter describes the epidemiology of TB and context for TB control in New Zealand. According to WHO criteria, New Zealand meets the criteria for being a low TB burden country, but the TB incidence in New Zealand is higher than the threshold for pre-elimination or elimination status. Furthermore, within New Zealand, the burden of TB falls disproportionately on migrant communities and Māori.

To eliminate TB, New Zealand faces a set of challenges that are common to many low-burden countries. These common challenges have led to the WHO listing a set of priority actions for TB elimination in low-burden countries, which has informed the recommendations made in this 2019 update of the New Zealand TB guidelines.

Global context

Globally 10 million people are diagnosed with TB annually, resulting in 1.5 million deaths and 50 million new *Mycobacterium tuberculosis* infections (WHO 2015). Fifty-six percent of TB cases occur in South East Asia and the Western Pacific – the countries nearest to New Zealand. Failed global TB control means all countries, including New Zealand, face the threat of new cases and drug resistance.

The WHO End TB Strategy sets global targets to eliminate TB as a public health problem by 2035: a 95 percent reduction in the number of TB deaths compared with 2015, a 90 percent reduction in the TB incidence rate compared with 2015 and zero TB-affected families facing catastrophic costs due to TB (WHO 2014). The global strategy emphasises the need for all countries, including low-incidence countries like New Zealand, to progress towards pre-elimination (<10 cases per million) and eventually elimination.

Achieving tuberculosis pre-elimination in New Zealand

Common features underlie TB epidemiology in low-incidence countries like New Zealand. This includes a low rate of transmission in the general population, occasional outbreaks, a majority of TB cases arising from reactivation of latent tuberculosis infection (LTBI) rather than recent transmission and a concentration of cases in risk groups or vulnerable populations. Accordingly, a specific set of priority action areas has been identified for low-burden countries (Lönnroth et al 2015). Of these, the management of MDR-TB patients, the diagnosis and treatment of LTBI and screening of migrants have been specifically addressed through these Guidelines. Neonatal bacille Calmette-Guérin (BCG) vaccination of certain neonates is also part of TB control in New Zealand, further details are in the *Immunisation Handbook 2017* (Ministry of Health 2018b).

Priority action areas for implementation of the post-2015 global TB strategy in low-incidence countries.

- Ensure political commitment, funding and stewardship for planning and essential services of high quality.
- Address the most vulnerable and hard-to-reach groups.
- Address needs of migrants and cross-border issues.
- Undertake screening for active TB and LTBI in TB contacts and selected high-risk groups.
- Provide appropriate treatment.
- Optimise the prevention and care of drug-resistant TB.
- Ensure continued surveillance, programme monitoring and evaluation and case-based data management.
- Invest in research and new tools.
- Support global TB prevention, care and control.

Source: Lönnroth et al (2015).

Tuberculosis epidemiology

For detailed and up-to-date epidemiological information, visit the Public Health Surveillance website <https://surv.esr.cri.nz/surveillance/AnnualTBReports.php>.

In New Zealand, TB is notifiable under the Health Act 1956, meaning a medical practitioner who suspects TB must notify the medical officer of health. For case definitions, see the *Communicable Disease Control Manual* (Ministry of Health 2018a).

Incidence

TB notification rates in New Zealand ranged between 6.2 and 7.0 per 100,000 from 2011 to 2015. New Zealand therefore meets the WHO definition of a low TB incidence country (<100 cases per million population). However, comparison with other developed, low-incidence countries suggests there is scope for improved TB control in New Zealand. In recent years, the TB incidence in New Zealand has been slightly higher than that in Australia (5.3 per 100,000 in 2015), the United States of America (3.0 per 100,000 in 2015) and Canada (4.6 per 100,000 in 2015) but lower than that in the United Kingdom (10.5 per 100,000 in 2015) (Australian Government Department of Health 2015; CDC 2016; Gallant et al 2017; Public Health England 2016).

The rate of TB in New Zealand-born children under the age of five years ranges between one and two cases per 100,000, suggesting that transmission in New Zealand is infrequent. However, some observations suggest this is not the case for Māori (Ministry of Health, ESR 2015). While TB cases in Māori have decreased in number, they still account for a disproportionate number of cases in the New Zealand-born population and genotyping results show that cases in Māori are more likely to be part of a cluster than other New Zealand-born cases, suggesting transmission is more likely among Māori.

Molecular epidemiology

Previously, molecular typing of *M. tuberculosis* isolates was performed by analysing restrictive fragment length polymorphism, but mycobacterial interspersed repetitive units (MIRU) was introduced in 2009 and has been used alone since October 2011. A case was categorised as having a non-unique molecular type if the combination of their MIRU 12 and MIRU 24 typing results matched at least one other case in the national database. If there was no matching strain type in the national database, the case was considered to have a unique strain. In the last five years (2011–2015), 1,131 TB cases had TB molecular typing results, of which 439 (38.8 percent) had non-unique molecular types and were in 169 separate molecular clusters.

The median cluster size, based on cases between 2011 and 2015, was two cases (range 1–38), and 91.1 percent (154/169) of clusters had fewer than five cases.² The remaining 15 clusters were distributed into the following cluster sizes: 5–9 cases (nine), 11–17 cases (four) and 20 or more cases (two).

Risk factors

As expected in a low-incidence setting, TB disease is strongly associated with vulnerable groups. For several years, the most frequently reported risk factors for TB cases have been being born outside New Zealand or living with someone born outside New Zealand. During 2011–2015, 78 percent (1,102 cases) of new TB cases notified were born outside New Zealand; an increase from earlier periods (61 percent for 1995–1999; 68 percent for 2000–2004 and 73 percent for 2005–2010). Of the cases born outside New Zealand, the majority were born in South and Central Asia, followed by the Pacific Islands and South East Asia, all high TB-burden areas. The most frequently reported country of birth was India, followed by the Philippines. The time since arrival in New Zealand and notification date for new TB in 2015 was recorded for 208 (87.8 percent) of the cases born overseas. Of these cases, notification occurred in the first year after arrival in New Zealand for 9.1 percent, and over 70 percent occurred more than two years after arrival in New Zealand.

A small proportion of New Zealand's TB notifications are detected through on-shore immigration screening (7 percent), meaning the majority of notifications in people born overseas is likely to arise from progression of LTBI acquired overseas. Consistent with this, the lineage of *M. tuberculosis* isolates from overseas-born cases is similar to that observed in their region of origin (Yen et al 2013).

Of the 312 new TB cases notified between 2011 and 2015 and born in New Zealand, the majority of cases were of Māori ethnicity (50.3 percent, 157/312) consistent with the high rates of TB in indigenous people around the world (Tollefson et al 2013). European or Other ethnicity (24.7 percent, 77/312), Pacific peoples (18.9 percent, 59/312), Asian (5.4 percent, 17/312) and Middle Eastern, Latin American and African – MELAA (0.6 percent, 2/312) comprised the remainder. Ethnicity was recorded for 98.1 percent (1,081/1,102) of new TB cases notified between 2011 and 2015 and born outside New Zealand. Most cases were of Asian ethnicity (76.1 percent, 823/1,081) followed by Pacific peoples (15.3 percent, 165/1,081), MELAA (5.3 percent, 57/1,081), European or Other (3.2 percent, 35/1,081) and Māori (0.1 percent, 1/1,081).

In 2015, an immunosuppressive illness was present in 58 (20.7 percent) of notifications of new TB cases and immune suppressive medications in 11 (3.9 percent) of notifications. Exposure in health care or other institutional settings was rarely reported. Human immunodeficiency virus (HIV) makes a small contribution to TB incidence in New Zealand (Das et al 2006; Ministry of Health and ESR 2015).

² A cluster can contain just one case when the other cases within that cluster were either not notified on EpiSurv or were notified before the last five years.

Deprivation and region

A high proportion of new TB cases lived in the most deprived parts of New Zealand, whether they were born in New Zealand or overseas. The notification rate was highest in Auckland and Wellington regions, but some smaller district health boards (DHBs) (Hawke's Bay and Hutt Valley) also have high rates.

Table 1.1: Proportion of new TB cases, 2011–2015, born in and outside New Zealand, by deprivation quintile

Quintile	Born in New Zealand		Born outside New Zealand	
	Cases	%	Cases	%
1	20	6.8	107	10.1
2	39	13.3	149	14.1
3	36	12.2	214	20.3
4	52	17.7	270	25.6
5	147	50.0	316	29.9
Total^a	294		1,056	

Deprivation is reported in quintiles. Quintile 1 represents the least deprived section of the population, and quintile 5 represents the most deprived section.

a Cases not included where quintile unknown. Quintile is unknown in about 5 percent of all cases where address was unable to be assigned an NZPep13 score.

Source: EpiSurv – Institute of Environmental Science and Research Ltd.

Age

The majority of TB cases occur in adults, with the highest average annual notification rates over the past 10 years in the 15–39 years age group (9.2 per 100,000), followed by the ≥60 years (7.9 per 100,000) and 40–59 years (5.9 per 100,000) age groups, whereas the rate for the <15 years age group during the same time was 2.0 per 100,000. Between 2011 and 2015, children under 15 years of age accounted for 3–6 percent of all cases, but this proportion varies significantly by ethnicity (43.5 percent of cases in Pacific peoples, 36.2 percent in Māori, 18.8 percent in Asian and 1.4 percent in Europeans or Other ethnic groups).

Table 1.2: Tuberculosis notification numbers and average rates by age, 2011–2015

Age group (years)	2011		2012		2013		2014		2015		Average (2011–2015)	
	Cases	Rate ^a	Cases	Rate ^a	Cases	Rate ^a	Cases	Rate ^a	Cases	Rate ^a	Cases	Rate ^a
<5	8	2.5	4	–	5	1.6	12	3.9	3	–	6	2.1
5–14	11	1.9	8	1.3	5	0.8	7	1.2	6	1.0	7	1.2
15–39	144	9.9	147	10.1	134	9.2	145	9.8	148	9.7	144	9.7
40–59	72	6.0	60	5.0	70	5.8	72	5.9	70	5.7	69	5.7
≥60	71	8.7	74	8.8	60	6.9	66	7.4	67	7.2	68	7.8
Total	306	7.0	293	6.6	274	6.2	302	6.7	294	6.4	294	6.6

a Rate per 100,000 based on mid-year population estimates; not shown for counts of less than five cases

Source: EpiSurv – Institute of Environmental Science and Research Ltd.

The three-year moving average rate of TB notifications in New Zealand-born children aged <15 years is an indirect indicator of recent transmission within the country. This rate decreased from 3.1 per 100,000 in 2007 to 1.7 per 100,000 in 2015.

Clinical characteristics of notified cases

Disease characteristics

The clinical characteristics of cases vary according to place of birth. For cases born in New Zealand, 73.7 percent were reported with pulmonary disease between 2011 and 2015, whereas for those born overseas, pulmonary disease was less frequently diagnosed (52.5 percent) in the same period. This potentially reflects a selection effect from off-shore chest X-ray screening of prospective migrants. Of 811 new TB cases in the 2011–2015 period with pulmonary disease, 755 had available information on whether acid-fast bacilli (AFB) were demonstrated in a direct smear of a clinical specimen. Of these, 54.3 percent (410/755) were smear positive, with sputum reported as the specimen site for 68.7 percent (277/403) of cases.

Between 2011 and 2015, the most common site of infection recorded for cases with extrapulmonary involvement was lymph node (excluding abdominal) (366 cases, 44.5 percent), followed by pleural (131 cases, 15.9 percent) and intra-abdominal (excluding renal) (98 cases, 12.2 percent). During this period, there were 32 cases (3.8 percent) of central nervous system (CNS) TB and 36 cases (4.3 percent) of miliary TB. There were three miliary TB cases aged less than five years, one an infant aged less than one year, one aged one year and the third aged three years, with none of the three having received the BCG vaccine. There were no cases of tuberculous meningitis in the less-than-five-years age group.

Completion of treatment

Between 2011 and 2015, 83.2 percent (1219/1466) of cases completed treatment to the satisfaction of the treating doctor. Others died (5.8 percent), went overseas (3.5 percent with transfer of care, 4.4 percent without) or had treatment stopped due to refusal (0.5 percent), adverse effects (1.2 percent) or pregnancy (one case). For 1.2 percent, the outcome was unknown.

Morbidity and mortality

The case fatality rate was 1.6 percent between 2006 and 2015. Between 2006 and 2015, adults aged 20–29 years had the highest number of hospitalisations (21.3 percent), followed by 30–39 years (17.6 percent) and 70 years and over (16.6 percent). During this period, mortality was highest in the 70 years and over age group (51.1 percent of total deaths).

Table 1.3: Morbidity and mortality of tuberculosis cases, 2006–2015

Year	Number of notifications	Number of hospitalisations	Annual case fatality rate (%)
2006	350	188	1.7
2007	283	154	1.1
2008	293	170	1.4
2009	298	181	1.3
2010	304	176	3.0
2011	306	170	1.0
2012	293	159	1.7
2013	274	166	1.1
2014	302	180	1.3
2015	294	176	2.0

Source: EpiSurv – Institute of Environmental Science and Research Ltd.

Antimicrobial susceptibility of *M. tuberculosis*

Culture data were available on 1,131 cases notified between 2011 and 2015. The majority (88 percent) were fully susceptible to antimycobacterial antibiotics. Isolated resistance to isoniazid was present in 6.4 percent of cases. Drug resistance was more frequent in patients who had relapsed TB, including when cases were previously

treated. Multidrug resistance (MDR), defined as resistance to at least the antibiotics isoniazid and rifampicin (R), was identified in eight isolates (0.8 percent).

Table 1.4: Antimicrobial resistance among new cases, relapses or reactivations, and previously treated cases, 2011–2015

	New cases (<i>n</i> = 1131) %	Relapse/reactivation cases			
		All (<i>n</i> = 41) % <i>p</i> -value ^b		Previously treated ^a (<i>n</i> = 32) % <i>p</i> -value ^b	
Fully susceptible					
	88	82.9	0.332	84.4	0.579
Resistant to: ^c					
Isoniazid ^d	6.4	14.6	0.050	15.6	0.055
Rifampicin	1.0	12.2	<0.001	12.5	<0.001
Ethambutol	0.5	0.0	1.000	0.0	1.000
Pyrazinamide	1.4	2.4	0.456	3.1	0.380
Streptomycin	6.8	9.8	0.522	9.4	0.479
MDR-TB ^e					
	0.8	12.2	<0.001	12.5	<0.001

n number of cases, MDR-TB: multidrug-resistant tuberculosis

a Information on previous treatment was reported for only 33 of the 41 relapse/reactivation cases, 32 of whom were recorded as being treated.

b Rate compared with that among new cases by the Chi-square test or Fisher's Exact test, as appropriate.

c Includes resistance alone or in combination with other antimicrobials.

d Isoniazid resistance at the standard concentration of 0.1 mg/L.

e MDR-TB, that is, resistant to at least isoniazid and rifampicin.

Case definitions: Tuberculosis disease: new case: Active TB in a person who has never been treated for TB before or has active disease from a new genotype; Tuberculosis disease: relapse or reactivation: Active TB in a person whose tuberculosis has been non-infectious or quiescent following full, partial or no treatment. See the Communicable Disease Control Manual (Ministry of Health 2018a).

Source: EpiSurv – Institute of Environmental Science and Research Ltd.

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Chapter 2: Diagnosis of tuberculosis disease

Executive summary

It is very important to maintain a high index of suspicion to make a diagnosis of tuberculosis (TB). TB should always be considered as a cause of illness in individuals with a history of exposure to TB or with previous prolonged residence, even in childhood, in high TB incidence countries, especially those who have arrived recently in New Zealand.

Testing for TB is indicated in everyone with signs and symptoms of TB or considered to be at high risk of TB disease. Common systemic symptoms include fever, night sweats, weight loss, anorexia and malaise, but active TB may also be asymptomatic.

Recommendation summary

- All patients referred with a diagnosis of possible TB should be assessed within two weeks or one to two days if they are thought to be infectious.
- A chest X-ray (CXR) and three sputum samples are recommended for the initial investigation of pulmonary TB.
- When inactive/fibrotic-type changes are seen on a CXR, they should not be attributed to inactive TB unless samples for mycobacteriological culture have been tested to exclude active pulmonary TB or previous CXRs show that the abnormalities have been stable for at least six months, or up to two years if extensive.
- Every effort should be made to confirm the diagnosis by culture. Histological or molecular tests can also confirm the diagnosis but do not give information on drug susceptibility.
- Three sputa are recommended for the diagnosis of pulmonary TB.
- Induced sputa are preferred to spontaneous cough samples, unless the patient has a productive cough.
- Three induced sputa are preferred over bronchoscopy and minimise risk to staff, if performed in an appropriate setting.
- Obtaining tissue samples in saline for TB culture is the preferred approach to diagnosing extrapulmonary TB, as testing fluid samples (pleural, ascitic) lacks sensitivity.

Tuberculosis natural history

The stages of the natural history of TB are described below and depicted in Figure 2.1. These clinical descriptions differ slightly from epidemiological case definitions listed in the *Communicable Disease Control Manual* (Ministry of Health 2018a). Inhaled *M. tuberculosis* replicates in the lungs in alveolar macrophages that migrate into lung parenchyma to form early granulomata. In many cases, these early infections are cleared (Verrall et al 2014), but in others, *M. tuberculosis* begins a period of logarithmic replication, infecting new cells and disseminating to distant sites. This early infection is usually asymptomatic.

The development of adaptive immunity is delayed in *M. tuberculosis*, meaning conversion of the tuberculin skin test (TST) or interferon gamma release assay (IGRA) to positive (see Chapter 7: Diagnosis and treatment of latent tuberculosis infection) usually occurs six to eight weeks after infection. Occasionally, a transient cough, fever or erythema nodosum (a characteristic skin rash) may occur during TST conversion (Poulsen 1950, 1957). Imaging performed at this time may show mediastinal lymphadenopathy or transient pulmonary infiltrates. The combination of a site of granulomatous inflammation in the lung and lymphadenopathy that occurs at this stage is called the Gohn complex, and it is the pathological correlate of **primary TB**.

In children under five years of age or people with immunocompromise, primary infection can progress to a disease called **primary progressive TB**. This occurs within six months of infection.

However, in most healthy adults, the development of adaptive immunity to *M. tuberculosis* leads to containment of bacterial replication. Bacilli can persist in a non-replicative state within cells, a state called **latent tuberculosis infection (LTBI)**. LTBI has no symptoms and is diagnosed by a positive TST or IGRA after the exclusion of active TB. Signs of healed primary infection, such as a scar or calcification may be present on a CXR, but it is usually normal.

LTBI progressing to **active TB** is also called **reactivation TB**. The 10-year risk for TB infection progressing from this latent phase to active TB disease is approximately 10 percent (Sloot et al 2014) but this risk is affected by: infecting dose, the age of the person, the presence of healed lesions on a CXR and immunocompromise (Getahun et al 2015). The risk of progression is greatest within the first five years after infection (Borgdorff et al 2011), but it can happen even decades later. In a low-transmission country like New Zealand, reactivation TB is the main form of active TB in adults. Although in clinical and public health practices, LTBI and active TB are conceptualised as discrete phenotypes (as represented in Figure 2.1), in practice, a spectrum of pathological states is likely to exist between latency and confirmed active disease (Lin et al 2014; Zak et al 2016).

The most common site of infection is the lung (pulmonary TB), where TB classically causes an asymmetrical pulmonary infiltrate. The 'classic' TB pathology of caseation, cavity formation and fibrosis occurs late and in a minority of cases. **In New Zealand, approximately one in three patients with active disease are asymptomatic at presentation.**

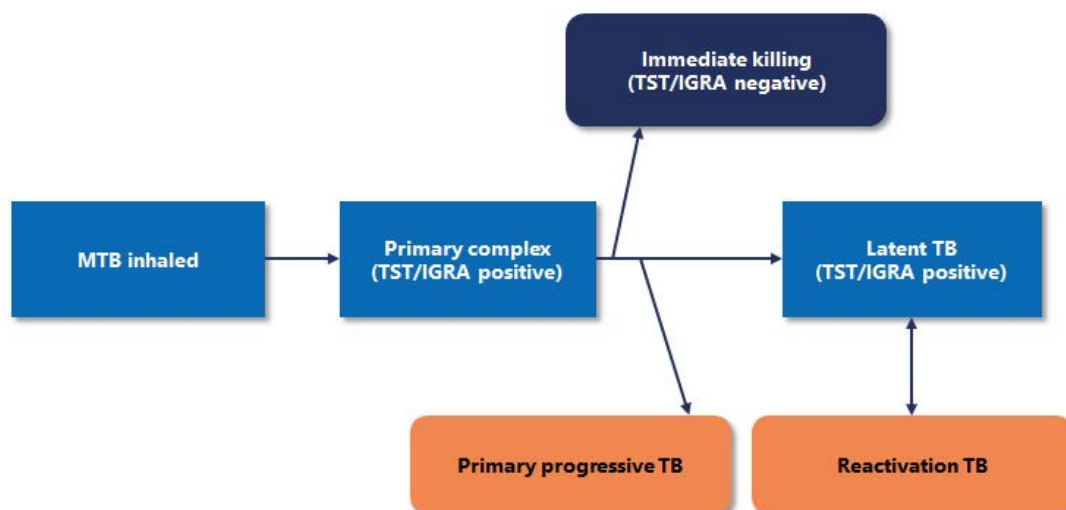
Young children with active TB may be asymptomatic or present with symptoms of fever, lassitude and failure to thrive. Older children and adults with active TB may present with symptoms of anorexia, fatigue, weight loss, chills, night sweats, cough, haemoptysis and chest pain.

Any organ can be affected by **extrapulmonary TB (EPTB)**, causing meningitis, pleurisy, pericarditis, bone or joint infection, renal infection, gastrointestinal tract infection, peritonitis or lymphadenitis, or disseminating via the bloodstream and affecting multiple organs (**disseminated TB**). Disseminated and meningeal TB are more common in very young children. Immunocompromise, like HIV, is associated with higher rates of disseminated TB and less specific clinical features (Cudkowicz 1952).

Inactive TB is sometimes used to refer to individuals with LTBI, who have more extensive CXR abnormalities and no history of previous TB treatment but who do not have microbiological evidence of active TB. Depending on the extent and stability of the changes, these individuals are often treated with a regimen as for active disease, as it is assumed they have a heavier burden of dormant tubercle bacilli and higher risk of progression. See Procedure for investigating extrapulmonary tuberculosis later in this chapter.

Active TB (in this text TB) refers to individuals with evidence of replicating *M. tuberculosis* organisms, demonstrated either by a smear and culture, histological evidence of characteristic granulomatous inflammation or other suggestive tests. TB may be asymptomatic particularly in the early stages of the disease.

Figure 2.1: Natural history of *M. tuberculosis* infection



TST: tuberculin skin test; IGRA: interferon gamma release assay; MTB: *Mycobacterium tuberculosis*; TB: tuberculosis.

Clinical approach

It is very important to maintain a high index of suspicion to make a diagnosis of TB. The need to evaluate a patient for TB is based on suspicion of TB on epidemiologic, clinical and radiographic grounds. TB disease should always be considered in individuals who have a history of contact with TB or with previous prolonged residence in high-TB-incidence countries (Ministry of Health 2018b), especially in people who have recently arrived in New Zealand.

TB may be asymptomatic until the condition is advanced. Common systemic symptoms when they occur include, malaise, fever, anorexia, weight loss and night sweats.

Every effort should be made to confirm the diagnosis by culture. Histological or molecular tests can also confirm the diagnosis but give limited information on drug susceptibility.

Mycobacteria bacilli can be identified by acid fast or fluorescence staining of fresh clinical samples and can provide early support for the diagnosis of TB in high-probability patients but will also be positive in non-tuberculous mycobacteria (NTM). In these situations, cartridge-based rapid molecular assays can be used to diagnose TB.

Because TB is a paucibacillary condition, negative microbiological tests do not necessarily exclude the condition. In a small number of cases, establishing a definitive diagnosis of TB may not be possible, and a presumptive clinical diagnosis is sufficient for commencing treatment.

All patients referred with a diagnosis of possible TB should be assessed within two weeks or one to two days if they are thought to be infectious.

Clinical investigation for TB requires a comprehensive history and physical examination. As well as identifying any presenting symptoms (including fever, night sweats, weight loss, cough and haemoptysis), it is also important to assess risk factors for TB, including previous TB, known TB contacts, country of origin and co-morbidities, including immunosuppression. Physical examination should include a careful assessment for lymphadenopathy. TB may occur at more than one site.

Notification of tuberculosis

Medical practitioners and laboratories must notify TB immediately to the local medical officer of health. In addition to confirmed cases, this also applies to patients reasonably suspected to have TB. Notification should not be delayed while microbiological confirmation is awaited (Ministry of Health 2018a).

Notification of TB encompasses all *Mycobacterium* species within *M. tuberculosis* complex, therefore including *M. bovis* and other species (see Classification in

Chapter 10: Laboratory methods and standards). Infections with non-tuberculous mycobacteria are not notifiable.

Investigations for pulmonary tuberculosis

Important initial tests are a CXR and an examination of sputum or other specimens for acid-fast bacilli (AFB) and mycobacterial culture. Smear positive samples should have a GeneXpert MTB/RIF performed to confirm *M. tuberculosis* and obtain early information on drug resistance (see Chapter 10: Laboratory methods and standards).

Pulmonary TB is the most common form of TB. Diagnostic investigations for pulmonary (including laryngeal TB) are outlined in Table 2.1.

Table 2.1: Diagnostic investigations for pulmonary (including laryngeal) TB

Suspected site of disease	Imaging techniques	Specimen	Routine test	Additional tests (if it would alter management)
Pulmonary or laryngeal	CXR ^a +/-CT thorax ^b	Three respiratory samples (preferably induced sputum or bronchoscopy and lavage. Spontaneously produced deep cough sputum samples may be suitable if the patient has a productive cough.)	Microscopy Culture GeneXpert MTB/RIF assay (Xpert MTB/RIF)	Nucleic acid amplification test (NAAT)

a Lateral and anteroposterior in children.

b CT (computed tomography) imaging is the preferred imaging for mediastinal and hilar lymphadenopathy, pleural and pericardial disease and for defining bronchogenic spread if required (Skoura et al 2015).

Adapted from: NICE Tuberculosis Guideline (NICE 2016).

Procedure for investigating pulmonary tuberculosis

The action taken for an individual case may vary, depending on the patient's age and the presence or absence of risk factors for reactivation of disease. In suspected cases of pulmonary TB, a physical examination and CXR should be performed at the first visit. Sputum samples should be obtained as soon as possible. It is strongly recommended that subjects undergoing investigation for active pulmonary TB are kept in isolation until disease activity and smear status are determined (see Chapter 11: Infection control and occupational health in tuberculosis disease).

When inactive/fibrotic-type changes are seen on a CXR, they should not be attributed to inactive TB unless samples for mycobacteriological culture have been sent to exclude active pulmonary TB or previous CXRs show that the abnormalities have been stable for at least six months, or up to two years if marked. This is of particular relevance in assessing candidates for 'immigration clearance' (see Chapter 9: Migration and screening and their impact on tuberculosis in New Zealand).

Chest X-ray in evaluation of tuberculosis

Features of active pulmonary disease should be followed up with sputum testing. These features include:

- possible patchy consolidation or infiltration
- definite infiltration or consolidation or cavitation.

Features of inactive/fibrotic-type changes with a high probability of progression should be followed up with sputum testing. These features include:

- minor lobar scarring or several tiny (less than 3 mm) dots of calcification
- larger focal areas of scarring
- possible patchy consolidation or infiltration
- definite infiltration or consolidation or cavitation.

Features of previous TB with a low probability of reactivation do not require sputum testing unless there is significant immunosuppression. These include:

- calcified lymph nodes or pleura, with normal parenchyma
- minor apical pleural thickening only
- single calcified granuloma less than 10 mm.

Opacities are often seen apico-posteriorly in the upper and, to a lesser extent, the apical segment of the lower lobes. As the disease progresses, there is more extensive consolidation and cavities develop, which are associated with increased infectivity. Cavity formation is uncommon in primary TB.

A 'miliary pattern' describes the CXR appearance of tiny, evenly distributed nodules. This pattern represents haematogenously disseminated TB (Kwong et al 1996).

Atypical or diminished CXR appearances are seen in conditions associated with varying degrees of immunosuppression, such as diabetes (Pérez-Guzmán et al 2001, 2000) and HIV/AIDS (Friedman and Selwyn 1994).

Pleural and mediastinal lymph node disease are classified as EPTB.

TB pleural effusion is classified as an EPTB. The CXR appearance of the lung parenchyma is often normal in active pleural TB. An abnormal chest radiograph is also common in patients with other forms of TB.

A normal CXR does not exclude EPTB, and testing for this should be pursued if there are suggestive systemic or site-specific symptoms.

Obtaining microbiological specimens for diagnosis of pulmonary tuberculosis

Sputum microscopy and culture

Three sputum specimens should be sent for TB testing. Ideally these are collected early in the morning on three separate days. Where this is not possible, collecting two specimens on the same day, ideally several hours apart, is an option. All three samples are processed for both smear and culture; although for smear-positive sputum specimens only two specimens need to be cultured as the yield is 100 percent. Spontaneously produced deep cough sputum samples may be suitable if the patient has a productive cough, however, induced sputum is preferred. Bronchoscopy with broncho-alveolar lavage (BAL) may be required if induced sputum testing is not available.

Induced sputum

Induced sputum testing requires a patient to inhale a mist of 3–7 percent hypertonic saline (through a mouthpiece or face mask) generated by an ultrasonic nebuliser. It is not the same as physiotherapist-aided coughing, which is not generally as effective. Although specimens often appear more watery than sputum, these are acceptable for testing (Dunlap et al 2000). The procedure has a very high level of patient safety and acceptability.

Induced sputum testing has been shown to be more sensitive than bronchoscopy in the diagnosis of pulmonary TB in subjects who are sputum-smear negative (McWilliams et al 2002).

Induced sputum testing for TB is a useful technique, with the following precaution:

- Respiratory isolation conditions are needed. The procedure must never be carried out in an open clinical area. Infected aerosols persist for a long time in a single room that is not equipped with an air extraction plus a high-efficiency particulate air

(HEPA) filtration system (see Chapter 11: Infection control and occupational health in tuberculosis disease).

The principal patient safety concern is precipitating worsening of air-flow obstruction. Nebulised bronchodilator should precede the hypertonic saline in people with asthma and chronic obstructive pulmonary disease (COPD).

Patients must be supervised by a person who has experience with the procedure. Nursing or physiotherapy expertise is needed to optimise sputum elimination and collection. Staff must wear particulate respirators (see Chapter 11: Infection control and occupational health in tuberculosis disease).

Bronchoscopy and broncho-alveolar lavage

Induced sputum is better than bronchoscopy for diagnosing pulmonary TB (McWilliams et al 2002).

Expert opinion is that BAL produces a better yield than 'bronchial washings' (the latter using 20–40 mL of lavage fluid) and should therefore be used at bronchoscopy. However, studies have not formally addressed this issue.

Bronchoscopy carries a greater risk of nosocomial infection from *M. tuberculosis* than induced sputum testing does, *provided* sputum induction is performed under respiratory isolation conditions.

Procedure for investigating extrapulmonary tuberculosis

In general, when TB is suspected, tissue biopsy is the preferred test and biopsy samples should be sent to the laboratory in saline. A negative test does not exclude TB and clinical review by a clinician experienced with TB is recommended. Site-specific diagnostic investigations for EPTB are outlined in Table 2.2.

Table 2.2: Site-specific diagnostic investigations for extrapulmonary TB

Suspected site of disease	Imaging techniques #	Specimen	Routine test	Additional tests (if it would alter management)
Pleural	CXR Bronchoscopy	Three respiratory samples (preferably induced sputum or bronchoscopy and lavage) Pleural biopsy	Microscopy Culture Histology	NAAT

Suspected site of disease	Imaging techniques #	Specimen	Routine test	Additional tests (if it would alter management)
		Pleural fluid	Microscopy Culture Cytology	Adenosine deaminase assay
Central nervous system	CT MRI	Biopsy of tuberculoma if possible	Microscopy Culture Histology	
		Cerebrospinal fluid	Microscopy Culture Cytology	Adenosine deaminase assay
Meningeal	CT MRI	Cerebrospinal fluid	Microscopy Culture Cytology	NAAT Adenosine deaminase assay
Lymph node	Ultrasound CT MRI	Biopsy	Microscopy Culture Histology	NAAT
Pericardial	Echocardiogram	Biopsy of pericardium	Microscopy Culture Histology	
Pericardial effusion	Echocardiogram	Pericardial fluid	Microscopy Culture Cytology	NAAT Adenosine deaminase assay
Gastrointestinal	Ultrasound CT Laparoscopy	Biopsy of omentum Biopsy of bowel Biopsy of liver	Microscopy Culture Histology	
		Ascitic fluid	Microscopy Culture Cytology	Adenosine deaminase assay
Genitourinary	Ultrasound Intravenous urography Laparoscopy	Early morning urine	Culture	
		Biopsy from site of disease (eg, endometrial curetting or renal biopsy)	Microscopy Culture Histology	
Bone or joint TB	X-ray CT MRI	Biopsy or aspirate of paraspinal abscess Biopsy of joint Aspiration of joint fluid	Culture	
Disseminated	CT of the thorax and head MRI Ultrasound of abdomen	Three respiratory samples Preferably induced sputum or bronchoscopy and lavage. Spontaneously produced deep cough sputum samples may be suitable if the patient is productive	Microscopy Culture	NAAT
		Urine	Culture ^b	NAAT

Suspected site of disease	Imaging techniques #	Specimen	Routine test	Additional tests (if it would alter management)
		Biopsy of the site of the disease, including liver and bone marrow	Microscopy Culture Histology	Additional tests appropriate to site
		Aspirate bone marrow	Microscopy	Additional tests appropriate to site
		Bronchial wash	Culture	
		Cerebrospinal fluid	Cytology	
Skin		Blood	Culture	
		Biopsy	Microscopy Culture Histology	
Tuberculous abscess – outside lymph node	Ultrasound or other appropriate imaging	Aspirate	Microscopy Culture Cytology	
		Biopsy	Microscopy Culture Histology	
Ophthalmological			IGRA/TST	If tissue is available for biopsy consider culture+/- NAAT

CT: computed tomography; CXR: Chest X-ray; IGRA: interferon gamma release assay; NAAT: nucleic acid amplification test includes Xpert MTB/RIF and Ultra; MRI: magnetic resonance imaging; TST: tuberculin skin test.

- a Taking into account the exact site of suspected disease and the availability of the test at the time of the assessment. CT imaging is the preferred imaging for abdominal TB, and MRI is the preferred imaging modality for tuberculous spondylitis and central nervous system TB (Skoura et al 2015).
- b Only if sterile pyuria present, see urine culture below.

Adapted from: NICE Tuberculosis Guideline (NICE 2016).

Additional information about laboratory tests is outlined below, with more detailed laboratory information available in Chapter 10: Laboratory methods and standards.

Consultation with the laboratory is important before ordering tests.

Urine culture

Urine mycobacterial cultures are almost never indicated unless sterile pyuria is present. Furthermore, there are multiple causes of sterile pyuria, and more common causes than *M. tuberculosis* should be excluded before mycobacterial urine cultures are performed, particularly in those with a low risk of exposure to *M. tuberculosis*.

In people with no urinary tract or abdominal symptoms, sterile pyuria, with or without red blood cells, is the main indication to proceed to early morning urine (EMU)

TB tests. In miliary TB, EMU tests may be culture positive without an anatomical urinary tract abnormality.

Sterile pyuria may be an indication for radiological or urological investigation of stenosis and other features of urological TB.

Blood culture for mycobacteria

Blood cultures are rarely positive in TB, with the highest yield in those with miliary disease and those with significant immunosuppression. Blood needs to be collected into Myco/F Lytic bottles (Becton Dickinson, Sparks, MD, USA) or BacT/Alert MB blood culture bottles (Biomérieux, Marcy-L'Etoile, France). Blood culture is preferred over bone marrow culture.

Pleural, pericardial and peritoneal investigations

In 90 percent of tuberculous pleural and peritoneal effusions, the fluid is an exudate with a lymphocyte predominance. Other causes of lymphocytic effusions include lymphoma, other malignancies, collagen vascular diseases and post-coronary artery bypass surgery. Early TB effusions may show neutrophil predominance, and an eosinophilic pleural effusion is occasionally seen (Bassiri et al 1997). A low pleural fluid glucose level is typical.

The sensitivity of the pleural and peritoneal fluid TB culture (10–35 percent) is less than that of pleural or peritoneal biopsy culture taken with pleuroscopy or laparoscopy (39–65 percent). Mycobacterial blood culture bottles are more sensitive than standard TB culture systems for examining these fluids. Histology can increase the diagnostic yield, and therefore, pleural biopsies are essential. In TB pleural effusions, induced sputum may be culture positive in just over 50 percent of cases so is a useful adjunct to investigations (Conde et al 2003). Pericardial fluid has similar biochemical properties to pleural fluid, but pericardial biopsies may be required for histology and culture and need to be obtained surgically.

An adenosine deaminase (ADA) is considered a useful adjunct to diagnosis in suspected TB pleural effusion (Trajman et al 2008). An ADA should be measured on fluid from patients with suspected pleural TB, peritoneal TB and pericardial TB (Nahid et al 2016; NICE 2016; Porcel et al 2010). There is a significant negative correlation between pleural fluid ADA level and age. The use of a lower ADA cut-off may reduce the number of false-negative results (Abrao et al 2014). Indeed, an Auckland study of ADA as an indicator of TB in pleural effusions showed a high negative predictive value when ≥ 15 (100 percent; 95 percent CI: 99.6 to 100) and ≥ 30 units/litre (99.7 percent; 95 percent CI: 99.3 to 99.9) (Blakiston et al 2018). An extremely high ADA should raise suspicion of empyema or lymphoma (Porcel et al 2010).

Lymph node tuberculosis

Because pulmonary TB co-exists in 70 percent of cases of supra-clavicular and cervical TB adenitis, a CXR is indicated. When pulmonary disease is also present, it may be easier to confirm the diagnosis with respiratory investigations.

A patient with lymphadenopathy may have other possible diagnoses, particularly malignancy. Therefore, it is important that clinicians performing this procedure have assistance from the laboratory in preparing cytological smears and putting a sufficient sample into a TB culture medium (usually a mycobacteria growth indicator tube, MGIT). Fluid or caseous appearing lymph nodes in patients at high likelihood of TB are often best sampled with an 18 G needle – the standard 25 G cytology needle often results in tiny, less useful samples. Direct smear of lymph nodes is of low yield, so cultures should be prioritised for scanty samples. Xpert MTB/RIF may be performed but will need to be discussed with the laboratory beforehand.

It is always desirable in this era of increasing drug resistance and given the propensity of TB lymphadenopathy to vary in size even during successful treatment, to obtain culture and sensitivity data. Therefore, if fine-needle aspirate smears and cultures are negative, a core biopsy or excision biopsy should be performed with a mycobacterial culture and cytology/histology. Ideally treatment should not be started until a positive culture has been obtained or until an abnormal node has been excised and is being cultured for mycobacteria.

In mediastinal adenopathy where TB is strongly suspected, it may be possible to obtain a transbronchial needle aspirate (TBNA) or an endobronchial ultrasound-guided TBNA (EBUS TBNA) (Steinfort et al 2009). Mediastinoscopy and biopsy is the usual sampling technique used when available. Intraabdominal lymphadenopathy may be sampled via laparoscopy.

Central nervous system tuberculosis

Central nervous system (CNS) TB causes significant morbidity and mortality, and diagnosis is often delayed. TB meningitis or CNS disease should be considered in anyone seriously ill with disseminated TB or in patients with TB exposure and meningism, encephalopathy or progressive neurological symptoms. In such cases, there should be a low threshold for performing a CT scan or MRI and/or lumbar puncture. CT/MRI is usually performed before a lumbar puncture in order to exclude raised intracranial pressure, posterior fossa disease or obstructive hydrocephalus. It is difficult to exclude these with clinical examination alone, especially as performing fundoscopy may be hazardous in infectious patients.

Characteristic findings on cerebrospinal fluid (CSF) examination include a leucocytosis (usually lymphocyte predominant, although polymorphs may predominate in a minority of patients with early disease), a raised protein in almost all patients and a low glucose (Thwaites et al 2009). At least 5 mLs of CSF should be cultured or sent for a nucleic acid amplification test (NAAT) as volumes less than this are associated with false negative results. AFB are found in less than 20 percent of cases. TB polymerase chain reaction (PCR) has excellent specificity but low sensitivity of around 50–60 percent, and up to

45 percent of patients with presumed TB meningitis have negative CSF cultures (Thwaites et al 2009). The Xpert MTB/RIF Ultra, a NAAT, may have higher sensitivity than culture (Bahr et al 2018). Routine blood test results are non-specific, but hyponatraemia is very common. It is important to search carefully for TB at other sites in patients with suspected CNS TB. Empiric treatment should be started early in patients with clinical features of CNS TB, even if rapid diagnostic tests are negative. Full neuroimaging is recommended in all cases of CNS TB (Darwish et al 2001).

Routine blood tests

Abnormal results that may be found with TB include the following.

- A mild leukocytosis – occasionally a leukaemoid reaction or a leukopaenia or raised monocyte or eosinophil count.
- Anaemia is common, especially with disseminated disease, and iron studies show non-specific features of chronic disease.
- Pancytopenia, which may indicate extensive bone marrow involvement.
- Hyponatraemia, which occurs in about 10 percent of cases and is due to the production of an anti-diuretic hormone-like substance in diseased tissue. When present, hypo-adrenalism should be excluded by a short synacthen test.
- Hypercalcaemia in about 5 percent of cases of TB – but it is usually mild and responds to treatment of the TB.
- Mild hepatic dysfunction, which is common with moderately extensive TB. More severe hepatic dysfunction may be due to a co-existing disease, such as viral hepatitis or alcoholism.
- Hypoalbuminaemia and other non-specific features of severe chronic disease, especially in disseminated TB.

HIV testing

It is recommended that all patients suspected to have TB or diagnosed with TB should be offered human immunodeficiency virus (HIV) testing on an opt-out basis. The clinical presentation of TB in HIV infection is influenced by the degree of immunosuppression. With increasing immunosuppression, the clinical presentation becomes less typical. HIV is the strongest risk factor for the development of active TB.

Tuberculin skin test or interferon gamma release assay

Positive TST and IGRA results do not distinguish between active TB disease and LTBI. In addition, false-negative TSTs and IGRAs may occur in patients with active TB disease (up to 30 percent in patients with TB pleuritis in one previous series) (Ferrer 1997).

False-positive TSTs may also occur in patients with previous bacille Calmette-Guérin (BCG) vaccination or exposure to NTMs; the risk of false-positives in this setting is less with IGRAs. The magnitude of the TST reaction does not predict the likelihood of current active TB disease (Al Zahrani et al 2000). Therefore, a positive TST or IGRA may help to support a diagnosis of active TB in appropriate clinical circumstances but is never conclusive.

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Chapter 3: Treatment of tuberculosis disease in adults

Executive summary

This chapter includes information on the treatment of active tuberculosis (TB), the monitoring of patients on TB treatment and the treatment of TB in special situations, including renal impairment, hepatic impairment and pregnancy. This chapter refers specifically to the treatment of TB in adults. The treatment of TB in children is discussed in Chapter 5: Tuberculosis in children.

Practitioners who are not familiar with TB and its management are advised to refer patients suspected with TB to a clinician experienced in the field. Patients with TB should be treated by a specialist multidisciplinary team with experience in managing TB.

All practitioners should refer to Medsafe data sheets for the latest safety and efficacy information when prescribing medicines for the treatment of TB. Data sheets can be viewed on the Medsafe website: <https://medsafe.govt.nz> or via The New Zealand Formulary: www.nzformulary.org/

The objective of anti-tuberculous treatment is to cure the disease while preventing the development of resistance.

Recommendation summary

- International best practice is for adults with pulmonary TB to be started on a standard six-month regimen consisting of an intensive phase of isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z) for two months followed by isoniazid and rifampicin for four months (2RHZE/4RH).
- International best practice is to include ethambutol in the initial regimen for the treatment of all TB patients until drug susceptibility testing (DST) establishes that it is not necessary.
- Regimens with daily dosing are recommended. Thrice-weekly directly observed therapy (DOT) is no longer recommended.

