

# Guidelines on the Prevention and Control of Tuberculosis in Ireland 2010

Health Protection Surveillance Centre



Féidhmeannacht na Seirbhíse Sláinte  
Health Service Executive





# Guidelines on the Prevention and Control of Tuberculosis in Ireland 2010

National TB Advisory Committee  
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## Terms of Reference

1. To review the guidance on prevention and control of tuberculosis in Ireland including:
  - I. Surveillance
  - II. Screening
  - III. Preventive therapy
  - IV. Clinical management
  - V. Laboratory diagnosis
  - VI. BCG vaccination
  - VII. HIV infection and tuberculosis.
2. To review the epidemiology of tuberculosis and provide advice as required to the Royal College of Physicians of Ireland (RCPI) Immunisation Committee on the use of vaccines to prevent cases of tuberculosis.
3. To act as a source of expert advice on tuberculosis when required to make interim recommendations.



## Foreword

Tuberculosis remains a significant cause of morbidity and mortality worldwide. In 2008, an estimated 8.9 to 9.9 million new cases and 1.7 million deaths were reported globally. In Ireland, the incidence of TB has fallen significantly from a high of 230 notifications per 100,000 population in 1952 when records first began to a low of 9.7 per 100,000 in 2001. The incidence has remained relatively stable since then with a rate of 11.3 per 100,000 in 2007 and an incidence rate of 8.0/100,000 in the indigenous Irish population in 2007.

The HIV epidemic has had a significant impact on TB rates globally as individuals with TB and HIV infection are more likely to develop active TB disease during their lifetime than those who are HIV negative. Drug resistance, including multidrug-resistant TB and extensively drug-resistant TB together with the increasing number of TB-HIV co-infected patients is also challenging TB control. The World Health Organization proposes to reduce the global incidence of active TB to less than 1 case per million population by 2050 and thus eliminate TB as a global public health problem. This offers a challenge to improve TB control in Ireland.

The first guidelines for the management and control of TB in Ireland were published in 1996. All the sections from the original guidelines have been updated and a new section on infection prevention and control has been added. The recommendations in these guidelines are based on a review of international literature and an extensive consultation process with relevant professionals.

I would like to thank all the members of the committee for their invaluable contribution to this report and also to acknowledge the work and commitment principally of Dr Joan O'Donnell who was ably assisted by Ms Sheila Donlon, Dr. Lorraine Hickey, Dr. Abaigeal Jackson, Dr. Kate O'Donnell, Mr. Noel Gibbons and Dr. Margaret O'Sullivan in producing this report.

**Dr. Darina O Flanagan**

Chairperson, National TB Advisory Committee.

February 2010

## Key Recommendations

### 1 Epidemiology and Surveillance of TB in Ireland

- 1.1 Case definitions specified by the European Commission should be applied for the purposes of notification and submission of data for epidemiological surveillance and disease control. These case definitions are available on the Health Protection Surveillance Centre (HPSC) website at [www.hpsc.ie/hpsc/NotifiableDiseases/CaseDefinitions/](http://www.hpsc.ie/hpsc/NotifiableDiseases/CaseDefinitions/) (section 1.4).
- 1.2 Once a diagnosis of tuberculosis (TB) is either laboratory confirmed or strongly suspected on clinical grounds, the medical officer of health (MOH) should be notified by the clinical director of the laboratory and/or clinician as soon as possible and ideally at the time of diagnosis (section 1.5).
- 1.3 Reporting of outbreaks of TB is a mandatory requirement (section 1.5).
- 1.4 Detailed surveillance information should be recorded on the national tuberculosis notification database (NTBSS) and submitted to the Health Protection Surveillance Centre (HPSC). It is planned that TB surveillance will be included in the Computerised Infectious Disease Reporting System (CIDR) (section 1.5).

### 2 Methods of TB Screening

- 2.1 The standard tuberculin skin test (TST) recommended for use in Ireland is the Mantoux 2TU/0.1ml tuberculin PPD. Mantoux 10TU/0.1/ml tuberculin PPD is not recommended for use in Ireland (section 2.3).
- 2.2 In all cases, the TST (Mantoux test) should be administered intradermally (section 2.3).
- 2.3 The TST (Mantoux test) result should be read within 48 to 72 hours of receiving the test. The transverse diameter of the area of induration (and not the erythema at the injection site) is measured with a ruler and the result recorded using millimetres (section 2.3).
- 2.4 The TST (Mantoux test) should be used as the first line test for the diagnosis of latent TB infection (LTBI) in contacts of infectious TB cases and others considered to be at high risk of LTBI. Those with positive TST results should be considered for Interferon Gamma Release Assay (IGRA) testing (section 2.6). IGRA should be considered on a case-by-case basis in adults and children as per the general recommendations in section 8.7.
- 2.5 IGRA tests should not be used in the first instance for the diagnosis of active TB disease. Appropriate microbiological and molecular investigations remain the gold standard for the diagnosis of active TB disease (section 2.6).
- 2.6 Chest X-ray is not considered the "gold standard" for the diagnosis of pulmonary TB (section 2.8).

### 3 Management of Latent TB Infection

- 3.1 The following groups should be prioritised for the treatment of LTBI: 1) Recent converters; 2) HIV-positive individuals; 3) Those aged less than 5 years; 4) Persons receiving immunosuppressive therapy e.g. Tumour Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) antagonists; 5) Persons with evidence of old healed TB lesions on chest X-ray; 6) Foreign-born persons from countries of high TB endemicity ( $\geq 40$  cases of TB/100,000 population notified per year); 7) Homeless persons; 8) Intravenous drug users and 9) healthcare workers (HCWs) (section 3.3).

- 3.2 For the treatment of LTBI in the groups outlined in 3.1, the following is recommended:
- 3.2.1 Groups 1-5: LTBI treatment should be offered to those in all age groups
  - 3.2.2 Groups 6-8: LTBI treatment should be offered to all those aged  $\leq 55$  years if supervised therapy i.e. directly observed therapy (DOT) is available. Otherwise, it should be offered to those aged  $\leq 35$  years. These groups should be closely monitored for isoniazid toxicity.
  - 3.2.3 Group 9: The age limit for LTBI treatment should be assessed on a case-by-case basis i.e. treat all HCWs where the risk of progression from LTBI to TB disease is high regardless of age. Where the risk of progression is low, the upper age limit for LTBI treatment is  $\leq 35$  years.
  - 3.2.4 For all other persons not mentioned above, the upper age limit for LTBI treatment should be  $\leq 35$  years (section 3.3).
- 3.3 Care should be taken when prescribing LTBI therapy for those with co-morbidities which increase the likelihood of hepatotoxicity (section 3.3).
- 3.4 Directly observed therapy (DOT) should be provided for those being treated for LTBI in groups 6, 7 and 8 i.e. immigrants from areas of high TB endemicity, homeless persons and intravenous drug users (section 3.4).
- 3.5 It is recommended that audits of compliance with LTBI therapy are undertaken (section 3.4).
- 3.6 The recommended treatment regimens for LTBI in adults are: (i) isoniazid for a minimum of six months with an optimum duration of nine months or (ii) rifampicin for four months or (iii) a combination of rifampicin and isoniazid for a duration of at least three months and an optimum of four months (section 3.4).
- 3.7 The recommended treatment regimens for LTBI in children are: (i) isoniazid for a minimum of six months with an optimum duration of nine months or (ii) rifampicin for six months or (iii) a combination of rifampicin and isoniazid for a duration of four months (section 3.4).
- 3.8 Physicians experienced in the management of children with LTBI should supervise therapy in children (section 3.4).
- 3.9 Consultation with a respiratory physician or infectious disease consultant should be sought for the management of persons with active TB or LTBI who have been exposed to patients with MDR-TB or XDR-TB (section 3.5).
- 3.10 Clinicians may choose to undertake baseline liver function tests (LFTs) for all patients aged over 14 years at the start of treatment for LTBI. However, this is not universally obligatory (section 3.6).
- 3.11 A consultant with expertise in TB should always be consulted when treating a patient with LTBI with documented hepatotoxicity (section 3.7).
- 3.12 Breastfeeding is not a contraindication to LTBI therapy. Isoniazid or rifampicin are not secreted in sufficient quantities in breast milk to harm the baby (section 3.7).
- 3.13 Ideally monthly clinical monitoring (or at the discretion of the physician) is indicated for all patients on LTBI treatment (section 3.7).
- 3.14 Prior to commencing TNF- $\alpha$  antagonists, patients should be thoroughly assessed by the treating physician for clinically active TB disease and for LTBI (section 3.8).