- Patients with some forms of extrapulmonary tuberculosis (EPTB) may require a more prolonged treatment course.
- Patients with miliary/disseminated TB should be assessed for evidence of central nervous system (CNS) TB.
- Single agents should not be added to an existing treatment regimen without the advice of a TB specialist, and particularly not to a failing regimen. The addition of two or more drugs is required if treatment failure is suspected.
- All cases of multidrug-resistant tuberculosis (MDR-TB) or extensively drug-resistant tuberculosis (XDR-TB) must be treated in consultation with the Ministry of Health TB clinical network (TBCN).
- A daily dosing schedule should be used for all patients with drug-resistant TB.
- Patients who are sputum-smear positive before treatment should have repeat sputum tests at least monthly to confirm sterilisation.
- If the specimen at the end of the third month is both smear and culture positive, repeat DST should be performed.
- As early detection of drug-resistant TB is important, repeat DST after two months of treatment may be appropriate in some patients where there are concerns that acquired drug resistance may have developed.
- Baseline blood count, creatinine, liver function tests, hepatitis B surface antigen and hepatitis C and human immunodeficiency virus (HIV) serology should be completed in all adults who are to be treated for TB disease or latent TB infection (LTBI).
- Regular monitoring of liver function tests should occur for all patients on treatment for TB, with the frequency determined by risk factors for hepatotoxicity.
- Patients should be advised of common and important side effects, such as those associated with hepatitis and ocular toxicity, and to report these promptly.
- The prompt recognition and appropriate management of adverse drug reactions is essential.
- Monthly monitoring of visual acuity and colour discrimination is recommended for all patients on ethambutol for longer than two months and for any patient with renal impairment.
- Some patients will require a temporary treatment regimen to be started following a drug reaction until the difficulties have been resolved.
- The interaction of TB drugs with other medications must always be considered when starting TB treatment.
- TB in patients with hepatic dysfunction and renal impairment is complex, and treatment regimens may require dose adjustment with regular patient monitoring.

Management principles in treating tuberculosis

The objectives of anti-tuberculous treatment are:

1. to cure the individual patient and minimise the risk of death and disability
2. to reduce transmission of *Mycobacterium tuberculosis* to other people
3. to prevent the development of drug resistance during therapy.

All patients who are diagnosed with TB disease must be notified immediately. Relapse of TB, whether this occurs during treatment or not, must be re-notified. Infectious cases of TB must be isolated to prevent further spread of disease. Isolation (in hospital or at home) is discussed in Chapter 11: Infection control and occupational health in tuberculosis disease.

Treatment regimens must contain multiple drugs to which the organisms are susceptible. **Single agents should not be added to an existing treatment regimen without the advice of a TB specialist**, and particularly not to a failing regimen. The addition of two or more drugs is required if treatment failure is suspected. Initial treatment should be modified if drug resistance is suspected (see Drug-resistant tuberculosis later in this chapter).

The treatment of TB-HIV co-infection is complex and well covered in guidelines (Department of Health and Human Services 2018). It is essential that all patients have optimal and timely management of both TB and HIV, and any co-infection should be discussed with an infectious disease clinician.

The natural history of TB infection is profoundly altered by HIV infection, and so the diagnosis of HIV needs to be kept in mind. All people being investigated for TB should be offered routine HIV testing.

Phases of treatment and abbreviations of treatment regimens

Commonly used abbreviations for the names of tuberculosis (TB) drugs in treatment regimens are:

- | | |
|---|---------------|
| E | ethambutol |
| H | isoniazid |
| M | moxifloxacin |
| R | rifampicin |
| Z | pyrazinamide. |

Treatment of active TB usually includes two phases:

- intensive phase of treatment (when more drugs are used) – bactericidal phase
- continuation phase (with fewer drugs) – sterilisation phase.

In a treatment regimen such as 2RHZE/4RH, the number and letters before the slash refer to the intensive phase, and those after it refer to the continuation phase. In this example, the treatment regimen is two months of daily isoniazid, rifampicin, ethambutol and pyrazinamide during the initial phase followed by four months of daily isoniazid and rifampicin in the continuation phase. The absence of a subscript number means the drug is taken daily.

Standard treatment regimens for susceptible pulmonary tuberculosis isolates

International best practice is for adults with drug-susceptible pulmonary TB to be treated with a standard six-month regimen, consisting of an intensive phase of isoniazid, rifampicin, ethambutol and pyrazinamide for two months followed by isoniazid and rifampicin for four months (2RHZE/4RH) (WHO 2009). No other agents can be substituted in the intensive or continuation phase of treatment as this would decrease the efficacy of the regimen and a longer duration of therapy would be required. International authorities recommend ethambutol be included in the initial regimen for the treatment of all TB patients (WHO 2009). Once full drug susceptibility is confirmed, ethambutol can usually be stopped (Nahid et al 2016). However, in patients with a significant disease burden, some authorities recommend continuing ethambutol for the entire first two months or until smear conversion has occurred (Nahid et al 2016; WHO 2009). An injectable agent or moxifloxacin may be used instead when ethambutol is not an option provided drug resistance is not suspected, in which case multiple additional agents may be required in the initial regimen. At the date of publication of these Guidelines, ethambutol is not an approved medication in New Zealand. Clinicians prescribing any unapproved medicine or a medicine for an 'off-label' use under section 29 of the Medicines Act 1981 should do so with the informed consent of the patient.

2RHZE/4RH is the international best practice for the treatment for all cases of susceptible TB. The duration of the intensive phase is for a minimum of two months, but continued until sputum is smear negative for pulmonary TB.

All treatment regimens suggested in this chapter give the minimum period of treatment required to achieve cure. Extensive TB, whether pulmonary or multi-system, requires a longer duration of treatment. In patients with cavitary disease or positive cultures after two months of treatment, the continuation phase of the six-month treatment regimen should be extended so that the patient receives at least nine months of treatment in total. Clinicians should also consider increasing the duration of treatment for patients with extensive TB or slow radiological improvement at the end of treatment.

Standard treatment regimens for extrapulmonary tuberculosis

EPTB is treated with the same regimens as pulmonary TB, except for central nervous system TB, miliary/disseminated TB and bone and joint TB.

Duration of treatment for extrapulmonary tuberculosis

Most patients with EPTB can be treated with a standard six-month short-course treatment if the isolate is fully susceptible. Meningeal TB, intracranial TB and TB of the bones and joints should be treated with a longer duration of treatment.

Studies on the treatment of EPTB are more limited, but reports on pleural, lymphatic, renal, abdominal, meningeal, and bone and joint TB show that outcomes are similar to those of pulmonary TB using similar short-course regimens (Dutt et al 1986; Dutt et al 1992; Goel et al 1990; Medical Research Council Working Party on Tuberculosis of the Spine 1986). However, as the ideal therapy for meningitis, miliary/disseminated disease or spinal disease with neurological complications has not yet been defined with certainty, some authorities have recommended longer duration of treatment.

At least 12 months of treatment is usually recommended for meningeal TB and 18 months of treatment for intracerebral TB (Choudhury 1989; Thwaites et al 2009; WHO 2009). Patients with disseminated TB should be treated for at least nine months and should be assessed for evidence of central nervous system involvement with imaging (ideally magnetic resonance imaging, MRI) and cerebrospinal fluid sampling where possible, and treatment should be extended to 12 months if this is present (National Collaborating Centre for Chronic Conditions 2006). Some experts recommend at least 9 to 12 months of treatment for bone and joint TB, given the difficulties in assessing treatment response (WHO 2009). A longer duration of treatment is also recommended in the presence of severe or extensive disease, drug resistance or clinical or radiological progress that is slower than expected. A daily dosing schedule throughout is considered optimal for patients with central nervous system TB, miliary/disseminated TB and bone and joint TB (Thwaites et al 2009).

Managing central nervous system (CNS) tuberculosis

Recommended treatment

TB meningitis: 2RHZE/10RH

Intracranial TB / tuberculoma: 2RHZE/16RH

All CNS tuberculosis should be treated in conjunction with a TB physician experienced in the management of CNS TB. Table 3.1 shows that isoniazid and pyrazinamide penetrate best into the cerebrospinal fluid. Rifampicin is also an excellent agent if the meninges are inflamed. Rifampicin, isoniazid and pyrazinamide are therefore the most important drugs for treating CNS tuberculosis (Loenhout-Rooyackers et al 2002). Some authorities recommend continuing pyrazinamide beyond two months in the setting of CNS TB.

There are no controlled trials to guide the selection of ethambutol versus an injectable or ethionamide as the fourth drug for TB meningitis (WHO 2009). The current American Thoracic Society guidelines recommend the routine use of ethambutol as the fourth drug (Nahid et al 2016).

An aminoglycoside can be used if the meninges are inflamed and can be an additional agent where drug resistance is suspected; isoniazid is the most common agent to which resistance is found. Fluoroquinolones may represent an effective agent for treating TB meningitis, however data concerning their cerebrospinal fluid pharmacokinetics and safety during prolonged therapy are limited (Alffenaar et al 2008, 2009). Protionamide may also be an option, as this does penetrate into the cerebrospinal fluid.

Intensified treatment of TB meningitis with higher dose rifampicin is controversial. A clinical trial (15 mg/kg rifampicin orally) did not detect a higher rate of survival among adults with TB meningitis than standard treatment (Heemskerk et al 2016). However, smaller un-blinded studies have shown a benefit with intravenous rifampicin (Ruslami et al 2013; van Crevel et al 2016).

Table 3.1: Treatment of tuberculous meningitis and intracranial tuberculosis

	Rifampicin R	Isoniazid H	Pyrazinamide Z	Ethambutol E	Streptomycin S
Drug penetration across the blood/brain barrier:					
• inflamed meninges	++	++	++	+/-	++
• non-inflamed meninges	+	++	++	-	+/-
Drug efficacy in central nervous system TB	++	++	++	-	+/-
Daily drug doses (for adults)*	10 mg/kg	5 mg/kg	25–35 mg/kg		20 mg/kg intramuscular (maximum 1 g)
No dose increase needed for central nervous system TB					
Oral steroid	Should be offered to all patients				

* For information about doses for children, see Chapter 5: Tuberculosis in children.

Frequency of tuberculosis medication dosing

The optimal dosing frequency for patients with pulmonary or EPTB is daily throughout the course of therapy. The use of thrice-weekly dosing is no longer recommended in both the intensive phase and the continuation phase as there is a higher risk of treatment failure, disease relapse and acquired drug resistance. The Ministry of Health recommends every TB case begin their treatment with DOT (see Chapter 4: Supervision and adherence to treatment for further details).

Drug-resistant tuberculosis

If MDR-TB is a possibility and immediate treatment is **clinically** necessary, sufficient drugs should be used initially to avoid the development of further resistance should the isolate subsequently prove to be resistant to all first-line agents. In practice, this may necessitate use of a MDR-TB regimen at the outset. Second-line regimens often present the best hope for cure and thus inappropriate management of a drug-resistant case can have life-threatening consequences.

All cases of MDR-TB must be treated in consultation with the New Zealand TBCN.

Information for activating the TBCN is provided in Appendix 3.1: Information sheet. A case summary will need to be provided to the group (Appendix 3.2: Case summary form). If a MDR-TB suspect is admitted to hospital, they should be in a negative pressure room.

The management of drug-resistant TB is often complicated by drug toxicities and the long duration of therapy. Successful treatment outcomes for drug-resistant TB are often difficult to achieve compared with drug-susceptible disease, especially when multidrug resistance is present.

The most important predictors of drug-resistant TB are:

- a previous episode of TB treatment
- progressive clinical and/or radiographic findings while on TB treatment
- origin from, history of residence in or frequent travel to a region/country with high rates of drug resistance
- exposure to an individual with infectious drug-resistant TB.

Treatment of drug-resistant tuberculosis

The duration of treatment needs to be re-evaluated when drug resistance is encountered. The treatment periods described below are a guide and represent the minimum duration of treatment for patients with TB without central nervous system involvement. A daily dosing schedule should be used for all patients with drug-resistant TB. Intermittent dosing schedules must not be used.

It is essential that exemplary infection control practices are maintained in all case of drug-resistant TB.

Isoniazid-resistant tuberculosis

Isoniazid-resistant tuberculosis should be treated with 6REZM (WHO 2019).

Rifampicin-resistant tuberculosis

Isolated resistance to rifampicin is very uncommon and should raise the suspicion of MDR-TB. The loss of rifampicin from the treatment regimen requires a longer duration of treatment.

Pyrazinamide-resistant tuberculosis

Mycobacterium bovis (or bacille Calmette-Guérin, BCG, related disease) is naturally resistant to pyrazinamide. 2RHE/7RH (or 9RH for minor extent of disease) is appropriate for treatment of patients with isolated pyrazinamide-resistant TB (Combs et al 1990). For patients with extensive disease, moxifloxacin should also be added to the regimen.

Multidrug-resistant tuberculosis

MDR-TB is defined as TB that is resistant to rifampicin and isoniazid. Resistance to other drugs may or may not be present. Resistance to rifampicin and isoniazid eliminates the two most important TB drugs from the treatment regimen. At the time of publication, the WHO has issued a rapid communication summarising key changes in MDR-TB treatment ahead of the release of the full guideline.

Key recommendations for the treatment of MDR-TB are as follows (WHO 2018):

- All cases must be referred/discussed through the NZ TBCN (see Appendix 3.1).
- Drug-resistant TB should be promptly diagnosed and appropriate therapy initiated.
- Patients with MDR-TB should always be treated with a regimen **composed of at least five drugs that are likely to be effective**. If five second-line TB medicines cannot be reached by using agents from groups A and B alone, drugs from group C should be added.
- Usually treatment is continued for at least 18 months after culture conversion.
- Adverse effects should be monitored for and, when found, treated immediately and adequately. They should also be reported to the Centre for Adverse Reactions Monitoring (CARM). Protocols for monitoring for drug toxicity during MDR-TB treatment are published by the Curry International Tuberculosis Center (Curry International Tuberculosis Center and California Department of Public Health 2016).
- Daily DOT is mandatory for all patients with MDR-TB.
- Clinical care should be provided in a way that does not stigmatise people with MDR-TB. As soon as possible, options should be explored to reduce the psychosocial impact of prolonged isolation. For example, by providing access to internet, telephone and television where possible as well as opportunities for walks outside.
- Elective partial lung re-section (lobectomy or wedge re-section) may be used alongside a recommended MDR-TB treatment regimen.

The WHO classifies three different groups of drugs available for use in treating MDR-TB. These groups provide a systematic method for allocating drugs to an MDR treatment regimen (Table 3.2). Treatment regimens should be designed with a consistent approach based on the hierarchy of the three groups of anti-TB drugs.

Table 3.2: Medicines for treating MDR-TB

Group	Drug
Group A – Medicines to be prioritised	Levofloxacin/moxifloxacin, bedaquiline and linezolid
Group B – Medicines to be added next	Clofazimine, cycloserine/terizidone
Group C – Medicines to be included to complete the regimens and when agents from groups A and B cannot be used	Ethambutol, delamanid, pyrazinamide, imipenem-cilastatin, meropenem, amikacin (streptomycin), ethionamide/prothionamide, p-aminosalicylic acid

At the time of publication of these Guidelines, ethambutol, cycloserine, prothionamide, streptomycin and capreomycin, and p-aminosalicylic acid were unapproved medicines, and their use in New Zealand was only possible under section 29 of the Medicines Act 1981. Moxifloxacin, linezolid, clofazimine are approved for other indications and their use for TB treatment is 'off label'. In both cases, patients should give informed consent for their use. For further information, clinicians should consult Medsafe approved data sheets www.nzformulary.org.

Source: World Health Organization (WHO 2018).

Group A: Include all three medicines unless they cannot be used. Treatment with a later generation fluoroquinolone antibiotic significantly improves treatment outcomes in adults with MDR-TB. Linezolid use for at least six months is highly effective although toxicity may limit its use. Bedaquiline should also be prioritised for inclusion, and this will require a Named Patient Pharmaceutical Assessment (NPPA) application unless the patient has XDR-TB.

Group B: Add both medicines unless they cannot be used – clofazimine and cycloserine or terizidone.

Group C: The drugs in this group are only used when a MDR-TB regimen with at least five effective drugs cannot otherwise be achieved.

In addition to expert consultation, current MDR-TB guidelines published by WHO and the Curry International Tuberculosis Center may be useful resources for clinicians involved in managing patients with drug-resistant TB (Curry International Tuberculosis Center and California Department of Public Health 2012, 2016; WHO 2016, 2018).

Extensively drug-resistant tuberculosis

XDR-TB is defined as MDR-TB that is resistant to one or more of the fluoroquinolones and injectable agents (WHO 2016). XDR-TB has a very high mortality rate, especially in the setting of HIV co-infection, and a low cure rate.

All cases of XDR-TB must be treated in consultation with the New Zealand TBCN. Information for activating the MDR-TB TBCN is provided in Appendix 3.1: Information sheet. A case summary will need to be provided to the group (Appendix 3.2: Case summary form).

Corticosteroid treatment in managing tuberculosis

Adjuvant corticosteroid treatment is recommended in the first eight weeks for both TB meningitis and TB pericarditis and may also provide benefit in life threatening cases of TB.

Corticosteroids should only be given when adequate anti-TB treatment is also being given.

Tuberculosis meningitis and intra-cerebral tuberculomas

Randomised controlled trials show improved survival with the use of corticosteroids in patients with all stages of severity of TB meningitis (Girgis et al 1991; Prasad and Singh 2008, 2016; Schoeman et al 1997; Thwaites et al 2004).

All patients with TB meningitis should receive adjunctive corticosteroids regardless of disease severity at presentation (Thwaites et al 2009). The optimal corticosteroid dose is not certain, but the following regimen was used in a recent controlled trial: adults were started on treatment with dexamethasone 0.4 mg/kg/24h with a reducing course over six to eight weeks (Thwaites et al 2004).

Tuberculous pleural effusion

Recommendations for managing tuberculous pleural effusions

- Steroid treatment is not routinely indicated for tuberculous pleural effusions (Lee et al 1998, Galarza et al 1995, Wyser et al 1996).but may be recommended for:
 - large, loculated effusions that cannot be adequately drained (Improvement is unlikely to occur after two months on steroid treatment.)
 - oral steroids may be required to obtain early control of symptoms (pain, fever or malaise).
- Full drainage of tuberculous effusions is desirable (Wyser et al 1996). Usually this can be achieved by repeated thoracentesis. In the past, intercostal tube drainage was avoided because of fears of causing a chronic fistula, but this is unlikely with concurrent modern chemotherapy.
- Follow-up is needed after drainage, as an effusion that has been fully drained may recur and need re-aspiration in the first two to three weeks of treatment.
- Repeat a chest X-ray (CXR) at the conclusion of treatment, as a baseline in case of future disease.

Tuberculous ascites

No well-controlled studies are available. In the absence of evidence to support steroid treatment for tuberculous pleural effusion, it is not recommended for tuberculous ascites.

Tuberculous pericarditis

Although uncommon, pericarditis is a dire complication of TB. Tuberculous pericarditis is almost invariably fatal without treatment and has up to a 40 percent mortality rate even with treatment. Early diagnosis and early institution of anti-TB therapy are important in preventing the development of constriction.

Constrictive pericarditis usually occurs early but can also be a late consequence and is associated with high morbidity and mortality. Although there have been no controlled trials, early surgical intervention is said to be technically easier and is associated with lower operative mortality and a lower rate of subsequent constriction than late pericardectomy.

The efficacy of corticosteroid treatment in tuberculous pericarditis may vary in the different stages of the disease (effusive, effusive-constrictive and constrictive), and many reports do not distinguish these stages. Oral steroids are unlikely to stop the progression from any stage to constrictive pericarditis but do improve survival and reduce the need for surgery (Hakim et al 2000; Strang et al 2004).

Miliary tuberculosis, advanced tuberculosis and suspected hypo-adrenalism

There is evidence to support the use of steroid treatment in patients with miliary TB, very advanced TB and suspected hypo-adrenalism (Dooley et al 1997). These situations are associated with unexpected death, the causes of which are often uncertain but may include:

- adrenal insufficiency – potentially, this could be made worse by the introduction of rifampicin, which may reduce the available endogenous cortisol
- paradoxical reactions, occurring soon after the start of TB treatment
- sudden death from myocardial infection
- other common medical complications that may be additive and contribute to cardiac arrhythmias and death in people with advanced TB, including electrolyte disturbances (from TB or from other conditions or their treatment), hypoxaemia caused by pulmonary TB or concurrent chronic air-flow obstruction or coronary artery disease.

A retrospective study of patients with pulmonary TB and acute respiratory failure also found that corticosteroid use may reduce the 90-day mortality rate (Yang et al 2016).

Because of the small risk and potential benefits from steroid treatment, steroid treatment of 20–60 mg/day should be considered:

- if the patient is very ill from TB (Dooley et al 1997)
- if the CXR shows a miliary appearance
- to reduce the mass effects and obstructive complications from mediastinal lymphadenopathy (Nemir et al 1963)
- in HIV-associated immune reconstitution syndrome resulting in worsening of clinical status in a patient with active TB.

Where clinical or laboratory features are compatible with hypo-adrenalism, a short synacthen test should be done before steroid treatment is started where possible. In severely ill patients or patients with radiologically advanced disease, steroid cover should start immediately. The duration of steroid treatment will be judged by the clinical circumstances but may continue for several weeks.

Renal-tract tuberculosis

Oral steroids have been used with anti-TB drugs for treating tuberculous renal-tract stenoses, especially if the stenosis was located at the pelvi-ureteric or uretero-vesical junction. The aim has been to avoid permanent stenoses from post-tuberculous scarring. Severe tuberculous cystitis has often been managed in the same way. However, benefits are unproven in both situations. Steroid treatment is likely to be helpful only if narrowing is due to acute inflammation caused by a hypersensitivity response to tuberculo-protein or to the infection.

Smoking cessation

Recent reviews have shown that smoking is strongly associated with increased rates of TB infection and the development of pulmonary TB and also increased risk of TB transmission to others (Slama et al 2007). Smoking also leads to faster progression and poorer prognosis of TB. Smokers are less likely to adhere to TB treatment and are more likely to relapse after successfully completing treatment according to some studies (Wang et al 2007).

All patients with TB who smoke should be advised – and offered support – to quit smoking. With regard to smoking cessation, it is important to note that rifampicin increases the clearance of bupropion, resulting in decreased levels of bupropion.

Nutrition

Malnutrition is associated with an increased risk of mortality and relapse of active TB disease. Patients should be encouraged to gain weight with supplemental calorie or protein intake if needed (Grobler et al 2016; Koethe and von Reyn 2016).

Drug dose administration

Drug doses

Table 3.3 shows the dosage recommendations for anti-TB medicines. In obese patients, ideal body weight should be used to calculate doses of the first-line TB drugs. Drug doses in obesity are also discussed below. Practitioners should refer to Medsafe data sheets for dosage and administration information when prescribing medicines for the treatment of TB (www.nzformulary.org).

Table 3.3: Dosage recommendations for anti-tuberculosis agents for adults

Medication	Daily dose
First-line agents	
Isoniazid^a	
Maximum dose/kg	5–10 mg
Maximum dose/day	300 mg
Rifampicin^b	
Maximum dose/kg	10 mg
Maximum dose/day	600 mg
Pyrazinamide	
Maximum dose/kg	25 mg
Maximum dose/day	2000 mg
Ethambutol	
Maximum dose/kg	15 mg
Maximum dose/day	1,600 mg
Second-line agents	
Protonamide and ethionamide^c	
Maximum dose/kg	15–20 mg
Maximum dose	1 g
Moxifloxacin	
Maximum dose	400 mg
Streptomycin	
Maximum dose/kg	15–20 mg
Maximum dose, intramuscular, intravenous	1 g
Amikacin	
Amount/kg	15 mg
Maximum dose, intramuscular, intravenous	1 g
Kanamycin	
Amount/kg	15–20 mg
Maximum dose, intramuscular, intravenous	1 g
Capreomycin	
Amount/kg	15–20 mg
Maximum dose intramuscular	1 g
Cycloserine	
Amount/kg	15–20 mg
Maximum dose	750 mg–1 g
P-aminosalicylic acid (4 g sachets)	
Amount/kg	150 mg
Maximum dose	8–12 g

a Isoniazid should be dosed at 300 mg unless the patient weighs less than 30 kg, in which case the dose should be discussed with a pharmacist. Sometimes doses up to 450 mg are used.

b An intravenous form of rifampicin is available.

c Protonamide and ethionamide are given in divided doses.

Sources: World Health Organization (WHO 2008, 2009); Curry International Tuberculosis Center and California Department of Public Health (2012).

Obesity and tuberculosis drug doses

Antimicrobial dosing in obese patients is complex and poorly understood, but some issues are discussed in a review by Wurtz et al (1997). Obesity leads to physiological changes with effects on antimicrobial pharmacokinetics; these factors may be interactive. Important considerations include:

- increased body mass (including lean body mass and adipose mass)
- increased cardiac output and blood volume
- increased renal clearance (equations to estimate creatinine clearance do not accurately predict the higher creatinine clearance observed in obesity)
- hepatic metabolic changes
- changes in serum protein levels.

Doses of first-line tuberculosis medicines in obesity

Maximum doses of the standard TB medicines are discussed under Drug dose administration earlier in this chapter.

With a short obese adult, standard maximum doses may be excessive. Here the ideal body weight (IBW) should be obtained, and the dose of the first-line agents should be based on this.

The calculation of IBW for:

- women is $45 \text{ kg} + 0.9 \text{ kg per centimetre of height above } 150 \text{ cm}$
- men is $50 \text{ kg} + 0.9 \text{ kg per centimetre of height above } 150 \text{ cm}$ (Hanley et al 2010).

Ethambutol

The daily dose of ethambutol should be 15 mg/kg, unless there is a good reason for a higher dose (Citron and Thomas 1986; Place and Thomas 1963). Ethambutol should be avoided in patients who have renal impairment and dialysis (see Special situations: Renal impairment and treatment of tuberculosis later in this chapter). The risk of optic neuritis is greater with higher doses.

Pyridoxine with isoniazid and cycloserine

In patients taking isoniazid, it is advisable to also give pyridoxine 10–25 mg/day. This is essential for people at risk of peripheral neuropathy from other causes, such as diabetes, chronic renal failure, malnourishment, alcoholism, HIV infection and pregnancy. In patients on isoniazid, a pyridoxine dose of 25 mg is sufficient as higher doses may interfere with isoniazid activity (Snider 1980).

In patients taking cycloserine, pyridoxine should be given at a dose of 50 mg for every 250 mg of cycloserine prescribed to reduce risk of neurotoxicity (WHO 2016).

Administration of amikacin

Aminoglycosides should be dosed once daily or at extended intervals. This results in a high-peak serum concentration, which declines over a 24-hour period, and a drug-free period at the end of the dosing interval.

Dose adjustments for weight

The correct dose of amikacin is based on body weight. The weight used to calculate the dose should be the actual bodyweight for non-obese individuals. For these patients, the usual daily dose is 15 mg/kg, given by intravenous infusion (or rarely, intramuscularly). The method of calculating the dosing weight with obese people is discussed in Obesity and tuberculosis drug doses earlier in this chapter.

Prolonged treatment with amikacin and normal renal function

Depending on the severity of TB, amikacin is generally given daily for five or six days a week. When necessary, amikacin can be continued at the same dose three times a week after an initial period of daily administration (Curry International Tuberculosis Center and California Department of Public Health 2012). Modifications are required to the dose and/or dosing interval when significant renal impairment is present, see Special situations: Renal impairment and treatment of tuberculosis later in this chapter.

Monitoring of patients on amikacin is discussed under Monitoring later in this chapter.

Pharmacological considerations with anti-tuberculosis drugs

The sections below discuss the pharmacological considerations with the following anti-TB agents: isoniazid, rifampicin, ethambutol, pyrazinamide, protionamide and ethionamide, fluoroquinolones and amikacin, and whether DOT should occur before or after food.

Isoniazid

Isoniazid is best taken on an empty stomach with no antacids taken for at least two hours afterwards (Melander et al 1976). Food and antacids may reduce the absorption of isoniazid.

Rifampicin

Rifampicin is best taken on an empty stomach. The peak serum concentration is reduced by one-third if rifampicin is taken after a fatty meal. Smaller reductions are seen with carbohydrate meals. Antacids do not affect the absorption of rifampicin (Effect of food on the absorption of rifampicin 1975). If the patient is taking iron supplements, these should be taken four or more hours after TB treatment.

Only free rifampicin (not plasma protein-bound rifampicin, which accounts for 75 percent of the total serum rifampicin level) is available to interact with mycobacteria. Therefore, to produce a concentration of 'free' rifampicin of 0.2–0.5 µg/mL (the minimal inhibitory concentration, MIC, of rifampicin for *M. tuberculosis*) a total serum concentration of 0.8–2.0 µg/mL is required. This is usually attained and persists for several hours, even if the drug was administered postprandially (Effect of food on the absorption of rifampicin 1975; Peloquin et al 1999).

Rifampicin is excreted in urine, sweat, tears and other bodily fluids and colours those fluids orange. It may permanently discolour soft contact lenses.

Ethambutol

Food does not affect the absorption of ethambutol (Matilla et al 1978).

Pyrazinamide

Food does not impair the absorption of pyrazinamide.

Protionamide and ethionamide

Protionamide and ethionamide drugs have a narrow therapeutic side-effect profile. They are well absorbed after food. The effect of antacids on absorption is unknown.

Fluoroquinolones

The ingestion of fluoroquinolones (Walker 1999) with food delays the time to peak serum concentration by one to two hours but does not change the extent of absorption (Walker 1999). Antacids or ferrous sulphate may interfere with the absorption of fluoroquinolones.

Amikacin

Amikacin is usually given by intravenous infusion over half an hour. If given intramuscularly, the peak serum concentration occurs an hour later.

Directly observed therapy – whether drugs should be taken before or after food

If feasible, a person undergoing DOT should take their drugs on an empty stomach. However, if this is not possible, the drugs can be taken without fasting, since the timing is often not critical. However, caution is required; rifampicin levels are lower when the drug is taken after food, especially after a fatty meal. Prescribers should give appropriate advice to people undergoing DOT.

Before a prescriber starts a person on DOT, they should ask the person about symptoms of malabsorption. The combination of malabsorption and postprandial administration of rifampicin during DOT may result in treatment failure or the selection of rifampicin-resistant organisms (Falade et al 1999).

Drugs in fixed-dose combinations

Fixed-dose combination (FDC) tablets contain two or more medicines within the same tablet or capsule. An advantage of FDCs is the reduced risk of resistance developing, because if a dose is missed, all the drugs are omitted and it is less easy to take an inadequate combination. Other advantages are that fewer medication errors occur with FDCs and fewer prescription items need to be ordered.

A disadvantage of many FDC formulations is reduced bioavailability of some drugs, in particular rifampicin, and the loss of flexibility in obtaining an optimal dose of some agents, such as pyrazinamide; the total number of tablets may not be reduced.

When prescribing FDC formulations ensure all drugs in the formulation are prescribed at the appropriate dose for weight.

Monitoring

Monitoring infectivity

Patients who are sputum-smear positive before treatment should have repeat sputum tests at least monthly to confirm sterilisation. Eighty-five percent of these patients are expected to be smear and culture negative after two months of treatment (ATS/US CDC and IDSA 2003).

If the specimen at the end of the third month is both smear and culture positive, repeat DST should be performed (WHO 2014). As early detection of drug resistant TB is important, repeat DST after two months of treatment may be appropriate in some patients where there are concerns that acquired drug resistance may have developed (WHO 2014).

The use of sputum-smear microscopy and culture as monitoring during TB treatment have low sensitivity and modest specificity for predicting failure and relapse (Datta et al 2015; Horne et al 2010).

A sputum sample should also be submitted for culture at the conclusion of treatment of all sputum culture positive cases. This documents cure and is a requirement for reporting to the WHO.

Radiological monitoring

Chest X-ray monitoring

CXR monitoring during treatment is required for all patients with CXR abnormalities consistent with TB. The intervals between films will depend on the clinical circumstances. At a minimum, a CXR should be performed at two to three months of treatment (at the end of the intensive phase) to ensure radiological response and then again at the end of treatment.

A patient's CXR that does not show improvement after the patient has received three months of treatment suggests:

- the diagnosis of TB may be wrong
- the TB may have produced scarring before treatment, so radiological improvement may not occur
- a mixed pathology may be present with TB co-existing with another condition
- the patient may not have followed their medication regimen and/or secondary drug resistance must be considered
- primary drug resistance may have been present from the outset.

Monitoring for drug toxicity

Hepatotoxicity

Pre-treatment

Baseline blood count, creatinine, liver function tests, hepatitis B surface antigen and hepatitis C, HbA1c and HIV serology should be completed in all adults who are to be treated for TB disease or LTBI.

All patients should be advised to avoid drinking alcohol while taking TB drugs.

Monitoring during treatment

Regular clinical monitoring of liver function is recommended as:

- serious hepatic dysfunction can develop before patients develop symptoms and can happen at any time during the treatment (Black et al 1975; Nolan et al 1999)
- hepatitis B carrier state or sero-positivity for hepatitis C or HIV increases the incidence of hepatotoxicity to TB drugs (Chang et al 2007; Fountain et al 2005)
- the prevalence of hepatitis B carriage in New Zealanders is 2.5 percent; it is highest in Pacific peoples (7.3 percent), Asian (6.2 percent) and Māori (5.6 percent) (Robinson et al 2005)
- risks of liver dysfunction are greater for those aged over 50 years than for those aged 35–50 years, but for simplicity, 35 years or over is the cut-off for higher risk
- regular alcohol use is a risk factor for hepatotoxicity
- even a rare death from TB-drug induced hepatitis is unacceptable
- iatrogenic hepatic failure sometimes requires liver transplantation.

Monitoring for hepatotoxicity

- After baseline screening, adults being treated for LTBI should have alanine aminotransferase (ALT) monitoring at one month and then every two months.
- After baseline screening, adults being treated for TB disease who have **no** risk factors for hepatotoxicity, should have liver function test (LFT) monitoring at one month, two months and then every two months thereafter.
- After baseline screening, adults being treated for TB disease who have risk factors for hepatotoxicity, should have complete LFTs every month and more frequently if clinically indicated.
- If a patient's ALT is more than three times the normal level, advice should be sought from a clinical TB expert promptly. See also Threshold for stopping LTBI treatment due to hepatotoxicity in Chapter 7: Diagnosis and treatment of latent tuberculosis infection.
- Any patient with jaundice should be referred to a liver unit or gastroenterologist, and all hepatotoxic drugs should be stopped immediately.
- Any patient whose TB treatment is stopped because of abnormal liver function should be notified to the Centre for Adverse Reactions Monitoring (www.medsafe.govt.nz/profs/adverse/reactions.asp).

Ocular toxicity

Ocular toxicity is the most important side effect of ethambutol; it is less likely if the dose is 15 mg/kg than if the dose is higher. All patients starting ethambutol should have a baseline visual acuity test and a red–green colour vision assessment. Patients with abnormalities should be referred to an ophthalmologist.

All patients on ethambutol should be asked to report new visual symptoms and visual acuity effects. Monthly testing of visual acuity and colour discrimination is recommended for patients receiving ethambutol for longer than two months and for any patient with renal impairment (ATS/ CDC and IDSA 2003). Ophthalmological review should occur if there are any abnormalities. Ethambutol should be avoided in people unable to report changes in vision and in people with moderate or severe renal insufficiency (WHO 2009).

Monitoring of patients on amikacin

Monitoring serum amikacin trough levels

Serum amikacin trough levels should be measured regularly just before giving a dose. The trough level should be less than 1 µg/mL to avoid toxicity. If the estimated creatinine clearance is less than 50 mL/min or serum creatinine is increasing, then trough levels should be monitored frequently. Serum peak levels may need to be assessed in some patients to confirm adequate levels.

Monitoring plasma creatinine concentration

In patients with normal renal function requiring long-term dosing, fortnightly creatinine clearance monitoring is recommended to monitor plasma creatinine concentration.

Monitoring ototoxicity and vestibular dysfunction

Audiometry testing should be completed at treatment initiation and fortnightly to monitor ototoxicity and vestibular dysfunction. Electronystagmography may be considered if vestibular symptoms develop.

Hypothyroidism

Patients on para-amino-salicylic acid (PAS) and ethionamide may develop hypothyroidism. All patients on these medications should have thyroid function tests at baseline and then every three months.

Weight and nutrition

Many patients with TB are poorly nourished. Weight and nutrition status are important markers of disease status. Patient's weight should be monitored throughout the course of treatment, and nutrition should be optimised.

Medical appointments

A medical review may be completed every two months provided there are no risk factors for poor compliance, the patient can be relied on to report symptoms and a monthly review by a public health nurse is being carried out.

Table 3.4: Assessments recommended before treatment initiation and while on treatment for pulmonary TB patients treated with first-line drugs

	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	End of treatment
Symptom review; clinical response and toxicity	✓	✓	✓	✓	✓	✓	✓	✓
Adherence review		✓	✓	✓	✓	✓	✓	✓
Review of concomitant medicines*	✓	✓	✓	✓	✓	✓	✓	✓
Weight	✓		✓		✓		✓	✓
Vision assessment	✓		✓		If ethambutol continued, then perform monthly checks			
Liver chemistries	✓	At least monthly checks in high-risk patients otherwise every two months (or sooner if symptoms develop)						
Creatinine	✓	If abnormal at baseline or comorbidities, then check at least every month						
Platelet count	✓							
HIV test	✓							
Hepatitis B and C screen	✓							
Diabetes screen	✓							
CXR or other chest imaging	✓		✓					✓
Sputum smear and culture	✓		✓					✓
Rapid molecular test on sputum	✓							
Drug susceptibility testing	✓							

* At the end of treatment, special attention should be paid to potential need for adjusting doses of any concomitant medications for which dose may have been adjusted previously to compensate for drug–drug interactions with anti-tuberculous drugs. Enzyme induction typically resolves over about two weeks.

HIV: human immunodeficiency virus; CXR: chest X-ray.

Modified from: Grosset and Chaisson (2017).

Therapeutic drug monitoring

Indications for therapeutic drug monitoring

Most patients with uncomplicated TB usually respond to standard treatment. However, there are several situations in which the monitoring of serum drug concentrations

might be helpful (Peloquin 2002; Ray et al 2003). Rifampicin and isoniazid therapeutic drug monitoring is recommended in the following circumstances:

- The disease does not show the expected improvement.
- Non-adherence or malabsorption is suspected. Malabsorption is particularly likely in patients with HIV infection, cystic fibrosis or diabetes mellitus. In patients with HIV, there may be up to a 70 percent reduction in serum TB drug concentrations compared with control subjects. Sub-therapeutic drug concentrations carry a significant risk of drug resistance developing.
- The patient has ascites (see Hepatic dysfunction (and ascites) and tuberculosis treatment later in this chapter).
- The patient experiences drug side effects, especially if the offending drug needs to be re-introduced.
- There are patients with isolates that are MDR or that have acquired drug resistance.
- Risk factors for drug toxicity are present.
- The patient has a body mass index >30 – see Obesity and tuberculosis drug doses earlier in this chapter.

Paradoxical reactions to tuberculosis treatment

A paradoxical reaction to TB treatment is defined as a 'worsening of disease at a pre-existing site or the development of new TB lesions following initiation of appropriate treatment' (Hawkey et al 2005; Orlovic and Smego 2001). These reactions generally occur about one to three months after the start of treatment but can occur even after treatment is complete.

A paradoxical reaction is thought to result from an immunological host response to mycobacterial products that have been released as a result of treatment-induced bacterial cell death and dissolution and the restoration of part of the host immune response as a result of treatment.

Paradoxical reactions may have local or systemic components or both. Their nature is the same in HIV-infected and non-HIV-infected people, but they occur more frequently in HIV-infected people who are receiving TB treatment and then start taking anti-retroviral agents (Narita et al 1998).

A paradoxical reaction is a diagnosis of exclusion. Investigations to detect other possible causes, including tissue sampling and repeat TB cultures, should be completed.

The differential diagnosis of apparent paradoxical reactions includes:

- incorrect or inadequate treatment, with worsening of the TB through non-adherence with drug treatment, malabsorption of TB drugs, the presence of primary drug resistance or the development of secondary drug resistance
- drug reaction
- concurrent infection or malignancy.

In critical scenarios such as CNS paradoxical reactions that do not respond to steroids, contact a clinical TB specialist for consideration of other immunomodulatory treatments.

Drug side effects

Common adverse side effects of TB drugs are listed in Table 3.5. All practitioners should refer to Medsafe data sheets for the latest safety information when prescribing medicines for the treatment of TB (www.nzformulary.org).

Table 3.5: Adverse effects of tuberculosis drugs

Drug	Adverse side-effects
Aminoglycosides (amikacin, capreomycin, kanamycin, streptomycin)	Ototoxicity (lowest incidence with streptomycin) and vestibular toxicity; nephrotoxicity, skin rashes, fevers. Hypersensitivity can include joint pains, lymphadenopathy and possible hepatitis. Neurotoxicity; circum-oral paraesthesia, neuromuscular blockade. Agranulocytosis and aplastic anaemia have been rarely reported.
PAS	Gastrointestinal effects and hypokalaemia, sodium overload. Hypothyroidism and goitre. Hypersensitivity reactions occur in 5–10 percent of patients; hepatitis, fever, rash, conjunctivitis, pruritis. Neutropenia and acute agranulocytosis rarely described.
Cycloserine	Dose-related central nervous system effects (drowsiness, vertigo, disorientation, confusion, coma and psychosis). Skin rashes.
Ethambutol	Optic neuropathy (dose-related); peripheral neuropathy, arthralgia, nephrotoxicity, rash or hypersensitivity are rare. Haematological abnormalities have also been reported very rarely.
Ethionamide	Gastrointestinal effects, liver toxicity; rarely hypothyroidism, hypotension, hypoglycaemia, alopecia, convulsions and neuropathy. Hypoglycaemia, gynaecomastia and alopecia have been described.
Fluoroquinolones	Gastrointestinal disturbances, dizziness, anxiety, depression, confusion and convulsions; rarely, Achilles tendon rupture, arthropathy and photosensitivity. Hypersensitivity reactions, cardiac toxicity, hepatotoxicity, haematological toxicity, hypoglycaemia. For use in children, consult a paediatric tuberculosis expert.

Drug	Adverse side-effects
Isoniazid	<p>Isoniazid hepatotoxicity.</p> <p>Hypersensitivity reactions are unusual.</p> <p>Peripheral neuropathy, optic neuritis, fever, hepatitis, ataxia, euphoria, convulsions, tinnitus, insomnia, hyperglycaemia, gynaecomastia, dry mouth, epigastric discomfort, urinary retention, anaemia, arthralgias. Contraindicated in manic states and porphyria.</p> <p>Idiosyncratic reactions may include a (usually reversible) lupus-like syndrome (fever, arthritis, pleuritis, pericarditis, positive rheumatoid factors, etc), and, very rarely, a rheumatoid arthritis-like syndrome, and agranulocytosis.</p> <p>Very rare hypersensitivity reactions include eosinophilia, angitis, toxic psychosis and meningo-encephalitis.</p> <p>Toxic doses decrease the synthesis of the inhibitory neurotransmitter gamma aminobutyric acid. Central nervous system depression or stimulation may result.</p> <p>Gastrointestinal side effects, including nausea, vomiting and diarrhoea.</p> <p>Rarely acute pancreatitis and diffuse interstitial nephritis has been described.</p>
Pyrazinamide	<p>Gastrointestinal side effects, hyperuricaemia, hepatotoxicity, fever, anorexia, nausea and vomiting; precipitation of gout (see Interactions with anti-tuberculosis drugs later in this chapter); arthralgias, urticaria, sideroblastic anaemia.</p> <p>Of the TB drugs, pyrazinamide is the most common cause of a rash.</p> <p>Anorexia and nausea and less commonly vomiting may occur in the absence of hepatotoxicity, but liver function tests should always be checked.</p> <p>Rare reports of thrombocytopenia.</p>
Rifabutin	<p>Rash, gastrointestinal disturbance, neutropaenia and thrombocytopenia, gastrointestinal symptoms, polyarthralgias, hepatotoxicity.</p> <p>Orange discolouration of body fluids.</p> <p>Uveitis, particularly in combination with macrolide antibiotics.</p> <p>Flu like syndrome is rare.</p>
Rifampicin	<p>Orange discolouration of body fluids.</p> <p>A cutaneous syndrome may occur with flushing and/or itch with or without rash.</p> <p>Gastrointestinal disturbance, cholestatic hepatic dysfunction, transient elevation of hepatic enzymes.</p> <p>Nausea, anorexia and abdominal pain have been reported.</p> <p>Danger with intermittent therapy: flu-like syndrome, shock, acute renal failure, death.</p> <p>Acute haemolytic anaemia, thrombocytopenia, leukopenia and granulocytopenia have all been described.</p> <p>Drug-induced lupus.</p> <p>Rare reports of rifampicin-induced light-chain proteinuria and renal failure, attributed to dehydration associated with fluid restriction for syndrome of inappropriate antidiuretic hormone.</p> <p>Hypersensitivity reactions are uncommon.</p>

Source: Winter et al (1984); Grayson et al (2010).

Adverse reactions should be reported to the Centre for Adverse Reactions Monitoring (CARM) NZPhvC, at the University of Otago Medical School: <https://nzphvc.otago.ac.nz>.

Dermatological side effects

Skin reactions can occur with any anti-TB drug. Pyrazinamide is the drug that most commonly causes skin reactions; in one study, it caused 26 out of 31 (84 percent) of all rashes in 1,317 patients (Ormerod and Horsfield 1996). Pyrazinamide also causes facial flushing or transient pruritis.

Isolated skin rash occurs in about 2 percent of people taking isoniazid but commonly occurs as part of a wider hypersensitivity reaction. Skin rash due to rifampicin is usually mild but can take many forms. Photosensitivity can occur with pyrazinamide and the fluoroquinolones.

Hepatotoxicity from tuberculosis drug treatment

TB treatment includes several potentially hepatotoxic drugs, including isoniazid, rifampicin and pyrazinamide. Monitoring is discussed earlier in this chapter. Ethambutol rarely causes hepatic dysfunction.

Toxicity of aminoglycosides

The toxicity of aminoglycosides can be auditory and vestibular toxicity or nephrotoxicity.

Auditory and vestibular toxicity

Aminoglycosides can cause auditory and vestibular toxicity. Auditory damage begins in the basal end of the cochlea and progresses to the apical end. Symptomatic hearing loss begins with high-frequency loss and, as administration continues, lower-frequency loss occurs. At least half the cases of auditory toxicity are irreversible. Vestibular damage may be reversible. Early detection helps prevent hearing loss in the frequency range that can affect communication, so it is essential to test high-frequency ranges.

High-trough serum levels and advanced age are the most important predisposing factors to ototoxicities. Other factors include the duration of administration, the total dosage, having a high fever and bacteraemia, dehydration and prior renal or ear disease. Ototoxicity occurs independently of nephrotoxicity.

Nephrotoxicity

Nephrotoxicity relates to dose, duration of treatment and age and is more likely in patients with pre-existing renal impairment, dehydration or liver disease and in patients receiving loop diuretics or other nephrotoxic agents.

Managing drug reactions

Need for a new temporary regimen

The patient's clinical situation determines the acceptable period for which the patient should stay off all TB treatment while awaiting resolution of TB-drug side effects.

If it is necessary to stop anti-TB treatment (**particularly** to give a steroid to counteract treatment side effects), consider whether a new, temporary regimen would be helpful. This regimen should continue until full doses of all drugs in the definitive regimen have been started. A person who is acutely ill with TB or is infectious should be put on a temporary regimen immediately. For a non-infectious, well person, four weeks without treatment is an arbitrary maximum period to be off anti-tuberculous treatment. It should be noted, however, that if a patient is off treatment for 14 or more days during the intensive phase, then the treatment course should be started from the beginning again (see Interrupted treatment, Chapter 4: Supervision and adherence to treatment) (Nahid et al 2016). The development of infectiousness or the spread of disease to other sites is likely after this time.

Progressive but non-effective partial regimens

The period for which a progressive but non-effective partial regimen may be given without inducing drug resistance is not certain but is in the order of days. In a person who is well despite TB, the period should not exceed 10 days. If the person is ill with TB, an alternative regimen should be started as soon as the original regimen is modified.

Repeated periods of partial or no treatment should be avoided. A second episode without treatment or partial treatment is an indication for a temporary regimen that should be continued for several weeks, until the difficulties have been fully resolved.

The development of resistance to moxifloxacin can appear relatively quickly and has been observed to occur in patients with TB who have been exposed to moxifloxacin monotherapy for as short a period as 10 days (Devasia et al 2009).

Agents in the temporary regimen

Agents in the temporary regimen could include amikacin (or streptomycin), moxifloxacin, ethambutol and ethionamide (or protionamide).

Practice point – managing side effects of TB drugs

The maximum period for a patient to be off all drugs is four weeks.

The maximum period for a patient to be on a partial regimen is 10 days.

A typical temporary regimen is amikacin (or streptomycin), ethambutol and moxifloxacin.

Managing drug challenges

When troublesome side effects occur, such as significant hepatotoxicity, stop treatment and allow the reaction to resolve. Then identify the agent or agents causing the reaction by re-introducing the drugs sequentially.

Give the patient a few days on each dose of each agent; the more severe the reaction, the more caution is required. It may be necessary to start with small incremental doses and build up to the full dose over several days. It may be necessary to cover the patient with a temporary regimen to prevent resistance emerging during the challenge period.

If the patient experiences no side effects, repeat the process with the next drug. With less-severe reactions, it may be possible to introduce full doses. The drug challenge doses for mild-to-moderate reactions are shown in Table 3.6.

If you are unfamiliar with conducting drug challenges, consultation with a clinical TB expert should occur.

Table 3.6: Drug challenge doses for mild-to-moderate reactions

Drug	Day 1 dose	Day 2 dose	Days 3 and 4 doses
Isoniazid	50 mg	100 mg	300 mg
Rifampicin	75 mg	150 mg	450–600 mg
Pyrazinamide	250 mg	500 mg	Full dose
Ethambutol	100 mg	400 mg	Full dose
Streptomycin	100 mg	500 mg	Full dose

Source: NHMRC (1989)

Managing drug desensitisation

Desensitisation should be considered only when suitable replacement drugs are not available. Rapid desensitisation protocols can be used for patients who are sensitive to rifampicin, ethambutol (Matz et al 1994) and isoniazid (Holland et al 1990). These Guidelines are based on experience treating penicillin allergy. Desensitisation should always be carried out cautiously and with full resuscitation resources available.

Managing skin side effects

A minor rash and itchiness are common with anti-TB drugs. Sometimes the skin side effects are short lived, so the drugs may not have to be stopped. If the drugs are stopped, it is sometimes possible to resume them successfully. Consider the following measures:

- Before assuming that the anti-TB drugs are the cause of the symptoms, check the patient has not recently changed their brand of soap.
- Skin moisturisers may help relieve dry, itchy skin.
- Pruritis may be helped by:
 - a non-sedating antihistamine, such as loratidine, although older antihistamines may be tolerated and are cheaper
 - Pinetarsol™ gel or solution
 - BK® bath oil or lotion.

Major skin rashes require all drugs to be stopped and the patient to be given test doses of each drug until the drug causing the reaction is identified.

Managing drug-induced hepatotoxicity

Generally, drugs that are closely related chemically should not be used if marked hepatotoxicity occurs with one of them. However, rifabutin may be tried cautiously after recovery from rifampicin hepatotoxicity.

If clinical hepatitis occurs (with anorexia, nausea, vomiting, hepatic tenderness and/or jaundice), stop all drugs and refer the patient to a liver unit or gastroenterologist.

Use your clinical judgement before reinstituting a drug that has caused hepatitis. In one series, reintroduction of rifampicin and isoniazid was possible in 41 out of 44 patients after resolution of marked biochemical and clinical hepatitis (Singh et al 1996). Most experienced physicians would try cautiously reintroducing isoniazid and rifampicin after an asymptomatic abnormality of liver function. However, in all but very minor circumstances, consult a clinical TB expert.

Managing uncontrollable vomiting

Nausea is common with anti-TB drug treatment, but usually it can be managed with common agents. Theoretically, drugs such as metoclopramide, which stimulate gastric emptying, may have an effect on anti-TB drug levels, but there is no literature on this subject. If prolonged use of such drugs is needed, it may be preferable to use prochlorperazine (Stemetil) or cyclizine (Marzine).

Managing paradoxical reactions

Once a paradoxical reaction has been investigated and other causes excluded, the need for treatment depends on the location and severity of the reaction. Pulmonary reactions may precipitate acute respiratory failure, and an expanding intracranial abscess may result in serious neurological sequelae or death. In these and similar life-threatening situations, corticosteroid treatment may be needed to control cytokine-induced inflammation. Painful, grossly enlarged lymph nodes may need to be excised.

Interactions with anti-tuberculosis drugs

The rifamycin–warfarin interaction and interactions with pyrazinamide are discussed below. For other drug interactions, see Table 3-7 and refer to medicines data sheets (www.nzformulary.org).

Rifamycin – anticoagulant interactions

The rifamycins interact with warfarin and other anticoagulants including dabigatran and rivaroxaban. This interaction can cause sub-therapeutic anticoagulation or a dangerous degree of over-anticoagulation when rifampicin is stopped.

Sub-therapeutic anticoagulation may occur when a patient on warfarin starts rifampicin (Lee and Thrasher 2001). Patients who are taking both agents and who have an absolute indication for anticoagulation, need monitoring at least weekly. If warfarin anticoagulation is difficult, use low-molecular-weight heparin.

Dangerous over-anticoagulation may occur when rifampicin is stopped, thereby effectively reducing the hepatic metabolism of warfarin.

Rifamycin – allopurinol interactions

Allopurinol may paradoxically increase serum urate levels if given with pyrazinamide (Lacroix et al 1988).

Pyrazinamide may need to be avoided in patients with troublesome gout, as it can precipitate acute attacks. Anecdotally, it may be possible to continue pyrazinamide after recovery from an attack of gout if the patient can tolerate colchicine in a dose of 0.5 mg twice a day (BID). If successful, the colchicine should be continued, and stopped when the pyrazinamide is discontinued.

Rifamycins – oestrogen interactions

Rifamycins are inducers of certain hepatic cytochrome P450 enzymes. Both oestrogens and progesterones are metabolised through this pathway. As a result, their elimination is accelerated in people taking rifampicin or rifabutin, and contraceptive efficacy is lost for both combined oral contraceptives and progesterone-only pills (Back et al 1979; Skolnick et al 1976). Rifampicin is the more potent inducer, and the induction of liver enzymes begins six days after commencing rifampicin and can be observed for up to one month after cessation of the drug (Consumers Association 1987).

A second mechanism by which rifamycins lower circulating blood oestrogen levels is by reducing their entero-hepatic circulation. This has been shown to occur with ethinyloestradiol. This mechanism does not operate with progesterone hormones.

An alternative contraceptive method should be used during rifamycin therapy and for one month after stopping, even if rifamycin was for less than a week (Consumers Association 1987; Hansten and Horn 1990).

Injectable progesterone, depot medroxyprogesterone acetate is considered an effective contraceptive during rifamycin therapy. The standard recommendation is a 12-weekly injection. It is uncertain whether a greater frequency is needed when rifamycins are being taken. The usual recommendation is to reduce the dosing interval to 10 weeks (one source advises eight weeks) in women taking rifampicin or rifabutin (British National Formulary 1996).

Rifampicin-corticosteroid interaction

Induction of hepatic enzymes due to rifampicin can result in a profound reduction in corticosteroid levels. Patients on corticosteroids therefore should have the dose of corticosteroid increased by two- to three-fold when rifampicin is commenced. Clinicians should also be aware that enzyme induction may persist for two to three weeks after the discontinuation of rifampicin.

Table 3.7: Clinically important interactions with tuberculosis drugs

All practitioners should refer to Medsafe data sheets for the latest information regarding interactions and contraindications when prescribing medicines for the treatment of TB (www.nzformulary.org/).

Tuberculosis drug	Interacting agent	Effect	Advice
Isoniazid	Antacids , containing aluminium	Reduced absorption of isoniazid	As for fluoroquinolones + antacids
	Anti-epileptics:		
	Carbamazepine	Inhibition of carbamazepine hepatic metabolism has been described	Monitor carbamazepine blood levels
	Phenytoin	Inhibition of phenytoin hepatic metabolism; phenytoin toxicity may develop over days to weeks	Monitor phenytoin levels and symptoms
	Valproic acid	Interferes with metabolism of valproic acid	Monitor valproic acid levels and symptoms
	Antipsychotics	Possible increased plasma haloperidol	Adjust dose if needed
	Anxiolytics and hypnotics	Possible delayed metabolic clearance of diazepam and triazolam, causing prolongation of their effects	Monitor effects; decrease dose if necessary
	Anti-fungals:		
	Ketoconazole	Possible decreased antifungal blood level	No problem using fluconazole
	Cyclosporin	Marked rise in cyclosporin levels	Monitor cyclosporin blood levels
	Disulfiram	Central nervous system toxic effects of disulfiram among 30 percent of people on both	Reduce dose or discontinue disulfiram
	Enflurane	Enhanced defluorination of this anaesthetic agent may lead to accumulation of nephrotoxic fluoride (more likely in isoniazid rapid acetylators)	Avoid concurrent use of these two agents
	Histamine-rich food: Cheese, sauerkraut, yeast extract, various types of fish, including tuna	Flushing, chills, headache, wheeziness, palpitations, diarrhoea, vomiting, burning	Advise on diet; give antihistamine, if necessary
Rifampicin and rifabutin	Tyramine-rich foods: Red wine, cheese, yeast extract (due to slight monoamine oxidase effect of isoniazid)		Advise on diet
	Antiarrhythmics:		
	Disopyramide Mexilitine Propafenone Quinidine		Monitor response Avoid use
	Verapamil, Nifedipine		Clinical monitoring recommended
	Diltiazem	Increased levels of rifampicin and decreased levels of diltiazem	

Tuberculosis drug	Interacting agent	Effect	Advice
Rifampicin and rifabutin (continued)	Propranolol, metoprolol	Decreased levels of propranolol and metoprolol	Clinical monitoring recommended; may require dose increase or change to an alternative cardiovascular agent
Antifungals			
	Itraconazole		Monitor serum level; may increase antifungal dose
	Fluconazole	Raised rifabutin level	As for clarithromycin
	Ketoconazole	Reduced absorption, halving the rifampicin level	Give at least 12 hours apart; check rifampicin level
	Posaconazole		Monitor posaconazole level
	Caspofungin	Avoid if possible	Increase caspofungin dose
Anti-retrovirals			
		Significant interactions occur between the rifamycin drugs and the protease inhibitors and the non-nucleoside reverse transcriptase inhibitors	Consider alternative anti-retrovirals
Antibiotics			
	Clarithromycin (and possibly other macrolides)	Raised rifabutin levels; risk of uveitis	Keep rifabutin dose at or below 300 mg/day; acute uveitis: stop rifabutin; ophthalmology review
	Doxycycline	Potential for decreased doxycycline efficacy	Monitor closely for therapeutic failure
	Dapsone	Reduced dapsone activity	Consider increasing dapsone dose or using alternative agent
	Atovaquone		Consider an alternative antibiotic
	Chloramphenicol		Consider an alternative antibiotic
	Mefloquine		Consider an alternative malaria prophylaxis
Corticosteroids			
	Glucocorticoids and mineralocorticoids	Profound reduction in steroid levels	Increase steroid dose two- to three-fold; reduce when rifamycin is discontinued
Digitalis preparations			
		Likely with renal impairment	Monitor levels; dose may need to be doubled
Immunosuppressive agents:			
	Cyclosporin	Levels reduced about 50 percent; significance uncertain	May need three- to five-fold increase in cyclosporin dose
	Tacrolimus		
	P-aminosalicylic acid	Possible increase in serum rifampicin	Ensure these two agents are taken eight hours apart

Tuberculosis drug	Interacting agent	Effect	Advice
Rifampicin and rifabutin (continued)	Phenytoin concurrent isoniazid	Markedly reduced anti-epileptic effect, especially in fast acetylators Isoniazid counteracts lowering of serum phenybin by rifampicin	
	Warfarin (see also interactions with anti-tuberculosis drugs)	Markedly reduced anticoagulation	Warfarin may not be effective, and alternative treatment such as low molecular-weight heparin may be required
	Methadone		May require methadone dose increase; rifabutin infrequently causes methadone withdrawal
	Hormone therapy Ethinyl estradiol, norethindrone Tamoxifen		Add a barrier method May require alternative therapy
	Levothyroxine		Monitor thyroid stimulating hormone (TSH), may require increased dose of levothyroxine
	Theophylline		Therapeutic drug monitoring recommended; may require theophylline dose increase
	Sulfonylurea hypoglycaemics: Tolbutamide Repaglinide Possibly others (eg, glibenclamide)		Monitor blood glucose; may require dose increase or change to another agent
	Hypolipidaemics: Simvastatin Fluvastatin		Monitor clinically; may require use of an alternative hypolipidaemic drug
	Psychotropic drugs: Nortriptyline Haloperidol, quetiapine Benzodiazepines (Diazepam, nitrazepam)		Monitor clinically, may require dose increase or change to an alternative drug
	Ethambutol	No interactions of note	
Pyrazinamide	Allopurinol (see also interactions with anti-tuberculosis drugs)	Acute gout	Avoid allopurinol; try colchicine instead
	Probenecid	Prolongation of the half-life of probenecid and its uricosuric action tends to be prolonged	May need to abandon use of pyrazinamide

Tuberculosis drug	Interacting agent	Effect	Advice
Fluoroquinolones	Antacids , containing aluminium, calcium and magnesium	Reduced absorption of fluoroquinolones	Avoid antacids; or give fluoroquinolone two hours before or four hours after antacid
	Warfarin	Occasional, unpredictable prolonged prothrombin time	Monitor anticoagulation carefully, if starting or stopping fluoroquinolones
	Iron and zinc	As for fluoroquinolones + antacids	
	Sucralfate	As for fluoroquinolones + antacids	
Ethionamide and Protionamide	Rifampicin, Isoniazid and Pyrazinamide	Increased risk of hepatotoxicity	
	Isoniazid and Cycloserine	May potentiate neurologic side effects associated with isoniazid and cycloserine	
PAS	Probenecid	Increases the serum levels of PAS	

Modified from: Grayson et al (2010).

Special situations

Renal impairment and treatment of tuberculosis

Isoniazid, rifampicin, pyrazinamide, ethionamide and protionamide are eliminated almost entirely by non-renal routes (ie, by metabolism or biliary secretion). When prescribing TB drugs for a person with significant renal impairment, monitoring of blood levels may be required. The dosing is summarised in Table 3.8.

Specific drugs

Isoniazid

It has been estimated that isoniazid of 5–6 mg/kg/day given to a slow acetylator with severe renal impairment would be equivalent to a dose of 7–9 mg/kg/day in a normal subject (Ellard 1993). Therefore, standard doses of isoniazid should be given in people on haemodialysis, peritoneal dialysis and with chronic renal failure. If side effects occur, therapeutic drug monitoring is indicated (see Monitoring earlier in this chapter).

Rifampicin

Up to 30 percent of rifampicin is excreted in urine (possibly as a result of the biliary route becoming saturated) but less than half of this is unaltered. Although the half-life of 600 mg rifampicin increases 30–40 percent in patients with renal insufficiency, it is well tolerated and no dosage adjustment is required in haemodialysis, peritoneal dialysis and with chronic renal failure.

Ethambutol

About two-thirds of the dose of ethambutol is excreted unchanged in urine.

Ethambutol should be avoided if possible in the setting of renal impairment. However, if ethambutol is given, the frequency of dosage should be reduced according to the severity of renal impairment. Alternatively, the daily dosage adjustment can be based on the glomerular filtration rate (GFR) but note the following:

- With normal renal function, corrected creatinine clearance is the best indicator of GFR.
- In the early stages of glomerular failure, the corrected creatinine clearance remains the most sensitive indicator of GFR. Because of the hyperbolic relationship between creatinine clearance and serum creatinine, the clearance will fall significantly during a period in which the serum creatinine remains normal.
- Once renal failure is established and the serum creatinine is significantly elevated (above 0.2–0.3 mmol/L, depending on muscle mass), the serum creatinine becomes a more sensitive indicator of any further deterioration of the GFR. The serum concentration will rise rapidly while the creatinine clearance will show little further change.

If ethambutol is used, regular ophthalmology assessments are essential.

Ethambutol – haemodialysis

For patients on undergoing haemodialysis three times a week, the ethambutol dose is 15–25 mg/kg given after dialysis.

Pyrazinamide

Pyrazinamide is primarily metabolised by the liver to pyrazinoic acid and other metabolites, 3 percent appearing unchanged in the urine and 30–40 percent as pyrazinoic acid.

Chronic renal failure: mild-to-moderate degrees of renal impairment do not require any adjustment of dose or frequency of administration.

Haemodialysis: Pyrazinamide is significantly removed by haemodialysis. Doses of 25–30 mg/kg must be given after haemodialysis, three times a week. Pyrazinoic acid, which is the primary metabolite of pyrazinamide, is partially removed by haemodialysis, but the extent of removal is uncertain.

Fluoroquinolones

The mode of excretion varies among the fluoroquinolone family, so drug management varies in the presence of renal impairment.

Moxifloxacin is excreted both by renal (20–30 percent) and biliary pathways, so no dose adjustment is needed, with or without haemodialysis (MacGowan 1999; Stass et al 2007).

Aminoglycosides

Streptomycin, kanamycin, amikacin and capreomycin are excreted almost exclusively by the kidneys, and dosages must be adjusted according to the degree of renal impairment. Serum concentrations of drugs should be monitored. However, these drugs are best avoided in renal impairment.

Other tuberculosis drugs

Ethionamide and para-aminosalicylic acid are not significantly dialysed (Malone et al 1999).

Cycloserine is significantly removed by dialysis, so doses should be given after dialysis. Usual doses, given three times a week after dialysis, are recommended.

Ethionamide is rapidly metabolised by the liver, so dose adjustment for renal failure or dialysis is unnecessary. The absorption of ethionamide may be delayed in long-term dialysis patients.

Clofazimine should be given in its usual dose of 100–200 mg daily, administered after dialysis.

Moxifloxacin can be given in usual doses with haemodialysis (Stass et al 2007).

Table 3.8: Doses of major anti-tuberculosis agents and renal impairment

Agent	Chronic renal failure	Peritoneal dialysis	Haemodialysis ^a
Isoniazid	Normal dose	Normal dose	Normal dose
Rifampicin	Normal dose	Normal dose	Normal dose
Ethambutol ^b	Avoid unless absolutely necessary GFR 30–50: 15 mg/kg every 24–36 hours GFR 10–30: 15 mg/kg every 36–48 hours GFR <10 mL/min: 15 mg/kg every 48 hours	Avoid unless absolutely necessary 15 mg/kg every 48 hours	Avoid unless absolutely necessary 15 mg/kg every 48 hours, after dialysis
Pyrazinamide	GFR <20 mL/min: 25 mg/kg every 48 hours	25 mg/kg daily	25 mg/kg three times a week, after dialysis
Aminoglycosides	Avoid if possible; or single dose and monitor serum levels		

GFR: glomerular filtration rate (mL/min).

a TB medicines are given after haemodialysis.

b Ethambutol should be avoided in renal impairment unless absolutely necessary.

Table modified from: World Health Organization (WHO 2008); Ashley and Currie (2009).

Timing of doses

Rifampicin, isoniazid and ethambutol may be administered after haemodialysis, and this may facilitate DOT.

Hepatic dysfunction (and ascites) and tuberculosis treatment

The monitoring of hepatotoxicity of TB drugs is discussed earlier in this chapter, under Monitoring for drug toxicity. Sometimes liver dysfunction is detected before treatment is started. Hepatic dysfunction before TB treatment may be due to TB. If this is the cause of the hepatic dysfunction, improvement should occur within the first few weeks of treatment. Other drugs taken when TB is diagnosed may also cause abnormal liver function. The section Monitoring for drug toxicity discusses the investigations of liver function that should be undertaken before starting treatment. If tests are abnormal, investigations should include appropriate clinical evaluation; an ultra-sound may be indicated if an obstructive pattern is present.

When severe liver disease is present before starting treatment

In hepatic failure, there is decreased total body clearance of isoniazid and rifampicin, resulting in drug accumulation and higher serum levels. The elimination half-life may increase 30–100 percent in hepatic failure (Peloquin 1991). Significant accumulation of pyrazinamide in icteric patients can occur. Although 50 percent of quinolone clearance occurs in the liver, its serum concentration is not substantially altered in hepatic disease.

If a person with active TB has severe liver disease, treatment should start with an effective, non-hepatotoxic regimen such as amikacin, ethambutol and moxifloxacin. If these do not cause side effects in the first three to four days, the potentially hepatotoxic agents may be added one at a time. Rifampicin would be the next agent of choice to add. **Consultation with a TB clinical expert and a hepatologist is strongly recommended.** Therapeutic drug monitoring of rifampicin and isoniazid may be helpful if it is felt that they can be used safely.

Ascites

Ascites presents a problem with many anti-TB drugs because those that distribute freely into water will display a larger volume of distribution and therefore a longer elimination half-life. Therapeutic drug monitoring is recommended for people with persistent ascites (see Therapeutic drug monitoring under Monitoring earlier in this chapter).

Hepatitis B, hepatitis C and HIV-infected patients

Patients with HIV infection or hepatitis B or C infection may have abnormal liver function when starting treatment and are also more likely to develop hepatotoxicity than other people. Liver function tests should be more closely monitored.

Pregnancy and lactation

Pregnancy

The risk of untreated TB to pregnant women is far greater than the risk of toxic effects from the drugs used in its treatment (Figueroa-Damian and Arredondo-Garcia 1998; Snider et al 1980). When active TB is diagnosed in pregnant women, it is essential that prompt, effective treatment is administered (Brost and Newman 1997). If there are strong indications of active TB disease but bacteriological confirmation is lacking, treatment may often be deferred until after the first trimester.

In pregnant women who have no symptoms, negative bacteriology, a lack of radiological change but evidence of past TB infection, delay initiation of preventive therapy for LTBI until after the birth unless the infection has been recently acquired or the woman has other medical conditions, such as HIV infection that places her at higher risk of developing TB disease. Selection of a treatment regime is a clinical decision that must consider the potential risks and safety and be undertaken in consultation with the woman. Standard first-line regimen for drug susceptible TB has been used effectively during pregnancy but is not without risks.

Little is known about the safety of second-line agents during pregnancy. These drugs should only be used in specific instances after consultation with a TB specialist.

All practitioners should refer to Medsafe data sheets for the latest safety information, including information about use in pregnancy (www.nzformulary.org). All pregnant women on isoniazid should receive pyridoxine to prevent neurotoxicity in the foetus.

Pyrazinamide

There is a lack of controlled data on the safety of pyrazinamide during pregnancy and international guidelines differ in their recommendations.

The WHO and the International Union Against Tuberculosis and Lung Disease both recommend the routine use of pyrazinamide during pregnancy, and toxicity to the foetus has not been documented (Caminero 2003; WHO 2009). The American Thoracic Society and United States Centers for Disease Control and Prevention (CDC) guidelines, however, do not recommend the general use of pyrazinamide with drug-susceptible TB due to a lack of controlled data in pregnancy (ATS/ CDC and IDSA 2003). The Curry International Tuberculosis Center guidelines for drug-resistant TB recommend that for women with HIV co-infection or drug-resistant disease, pyrazinamide should be included in the TB regimen if the isolate is susceptible (Curry International Tuberculosis Center and California Department of Public Health 2016). In cases with drug resistance, the risk of taking pyrazinamide is less than the risk of not curing TB.

Pregnant women with TB should be counselled appropriately, and if pyrazinamide is not used, the minimum duration of treatment is nine months.

Lactation

Treatment with first-line agents for TB is not necessarily a contraindication for breastfeeding as the small concentrations of these drugs in breast milk do not produce toxic effects in the newborn (Snider and Powell 1984). The benefits of effective treatment of the mother, the potential benefit of breastfeeding and risk to the newborn of the anti-TB drugs need to be discussed with the patient, especially if their use while breastfeeding is not consistent with the medicine's datasheet (www.nzformulary.org). It is also important to note that anti-TB drugs in breast milk do not provide an effective treatment for disease or LTBI in a breastfed infant.

Appendix

Appendix 3.1: Information sheet



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MULTIDRUG-RESISTANT TUBERCULOSIS **Information for Activating the Tuberculosis Clinical Network**

- 1 The testing laboratory³ informs:
 - firstly, the patient's clinician on the results for the case of multidrug-resistant tuberculosis (MDR-TB)
 - secondly, the relevant public health unit / medical officer of health on the results for the case of MDR-TB.
- 2 The medical officer of health contacts the Ministry of Health's Communicable Diseases Team⁴ as soon as possible, informing it that results for a case of MDR-TB have been received.
- 3 The Communicable Diseases Team sends a request to the medical officer of health for anonymised summary case information about the case. This information will be reviewed by the tuberculosis clinical network (TBCN). The EpiSurv⁵ number for the case is used as the unique identifier.
 - The medical officer of health discusses with the clinician handling the case and arranges for the anonymised summary case information to be documented for case review by the TBCN.
 - The medical officer of health passes the anonymised summary case information to the Communicable Diseases Team who then arranges for a teleconference with the TBCN, the clinician managing the case and the local medical officer of health.
 - The TBCN teleconference will discuss the case and provide advice around development of a treatment plan and an overall care plan for the MDR-TB case.
 - The Communicable Diseases Team member at the teleconference will act as secretary for the teleconference.

³ Presently, three laboratories offer services for identification and susceptibility testing for mycobacteria in New Zealand (Auckland, Waikato, and Christchurch Hospital laboratories).

⁴ Contact: Communicable Diseases Team via email notifycommndiseases@moh.govt.nz

⁵ EpiSurv is the national notifiable disease surveillance database operated by ESR on behalf of the Ministry of Health.

Appendix 3.2: Case summary form



133 Molesworth Street
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SUMMARY CASE INFORMATION FOR TB CLINICAL NETWORK

MDR-TB case location:

EpiSurv number:

Clinician's name:

Demographics

- Age / DOB
- Gender
- Ethnicity
- Country of birth
- Country/countries where lived for three months or more

Weight (kg)

Site(s) of disease

Chest X-ray

- Cavities

Other radiology

- MRI
- CT

Bacteriology result

- Microscopy
- Culture
- Molecular

Drug susceptibility testing

Key:

S = susceptible

R = resistant

NT = not tested

Antibiotic	Phenotypic result (S, R or NT)	Genotypic result (S, R or NT)
Isoniazid		
Rifampicin		
Ethambutol		
Pyrazinamide		
Amikacin		
Ethionamide		
Moxifloxacin		

Patient's TB treatment history

- Year of treatment
- Location
- Date of MDR-TB treatment commencement
- Treatment given
- Outcome
- Date of smear negative status (when known)
- Date of release from isolation (when known)

Were fixed dose combinations or individual drugs used?**Previous exposure to quinolones or aminoglycosides?**

- Include details if yes

Current clinical assessment and medical history

Details of co-morbidities

Include details of:

- diabetes
- renal impairment
- liver impairment
- immunosuppression
- visual impairment
- hearing impairment
- significant psychiatric history

Medications

Allergies

Baseline laboratory information

- Creatinine
 - Liver function tests
 - Haemoglobin
 - HIV test
 - HbA1c
 - Chest X-ray
-

Social

- Occupation
 - Smoking history
 - Alcohol history
 - Current housing situation
(including details of other
occupants – children, etc)
-

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Chapter 4: Supervision and adherence to treatment

Executive summary

Tuberculosis (TB) control requires a high level of adherence to the treatment regimen. If adherence is poor, drug resistance, prolonged infectiousness or reactivation may develop. Health care staff must support patients and enable them to adhere to the full course of treatment. This chapter discusses the different levels of supervision for treatment, including the use of directly observed therapy (DOT). It is primarily intended for public health nurses and clinicians with TB patients.

Recommendation summary

Clinical and public health services providing treatment, supervision and follow-up for TB must provide:

- free service
- free TB medications
- good case management
- appointment reminders and follow-up of non-attendance
- a comfortable clinic environment with minimal waiting times
- clear advice about side effects
- clear communication, including written and oral health education materials
- interpreters, if required, and culturally competent workers.

TB programmes may need to use multiple strategies to ensure patients adhere to the treatment regimen. The most successful programmes combine DOT observers, supervised therapy, thorough case management, excellent patient–provider communication and additional assistance or incentives to patients if required.

Public health services should ensure that information on DOT is carefully completed on the EpiSurv Case Report form.

Treatment supervision in New Zealand

The Ministry of Health recommends every TB case begins their treatment with DOT.

Levels of treatment supervision

All TB patients should commence treatment with DOT. After they have been observed taking treatment in their home environment, they can be assigned one of three levels of supervision:

- DOT
- Close supervision
- Self-administered treatment.

The optimal level of supervision is influenced by patient factors, clinical factors (such as drug resistance and the presence of side effects) and social factors (see Table 4.1).

The required level of supervision may change throughout the course of treatment.

Table 4.1: Recommended level of supervision

Risk factor	Level of supervision
One or more of: <ul style="list-style-type: none">• resistance to isoniazid or multidrug resistance (resistance to isoniazid and rifampicin) and other cases of multiple drug resistance• all relapses and re-activations• delayed culture conversion• human immunodeficiency virus (HIV) infection• inability or unwillingness to self-medicate (eg, substance abuse, denial of diagnosis, homelessness, intellectual limitations)• consistent failure to comply with ward or outpatient clinic requests• poor adherence during close supervision• extensive disease and high infectiousness• multiple risk factors in the 'close supervision' category• residence at a long-term care facility or prison• intermittent regimens (thrice-weekly doses)*	DOT
Any one of: <ul style="list-style-type: none">• weak or absent social support• psychiatric illness• troublesome drug side effects• complex treatment regimen• record of previous non-adherence with regard to treatment for other diseases	Close supervision: consider DOT
None of the above risk factors	Self-administered treatment

* Intermittent regimens are no longer recommended. If they are ever used, then they must be used with DOT.

Directly observed therapy – face to face and TeleDOT

The World Health Organization (WHO) directly observed therapy, short course (DOTS) strategy includes a comprehensive strategy for TB control that is relevant for resource limited settings.

DOT, as discussed here, describes the process where a trained observer watches the patient swallowing the medication for all doses during the course of treatment. It is one component of the DOTS strategy.

Close supervision

Medication is taken daily by the patient (or for a child, administered by the parent/caregiver). The public health nurse visits at least every week.

Where possible, medications should be dispensed in blister packs that are delivered every 28 days by a public health nurse. At each weekly visit, the public health nurse assesses adherence. Throughout the treatment course, the public health nurse explores and tries to alleviate potential barriers to non-adherence.

Self-administered treatment

Self-administered treatment is when medication is taken daily by the patient (or for a child, administered by the parent/caregiver). The public health nurse visits at least once every 28 days.

Self-administered treatment is possible if there are no risk factors and regular monitoring confirms good adherence. The patient self-administers medications daily with oversight by a public health nurse. Where possible, medications should be dispensed in blister packs that are delivered every 28 days by a public health nurse who takes this opportunity to assess adherence. Throughout the treatment course, the public health nurse explores and tries to alleviate potential barriers to non-adherence.

Definitions

- Face-to-face DOT: the patient is given the prescribed medication by a DOT observer and is observed swallowing the medication at a face-to-face meeting. The observer remains present until all medication has been swallowed.
- TeleDOT: the patient records themselves swallowing the medication by video and uploads to a secure server for later review by a DOT observer. Also referred to as Video Observed Therapy.

Accepted regimens are outlined in Chapter 3: Treatment of tuberculosis disease in adults and Chapter 7: Diagnosis and treatment of latent tuberculosis infection.

DOT observers

Ideally, DOT is provided by a public health nurse who also supervises the treatment course, monitors for medication side effects, oversees regular lab test monitoring and provides support for patients to attend clinic appointments.

Other staff can become trained DOT observers. This includes community workers, public health assistants or administrative staff without formal health care training. In other circumstances, health care professionals from outside the public health workforce can be recruited to administer DOT, eg, practice nurses, pharmacists. In either situation, the public health nurse remains the case manager with overall responsibility for DOT, and close communication is essential.

Data on DOT are recorded on EpiSurv by public health service staff. Data are captured for cases who received DOT for the entire duration of their treatment and for those who received DOT through the intensive phase of treatment. Between 2012 and 2015, 48 percent of TB cases in New Zealand had DOT during the intensive phase and 25 percent throughout the full course treatment.⁶

Thrice-weekly DOT

Thrice-weekly DOT is no longer recommended. (see Chapter 3: Treatment of tuberculosis disease in adults, for further information).

Adherence

Adherence refers to the extent to which a patient follows the instructions given for prescribed treatment. Adherence is critical for successful TB control. Patients who do not adhere to their treatment regimen remain infectious longer, take longer to complete treatment and are more likely to relapse or develop drug resistance than patients who do adhere.

Low adherence with any prescribed treatment is common, with typical adherence rates estimated to be about 50 percent (Haynes et al 2008). A meta-analysis of interventions to improve adherence with long-term medication found that almost all the effective interventions were complex, including drug combinations, information, counselling, reminders, self-monitoring, reinforcement, family therapy and other forms of additional supervision or attention (Haynes et al 2008).

⁶ EpiSurv – Institute of Environmental Science and Research.

Adherence and tuberculosis medication

Patients need support to adhere to a course of TB medication because:

- it is difficult to remember to take long courses of treatment
- the pills prescribed are sometimes hard to swallow
- large numbers of pills have to be taken
- the medication can have unpleasant side effects
- patients must abstain from or reduce their intake of alcohol
- stigma and negative attitudes associated with TB can affect the patient's acceptance of their diagnosis and willingness to adhere to treatment
- medication for other conditions may result in a very large total number of pills, and interactions may compound difficulties
- the patient usually feels better long before the treatment has been completed.

These factors are also relevant in the treatment of latent tuberculosis infection (LTBI), where the patient does not even feel unwell before starting treatment (see Chapter 7: Diagnosis and treatment of latent tuberculosis infection).

Factors influencing adherence

A number of factors influence the likelihood of adherence including:

- the accessibility and responsiveness of the health service (health care factors)
- the nature of the treatment (treatment factors)
- stigma and cross-cultural concepts of TB (cultural factors)
- the existence of more pressing personal problems (patient factors).

A New Zealand study of older people found that the public health nurse, resourced to deliver a patient-centred model of care, is a key support during TB treatment (Searle et al 2007).

Assessing adherence

Risk factors for non-adherence must be formally assessed for each patient at the beginning of treatment to determine the optimal level of supervision.

Risk factors for non-adherence

Recognised risk factors for non-adherence to the treatment regimen include:

- homelessness
- a history of TB
- substance abuse

- denial of diagnosis
- living alone
- patients believing that they are likely to have poor adherence (Davidson et al 2000; Pablos-Mendez et al 1997).

It is difficult for health care workers to predict a patient's adherence with accuracy. Care should be taken not to assume adherence or non-adherence on the basis of demographic variables such as age, gender and ethnicity.

Monitoring adherence

All patients on TB medication must be systematically monitored for adherence to their treatment regimen.

Methods for monitoring adherence

Monitoring methods include patient interviews, pill counts and, rarely, urine assays. Record-keeping sheets help public health nurses to record doses and detect adherence problems (see Appendix 4.1: Sample medication record for patients on self-medication at the end of this chapter). Where possible, medications should be provided in blister packs as this facilitates better adherence for the patient as they provide a visual cue and also make it easier for a public health nurse or trained observer to monitor missed doses.

Table 4.2: Routine activities for monitoring adherence

Clinical activities	Public health activities	Clinical and public health activities
Monitoring: <ul style="list-style-type: none"> • clinic non-attendance • adherence (physician assessment) • rate of clinical response to medication • induced sputum at the completion of the intensive phase (WHO 2009) 	Regular assessment of patient by a public health nurse, which includes: <ul style="list-style-type: none"> • discussing progress and problems, including side effects and adherence • making monthly pill / blister pack counts or syrup volume checks • checking medications are dispensed as prescribed • monitoring changes to risk factors for non-adherence 	Good communication among case workers, clinicians and patient Rapid communication if concerns about adherence Regular case review meetings between clinical and public health services

Trigger points that might lead to closer supervision (or DOT) include:

- the patient not attending one clinic visit without a good reason
- the patient not presenting for one pre-arranged public health nurse visit
- the public health nurse or hospital staff being concerned about non-adherence
- pill or blister pack counts or syrup levels indicating consistent missing doses (more than 15 percent).

Treatment contracts

Treatment contracts can be used at all levels of supervision, if the patient's adherence is in doubt. A treatment contract includes:

- the time and place for delivering supplies of medication (or delivering DOT)
- the patient's agreement to contact the case worker if plans change
- the patient's intention to attend all appointments.

After the patient has dated and signed the treatment contract, the public health nurse or medical officer of health should date and countersign the contract.

Adherence to treatment of latent tuberculosis infection

Treatment for LTBI requires a long course of treatment in a well person. Adherence is even more difficult than in cases on full treatment for active TB disease. Various approaches have been studied to improve adherence to treatment for LTBI. It has been found that shorter courses of treatment for LTBI are associated with better adherence, (Trajman et al 2010) as are a range of social interventions (Stuurman et al 2016). Offering the patient the choice of medication regimen for LTBI is also associated with better adherence (Rennie et al 2007).

DOT is associated with higher completion rates of LTBI treatment (Gourevitch et al 1998; White et al 2003). It should be considered if the patient has risk factors for non-adherence and one or more of the following apply:

- full DOT treatment of TB disease is being given at the same time to a person in the same household or neighbourhood
- the patient is aged under five years
- there are risk factors for progressing from infection to disease (see Who should be offered treatment for LTBI under Treatment in Chapter 7: Diagnosis and treatment of latent tuberculosis infection)
- the patient is a contact of a multidrug-resistant TB (MDR-TB) case, and treatment has been recommended.

Interrupted treatment

Interruptions to the treatment plan occur when a patient misses a dose of medication and are common in the treatment of TB. When they occur, the responsible clinician must decide whether to restart a complete course of treatment or simply to continue as intended originally. Interruptions that occur early in treatment and longer interruptions are thought to be more serious, and treatment may need to be restarted from the beginning. There is no evidence to guide management of interruptions; approaches have been developed based on expert opinion. An example, published by the American

Thoracic Society (ATS), the United States Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA) is shown in Table 4.3.

Table 4.3: Management of interrupted treatment

Time of interruption	Details of interruption	Approach
During intensive phase	Lapse is <14 days in duration	Continue treatment to complete planned total number of doses (as long as doses are completed within three months)
	Lapse is >14 days in duration	Restart treatment from beginning
During continuation phase	Received ≥80 percent of doses and sputum was AFB smear negative on initial testing	Further therapy may not be necessary
	Received ≥80 percent of doses and sputum was AFB smear positive on initial testing	Continue therapy until all doses are completed
	Received <80 percent doses and cumulative lapse is <3 months duration	Continue therapy until all doses are completed (full course), unless consecutive lapse is >2 months If treatment cannot be completed within recommended timeframe for regimen, restart therapy from the beginning (ie, restart intensive phase to be followed by continuation phase)*
	Received <80 percent of doses and lapse is ≥3 months duration	Restart therapy from the beginning, new intensive and continuation phases (ie, restart intensive phase, to be followed by continuation phase)*

AFB: acid-fast bacilli.

Note: According to expert opinion, patients who are lost to follow-up (on treatment) and brought back to therapy, with interim treatment interruption, should have sputum resent for AFB smear culture and drug susceptibility testing.

* The recommended timeframe for regimen, in TB control programmes in the United States of America and in several European countries, is to administer all the specified number of doses for the intensive phase within three months and those for the four-month continuation phase within six months so that the six-month regimen is completed within nine months.

Source: Nahid et al (2016).

The treating clinician and the medical officer of health should be advised if the patient misses a treatment dose. In particular, concerns should be raised without delay if a patient misses:

- more than one DOT dose per week (for daily treatment)
- more than one DOT dose per month (for intermittent treatment).