## 4 Laboratory Diagnosis of Tuberculosis

- 4.1 It is a mandatory requirement for clinical directors of diagnostic laboratories to notify cases of active TB disease to the MOH (director of public health (DPH) or designate) (section 4.1).
- 4.2 Culture is necessary to achieve the "gold standard" for the diagnosis of active TB disease (section 4.1).
- 4.3 Microscopy and culture for TB should only be performed in those laboratories where there is sufficient throughput to ensure proficiency (section 4.1).
- 4.4 Laboratories should aim to meet the "goals" set down by CDC and others (section 4.1).
- 4.5 All mycobacterial isolates should be referred to the Irish Mycobacteria Reference Laboratory (IMRL) for identification and susceptibility testing once its new facility is opened (section 4.1).
- 4.6 All *M. tuberculosis* complex isolates should be referred to the IMRL with immediate effect for molecular typing where typing is now offered. (section 4.1).
- 4.7 The results of all *M. tuberculosis* complex isolates which have already had identification, susceptibility and molecular typing performed should be forwarded to the IMRL for incorporation into a national repository of *M. tuberculosis* complex isolates (section 4.1).
- 4.8 Reasonable efforts should be made to obtain the best quality sample possible depending on the site of disease and to deliver it in a timely fashion to the analysing laboratory (section 4.2).
- 4.9 It is recommended that solid media is used in combination with a liquid culture system (section 4.3).
- 4.10 All those wishing to undertake nucleic acid amplification tests (NAAT) on suspected cases of pulmonary TB should seek advice from the local consultant microbiologist. It is recommended that NAAT should be made available at the IMRL (section 4.3).
- 4.11 Recommendations in the Seventh Schedule of S.I. 146/1994 Safety, Health and Welfare at Work (Biological Agents) Regulations 1994 should be interpreted as mandatory in relation to working with *M. tuberculosis* complex (section 4.7).
- 4.12 All relevant legislation (national and international) for the transport and handling of specimens and cultures for TB should be strictly adhered to at all times (section 4.7).
- 4.13 Laboratories should participate in internal and external quality assurance schemes for all tests performed (section 4.8).

## 5 Clinical Management

- 5.1 All persons with an otherwise unexplained productive cough lasting three or more weeks with at least one additional symptom, including fever, night sweats, weight loss or haemoptysis should be evaluated for TB. This will include clinical, radiological and bacteriological examinations (section 5.1).
- 5.2 All cases of suspected active TB should be referred to a TB clinic and have a clinical assessment at the next available clinic. If immediate evaluation is required, consult with the clinical team regarding the need for more urgent clinical assessment. The management of suspect TB cases can be undertaken in collaboration with the clinical team (respiratory or infectious diseases) who will advise on sputa collection and the clinical management (including commencement of therapy, if the sputa are positive for acid-fast bacillus (AFB)), until the next clinic appointment (section 5.1).
- 5.3 Treatment of TB should be directed by a consultant respiratory physician/consultant in infectious diseases with appropriate training in the management and treatment of TB (section 5.2).

- 5.4 There should be active case management with a dedicated case manager or health care professional who liaises with and follows the patient during the entire treatment course to monitor and enhance adherence (section 5.3).
- 5.5 More widespread establishment of combined clinics attended by both respiratory physicians and public health doctors for the diagnosis and treatment of TB (and LTBI) and the evaluation of contacts is recommended. Such clinics should be appropriately staffed with medical, nursing, pharmacy, administrative staff and medically qualified interpreters and should be integrated with the hospital system (section 5.3).
- 5.6 Isoniazid and rifampicin, with pyrazinamide and ethambutol for the initial two months (intensive phase), followed by isoniazid and rifampicin for a further four months (continuation phase) is recommended in patients with sensitive strains of tuberculosis and where there are no contraindications (section 5.4).
- 5.7 Six months of chemotherapy is usually adequate for the treatment of active disease caused by sensitive strains. However, it should be extended to nine months for the following patients:
- 5.7.1 Patients with drug-susceptible pulmonary TB with initial cavitation on chest X-ray and whose sputum cultures remain positive after the intensive phase ( i.e. the first two months of treatment)
  - 5.7.2 Other patients who are still culture positive at two months regardless of chest X-ray results
  - 5.7.3 Patients whose treatment regimen did not include pyrazinamide in the intensive phase or whose organism is resistant to pyrazinamide
  - 5.7.4 Patients being treated with once weekly isoniazid and rifampicin whose sputum culture remains positive after the two month intensive phase of treatment (section 5.4).
- 5.8 Follow-up sputum specimens for smear and culture should be obtained monthly in patients with drug-susceptible pulmonary disease. Requests for more frequent testing should only be undertaken following discussion between the treating physician and consultant microbiologist. For patients with isoniazid- and rifampicin-susceptible TB there is no need to examine sputum monthly once culture conversion is documented (i.e. two negative cultures taken at least two to four weeks apart). It is recommended that identification and sensitivities are repeated in cases who are still culture positive at  $\geq$  two months (section 5.4).
- 5.9 To enhance compliance and to minimise potential problems from the development of drug resistance, it is strongly recommended that only combination tablets should be used whenever possible (section 5.4).
- 5.10 It is recommended that the supraregional TB centre at St James's Hospital and a number of regional centres should have a small number of non-acute beds available to facilitate the inpatient care of patients who are non-compliant or have drug-resistant TB (section 5.5).
- 5.11 Prioritising the establishment of a structured national DOT programme is recommended for more effective management and control of TB (section 5.6).

## **6 Infection Prevention and Control**

- 6.1 Patients with known or suspected pulmonary or laryngeal TB should be admitted to an airborne isolation room (negative pressure isolation room with an ante room or a neutral pressure design as outlined in HBN 04 supplement 1). Hospitals need to have a risk assessment process to ensure the appropriate provision of isolation facilities (section 6.5).

- 6.2 All patients with suspected or known pulmonary or laryngeal TB must have a risk assessment for MDR-TB (section 6.5).
- 6.3 Patients with suspected or confirmed MDR-TB must be admitted to an airborne isolation room (negative pressure isolation room with an ante room or a neutral pressure design as outlined in HBN 04 supplement 1). (This may require transferring the patient to another institution where the facilities, together with a physician experienced in the management of complex drug-resistant cases are available) (section 6.5).
- 6.4 Healthcare Workers (HCWs) (including HCWs visiting a patient in their own home) should wear FFP2 masks when caring for patients with suspected or confirmed infectious TB where MDR-TB or XDR-TB is not suspected. These patients are usually non-infectious after a minimum of two weeks treatment. The supervising clinician should be consulted before the use of masks is discontinued (section 6.5).
- 6.5 HCWs should wear FFP3 masks when undertaking cough-inducing procedures on all patients (fully susceptible and resistant strains included) e.g. sputum induction, bronchoscopy, administration of aerosolised medications, airway suctioning, endotracheal intubation, caring for patients on mechanical ventilation and during treatment of lesions/abscesses when aerosolisation of drainage fluid is anticipated (section 6.5).
- 6.6 HCWs (including HCWs visiting a patient in their own home) should wear FFP3 masks when caring for patients with suspected or confirmed infectious MDR-TB or XDR-TB. The supervising clinician should be consulted before the use of masks is discontinued (section 6.5).
- 6.7 A respiratory protection programme should be provided for all HCWs who may be required to use respiratory masks during the course of their work. HCWs should be fit tested by a trained professional as part of this programme. All HCWs should fit check each time a mask is donned (section 6.5).
- 6.8 Patients should wear a surgical mask while they are infectious when they are outside their room e.g. visiting the X-ray /OPD departments (section 6.5).

## 7 BCG Vaccination

- 7.1 The continuation of a universal programme of neonatal BCG vaccination is recommended in Ireland at this time (section 7.2).
- 7.2 When BCG is given to infants there is no need to delay the primary immunisations. No further immunisation should be given in the arm used for BCG immunisation for at least three months because of the risk of regional lymphadenitis (section 7.3).
- 7.3 Training for health professionals in the correct administration of BCG vaccine is recommended. Those administering vaccine should be aware of indications, contraindications, immunisation and adverse reactions associated with BCG (section 7.4).
- 7.4 BCG should not be administered to an individual with a positive tuberculin (or interferon-gamma) test (section 7.10).

## 8 Contact Tracing

- 8.1 Contact tracing should be conducted according to the concentric circle approach, whereby contacts with greatest exposure to the index case are prioritised for screening (chapter 8).
- 8.2 Infectious pulmonary and laryngeal cases are priorities for contact investigation. A precautionary approach should be taken with bronchoalveolar lavage (BAL) smear positive cases (section 8.1).

- 8.3 Those BAL smear positive cases with cavitation on chest X-ray, MDR-TB or XDR-TB or where contacts are immunosuppressed or less than 5 years of age should be presumed infectious for contact tracing purposes (section 8.1).
- 8.4 The determination of infectivity of all other BAL smear positive patients should be considered on a case-by-case basis (clinical/microbiology/public health input) (section 8.1).
- 8.5 Young children under 10 years of age with pulmonary disease are rarely infectious. Such contact tracing investigations should be focused on finding a source and co-primary cases (section 8.1).
- 8.6 The recommended interval between first and second screening rounds (TST ± IGRA) in contact investigations is eight weeks. If the last contact with the infectious case exceeded an eight-week period, one TST is sufficient (section 8.6).
- 8.7 Contact tracing of infectious or potentially infectious TB cases on aircraft should be limited to flights which were ≥8 hours duration and took place during the previous three months. All cases of respiratory TB who are sputum smear positive and culture positive (if culture available) are deemed infectious. All cases of respiratory TB who are sputum smear negative and culture positive are deemed potentially infectious. The following criteria should also be used when determining the infectiousness of a case at the time of travel: (i) presence of cavitations on chest X-ray, (ii) presence of symptoms at the time of the flight and (iii) documented transmission to close contacts (section 8.12).
- 8.8 If the index case is a passenger, obtain contact details of passengers sitting in the same row and the two rows ahead and behind (from one side of the aircraft to the other because of ventilation patterns) the index patient. Inform contacts of possible exposure and advise screening of these contacts and of cabin crew who serviced the section in which the TB case was seated (section 8.12).
- 8.9 If the index case is an aircraft crew member, contact tracing of passengers should not routinely take place. Contact tracing of other members of staff is appropriate, in accordance with the usual principles for screening workplace colleagues (section 8.12).
- 8.10 A multidisciplinary team approach to effectively manage TB contact tracing in prisons is required. The team should be led by the local public health department who will undertake contact tracing (section 8.13).
- 8.11 DOT is recommended for all prisoners receiving treatment for active disease and should be considered for those receiving treatment for LTBI (section 8.13).
- 8.12 Evaluation of all contact tracing activities is recommended. The following information should be collected: (a) number of contacts identified (b) number of cases of active disease and LTBI and (c) the number of persons who accepted and completed preventive therapy (section 8.16).

## 9 Screening in Special Situations

- 9.1 A pre-placement screen is recommended for all clinical staff working with patients or clinical specimens (this may also be applicable to ancillary staff, as determined by a risk assessment) (section 9.1).
- 9.2 If an employee has unexplained and suggestive symptoms such as cough lasting three or more weeks that is unresponsive to usual interventions and weight loss or fever, a chest X-ray and sputum examination should be carried out. Such employees should not start work. If an employee has no suspicious symptoms, completion of the pre-placement questionnaire should be followed by an appropriate medical evaluation (section 9.1).
- 9.3 HCWs from countries of high TB incidence (≥ 40 cases of TB per 100,000 per year) with a positive TST (Mantoux test) defined as ≥10mm (table 2.1) should be referred to a respiratory or infectious



disease clinician (with a chest X-ray) for a medical assessment to rule out TB disease or LTBI. However, an occupational medicine consultant may wish to treat these patients if appropriate protocols, audit of care and resources are in place (section 9.1).

- 9.4 Irish HCWs or HCWs from low incidence countries (< 40 cases of TB per 100,000 per year) with a positive TST (Mantoux test) defined as  $\geq 15\text{mm}$  should be referred to a respiratory or infectious disease clinician (with a chest X-ray) for a medical assessment to rule out TB disease or LTBI. However, an occupational medicine consultant may wish to treat these patients if appropriate protocols, audit of care and resources are in place (section 9.1).
- 9.5 All new entrants to Ireland who originate from a country with a high incidence of tuberculosis ( $\geq 40$  cases per 100,000 population per year) and will be spending at least three months in Ireland should be provided with an opportunity to be screened for TB (section 9.2).
- 9.6 An expanded programme of screening for TB including voluntary screening for HIV in new entrants should be established. The committee believes that this should be part of a broader health screening programme to improve the health of new entrants to Ireland (section 9.2).
- 9.7 A programme of screening for TB in prisoners should be provided (section 9.3).
- 9.8 Prisoners should receive chemotherapeutic treatment for active disease or LTBI by DOT, as high rates of treatment failure have been observed in this population. Patients undergoing any form of TB treatment should be assigned a key worker (a health professional) to promote compliance, monitor treatment effectiveness and the occurrence of adverse events (section 9.3).
- 9.9 Prison medical services should liaise with community TB services to ensure the continuation of DOT after release from prison (section 9.3).
- 9.10 An opportunistic active case finding strategy is advised among homeless individuals. Screening by chest X-ray is recommended. TST and IGRA are believed to be less useful, as people may move before test reading /results are available (section 9.4).
- 9.11 Nomination of a key worker for homeless patients receiving treatment and the provision of DOT are considered an optimal strategy for treatment completion (section 9.4).

## 10 Tuberculosis and HIV Infection

- 10.1 Cases of TB/HIV should always be managed by physicians with expertise in treating both TB and HIV (chapter 10).
- 10.2 A high index of suspicion should be maintained for TB in all HIV-infected individuals (section 10.1).
- 10.3 In HIV-infected individuals, routine screening for TB is advisable. HIV-infected children should be screened annually for TB, beginning at age three to 12 months (section 10.5).
- 10.4 All TB cases should be offered HIV testing (section 10.4).
- 10.5 The recommended treatment regimens for LTBI in adults who are HIV positive are: (i) isoniazid for an optimum duration of nine months or (ii) rifampicin for four months or (iii) a combination of rifampicin and isoniazid for four months (section 10.7).
- 10.6 The recommended treatment regimens for LTBI in children who are HIV positive are: (i) isoniazid for a minimum of six months with an optimum duration of nine months or (ii) rifampicin for six months or (iii) a combination of rifampicin and isoniazid for four months (section 10.7).
- 10.7 DOT is recommended for the treatment of all HIV-infected TB cases (section 10.7).



## 11 Education, Research and Information

- 11.1 Given the increased importance of LTBI and TB diagnosis and treatment: TB education in the undergraduate and postgraduate medical/nursing/pharmacy disciplines needs to be strengthened (section 11.1).
- 11.2 Research that seeks to improve our understanding of the pathobiology of TB as well as the nature of the disease in our country is to be encouraged; research funding agencies should foster such activity which has potential to improve the treatment of the disease both locally and internationally (section 11.2).
- 11.3 Studies to determine the prevalence rate of LTBI should be initiated and supported (section 11.2).

## Abbreviations

|                      |  |
|----------------------|--|
| <b>ACDP</b>          | Advisory Committee on Dangerous Pathogens (UK)             |
| <b>AFB</b>           | Acid Fast Bacilli  |
| <b>AIDS</b>          | Acquired-Immune Deficiency Syndrome                        |
| <b>ALT</b>           | Alanine Transaminase                                       |
| <b>AS</b>            | Aspartate Transaminase                                     |
| <b>ATS</b>           | American Thoracic Society                                  |
| <b>BAL</b>           | Bronchoalveolar Lavage                                     |
| <b>BCG</b>           | Bacille Calmette-Guérin                                    |
| <b>BHIVA</b>         | British HIV Association                                    |
| <b>CDC</b>           | Centers for Disease Control and Prevention                 |
| <b>CF</b>            | Cystic Fibrosis  |
| <b>CIDR</b>          | Computerised Infectious Disease Reporting System           |
| <b>CL3</b>           | Containment Level 3  |
| <b>CNS</b>           | Central Nervous System                                     |
| <b>COSHH</b>         | Control of Substances Hazardous to Health (UK Regulations) |
| <b>CPA (UK)</b>      | Clinical Pathology Accreditation Ltd (UK)                  |
| <b>CPHM</b>          | Consultant in Public Health Medicine                       |
| <b>CXR</b>           | Chest X-ray  |
| <b>DOT</b>           | Directly Observed Therapy                                  |
| <b>DOTS Strategy</b> | Directly Observed Therapy Short-course Strategy            |
| <b>DPH</b>           | Director of Public Health                                  |
| <b>E</b>             | Ethambutol   |
| <b>EC</b>            | European Commission  |
| <b>ECDC</b>          | European Centre for Disease Prevention and Control         |
| <b>ELISA</b>         | Enzyme-Linked Immunosorbent Assay                          |
| <b>EU</b>            | European Union   |
| <b>EuroTB</b>        | European Network for Surveillance of TB                    |
| <b>FDA</b>           | Food and Drug Administration (USA)                         |
| <b>H</b>             | Isoniazid  |
| <b>HAART</b>         | Highly Active Antiretroviral Therapy                       |
| <b>HCW</b>           | Healthcare Worker  |
| <b>HIV</b>           | Human Immunodeficiency Virus                               |
| <b>HPSC</b>          | Health Protection Surveillance Centre                      |
| <b>HRZ</b>           | Three-Drug Regimen: Isoniazid, Rifampicin and Pyrazinamide |
| <b>HSE</b>           | Health Service Executive                                   |
| <b>IATA</b>          | International Air Transport Association                    |
| <b>IGRA</b>          | Interferon-gamma release assay                             |
| <b>IL-1</b>          | Interleukin-1  |