Use of legislation to support adherence

If the patient misses a dose, the medical officer of health and treating clinician should be advised. In centres with a large number of cases, this reporting could occur weekly. The medical officer of health may meet the patient to discuss any obstacles to adherence to the DOT regimen. Under Part 3A of the Health Act 1956, a patient must be given the opportunity to voluntarily adhere to their treatment programme. Cases who have missed medication doses can be given a formal direction to be available for DOT at specified times and places, be examined, stay away from work, etc, for a specified period up to six months.

Under Part 3A, no directions can be given to cases or contacts compelling treatment. If adherence cannot be achieved through the use of directions, education, incentives and support and the patient poses a public health risk (a substantial risk of harm to others), the medical officer of health still has other options. Provided the specific statutory preconditions are met for a particular measure, the medical officer of health can arrange for contact tracing, issue an urgent public health order to detain the case for 72 hours until a court order can be obtained or apply for a court order for treatment. A court order must be applied for and granted in order to require treatment. The case has a right to appeal public health directions and court orders. Prosecution for breach of directions or orders is a last resort.

Optimising tuberculosis health services to improve adherence

Person-centred care

There are many factors that can support patients to adhere to anti-TB treatment, including ensuring TB services are person- and whānau-centred. Person-centred care is personalised, enabling and coordinated (The Health Foundation 2016), where the clinician truly empathises with the patient, shows unconditional positive regard and is genuinely respectful and honest with the patient (Stewart et al 2014; Wilson and Cunningham 2014).

Whānau-centred care

Within New Zealand, TB has been a neglected condition within Māori communities. Providers of TB services need to work hard for Māori to address this inequity and enable personalised, enabling and coordinated care within the TB health service. Clinicians should be expected to work with Māori people with TB in a culturally competent manner (MCNZ 2006; NCNZ 2011). Like all people, Māori are entitled to receive services that are culturally safe for them (New Zealand Public Health and Disability Act 2000; MCNZ 2006; NCNZ 2011). Building a relationship based on trust and mutual respect is critical when working with people and their whānau (Lacey et al

2011). Clinicians delivering TB services need to consider the whole person, including their wider social, practical and emotional needs.

Focusing on strengths and processes that work for whānau may help identify strategies for successfully delivering services despite challenges such as rurality and work and whānau commitments. People delivering TB services should do their utmost to remove all barriers to accessing required services. This could include considering alternative strategies for delivering DOT and highlighting the availability of free services, medication and other enablers and incentives described below.

Health care system factors

Health and Disability Services Consumers' Rights

The Code of Health and Disability Services Consumers' Rights (the Code of Rights) describes a series of rights for all users of health services in New Zealand (including the right to be treated with respect, to effective communication, to full information and to confidentiality). These rights are part of best clinical practice.

In addition, the Health Act 1956 sets out a number of patient rights with respect to public health directions and orders. Notably, there must be respect for individuals, patients must be given the opportunity to voluntarily comply, individuals must be informed and the least restrictive alternative must be used. If public health directions or orders are served, then the patient has a right of appeal to the District Court.

Free services and medication

People who have or who are suspected of having an infectious and/or quarantinable disease are eligible for publicly funded health services to address the risks to other people. This includes TB, which is a notifiable disease under the Health Act 1956. This is true irrespective of a person's citizenship or immigration status under Criteria B23 of the Health and Disability Services Eligibility Direction 2011 (Ministry of Health 2011; 2012a).

These free services include diagnostic investigations, clinic visits, hospital admissions, medications, laboratory testing for monitoring, supervision and contact tracing. This means treatment of LTBI identified in the course of contact tracing is free.

Case management

Ideally, a designated physician and a single case worker (usually a public health nurse) would communicate regularly with the patient and each other (NICE 2016).

Patient reminders should be issued for follow-up of non-attendance at clinics. A copy of the appointment should be sent to the public health service as the public health staff may know about changes affecting the patient's ability to attend.

TeleDOT

TeleDOT is one of a number of digital technologies that support TB medication adherence (WHO 2017). The use of video phone technology for directly observing anti-TB medication being taken has been successfully implemented in a number of settings (Chuck et al 2016; DeMaio et al 2001; Mirsaeidi et al 2015), including Washington DC, Illinois, New York, Adelaide and Auckland. It has been found to be acceptable to patients and to result in cost savings (Krueger et al 2010; Mirsaeidi et al 2015) and, in one study, to have higher adherence than DOT. TeleDOT will not be appropriate for every patient, and best practice for teleDOT is still being defined. It requires an internet connection to upload videos.

Case study: TeleDOTS at Auckland Regional Public Health Service

In December 2012, Auckland Regional Public Health Service (ARPHS) secured funding for a pilot telehealth project called TeleDOT. This project aimed to increase the proportion of TB patients receiving DOT in the greater Auckland area, using telehealth technology while staying within current staffing levels and improving cost-effectiveness.

TeleDOT is a cloud-based system, where patients take video recordings of themselves taking their medications daily, at a time that is convenient for them. The recording is stored in the cloud and viewed by the patient's public health nurse, usually later the same day or the following day. There is also the option to have live teleconferences for patients who require further input. Rather than being visited up to twice a day at their homes, patients only need to be seen in person once a month to replenish their antibiotic supply. This new approach is patient-centred, giving patients greater flexibility over the timing for taking their medication and maintaining their privacy, thereby minimising interference in their busy lives. In order to improve access to TeleDOT, ARPHS has a pool of tablet devices it loans to patients who do not have smartphones.

The move to TeleDOT at ARPHS has had benefits both to the patients and to the health system (Table 4.4). ARPHS is continuing to invest in this technology, with future improvements aimed to support the continuation of DOT in patients who are outside the Auckland region for a period of their treatment programme.

Table 4.4: Benefits of ARPHS expanding their TB programme to include TeleDOT

Benefits to the patients	Benefits to the health system
<ul style="list-style-type: none">• The patient is in control of the time that they take their medication, fitting it in around work, school and social commitments – they can decide where, when and how to take their medication.• Flexibility – patients can do TeleDOT at home, work or anywhere that has an internet connection.• Smartphone-based technology meets adolescents and youth in their natural online space.• The system decreases the stigma of having a health worker come to their house every day and increases patient privacy in their own home.	<ul style="list-style-type: none">• Cost-per-patient estimates show that TeleDOT cut the cost of regular DOT before recorded sessions were introduced by 75 percent. Recorded sessions add cost-effectiveness as they decrease the weekend staff workload.• The system improves the use of ARPHS staff time and resources. It increases the percentage of patients we are able to provide with DOT from 30 percent to 60 percent of active pulmonary TB cases, improving overall control of the disease in Auckland.• Public health nurses can easily hand over patients, meaning there are fewer disruptions when staff are away or change geographical areas.• The system uses all electronic records – no more paper notes are taken in the community and transcribed to the computer.• There is the potential for the system to be scaled up and shared between district health boards throughout New Zealand.

Enablers and incentives

Adhering to any medication regimen can be difficult. Anti-TB medication adherence is particularly challenging because of the number of medications required, the long course, possible side effects and interactions with other medications, etc. All patients will need some level of support to complete their treatment plan successfully. Enablers make it easier for a patient to participate in a treatment programme, and incentives are used to coerce or reward adherence. Below are enablers and incentives that have been found to be useful in a number of settings (Bock et al 2001; Calder et al 2001; Chaulk and Pope 1997; Davidson et al 2000; Fujiwara et al 1997; Nahid et al 2016; NICE 2016; San Sebastian and Bothamley 2000; Schechter 1997). They may or may not apply to individual settings across New Zealand.

Table 4.5: Enablers and incentives

Enablers	Incentives
<ul style="list-style-type: none"> • Health education counselling • Advice about side effects • Discussion of barriers and attempts to overcome these • Transportation vouchers (taxi chits, petrol vouchers, public transport cards) • Convenient clinic hours and locations • Clinic personnel who speak the languages of the populations served • Reminder systems (eg, phone and text reminders) and follow-up of missed appointments • Social service assistance (eg, income support, housing and other services) • Addiction service referrals for substance abuse treatment and counselling • Outreach workers (bilingual/bicultural as needed; can provide many services related to maintaining patient adherence, including provision of DOT, follow-up on missed appointments, monthly monitoring, transportation, social service assistance and educational reinforcement) • Integration of TB care with care for other conditions • Advice and support for parents and carers 	<ul style="list-style-type: none"> • Interventions to motivate the patient, tailored to individual patient wishes and needs and, thus, meaningful to the patient • Food vouchers or snacks and meals • Other monetary incentives, eg, mobile phone top-ups • Petrol vouchers • Patient's contract

Advice on the use of interpreters

Effective communication, given in a form, language and manner that the patient understands, is one of the rights in the Code of Rights. At the first contact with the health service, any patient whose first language is not English should be assessed to establish whether or not an interpreter is needed. If there is any doubt, an interpreter should be used. Ensure that written information is available in the patient's language to complement verbal information.

When an interpreter is needed, a professional interpreter (ie, an interpreter with specialised training) should be used whenever possible. In general, untrained interpreters (eg, family members or friends) should not be used except in emergency situations as this compromises the patient's confidentiality and there is a risk of miscommunication. A telephone interpreting service can be used.

Tips for communicating through an interpreter

Speak slowly and clearly, using one or two sentences at a time.

Focus your attention on the patient, not the interpreter.

Use simple English – try to avoid medical terms and colloquialisms.

Avoid non-patient-related conversations with the interpreter in front of the patient. If this cannot be avoided, try to include the patient or explain what is happening.

Source: Ministry of Health (2012b)

Appendix

Appendix 4.1: Sample medication record for patients on self-medication

Place sticky label here PATIENT NAME / NHI / DATE OF BIRTH / ADDRESS				Medication record for patients on self-medication Blister pack medications: _____ _____ _____				
				Number of tabs per dose _____				
A	B	C	D	E	F	G	Comments	
Date	No. of days since last visit	No. of doses left at last visit	No. of doses present today	Expected doses today (C–B)	Doses missed (D–E)	Percentage of doses missed 100 (F/B)		PHN initials

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Chapter 5: Tuberculosis in children

Executive summary

Tuberculosis (TB) in children under 15 years of age accounts for approximately 5–10 percent of all TB disease in New Zealand. This means many clinicians in New Zealand will rarely diagnose a case of TB in a child. Along with this, paediatric TB disease has some distinct characteristics, particularly in the young infant, which can make it a challenge to diagnose and treat.

As TB in children is an indicator of recent acquisition and a marker of ongoing transmission in a community, it needs to be diagnosed early to identify source cases and prevent further transmission (Newton et al 2008; Perez-Velez and Marais 2012). A source case within the family or close contacts is usually found. *Mycobacterium tuberculosis* infection progresses to disease more rapidly in children than in adults.

Children with intrathoracic TB have minimal symptoms and signs, therefore an approach that includes awareness of the diagnosis, epidemiological information, clinical findings and appropriate investigations will help to make an early and accurate diagnosis. Children have a higher risk of developing severe or disseminated forms of TB than adults. Diagnosis of TB in children is usually based on history and examination along with a combination of a positive tuberculin skin test (TST), known contact with an adult case of TB and clinical or radiological features suggestive of TB. Microbiological confirmation should be sought but is not always possible due to the low number of bacilli present. This chapter includes recommendations on diagnosis, drug dosage, treatment setting, monitoring and when to consult a paediatrician expert in TB.

Other chapters in this guideline will include details of managing a child's exposure to a case of active TB (see Chapter 6: Contact investigation), managing latent TB infection (LTBI) in children (see Chapter 7: Diagnosis and treatment of latent tuberculosis infection) and details on drug toxicities (see Chapter 3: Treatment of tuberculosis disease in adults). Bacille Calmette-Guérin (BCG) vaccination is now covered in the *Immunisation Handbook 2017* (Ministry of Health 2018).

Recommendation summary

- In most cases of superficial lymph node enlargement, a tissue biopsy for histology and culture is required to exclude TB.
- When a child suspected of TB with no identified source case does not produce sputum, clinicians should still seek a microbiological diagnosis, using a combination of three early morning gastric aspirates on consecutive days, induced sputums or bronchial secretions from bronchoscopy.
- Children under one year of age with miliary TB should have a lumbar puncture to exclude meningitis.
- All hospitalised children with suspected TB and their caregivers and visitors should be isolated initially.
- For children with paucibacillary disease without risk factors for drug resistance a three-drug intensive phase is recommended (2RHZ/4RH). All TB patients should commence treatment with directly observed therapy (DOT) (see Chapter 4: Supervision and adherence to treatment).
- Higher dose rifampicin (R) is now recommended for infants, toddlers and children of any age with TB meningitis.
- A fourth drug is recommended in all cases of disseminated and meningeal TB, severe disease, co-infection with human immunodeficiency virus (HIV), and smear positive pulmonary TB if no source case identified.
- Consider consulting all cases of TB in a young child with a paediatric infectious diseases specialist. Early discussion with a paediatric TB expert is recommended for neonates and in cases of disseminated TB, slow clinical resolution, comorbidities especially HIV co-infection and suspected or proven drug resistance. All cases of multidrug-resistant tuberculosis (MDR-TB) must be treated in consultation with the New Zealand tuberculosis clinical network (TBCN).
- Liver function tests (LFTs) should be measured at baseline and, if normal, children should be followed clinically for symptoms of liver dysfunction.
- Clinical follow-up should include assessment of growth, symptoms, adherence and adverse events, as well as dose adjustments for weight gains.
- If a neonate's mother has known or suspected MDR-TB, an expert in managing TB should be consulted.

Clinical and diagnostic differences from adult tuberculosis

The same basic principles that apply to diagnosis and management of TB in adults apply to children. This chapter should be read in conjunction with Chapter 2: Diagnosis

of tuberculosis disease and Chapter 3: Treatment of tuberculosis disease in adults. However, there are some important clinical and diagnostic differences.

- Children under five years of age have a higher risk of progressing from infection to disease than adults. This can occur within one year of infection and can be as short as a few weeks (Starke 2004). Reasons for this relate to the relative immaturity of immune function (Marais 2014; Newton et al 2008).
- Children under five years of age have a higher risk of developing extrapulmonary TB (EPTB), particularly miliary or meningeal TB. The proportion of TB cases with disseminated TB or tuberculous meningitis is 10–20 percent under one year of age and 0.5 percent over two years (Newton et al 2008).
- TB in children is usually an immediate complication of primary infection with a closed caseous paucibacillary lesion. Cavitory TB is rare in young children and is more likely to occur in children over 10 years of age (Hoskyns 2003; Newton et al 2008; Van Hest et al 2004). Uncomplicated hilar adenopathy is the most common disease manifestation in children.
- Before the use of chemotherapy, studies found that children under two years of age with primary infection progressed to serious disease within the first 12–24 months without significant prior symptoms. This progression rarely occurred in those aged 2–10 years, but when it did, they usually had significant symptoms (Marais et al 2004).
- Children with HIV infection or other immunocompromising conditions can have similar progression to young children (Schaaf and Zumla 2009; Swaminathan and Rekha 2010).
- Just over half of childhood TB occurs in infants and children under five years of age, with a second peak again in late childhood and adolescence. TB is much less common in children aged between 5 and 14 years. Most children are infected from an infectious adult within their own immediate or extended family (Munoz et al 2002; Sun et al 2002).
- Other factors associated with progression of LTBI to disease in children include recent infection, immunodeficiency, immunosuppressive therapy, certain diseases (eg, diabetes mellitus, chronic renal failure and use of biologic response modifying drugs, eg, infliximab).

Signs and symptoms

- The majority of children with intrathoracic TB have minimal symptoms and signs (Cruz and Starke 2007). Over one-half of children will have no symptoms or signs but will have significant changes on chest X-ray (CXR). The younger the age, the more likely the child will have symptoms. Non-productive, unremitting cough, mild dyspnoea and fever are the most common symptoms, and young infants may fail to thrive (Marais et al 2005). Findings on chest examination are uncommon. The characteristic CXR finding is lymphadenopathy with or without parenchymal involvement. A study from South Africa found significant limitations in interpretation of mediastinal adenopathy on CXR and suggests caution in interpreting radiographic lymphadenopathy (Swingler et al 2005). Further imaging may be required.

- Miliary disease results from lymphohaematogenous spread and occurs early after infection within the first two to six months. The clinical manifestations are variable with onset that can be insidious (malaise, anorexia, low-grade fever, weight loss) and non-specific or rapid and overwhelming. TB meningitis can also have an insidious onset over several weeks but is universally fatal without treatment, and delayed diagnosis can result in significant morbidity (Schaaf and Zumla 2009).
- Early suspicion and diagnosis is a crucial part of detection of TB in children. There have been a number of large outbreaks reported due to delayed diagnosis in the source case. A number of these have involved schools (Calder et al 2008; Hoskyns 2003).
- Superficial lymph node enlargement is more commonly due to non-tuberculous mycobacteria (NTM) in children in New Zealand, particularly in the under-five year olds. However, TB needs to be excluded, particularly if the child was born overseas or born to a family from a high prevalence country. In most cases, a tissue biopsy for histology and culture is required to confirm diagnosis.

Diagnosis

- Diagnosis of TB in children is usually based on history and examination along with epidemiology, such as contact with a case of TB, results of TST or interferon gamma release assay (IGRA) test, along with radiological findings consistent with TB. Positive cultures are uncommon in children, and the above factors are the mainstay of the diagnosis despite introduction of new diagnostic tests (Lewinsohn et al 2017; Newton et al 2008; Starke 2004). Negative cultures never exclude TB in a child (Starke 2004).
- Systematic reviews suggest TST and IGRAs have similar limitations diagnosing either latent or active TB in children. However, in children under five years old, it is difficult to obtain the volume of blood required for an IGRA, and this is why a TST is preferred. Where TST is unavailable, an IGRA can be used in children over two years old (Starke 2014). These tests should only be used as one part of the clinical diagnosis of TB (Machingaidze et al 2011; Mandalakas et al 2011).
- As sputum is rarely available from young children, alternatives are three early-morning gastric aspirates on consecutive days, three induced sputums (Marais and Pai 2006; 2007) or bronchial secretions from bronchoscopy, if available (see Chapter 2: Diagnosis of tuberculosis disease). Bronchoscopy is invasive and should be used with caution in the unwell child with respiratory compromise but may be useful if another diagnosis is under consideration. A combination of specimens provides the best yield (Nicol and Zar 2011).
- Although Xpert MTB/RIF has been very valuable in improving diagnosis of TB in adults, it has not overcome the difficulty with diagnosing paucibacillary disease, with reduced sensitivity in children of only 60–70 percent (Detjen et al 2015). A negative result does not rule out TB in children.
- Biopsy of appropriate tissue specimens for microscopy, culture and polymerase chain reaction (PCR) should be undertaken if possible, eg, pleura, cerebrospinal fluid (CSF) or lymph node. Miliary TB has a high risk of meningeal involvement in over 50 percent of cases.

- Children under 12 months of age who are suspected of having pulmonary or extrapulmonary TB, with or without neurologic symptoms, should have a lumbar puncture (WHO 2014). Children 12–24 months should be considered for a lumbar puncture, but over 24 months lumbar puncture is only required if they have neurologic signs and symptoms (American Academy of Pediatrics 2018).
- PCR will frequently be negative in pulmonary TB in children due to the low bacillary load but can be very useful in diagnosing EPTB (Marais and Pai 2007).
- Bacteriological confirmation is particularly important:
 - if an isolate from a source case is not available
 - if the child has HIV
 - if there is suspected drug resistance or known drug resistance in the probable source case
 - in severe disease
 - if the diagnosis is unclear (WHO 2014).
- If suspected TB disease has not been confirmed microbiologically, a decision to treat requires careful consideration before initiating treatment. Good treatment outcomes would be expected provided treatment is started promptly. The risk of developing drug resistance during drug treatment is low.

Isolation requirements

It is recommended to isolate all hospitalised children with suspected TB and their caregivers and visitors initially, as although paediatric TB is rarely infectious, an undiagnosed relative may be the source case (American Academy of Pediatrics 2018; Munoz et al 2002).

The vast majority of children under 10 years old with TB are not infectious. The reasons for this are that most children have no significant cough, lack the tussive force necessary to spread disease, rarely produce sputum and have a low concentration of organisms in endo-bronchial secretions (Schaaf and Zumla 2009). Any child who develops adult-type TB, including upper lobe infiltrates or cavities, has a higher load of organisms and should be considered infectious until sputum results are available.

Children that require isolation include children with: cavitary TB, positive sputum smears for acid-fast bacilli (AFB), laryngeal involvement, extensive pulmonary infection, congenital TB undergoing procedures that involve the airway (American Academy of Pediatrics 2018).

Treatment of tuberculosis in children

Principles of management

For paucibacillary childhood TB, a three-drug intensive phase is sufficient if resistance is not suspected (Donald and Schaaf 2007). If no isolate is available from the source case or for complicated disease, including miliary and meningeal disease, four drugs should be started.

Basic principles of drug treatment in children are the same as for adults (Marais et al 2006). However:

- due to different patient pharmacokinetics, children's dosages are based on mg/kg
- medication doses need to be adjusted for weight increases with growth to prevent under dosing
- in younger children, it is better to dose at the higher end of recommended ranges
- children have a lower risk of adverse effects
- limited paediatric drug formulations can result in difficulties with administration
- children are dependent on caregivers for adherence.

See Chapter 3: Treatment of tuberculosis disease in adults, for discussion of drug toxicities and interactions.

Managing tuberculosis in children

Early discussion with a paediatric TB expert should be undertaken in cases of:

- disseminated TB
- poor or slow resolution of TB despite adequate treatment
- presence of comorbidities, especially HIV co-infection
- suspected or proven drug resistance
- drug toxicity
- neonatal TB.

Treatment regimens

Optimal treatment regimens and dosages are not known for children, but most children using current regimens have good outcomes. Treatment regimens are available from a number of different international organisations (see Chapter 3: Treatment of tuberculosis disease in adults) (Shingadia and Novelli 2003). Many studies have confirmed that the regimen of six months of isoniazid (H) and rifampicin (R), with

pyrazinamide (Z) in the first two months cures over 99 percent cases of drug susceptible pulmonary TB.

As most cases of TB in children do not have an isolate available, the treatment regimen is based on sensitivities from the source case. Usually three drugs alone are started, but if a fourth drug is required, ethambutol (E) is most common but penetrates poorly into CSF except in the presence of inflamed meninges (WHO 2014).

A fourth drug is recommended in all cases of disseminated and meningeal TB, severe disease, co-infection with HIV and smear-positive pulmonary TB if no source case is identified. Consider a fourth drug if there is a high risk of drug resistance based on epidemiologic characteristics of the child or source case (Starke 2004).

Prothionamide has better CSF penetration, maybe considered as an alternative to ethambutol in TB meningitis and is generally well tolerated. Rifampicin also penetrates poorly into CSF. Some experts recommend a longer continuation phase (10 months, ie, 12 months total) for miliary and meningeal TB (Marais et al 2006; WHO 2014).

Intermittent treatment regimens have been used in children, but these studies have enrolled children with less severe disease (Donald and Schaaf 2007). Intermittent treatment regimens are no longer recommended in New Zealand.

Adherence issues are the same as for adults (see Chapter 4: Supervision and adherence to treatment).

Table 5.1: Treatment regimens for children

TB disease	Intensive phase	Continuation phase
Pulmonary disease or TB peripheral lymphadenitis (HIV negative)	2RHZ	4RH
Extensive pulmonary disease	2RHZE	4RH
TB meningitis*	2RHZE	10RH
Miliary/disseminated TB*	2RHZE	10RH
Osteoarticular TB*	2RHZE	10RH
MDR-TB	Refer to paediatrician experienced in TB	

2: 2 months; 4: 4 months; 10: 10 months; E: ethambutol; H: isoniazid; R: rifampicin; Z: pyrazinamide.

HIV: human immunodeficiency virus; MDR-TB: multidrug-resistant tuberculosis; TB: tuberculosis

* Treatment duration can vary and discussion of management regimen with a paediatrician experienced in TB management is recommended. In managing TB meningitis, higher dose rifampicin is sometimes used (see text) and a longer duration of the intensive phase maybe considered in some individuals. Clinicians prescribing these drugs should be familiar with the content of the datasheet (www.nzformulary.org).

Adapted from World Health Organization (WHO 2010).

Fixed dose combination tablets of isoniazid/rifampicin are available. The American Academy of Pediatrics has indicated that many experts recommend a daily rifampicin dose of 20–30 mg/kg/day based on pharmacokinetic/pharmacodynamic modelling for infants, toddlers and children of all ages with serious forms of TB, such as meningitis or disseminated disease (Savic et al 2015; American Academy of Pediatrics 2018).

Rifampicin is the only first-line TB drug with a commercially available suspension. Isoniazid is available as 100 mg tablets. There is no commercial suspension available, and there are no stability data for extemporaneously compounded liquids. The tablets can be crushed and mixed with water immediately before administration. The mixing agent should not be apple sauce or a vitamin C containing product as these can alter the bioavailability of the drug. Pyrazinamide is only available as 500 mg tablets, which can be halved and crushed. This should be closely supervised until tolerance and adherence is consistently achieved.

Adverse effects are uncommon, but hepatotoxicity can be caused by isoniazid, rifampicin and pyrazinamide. If baseline liver functions are normal, no further routine laboratory monitoring is required, but clinical symptomatology should be assessed regularly. If symptoms suggestive of liver toxicity occur, such as jaundice, nausea, abdominal pain, anorexia, dark urine or pale stools, medication should be discontinued and a full evaluation should take place.

In cases with an adverse event or intolerance, advice should be sought from a paediatrician with experience in managing TB.

Anti-tuberculosis drug doses

Table 5.2: Dosage recommendations for anti-tuberculosis agents for children

Medication	Daily dose mg/kg (range)	Max dose/day
First-line agents		
Isoniazid (H)	10 (10–15)	300 mg
Rifampicin (R)	15 (10–20)	600 mg
Ethambutol (E)	20 (15–25)	1.0 g
Pyrazinamide (Z)	35 (30–40)	2.0 g
Prothionamide	20 (15–20)	1.0 g
Second-line agents (Marais et al 2011)		
Prothionamide and ethionamide	15–20	1.0 g
Rifabutin	10–20	300 mg
Moxifloxacin	7.5–10	400 mg
Streptomycin (intramuscular, intravenous)	20–40	1.0 g
Amikacin (intramuscular, intravenous)	15–30	1.0 g
Kanamycin (intramuscular, intravenous)	15–30	1.0 g
Capreomycin (intramuscular)	15–30	1.0 g
Cycloserine	10–20	1.0 g
P-aminosalicylic acid (4 g sachets)	200–300	10 g

Refer to datasheets for additional information (www.nzformulary.org). Ethambutol and Prothionamide are not approved medicines in New Zealand, and clinicians prescribing them under section 29 should do so with the informed consent of the patient.

The child's weight needs to be monitored frequently and dose adjustments made accordingly (Lewinsohn et al 2017; WHO 2010).

- Ethambutol has been associated with optic neuritis, and this has resulted in limited use in young children due to difficulty monitoring visual symptoms. A WHO review has concluded that ethambutol is safe to use in children if recommended doses are adhered to. Children requiring ethambutol should have regular vision checks, using the Ishihara test and ophthalmology review at baseline and monthly while on medication. Renal function should be monitored if the child has, or is at risk of, renal impairment as ethambutol is renally excreted (Schaaf and Zumla 2009).
- Prothionamide causes gastrointestinal discomfort and vomiting in 50 percent patients. This can be modified by starting with a twice-daily dose.
- Renal function will need to be closely monitored when using an aminoglycoside. Audiology should be done at baseline and monthly while on an injectable aminoglycoside and at six months after completion.

Pyridoxine

Isoniazid peripheral neuritis is rare in children, so most do not require pyridoxine supplementation. Pyridoxine (5–10 mg/day) should be given to:

- breastfeeding infants
- adolescents (because of their rapid growth, using adult dosing)
- malnourished children or children with inadequate diets (eg, meat- or milk-deficient diets)
- breastfeeding infants whose mothers are taking isoniazid
- HIV-infected children
- children who develop paraesthesiae.

For children, the dose can be achieved by halving a tablet or requesting the pharmacy suspend the tablet and provide instructions for oral administration measured by a needle-less syringe.

Corticosteroids

Corticosteroids are indicated for children with TB meningitis. There may be some other situations in managing TB when the use of corticosteroids should be considered, although limited evidence is available (Nahid et al 2016). These include cases of TB meningitis, airway obstruction secondary to enlarged lymph nodes, severe miliary disease and pericardial TB (Prasad et al 2000).

- When indicated, a prednisone dose of 2 mg/kg per day (maximum 60 mg/day) tapered over four to six weeks should be used.
- Corticosteroids should only be given with appropriate anti-TB therapy (WHO 2014).

Monitoring

Clinical and radiological follow-up are used to evaluate a child's response to treatment.

- Clinical follow-up should include assessment of growth, symptomatology, adherence and adverse events, as well as dose adjustments for weight gains. As a guide, this should occur two weeks after initiation of treatment, at the end of the eight-week intensive phase and two-monthly after that. This will vary according to a number of factors, including age of child, severity of disease and tolerance to medication.
- CXR – radiological changes usually require longer than six months for complete resolution. A normal CXR is not necessary for discontinuing anti-TB medication.
- Long-term complications such as development of bronchiectasis are uncommon, but awareness of this risk is needed.

Managing neonates

(Australasian Society of Infectious Diseases 2014)

TB in neonates is uncommon and can occur as congenital infection or postnatal TB (Schaaf et al 2010).

Congenital TB is rare (Connelly Smith 2002). A neonate may acquire TB in utero through direct spread through the umbilical cord, haematogenous spread or aspiration of infected amniotic fluid or vaginal secretions. Definitions developed by Cantwell et al (1994) distinguish between congenital and postnatal transmission.

Transmission in utero is most likely to occur in pregnant women with recent TB infection or EPTB, such as disseminated TB or pleural effusion, rather than cavitating disease, which is more likely to cause postnatal infection.

- Perinatal TB from airborne spread from an adult case, including from health care workers, has been well documented over the years (Isaacs et al 2006).
- Symptoms of TB in the neonate are non-specific: lethargy, poor feeding, low birth weight, unresolving or recurrent pneumonia and possible mimicking of other congenital viral infections or bacterial sepsis. The commonest reported symptoms are hepatosplenomegaly and respiratory distress, less commonly fever and lymphadenopathy.
- The presence of a hepatic granuloma is consistent with congenital TB.
- Postnatal TB is more likely to present with cough, tachypnea, wheeze and stridor. The diagnosis can be difficult but should be considered in the child who is not responding to broad-spectrum antibiotics, tests negative for other congenital infections and in whom TB is suspected in the mother.
- Overt expression of disease often does not occur until the second or third week of life.

- A high index of suspicion should be kept when evaluating an unwell infant with symptoms not able to be explained by other causes and born to a mother at high risk for TB.
- If a TB diagnosis is suspected, a TST, CXR, lumbar puncture and appropriate cultures should be performed. Diagnosis is usually made on clinical suspicion and microscopy and culture from gastric aspirates, biopsy tissue (lymph nodes, bone marrow, liver) or placental tissue. The TST is usually negative in neonates, so does not rule out the diagnosis of TB disease.
- Treatment should be initiated promptly if examination findings and CXR support diagnosis of TB.

Managing neonates exposed to maternal tuberculosis

Management will depend on the stage of maternal disease (Australasian Society of Infectious Diseases 2014; Ormerod 2001). Case management can be complex and should be discussed with an expert in paediatric TB.

Mother with active disease

If the neonate presents with symptoms, the infant should be assessed for congenital TB. For the asymptomatic infant (when congenital TB has been excluded):

- treat with isoniazid (10 mg/kg) for three to four months (if maternal isolate is known to be sensitive)
- when the infant is three to four months old, perform a TST (If the TST and CXR are normal and the infant is asymptomatic, stop isoniazid and consider BCG vaccination.)
- if the TST is positive, reassess for TB disease. If the infant's examination and radiology is normal treat with isoniazid for six months.

Breastfeeding is recommended irrespective of the mother's TB status. First-line anti-TB drugs cross into breast milk in variable amounts, although at an inadequate level to treat the infant and are considered safe.

Isolation of the neonate from mother is rarely required if the mother who has drug susceptible TB wears a mask and follows infection control measures (Isaacs et al 2006). Once the infant is receiving isoniazid, a mask is no longer necessary.

Isolation of the neonate from the mother may be required if the mother has MDR-TB or has poor adherence (American Academy of Pediatrics 2018; Ormerod 2001).

Mother with latent tuberculosis infection but no disease

The neonate of a mother with latent tuberculosis infection (LTBI) but no disease is not at risk and requires no special evaluation or treatment (American Academy of Pediatrics 2018).

Household contacts should be evaluated for an infectious source case.

Mother with MDR-TB or suspected MDR-TB

If the mother has known or suspected MDR-TB, an expert in the management of TB should be consulted.

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Chapter 6: Contact investigation

Executive summary

The chapter is a guide for public health staff who may be involved in contact tracing of tuberculosis (TB), including district health board (DHB) occupational health and infection control staff. This chapter provides guidance on conducting a contact investigation, including identifying contacts, prioritising their screening and arranging their medical management. Special situations including management of contacts of multidrug resistance (MDR) cases, pregnant contacts and contacts on aircraft. School and health care facility contact investigations are also covered.

Recommendation summary

- Case contact investigations should be overseen by the medical officer of health of the region in which the index case is notified.
- Contacts should be prioritised for assessment according to their exposure to *Mycobacterium tuberculosis* and their risk of progressing to active TB if infected.
- In the first instance, all first-circle (close) contacts should be traced, as should second-circle contacts with risks for progression to TB (Figure 6.1).
- High-priority contacts aged under five years should have a chest X-ray (CXR), tuberculin skin test (TST) or interferon gamma release assay (IGRA) and specialist clinical evaluation by a paediatrician.
- Contacts aged over five years, with symptoms of pulmonary TB or a positive TST or IGRA require a CXR. A CXR may also be considered following a negative TST or IGRA in a person aged over 60 years or with another risk factor for a false-negative TST or IGRA.
- Contacts of infectious TB cases who are TST or IGRA positive and with a normal CXR must be considered for latent tuberculosis infection (LTBI) treatment.
- Contacts of multidrug-resistant tuberculosis (MDR-TB) cases should be managed by, or in consultation with, practitioners experienced in this rapidly changing area.
- Bacille Calmette-Guérin (BCG) vaccination should be offered to unvaccinated TST negative contacts under five years of age.
- For TB cases on aircraft, only contacts seated within two rows of an infectious case on flights lasting longer than eight hours need to be traced.
- The medical officer of health in the DHB area in which a case is notified must coordinate and finalise the contact investigation.

- Medical officers of health must ensure general practitioners (GPs) in their districts are aware of TB policy and procedures and advise them of the investigation and public health management of their patients.
- Contact tracing activity should be audited periodically to ensure quality and consistency with guidelines and to inform future work.

Contact investigation

Objectives

The objectives of contact investigation are to:

- reduce TB morbidity and mortality by early identification and adequate treatment of contacts with TB
- arrest further transmission by early detection of possibly infectious TB cases
- contribute to TB elimination by preventing future cases of TB in the population by detection and preventive treatment of infected contacts at risk of developing TB.

In some situations, a further objective of contact investigation is to identify the source case where recent transmission is suspected (in particular, if the index case is a child).

Overview

Material in this chapter is based on the frameworks provided by the United States Centers for Disease Control and Prevention (CDC) and by Erkens et al (CDC 2005; Erkens et al 2010). The principal steps in contact investigation of a potentially infectious index case are:

- assessing the risk, which includes considering:
 - the index case's relative infectiousness
 - the index case's infectious period
 - locations of possible transmission
 - susceptibility of contacts
- identifying and prioritising contacts for investigation
- developing a screening plan
- contact investigation.

Index case's relative infectiousness

(Riley et al 1962; Sultan et al 1960)

- Anatomical site of infection: with few exceptions, only patients with TB of the lung parenchyma or airways transmit tubercle bacilli. Pulmonary TB should be sought and excluded in patients with pleural disease (Conde et al 2003). Extrapulmonary TB (EPTB) may be transmissible if lesions are subject to procedures that release aerosol (eg, dressing change of tuberculous abscess) (Keijman et al 2001).
- Production of sputum: those who were unable to expectorate sputum (and therefore required sputum induction or broncho-alveolar lavage (BAL) for specimen collection) are likely to be less infectious than others.
- Ability to aerosolise bacilli (Jones-López et al 2016): aerosols are produced by respiratory actions, such as coughing, talking, singing and sneezing; the larger the physical force of the action, the larger the number of expelled small droplets that evaporate into droplet nuclei. The presence and frequency of cough is therefore relevant to infectiousness (Jones-López et al 2014).
- Results of sputum-smear examination: Patients with detectable acid-fast bacilli (AFB) in their sputum smears (sputum-smear positive) are more infectious than those who are sputum-smear negative but culture positive (Barnes et al 1988). Of those who are smear positive, the higher smear grades are associated with greater transmission to contacts (Rutherford et al 2012).
- Chest radiographic findings: among those with lung parenchymal disease, those with cavities are more infectious than those without (Bailey et al 2002).
- As young children and those with compromised immunity, specifically human immunodeficiency virus (HIV), tend to have paucibacillary non-cavitating disease, they are usually less infectious.

Infectious period

In general, it is not possible to objectively determine the onset of infectivity. However, start of cough is commonly used as a proxy. For contact investigation purposes, the following rules have been suggested:

- Smear-positive pulmonary cases should be considered to have been potentially infectious for the period known to have been coughing or with respiratory symptoms initially to a maximum of three months.
- Culture-positive smear-negative may be considered potentially infectious for one month before diagnosis (Erkens et al 2010).

In the absence of suspicion or proof of MDR-TB, infectiousness should be considered to continue until the person has completed at least two weeks of appropriate treatment if symptoms have improved. Further information on the effect of treatment on infectiousness can be found in Chapter 11: Infection control and occupational health in tuberculosis disease.

Locations of possible transmission

Transmission outdoors is highly improbable unless the source and susceptible person are within talking distance: bacilli are dispersed immediately and are rapidly killed by daylight.

In an indoor environment, bacilli may remain viable and suspended for a prolonged period of time; proximity is therefore less important. Room size, air circulation and ventilation all affect dispersion and dilution of bacilli in ambient air.

Information should be gathered on locations where transmission may have occurred, ideally, this will include visits to the site(s).

Susceptibility of contacts

Contacts at highest risk of TB following infection are those with conditions or characteristics listed in Table 6.1 below. These contacts should be accorded a higher priority for assessment. Note that TSTs or IGRA tests may be falsely negative in immunocompromised contacts.

The presence of drug resistance in the index case does not increase infectivity. However, the priority for rapid identification and assessment of contacts is increased, particularly if young (aged under five years old) or immunocompromised.

Identifying contacts

Information on potentially exposed contacts should be collected from the index case or other informants during initial assessment. The question should be asked again in subsequent weeks, as a patient may not remember every contact at the first interview or may initially be reluctant to divulge names and details.

Note, not all contacts identified in this information collection will necessarily require screening; the objective at this stage is to gain the fullest appreciation of the case's activity during the estimated infectious period.

Structure the interview so that full ascertainment of potential contacts is undertaken, including:

- contacts in the patient's home environment and other settings where the patient has stayed overnight
- contacts in the patient's workplace or place of learning including early education centres
- social contacts in the patient's leisure time and non-work activities

- people exposed during the patient's health care attendances
- people exposed to the patient during travel, particularly in closed environments (eg, shared vehicle).

Prioritising contacts for assessment

Contacts are prioritised for assessment based on two factors (CDC 2005):

- 1) degree of exposure to the *M. tuberculosis* (a combination of duration and proximity of exposure to the index case and infectivity of that case)
- 2) risk of progression to TB if infected, as suggested in Table 6.1.

This range of contacts may need to be broadened in certain circumstances, for example cases in confined spaces.

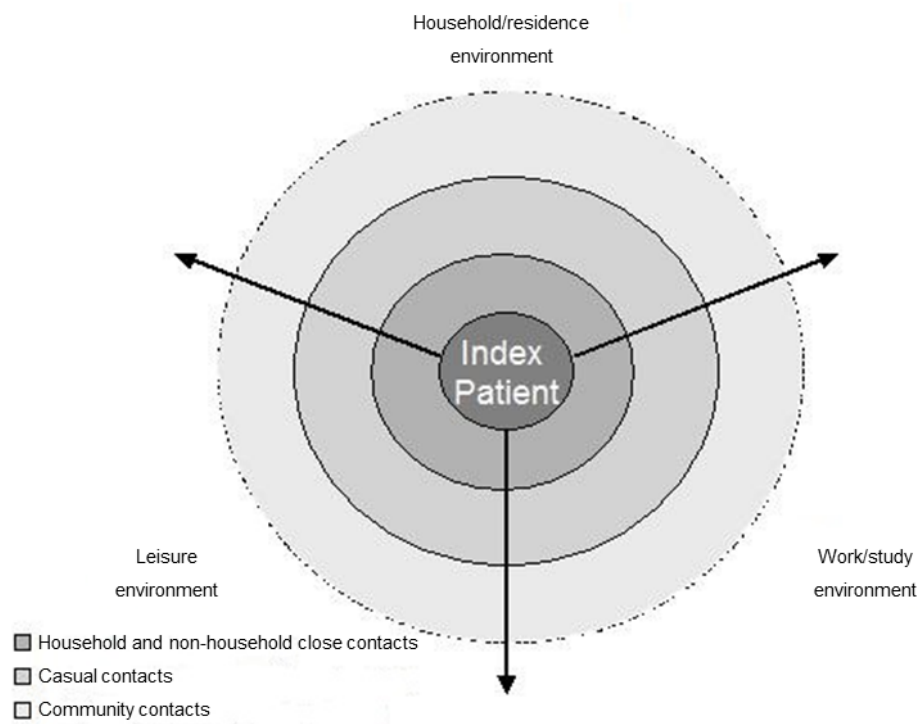
Degree of exposure

A frequently-used system classifies contacts into three circles related to their approximate degree of exposure to the index case (Etkind and Veen 2006; Veen 1992). As shown in Figure 6.1, exposures can occur in different contexts: household or residence, work or study environments and leisure environments.

The risk of infection is greatest for contacts who have been closest to the source case for the longest time.

Usually it takes many hours or days to transmit an infectious dose, but casual exposures may lead to transmission if the case is sufficiently infectious and the environmental air conditions are favourable (Golub et al 2001).

Figure 6.1: Concentric circle approach to contact tracing



Source: Adapted from: Etkind and Veen (2006), courtesy of Marcel Dekker Inc.

First circle of contacts (inner circle)

Close household contacts: people who live in the same household and share breathing space with the source case on a daily basis.

Close non-household contacts, including:

- those with intense short-duration, face-to-face exposure to particularly high densities of droplet nuclei, such as during medical procedures involving the respiratory tract
- close friends or colleagues who have had regular, prolonged contact with the source case, particularly if this has occurred in confined poorly ventilated spaces.

Second circle of contacts (middle circle)

Casual contacts: those who have spent less time with the infectious case. These may include frequent visitors to the home, friends, relatives, school or classmates, colleagues at work or leisure contacts.

Third circle of contacts (outer circle)

Community contacts: Those living in the same community or attending the same school, sports club or workplace who may have had sporadic contact.

Determining priorities

High-priority contacts

- i. Any first-circle contacts
- ii. Second-circle contacts with risk factors for progression to TB.

Medium-priority contacts

- i. Second-circle contacts
- ii. Third-circle contacts with risk factors for progression to TB.

Low-priority contacts

- i. Third-circle contacts.

Table 6.1: Characteristics increasing risk of progression to tuberculosis, with odds ratio (OR) or relative risk (RR)

Condition or characteristic	OR RR
Age <5 years	2–5
Immune suppression	
HIV positive and TST positive	50–110
AIDS	110–170
Solid organ transplant related to immunosuppressant therapy	20–74
Receiving anti-TNF- α treatment	1.5–17
Corticosteroids equivalent to >15 mg prednisolone daily for >two to four weeks*	4.9
Malignancy	4–8
Haematological (leukaemias, lymphomas)	16
Carcinoma of the head, neck or lung	2.5–6.3
Gastrectomy	2.5
Jujenoileal bypass	27–63
Silicosis	30
Chronic renal failure / haemodialysis	10–25
Diabetes mellitus	2–3.6
Smoking	2–3
Excessive alcohol use	3
Underweight	2.0–2.6

AIDS: Acquired immunodeficiency syndrome; HIV: Human immunodeficiency virus; TNF- α : Tumour necrosis factor alpha; TST: Tuberculin skin test.