|                                |   |
|--------------------------------|---|
| <b>IMRL</b>                    | Irish Mycobacteria Reference Laboratory           |
| <b>IRIS</b>                    | Immune Reconstitution Inflammation Syndrome       |
| <b>ISTC</b>                    | International Standards of TB Care                |
| <b>IUATLD</b>                  | International Union against TB and Lung Disease   |
| <b>LFTs</b>                    | Liver Function Tests                              |
| <b>LHO</b>                     | Local Health Office                               |
| <b>LIP</b>                     | Lymphoid Interstitial Pneumonia                   |
| <b>LTBI</b>                    | Latent TB Infection                               |
| <b>MAC</b>                     | <i>Mycobacterium avium</i> Complex                |
| <b>MDG</b>                     | Millennium Development Goal                       |
| <b>MDR-TB</b>                  | Multidrug-Resistant TB                            |
| <b>MOH</b>                     | Medical Officer of Health                         |
| <b>MTC</b>                     | <i>Mycobacterium tuberculosis</i> Complex         |
| <b>NAAT</b>                    | Nucleic Acid Amplification Tests                  |
| <b>NEQAS</b>                   | National External Quality Assessment Service (UK) |
| <b>NICE</b>                    | National Institute of Clinical Excellence (UK)    |
| <b>NTBSS</b>                   | National TB Surveillance System                   |
| <b>NTM</b>                     | Non-tuberculous Mycobacteria                      |
| <b>OCT</b>                     | Outbreak Control Team                             |
| <b>PGL</b>                     | Persistent Generalised Lymphadenopathy            |
| <b>PPD</b>                     | Purified Protein Derivative                       |
| <b>R</b>                       | Rifampicin  |
| <b>SGOT</b>                    | Serum Glutamic Oxaloacetic Transaminase           |
| <b>SGPT</b>                    | Serum Glutamate Pyruvate Transaminase             |
| <b>SI</b>                      | Statutory Instrument                              |
| <b>SMO</b>                     | Senior Medical Officer                            |
| <b>SSI</b>                     | Statens Serum Institut (Denmark)                  |
| <b>TB</b>                      | Tuberculosis                                      |
| <b>TNF-<math>\alpha</math></b> | Tumour Necrosis Factor- $\alpha$                  |
| <b>TST</b>                     | Tuberculin Skin Test                              |
| <b>UK</b>                      | United Kingdom                                    |
| <b>USA</b>                     | United States of America                          |
| <b>WHO</b>                     | World Health Organization                         |
| <b>XDR-TB</b>                  | Extensively Drug-Resistant TB                     |
| <b>Z</b>                       | Pyrazinamide                                      |
| <b>ZN</b>                      | Ziehl Neilsen                                     |

## 1. Epidemiology and Surveillance of Tuberculosis

Human tuberculosis (TB) is caused by infection with bacteria of the *Mycobacterium tuberculosis* complex (*M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, *M. canettii*, *M. caprae* or *M. pinnipedii*). The organism may infect any part of the body. However, the majority of cases involve the respiratory system.

### 1.1 Global Trends

TB remains a significant cause of morbidity and mortality worldwide. An estimated 9.3 million new cases were reported in 2007, of which 7.8 million were detected in Asia and Africa. Of the 9.3 million new cases, 1.4 million (15%) were co-infected with human immunodeficiency virus (HIV). Approximately 1.8 million deaths occurred due to TB, of which 456,000 individuals were co-infected with HIV, accounting for 25% of these deaths. Worldwide, the incidence of disease is stable, although case numbers particularly in Africa, South-Eastern Asia and Eastern Mediterranean countries continue to rise.<sup>1</sup> In 1993, the World Health Organization (WHO) declared TB a 'global emergency' in response to a resurgence in cases, following nearly a century of decline.<sup>2</sup> To improve control, targets for TB control recommended by WHO's World Health Assembly<sup>3</sup> were defined within the United Nations Millennium Development Goals (MDG 6, target 8), and indicators to measure progress towards these goals were proposed by the Stop TB partnership in 2006.<sup>4,5</sup>

**Table 1.1:** Indicators of progress towards Millennium Development Goals<sup>5</sup>

#### STOP TB PARTNERSHIP TARGETS

- By 2005: At least 70% of new sputum smear positive TB cases will be detected and at least 85% of these cases cured
- By 2015: Reduce prevalence of and death due to TB by 50% relative to 1990
- By 2050: The global incidence of active TB will be less than 1 case per million population (i.e. elimination of TB as a global public health problem).

The HIV epidemic has had a significant impact on TB rates. Individuals with TB and HIV infection are more likely to develop active TB disease during their lifetime than those who are HIV negative, making HIV the most potent predictor of progression to active TB.<sup>4,6</sup> Drug resistance, including multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) (see table 1.2), together with an increasing number of TB-HIV co-infected patients is challenging TB control.

**Table 1.2:** Definitions of drug resistance

#### DRUG RESISTANCE DEFINITIONS

- Multidrug-resistant TB (MDR-TB): TB bacilli resistant to at least isoniazid and rifampicin with or without resistance to ethambutol and streptomycin
- Extensively drug-resistant TB (XDR-TB): is resistance to at least isoniazid and rifampicin (i.e. MDR-TB), plus resistance to any fluoroquinolone, and any one of the following second line anti-TB injectable drugs (capreomycin, amikacin or kanamycin).

Incomplete and incorrect treatment regimens may result in patients remaining infectious, and bacilli in their lungs may develop resistance to anti-TB medicines. While drug-resistant TB is generally treatable, it requires extensive chemotherapy (for up to two years) that is often prohibitively expensive (often more

than 100 times more expensive than treatment of drug susceptible TB) and is also more toxic to patients. Recent findings from a survey conducted by WHO and the US Centers for Disease Control and Prevention (CDC) on data from 2000-2004 found that XDR-TB has been identified in all regions of the world but was most frequent in the former Soviet Union and in Asia.<sup>7</sup> A recent outbreak of XDR-TB in HIV-infected individuals in South Africa highlighted a worrying situation whereby 52 of 53 XDR-TB patients died within a median of 16 days.<sup>8</sup>

## 1.2 Tuberculosis in Europe

In European countries, the decline of TB in the latter half of the twentieth century was accelerated by a combination of improved socioeconomic conditions such as better housing and reduction of overcrowding and biological factors e.g. improved nutrition, advent of chemotherapeutic drugs, BCG immunisation programmes.<sup>9</sup> However, in the last decade overall rates in the WHO European region began to increase steadily from 28 notifications per 100,000 population in 1994 to 54 notifications per 100,000 population in 2007.<sup>10</sup> Disparities in rates between Western and Eastern European countries are apparent and have diverged further in recent years. The incidence of disease in the Eastern European region (comprising mostly of states of the former Soviet Union) continues to increase annually and in 2007 rates in excess of 131 cases per 100,000 population were reported. Former Soviet Union countries have the greatest burden of disease and the highest rates of multidrug-resistance and mortality rates ranging from 3.0 to 22.3 deaths per 100,000 population. This region remains a priority for TB control.<sup>10</sup>

The Western European region (European Union and Western European countries) reported a rate of 17 cases per 100,000 population in 2007. This region experienced a steady decrease in overall TB incidence for a number of decades, briefly reversed in certain countries in the early 1990s.<sup>11</sup> This pattern was also first observed in the United States of America during the 1980s and early 1990s due in part to the impact of HIV but also due to the problems of homelessness, drug abuse, immigration from high incidence countries and deterioration in living conditions and health care delivery to the poor.<sup>12</sup> A concerted effort to control TB in the US resulted in a 45% reduction in cases and halved the incidence rate to 5 cases per 100,000 population between 1992 and 2002.

In low-incidence European countries, specific challenges to TB control have emerged as a result of this shift from high to low incidence.<sup>13</sup> These include a declining incidence in native populations, the increasing importance of LTBI, disease in immigrant populations, groups at high risk (HIV-infected, homeless and prisoners) and importation of drug resistance (e.g. multidrug-resistance from Eastern Europe and other countries). In the United Kingdom, national rates have remained low overall but have gradually increased in England by 25% (1994-2004).<sup>14</sup> The London region accounted for the highest proportion of cases in 2007 at 41% of all UK cases notified and had the highest TB notification rate at 44.8 per 100,000. Most TB cases continue to occur in young adults (61% were aged 15-44 years) and in the non-UK born population (72%).<sup>15</sup> In 2004, an action plan entitled 'Stopping Tuberculosis in England'<sup>16</sup> was published by the UK Department of Health, to focus efforts on controlling increasing TB levels.

In 1996, a European network for surveillance (EuroTB) was introduced, based on the participation of national TB surveillance institutions in the 53 countries of the WHO European Region. Its aims were to improve the contribution of surveillance to TB control in the WHO European region, through the provision of valid, comparable epidemiological information on TB. Annual reports indicate that Cyprus had the lowest notification rate of disease in 2007 in the 27 EU countries (EU-27) at 5.3 cases per 100,000, while Ireland ranked in sixteenth position (table 1.3).

**Table 1.3: Notification and mortality rates per 100,000 reported by EuroTB<sup>10</sup> for all 27 EU countries: 2007, 2006.**

| Country                       | Notification rate per 100,000 (2007) | Mortality rate per 100,000 (2006) |
|-------------------------------|--------------------------------------|-----------------------------------|
| Cyprus                        | 5.3                                  | 0.26                              |
| Sweden                        | 5.4                                  | na                                |
| Finland                       | 5.9                                  | 1.14                              |
| Greece                        | 5.9                                  | 0.73                              |
| Netherlands                   | 5.9                                  | 0.46                              |
| Germany                       | 6.1                                  | 0.53                              |
| Denmark                       | 7.2                                  | 0.17                              |
| Luxembourg                    | 8.1                                  | 0.00                              |
| Malta                         | 9.3                                  | 0.25                              |
| Italy                         | 7.6                                  | na                                |
| France                        | 8.8                                  | na                                |
| Czech Republic                | 8.4                                  | 0.51                              |
| Austria                       | 10.5                                 | 0.68                              |
| Slovenia                      | 10.8                                 | 0.90                              |
| Belgium                       | 9.7                                  | na                                |
| Ireland                       | 10.9                                 | 0.94                              |
| Slovakia                      | 12.6                                 | na                                |
| United Kingdom                | 13.8                                 | 0.79                              |
| Spain                         | 17.3                                 | na                                |
| Hungary                       | 17.4                                 | na                                |
| Poland                        | 22.6                                 | 1.99                              |
| Portugal                      | 29.5                                 | 0.21                              |
| Estonia                       | 36.3                                 | 4.99                              |
| Bulgaria                      | 39.8                                 | 3.51                              |
| Latvia                        | 55.1                                 | 7.95                              |
| Lithuania                     | 71.3                                 | 10.87                             |
| Romania                       | 118.3                                | 7.89                              |
| <b>Total all EU countries</b> | <b>17.0</b>                          | <b>na</b>                         |

(na: not available)

### 1.3 Tuberculosis in Ireland

Following the introduction of compulsory notification of all forms of TB in 1948, declining rates of morbidity and mortality were observed in Ireland throughout the latter half of the twentieth century<sup>17</sup> (figure 1.1). The first national survey of TB in Ireland reported 6,795 notifications in 1952, giving a notification rate of 230 cases per 100,000 population.<sup>18</sup> A downward trend was sustained until 2001 (381 cases, 9.7 per 100,000 population) after which case rates became stable, with minor fluctuations in annual figures thereafter. In 2006, there were 465 cases of TB notified in Ireland, representing a rate of 11.0 per 100,000 population.<sup>19</sup> Mortality rates also declined, from 266 per 100,000 population in 1901<sup>18</sup> to 0.94 per 100,000 in 2006, and are now amongst the lowest reported in Western Europe.<sup>10</sup> The majority of deaths from TB now occur in those aged 65 years and older.

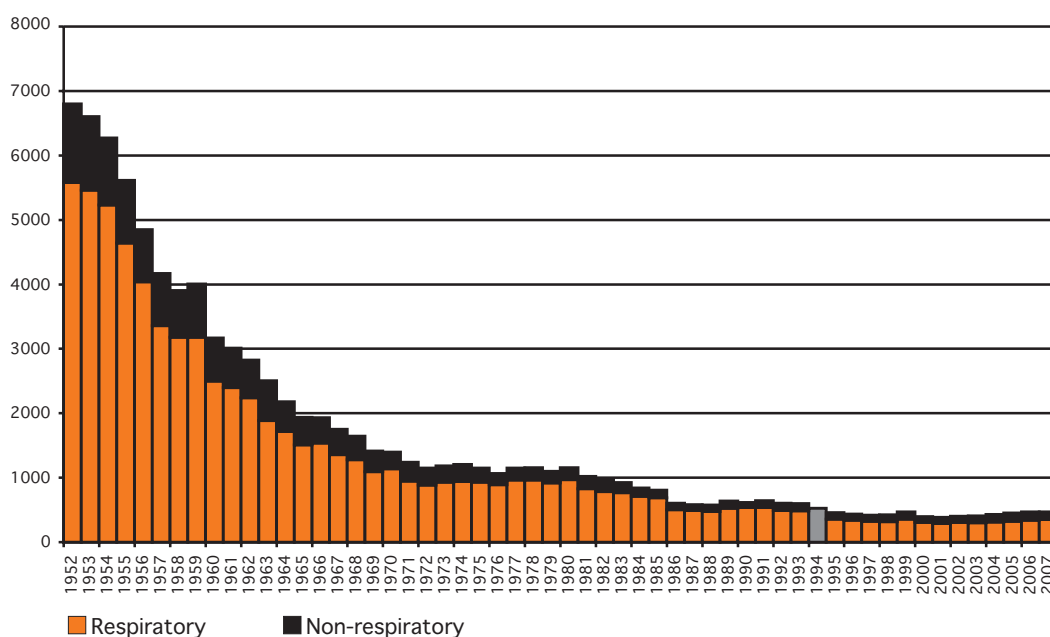


Figure 1.1: TB cases notified to the Department of Health and HPSC, 1952-2006 (breakdown by respiratory /non-respiratory not available for 1994)<sup>19</sup>

### Geographical distribution

Considerable variation exists in TB notification rates between HSE areas in Ireland (table 1.4). Overall, annual incidence rates in HSE areas fluctuate, with no discernable increasing/decreasing pattern in any region. HSE South (Cork and Kerry) typically reports the highest annual crude case rate, with rates ranging between 12.4 and 15.3 per 100,000 between 2000 and 2006. Since 2000, case rates have remained above 10 per 100,000 in both HSE East and HSE South (Cork and Kerry), and consistently below 10 per 100,000 in HSE Midlands and HSE Northwest. This distribution differs from that documented in the 1950s when the proportion of the population with pulmonary disease in Dublin was nearly twice that in any other area in Ireland.<sup>18</sup> In 2006, the largest number of notifications was reported by HSE East (193 notifications).<sup>19</sup>

In Northern Ireland, 62 cases were notified in 2006, and since 1990, an incidence rate of 3 to 5 cases per 100,000 population per year has been recorded.<sup>15</sup>