* Estimated.

Adapted from: Erkens et al (2010).

Developing an assessment plan

The focus of contact investigation should be on high-priority contacts. Expansion of the investigation to screen medium-priority contacts can be considered if there are indications that recent TB transmission has occurred to high-priority contacts. Signs this may be necessary include:

- unexpectedly high rates of LTBI or TB
- TB disease in any contacts who were not considered high priority
- infection of contacts aged under five years
- contacts with TST or IGRA test conversion.

Screening of medium-priority contacts of sputum-smear-negative TB patients is unlikely to be necessary.

Low-priority contacts are not screened unless transmission appears to have occurred to medium-priority contacts.

Periodically review the findings to determine whether to stop or extend the investigation.

Timeliness

Screening of contacts by the public health service should begin as soon as possible after notification. The recommended timeframes for starting the contact assessment are within:

- three days for contacts of a smear-positive pulmonary case
- three days for child contacts (under five years of age) of any pulmonary case
- seven days for contacts of a smear-negative pulmonary case
- seven days for all other cases.

Assessing and managing high-priority contacts

Assessing and managing high-priority contacts aged under five years

In young children (aged under five years), the risk of developing TB disease within five years after infection could be greater than 50 percent (Trauer et al 2016), and infants are especially vulnerable. Disease in young children can develop within weeks of infection (Comstock et al 1974).

Those with symptoms of TB will require urgent clinical review.

All children under five years of age need to be seen by a specialist for clinical and CXR review regardless of the TST or IGRA result to rule out active disease. For these children, TST rather than IGRA is recommended, especially for those under two years (see Chapter 7: Diagnosis and treatment of latent tuberculosis infection).

- Those who are TST or IGRA positive should receive treatment for presumed LTBI if active disease has been excluded.
- Those who are TST or IGRA negative should be considered for isoniazid (H) preventative therapy until a repeat test is performed at eight weeks since last exposure to infectious case.

Assessing and managing high-priority contacts aged over five years

Step 1: Symptom screen

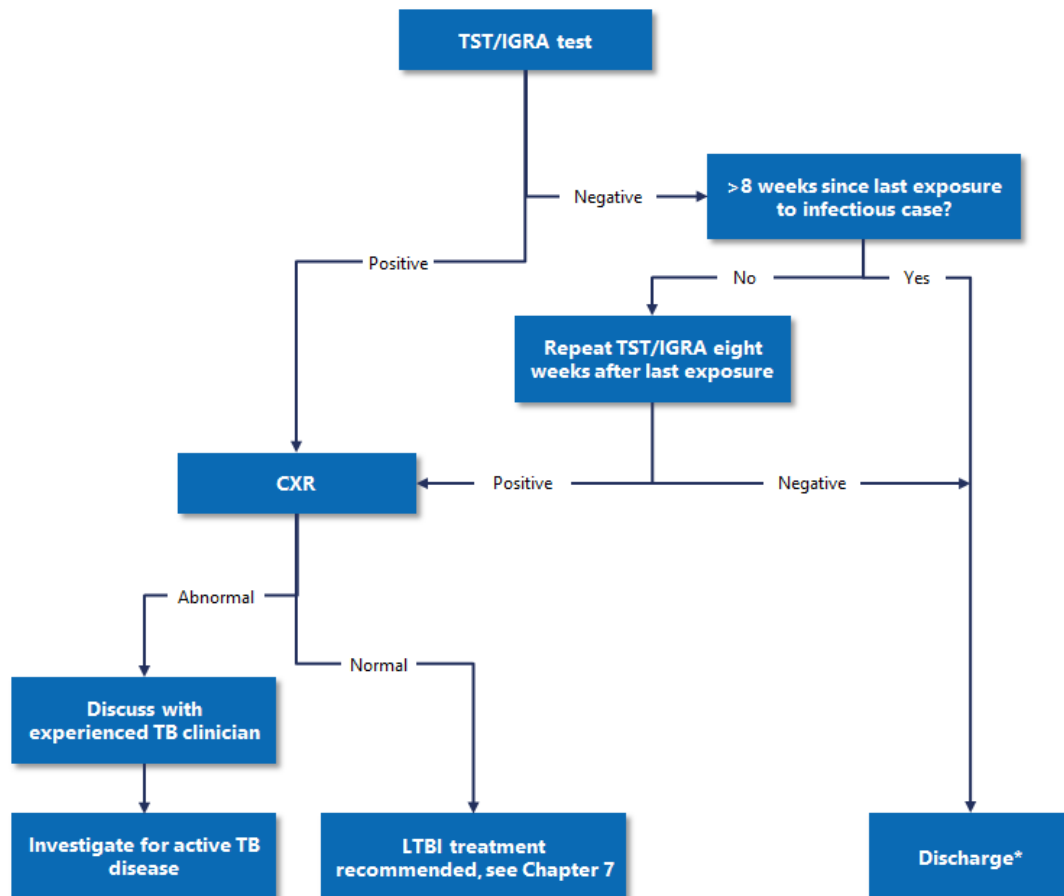
The first step in screening high-priority contacts is to enquire about TB symptoms: cough, haemoptysis, fever, night sweats or unexplained weight loss.

Those with symptoms require investigation for active TB, see Chapter 2: Diagnosis of tuberculosis disease. Note that TST or IGRA testing in those with active TB may give a false-negative result.

Step 2: Screening contacts without TB symptoms

An overview of the screening algorithm for high-risk contacts is shown in Figure 6.2. Details on TST and IGRA tests are provided in Chapter 7: Diagnosis and treatment of latent tuberculosis infection.

Figure 6.2: Algorithm for investigating high-priority contacts aged ≥ 5 years without symptoms of TB disease



CXR: Chest X-ray; IGRA: Interferon gamma release assay; LTBI: Latent tuberculosis infection; TB: Tuberculosis, TST: Tuberculin skin test.

* Consider CXR as a precaution if contact is aged over 60 years or if there is a possibility the TST/IGRA may be falsely negative (see Chapter 7: Diagnosis and treatment of latent tuberculosis infection).

Assessing and managing medium-priority contacts

Medium-priority contacts normally do not require screening unless transmission to high-priority contacts appears to have occurred.

Medium-priority contacts aged under five years

Children aged under five not classified as high-priority following exposure to a pulmonary case should be referred to a paediatrician only if the TST or IGRA is positive or becomes positive on a second test.

Medium-priority contacts aged over five years

Should screening of medium-priority contacts be required, TB symptoms should be checked for as for high-priority contacts. Further investigation is required for those with symptoms.

For those who are asymptomatic, screening with TST or IGRA tests should occur only after the window period: typically eight weeks from last exposure to the infectious case.

Further testing and management

Initial chest X-rays

Contacts require a CXR if:

- they have symptoms of TB
- they have a positive TST or IGRA or a conversion
- they are a child aged under five years old who is a contact of a pulmonary case
- a false-negative TST or IGRA is suspected, especially in patients with immuno-suppression or aged over 60 years (see Chapter 7: Diagnosis and treatment of latent tuberculosis infection).

Treatment of latent tuberculosis infection

People who are TST or IGRA positive should be evaluated for treatment of LTBI (see Chapter 7: Diagnosis and treatment of latent tuberculosis infection).

Monitoring people who are not being treated

People at higher risk of developing TB disease, who have declined treatment or for whom the decision has been made not to treat for LTBI should be monitored with CXRs every six months until 24 months after exposure. This group includes:

- children aged under five years who are close contacts of smear- or culture-positive cases
- HIV-positive contacts
- contacts of MDR-TB source cases
- people with inactive fibrotic scars on CXR.

CXR monitoring of other people who are untreated for LTBI is not recommended.

Tuberculosis contact investigations in special situations

TST or IGRA positive individual in a house containing an infant

If a TST or IGRA positive individual is found in a house containing an infant (under one year old), enquire about TB symptoms in all adults and adolescents in the household in case there is a source case who may infect the infant.

Pregnancy

The TST test is safe in pregnancy. TST or IGRA positive contacts need investigation, with the following modifications if the contact is pregnant:

- If there are no symptoms of TB disease, CXR can usually be deferred until after the pregnancy, or at least until after the first trimester. CXR should be done with shielding.
- Discuss with a TB specialist if there are concerns about symptoms or the risk factor profile in those with a TST test greater than 15 mm or positive IGRA. The public health and clinical TB specialists should discuss with the lead maternity carer and woman to determine if the risk justifies investigation for TB disease or treatment of LTBI.

Contacts of MDR-TB cases

The balance of benefits and harms associated with treating LTBI in people exposed to MDR-TB is unclear. Contacts of MDR-TB cases should be managed by, or in consultation with, specialists experienced in the treatment of MDR-TB contacts. Whether they are treated for LTBI or not, all contacts of MDR-TB cases should be educated about the need for lifelong awareness of the symptoms and signs of active TB disease and should be monitored with symptom screening and CXRs every six months for at least two years.

Contacts suspected of having tuberculosis who refuse follow-up

Alert the medical officer of health if a person has symptoms and/or signs of active TB but is refusing to be investigated further. This situation may apply if contacts of active TB cases refuse to be investigated or followed up.

Part 3A of the Health Act 1956 provides the medical officer of health with a legislative framework to manage public health risks associated with people with infectious diseases and their contacts. This framework includes the ability to provide direction to contacts to have medical examinations and to comply with instructions to prevent spread of the infectious disease until those examinations have been completed. The document *Guidance on Infectious Disease Management under the Health Act 1956* provides assistance on contact tracing measures incorporated into the Health Act in 2017 (Ministry of Health 2017).

BCG vaccination

A BCG vaccination should be offered to unvaccinated TST or IGRA-negative contacts (<5 mm) aged under five years.

If two TST tests are needed to test for conversion, a BCG vaccination should not be given until after the second test has been confirmed to be negative.

Non-tuberculous mycobacteria

Patients with non-tuberculous mycobacteria (NTM) disease, such as *Mycobacterium avium-intracellulare*, are of negligible infectivity and do not represent a disease threat to healthy contacts. They do not need public health follow-up.

If the notifying physician suspects that the diagnosis might be NTM, the public health service should be told this at the time of notification so contact tracing can be restricted until the diagnosis is confirmed.

Contact investigations in hospitals and other health care facilities

If a case of pulmonary disease has been in a hospital or another health care facility before diagnosis of TB and isolation, staff and patients may need assessment. Good communication between the public health service and the infection control and occupational health services in the facility is needed. These contact investigations are overseen by the medical officer of health of the region in which the index case is notified.

A risk assessment should be undertaken that takes into account:

- the degree of infectivity of the index case
- the length of time before the infectious person was isolated
- whether other patients are unusually susceptible to infection
- the proximity of contact.

In general, patients should be regarded as at risk of infection if they have spent more than eight hours in the same bay or room as an inpatient with smear-positive TB who had a cough.

The United Kingdom National Institute for Health and Care Excellence (NICE) guidelines (NICE 2016) advise that staff should 'inform and advise' such patients and their GP should be informed. If patients were exposed to a patient with sputum-smear-positive TB for long enough to be equivalent to a household contact or an exposed patient is known to be particularly vulnerable to infection, they should be managed as high-priority contacts.

Exposed patients may have been discharged by the time the contact investigation begins, and public health should follow up these contacts.

Health care workers may be less likely to comply with screening recommendations than non-health professionals (Stuart and Grayson 2000), so management support may be needed. If a health care worker, who has a documented TST or IGRA test result within the past 12 months, is exposed to infectious TB, only one test is necessary to detect conversion. This test should be done eight weeks after the date of last exposure.

The medical officer of health should maintain an overview of the investigation, both of patients and staff. Data on the outcome of contact investigation in hospitals should be supplied to the medical officer of health, who should also provide feedback to hospital infection control and occupational health staff about the outcome of contact investigations, so that all parties have the same picture of the infectivity of the source case.

Contact investigations in schools, early childhood education centres and crèches

TB in schools, early childhood education centres and crèches requires particular care because of the potential for spread of infection and the likely level of anxiety among parents and staff. A review of TB transmission in schools suggests that transmission rates to close contacts in school outbreaks is higher if the index case is a child rather than an adult (Roberts et al 2012). Following diagnosis of TB in a school pupil or staff member, and after discussion with the patient and family, the public health service should make contact with the school principal. Prevention and control activities will need to be clearly explained to staff, parents and, if necessary, the media.

If a pupil has sputum-smear-positive TB, carry out a risk assessment of the need to test the rest of their class (if there is a single class group) or the rest of the year group who share classes, as part of contact tracing (NICE 2016).

If a teacher has sputum-smear-positive TB, the pupils in their classes in the preceding three months should be screened.

Consider extending the contact tracing on the basis of:

- high infectivity of the index case
- the length of time of contact
- whether contacts are unusually susceptible to infection
- the proximity of the contact.

If an index case cannot be found among the case's household or other close contacts, consider extending the screening to all staff to search for a source case.

Contact investigations in correctional facilities

See also Chapter 8: Tuberculosis control in prison.

When an infectious TB case is discovered in prison, the clinician should alert the Department of Corrections and public health teams about the infectious potential and treatment plan. The prison medical service and public health service need to liaise closely throughout the treatment period and follow-up, and communications must be well documented.

Public health staff are responsible for conducting education and contact investigation among staff and people in prison. Prison contacts will often be released before their investigation and management is complete. Good liaison between prison services and public health will allow identification and education of families at risk of TB exposure.

Aircraft contact investigations

Transmission of TB on aircraft has been documented, but the risk is very low.

Following notification, the medical officer of health should conduct a risk assessment to determine whether a contact investigation is needed. The risk of *M. tuberculosis* transmission should be evaluated before it is decided whether it is necessary to inform travellers who may have been in close contact with the index case of the potential exposure. Risk assessment should consider the infectiousness of the person with TB at the time of travel; sputum-smear examination; presence of cavitations on CXR; documented transmission to close contacts; presence of symptoms (eg, cough, haemoptysis) at the time of the flight; and the consequences of transmission (ie, whether the case has MDR-TB).

As a general rule, exposure to an infectious case as defined above should only result in contact tracing if the elapsed time between the flight(s) and notification of the case is less than three months. Only contacts seated within two rows of an infectious case, on flights lasting longer than eight hours, need to be traced. Although a recent review suggests that the risk of TB transmission on aircraft seems to be very low (Kotila et al 2016), this remains the current World Health Organization (WHO) recommendation (WHO 2008).

Passenger information can be divulged to the medical officer of health under Principle 11 of the Privacy Act 1993. The aircraft seating diagram and passengers' seat numbers can be obtained from the airline. Passenger arrival cards (often with limited address information) can be obtained from the New Zealand Customs Service. Details of exposed passengers who are no longer in New Zealand can be referred to an overseas public health service for follow-up (see Communication: Notification to overseas health authorities later in this chapter).

If the TB index case is a crew member, contact tracing of passengers should not routinely take place. Staff should be traced following the usual principles for workplace colleagues.

Outbreaks

An outbreak of TB is defined as two or more cases known to be linked by epidemiological investigation or DNA fingerprinting supported by time, place or person commonalities: a cluster of cases all living in a single household is not considered an outbreak. Outbreak control activities that must be considered include:

- workforce planning
- communications with the affected group
- inter-district communication
- communication with the Ministry of Health
- media management
- notification of the outbreak on EpiSurv.

Practical aspects of contact investigation

Documentation

Collect data about each contact in a standardised form and compile a summary of the full contact investigation, preferably electronically.

Education

Contacts should be provided with information about the:

- contact investigation procedures and role of public health in supervising community treatment
- symptoms of TB disease

- transmission of TB
- difference between TB disease and LTBI
- success of treatment for TB infection and disease
- importance of early medical assessment of TB symptoms
- principles of privacy, confidentiality and their rights as health care consumers.

At the end of screening, contacts with abnormal findings should be given a summary of their results, and a copy should be sent to their GP. Stress the importance of lifelong awareness of the symptoms of TB for infected contacts (even if treated for LTBI) and the need to seek medical attention promptly if symptoms occur.

Cross-cultural communication

Public health workers conducting contact investigations should be trained and ready to address cross-cultural issues in their interactions with contacts. If necessary, use a trained interpreter. Cross-cultural advisors may also be helpful in complex situations.

Public health follow-up of non-infectious tuberculosis

During the public health follow-up of non-infectious TB cases, it is important to consider whether it is necessary to search for the person who is the *source* of this TB case's infection. This is particularly important if the case is a young child.

Different public health follow-up is advised in the following three scenarios.

Scenario 1: Adult case, normal chest X-ray, non-respiratory tuberculosis (such as bone or kidneys)

A source case is unlikely to be found because the infection leading to the TB disease probably occurred many years ago. The search for a source case is confined to asking whether any of the current close contacts of the case have symptoms of TB, such as fever, sweats, chronic cough, weight loss. Anybody answering 'yes' to any of these symptoms should be offered a TST or IGRA test and CXR. Otherwise, TST or IGRA testing and CXRs for the case's social circle are not necessary.

Contact tracing is not necessary because the case is not infectious.

Scenario 2: Paediatric case, with or without pulmonary disease

The child is likely to have been recently infected by an adult so an urgent search for a source case is essential. All those in the child's immediate social circle should be screened. It is efficient to focus screening for the adult source on adults with a history of TB or symptoms of TB (Eckhoff 2000).

Contact tracing is seldom necessary. Children aged under 12 years with pulmonary disease seldom infect others because:

- the natural history of primary TB means children rarely form cavities
- children are usually diagnosed relatively early
- younger children do not generate a sufficiently powerful cough to disseminate many AFB.

However, it is incorrect to assume that a child can never transmit disease (Cardona et al 1999). The paediatrician must assess the infectious potential of children with pulmonary disease and discuss the case with the public health service.

Scenario 3: Person placed on preventive treatment for inactive tuberculosis with up to four drugs

A person placed on preventive treatment for inactive TB may have had active pulmonary disease in the past. Treatment is given preventively because the prescribing clinician is concerned about a possibility of relapse.

It is unnecessary to search for a source case or to undertake a contact investigation because it is likely the case has been non-infectious for a long time. As a precaution, current close contacts should be asked about symptoms of TB, such as fever, sweats, chronic cough and weight loss. Contacts with these symptoms should be offered a TST or IGRA test and CXR. Contacts without symptoms do not need to be investigated.

Repeat contact tracing for re-exposed contacts

It is possible to develop disease following re-infection with TB (Bandera et al 2001; du Plessis et al 2001; Sonnenberg et al 2001). Therefore, people re-exposed to infectious TB must be re-evaluated, even if they have been treated for LTBI in the past (see Chapter 7: Diagnosis and treatment of latent tuberculosis infection).

Molecular typing

The purpose of molecular typing is to detect clustered isolates of TB. The molecular reference laboratory should report to the relevant public health service if a new isolate is clustered with a previously submitted isolate. This should occur within four weeks of a positive isolate being submitted to the reference laboratory. At the time of publication, this analysis used automated 24 loci mycobacterial interspersed repetitive units (24-MIRU) typing. Newer techniques, like whole genome sequencing, have greater resolution and can define clusters with greater specificity. Clustered isolates may arise from links between cases that were not detected in initial contact tracing investigation and may require further investigation and action.

Contacts newly exposed to cases in isolation

All contacts newly exposed to a case who is still in isolation should be identified and receive two TST or IGRA tests eight weeks apart. Any conversions should be drawn to the attention of the medical officer of health, who should discuss with the clinician treating the case the need for a review of treatment efficacy and for induced sputum testing.

Communication

Communication between district health boards

The public health service in the DHB area in which a case is notified must coordinate and finalise the contact investigation and enter all data onto EpiSurv.

They must ensure:

- contacts are followed up if they move to another DHB area
- complete assessment information is obtained on the outcome of screening in all DHB areas.

When requesting that a public health service in another DHB investigate contacts in their area, provide a fully completed TB case report form on the index case and communicate culture and sensitivity results as soon as available.

When asked by another public health service to investigate contacts residing in your own DHB area, supply interim and final outcome information to the requesting DHB. Do not enter these cases or contacts onto EpiSurv in your area.

General practitioners

Contact investigation and medical evaluation are specialised tasks and should be provided by public health. GPs who are consulted by contacts need to refer those contacts to the local public health service.

Medical officers of health need to:

- ensure GPs in their DHB areas are aware of the local TB policy and procedures
- provide information and support to GPs to ensure smooth and effective service delivery for patients
- advise a GP if their patients have LTBI following TB contact tracing and communicate any abnormal results, hospital referrals and problems
- alert the GP to the possibility of future TB in all TST- or IGRA-positive contacts, particularly those not receiving treatment for LTBI, and the need for a repeat CXR if the person develops symptoms.

GPs should:

- understand the process the public health service follows for contact investigation
- refer contacts according to local referral pathways, either to the medical officer of health or to an experienced clinician for evaluation for LTBI treatment
- know the indications for BCG vaccination and the local arrangements for BCG vaccinations.

DHB and private specialists

All specialists treating cases of TB disease must contact the local public health service to notify the case and enable appropriate contact investigation.

Notification to overseas health authorities

Medical officers of health must notify overseas health authorities about:

- TB cases diagnosed in New Zealand who temporarily or permanently travel overseas
- overseas contacts of cases diagnosed with TB after arrival in New Zealand
- overseas source cases of TB diagnosed in New Zealand.

This is done via the Ministry of Health Focal Point and is a requirement of the International Health Regulations 2005 (WHO 2016).

Media management

Responsibility for media comment should be agreed between those involved and should usually be carried out by the medical officer of health, unless a health facility is involved.

Reviewing local findings

Regular audits are important to ensure screening activities are optimal and to avoid unnecessary screening. Medical officers of health should collect and periodically analyse contact investigation data, including molecular typing data, to evaluate local screening activities.

Cascade of care

An important framework on which to base audits of contact investigation and management is the 'cascade of care' model (Alsdurf et al 2016). The cascade of care describes the steps at which contacts can be lost to follow-up or otherwise fail to proceed to eventual completion of LTBI treatment. A systematic review of international studies indicates that of those intended for screening, only 71.9 percent complete screening, 43.7 percent complete medical evaluation, 35.0 percent are recommended for treatment and 18.8 percent complete treatment.

Public health services should audit their contact investigation procedures at regular intervals. Potential indicators for evaluating contact investigations include:

- the proportion of pulmonary index cases who had at least one contact identified
- the proportion of identified contacts of pulmonary index cases who were evaluated for TB disease and LTBI
- the proportion of all evaluated contacts who had active TB ('Yield of active disease per contact'). The expected average is approximately 2 percent (Jackson-Sillah et al, 2007)
- the proportion of all evaluated child contacts who had LTBI ('Yield of LTBI per child contact')
- the proportion of infected contacts who begin treatment for LTBI
- the proportion of LTBI-treated contacts who complete treatment.

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Chapter 7: Diagnosis and treatment of latent tuberculosis infection

Executive summary

This chapter deals with the diagnosis and management of latent tuberculosis infection (LTBI). It is primarily intended for specialist medical practitioners and public health service staff who treat people with LTBI.

LTBI is 'latent' because *Mycobacterium tuberculosis* bacteria are sequestered in the tissues but are not clinically apparent. The purpose of testing for LTBI is to identify people who are at high risk for developing active tuberculosis (TB) disease and who would therefore benefit from treatment of LTBI. The diagnosis of LTBI depends on finding evidence of latent TB infection in the absence of active or inactive TB disease. In LTBI, the chest X-ray (CXR) is normal or shows trivial and stable evidence of past TB (eg, a small scar or patch of calcification). The number of *M. tuberculosis* bacteria is low, and less than 10 percent of people with LTBI ever develop active TB disease. People with LTBI are not infectious. A detailed description of TB natural history, including LTBI, is in Chapter 2: Diagnosis of tuberculosis disease, which also describes the approach to inactive / fibrotic-type changes on CXR.

The tests used to diagnose LTBI are tuberculin skin tests (TSTs), such as the Mantoux test and interferon gamma release assays (IGRAs), such as the QuantiFERON®-TB Gold In-Tube assay (QFT-GIT).

Worldwide about one-quarter of the population is thought to have LTBI (Houben and Dodd 2016). The prevalence of LTBI in New Zealand is not known. However, prevalence most likely varies in different subgroups within the population. The risk of progression is greater in some groups of people with LTBI, including recently infected people and people with risk factors for progression to active TB disease (including children under five years of age, people living with human immunodeficiency virus (HIV) and certain immunocompromised people with other predisposing medical conditions and/or on immunosuppressive treatments).

People from high TB-burden countries are an important group for extending LTBI testing and treatment to, as residence in a high TB-burden country is the predominant risk factor for active TB in New Zealand. Practitioners need to align any activities with local pathways in conjunction with their local diagnostic microbiology laboratory, public health service and respiratory or infectious diseases service to ensure that service use is prioritised to maximise clinical and public health gain.

Treatment of LTBI in an individual at high risk of developing active TB disease is effective in reducing the individual's future risk of developing TB disease. There are a number of recommended drug regimens for the treatment of LTBI in HIV-negative and HIV-positive people. In New Zealand, where a large proportion of the population do not have LTBI, a targeted approach to LTBI testing and treatment has been adopted, similar to that used in the United States of America (CDC 2000).

Treatment of LTBI should be undertaken by specialist medical practitioners with knowledge and experience in the area (including appropriate medical and nursing staff in public health services).

Recommendation summary

LTBI testing should not be performed on people who would not be considered for treatment. The following groups of people may be considered for testing for LTBI:

- high-priority contacts of pulmonary TB cases
- immigrants from a high-TB-prevalence country
- people with HIV
- people starting tumour necrosis factor alpha (TNF- α) inhibitor treatment or undergoing solid organ transplant
- people who have potentially been exposed to a TB case and have an increased risk of developing active TB disease, due to impaired immunity (eg, people on high doses of steroids or those with renal failure or on haemodialysis)
- health care workers (HCWs) with an exposure history (see Chapter 11: Infection control and occupational health in tuberculosis disease).

In most situations, either an IGRA or a TST is suitable. In children under five years of age, a TST is preferred.

People with clinical, radiological or laboratory evidence of active or inactive TB disease requiring full multidrug treatment should not be treated for LTBI.

Evidence for LTBI treatment in people who are close contacts of a multidrug-resistant TB (MDR-TB) is emerging. Clinicians managing multidrug resistance (MDR) contacts should be experienced in the area or refer the case to a specialist for advice about 'second-line' treatment options.

In people being treated for LTBI, monitoring of liver function tests (LFTs) should generally be done at baseline, one month after starting treatment and then every second month in those over 15 years of age. For children, LFTs should be performed at baseline. If there are no risk factors for hepatotoxicity identified at baseline, then further monitoring can be by regular screening for symptoms of hepatotoxicity.

Diagnosis

Who should be tested for LTBI

The purpose of testing for LTBI is primarily to identify people who are at high risk for developing active TB disease and who would therefore benefit from treatment of LTBI. This includes people who were recently infected and others with LTBI with risk factors for progression. Health care workers are also targeted as they have some risk of occupational infection and work with a vulnerable population.

- **People who are recently infected.** There is an inverse association between time since infection and incidence of disease (Ferebee 1970). High-priority contacts (as defined in Chapter 6: Contact investigation) of recently diagnosed pulmonary TB patients should be tested for LTBI.
- **Recent migrants from high-burden countries.** Being from a high-incidence country is the predominant risk factor for TB in New Zealand. While the majority of these cases are diagnosed after residing in New Zealand for more than two years, the risk of TB for immigrants from high-incidence countries attenuates gradually over time while staying elevated relative to the population throughout their lives (MacIntyre and Plant 1999; Wilcke et al 1998) (see Chapter 9: Migration and screening and their impact on tuberculosis in New Zealand, Figure 9.1). This suggests many of the cases that arise after screening result from the reactivation of LTBI. Before routinely offering LTBI testing to this group, practitioners must consult their local diagnostic microbiology laboratory and local respiratory / ID service to ensure diagnostic and referral pathways have adequate capacity to cope with any resulting increased demand.
- **Immunocompromise and immunosuppression.** A number of immune compromising conditions and immune suppressing medications increase risk of TB (CDC 2000). In New Zealand, in 2014, an immunocompromising condition was identified as a risk in 15 percent of TB notifications. In general, a handful of conditions are associated with profoundly increased risk, namely: HIV infection, use of TNF- α inhibitors, renal failure and haemodialysis, corticosteroid use and solid organ transplant. Physicians treating these populations or using these medications should have a systematic approach to the diagnosis of LTBI.

Specific recommendations for these groups are as follows:

- People with HIV infection should be tested for LTBI when diagnosed with HIV (Antonucci et al 1995; Guelar et al 1993; Ministry of Health 2014; Selwyn et al 1989; Selwyn et al 1992).
- People undergoing solid organ transplant and, where possible their donors, (Subramanian and Morris 2013) should be tested before transplantation (Singh and Paterson 1998).
- Patients starting anti-TNF- α therapy should undergo testing for LTBI before commencing anti-TNF- α treatment. Treatment is indicated in all patients with a positive test. Patients with a negative test and risk factors may also benefit from treatment and should be discussed with a TB specialist (Byun et al 2015; Solovic et al 2010).

- Patients with renal failure (Chia et al 1998; Verrall et al 2010) hematologic, head and neck, and lung cancers (Cheng et al 2017) or using corticosteroids (equivalent to prednisone 15 mg per day or more), (Jick et al 2006) should be evaluated for risk of potential TB exposure and, when any are present, tested. Risk factors include exposure to a TB case, residence in a high-burden country, incarceration and high-risk occupations.
- Patients on haemodialysis should also be tested if they have potential TB exposure.
- **Health care workers.** Due to their risk of occupational exposure (see Chapter 11: Infection control and occupational health in tuberculosis disease).

LTBI testing or treatment in situations other than those described above should be in consultation with a specialist experienced in LTBI. Usually we would not recommend treatment but it is a matter for balanced clinical judgement and discussion with the patient. It should be remembered that tests for LTBI have low positive predictive value in the absence of a history of potential TB exposure (see Chapter 10: Laboratory methods and standards).

Research gaps

Studies of LTBI prevalence and risk factors in Māori, immigrants and selected clinical populations are needed to inform future adjustments to the targeted approach.

Tests used to diagnose LTBI

There is no gold standard test for the diagnosis of LTBI.

TSTs, such as the Mantoux test, have been used for many decades. The Mantoux test is a TST using an intradermal injection of five tuberculin units (TU) of purified protein derivative (PPD), which is derived from cultures of *M. tuberculosis*. In a person previously infected with *M. tuberculosis*, a delayed type hypersensitivity reaction occurs at the site of injection. The Mantoux test is the only TST currently used in New Zealand. See Appendix 7.1: Special considerations regarding TST administration, reading and administration later in this chapter for further information regarding the TST, including how to administer and read the test.

Strengths of the TST are the long history and associated evidence base (Comstock et al 1974) and its high sensitivity especially in immunocompetent individuals. Limitations include the potential for confounding of the test result by prior bacille Calmette-Guérin (BCG) vaccination and the fact that injection of *M. tuberculosis* antigens can cause boosting of previous immunity to both *M. tuberculosis* and non-tuberculous mycobacteria (NTM) (see Test interpretation later in this chapter).

A recent development (not yet available in New Zealand) is the C-Tb test, which is a skin test based on the same core antigens (ESAT-6 and CFP-10) as used in IGRA tests. Formal evaluation suggests similar specificity at a 5 mm cut-off to the TST at 15 mm and reasonable sensitivity (Ruhwald et al 2017).

IGRAs have been developed as an alternative to the TST for diagnosing LTBI. IGRAs work on the principle that if a person is infected with *M. tuberculosis*, T-lymphocytes circulating in their blood will produce interferon-gamma (IFN-gamma) if re-exposed to TB antigens in vitro. They use antigens that are not present in BCG or in the majority of NTM, so at least in theory are more specific than the TST. They require only one patient visit for the test and are not subject to boosting and sensitisation, although their results may be slightly affected by a TST within the previous few months (van Zyl-Smit et al 2009).

Disadvantages of IGRAs compared with TSTs are that they have higher upfront costs, require laboratory expertise and undergo unexplained reversions of a positive to a negative test result. Such reversions can be due to small changes around the test cut-off, but many others remain unexplained and do not appear to reliably relate to clearance of *M. tuberculosis*. Furthermore, there are few studies comparing the ability of TSTs and IGRAs to predict who will progress to develop TB disease (Auguste et al 2017).

The United States Centers for Disease Control and Prevention (CDC) guidance recommends that QuantiFERON®-TB Gold assay (QFT-Gold) may be used in all circumstances in which TSTs are used (CDC 2005). The United Kingdom National Institute for Health and Care Excellence (NICE) TB guidelines previously recommend that a TST be done and that, in people with positive TSTs, IGRAs then be considered (if available) (National Collaborating Centre for Chronic Conditions 2006). This approach tends to reduce the sensitivity of the screening process overall, with a small gain in specificity. The updated guideline only recommends two tests in severe immune compromise (NICE 2016a).

There are some situations where one test is preferred over the other. Better specificity in some groups who have received the BCG vaccine, especially when given beyond infancy (Farhat et al 2006), or who have high exposure to NTM suggests that IGRAs are preferred in such individuals (Pai et al 2008). There are some situations where more evidence is needed to be clear which test is preferred. These include those who are living with HIV and others who are immunocompromised. In such individuals, all tests for LTBI have a sensitivity performance drop. One test might also be preferred for practical reasons.

Test interpretation

Definition of a positive TST test

The predictive value of TST readings in different clinical situations allows the establishment of 'cutting points'. Readings at the cutting points or higher are defined as positive. The cutting points are summarised in Table 7.1. Children are at greater risk of severe and life-threatening TB disease than adults, so the cutting points shown in Table 7.1 are conservative (Starke et al 1992; Sutherland 1966; Veening 1968).

Table 7.1 shows that previous BCG vaccination affects the cutting point in New Zealanders who have not resided in high-incidence countries. However, previous BCG vaccination does not affect the cutting point of a person who has resided in a high-incidence country.

Table 7.1: Definition of a positive TST test in New Zealand (cutting points)

Category	Adults (≥15 years)	Older children (5–14 years)	Younger children (<5 years)
New Zealand born			
• No BCG vaccination	≥10 mm	≥10 mm	≥5 mm
• Previous BCG vaccination	≥15 mm	≥10 mm	≥10 mm
Following residence in a high-incidence country*			
• No BCG vaccination	≥10 mm	≥10 mm	≥5 mm
• Previous BCG vaccination	≥10 mm	≥10 mm	≥10 mm
With immunosuppressive illness or taking immunosuppressive drugs (with or without BCG vaccination)	5–10 mm [†]	≥5 mm	≥5 mm
HIV/AIDS (with or without BCG vaccination)	≥5 mm	≥5 mm	≥5 mm
Close contacts of smear-positive cases (any origin) (with or without BCG vaccination)	≥10 mm	≥10 mm	≥5 mm

BCG vaccination: bacille Calmette-Guérin vaccination, HIV: human immunodeficiency virus, AIDS: acquired immunodeficiency syndrome

* As per the BCG chapter of the Ministry of Health's *Immunisation Handbook 2017* (Ministry of Health 2018a).

† See the discussion following the table. In adults with immunosuppressive illness or taking immunosuppressive drugs, the degree and duration of immunosuppression should be documented and the appropriate cutting point selected as described here.

The 5 mm cutting point is appropriate with:

- immunosuppressive treatment for organ transplantation
- aggressive immunosuppressive cancer treatment
- cytotoxic immunosuppressive agents such as cyclophosphamide or methotrexate
- systemic corticosteroid treatment that is prolonged (eg, for more than six weeks) and in a dose of prednisone of 15 mg or more per day (or equivalent with another steroid); the higher the dose, the greater the risk of reactivation of TB
- combinations of immunosuppressive conditions (eg, prednisone of less than 15 mg per day plus diabetes mellitus (on treatment), moderate or severely advanced malignancy, or malnutrition (this advice is empirical not evidence-based))
- end-stage renal failure.

The 10 mm cutting point is appropriate with:

- doses of prednisone less than 15 mg per day long term
- diabetes mellitus (including insulin-dependent)
- alcoholism

- malnutrition
- disseminated malignancy.

There is no correlation between size of reaction and likelihood of current active TB disease, ie, the TST test has a poor positive predictive value for current active TB disease (Al Zahrani et al 2000). However, the size of the TST reaction positively correlates with future risk of developing active TB disease (Jeyakumar 1999; Marks et al 2000; Watkins et al 2000).

Definition of a positive IGRA test

IGRA tests, like the TST, produce a quantitative read-out. The cutting points for a positive or negative result have been set by the manufacturers on the basis of their own in-house testing and a limited amount of independent research evidence.

The quantitative IGRA test result is available, although there is little evidence to suggest that it correlates with changing likelihood of true LTBI or TB disease. Intuitively, a strongly positive IGRA test result is reassuring with respect to making a firm diagnosis of LTBI. A positive or negative result close to the cut-off is certainly more likely to change on a subsequent test (Felber and Graninger 2013) but, because the second result is no more valid than the first, a repeat test when the result is close to the cut-off is not recommended. Furthermore, changing quantitative IGRA results do not correlate well with treatment efficacy in LTBI (Adetifa et al 2013).

Repeat testing, conversions and reversions

A person should have a repeat TST or IGRA test if they are a TB case contact, their initial test is within eight weeks of their first exposure to the index case and the initial test result was negative. Health care workers should not have routine repeat testing unless they have a new known exposure (see Chapter 11: Infection control and occupational health in tuberculosis disease).

TST test boosting, conversion and reversion

As opposed to the IGRA test, the TST exposes the immune system to *M. tuberculosis* antigens, which may influence subsequent test results.

A 'boosting phenomenon' can occur, whereby the test may stimulate immune memory of previous mycobacterial exposure, affecting the next test. The effect is maximal if a second test is placed one to five weeks after the initial test, and it may continue to be observed for up to two years (Menzies and Doherty 2006). This is a major reason why an IGRA test is recommended for those requiring serial testing.

TST conversion when a second test is done is defined as an increase in the TST reaction of 10 mm or more (ATS 2000). It has been associated with an annual incidence of TB disease of 4–6 percent (Sutherland 1966; Veening 1968). An increase of 10 mm or more is unlikely to be due to the boosting phenomenon. Furthermore, a second test result of 15 mm or more, regardless of the size of a previous reaction, should be regarded as positive.

TST reversion is the change to a negative TST result after a previous positive result. This phenomenon occurs in less than 10 percent of people (Hill et al 2007). There is no clinical or epidemiological information available to interpret the significance of a TST reaction that reverts to negative and then becomes positive again (Menzies and Doherty 2006). It should be regarded as a positive test result for re-infection with *M. tuberculosis*.

IGRA test boosting, conversion and reversion

While a repeat IGRA test cannot be subject to boosting from a previous IGRA test, there is evidence that a previous TST test may influence the IGRA test. This effect appears to be limited in time to around four weeks. Therefore, an IGRA test should not be performed within four weeks of a TST test. And if performing the two tests on the same day, blood should be drawn for the IGRA test before the TST test is administered. Debate exists in the international literature about the most valid cut-off point for defining a true IGRA conversion in the context of serial testing (Pai et al 2006; Veerapathran et al 2008). In line with guidelines from the CDC (CDC 2005), a change from a negative to positive IGRA result should be considered to be a test conversion. Similarly, a change from a positive to a negative IGRA test result should be considered to be a test reversion.

Specific approaches by target group

Contact investigation for LTBI

Practice points

All high-priority contacts should be tested, even if they have had LTBI or TB disease previously. People with a known previous positive IGRA or TST should be tested with IGRA.

Contacts aged five years and under: use TST, especially if under two years of age.

Contacts aged over five years: use TST *or* IGRA.

An IGRA is particularly recommended:

- in BCG-vaccinated people
- when it is considered a high risk that the person will not return for the reading of their TST
- when it is impractical for the person to make repeat visits for sequential testing
- when the contact has had LTBI or TB disease previously and has been tested with the TST.

Rationale

The recommendation to use the TST in children aged under five is pragmatic as phlebotomy is relatively invasive for children and studies have shown a relatively high rate of indeterminate results with IGRAs in children aged under five (Bergamini et al 2009; Ferrara et al 2006; Haustein et al 2009). Where TST is not possible, IGRA may be used in children over two years of age (Starke and Committee on Infectious Diseases 2014).

The specificity of IGRAs is higher than that of TSTs in people who have had a BCG vaccination (Pai et al 2008). The age at which BCG vaccination was performed affects subsequent TST reactivity (Farhat et al 2006; Menzies and Vissandjee 1992; WHO Tuberculosis Research Office 1955). Among people who received BCG in infancy, 3–5 percent have a subsequent positive TST reaction, whereas 30–35 percent of people who received BCG at an older age may have a subsequent positive TST reaction (Menzies and Doherty 2006). A TST reaction larger than 15 mm induration should not be attributed to BCG vaccination.

Individuals with a history of LTBI or TB disease remain at risk for reinfection and TB disease in the future, although they are less likely to develop TB disease rapidly after exposure to a TB case than if they were exposed for the first time (Bandera et al 2001; du Plessis et al 2001; Schwander and Ellner 2006; Sonnenberg et al 2001). If they have previously had a TST, it is likely to be positive again, while a previous IGRA test may have undergone test reversion. Therefore, a positive IGRA in a recently exposed contact who was treated more than two years ago is an indication for re-treatment.

Health care worker screening for LTBI

Practice point

Use IGRAs to screen HCWs for LTBI.

Rationale

HCWs are at risk of occupational exposure to TB so may need multiple tests for LTBI during their working life. Use of IGRAs avoids the need for baseline two-step testing, as well as the occurrence of boosting and sensitisation that can have complications of serial TSTs. The recommendations for HCW testing based on risk of exposure are described in Chapter 11: Infection control and occupational health in tuberculosis disease.

Interpretation of results in health care workers

If an IGRA is positive, the HCW should be referred for further investigation to exclude TB disease and offered treatment for LTBI if they are clear of disease.

If an IGRA is negative, they do not need any further investigation, unless they have symptoms of TB disease.

If an IGRA is indeterminate, it should be repeated. If it remains indeterminate, the HCW should be offered a TST test.

Refugees and other immigrants from high-incidence countries testing for LTBI

Practice points

Children aged five years and under: use TST.

Children aged 6–15 years and adults: use TST *or* IGRA.

An IGRA is particularly recommended in:

- BCG-vaccinated children
- immunocompromised children.

The Ministry of Health lists countries with high incidence (>40/100,000) on its website (Ministry of Health 2018b).

Rationale

As for contact investigation for LTBI (see earlier in this chapter).

Interpretation of results in refugees or immigrants from high-burden countries

If an IGRA or a TST test is positive, the person should be referred for further investigation and assessed for active TB disease. If they do not have active TB disease, they should be offered LTBI treatment.

If an IGRA is done but is indeterminate, it should be repeated. If indeterminate again, the person should be offered a TST test.

Screening for LTBI in immunocompromised people

Practice points

Use TST or IGRA to screen immunocompromised people where indicated, eg, before starting anti-TNF- α therapy.

In some situations, a clinician may elect to use both a TST test and an IGRA to screen for LTBI in an immunocompromised person.

Rationale

There are mixed results from studies comparing IGRAs with TST tests in people who are immunocompromised (Bocchino et al 2008; Kobashi et al 2007; Nagai et al 2007; Stephan et al 2008). Essentially, both tests have reduced sensitivity in immunocompromised people (Pai et al 2014).

Interpretation of results in immunocompromised people

If an IGRA or a TST test is positive (ie, only one test was done), the immunocompromised person should be treated for LTBI, after being cleared of having TB disease.

If IGRA and TST results are discordant in an immunocompromised person (ie, both tests were done and the TST is positive but the IGRA is negative *or* the IGRA is positive but the TST is negative), the person should be treated for LTBI.

If an IGRA is indeterminate, it should be repeated. If indeterminate again, the person should be offered a TST.