Table 1.4: Crude TB incidence rates per 100,000 population by HSE area, 1992-2006<sup>19</sup>

|      | HSE E | HSE M | HSE MW | HSE NE | HSE NW | HSE SE | HSE S | HSE W | Total |
|------|-------|-------|--------|--------|--------|--------|-------|-------|-------|
| 1992 | 16.1  | 18.7  | 20.9   | 10     | 15.9   | 12.3   | 21.4  | 22.2  | 17.1  |
| 1993 | 11.9  | 10.8  | 16.1   | 10     | 37.5   | 16.7   | 23.9  | 23    | 17    |
| 1994 | 12.9  | 14.6  | 17.3   | 11.4   | 9      | 11     | 17.4  | 22.7  | 14.5  |
| 1995 | 11.9  | 8.8   | 15.1   | 8.5    | 11.4   | 9.5    | 20.5  | 11.1  | 12.6  |
| 1996 | 8.7   | 8.3   | 17.7   | 12.1   | 7.1    | 6.9    | 22.5  | 13.1  | 12    |
| 1997 | 9.9   | 9.2   | 12.6   | 9.1    | 10.4   | 12.8   | 16.5  | 11.1  | 11.5  |
| 1998 | 11.7  | 4.9   | 14.8   | 9.5    | 9      | 8.9    | 14.3  | 15.3  | 11.7  |
| 1999 | 13.9  | 7.3   | 17     | 8.2    | 9      | 7.9    | 13.7  | 19.9  | 12.9  |
| 2000 | 10.2  | 7.1   | 13.8   | 6.1    | 4.1    | 9.7    | 13.8  | 10    | 10.1  |
| 2001 | 12.3  | 3.1   | 7.1    | 11     | 5.9    | 4.7    | 12.4  | 8.9   | 9.7   |
| 2002 | 11.6  | 8.4   | 9.4    | 7      | 5.4    | 11.6   | 13.3  | 8.7   | 10.4  |
| 2003 | 11.9  | 5.3   | 12.4   | 7.5    | 4.1    | 8.3    | 16    | 6     | 10.4  |
| 2004 | 12.6  | 3.6   | 12.2   | 5.8    | 6.7    | 7.4    | 11.8  | 10.6  | 10.2  |
| 2005 | 13    | 6.4   | 14.7   | 3.3    | 6.3    | 8      | 12.2  | 10.9  | 10.6  |
| 2006 | 12.9  | 6.0   | 10.2   | 8.4    | 3.8    | 11.1   | 15.3  | 7.7   | 11.0  |

### Age and sex

As in other developed countries, more TB cases are notified annually in males than females in Ireland and the rate is consistently higher in males across all age groups. There were 280 (60.2%) notifications for males in 2006, giving a male to female ratio of 1.5:1. The median age of cases was 45 years (range 0 to 93 years) in 2006. As reflected in other European countries, the majority of foreign-born cases occur in younger age groups. In 2006, the majority (83.2%) of foreign-born cases occurred in those aged 15 to 44 years (median 31 years). Over one-third (39.1%) of Irish cases occurred in persons aged 55 years and older in the same year.<sup>19</sup>

### Ethnicity and place of birth

Since 1998, the number of foreign-born cases has tripled, while Irish born case numbers have declined overall. In 2006, the crude rate of TB in the indigenous population was 8.3 per 100,000 and 26.3 per 100,000 in the foreign-born. Approximately, two-thirds (63.2%) of all cases notified in 2006 were Irish born. Of those born outside Ireland, 37% were born in Asia and 36% in Africa.<sup>19</sup>

### Drug resistance

Between 2001 and 2006, 10 to 27 cases per annum were resistant to at least one front-line anti-TB therapy. Of these an average of two cases had MDR-TB. In 2006, four cases of MDR-TB were reported.<sup>19</sup> In 2005, the first reported case of XDR-TB was detected in Ireland.<sup>20</sup>

## 1.4 Surveillance of TB

Clinical notification of TB was introduced in 1948<sup>17</sup> and the Infectious Diseases Regulations 1981 as amended by the Infectious Diseases (Amendment) (No. 3) Regulations 2003 (S.I. No. 707 of 2003) extended the scope of this legislation.<sup>21</sup> From 2004, it became mandatory for clinical directors of laboratories to notify a case of TB to the regional director of public health (DPH) under their role as medical officer of health (MOH).<sup>21</sup>

The 2003 amendment also made reporting of outbreaks a mandatory requirement.<sup>21</sup> The legislation describes outbreaks as “*an unusual cluster or changing pattern of illness*” which is defined as an aggregation of health events, grouped together in time or space that is believed or perceived to be greater than could be expected by chance. This may apply to a geographic area, facility or a specific population group. This definition relates to cases of TB disease only and not to cases of LTBI. LTBI is not a notifiable disease.

### Case definitions

A decision of the European Commission (Decision No. 2002/253/EC) specified the case definitions to be applied by Member States for the purposes of submitting data for the epidemiological surveillance and control of communicable disease.<sup>22</sup> In April 2008, the above decision was amended (Decision No. 2008/426/EC) updating these case definitions.<sup>23</sup> The updated standardised European case definitions are used for notification of TB in Ireland (table 1.5).<sup>23</sup>



Table 1.5: EU standardised case definitions for notification of a TB case<sup>23</sup>**TUBERCULOSIS (*Mycobacterium tuberculosis* complex)****Clinical Criteria**

Any person with the following two:

- Signs, symptoms and/or radiological findings consistent with active tuberculosis in any site

**AND**

- A clinician's decision to treat the patients with a full course of anti-tuberculosis therapy

**OR**

- A case discovered post-mortem with pathological findings consistent with active tuberculosis that would have indicated anti-tuberculosis antibiotic treatment had the patient been diagnosed before dying.

**Laboratory Criteria****Laboratory criteria for case confirmation**

At least one of the following two:

- Isolation of *Mycobacterium tuberculosis* complex (excluding *Mycobacterium bovis*-BCG) from a clinical specimen
- Detection of *M. tuberculosis* complex nucleic acid in a clinical specimen **AND** positive microscopy for acid-fast bacilli or equivalent fluorescent staining bacilli on light microscopy.

**Laboratory criteria for a probable case**

At least one of the following three:

- Microscopy for acid-fast bacilli or equivalent fluorescent staining bacilli on light microscopy
- Detection of *M. tuberculosis* complex nucleic acid in a clinical specimen
- Histological appearance of a granuloma.

**Epidemiological Criteria:** Not applicable.

**Case Classification**

**Possible case:** Any person meeting the clinical criteria

**Probable case:** Any person meeting the clinical criteria and the laboratory criteria for a probable case

**Confirmed case:** Any person meeting the clinical criteria and the laboratory criteria for a confirmed case.

**Recommendation:**

Case definitions specified by the European Commission should be applied for the purposes of notification and submission of data for epidemiological surveillance and disease control. These case definitions are available on the Health Protection Surveillance Centre (HPSC) website at [www.hpsc.ie/hpsc/NotifiableDiseases/CaseDefinitions/](http://www.hpsc.ie/hpsc/NotifiableDiseases/CaseDefinitions/).

Patients with pulmonary TB are further subdivided into sputum smear positive and sputum smear negative cases.

### Sputum smear positive TB

The revised WHO definition of a new sputum smear positive pulmonary TB case is based on the presence of at least one acid fast bacillus (AFB+) in at least one sputum sample in countries with a well functioning external quality assurance (EQA) system in their laboratories.<sup>24</sup>

### Sputum smear negative TB

A sputum smear negative patient has:

- At least three negative sputum smears (including at least one early morning specimen)
- Chest X-ray findings consistent with TB and
- Lack of response to a trial of broad-spectrum antimicrobial agents (**Note:** because the fluoroquinolones are active against *M. tuberculosis* complex and thus may cause transient improvement in persons with TB, they should be avoided).<sup>25</sup>

It should be noted that in making a diagnosis of sputum smear negative TB based on the above three criteria, a clinician who decides to treat with a full course of anti-TB chemotherapy should report this as a case of sputum smear negative pulmonary TB to the MOH. Although the results of culture may not be available until after a decision to begin treatment has to be made, treatment should be stopped subsequently if cultures are negative, the patient has not responded clinically and the clinician has sought other evidence in pursuing the differential diagnosis.<sup>25</sup>

### TB outbreaks

The following are examples of situations to report:

1. An unexpected increase (significantly above baseline) of newly identified confirmed or suspected cases in any setting
2. Two or more TB cases on treatment from a congregate (e.g. school or prison) or high risk setting e.g. HIV positive individuals occurring within a relatively short space of time
3. Three or more TB cases on treatment in a household
4. Three or more cases on treatment from a community setting (outside a household) occurring within a relatively short period of time who may be related
5. Two or more cases of MDR-TB or XDR-TB that may be related and occur outside a household.

When assessing whether a cluster of TB cases represents an outbreak, indicators to look for include:

- Epidemiological links between cases
- Similar unique characteristics among cases
- Matching drug resistance patterns of isolates
- Matching DNA fingerprint patterns of isolates.

Outbreaks of particular concern are MDR-TB or XDR-TB outbreaks, outbreaks among immunocompromised populations, children or other vulnerable groups.