Treatment

Who should be offered treatment for LTBI

Treatment should be offered to patients who are targeted for testing who have a positive test, subject to the contraindications and precautions below. The patient should be fully informed of what LTBI treatment entails, along with a discussion of the risks and benefits of effective treatment of LTBI. Patients offered LTBI treatment under the indications in these Guidelines should understand that treatment is recommended but not compulsory, they have the right decline treatment for LTBI.

Chest X-ray before starting treatment

The final diagnosis of LTBI depends on the *absence* of radiological or other signs of active or inactive TB disease. Therefore, a CXR is essential before starting LTBI treatment. In people with LTBI, the CXR may show evidence of past processing of initial *M. tuberculosis* infection (eg, a small scar or patch of calcium).

LTBI treatment contraindications and precautions

Practice points

People with clinical, radiological or laboratory evidence of active or inactive TB disease requiring full multidrug treatment should not be treated for LTBI.

Caution is needed, and the risks versus the benefits of LTBI treatment need to be assessed carefully when deciding whether or not to treat:

- a pregnant woman
- a woman who is breastfeeding
- a person who has acute or chronic liver disease
- a person who is taking concurrent medications that can cause hepatotoxicity
- a person with a high alcohol intake or alcohol abuse, especially if they are not willing/able to stop or reduce their intake.

Age is no longer considered a contraindication to treatment. Modelled data from meta-analyses show the harms of treatment toxicity are clearly outweighed by benefits in every age group (NICE 2016b).

Clinical, radiological or laboratory evidence of tuberculosis disease

Treatment for LTBI is contraindicated if there is clinical, radiological or bacteriological evidence of active or inactive (old, healed) TB disease. When these conditions are met, the risk of drug resistant TB after LTBI treatments is very low (Balcells 2006; den Boon et al 2016a). Prompt investigation is needed to assess whether the disease is active or inactive (see Chapter 2: Diagnosis of tuberculosis disease, Table 2.1).

Close contacts of MDR-TB cases

No definitive recommendation on the best management for contacts of MDR cases could be made at the time of publication. However, several current international studies on this question will report in the near future. Contacts of MDR-TB cases should be managed by a public health physician or medical officer experienced in the area or co-case managed with a hospital specialist experienced in the treatment of MDR-TB cases and their contacts. Contacts who are not treated should be monitored for the development of TB with CXRs every six months for two years.

Pregnancy and breastfeeding

Testing and treatment of LTBI in pregnant women is usually delayed until after the birth of the baby, except in HIV-positive pregnant women or those who are identified as high priority contacts of a TB case. The risks and benefits of effective treatment of LTBI for the mother, the benefits of breastfeeding and risk to the newborn of the anti-tuberculosis drugs need to be discussed with the patient, especially if their use while pregnant or breastfeeding is not consistent with the medicine's datasheet (www.nzformulary.org). It is also important to note that anti-tuberculosis drugs in breast milk do not provide an effective treatment for LTBI in a breastfed infant.

Selection of a LTBI treatment regime is a clinical decision that must consider the potential risks and safety and be undertaken in consultation with the woman. Standard first-line regimen for LTBI has been used effectively during pregnancy and in breastfeeding women but is not without risks. Pregnant or breastfeeding women taking isoniazid should also receive pyridoxine (vitamin B6). Exclusively breastfed infants under six months should also receive pyridoxine.

Acute and chronic liver disease

Treatment of LTBI is not contraindicated in hepatitis B surface antigen-positive carriers who have no evidence of active liver disease or in people with hepatitis C. However, such subjects may be more likely to develop hepatotoxicity, and hepatitis Be antigen (HBeAg) positivity represents an important risk factor for severe isoniazid hepatitis (Grzybowski et al 1975; Patel and Voigt 2002). Frequent monitoring of liver function is indicated (see Monitoring in Chapter 3: Treatment of tuberculosis disease in adults).

Treatment of LTBI may need to be considered in a person who has acute liver disease and a high risk of TB infection progressing to disease after they have had close and prolonged contact with a highly infectious TB case.

Who should prescribe treatment and follow-up for LTBI

Prescribing

In New Zealand, TB medications may only be prescribed by specialist medical practitioners (eg, respiratory physicians, infectious diseases physicians, renal physicians, paediatricians, occupational health physicians, public health physicians).

Follow-up

Investigation and follow-up of contacts of TB cases notified to the medical officer of health is the responsibility of the local public health service's medical and public health nursing staff. In some public health units, the public health service refers contacts to specialists for diagnosis and management of LTBI. Follow-up of non-contacts prescribed LTBI treatment is the responsibility of the prescribing clinician, unless that responsibility has been transferred to and accepted by another practitioner.

LTBI treatment regimens

A note about abbreviations in this section: the commonly accepted abbreviations for TB drugs are used, ie, isoniazid (H), rifampicin (R), rifapentine (RPT), pyrazinamide (Z) and ethambutol (E). A number before a capital letter refers to the number of months of daily treatment in that regimen, for example, 3RPT H means three months of daily rifapentine and isoniazid.

Practice points

The choice of drug regimen for treating LTBI in an individual depends on:

- the presence or absence of risk factors for progressing to TB disease, (see: Who should be tested for LTBI, earlier in this chapter)
- assessment of the individual's likely level of adherence to treatment
- whether there are time constraints (ie, a need for a short course)
- the antibiotic susceptibility of the presumed source case (if known)
- whether the individual is likely to tolerate the drug(s) and the likelihood of drug interactions.

Recommended drug regimens for treating LTBI are listed in: Table 7.2 for adults and Table 7.3 for children. Current evidence suggests rifamycin containing regimens are non-inferior to isoniazid-based regimens (Menzies et al 2018). For immunocompetent patients who are adherent and tolerate treatment with isoniazid, there is likely to be additional benefit in extending treatment from six to nine months (Comstock 1999).

Pharmacological considerations and side effects are discussed in Chapter 3: Treatment of tuberculosis disease in adults.

Table 7.2: Drug regimens for treating LTBI in adults

Clinical situation	Drug	Administration	Duration (months)
Short-course regimen for adherent patients	R	Self, daily	4
Short-course regimen for adherent patients	RPT ^a + H	Self, weekly	3
Short-course regimen for adherent patients	R + H	Self, daily	3
Source case H-resistant	R	Self, daily	4
Established regimen for adherent patients	H	Self, daily	6 ^c
Established regimen for non-adherent patients	H	DOT, thrice weekly	6 ^c
Patient HIV-positive or other immunocompromise	H	Self, daily	9
Source case multidrug-resistant ^b (see important note below)	Individually tailored (eg, Z + E or Z + quinolone)	Self, daily	6 (if immunocompetent) or alternatively no treatment 12 (if immunosuppressed)

DOT: directly observed therapy; E: ethambutol; H: isoniazid; R: rifampicin; Z: pyrazinamide; RPT: rifapentine.

- a At the time of publication, RPT was not licenced or available in New Zealand. Clinicians prescribing any unapproved medicine or a medicine for an 'off-label' use under section 29 of the Medicines Act 1981 should do so with the informed consent of the patient.
- b Consultation and co-case management with a hospital specialist experienced in treating MDR-TB/contacts of MDR-TB is essential.
- c For immunocompetent patients who are adherent and tolerate treatment with H, there is likely to be additional benefit in extending treatment from six to nine months.

Table 7.3: Management of children with TB exposure or infection

Clinical situation	Drug	Administration	Dose mg/kg (max mg)	Indications for use	Duration
Exposure	H	Daily	10–15 (300)		Until second TST placed (usually 8 weeks after last contact) ^a
	H	3 times a week	20–30 (900)	Intermittent therapy requires DOT	If negative, stop
	R	Daily	10–20 (600)	H monoresistance in source case, H intolerance	If positive, complete full course for LTBI
Infection (LTBI) ^b	H	Daily	10–15 (300)		6 months
	H	3 times a week	20–30 (900)	Intermittent therapy requires DOT	6 months
	R	Daily	10–20 (600)	H monoresistance in source case, H intolerance	4 months
	R + H	Daily	R 10–15 (600) H 10–15 (300)	Shorter course regimen may improve adherence	3 months

H: isoniazid; R: rifampicin; DOT: directly observed therapy; TST: tuberculin skin test; LTBI: latent tuberculosis infection.

a May be longer than eight weeks in young infants.

b Equivalence has been shown between 6H monotherapy and 3RH combination therapy. H monotherapy should be used in children on concurrent medication that may interact with R (Ena and Valls 2005).

Adapted from: Cruz and Martinez (2015)

LTBI treatment regimens in HIV-negative people

Isoniazid

A Cochrane review of treatment of LTBI in HIV-negative people included 11 randomised trials (with a total of 73,375 participants) comparing isoniazid versus a placebo (Smieja et al 2000). This review showed that in HIV-negative individuals, treatment of LTBI with isoniazid for 6–12 months prevents the development of TB disease (RR 0.40, 95 percent CI 0.31 to 0.52) and reduces deaths from TB disease but does not reduce all-cause mortality. The number needed to treat (NNT) to prevent one case of TB disease was 100 overall. Efficacy and NNT vary, depending on an individual's risk of progression to TB disease. In this review, durations of isoniazid of longer than six months (RR 0.38, 95 percent CI 0.28 to 0.50 for 12 months) had little additional benefit, compared with a duration of six months (RR 0.44, 95 percent CI 0.27 to 0.73).

Isoniazid hepatotoxicity occurs more frequently with increasing age (Fountain et al 2005; Saukkonen et al 2006). Elevated baseline transaminases and excessive alcohol consumption are other risk factors for hepatotoxicity (Fountain et al 2005; Saukkonen et al 2006). A literature review found limited data suggesting an association between chronic viral hepatitis infection (hepatitis B and hepatitis C) and isoniazid-associated hepatotoxicity during LTBI treatment (although there is substantial evidence suggesting an association in people treated for TB disease with isoniazid-containing multidrug regimens) (Bliven and Podewils 2009).

To prevent symptoms and signs of peripheral neuropathy in patients on isoniazid or isoniazid-containing LTBI regimens, 25 mg of pyridoxine daily should be prescribed for all adults, including pregnant women and mothers of fully breastfed infants. Breastfeeding infants who are on isoniazid should be prescribed pyridoxine, even if their mother is also taking it. The following groups of children may also need to take pyridoxine: older (ie, adult-sized) children and adolescents; those who develop paraesthesia; those with poor nutritional status and those with co-morbidities that may increase the risk of pyridoxine deficiency (seizure disorders, diabetes, uraemia, HIV).

The NICE TB guidelines recommend 6H (or 3RH) for HIV-negative adults and children (National Collaborating Centre for Chronic Conditions 2006). The recommended standard treatment regimen for LTBI in HIV-negative people in the United States of America and Canada is 9H (CDC 2000; Long and Ellis 2007).

Contacts of isoniazid-resistant cases

For contacts of isoniazid-resistant TB cases, rifampicin is usually used to treat LTBI (Cohn and El-Sadr 2006). However, evidence is sparse in this area. In the United States of America and Canada, the recommended regimen for contacts of isoniazid-resistant TB cases is 4R (CDC 2000; Long and Ellis 2007).

Rifampicin (4R)

A recent randomised controlled trial (RCT) found 4R to be non-inferior to 9H (Menzies et al 2018). The regimen has a number of practical advantages over isoniazid-based regimes that mean it will be the preferred regimen for many patients. A recent meta-analysis of 4R versus 9H included four studies (including two RCTs, and two non-randomised studies) with pooled data from a total of 3,586 patients (Ziakas and Mylonakis 2009). Compared with 9H, treatment with 4R was associated with better compliance, showing a significant reduction in the risk of non-completion (RR 0.53, 95 percent CI 0.44 to 0.64). A large trial to define the risks of TB disease among people who received 4R was completed in 2017, and the results are awaited.

A meta-analysis found that 4R was associated with significantly less hepatotoxicity than 9H (Ziakas and Mylonakis 2009).

Rifampicin plus isoniazid (3–4RH)

A meta-analysis of five RCTs in adults found that daily therapy with isoniazid plus rifampicin for three months (3RH) and standard therapy with isoniazid 6–12 for months (6–12H) were equivalent with respect to efficacy, severe side effects and mortality (Ena and Valls 2005). An RCT in children under 15 years of age found that four months of isoniazid plus rifampicin (4RH) was at least equivalent to 9H (Spyridis et al 2007). It is likely however that 4R will make 3–4RH obsolete, on the basis of equivalent efficacy and the likelihood of fewer side effects.

Rifapentine plus isoniazid (3RPT H)

Twelve doses of weekly directly observed rifapentine plus isoniazid has been shown to be equivalent to nine months of isoniazid alone in preventing disease progression (Sterling et al 2011), while treatment completion was substantially higher and toxicity lower. The regimen has also been shown to be equivalent to isoniazid among children aged two to 18 years (Villarino et al 2015) and among people living with HIV (Sterling et al 2016). A retrospective cohort study found higher rifapentine/isoniazid treatment completion than those taking isoniazid (Simkins et al 2017). There is now a significant history of routine rifapentine/isoniazid practice in the United States of America. At the time of publication, rifapentine was not licenced in New Zealand.

LTBI treatment regimens in people living with HIV

Efficacy against the development of TB disease in adults with HIV and LTBI is similar for all regimens, regardless of drug type, frequency or duration of treatment (Akolo et al 2010). Isoniazid does not have any significant interactions with anti-retroviral therapy.

The preferred treatment regimen for LTBI in HIV-positive people in the United States of America and Canada is 9H (US Department of Health and Human Services (DHHS) 2017) and rifapentine plus isoniazid with DOT is also included in the DHHS guidelines as an effective option. The British HIV Association recommends 6H, based on the results of the Cochrane review (Akolo et al 2010) or 3HR. In TB-endemic countries, the recommended duration of preventive treatment is for at least 36 months, because of the ongoing risk of reinfection with *M. tuberculosis* (den Boon et al 2016b). The need for a longer duration of preventive treatment for HIV positive people in countries like New Zealand has not been established.

The recommended treatment for a HIV infected child is isoniazid for six months.

Interactions with antiretroviral medicines should be considered before starting a rifamycin containing regimen.

Antibiotic susceptibility of source case

The antibiotic susceptibility of the presumed source case must be established (where possible). If the person with LTBI has been started on treatment before the antibiotic susceptibility of the source case is known, their regimen may need to be changed. If so,

it should be started from scratch (ie, the period during which the contact took the ineffective drug should not be counted).

The most common scenario necessitating a change in the LTBI regimen is a source case who is found to be isoniazid-resistant, in which case isoniazid should be stopped and 4R should be started. In the United States of America, for contacts of isoniazid-resistant TB cases (both HIV-positive and HIV-negative), the recommended regimen is 4R (CDC 2000). The NICE TB guidelines recommend 6R for contacts aged 35 years or younger of isoniazid-resistant TB cases (National Collaborating Centre for Chronic Conditions 2006).

Evidence to support guidelines regarding treatment regimens for contacts of MDR-TB patients is limited to observational studies. Tailored regimens, including a daily fluoroquinolone (moxifloxacin or levofloxacin) with ethambutol or ethionamide, according to the drug susceptibility testing (DST) of the source case, showed encouraging results in the Federated States of Micronesia (Bamrah et al 2014). Similarly, a six-month regimen of ofloxacin, ethambutol and high-dose isoniazid appeared to be highly effective in an uncontrolled cohort study in South Africa (Seddon et al 2013). The results of randomised controlled clinical trials are awaited.

Practical considerations in treating LTBI

Reporting LTBI under treatment to the medical officer of health

Although LTBI is not notifiable, if a clinical decision is made to offer treatment to a person with LTBI, the treating clinician should seek the person's consent to report them as a case of 'LTBI under treatment' to the local medical officer of health. No public health action is required, but the case details are entered into the national surveillance database so that LTBI trends can be monitored.

Communication with the patient's usual doctor

When prescribing treatment for LTBI, the prescribing clinician should advise the patient's doctor (usually the general practitioner, GP) in writing of the indications, drug(s), dosage and duration of treatment, and the management of adverse reactions and potential drug interactions, including the potential for hepatotoxicity. See Chapter 3: Treatment of tuberculosis disease in adults for further details regarding adverse reactions associated with TB medications.

Baseline investigations

Adults (and children who are considered at risk of HIV) should be tested for HIV when a decision has been made to commence LTBI treatment.

Other recommended pre-treatment baseline tests in adults include haematology, creatinine, alanine aminotransferase (ALT) followed by full LFTs if elevated, hepatitis B and hepatitis C serology. Children have a lower risk of hepatotoxicity from TB drugs than adults, therefore they might not always require baseline tests.

Education

Patient education (using interpreters and written translations if needed) should include:

- the difference between TB disease and LTBI
- the fact that LTBI is not infectious to others
- the possible adverse effects of treatment (including written information about the symptoms of hepatotoxicity and other adverse effects)
- timing for monitoring visits and blood test
- the contact person/contact details if the patient needs further advice.

Alcohol

Patients should be advised that drinking alcohol is an important risk factor for hepatotoxicity and that they should abstain from alcohol while taking drugs for LTBI.

Follow-up and monitoring for adverse effects and for adherence

In people being treated for LTBI, monitoring of LFTs should generally be done at baseline, one month after starting treatment and then every second month for those over 15 years of age without risk factors for hepatotoxicity. In people with risk factors for hepatotoxicity, LFTs should be done monthly (or more frequently if necessary; see Chapter 3: Treatment of tuberculosis disease in adults). For children, LFTs should be performed at baseline. If there are no risk factors for hepatotoxicity identified at baseline, then further monitoring can be by regular screening for symptoms of hepatotoxicity.

Follow-up should be at monthly intervals (or more frequently if necessary, eg, if there are adverse effects). Monthly follow-up of contacts with LTBI being treated by public health services is usually done by public health nurses. Follow-up of non-contacts prescribed LTBI treatment is the responsibility of the prescribing clinician.

Prescriptions can be written three monthly but dispensed monthly.

Symptoms and signs of possible hepatotoxicity for which patients should be alert include loss of appetite, nausea, vomiting, abdominal discomfort or pain, and unexplained fatigue or feeling generally unwell (symptoms), jaundice and dark urine (signs). **Patients should be reminded that it is essential to stop their LTBI drug(s) at the first symptom or sign of a possible adverse effect and then to contact their prescribing clinician or GP immediately for further advice as urgent LFTs are indicated.**

Threshold for stopping LTBI treatment due to hepatotoxicity

If aspartate transaminase (AST) or ALT reach three times the upper limit of normal, consult with a clinical TB expert. If the patient has no symptoms, treatment can usually

be continued, but the patient should be closely monitored. Re-check for symptoms and repeat LFTs three to four days later.

In an asymptomatic person, with very close monitoring, AST or ALT may be allowed to rise up to five times the upper limit of normal. If AST or ALT reach three times the upper limit of normal and the patient has symptoms, treatment should be stopped. When LFTs have normalised, treatment with a different drug can be considered, with very close monitoring.

Changing regimens because of adverse effects

If a patient's regimen is changed because of side effects or adverse effects from the first agent given, the whole period of treatment on the first agent counts toward the eradication of LTBI and a lesser period is needed on the second regimen. It is reasonable to adopt a proportional approach; for example, if half of a course of the first regimen has been completed, then half of the recommended course of the second regimen should be completed.

Ending treatment

The patient should be given a written record of their TST or IGRA result, the LTBI treatment they received and a reminder of the need for lifelong awareness of the symptoms and signs of TB.

If treatment is not given

If treatment is contraindicated, declined or considered inappropriate (eg, because of likely non-adherence), the patient and their GP should be alerted to the risk of future TB disease.

Impact of LTBI treatment on antibiotic susceptibility of tuberculosis

Concern that drug treatment for LTBI might generate drug-resistant strains does not seem to have come to fruition, but this issue requires further study (Cohn and El-Sadr 2006). In New Zealand, isoniazid LTBI treatment regimens have been used for over 30 years, but the rate of isoniazid resistance among New Zealand-born TB cases has not increased (see Chapter 1: Introduction).

Appendix

Appendix 7.1: Special considerations regarding TST administration and reading

Administering and reading the tuberculin skin test

Those administering and reading the TST must be trained in the technique and should follow these Guidelines. Medical officers of health should work with organisations offering TST to facilitate the initial and ongoing training of those undertaking TSTs.

Mantoux testing should be performed by a person who is proficient with the procedure and has had experience in reading the results. Only authorised vaccinators with BCG endorsement are able to administer BCG vaccine.

The TST is usually placed in the right arm (second step, if necessary, in the opposite arm).

Storage of tuberculin solution

- Store between 2°C and 8°C.
- Protect from light.
- Once opened, date the vial and discard after one month.

Administering the test – see Figure 7.1

The Mantoux (TST) is placed by injecting 0.1 mL 5TU PPD (5 tuberculin units purified protein derivative) intradermally into the flexor surface of the mid-forearm.

Use either an insulin syringe or a tuberculin syringe with a 20-gauge (G) needle. If the vial has been previously opened, swab the vial with an alcohol swab and allow it to dry before use.

- With an insulin syringe, there is no need to change the needle. The needle is very fine and does not become blunt or dislodged.
- With the tuberculin syringe, it is necessary to change the needle to a new 26G or 27G needle, because:
 - they are the correct size for administration
 - penetrating the bung may blunt the needle.

Draw 0.1 mL of tuberculin into the syringe and remove any air bubbles.

Insert the needle into the most superficial layers of the skin with the bevel of the needle upward, until the bevel is just covered and slowly inject the solution.

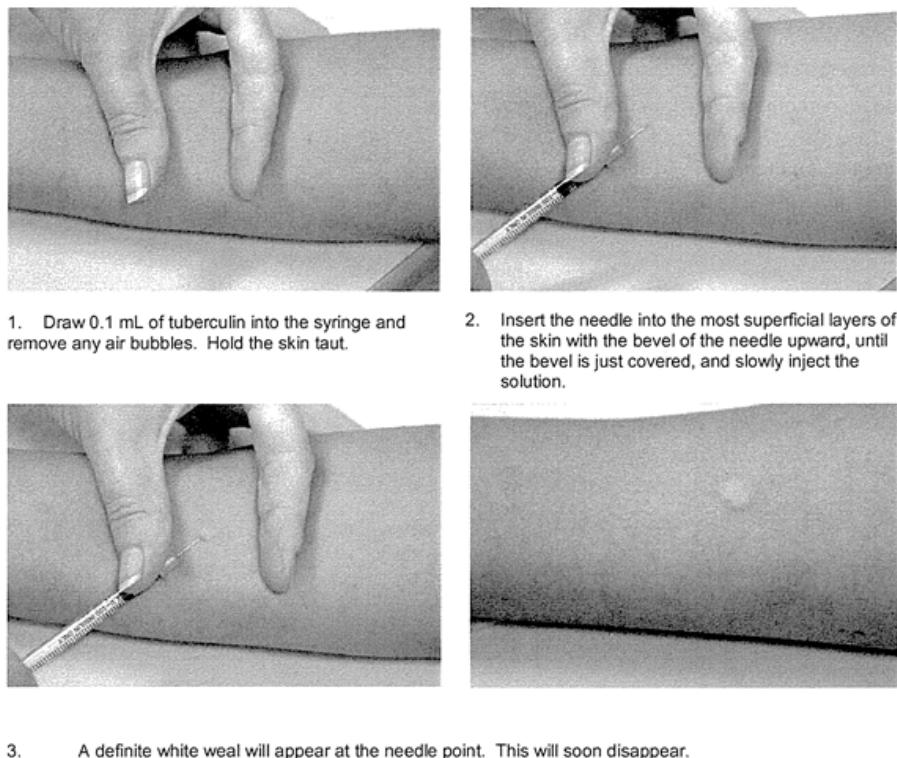
If the intradermal injection is carried out correctly, a definite white weal at least 6 mm in diameter will appear at the needle point. This will soon disappear. No dressing or use of alcohol swabs is required on the site.

If the weal is less than 6 mm in diameter, then the test should be administered again. The needle bevel may have been inserted too deeply or an inadequate dose administered.

If leaks occur at the insertion site, the needle bevel may not have been inserted far enough for the bevel to be covered by the skin.

If the TST must be repeated, use another site at least 50 mm from the original site.

Figure 7.1: Administering the Mantoux test



Source: Auckland Regional Public Health Service.

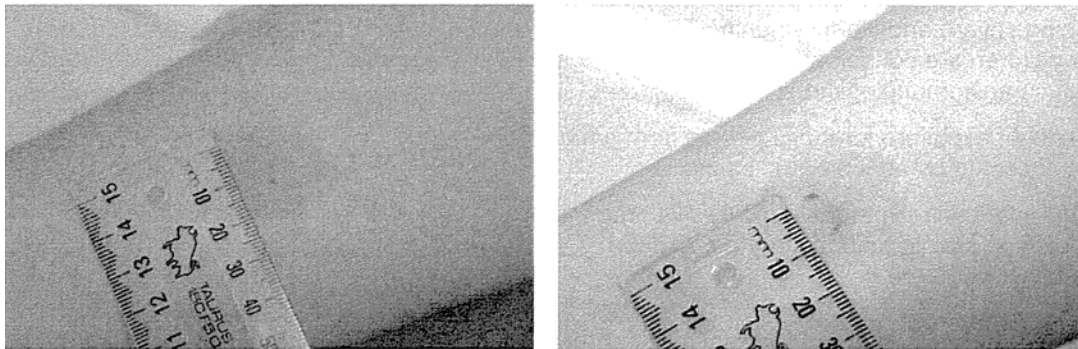
If it is not possible to read a TST test at 72 hours, a reading at 48 hours is acceptable (CDC 2000; Menzies and Doherty 2006). If this is not possible, readings may be done between 72 hours and seven days. However, as all the literature regarding the risk of developing TB is based on reading TST tests at 48–72 hours, the interpretation of TST tests that are read between 72 hours and seven days is uncertain (Menzies and Doherty 2006).

The exception to this is when the two-step Mantoux is done to identify the booster effect, which should be read at 48 hours.

The TST is read observing the presence or absence of induration (the area of raised tissue that can be felt and seen) not redness. The induration may be determined by inspection and palpation. It is important that readings are carried out in good light.

Use a transparent ruler, marked in millimetres, to measure the induration (and only the induration – not the entire area of redness). Measure transversely to the long axis of the forearm (ie, across the width of the forearm) and record the result in millimetres. This is the method recommended by the American Thoracic Society and allows international comparability of data (see Figure 7.2).

Figure 7.2: Reading the Mantoux test



Source: Auckland Regional Public Health Service photos showing Mantoux reactions: a) 15 mm and b) 9 mm.

Practice points

Read a TST as close as possible to 72 hours after placement.

A TST is read by measuring the presence or absence of induration (not redness). The result should be recorded in millimetres (mm).

Situations in which people should not receive a TST test

The following people should not receive a TST test (incorporating guidance from the Canadian Tuberculosis Standards) (Long and Ellis 2007).

- Those with documented active TB or a documented history of adequate treatment for LTBI or TB disease (because the test is of no clinical utility and discomfort is likely).
- Those with documented TST reactions 15 mm or greater (because no new diagnostic information will be gained and discomfort is likely).
- Those with severe blistering TST reactions in the past or with extensive burns or eczema present over TST testing sites (because of the greater likelihood of adverse reactions or severe reactions).
- Those with major viral infections.

- Those who have received measles vaccination within the past four weeks, because this has been shown to increase the likelihood of false-negative TST results. No data are available regarding the effect on TST results of other live virus vaccinations – eg, mumps, rubella, varicella and yellow fever – but it would seem prudent to follow the same guidance. However, if the opportunity to perform the TST test might be missed, the test should not be delayed for live virus vaccines as these are theoretical considerations. Note that a TST test may be administered before or on the same day as live virus vaccinations but at a different site (CDC 2006).

Adverse reactions following TST

Adverse reactions are unusual. Rarely, people may experience a sore arm and mild flu-like symptoms for a few days. Severe systemic hypersensitivity reactions following administration of the TST are also rare. Where hypersensitivity has occurred, reactions have resulted in angioedema, upper respiratory stridor, dyspnoea, skin rash, generalised rash and/or urticaria within 24 hours of TST placement.

Adverse reactions should be reported to the Centre for Adverse Reactions Monitoring (CARM) NZPhvC, at the University of Otago Medical School:
<https://nzphvc.otago.ac.nz>.

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Chapter 8: Tuberculosis control in prisons

Executive summary

Prisons are a significant source of tuberculosis (TB) infection in most parts of the world. In many countries, there are reports of disproportionately high rates of TB disease in prisons.

Recommendation summary

- Refer to the Ministry of Health's *Tuberculosis Case Management for People in Correctional Facilities* for further information (Ministry of Health 2018).
- Directly observed therapy (DOT) is essential for treating latent tuberculosis infection (LTBI) or TB disease in prisons.

Tuberculosis rates and risk factors

Prisons are an important site of TB transmission in most parts of the world, irrespective of the economic status or burden of TB in that country (WHO 2000). A systematic review estimated that 8.5 percent of national TB incidence in high-income countries is attributable to exposure in prisons (Baussano et al 2010). In the United States of America, up to 40 percent of TB cases have a history of incarceration (Hayden et al 2004). In Eastern Europe and Central Asia, the rate of incarceration associated with TB and the prevalence of multidrug-resistant tuberculosis (MDR-TB) is at a national level (Stuckler et al 2008). LTBI prophylaxis is underutilised in prisons internationally (Al-Darraj et al 2012). Overcrowding, inadequate infection control measures and a low priority for prison health care generally can contribute to the spread of infection (Dara et al 2015).

Prison incarceration was linked to an outbreak of TB in the North Island between 1996 and 2000 (De Zoysa et al 2001). The outbreak included at least 61 TB cases who were dispersed across the seven North Island districts following repatriation of people who have been in prison. The outbreak required 762 contacts to be traced, including 206 in prisons. The outbreak highlights the public health consequences of TB in this setting. Cases of MDR-TB in prison have not been reported in this country but contribute a large proportion of cases in other countries (Coninx et al 1998; Valway et al 1994).

Factors that may predispose the prison population to TB infection and disease include:

- high representation of people from low socioeconomic backgrounds
- high rates of substance abuse
- poor health or nutrition
- over-representation of Māori and Pacific peoples, who have higher rates of TB (ESR 2015).

Treatment of tuberculosis cases in correctional facilities

Internationally there is a higher rate of treatment failure in TB cases in correctional facilities (White et al 2002). Short duration of incarceration and high turnover rates in institutions are major factors.

Refer to the Ministry of Health's *Tuberculosis Case Management for People in Correctional Facilities* (Ministry of Health 2018), which is a joint protocol between the Department of Corrections (Health Services) and TB treatment supervising services (usually the public health service in most regions of New Zealand, but occasionally the clinical TB service).

Successful treatment requires:

- DOT for all cases of TB
- close liaison between correctional facility medical and nursing staff, specialists and public health authorities
- completion of treatment.

When people who have been in correctional facilities are released into the community, appropriate transfer of responsibility must be made to the medical officer of health and district health board (DHB) in the area where the patient will be residing.

A probation officer may help with follow-up and completion of treatment.

Contact investigation in prison

Department of Corrections Health Services should seek early guidance from the local public health service if a case of TB disease is diagnosed or where it is suspected. Because contacts within the correctional facility will often be released before their investigation and treatment is complete, the local public health service will maintain overall responsibility for managing contacts held in custody. The joint protocol, *Tuberculosis Case Management for People in Correctional Facilities* (Ministry of Health 2018), provides specific information on the roles of both the public health nurse and the Department of Corrections nurses.

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Chapter 9: Migration and screening and their impact on tuberculosis in New Zealand

Executive summary

Most challenges posed by tuberculosis (TB) for low-incidence countries like New Zealand are brought about by cross-border migration (Lönnroth et al 2015). The epidemiology of TB in most of these countries is characterised by a low rate of transmission in the general population and higher risk among people from high-burden countries or their close contacts. Seventy-eight percent of TB cases in New Zealand occur in individuals who have been born overseas. This is an important health issue for these individuals and the people they are in close contact with. Existing control measures mean TB in people born overseas does not act as an important source of TB for New Zealand-born people.

This chapter summarises immigration screening requirements for TB and latent tuberculosis infection (LTBI) screening and management of people from high-prevalence countries, including the management of an abnormal immigration chest X-ray (CXR). A statement is also made on travellers planning to spend extended time in high-incidence countries.

Recommendation summary

General practitioners (GPs), particularly those with patients from high-incidence countries, should be aware of the need to detect TB early to improve clinical outcomes and limit the spread to others. The Ministry of Health lists countries with high incidence (>40/100,000) on its website, (Ministry of Health 2018b) and more detailed statistics are published by the World Health Organization (WHO). GPs should inform new patients from high-incidence countries about TB, including:

- the need for early investigation of signs and symptoms of TB
- the fact that TB is a treatable disease
- the fact that treatment of TB in New Zealand is free.

This chapter is intended as a reference for clinicians, public health practitioners and immigration officials who work with people from high-incidence countries.

The WHO targets for global incidence of tuberculosis

The WHO has recently proposed an ambitious set of targets with the aim of 'ending the global tuberculosis epidemic'. The WHO calls for a reduction in the global incidence of TB of 90 percent by 2035, which would result in a rate of less than 10 cases per 100,000 people worldwide (WHO 2014a). To achieve this, low-incidence countries are called upon to progress even further by focusing control on risk groups, including migrants (Lönnroth et al 2015). Having endorsed the United Nation's international Sustainable Development Goals (SDGs),⁷ New Zealand also has a responsibility to contribute to global TB control, but this is not covered in this chapter.

Influence of immigration on tuberculosis in New Zealand

Tuberculosis in foreign-born people in New Zealand

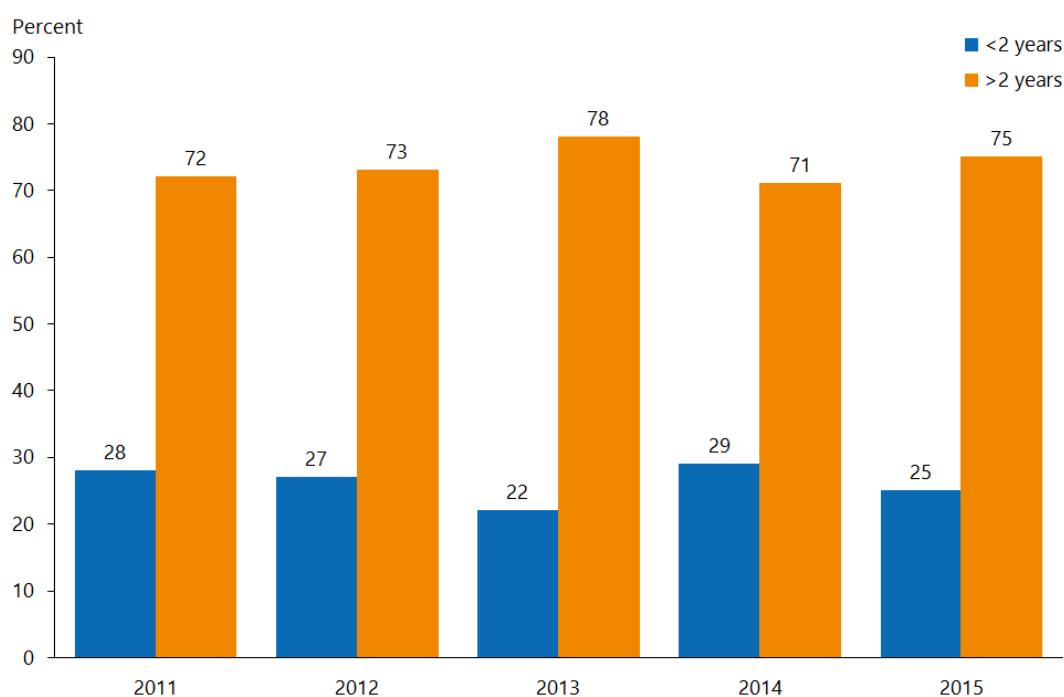
Seventy-eight percent of individuals diagnosed with TB between 2011 and 2015, in New Zealand were born overseas, and this figure has continued to rise (ESR 2015). However, it is important to note that the percentage of the New Zealand resident population that was born overseas has also continued to rise – from 22.9 percent of the population in 2006 to 25.2 percent in 2013 (Statistics NZ 2013).

Immigration screening is targeted towards identifying active disease, and New Zealand does not currently have an LTBI screening programme. A review of data from the Institute of Environmental Science and Research (ESR) indicates that the majority of individuals diagnosed with TB have been in New Zealand for more than two years (Figure 9.1). This suggests many of the cases that arise after screening result from the reactivation of LTBI.

Immigration New Zealand (INZ) annually screens around 200,000 individuals who are entering or staying in New Zealand to ensure that visa applicants have an acceptable standard of health. Around 60 percent of those individuals are screened before they arrive in New Zealand. In 2016, 77 TB cases were detected as part of an immigration medical examination, corresponding to a rate of 37.3 per 100,000.

⁷ United Nations: Sustainable Development Goals, see: www.un.org/sustainabledevelopment/sustainable-development-goals.

Figure 9.1: Percentage of overseas-born individuals, with known date of arrival in New Zealand, whose TB was diagnosed within or after two years, 2011–2015



On average, the arrival date was unknown for 18 percent of cases (2011: 26 percent, 2012: 11 percent, 2013: 22 percent, 2014: 20 percent, 2015: 13 percent).

Source data: ESR.

Multidrug-resistant tuberculosis

Over the last 10 years, the proportion of cases (both new disease and relapses/reactivations) with multidrug-resistant tuberculosis (MDR-TB) was 1.3 percent or 31 MDR-TB cases. Of these, 29 were born overseas, and it is assumed they acquired their resistant organisms overseas (ESR 2015). Although the incidence of MDR-TB has remained low in New Zealand, it is critical that New Zealand remains vigilant to the increasing global movement of people and the risk this movement poses to New Zealand.

Immigration screening for tuberculosis

Purpose of tuberculosis screening

The objective of INZ's health screening requirements is to ensure that visa applicants have an acceptable standard of health. A person has an acceptable standard of health if, amongst other requirements, they are unlikely to be a danger to public health (A4.5 of INZ's operational manual, Immigration New Zealand 2017).

People with risk factors for TB intending to stay in New Zealand for more than six months, or all people intending to stay in New Zealand for more than 12 months are screened to detect active TB disease (Immigration New Zealand 2017). This provides a public health benefit of improved TB control. The application for a temporary visa or residence provides a unique opportunity for screening and may represent one of the few reliable points of contact for new arrivals to New Zealand (Verver and Veen 2006).

Immigration New Zealand tuberculosis screening requirements

INZ requires people intending to stay in New Zealand for more than 12 months to have a medical examination and a CXR before they arrive in New Zealand (see Table 9.1). If they are already in New Zealand when they decide to extend their stay, this process is done in New Zealand.

The immigration medical examination and CXR must be completed by an INZ-approved doctor (panel physician) in countries with panel physicians. INZ has panel physicians in New Zealand and in most other countries around the world (Immigration New Zealand nd). In the majority of countries, the examination is recorded electronically in eMedical (an online health processing system) and must not be more than three months old when the person lodges their visa application. If the examination was completed more than three months previously, the applicant is usually required to undergo another examination and CXR. However, once an application for a temporary visa has been made, the immigration medical examination can be used for further applications within the next 36 months if the applicant has been found to have an acceptable standard of health. All CXRs are reviewed by a radiologist appointed to the panel physician network and then, if required, are reviewed by an INZ medical assessor, who provides comment on whether the person has an acceptable standard of health to enter or remain in New Zealand.

If an individual is intending to stay more than six months but less than 12 months, people assessed as having risk factors for TB must have a CXR. The CXR is reviewed by a radiologist with any abnormalities noted. Risk factors for TB are:

- holding a passport of a country not on the INZ list of low-TB prevalence countries
- having spent a total of three months or more in the past five years in a country that is not on the INZ list of low-TB prevalence countries (Immigration New Zealand 2018).

A visa applicant who has provided a CXR within the previous 36 months but has spent six consecutive months in one or more countries not on the INZ list of low-TB prevalence countries must also provide a CXR that is less than three months old.

INZ cannot require TB screening for:

- people with New Zealand or Australian passports
- people from the Cook Islands, Tokelau and Niue (who hold New Zealand passports)
- children involved in overseas adoptions (who have been granted New Zealand citizenship before arrival).

People travelling on New Zealand passports have an unfettered right of entry to New Zealand and cannot be subjected to immigration screening or controls. People travelling on Australian passports are not subject to normal immigration controls as they have the right to travel to New Zealand without a visa and remain in New Zealand indefinitely. Equally, individuals who have a valid temporary visa are free to enter and leave New Zealand during the validity of their visa, which may be up to three years (although, in some cases, this may be five years) and will not be rescreened during the validity of that visa.

INZ does not require TB screening for:

- people who hold Australian permanent residence (who are treated for immigration purposes as though they have New Zealand permanent residence)
- asylum seekers (who are however strongly encouraged to undertake (free) screening, through information provided with the letter sent advising that their asylum claim has been received)
- children under 11 years of age and pregnant women (unless a CXR is specifically requested by INZ).

Quota refugees are screened for TB offshore and again after arrival in New Zealand (see Table 9.2 under New Zealand health screening requirements later in this chapter).

Immigration New Zealand tuberculosis screening tools

Applicants' immigration examination results are predominantly captured in eMedical, however, a proportion are still recorded in a paper-based format.

The paper-based examination records are referred to as 'medical certificates'. In eMedical, the examinations are recorded under a different title. The questions regarding any history or evidence of TB are listed in Table 9.1 under both the name of the paper-based certificates and relevant eMedical examination title.

Table 9.1: Questions on tuberculosis in the immigration medical examination

Certificate	Section	Question asked
General Medical Certificate (INZ 1007) (The eMedical equivalent is a 501 Medical Examination)	Section B: Medical history	B1: Have you ever been diagnosed with tuberculosis (TB)? Have you ever had to take treatment for TB? B2: Have you ever been in close contact at home with a person known to have TB?
	Section D: Physical examination	D10: Respiratory system (Normal/Abnormal) D21: Skin and lymph nodes (Normal/Abnormal)
	Section F: Examination grading	Please consider the information you have recorded regarding this applicant, taking into account the New Zealand Immigration Panel Member Instructions (INZ1216), and provide a grading on their medical examination below. Supporting comments are mandatory if you provide a B grading. If you provide an A grading, comments are optional.
Limited Medical Certificate (INZ 1201) <i>(to be completed by partners/children of New Zealand residents/citizens; and refugees)</i> (The eMedical equivalent is a 512 Limited Medical Examination)	Section B: Medical history	B4: Do you have any personal history of tuberculosis (TB), or any household or occupational contact with someone who has TB, or have you ever needed medication for TB?
	Section D: Physical examination	D5: Are there any symptoms or signs of previous or current TB, of any form? Examples: has a history of cough persisting longer than three weeks, night sweats, haemoptysis, chest pain, unexplained weight loss, HIV, close contact with TB; or history of abnormal CXR, abnormal sputum, skin or blood tests?
	Section F: Examination grading	Please consider the information you have recorded regarding this applicant, taking into account the New Zealand Immigration Panel Member Instructions (INZ1216), and provide a grading on their medical examination below. Supporting comments are mandatory if you provide a B grading. If you provide an A grading, comments are optional.
Chest X-ray Certificate (INZ 1096) (The eMedical equivalent is a 502 Chest X-ray Examination)	Section C: Results of chest X-ray examination	C4: Hilar and lymphatic glands (Normal/Abnormal) C5: Hemidiaphragms and costophrenic angles C6: Lung fields C7: Evidence of TB C8: Evidence suspicious of active TB
	Section D: Examination grading	Please consider the information you have recorded regarding this applicant and provide a grading on their radiology examination below. Supporting comments are mandatory if you provide a B grading. If you provide an A grading, comments are optional. A – No evidence of active TB, or changes consistent with old or inactive TB, or changes suggestive of other significant diseases identified. B – Evidence of active TB, or changes consistent with old or inactive TB, or changes suggestive of other significant diseases identified. Please list abnormal findings.

HIV: human immunodeficiency virus; INZ: Immigration New Zealand; TB: tuberculosis.

Source: INZ.

New Zealand health screening requirements

Table 9.2 summarises the health screening requirements for the various visa types that people entering or in New Zealand may hold. INZ also reserves the right to ask any person applying for a visa to be in New Zealand to undertake a medical examination and CXR before the visa is issued, even if their stay is for less than 12 months.

Table 9.2: Current Immigration New Zealand visas and health screening requirements

Visa type	Description	Permitted length of stay	Medical exam and X-ray ^a
Visitor visa	Required for visits to New Zealand unless from a visa-waiver country	Nine months in an 18-month period (may be extended for three extra months)	Required if applicant is intending to stay in New Zealand longer than 12 months (medical exam and CXR) or is intending to stay between six and 12 months if the applicant has risk factors for TB (CXR) ^b
Work visa	Required for those offered employment in New Zealand	Generally up to three years (although can be up to five years)	Note: The need for students to provide a medical exam and/or a CXR varies depending on a combination of factors, including whether they are considered a domestic or foreign fee-paying student
Student visa	Required for study in New Zealand of over three months' duration	No maximum applied – depends on the length of the course being studied	
Limited-purpose visa	Required if entering New Zealand for a specific purpose	No maximum applied – depends on the purpose of visit but is usually brief	
Recognised seasonal employer limited-purpose visa	Required if entering New Zealand under the recognised seasonal employer scheme	Up to nine months	Required, regardless of intended length of stay in New Zealand, if the applicant has risk factors for TB (CXR) ^b
Residence visa	Required if wanting to live in New Zealand indefinitely	Indefinite	Required ^b
Asylum seeker	A person who has made a claim for refugee or protection status while in New Zealand	Dependent on length of time required to determine the claim	Required on application for residence (encouraged beforehand)
Quota refugee (residence)	A refugee outside New Zealand selected for New Zealand's annual refugee quota programme	Indefinite	Screened before travel and on arrival
Samoan quota and Pacific access category (residence)	Schemes that allow citizens of the Pacific Islands to enter a ballot to be considered for a grant of residence	Indefinite	Required before arrival ^b

TB: tuberculosis; CXR: chest X-ray.

a Must be completed before arriving in New Zealand if stay is intended to be at least 12 months, and must be completed in New Zealand if stay is extended to longer than 12 months.

b Applicants must:

- not be likely to be a danger to public health
- not be likely to impose significant costs or demands on health or special education services
- be fit for the purposes of entry.

Source: INZ (Immigration New Zealand 2017)

Offshore screening of quota refugees

The goal of offshore screening is to diagnose and treat refugees before they travel to and resettle in another country. An annual quota of refugees is accepted for permanent resettlement in New Zealand, mandated by the United Nations High Commissioner for Refugees (UNHCR). Since 2005, INZ has screened quota refugees for TB and HIV in approved offshore facilities. If found to have infectious TB, entry to New Zealand is delayed while treatment is provided, according to the WHO guidelines. Quota refugees also undergo medical examination (including a further CXR) on arrival at the National Refugee Health Screening Service (RHSS) at the Mangere Refugee Resettlement Centre.

Communication between countries

Communication between national health authorities and health care providers in different countries is important in the international control of TB.

Under the International Health Regulations 2005 (WHO 2016), the health governing body in each participating country has a nominated 'national focal point'. Information on people with TB who are travelling between countries or about international contact tracing for people exposed to TB, should be transferred through this mechanism. In addition, it may be necessary for clinicians to communicate directly with treating clinicians in other countries around case management.

INZ is a member of the Immigration and Refugee Health Working Group (IRHWG). The IRHWG is a partnership of member states that gathers government officials from Australia, Canada, New Zealand, the United Kingdom and the United States of America on a regular basis for information exchange, agreement and cooperation. The member states share a common goal of optimising international best practices for screening and treating prospective migrants and effectively managing communicable health risks, with the overriding priority of protecting public health. The group is a consultative forum and not a legally-constituted body. It seeks to jointly enhance the health security of migrants and receiving countries, the health services provided to migrants and TB control globally.

Tuberculosis in people being deported

A diagnosis of TB during reapplication for a visa may lead to a person being unable to demonstrate an adequate standard of health, and their application could be declined. A migrant who has breached the requirements of their visa may also be declined a further visa. This means a migrant may lose the right to remain in New Zealand. Deportation risks interruption to the patient's treatment, thereby posing a risk to TB control in their country of origin and, if they return, New Zealand. New Zealand has committed to the WHO's eight-point framework *Towards Tuberculosis Elimination: An action framework for low-incidence countries* (WHO 2014b). This identifies stigmatising immigration practices, such as deportation, as obstacles to timely, free access to early

TB detection and care. The framework also encourages offering a guarantee of non-deportation to foster adherence.

Investigation of abnormal immigration chest X-rays

Physicians are often asked to investigate a person in whom TB is suspected as a result of a CXR taken for immigration purposes.

Immigration clearance for tuberculosis

When a person applies for residence or a temporary entry visa, an opinion will be sought from an INZ medical assessor, or where appropriate, a contracted respiratory physician, if an abnormality is found on a CXR. Visa applicants who have a history of, diagnostic findings of, or treatment for MDR-TB or extensively drug-resistant TB can only be approved if:

- they have been cleared by a New Zealand respiratory or infectious diseases specialist upon review of their file or review of the applicant according to these Guidelines and
- the applicant continues to meet all other requirements.

Non-residents who are currently in New Zealand and elect to undergo private medical assessment for CXR abnormalities must pay for the ensuing costs, including TB screening costs. However, if a person has, or is suspected of having, an infectious disease or quarantinable disease within the meaning of the Health Act 1956, they are entitled to the same level of funded health services as New Zealand citizens can expect. This includes for surveillance, quarantine, diagnosis, treatment, follow-up and contact tracing for the extent appropriate in the circumstances to prevent risks to other people (as defined in the Minister of Health's gazetted notice *Health and Disability Services Eligibility Direction 2011*, Ministry of Health 2011). The cost of investigating and treating TB disease in non-residents is borne by the New Zealand government.

In practice, this applies only to investigations and treatment obtained through the public system; investigations performed privately are not reimbursed from public funds. Therefore, in order to ensure that non-residents are not required to pay for an investigative work-up for suspected TB, the physician must (a) arrange for the investigations to be performed in the public system and (b) clearly state on the referral or request form that the investigations are being ordered because TB is suspected or has been identified. The medical officer of health may be able to help if problems are encountered with this process.

Role of the panel physician in an immigration medical examination

(Refer INZ1216, Immigration New Zealand 2015.)

The panel physician needs to exclude or diagnose active TB disease; currently there is no guidance on LTBI.

The clinician must also consider other possible diagnoses (eg, lung cancer, chronic obstructive pulmonary disease (COPD), or bronchiectasis).

In addition to obtaining the applicant's history, a recent CXR and physical examination, the investigation may include:

- a review of old CXRs for comparison (if available)
- a repeat posteroanterior image at the completion of cultures
- a review of any previous reports regarding treatment of TB
- results of three current smears and cultures (sputum samples taken on three different mornings or other appropriate specimens as clinically indicated) and cultures for *Mycobacterium tuberculosis*, incubated for six to eight weeks (plus drug susceptibility testing (DST), where available, if cultures are positive).

Notifying the medical officer of health of cases of active tuberculosis

Under the Health Act 1956, section 74 and 74AA, every medical practitioner and medical laboratory is required to notify the medical officer of health if they have reason to believe that a person consulting them may have (or has been confirmed to have) active TB. Therefore, if active TB is suspected, for example, because the person has symptoms of TB and/or the CXR shows evidence suggestive of active TB, the medical practitioner concerned must notify the medical officer of health at the local public health service. This applies to all medical practitioners, including radiologists reporting CXR results for X-ray certificates for temporary entry as well as physicians undertaking immigration medical examinations or examining people referred for further investigation because of an abnormal temporary entry CXR. A list of contact details for all public health units is available on the Ministry of Health website (Ministry of Health 2017).

Screening and managing LTBI in people from high-incidence countries

LTBI screening is not required for immigration procedures, with the exception of a tuberculin skin test (TST) for refugee children aged under 16 years as part of their evaluation for TB.

Nonetheless, over half of TB cases in people born overseas occur more than two years after arrival in New Zealand (Figure 9.1), suggesting reactivation of latent infection acquired overseas could make a significant contribution to the TB burden in New Zealand. Other low-burden, high-migrant-receiving countries such as the United States of America do screen immigrants for LTBI (Taylor et al 2016), and Australia has recently introduced LTBI screening for children (Australian Government Department of Home Affairs nd).

See Chapter 7: Diagnosis and treatment of latent tuberculosis infection for recommendations on when people born overseas should be tested and treated for LTBI.

Travel to high-incidence countries

The risk for travellers to high-incidence countries will relate to the length of stay, activity while overseas and prevalence of TB within the country visited.

Bacille Calmette-Guérin (BCG) vaccination (if not previously administered) should be offered to children aged under five if travel to a high-prevalence country is likely to exceed three months. Details are available in the New Zealand *Immunisation Handbook 2017* (Ministry of Health 2018a).

BCG vaccination is unnecessary in adult travellers.

A TST or interferon gamma release assay (IGRA) should be done before visits of more than three months to a high-prevalence country, if there has not been a previous positive test.

Those travelling to undertake health care work and other high-risk activities should have pre-travel testing even if they are travelling for shorter durations. The test should be repeated eight weeks after return. Further evaluation and management are as described in Chapter 7: Diagnosis and treatment of latent tuberculosis infection.

A high index of suspicion and early investigation are required if a returning traveller presents with symptoms suggestive of active TB.

The importance of early detection

It is important that primary health care physicians with patients from high-incidence countries are aware of the increased risk of TB in these patients and the importance of early detection. Primary health care physicians should inform new patients from high-incidence countries about TB, including:

- the need for early investigation of signs and symptoms of TB
- the fact that TB is most likely to occur in migrants, and doctors need to be vigilant for TB in migrants not only shortly after their arrival but also throughout their time in New Zealand
- the fact that TB is a treatable disease
- the fact that TB treatment is free in New Zealand.

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Chapter 10: Laboratory methods and standards

Executive summary

Mycobacteriology laboratories play a central role in the control of *Mycobacterium tuberculosis* by ensuring that it is isolated; identified and tested against appropriate drugs in a timely manner (ATS 1997b; 2000; Hale et al 2001; Salfinger and Morris 1994; Schluger 2001; Tenover et al 1993).

This chapter contains guidelines for New Zealand diagnostic laboratories handling mycobacterial samples, including smear staining and microscopy, culture, nucleic acid amplification tests (NAATs) and drug susceptibility testing (DST). It also covers interferon gamma release assays (IGRAs) and molecular typing of *M. tuberculosis* isolates and updates the issues relating to quality, performance and safety in mycobacteriology laboratories. Standards are referenced when applicable.

Although many mycobacterial species other than *M. tuberculosis* cause human disease, the focus of this chapter is *M. tuberculosis* (ATS 1997a).

Recommendation summary

Smear staining and microscopy

- Sputum-smear results (or rapid molecular testing) should be available within 24 hours, even on weekends, for specimens considered urgent. All urgent requests should be discussed with the on-call clinical microbiologist.
- Fluorescence staining is preferred to conventional microscopy for its greater sensitivity.
- All smear positive respiratory specimens should have a GeneXpert MTB/RIF (Xpert MTB/RIF) assay performed within 24–72 hours, either in the testing laboratory or at a referral laboratory.
- Laboratories performing smear microscopy must meet the requirements of a physical containment level 2 (PC2) facility.

Culture

- A PC2 laboratory with additional equipment and work practices is an appropriate facility for performing the large majority of tuberculosis (TB) cultures in New Zealand.
- To maintain technical competency, a TB culture laboratory should process at least 20 specimens for culture per week.
- Laboratories performing cultures but referring isolates for identification and DST must send all positive cultures to the reference laboratory within 48 hours of culture positivity.

Nucleic acid amplification tests

- If there is insufficient specimen to process for both culture and NAAT, priority should be given to culture.
- Each mycobacteriology laboratory should develop a NAAT testing algorithm based on the particular characteristics of their patient population, the local prevalence of TB and non-tuberculous mycobacteria (NTM), the performance characteristics of the particular NAAT being used and the laboratory size and resources.

Interferon gamma-release assays

- When IGRAs are used as a tool to screen health care workers and other groups before beginning work, the pre-test probability of latent tuberculosis infection (LTBI) must be considered. Routinely screening populations at low risk of TB infection will lead to the test having a low positive predictive value and is generally not recommended.
- Positive results near the cut-off of 0.35 IU/mL are more likely to be non-specific than highly positive results.

Phenotypic drug susceptibility testing

- Laboratories performing DST must meet the requirements of a physical containment level 3 (PC3) facility.
- All DST must be performed using a liquid culture system so that results are made available within 30 days from specimen reception.
- DST must be performed in:
 - all initial isolates of *M. tuberculosis*
 - isolates from patients who remain culture-positive after three months of treatment
 - isolates from patients who are clinically failing treatment
 - an initial isolate from a patient relapsing after previously successful TB treatment.

- At a minimum, second-line testing should include amikacin, capreomycin and moxifloxacin.

Related guideline documents

This chapter has drawn heavily on the Australian National Tuberculosis Advisory Committee (NTAC) 2017 TB Laboratory Guidelines (NTAC 2017). In many places, the wording of NTAC recommendations has been adopted unchanged based on the principle that there are benefits in aligning practices where possible.

This chapter also draws on the WHO Global Laboratory Initiative (GLI) guidelines (Global Laboratory Initiative 2014). This guideline was developed to ensure high-quality results and comparability of data from a network of international TB laboratories handling sputum specimens for multidrug-resistant tuberculosis (MDR-TB) clinical trials.

Background

Description of mycobacteria

Mycobacteria are aerobic bacilli (ie, rod shaped) that are considered gram-positive but do not readily stain by the Gram stain method. Special techniques must be used to promote the uptake of dye and, once stained, mycobacteria are not easily decolourised. Their resistance to decolourisation is termed 'acid fastness', hence the term 'acid-fast bacilli' (AFB).

Growth rates for mycobacteria are slow compared with most other bacteria (16–18 hours to undergo one cycle of replication compared with 20 minutes for most bacteria).

Classification

Mycobacterium tuberculosis complex

The *Mycobacterium* genus is divided into the *Mycobacterium tuberculosis* complex (MTBC) and NTM. The MTBC includes *M. tuberculosis*, *M. bovis* (*M. bovis* subsp. *bovis*, *M. bovis* subsp. *caprae* and *M. bovis* BCG), *M. microti*, *M. canettii*, *M. africanum*, *M. pinnipedii* (ATS 2000) and *M. orygis* (Dawson 2012; van Ingran et al 2012). The bacille Calmette-Guérin (BCG) is a vaccine against TB that is derived from *M. bovis* and has attenuated pathogenicity.

Non-tuberculous mycobacteria

A variety of terms have been used to describe the rest of the *Mycobacterium* genus, including mycobacteria other than tuberculosis (MOTT), environmental mycobacteria, atypical mycobacteria (ATM) and NTM (ATS 1997a). However, the term NTM is now preferred (ATS 1997a) and is used in this chapter to refer to these species as a group.

Specimen types, collection and transport

Specimen collection

- Relevant clinical details must be written on the request form as well as a clear statement regarding the tests requested (eg, routine culture, cytology).
- Sterile, leak-proof disposable plastic containers must be used to send specimens to the laboratory. Containers must be clearly labelled with the patient's name, the specimen type and the time and date of collection.
- Sufficient material must be collected for all the tests required. Do not use fixatives or preservatives for culture specimens.
- Swabs are not recommended for the isolation of mycobacteria. Transport time should be minimised to avoid overgrowth by contaminating commensal flora.
- If transport is delayed, specimens should be refrigerated at 4°C.

Specimen types

Sputum

- Spontaneously produced deep-cough sputum samples may be suitable if the patient has a productive cough, however, induced sputum is preferred. Bronchoscopy with broncho-alveolar lavage (BAL) may be required if induced sputum testing is not available. Expecterated sputum should be collected early in the morning from a deep productive cough. Three consecutive specimens (either spontaneous or induced) should be collected at 8- to 24-hour intervals.

Other respiratory specimens

- Bronchial washings and lavages should be sent in sterile containers.

For information on the role of sputum induction in the diagnosis of TB, see Chapter 2: Diagnosis of tuberculosis disease.

Early morning urines

- The entire volume of early morning urine should be collected into a clean container.
- The minimum volume required is 40 mL.

Send one specimen on three consecutive mornings. Indications for early morning urine tests are discussed in Chapter 2: Diagnosis of tuberculosis disease.

Tissues, curettings, bone and aspirates

- Tissues and aspirates should be collected into sterile containers.
- The request for mycobacterial culture should be clearly noted on the request form.
- If histopathology is also required, the specimens should first be processed for microbiology and then sent on to histopathology.

Blood and bone marrow

- Blood and bone marrow specimens must be inoculated immediately into the mycobacterial blood culture tubes used by the receiving laboratory. This must be done at the bedside.
- The minimum volume of blood for culture is 5 mL for adults and 1 mL for children.

Swabs

- The rate of recovery of mycobacteria from swabs is poor.
- Swabs are only acceptable if a biopsy or aspirate cannot be obtained. Under these circumstances, the swab should be placed in a transport medium before transporting to the laboratory.

Gastric aspirate (lavage)

- If possible, gastric aspirate (lavage) specimens should be processed within four hours of collection.
- When transportation is expected to be delayed, the specimen should be collected into 10 percent sodium carbonate.
- Early morning specimens should be sent on three consecutive days.

Nasopharyngeal aspirate

- In children, nasopharyngeal aspirates (NPA) are also a useful specimen for testing by the GeneXpert MTB/RIF.
- Two NPAs may be collected as an interim specimen where the GeneXpert MTB/RIF is available and where induced sputa and gastric aspirates will be delayed or are unfeasible.

- However, the sensitivity of NPA culture is very low, and induced sputa are preferred for culture.

Smear staining and microscopy

Background

Three staining techniques are commonly used to detect AFB: two carbol fuchsin-based stains (Ziehl-Neelsen (ZN) and Kinyoun) and fluorochrome stains. The classic ZN stain involves heating to enhance dye uptake. The Kinyoun acid-fast stain is a similar method but without the heating requirement. Both methods stain mycobacterial cells red against a blue counter-stain. Both are examined under oil immersion at 1,000 times magnification.

- **At least 300 fields should be examined before a slide is reported as 'negative'.**

A fluorochrome stain (auramine O or auramine-rhodamine) is the screening method recommended for laboratories with a fluorescent (ultraviolet) microscope. These stains fluoresce under ultraviolet illumination, so that mycobacteria appear bright yellow against a dark background. Fluorochrome smears can be read at lower magnification and in less time than carbol fuchsin based smears. Fluorescence microscopy is more sensitive than conventional microscopy and has similar specificity (Public Health Agency of Canada and the Canadian Lung Association / Canadian Thoracic Society 2014).

For a sputum specimen to be smear-positive, it must contain approximately 10⁵ AFB/mL. Positive cultures can be expected when the sputum specimen contains 10–100 AFB/mL.

Acid-fast smears have high specificity, but some other organisms may also stain acid-fast, including *Nocardia* species, *Rhodococcus* species, and *Legionella micdadei*.

Guidelines for laboratories performing smear microscopy

Turnaround time and reporting

- Sputum-smear results (or alternatively rapid molecular testing using a platform such as the Xpert MTB/RIF) should be available within 24 hours of specimen reception. Results should be available within 24 hours even on weekends for specimens considered urgent; results for non-urgent requests should be available the following Monday.

- After-hours urgent smear microscopy may, by necessity, be performed directly on unprocessed sputum with sputum concentration and decontamination for culture occurring later during routine hours. Such requests should be discussed with the on-call clinical microbiologist.
- All specimens, except urine, pleural, peritoneal and cerebrospinal fluid, should have a stained smear performed. Smears of urine are rarely positive and not usually cost effective.
- For cerebrospinal fluid (CSF), the preferred minimum volume for culture and NAAT is >5 mL (Pfyffer 2015).
- For low-volume CSF samples, culture should be performed in preference to stained smears.
- Positive smear results should be quantified using the International Union against Tuberculosis and Lung Disease (IUATLD) / WHO scale (IUATLD 2000). The wording of reports and the corresponding number of AFB present in the smear for both systems are summarised in Table 10-1. It is also recommended that laboratories report the numerical result in brackets alongside the 1+ to 4+ result (eg, 2+ AFB seen (1–9 AFB/10 fields)).
- A GeneXpert MTB/RIF must be performed on a smear-positive respiratory specimen within 72 hours, either in the testing laboratory or by referral to a larger central laboratory.

Biosafety

- Laboratories performing smear microscopy must meet the requirements of a PC2 facility as described in the Standards Australia / Standards New Zealand standard (Standards Australia / Standards New Zealand 2010).
- The smear preparation procedure must take place within a Class I or Class II biosafety cabinet (BSC).
- Any manipulation involving vortexing, shaking, mixing or sonication must be performed in the BSC and a period of at least 10 minutes must elapse before the container is opened within the BSC.
- The operator must wear an impervious long-sleeved gown and gloves, where the glove and sleeve cuff overlap.

Quality assurance

- A laboratory performing smear microscopy should process a minimum of 10 requests per week to maintain expertise. A scientist should read no more than 25 ZN smears per day on average. Up to 75 slides per day can be read if a fluorochrome stain is used.
- A positive and negative control smear should be included with each batch of smears.

- The staining reagents must be labelled with their identity, concentration, preparation date, expiration date, initials of the scientist who prepared the reagent, and the relevant safety symbols. Laboratories are reminded of the recent changes recommended by the GLI (Global Laboratory Initiative 2014) to the reagent formulations for ZN and fluorescent microscopy.
- The staining method should be clearly described in the laboratory method manual, which should also list the remedial actions if the positive or negative control slide fails.
- Larger laboratories that process many specimens (and perform cultures) may use a fluorochrome stain. It is not necessary for smears from new smear-positive patients to be checked by ZN stain.
- The laboratory must participate in an external quality assurance programme (QAP). The Royal College of Pathologists of Australasia (RCPA) programme sends 8–10 AFB smears per year. Quantitation errors are of minor significance. Low false-negative results are understandable if the QAP sends a slide with 1–9 AFB/100 fields. Any low or high false-positive result or any high false-negative result should trigger immediate remedial action.

Table 10.1: IUATLD acid-fast smear evaluation and reporting

Report	AFB seen by staining method and magnification		
	Carbol fuchsin stain x 1000	Fluorochrome stain	
		x 200	x 400
No AFB in at least 100 fields	0/negative	No AFB in one length ^a	No AFB in one length ^a
Confirmation required ^b	–	1–4 AFB in one length ^a	1–2 AFB in one length ^a
Actual AFB count	1–9 AFB in 100 fields ^c	5–49 AFB in one length ^a	3–24 AFB in one length ^a
+	10–99 AFB in 100 fields	3–24 AFB in one field	1–6 AFB in one field
++	1–10 AFB per field in at least 50 fields	25–250 AFB in one field	7–60 AFB in one field
+++	> 10 AFB per field in at least 20 fields	> 250 AFB in one field	> 60 AFB in one field

AFB: acid-fast bacilli; IUATLD: International Union against Tuberculosis and Lung Disease

a One length is equivalent to 2 centimetres.

b Confirmation is required by another technician or prepare another smear, stain and read.

c A finding of 1–3 bacilli in 100 fields does not correlate well with culture positivity.

Source: Adapted from Kent and Kubican (1985).

Culture

Decontamination process

Background

Sputum specimens contain oropharyngeal flora, which, unless eliminated, will overgrow *M. tuberculosis* cultures. Optimal recovery of mycobacteria requires special decontamination procedures designed to eliminate contaminating bacteria while releasing mycobacteria trapped in organic material (mucus, cells and other proteinaceous material) (Pfyffer 2015).

Many laboratories decontaminate and liquefy sputum samples using sodium hydroxide. Other decontamination/mucolytic agents include dithiothreitol (sputolysin) and N acetyl-L-cysteine (NALC).

- Non-sterile specimens other than sputum also require decontamination to eliminate contaminating bacterial flora (Pfyffer 2015).
- Tissues and aseptically collected body fluids do not usually require decontamination.
- Body fluids infected with *M. tuberculosis* usually contain only a few mycobacteria and should be concentrated by centrifugation to maximise recovery.
- Tissues can be ground and inoculated directly to both solid and liquid media.

During the decontamination process, there are many opportunities for generating splashes and aerosols that can lead to cross-contamination of specimens, and unnecessary treatment (Burman and Reves 2000).

Technical guidelines for decontamination

- Contamination rates should be monitored.
- For liquid culture systems, contamination rates of 8–10 percent are acceptable and represent the best balance between excessive contamination and overly stringent decontamination (that risks false-negative culture results).
- For solid media, contamination rates of 3–5 percent are acceptable.
- Laboratories must be alert to cross-contamination between specimens resulting in false-positive results. In studies from the United States of America and Europe, 1–4 percent of cultures may be false-positive cultures, and the consequences for the patient may be substantial (De Boer et al 2002). Laboratory cross-contamination should be considered in the following circumstances:
 - A single smear-negative *M. tuberculosis*-culture-positive specimen when other samples from the patient are smear- and culture-negative.
 - The patient's clinical presentation or course is inconsistent with TB.
 - Unusual clustering of positive-culture results processed on the same day.
 - Isolates with unusual DST profiles that were processed on the same day.

- Five colonies grown on solid media, or time to growth detection is more than 30 days in automated broth cultures or discordant results are obtained when solid- and broth-based media are inoculated with the same specimen (Standards Australia / Standards New Zealand 2010).
- Suspicions of laboratory cross-contamination events should be investigated by:
 - reviewing the laboratory records for other culture-positive specimens processed at the same time
 - reviewing the patient’s history, radiological investigations, clinical course and response to therapy
 - molecular typing of the suspicious isolates, which may demonstrate identical profiles to laboratory control strains (eg, H37Rv) or to isolates from epidemiologically-unrelated patients processed on the same day
 - reviewing the laboratory procedures.

Culture process

Background

A variety of media are available to use for recovering mycobacteria, including solid and liquid (broth) media (Global Laboratory Initiative 2014; Pfyffer 2015).

Liquid media reduce the time to detect the growth of mycobacteria by about seven days. Liquid media also recover more isolates than solid media and detect mixed mycobacterial cultures more frequently.

Modern mycobacteriology laboratories use automated, continuously monitored systems to culture mycobacteria in liquid media. These systems use specialised vials/tubes into which processed specimens are inoculated. For example, the mycobacteria growth indicator tube (MGIT) 960 system detects bacterial growth using a fluorescence-quenching based oxygen sensor within each tube. As mycobacteria multiply within the tube, oxygen is consumed, and the system detects fluorescence (Pfyffer 2015). The contents of the tube can then be stained to look for the presence of mycobacteria and tested for the presence of *M. tuberculosis* using *M. tuberculosis* antigen tests. Examples of different continuously automated systems include the BACTEC MGIT 960 (BD), the BACTEC 9000 MB (BD) and the MB/BacT Alert 3D (Biomérieux).

Technical and quality assurance guidelines for laboratories performing mycobacterial culture

Quality assurance recommendations

- A scientist with a relevant university degree (or equivalent training) should be responsible for the mycobacteriology laboratory. All staff working in the mycobacteriology laboratory should be suitably trained and have evidence of ongoing training. A clinical microbiologist should have active input into the laboratory planning, procedures and supervision and should be available to communicate any positive culture results, where necessary.
- To maintain technical competency, a TB culture laboratory should process at least 20 specimens for culture per week.
- Laboratories performing mycobacterial cultures must participate in a recognised QAP programme. The RCPA QAP programme distributes eight specimens for mycobacterial culture per year. Results should be reviewed by the institution's quality services section and laboratory procedures reviewed when any false-positive or false-negative culture results occur.
- A laboratory performing mycobacterial cultures but not meeting the minimum recommended workload (ie, 20 specimens for culture per week) or fulfilling QAP or other requirements must consider referring their mycobacteriology workload to a larger laboratory facility.

Technical recommendations

- Ideally, specimens should be processed on each day of the working week. Smaller laboratories culturing 20–50 specimens per week may choose to process cultures three to four times per week. In these circumstances, smears are to be prepared and read daily.
- All specimens should be inoculated in a liquid culture system +/- onto solid media. Liquid culture provides appreciably faster turnaround times (TATs) than those achieved by culture on solid media. Liquid culture systems should therefore be used by default. Various authorities recommend that each specimen also be inoculated onto solid media to detect strains that may not grow in broth (Association of Public Health Laboratories 2013; European Centre for Disease Prevention and Control 2016; Public Health Agency of Canada and the Canadian Lung Association / Canadian Thoracic Society 2014; Public Health England 2018). Growth on solid media only in comparative studies may be due to the 'splitting' of samples with low AFB counts across multiple media and may not be a major problem if all the sediment is inoculated into the broth.
- Processing of multiple specimens from each presumptive TB case increases the sensitivity of culture.
- Specimens from skin, lymph nodes and abscesses that may contain pathogenic NTM should also be inoculated onto/into additional media for incubation at 30°C.
- Environmental samples may also be tested for the presence of NTM, most commonly endoscopic instrument washings. In addition, recommendations have been published for mycobacterial culture of water from heater cooler units (HCUs)

used for cardiopulmonary bypass and other applications (Public Health Laboratory Network 2016, Ministry of Health 2018).

- The inclusion of positive- and negative-culture controls with every batch of specimens for culture is not necessary. Positive controls represent a potential source of contamination and should only be included when a new batch of media is used. Negative controls will only reliably detect gross cross-contamination that will be self-evident. Low-level contamination will be inconsistent and may not be detected in negative control vials. It is more important to record background bacterial contamination rates.
- Automated liquid-based cultures are incubated and monitored continuously for six weeks. Non-automated liquid-based cultures should be read every two to three days for weeks one to three and weekly thereafter for at least six weeks but longer if required, depending on the specimen type and smear result. Solid media should be read twice weekly for weeks one to four, then weekly thereafter for at least eight weeks but longer if required.
- All positive broth-based cultures must be: ZN stained, sub-cultured to solid media (to detect mixed mycobacterial growths) and sub-cultured to blood agar (to detect bacterial contamination). Repeat positive cultures must have a ZN-stained smear performed to confirm presence of AFB and sub-cultured where appropriate.
- Laboratories performing cultures but referring isolates for identification and DST must send all positive cultures to the reference laboratory within 48 hours of culture positivity. The sample should be sub-cultured to a blood agar plate and incubated for a minimum of 24 hours to exclude bacterial contamination before sending to the higher-level laboratory.
- Shipment of isolates must comply with relevant national regulations (Standards Australia 2007; Standards Australia / Standards New Zealand 2010). Depending on the transport regulations, the isolate may be sent in liquid or on solid media. The isolate must be accompanied by the original request form and documentation of all relevant clinical and laboratory information (eg, patient details, original specimen type, AFB smear result, associated histological investigations that may have been performed on the same specimen).
- Laboratories should aim to report positive *M. tuberculosis* complex cultures within an average of 14–21 days from time of specimen reception (Association of Public Health Laboratories 2013). These turnaround times are achievable using broth-based culture systems (Therapeutic Goods Administration 2015).
- All positive culture and DST results that will affect patient management should be phoned and sent electronically and/or in printed form to the treating doctor and the responsible district health board (DHB) public health service as soon as the results become available. For example, the initial results on all new patients, relapses and failure cases must be phoned and sent directly to the treating doctor. Repeat results on subsequent specimens from the same episode can be sent in printed form.
- TB is a notifiable disease in New Zealand. Microbiological laboratories performing mycobacterial cultures should ensure that they, or the reference laboratory to which their cultures are referred, comply with all legal requirements for direct laboratory notifications.

- All primary MTBC isolates should be retained for at least six months by the primary laboratory and for at least five years by the laboratory performing molecular typing.

Biosafety and laboratories performing *M. tuberculosis* culture

For mycobacterial culture, the processing and concentration of specimens for inoculation on to primary media or for sample preparation for line probe assay (LPA) is considered to carry moderate risk. Although there is usually a low concentration of infectious particles, specimens are liquefied during the processing procedure, increasing the chance of generating infectious aerosols. In a retrospective study by Kim et al, laboratory staff performing mycobacterial culture procedures had a relative risk of TB of 2.0 (95 percent CI 0.2–13.3) compared with non-laboratory staff (Kim et al 2007).

Biosafety guidelines for laboratories performing tuberculosis culture

- **A PC2 laboratory with additional equipment and work practices would appear to be an appropriate facility for performing primary processing of the large majority of clinical specimens requesting *M. tuberculosis* cultures in New Zealand.**
- Laboratories undertaking more than 5,000 cultures per year, performing susceptibility tests or knowingly handling MDR-TB strains should be undertaking *M. tuberculosis* culture within a fully compliant PC3 facility.
- The mycobacterial culture laboratory must be in a self-contained room physically separated from other areas. The laboratory should be divided into areas where 'clean' activities (administration, microscopy, staining, storage of consumables and reagents) and 'dirty' activities (processing of specimens, handling cultures, BSC, centrifuge, incubators) are located.
- The 'clean' area should be near to the entry/exit point of the laboratory and have a hand-washing station and hooks for gowns. The 'dirty' area must be located away from the entry/exit point.
- Access to the mycobacteriology laboratory must be limited to staff trained to work in the area. Access should be restricted by lockable doors.
- A pressure steam steriliser must be available for decontaminating laboratory waste, preferably within the mycobacteriology laboratory but otherwise within the laboratory facility. Any non-sterilised infectious waste taken out of the mycobacteriology culture laboratory must be placed within a container with a lockable lid and taken directly to the pressure steam steriliser.
- A directional air flow from the entry/exit point to the 'dirty' area shall be maintained by extracting room air. Recirculation is permitted but not into areas outside the PC2–PC3 facility.
- All procedures must be performed in a Class I or Class II BSC. The BSC must undergo at least an annual maintenance check and be certified for use.
- For personal protective equipment, staff must wear gloves and a long-sleeved gown, where the glove and sleeve cuff overlap. These personal protection items must not be worn outside the TB laboratory.

- Laboratory coats must not be used for *M. tuberculosis* culture as they do not provide the user with adequate coverage.
- N95 particulate respirators should be included in the spill kit and worn if a spill event occurs outside the class II biosafety cabinet (BSC-II). N95 particulate respirators should be available to use when performing high-risk activities. Such respirators are not a substitute for poorly functioning BSC. Local risk assessments are recommended to determine the appropriate level of respiratory protection required for each activity. Respirators must be correctly fitted, which may be achieved by fit testing (Coulter and the NTAC 2016). Wearers must be trained in respirator selection, performing a 'fit check', donning and removal, proper use and limitations.
- Any manipulation of specimens involving vortexing, shaking, mixing or sonication must be performed in the BSC, and a period of at least 10 minutes must elapse before the container is opened in the BSC.
- When cultures are vortexed, shaken or sonicated, at least 15 minutes should elapse before opening the container (WHO 2012).
- A centrifuge with sealed rotors or safety cups must be used and must be capable of reaching and maintaining 3,000 g to reliably sediment AFB (Ratnam and March 1986). The specimen must not be heated above 37°C during centrifugation.

Summary of laboratory biosafety and quality assurance requirements

Table 10.2: Biosafety and quality assurance recommendations

Laboratory capability	Physical containment level	Quality assurance recommendation
Smear only	PC2	Yes, RCPA smear QAP
Culture		Yes, RCPA smear and culture QAP or equivalent
1 <5,000 cultures per year	PC2	
2 ≥5,000 cultures per year	PC3	
3 Knowingly handling MDR-TB	PC3	
Susceptibility testing	PC3	Yes, as above and other external programmes that include DST, such as the RCPA MSIG EQA programme or WHO QAP

PC: physical containment level; QAP: Quality assurance programme; DST: drug susceptibility testing; RCPA: The Royal College of Pathologists of Australasia; RCPA MSIG EQA: The Royal College of Pathologists of Australasia Mycobacterium Special Interest Group External Quality Assurance; MDR-TB: multidrug-resistant tuberculosis.

Source: Australian National Tuberculosis Advisory Committee (NTAC 2017)

Mycobacterial identification process

Nucleic acid probes

Two-line probe kits have been developed: LiPA Mycobacterial kit (Innogenetics) and GenoType® Mycobacteria (Hain Lifescience). These kits can be used to identify *M. tuberculosis* and some commonly encountered NTM from either solid or liquid media. LPAs have the advantage of allowing several species to be identified from a single polymerase chain reaction (PCR) and thus do not require pre-selection of the appropriate probe (Greco et al 2006).

MPT64 antigen tests

Three commercial immunochromatographic tests (ICTs) are available that detect MPT64, a secretory protein specific to the *M. tuberculosis* complex, in liquid and solid cultures (Brent et al 2011; Yin et al 2013). These assays are simple to perform, have a 30-minutes turnaround time and allow rapid identification of *M. tuberculosis* in positive liquid cultures, such as MGIT. A meta-analysis of commercial immunochromatographic tests (ICTs) reported a pooled sensitivity of 97 percent (95 percent CI, 96–97 percent) and a pooled specificity of 98 percent (95 percent CI, 98–99 percent) (Yin et al 2013). False-negative results occur for some but not all BCG strains, some *M. bovis* isolates and with *M. tuberculosis* isolates containing MPT64 gene mutations. Rare false-positive results have been reported with NTM, including *M. kansasii*, *M. gastri* and *M. terrae* (Brent et al 2011; Hopprich et al 2012; Roberts et al 2012).

Guidelines for Mycobacterial identification

- The laboratory's testing algorithm must contain access to a secondary (molecular) identification test to detect MPT64-negative *M. tuberculosis* isolates. Typically this is by performing GeneXpert MTB/RIF on the MGIT broth.
- Mycobacteriology laboratories working in PC3 facilities (or suitably-risk-assessed PC2 facilities) should perform MPT64 ICTs (or a similar rapid identification test, such as a GeneXpert MTB/RIF assay) within 24 hours of the first positive mycobacterial culture from a patient. However, the laboratory's testing algorithm must contain a secondary (molecular) identification test to detect MPT64-negative *M. tuberculosis* isolates. *M. tuberculosis* and NTM may also be identified by matrix-assisted laser desorption ionization – time of flight (MALDI-TOF) mass spectrometry (Buckwalter et al 2016; Girard et al 2016). This technology has demonstrated rapid and accurate identification, but users must optimise protein extraction techniques (particularly from liquid cultures) and develop a customised spectral library. Most importantly, MALDI-TOF users must confirm that their extraction technique inactivates pathogenic *M. tuberculosis* so that target plates can be safely moved from the (PC3) mycobacteriology laboratory to the mass spectrometer.

Nucleic acid amplification

Xpert MTB/RIF

The Xpert MTB/RIF is a commercial real-time PCR assay where the extraction, amplification and detection steps lie within a closed cartridge. The assay detects both *M. tuberculosis* and rifampicin (R) resistance within two hours. It has been used most extensively on respiratory specimens, but the World Health Organization (WHO) has also recommended testing CSF (strong recommendation, very low quality evidence), lymph node and other tissues (conditional recommendation, very low quality evidence) (WHO 2014).

In making these recommendations, the WHO recognised ‘substantial heterogeneity’ in the performance of the MTB/RIF assay on extrapulmonary specimens. For example, lymph node tissue/aspirates and CSF were found to have pooled sensitivity of 84.9 percent and 79.5 percent respectively, whereas pleural fluid was found to have a pooled sensitivity of 43.7 percent. Table 10.3 summarises the performance characteristics of different NAATs on different specimen types. For smear-negative respiratory specimens, the sensitivity may be enhanced by sending a second specimen. Note, a new generation of the Xpert MTB/RIF has been developed known as Xpert MTB/RIF Ultra. This assay has improved sensitivity with a small reduction in specificity (WHO 2017).

- **The appropriateness of sending more than one specimen for Xpert MTB/RIF will depend on the clinical setting, and consultation with a clinical microbiologist is recommended.**

Line probe assays

LPAs such as the MTBDR_{plus} assay (Hain Lifesciences) allow direct detection of *M. tuberculosis* as well as isoniazid and rifampicin resistance from smear positive specimens.

Table 10.3: Performance characteristics of different *M. tuberculosis* NAATs

	Smear-positive respiratory		Smear-negative respiratory		Extrapulmonary	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Xpert MTB/RIF	98–100%	>98%	57–83%	99%	53–95%	98–99.6%
LPA	93.4%	85.6%	N/A	N/A	N/A	N/A
In-house NAAT	Sensitivity 84–100% Specificity 83–100%					

LPA: line probe assay; N/A: not applicable; NAAT: nucleic acid amplification test.

Source: Australian National Tuberculosis Advisory Committee TB Laboratory Guidelines (NTAC 2017)

- Despite the faster turnaround time for NAATs compared with culture methods, culture should always be performed alongside NAATs for two reasons:
 - Culture methods remain more sensitive (sensitivities shown in Table 10.3 are all relative to culture).
 - Culture of *M. tuberculosis* allows phenotypic susceptibility testing, molecular typing and whole genome sequencing (WGS) to be performed (ATS 1997b; Schluger 2001).

Recommendations for nucleic-acid amplification testing

- Use of an Xpert MTB/RIF is recommended on all sputum samples, either for confirmation of TB or rapid evaluation of rifampicin resistance. Detection of rifampicin resistance should lead to early consultation with the tuberculosis clinical network (TBCN) (see Chapter 3: Treatment of tuberculosis disease in adults, appendices 3.1: Information sheet and 3.2: Case summary form). All samples should also be cultured.
- If there is insufficient specimen to process for both culture and NAAT, priority should be given to culture.
- The decision to perform NAAT and resulting interpretation should involve close liaison between the requesting clinician and the clinical microbiologist, particularly for paucibacillary specimens (such as pleural and ascitic fluid).
- Laboratories undertaking NAATs for mycobacteria must participate in quality assurance programmes.
- To avoid cross-contamination and false-positive results:
 - wherever possible, NAAT should be performed on aliquots taken before other tests are performed
 - for in house NAATs other than the GeneXpert, three physically separated areas are required for DNA extraction, reagent preparation and amplification/product detection. The movement of specimens must be unidirectional from pre-amplification to post-amplification areas.
- For specimens such as paraffin-embedded tissue, in-house PCR may be preferred over the GeneXpert. If this is the case, at least one negative control and a weak positive control must be subject to the whole test process, including DNA extraction.

Some additional settings in which NAATs should be considered for inclusion in a testing algorithm include:

- selected non-respiratory specimens where prompt management decisions are necessary (recognising that such tests tend to have been poorly validated and limited supporting evidence exists)
- immunocompromised patients at high risk of TB, where delay in diagnosis may compromise the prognosis or lead to inappropriate empirical treatment of other conditions

- when culture is not possible (eg, paraffin embedded tissue)
- when a patient at risk of MDR-TB presents with signs and symptoms of TB.

Immunological and biomarker tests for latent tuberculosis infection

See also Chapter 7: Diagnosis and treatment of latent tuberculosis infection.

The traditional test for LTBI is the tuberculin skin test (TST). Problems with the TST include the need for return visits, subjectivity in reading results and cross-reactivity with the BCG vaccine. Several immunological methods to diagnose LTBI have been evaluated as alternatives to the TST.

Immunological tests for TB measure some aspect of the immune response to TB (humoral or cellular) in order to infer the presence of TB infection (Andersen et al 2000). TB infection may be latent or active. Unlike culture and NAATs, immunological tests do not differentiate between active TB and LTBI.

Interferon gamma release assays – underlying principle

IGRAs involve incubation of peripheral blood lymphocytes with mycobacterial antigens. The underlying principle of IGRAs is that specific lymphocytes that have been previously exposed to mycobacterial antigens will release interferon-gamma (IFN-gamma) on re-exposure. IFN-gamma is then measured using either an enzyme immunoassay or elispot technique (Mazurek et al 2001; Pottumarthy et al 1999). The currently available commercial assays use antigens that are present in *M. tuberculosis* but absent from BCG, for example, CFP-10 and ESAT-6. These antigens are encoded by genes located within the region of difference 1 (RD1) of the *M. tuberculosis* genome. This is a region of the genome that is absent in BCG and most NTM.

Interferon gamma release assays

See also Chapter 7: Diagnosis and treatment of latent tuberculosis infection.

Two commercial IGRAs are available: The QuantiFERON®-TB Gold Plus assay (QFT-Plus) (Cellestis Limited, Carnegie, Victoria, Australia) and the T.SPOT TB assay (Oxford Immunotec, Oxford, United Kingdom). The QFT method is used by all labs in New Zealand offering IGRA. It uses an enzyme immunoassay (EIA) method to measure the amount of IFN-gamma released.