## 1.5 Notification Procedures

Once a diagnosis of TB is either laboratory confirmed or strongly suspected on clinical grounds, the MOH should be notified by the clinical director of a diagnostic laboratory and/or clinician as soon as possible and ideally at the time of diagnosis (appendix 2). Infection prevention and control staff or other laboratory medical or scientific staff to whom the function of providing notification of infectious diseases has been delegated by the clinician/clinical director of the laboratory may notify the case (s) also if authorised to do so by the clinician. Notification should be made using the infectious disease notification form available at: [www.hpsc.ie/hpsc/NotifiableDiseases/NotificationForms/](http://www.hpsc.ie/hpsc/NotifiableDiseases/NotificationForms/).

Once notified, the MOH or designated medical officer, usually a Consultant in Public Health Medicine (CPHM) shall inform the designated members of the contact tracing team of cases of new and re-treatment TB as they occur. Immediate notification enables prompt contact tracing and facilitates successful contact investigation. The practitioner notifying presumed cases of TB is also required to inform the MOH or designated medical officer if the diagnosis subsequently proves not to be TB. If the case of TB is from another HSE area, the MOH or designated medical officer should notify his/her opposite number in the relevant HSE area. The responsible MOH is required to report possible, probable and confirmed cases of TB to the Health Protection Surveillance Centre (HPSC).

**Recommendation:**

Once a diagnosis of TB is either laboratory confirmed or strongly suspected on clinical grounds, the MOH should be notified by the clinical director of the laboratory and/or clinician as soon as possible and ideally at the time of diagnosis.

In the case of unusual incidences or clusters of TB cases, they should be notified by the MOH or designated medical officer to the HPSC as they occur.<sup>21</sup>

**Recommendation:**

Reporting of outbreaks of TB is a mandatory requirement.

Following notification of a case of TB, the MOH or designated medical officer shall seek further clinical data on the case as an aid to contact tracing and detailed TB surveillance. The national TB notification form is available at: <http://www.hpsc.ie/hpsc/AZ/VaccinePreventable/TuberculosisTB/SurveillanceForms/> (appendix 3).

**Enhanced surveillance**

The specific objectives of surveillance are to:

- Support local management of identified cases, contacts and screening programmes
- To monitor the incidence and distribution of TB disease at both local and national level
- To identify risk factors to support interventions aimed at the prevention of TB
- To monitor the process and outcome of disease control and screening programmes so that improvements can be introduced
- To monitor antibiotic susceptibility to *M. tuberculosis* and *M. bovis* to guide appropriate use of antibiotics.

Notification of cases of TB forms the basis of surveillance and public health follow-up of cases and contacts. The early identification of cases of TB is essential to the effective management and control of the disease.

National epidemiological data on TB have been collated by the HPSC, formerly the National Disease Surveillance Centre (NDSC) since 1998. Prior to the establishment of HPSC, limited epidemiological data had been collated for TB in Ireland. An enhanced national TB surveillance system (NTBSS) became operational in 2000, following consultation with the eight health boards and the National Tuberculosis Advisory Committee. The NTBSS is based on the minimum dataset required to be reported by Ireland to EuroTB,<sup>10</sup> the European TB surveillance centre located at the European Centre for Disease Prevention and Control (ECDC), which collates national TB data within Europe and contributes epidemiological data to the WHO global TB control programme for Europe.

TB notification forms summarise all available clinical, microbiological, histological and epidemiological data (see appendix 3). Forms collated in regional departments of public health are anonymised and submitted electronically to HPSC for the production of reports on a quarterly basis. HSE areas make quarterly returns to HPSC of TB notifications (which consist of disaggregate data on new TB notifications) in their area six weeks after the end of each quarter. Data in quarterly reports are provisional until a process of validation has been completed at the end of that notification year. At the end of each year and early into the following year, information on all cases is updated and validated by each HSE area to include outcome data. Annual reports are generally produced eighteen months after the end of the notification year to allow for the collection of complete treatment outcome information. Annual national TB reports are accessible at: [www.hpsc.ie/hpsc/A-Z/VaccinePreventable/TuberculosisTB/Publications/AnnualReportsontheEpidemiologyofTBinIreland/](http://www.hpsc.ie/hpsc/A-Z/VaccinePreventable/TuberculosisTB/Publications/AnnualReportsontheEpidemiologyofTBinIreland/).

It is proposed to incorporate the enhanced TB surveillance system into the Computerised Infectious Disease Reporting (CIDR) system in the future. CIDR is an integrated surveillance system providing laboratory and clinical data. This should lead to more complete and timely data on the epidemiology of TB in Ireland.

**Recommendation:**

Detailed surveillance information should be recorded on the national tuberculosis notification database (NTBSS) and submitted to HPSC. It is planned that TB surveillance will be included in the Computerised Infectious Disease Reporting (CIDR) system.

## 1.6 *Mycobacterium Bovis*

TB due to *M. bovis* infection accounts for a very small proportion of cases of locally acquired TB in Ireland and consequently there is no evidence that zoonotic TB is a major public health problem in Ireland at present. However, when it does occur, infection with *M. bovis* may produce a clinical picture indistinguishable from that caused by other members of the *M. tuberculosis* complex. The individual species within the complex cannot be distinguished from each other based on microscopic examination of stained tissues or other clinical specimens.

The majority of individuals are thought to have a very low risk of *M. bovis* infection but possible occupational exposures may occur in those in close contact with animals or animal carcasses such as farmers, veterinary practitioners and others who work with animals or their products or those consuming home produce such as unpasteurised milk on farms. Certain groups of people such as the very young, elderly people or people with suppressed immune systems may be particularly vulnerable.

Programmes for the early detection and elimination of *M. bovis*-infected cattle represent a safeguard against exposures and in particular milk borne transmission of *M. bovis*, by ensuring the elimination of infected animals from milk-producing herds. All cattle herds are required to have an annual test for TB on the animals within the herd, each year approximately 10 million animal tests are carried out (personal communication, Department of Agriculture, Fisheries and Food). This level of testing ensures that there is little opportunity for the development of advanced cases of TB in cattle, thus minimising the possible source of infection for humans. The risk from occupational and food borne infection is therefore now very low. The risk is further reduced in Ireland by the present requirement that all milk intended for sale and supply for human consumption, with the exception of milk for preparation of certain types of cheese, must be pasteurised.

Unquestionably, contaminated milk was a major source of human infection with *M. bovis* until recent decades. As the principal route of human food borne infection with *M. bovis* is via ingestion rather than by inhalation, infection of the tonsils, cervical lymph nodes, gastrointestinal tract, genitourinary infection and TB of the bones and joints has been considered to be associated with *M. bovis*.<sup>26</sup> Over 75% of those infected are now aged fifty years and over, suggesting the reactivation of latent infection acquired early in

life (personal communication, HPSC). Although there is much less complete information available for other animal species, infection with *M. bovis* does occur in other species of domestic and wild animals including goats, badgers and deer.<sup>26</sup>

## 1.7 Non-Tuberculous Mycobacteria

Species of mycobacteria other than *M. tuberculosis* complex are pathogenic to humans. Often the clinical presentation of non-tuberculous mycobacteria (NTM) is similar to that caused by *M. tuberculosis* complex. In the past, NTM was not often responsible for clinical disease but infections due to NTM are increasingly observed in immunocompromised individuals. A study in the Southwest of Ireland reported that the mean incidence of NTM has risen since 1995 (0.4/100,000 population), principally due to pulmonary *Mycobacterium avium intracellulare* complex (MAC).<sup>27</sup>

## 2. Methods of Tuberculosis Screening

Diagnosis of active or latent TB involves a number of tests. There is no gold standard for determining whether a person is infected with *M. tuberculosis* but in practice the tuberculin skin test (TST) is the standard method used. Recently immunological blood tests i.e. interferon-gamma release assays (IGRA) have been developed to aid diagnosis. However, neither the TST nor IGRA can be used to distinguish latent infection from active disease.

### 2.1 Definition of Active TB

Active TB is defined as infection with mycobacteria of the *M. tuberculosis* complex, where mycobacteria are growing and causing symptoms and signs of disease. This is distinct from LTBI where mycobacteria are present but are inactive and not causing symptoms of disease. The diagnosis of active TB is made most often on the basis of positive bacteriology but in approximately 15%-25% of cases on the basis of appropriate clinical and/or radiological and/or pathological presentation as well as treatment response (see chapters 4 and 5).

### 2.2 Definition of Latent TB Infection

A person with LTBI usually has a positive TST or IGRA test but has no physical findings of TB disease and the chest X-ray is normal or only reveals evidence of healed infection i.e. granulomas or calcification in the lung, hilar lymph nodes or both. Persons with LTBI are asymptomatic and are not infectious (see table 3.1, chapter 3).