Interpretation of interferon gamma release assay results

A positive result suggests TB infection but will not differentiate between LTBI and active TB.

A negative result should not be used to definitively exclude TB in someone who has clinical features of TB because the sensitivity of IGRA for active TB is only approximately 80 percent.

An indeterminate result may indicate immunocompromise or reflect poor processing (eg, inadequate mixing of tubes after inoculation for the QFT-GIT).

When IGRAs are used as a tool to screen health care workers and other groups before beginning work, the pre-test probability of LTBI must be considered. Routinely screening populations at low risk of TB infection will lead to the test having a low positive predictive value and is generally not advisable.

Grey zones and quantitative reporting

Although the manufacturer recommends that the QFT-GIT be used as a qualitative assay, a raw quantitative measurement expressed in international units/mL (IU/mL) can be obtained from each of the two antigen tubes minus the nil tube. Positive results near the cut-off of 0.35 IU/mL are more likely to be non-specific than highly positive results. To account for this, some laboratories in New Zealand report a 'grey zone' around the cut-off, while others have elected for routine quantitative reporting.

- It should be noted that for laboratories using a grey zone, there is currently no universal agreement as to what this grey zone should be.
- Regardless, there is general agreement that access to quantitative results may be useful in some clinical settings, particularly when positive results are obtained in people for whom the pre-test probability for TB infection is low or when serial testing results are discordant.
- Interpretation of quantitative QFT-GIT results requires close liaison with a clinical microbiologist.

Adenosine deaminase for diagnosis of pleural tuberculosis

Pleural fluid adenosine deaminase (ADA) has a sensitivity of approximately 92 percent, and a specificity of 90 percent, for identifying TB (Goto et al 2003; Greco et al 2003; Gui and Xiao 2014; Liang et al 2008; Morisson and Neves 2008). The most widely accepted threshold ADA value is 35–40 U/L, but some studies have suggested that lower cut-offs should be considered in older patients to reduce the number of false-negative results (Abrao et al 2014; Lee et al 2014). A New Zealand study found a high negative predictive value with cut-offs of 15 and 30 IU/L (Blakiston et al 2018).

Molecular typing of *M. tuberculosis*

The routine typing of *M. tuberculosis* isolates in New Zealand started in July 2002. Applications for molecular typing for TB control were proposed in 2003. The applications are:

- evaluating contact investigation and management
- reinforcing (or disproving) epidemiological links
- identifying outbreaks
- detecting cross-contamination of clinical specimens and isolates
- differentiating between relapse and exogenous re-infection
- providing a basis for the study of TB epidemiology.

Mycobacterial interspersed repetitive units – variable number tandem repeat – typing

Mycobacterial interspersed repetitive units – variable number tandem repeat – (MIRU-VNTR) genotyping involves PCR amplification of 24 loci mycobacterial interspersed repetitive units (24-MIRU) followed by determination of the size of each of the PCR products. Each PCR product is assigned a numerical value based on its size, so that a 24-digit profile is obtained. The size of each product is determined by the number of 'repeats' at each locus. The numerical profile generated for any given isolate can be used to make comparisons with MIRU profiles obtained from isolates processed at other laboratories. 24-MIRU is more discriminatory than some of the older typing techniques but less so than whole genome sequencing (WGS).

Molecular typing of *M. tuberculosis* in New Zealand

Methods for molecular typing of *M. tuberculosis* have advanced rapidly. New Zealand currently uses MIRU-VNTR testing to distinguish between strains of *M. tuberculosis*. WGS of isolates is increasingly accessible in New Zealand and internationally. WGS data enable greater accuracy in identifying clustered isolates, enhancing the ability to detect transmission chains that may not have been identified by conventional contact tracing. Furthermore, bacterial genotype, as identified by WGS, can correlate with drug resistance.

Drug susceptibility testing

Biosafety considerations

DST is regarded as the activity with the highest risk in the mycobacteriology laboratory because the manipulation of high-concentration liquid cultures carries a high risk of generating aerosols.

- **Laboratories performing DST must therefore meet requirements of a PC3 facility.**

Phenotypic drug susceptibility testing methods

For each anti-tuberculous drug, phenotypic DST methods for *M. tuberculosis* use 'critical concentrations' (or 'breakpoints'). Critical concentrations for the MGIT 960 system have been published by the WHO (WHO 2008). These represent the lowest drug concentration that inhibits 95 percent of 'wild *M. tuberculosis* strains' (ie, strains that have never been exposed to the drugs), without inhibiting growth of resistant strains (see Table 10.4). An isolate is considered to be 'resistant' to a drug when growth in the presence of a critical drug concentration exceeds growth of the same isolate diluted 1:100 in drug-free media.

- All DST must be performed using a liquid culture system so that results are made available promptly.
- Using these methods, the aim should be to report DST results within an average of 15–30 days from the time of specimen reception in the laboratory. DST itself can usually be completed within 7–21 days of obtaining *M. tuberculosis* from the primary cultures.

Table 10.4: WHO MGIT 960 critical concentrations for first- and second-line drug susceptibility testing of *M. tuberculosis*

Drug group	Drug	DST critical concentration µg/mL
First-line oral anti-TB agents	Isoniazid (low, high)	0.1, 0.4
	Rifampicin	1.0
	Ethambutol	5.0
	Pyrazinamide	100
Medicines recommended for treating MDR-TB		
Group A – Fluoroquinolones	Levofloxacin	1.0
	Moxifloxacin	0.25
	Moxifloxacin (CB) ^a	1.0
	Gatifloxacin ^b	0.25
Group B – Second-line injectable agents	Amikacin	1.0
	Capreomycin	2.5
	Kanamycin	2.5
	(Streptomycin)	1.0
Group C – Other second-line agents	Ethionamide	5.0
	Prothionamide	2.5
	Cycloserine / terizidone	–
	Linezolid	1.0
	Clofazimine	1.0
Group D – Add-on agents (not part of the core MDR-TB regimen) ^d	D2: Bedaquiline ^c	1.0
	Delamanid ^c	0.06
	D3: p-aminosalicylic acid	4.0
	Imipenem-cilastatin	–
	Meropenem	–
	Amoxicillin-clavulanate	–
	(Thioacetazone)	–

All concentrations apply to the proportion method, with 1 percent as the critical proportion.

CB: clinical breakpoint; DST: drug susceptibility testing; MGIT: mycobacteria growth indicator tube; TB: tuberculosis; WHO: World Health Organization.

a CB applies to high-dose moxifloxacin (ie, 800 mg daily).

b Gatifloxacin critical concentration for MGIT established despite very limited data.

c Interim critical concentrations established.

d Routine DST is not recommended for Group D3 anti-TB medicines as these agents are only to be used when a MDR-TB treatment regimen with five effective medicines cannot otherwise be composed.

Source: World Health Organization (WHO 2008, 2018).

Isoniazid drug susceptibility testing

Isolates that grow at the lower concentration of 0.1 µg/mL but not 0.4 µg/mL (CLSI 2011; Reller et al 2000), are reported as low-level resistance to isoniazid. Some experts believe that patients infected with strains exhibiting low-level isoniazid resistance may benefit from continued isoniazid therapy. Management should be discussed with a specialist in TB treatment.

Fluoroquinolone drug susceptibility testing

The WHO recommends that laboratories perform susceptibility testing for the fluoroquinolone used in their country. Therefore, moxifloxacin should be tested in New Zealand. The recently updated critical concentration for moxifloxacin is 0.25 mg/L (Table 10.4). Ideally moxifloxacin should be tested as a first-line agent to cover for the possibility of drug intolerance to standard first-line agents.

Resistance at the low breakpoint is associated with resistance to earlier-generation fluoroquinolones (Chien et al 2016; Coeck et al 2016). Patients with low-level-moxifloxacin-resistance may benefit from (high-dose) moxifloxacin treatment. A critical concentration of 1.0 mg/L can be used to determine if higher dose (800 mg/day) of moxifloxacin can be used.

Pyrazinamide drug susceptibility testing

Multiple international authorities now recommend pyrazinamide (Z) DST as part of routine first-line testing (Association of Public Health Laboratories 2013; Public Health Agency of Canada and the Canadian Lung Association / Canadian Thoracic Society 2014; Public Health England 2018). Unfortunately, pyrazinamide DST still remains technically challenging for two reasons. First, the requirement for testing at low pH is itself inhibitory to most *M. tuberculosis* isolates. Second, the MGIT 960 method is prone to false-resistant results due to high inocula (Piersimoni et al 2013). Molecular detection of pyrazinamide resistance is confounded by the heterogenous mutations encoding resistance along the 558 bp length of the *pncA* gene, the gene encoding pyrazinamidase and the presence of other pyrazinamide-resistance mechanisms.

- Recognising the above limitations, it is still recommended that pyrazinamide DST be performed routinely as a first-line test.
- Phenotypic DST by the MGIT pyrazinamide test may be used as a screening test for Z susceptibility (Simons et al 2012). An initial pyrazinamide-resistant result could then be followed by *pncA* gene sequencing to confirm the presence of pyrazinamide resistance.
- Laboratories and clinicians must recognise the vagaries of pyrazinamide DST and that the WHO considers the use of pyrazinamide (as an ancillary drug) to be an acceptable practice even when a laboratory result demonstrates resistance (WHO 2016).

Note, phenotypic testing for pyrazinimidase activity (Wayne's test) is also available but, due to longer turnaround times and difficulties with interpretation, this assay has largely been superseded by *pncA* gene PCR and sequencing.

When to perform drug susceptibility testing for *M. tuberculosis*

DST must be performed in the following circumstances:

- all initial isolates of *M. tuberculosis*
- isolates from patients who remain culture-positive after three months of treatment
- isolates from patients who are clinically failing treatment
- an initial isolate from a patient relapsing after previously successful TB treatment (CLSI 2011; Reller et al 2000).

Second-line drug susceptibility testing

Any isolate with rifampicin resistance detected by a rapid molecular method must have second-line DST performed in parallel with first-line DST. At a minimum, second-line testing should include, amikacin, capreomycin, ethionamide/prothionamide and moxifloxacin.

Second-line DST should also be performed on:

- all MDR-TB isolates (isolates resistant to rifampicin and isoniazid +/- other agents)
- all isolates demonstrating resistance to two or more first-line drugs; and
- isolates from patients experiencing severe adverse reactions to first-line agents.

Currently LabPlus, Auckland Hospital is the only laboratory in New Zealand that performs second-line phenotypic DST. The second-line drugs that can be tested in New Zealand include amikacin, capreomycin, ethionamide/prothionamide, linezolid and moxifloxacin. Other core second-line or 'add-on' agents, such as meropenem and amoxicillin-clavulanate, may be able to be tested following discussion with the clinical microbiologists overseeing the laboratory. Bedaquiline DST will be able to be performed once analytical grade bedaquiline powder becomes more easily available.

Avoiding 'false resistance' due to contamination

Before reporting a DST result, it is most important to exclude contamination in any drug tube that shows resistance. This can be done visually by checking the tubes for micro-colonies, confirming the absence of turbidity (which indicates non-MTBC contamination), and performing a ZN-stain, looking for cording AFB. Exclusion of contamination as a cause of false resistance is especially important when reporting a putative MDR-TB or extensively drug-resistant tuberculosis (XDR-TB) case.

All of the following checks should be performed:

- Visual check of the tubes for microcolonies to confirm the absence of turbidity (which indicates non-MTBC contamination).
- Inoculation of a blood agar plate to detect bacterial contamination after 72 hours incubation.

- A test to detect *rpoB* gene mutations as supporting molecular evidence of at least rifampicin resistance.
- A Hain second-line (MTBDRsl) assay as supporting molecular evidence of resistance to second-line injectable agents and quinolones.
- Most importantly, inclusion in the second-line DST of an additional tube containing 500 µg/mL of *p*-nitrobenzoic acid (PNB) to detect mixed cultures with NTM. Growth of *M. tuberculosis* complex is inhibited by PNB, while almost all NTM are resistant (Giampaglia et al 2007).

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Chapter 11: Infection control and occupational health in tuberculosis disease

Executive summary

Tuberculosis (TB) is a communicable disease that is a risk to health care workers (HCW). Isolation of TB cases in hospital or the community can protect HCW and the public.

This chapter covers the responsibilities and administration of hospital infection prevention and control (IPC) services and obligations on employers and employees under the Health and Safety at Work Act 2015 (HSWA). The decision to isolate patients, assess their infectivity and de-isolate are discussed. The correct use of personal protective equipment (PPE) and PPE policies are described. Hospital engineering standards and staff screening procedures are recommended. Risks in other (non-health care) work places are also outlined.

Recommendation summary

- Isolation of patients with infectious TB is an important public health intervention and may take place in a hospital or the community.
- Children who are sputum-smear positive need to be treated with the same precautions as adults.
- If infectious patients are sufficiently unwell to require hospital admission or cannot comply with community infection control precautions, they should be isolated in an airborne infection isolation room (AIIR – more commonly known as negative pressure rooms) in hospital.
- For infectious patients who are not acutely ill, home isolation and treatment is often preferred.
- Patients with smear-positive pulmonary TB may be removed from isolation after they have had a minimum of two weeks' effective chemotherapy.
- Multidrug-resistant TB (MDR-TB) should be managed by a multidisciplinary team, which includes the medical officer of health and an IPC practitioner.

- People should be isolated in AIIRs if pulmonary TB has been diagnosed or is suspected or if there are open wounds or drains involving extrapulmonary TB.
- Health care staff and students should be screened for TB infection at least through a questionnaire before they start employment.
- HCWs providing care for adult patients with known or suspected infectious pulmonary TB must wear N95/P2⁸ particulate respirators.
- Bacille Calmette-Guérin (BCG) vaccination of staff and students is not routinely advised.
- All staff contacts of infectious TB cases should be followed up and questioned about whether appropriate PPE was used and, if not, why not.

Infection prevention and control principles for tuberculosis

IPC's guiding principle is to prevent or minimise the spread of communicable diseases in health care settings. This applies to patients, workers and visitors. IPC policies in the hospital setting are the responsibility of the chief executive of the district health board (DHB). The medical officer of health also has powers to investigate and address health threats in hospitals.

TB poses particular challenges because it is spread largely by the airborne route, and the diagnosis is often thought of and made some weeks or months into the illness. It is during this period that the rate of transmission is greatest. The challenge therefore is to encourage all HCWs to think of TB when seeing and assessing patients and for the HCW to put controls in place on suspicion whenever they are in a health care environment.

The central elements of control are identical to those of public health:

- early identification of infectious people
- isolation of suspected and confirmed cases
- screening of high-risk patients
- screening of high-risk staff
- contact tracing of patients, staff and visitors with appropriate management of those with active or latent infection.

⁸ The N95/P2 mask is a particulate filter personal respiratory protection device, capable of filtering 0.3 µm particles. It complies with the AS/NZS 1716:2012.

- N95 classification means the mask complies with United States of America testing requirements.
- P2 classification indicates compliance with European testing requirements.

The general rule that only pulmonary TB with cough is infectious to others has many exceptions in the hospital environment because aerosols of infectious material can occur:

- when aspirating a lesion
- when irrigating or packing a wound (D'Agata et al 2001; Keijman et al 2001)
- when changing a urine catheter bag
- when performing a chest aspirate
- when performing a surgical procedure
- when intubating or performing respiratory procedures
- when manipulating samples in a laboratory outside a biosafety cabinet.

Therefore, a HCW should practice standard and airborne precautions when performing the above tasks whenever there is a possibility that the patient has TB. This means gloves, eye protection (if needed) as well as a N95/P2 particulate respirator.

It is generally the responsibility of IPC to advise the clinical teams as to the specific practicalities of how patients are managed in the health care environment. This includes:

- the need for and duration of isolation
- whether the patient should be in a AIIR
- identification of particular hazards, such as those listed above
- specific details of how the patient can safely receive care outside their room, including radiology and other investigations or family visits.

The increasing prevalence of MDR-TB internationally drives an even greater need for vigilance and consistent application of controls. Whilst MDR-TB is prevented by the same control measures, the consequences of being infected are much greater because of the difficulty of treatment.

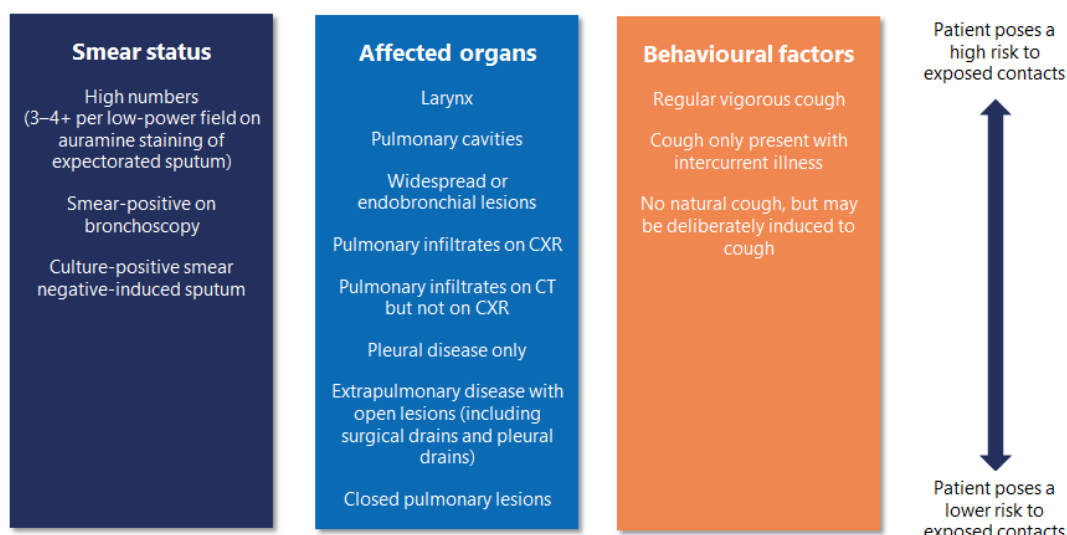
A number of international guidelines may assist practitioners (WHO 2009; Tuberculosis Coalition for Technical Assistance 2009; Curry International Tuberculosis Center 2011; Public Health Agency of Canada and the Canadian Lung Association / Canadian Thoracic Society 2014).

Infectivity of people with pulmonary tuberculosis

The traditional determinant of infectivity is regarded as the sputum smear for acid-fast bacilli (AFB). The most sensitive method is the auramine stain, which will detect lower numbers of bacilli than the Ziehl-Neelsen (ZN) stain (for more information see Chapter 10: Laboratory methods and standards).

In general, a scale of infectivity can be constructed, and that scale and risk to exposed contacts is shown in Figure 11.1 below.

Figure 11.1: Scale of infectivity and risk to exposed contacts



CT: computed tomography; CXR: chest X-ray.

This schematic represents the risk of transmission to contacts according to microbiological, clinical and behavioural factors. Risk is higher when factors higher in the columns are present. This figure may help assess the risk of exposure to others in the health care setting when the patient has not commenced therapy. All patients with diagnosed TB should be in AIIR / negative pressure room, or home isolation until approved by an IPC practitioner or a medical officer of health for de-isolation.

Infectivity of children

Children under 12 years old are rarely infectious. They usually have primary rather than post-primary TB and do not usually have laryngeal or bronchial disease. Generally, they do not have a cough of adequate strength to expel significant numbers of TB bacilli. However, some children, such as those with endobronchial disease and older children whose disease may more closely resemble adult TB, may be infectious. Sputum-smear-positive children need to be managed with the same precautions as adults.

Isolation of patients suspected of having tuberculosis

The most common avoidable need for contact tracing of patients and staff in the hospital setting occurs when there has been a failure to isolate the patient in AIIR / negative pressure room on suspicion of TB.

A pragmatic approach is to isolate patients with a clinical syndrome compatible with open TB and a risk of previous TB exposure. A compatible syndrome means whenever laryngeal or pulmonary disease could be TB, because TB is a great 'mimic' and presents in a myriad of ways. The classic triad of weight loss, chronic cough and characteristic chest X-ray (CXR) are only present in approximately 30 percent of cases (Miller et al 2000). Risk of *Mycobacterium tuberculosis* exposure includes:

- previous TB
- being brought up in a high-TB incidence country
- a household or other close contact with a TB case or someone with unexplained respiratory disease. Even in the elderly, there is a need to consider the prevalence of TB when they were younger. Stigma often prevents people from being honest about family members with TB, and caregivers and other household residents need to be enquired about carefully
- occupational or other institutional exposure (eg, prisons).

If TB cannot be reasonably excluded, it is much better to isolate until two negative sputa are obtained (see Chapter 2: Diagnosis of tuberculosis disease). It is prudent to place patients suspected of having extrapulmonary disease and risk of TB in an AIIR as well because these patients may require interventions, such as pleural aspiration, which may render them infectious by the airborne route.

Isolation of infectious cases in hospital: non-multiresistant tuberculosis

Infectious patients should be admitted to hospital for airborne isolation, if they are:

- sufficiently unwell to require admission to hospital
- at increased risk of drug toxicity or side effects
- unable to comply with the community infection control precautions.

Patient leaving negative pressure isolation

A patient with infectious TB will have to leave the isolation room at times for investigations in the hospital. They should wear an approved mask (see below) and have water- and air-tight dressings applied to open wounds or drains if required.

Isolation of infectious cases at home

It is possible to initiate anti-TB therapy at home. If the patient is not acutely ill, home isolation and treatment is often the preferred option. Home isolation and treatment minimises the possibility of previously unexposed vulnerable people being exposed to TB. The decision to manage a case at home should be shared between the medical officer of health and secondary health care services.

A public health nurse experienced in TB control should visit the home of the isolated patient within 24 hours of diagnosis and discuss isolation requirements with the patient and their family. The nurse must explain that:

- the patient should stay at home and not visit places where there will be previously unexposed or casually exposed people
- the family should minimise the duration and number of visits by previously unexposed or casually exposed people (this is especially important if visitors are children – all visiting by children from outside the family should be strongly discouraged until the patient is smear-negative or has received two weeks of treatment)
- where possible, the patient should minimise contact with children less than five years old
- previously unexposed people should not come to live with the family until the patient is smear negative or has received two weeks' treatment
- the patient should wear a mask when previously unexposed or casually exposed people (including visiting public health nurses) visit the home
- the patient should cover their mouth when sneezing or coughing
- the patient needs to adhere to the schedule of medication and side-effect monitoring.

The nurse must also educate the family about disease transmission and disease control.

Change in infectivity with treatment and decision to de-isolate

The decision to de-isolate a patient after commencing treatment should be based on when the patient is no longer spreading viable bacteria that can establish infection in others via the airborne route. The literature is heavily focused on measures such as time for sputum conversion by either smear or culture, but treatment will sufficiently damage mycobacteria to affect transmissibility of organisms much earlier than the damage required to prevent growth in liquid culture in the laboratory. The practice of repeating cultures at two months in patients who are still coughing is to check that the organisms remain drug-susceptible rather than to assess potential for transmission.

Studies in guinea pigs are an established model for TB transmission and convincingly shows that infectivity drops dramatically even after the first day of effective therapy. The greatest risk therefore is from patients who have resistant TB and those who are not treated promptly with standard regimens (Iseman 1997; Noble 1981; Riley et al 1962; Sultan et al 1960). A succinct review of the literature describing rapid reduction in infectivity is provided by Dharmadhikari and Nardell (2011).

A pragmatic approach may be to isolate cases of pulmonary TB until the full susceptibility results are back from the laboratory. This would mean that most patients are in airborne isolation for up to two weeks, by which time infectivity of even heavily smear-positive patients will have fallen to negligible levels.

The decision of where to isolate a patient may need to be discussed between the IPC practitioner and the medical officer of health. It is the role of the IPC service and Occupational Health to protect other patients, visitors and staff, so the default position is to isolate for at least two weeks. A patient who is tolerating treatment and is likely to comply with requests to not have any new contacts may be discharged quite promptly.

Factors favouring early removal from AIIR include:

- absence of cough
- low smear score on sputum
- compliance with requests to wear masks, etc, outside the isolation room.

Factors favouring longer isolation include:

- drug resistance
- treatment interruption
- cavitary disease
- vigorous cough
- three or 4+ sputum-smear score.

Multidrug-resistant tuberculosis

Due to the use of GeneXpert MTB/RIF (Xpert MTB/RIF) or similar testing, it is often possible to recognise MDR-TB soon after diagnosis. The presence of MDR-TB elevates the need for strict isolation because it may take some time to establish the patient on effective therapy. Depending on resistance and drug tolerability, it may take weeks or months before one may be confident that the patient is no longer infectious.

All patients with MDR-TB are to be discussed with the New Zealand tuberculosis clinical network (TBCN), hosted by the Ministry of Health (See Chapter 3: Treatment of tuberculosis disease in adults, appendices 3.1: Information sheet and 3.2: Case summary form).

Administrative measures for infection control

All health care facilities should have administrative measures in place to reduce the risk of exposure for other patients, staff and visitors.

Infection control policy

This document should be a useful starting point for a DHB-specific IPC policy. Special areas should have detailed procedures and training manuals for all staff working in the area. These areas include:

- wards with AIIR / negative pressure rooms
- respiratory equipment or departments where induced sputum procedures may be conducted
- cardiothoracic wards
- theatres
- radiology
- pathology:
 - fine-needle aspirate (FNA)
 - wet tissue
 - microbiology
 - mortuary
- laparoscopic and other abdominal surgery
- post-bronchoscopy and surgical recovery areas
- Ear Nose and Throat clinics.

Hospital engineering controls

Background

International recommendations and standards are used in New Zealand for ensuring that the ventilation requirements for AIIR / negative pressure rooms are met (ASHRAE 2017; Facility Guidelines Institute 2018; Jensen et al 2005).

Placing a person in an AIIR / negative pressure room minimises the risk to others outside the room, which allows the care of highly vulnerable patients on the same ward or care area. The room itself will still contain infectious bacilli, which are removed by exhausting the air to the outside, usually after high efficiency particulate air (HEPA) filtration. The number of infectious bacilli in the room air is kept to a minimum through

the use of dilution through air changes from the ventilation system. There is a practical limit to the number of air changes per hour because of noise and chill factor.

Number and placement of negative pressure rooms

It is important that hospitals in New Zealand have sufficient AIIR / negative pressure isolation rooms to enable safe care of patients with TB, as well as other airborne diseases such as measles, varicella and other emerging respiratory infections.

Patients may need to spend two weeks or more in airborne isolation, and it is therefore important to have sufficient properly designed rooms. A standard room would include:

- an anteroom (maybe shared with another room)
- monitoring gauges visible to HCWs using the room
- a lockable door to prevent direct entry and exit without going through anteroom
- easily serviceable HEPA filters
- at least 12 air changes per hour
- HEPA filtration of recirculated or exhaust air
- automatic dampers to prevent mixing the room's exhaust with other air handling systems
- visible and appropriate signs outside the room when in use as an AIIR.

Maintenance

There must be scheduled filter changes, or when pressure differences across the filter exceed specification. A process of decontamination and safe handling of the filters must be followed.

Monitoring

- Regular monitoring of pressure gradients across filters.
- Central monitoring by the hospital engineering controls.
- External monitoring by accredited experts, assessing that all engineering components are performing to standard.
- Monitoring reported to the IPC service.

Cleaning and clearing of room before use by another patient

It takes a long time to completely clear a room from the aerosol generated by a cough. Even at the recommended air change rate of 12 air changes per hour, the room will not be completely clear (99.9 percent removal of bacilli) for 35 minutes (Jensen et al 2005).

Proper cleaning and sterilising or disinfection of medical equipment

Instruments such as bronchoscopes and nebulisers used for patients with TB and other mycobacterial diseases become contaminated and unless adequately reprocessed become a source of cross-infection.

Each DHB should have a policy for the microbiological surveillance of endoscopes that is supervised by an IPC committee.

Standards New Zealand has published advice on cleaning and sterilising instruments (Standards New Zealand 2001). The GESA/GENCA *Endoscopy – Infection Control (2010)* guideline for monitoring endoscopes and bronchoscopes should be followed (Gastroenterological Society of Australia 2010).

Health and Safety at Work Act (General Risk and Workplace Management) Regulations 2016

This new legislation has clarified the roles of the employer and the employee in workplace safety and is particularly relevant for how TB is managed. It makes more explicit the requirement for employers to protect their staff and customers and for staff to have access to appropriate PPE.

Employer's responsibilities under the Health and Safety at Work Act (General Risk and Workplace Management) Regulations 2016

Relevant extracts from the explanatory notes to the legislation are as follows:

- A person conducting a business or undertaking (PCBU) may be an individual person or an organisation.
- Under the HSWA, a PCBU must look after the health and safety of its workers and any other workers it influences or directs. The business or undertaking is also responsible for the health and safety of other people at risk from its work, including customers, visitors or the general public. This is called the 'primary duty of care'.
- PCBUs must ensure all people are provided with the information, training, instruction or supervision they need to protect them from health and safety risks arising from the PCBU's work.
- PCBUs must ensure workers use or wear the PPE, so far as is reasonably practicable. Workers have their own duty to wear PPE (see Personal protective equipment and patient place of care and Personal protective equipment later in this chapter).
- PCBUs must ensure that any PPE they provide or that is provided by the worker (see Personal protective equipment and patient place of care and Personal protective equipment later in this chapter) is selected to minimise health and safety risks, including being: suitable for the nature of the work and any hazard associated with the work, a suitable size and fit and reasonably comfortable for the worker who is to wear or use it and compatible with any other PPE that is required to be worn or used by the worker.
- Workers have their own duties in relation to the PPE they must wear. They must use or wear the PPE (provided by themselves or the PCBU) in line with the information, training or reasonable instruction given to them by the PCBU. They must not intentionally misuse or damage the PPE and must tell the PCBU if the PPE is damaged or defective or when it needs to be cleaned or decontaminated.
- PCBUs must monitor the health of workers as described in the Health and Safety at Work (General Risk and Workplace Management) Regulations 2016 when regulations specify this. Currently, health monitoring as described in these Guidelines must take place 'if the worker is carrying out ongoing work using a substance hazardous to health that is specified in a safe work instrument as requiring health monitoring and there is a serious risk to the worker's health because of exposure to the substance hazardous to health'.

It is clear that the legislation places responsibility on the employer and the HCW to ensure that TB is not transmitted in the health care settings. The specific measures are discussed later in this chapter.

Personal protective equipment and patient place of care

- Particular emphasis should be on the correct use of PPE, especially N95/P2 particulate respirators, including fit checking.
- Standard precautions and airborne precautions must be used when providing clinical care for patients if pulmonary TB is suspected or has been diagnosed.
- The patient should be placed in an AIIR / negative pressure room (see Hospital engineering controls earlier in this chapter).
- Staff conducting aerosol-generating procedures, such as bronchoscopy and sputum induction, should wear particulate respirators even if the risk of TB is remote: prevention is better than treatment.
- Staff examining the upper airway or performing laryngoscopy or intubation in patients at higher risk (see above) should wear a N95/P2 particulate respirator.
- It should be noted that patients often cough after bronchoscopy, which is both a hazard and an opportunity for sample collection.
- Infectious TB patients should wear surgical masks when they leave the isolation room for investigations in other parts of the hospital.
- Standard and airborne precautions are required for TB wound care (Keijman et al 2001) This means gloves, eye protection (if needed) as well as a N95/P2 particulate respirator.

Personal protective equipment

HCWs providing care for adult patients with known or suspected infectious pulmonary TB must wear a N95/P2 particulate respirator that is properly fitted. The choice and style of masks will be determined by the district health board's (DHB's) IPC service and procurement policies.

The following are important requirements for IPC policies:

- Training and education should be given for using masks, including donning and doffing procedures to ensure the wearer has achieved a satisfactory seal around their nose and mouth. Periodic fit checks are recommended.
- N95/P2 particulate respirators have to be used properly to be effective, and it is easy to contaminate hands and face when removing masks. Hand hygiene must always be practiced immediately after removing a mask.
- Disposable particulate respirators are a single-use item and not to be used multiple times.

- Reusable or multi-use particulate respirators must be labelled for a single staff member's use and maintained according to the manufacturer's instructions.
- Particulate respirators do not usually fit well on men with beards. Obtain advice from the IPC service.

Occupational health and safety

Staff screening

For the purposes of this discussion, staff refers to workers who regularly come within 1 metre of patients in a health care facility.

The aim of staff screening is to find and treat those staff who may pose a risk to other staff or patients by developing infectious TB and transmitting the disease in the workplace. This practice is targeted at HCW who were born in or have worked in high-TB-prevalence countries.

Routine screening of HCW who do not have an exposure history for *M. tuberculosis* infection is not recommended. Contact tracing of diagnosed cases of TB is more cost effective and easier to administer consistently.

Risk of tuberculosis in health care workers

Historically, HCW had higher rates of TB infection than the general population, but this should no longer be the case in an era of greater attention to the use of PPE and environmental controls.

The greatest risk therefore for staff exposure is working in or having worked in an environment overseas, where TB is prevalent and there are poor IPC practices. This is in addition to the risk at home and in general society. In short, almost all TB infection occurs in staff from overseas, usually Asian countries.

Pre-employment screening

It is recommended that all HCW including those working in hospitals in New Zealand undergo pre-employment screening. This screening aims to:

- detect applicants who may have TB disease, and therefore prevent transmission to patients and colleagues
- identify those with latent TB infection so that their treatment can be discussed
- obtain baseline data regarding previous exposure, tuberculin skin test (TST) or interferon gamma release assay (IGRA) status to inform any future contact tracing exercise.

Similar screening by educational institutions is required for students of nursing, medicine and allied health. This screening should be included in the agreements between hospitals and educational institutions. When hospitals employ agency (bureau) staff, the contract should specify similar screening for the agency workers.

It is important that any results from screening on entry into health education courses or from previous employers is reviewed before repeating unnecessary tests. The IGRA tests are expensive and often needlessly repeated without considering whether there were any new exposures after the latest test.

Larger hospitals should have an in-house occupational health unit to facilitate cooperation with other services, such as infection control and public health.

Pre-employment questionnaire

Pre-employment screening should always start with an assessment of risk of *M. tuberculosis* infection by questionnaire. This is used to establish the previous TB-exposure risk, which is required before deciding whether to take any further actions. Currently, there is a widespread practice of arranging testing by IGRA irrespective of exposure risk, which is wasteful and poor practice. IGRA results are only interpretable with a knowledge of an exposure history as false-positives occur commonly in those at no significant risk.

For those at higher risk of exposure, the most important thing to establish is whether the person has symptoms compatible with TB. **Such a person should not be allowed to start work until they have been assessed appropriately.**

The pre-employment questionnaire should cover:

- birth, residence and extended travel in countries of high TB incidence
- previous TB and how it was treated
- previous TST or IGRA results
- TB exposure, particularly from household contacts
- previous roles, particularly working on medical wards in high-TB-incidence countries
- proposed new occupation
- health problems associated with immunosuppression.

The point of the screening is to allocate staff into one of three groups, akin to a traffic light system, as shown in Figure 11.2:

- A negative IGRA is most useful for excluding latent tuberculosis infection (LTBI) in a person with a positive exposure history.
- Treatment of LTBI enables a person to be allocated into the 'green' group, not requiring ongoing recalls and follow-up.
- The frequency and process for monitoring those at intermediate risk for developing TB infection should be based on a risk-based approach, with particular attention

paid to those most recently arrived in the country who are at the greatest risk of developing active TB.

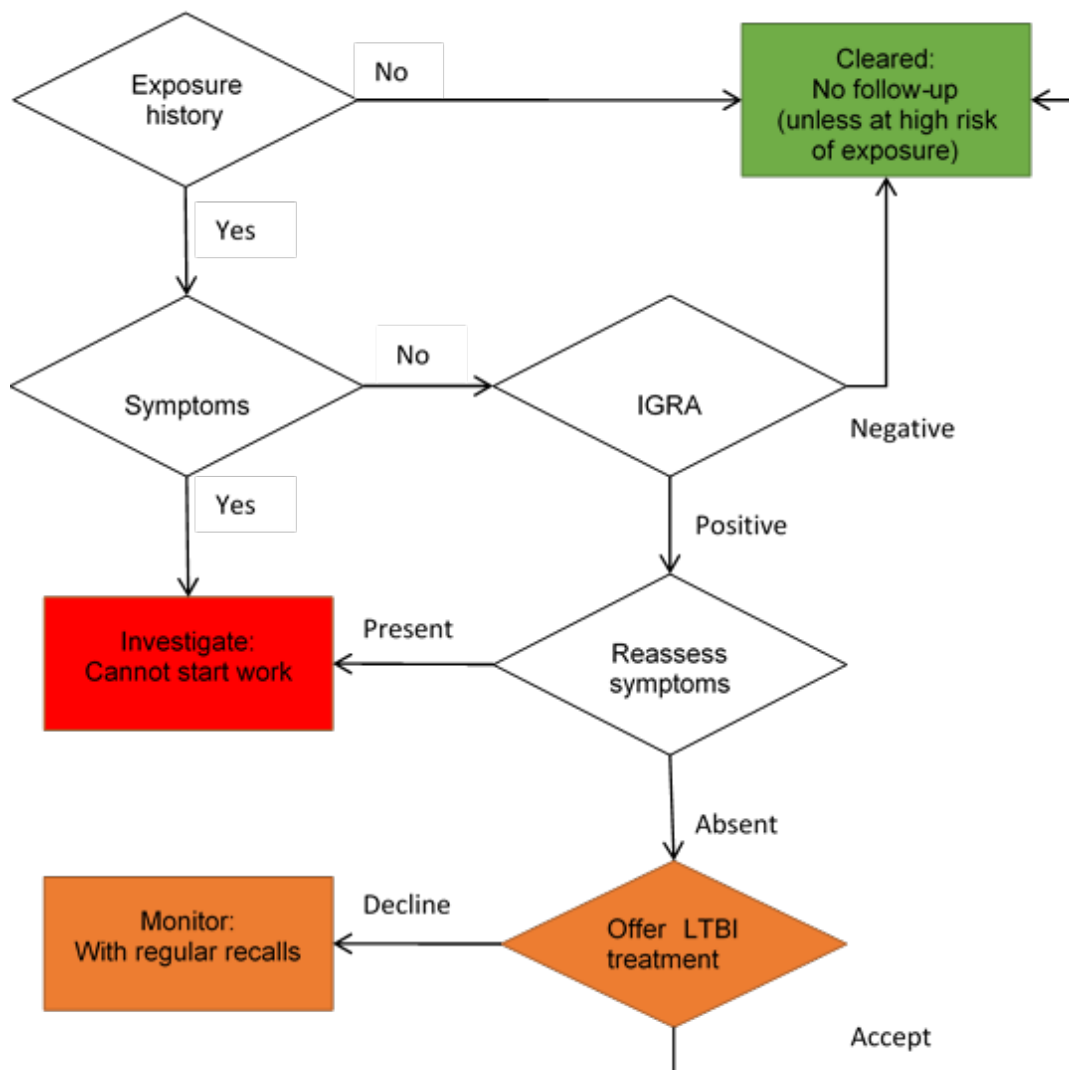
- Follow-up of those with no evidence of previous TB exposure is only indicated for those at high risk of exposure (see Figure 11.2).

Those who have refused treatment for LTBI

Staff, like other people, have the right to refuse treatment for LTBI. A staff member with untreated LTBI should be regularly monitored for TB symptoms and by CXR.

Staff are assigned to three groups according to their exposure history and symptoms.

Figure 11.2: Screening new staff for tuberculosis



IGRA: interferon gamma release assay; LTBI: latent tuberculosis infection.

Pre-employment bacille Calmette-Guérin vaccination

BCG is no longer recommended for HCW (Ministry of Health 2018a). It has a low efficacy in adults and makes the further use of TST as a diagnostic tool more difficult. The preferred strategy is appropriate infection control measures, including staff education and a TST programme that identifies and treats the at-risk infected HCW.

Surveillance during employment

Those at highest risk for TB exposure

Baseline testing at entry is recommended by most authorities for those working in high-risk areas, such as respiratory medicine and TB laboratories (Australian National Tuberculosis Advisory Committee 2006).

It is not clear however what level of exposure risk is required before recommending that staff with negative TST or IGRA should have an annual test. Even recommending serial testing or follow-up is explicit acknowledgment that ongoing exposure risk has not been mitigated. This could be due to inconsistent N95 particulate respirator use by clinical personnel combined with ineffective contact tracing. Similarly, modern laboratory practices mandate the use of biosafety cabinets for all hazardous procedures, so staff should only be at risk if correct procedures are not followed.

Contact tracing of staff should be properly conducted when there has been a case of infectious TB in a health care setting, with particular attention paid to whether masks were used appropriately. If this is done systematically, there should be little or no extra advantage for routine serial testing of employees with negative TST or IGRA results from pre-employment testing. The employer's responsibility is to ensure that those in high-risk settings are well trained and consistent in their use of PPE and negative pressure facilities.

If a decision is made to screen staff routinely during employment, a structured approach should be taken that includes:

- TB symptom questionnaires
- TST or IGRA
- CXR, if applicable.

The United States Centers for Disease Control and Prevention (CDC) recommends such an approach (Jensen et al 2005). Staff who are unwell with respiratory symptoms should be supported in taking sick leave, and staff with prolonged symptoms of cough should be investigated for TB.

Staff potentially exposed to patients with infectious tuberculosis

The clinical management of staff exposed to an infectious TB case is the same as for other contacts (see Chapter 7: Diagnosis and treatment of latent tuberculosis infection).

Infection control and tuberculosis in long-term care facilities

The main risk relates to staff from high-TB-prevalence countries developing TB and exposing patients and colleagues. See pre-employment screening earlier in this chapter.

Infection control in non-health care settings

Infection control in correctional facilities

Internationally there are higher rates of TB in correctional and detention facilities. In New Zealand, from 2011 to 2016, there were 15 cases of TB with a history of being incarcerated (see Chapter 8: Tuberculosis control in prisons). People in prison are at high risk of contracting TB for many reasons; most come from groups at higher risk of TB within the community, and many people in prison have had minimal or no access to primary health care before their incarceration. The physical structure of the prison facilities may contribute to disease transmission, as facilities often provide close-living quarters. Further compounding this is the movement of people between one correctional facility and another, making the possibility of transmission of TB more likely and hindering TB-control measures.

The key activities required to prevent transmission of TB in correctional facilities are:

- screening – finding people with an active disease
- containment – preventing transmission of TB and treating the person who has TB
- supervision of the person's TB treatment
- maintenance of uninterrupted care by liaising with public health services before release into the community.

During their screening process on admission to a correctional facility, people may give a history of being on current treatment for active TB disease (diagnosed in the community), past treatment for active TB disease or treatment for LTBI or past diagnosis of LTBI without treatment. Infectious TB may also be suspected and diagnosed for the first time in a person already being held in a correctional facility. It is important to raise awareness of signs and symptoms among people in prison, prison staff and HCWs working in these settings.

An infectious case should be immediately transferred to a hospital and placed in an AIIR until they have completed at least two weeks of appropriate anti-TB treatment.

All staff in correctional facilities should be familiar with the national infection control policy, including how to access N95 particulate respirators if the possibility of infectious TB in a person in prison arises.

When an infectious TB case is discovered or managed in prison:

- the clinician should alert the health centre manager of the prison and public health teams about the infectious potential and treatment
- written communication should continue throughout the period of treatment and follow-up
- public health staff must be available to conduct education and contact investigation among prison staff
- liaison between prison services and public health will allow identification and education of families at risk of TB exposure.

The management of people in prison with TB should be in accordance with *Tuberculosis Case Management for People in Correctional Facilities* (Ministry of Health 2018b).

Screening for health care workers in correctional facilities

In some studies, the higher incidence of TB cases in correctional facilities is associated with an increased rate of TB transmission to prison workers as well as to other people in prison (Jochem et al 1997; Jones et al 1999; Steenland et al 1997; Valway et al 1994; Walls et al 2000). However, a recent study looking at the risk factors for infection among HCWs in correctional facilities in the United States of America reported that the risk factors were predominantly demographic rather than occupational (Mitchell et al 2005).

HCWs working in correctional facilities should undergo the same screening processes as HCWs in health care settings (see Staff screening earlier in this chapter).

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