The three screening methods discussed in this chapter are:

1. Tuberculin skin test
2. Interferon-Gamma Release Assays (IGRA)
3. Chest X-ray.

### 2.3 Tuberculin Skin Test

The main tool to diagnose TB infection is the TST. It is also used as an aid to the diagnosis of active TB disease. In Ireland, the Mantoux test is the TST used. This test consists of the intradermal injection of a small amount of purified protein derived from *Mycobacterium tuberculosis* bacteria (PPD). The local skin reaction to PPD is used to assess an individual's sensitivity to the tuberculin protein. In a person who has cell-mediated immunity to these tuberculin antigens, a cell-mediated delayed hypersensitivity reaction will occur within 48 to 72 hours. The reaction will cause localised swelling and will be manifest as induration of the skin at the injection site. The greater the reaction, the more likely it is that an individual is infected or has active TB disease. In persons who are newly exposed and become infected with TB, this cell-mediated reaction to tuberculin will develop 3 to 8 weeks later.<sup>28</sup>

WHO recommends that the Mantoux 2TU/0.1ml tuberculin PPD should be used and this is the standard test recommended for use in Ireland. A comparative study undertaken by Comstock *et al* revealed that 2TU has almost identical sensitivity to the use of 5TU for tuberculin testing although specificity was slightly lower with 2TU.<sup>29</sup> However, it was concluded that the results of testing with 2TU and 5TU were sufficiently similar to deem them biologically equivalent.<sup>29</sup>

#### **Recommendation:**

The standard tuberculin skin test (TST) recommended for use in Ireland is the Mantoux 2TU/0.1ml tuberculin PPD. Mantoux 10TU/0.1ml tuberculin PPD is not recommended for use in Ireland.

In general testing for LTBI is indicated when the risk of development of disease is increased if the patient is infected.

**There are three general situations when the disease risk is increased:**

- **Recent infection:** most commonly contacts of a patient with a recent diagnosis of infectious TB disease **or** immigrants or persons from countries of high TB incidence ( $\geq 40$  per 100,000 TB cases notified per year) within 2 years of arrival in Ireland
- **Increased risk of reactivation due to impaired immunity:** This includes HIV infection and immunosuppressed conditions e.g. diabetes, renal failure, immunosuppressant medications and pulmonary silicosis
- **When there is radiological evidence of old, healed inactive TB but no prior treatment.**<sup>30</sup>

**The following persons should not receive a TST:**

- Those who had 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 or severe reactions
- Those with documented active TB disease or a well-documented history of adequate treatment for TB infection or disease in the past. In such patients the test is of no clinical utility.
- Those with major viral infections e.g. varicella (chickenpox), measles, mumps, infectious mononucleosis **BUT** not the common cold or minor viral infections
- Those who received MMR vaccines in the previous four weeks as this has been shown to increase the likelihood of false negative TST results. No data are available in relation to the effect of other live virus vaccines e.g. varicella or yellow fever but it would be prudent to follow the same four week guidance.<sup>30</sup>

**The following persons can receive a TST:**

- Those with a common cold
- Those who are pregnant or breastfeeding
- Those immunised with any vaccine on the same day
- Those immunised within the previous 4 weeks with inactivated vaccines
- Those who give a history of a positive TST reaction (other than blistering) that is not documented
- Those taking low doses of systemic corticosteroids, < 15mg prednisolone (or equivalent) daily. It generally takes a steroid dose equivalent to  $\geq 15$ mg prednisolone daily for 2-4 weeks to suppress tuberculin reactivity.<sup>30,31</sup>

**Administration of the Mantoux test**

In all cases, the Mantoux test should be administered intradermally. This is also sometimes referred to as intracutaneous administration. The Mantoux test is normally performed on the flexor surface of the left forearm at the junction of the upper third and the lower two-thirds. If the skin is visibly dirty, it should be washed with soap and water. The Mantoux test is performed using a 0.1ml tuberculin syringe or alternatively a 1ml graduated syringe fitted with a short bevel 26G (0.45x10mm) needle. A separate syringe and needle must be used for each subject to prevent cross-infection. Then 0.1ml of PPD should be drawn into the tuberculin syringe and the 25G or 26G short-bevelled needle attached to give the injection. The needle should be firmly attached and the intradermal injection administered with the bevel facing uppermost.

The operator stretches the skin between the thumb and forefinger of one hand and with the other hand slowly inserts the needle with the bevel upwards for about 5mm into the superficial layers of the dermis almost parallel to the surface. The needle can usually be seen through the epidermis. A correctly given intradermal injection results in a tense blanched raised bleb and considerable resistance is felt when the fluid is being injected. A bleb is typically of 7mm diameter following a 0.1ml intradermal injection. If little resistance is felt when injecting and a diffuse swelling occurs rather than a tense bleb the needle is too deep and should be withdrawn and reinserted intradermally on the opposite forearm or on the same forearm at a site at least 10cm away from the previous injection. Do not cover the site with a bandage. Inform the patient that he or she should not scratch the site but may perform all normal activities including showering or bathing. Record the following details: a) date of injection; b) dose (2TU, 0.1ml); c) manufacturer; d) lot number; e) expiry date; f) site of injection and g) person who administered the injection.

Detailed instructions on performing a Mantoux test are available on the National Immunisation Office website at [www.immunisation.ie/en/Downloads/PDFFile\\_14983\\_en.pdf](http://www.immunisation.ie/en/Downloads/PDFFile_14983_en.pdf).

Similar instructions are also available on the Staten Serum Institut (Denmark) website at [www.ssi.dk/sw11710.asp](http://www.ssi.dk/sw11710.asp).

#### **Recommendation:**

In all cases, the TST (Mantoux test) should be administered intradermally.

#### **Storage**

Care should be taken to store PPD Mantoux tests and BCG vaccine in separate areas of the fridge to ensure the correct product is administered. If using the vial of Tuberculin PPD (Mantoux) on more than one patient, it is recommended that once the vial is in use, it should be used immediately. Otherwise it should not be in use for longer than 24 hours and stored between 2 and 8°C as per Tuberculin PPD product specific details from Statens Serum Institut (SSI) in Copenhagen.<sup>32</sup> In light of the need for the immediate use of the vial of PPD as indicated above, it is recommended that where possible a clinic should be arranged to undertake Mantoux testing on more than one person.

#### **Reading the TST (Mantoux test)**

The TST should be read by a trained health professional. Individuals without experience in reading a TST may not feel slight induration and the result may be mistakenly recorded as 0mm.

TST interpretation depends on a number of factors as follows:

- Measurement of the induration in millimetres
- The person's risk of being infected with TB and of progression to disease if infected
- Prior BCG vaccination or exposure to non-tuberculous mycobacteria (NTM) (section 2.4)
- Conditions resulting in a false negative result (section 2.4).

The results should be read within 48 to 72 hours of receiving the test but a valid reading can usually be obtained up to 96 hours later. The transverse diameter of the area of induration and not the erythema at the injection site is measured with a ruler and the result recorded using millimetres. As several factors affect interpretation of the test, the size of the induration should be recorded and **NOT** just as a positive or negative result.

It is recommended that the following items are recorded:

- Date the induration was read
- Measurement of the induration if any in millimetres
- Any adverse reactions e.g. blistering (can occur in 3-4% of subjects) and
- The name of the individual who read the test.

There is some variability in the time at which the test develops its maximum response. The majority of tuberculin-sensitive subjects will be positive at the recommended time of reading. The predictive value can be enhanced by using cut-off points dependent on the infection risk. The reaction to a TST is classified as positive based on the individual's risk factors (see table 2.1). In general, a negative TST result is  $\leq 5$ mm. For the interpretation of TST results in contact tracing situations and in screening of HCWs and new entrants, see chapters 8 and 9.



**Recommendation:**

The TST (Mantoux test) result should be read within 48 to 72 hours of receiving the test. The transverse diameter of the area of induration (and not the erythema at the injection site) is measured with a ruler and the result recorded using millimetres.

**Note:**

- A delay in reading the TST if the result is positive i.e. >5mm does not affect the validity of the results
- A strongly positive TST resulting from inadvertent subcutaneous administration does not affect the validity of the reading.

**Deciding that a TST is positive**

The health professional reading the TST must decide whether the test result is positive. This is based on the size using the criteria listed in table 2.1. Once a TST is considered positive the individual should be referred for a medical evaluation. There is no clinical utility in performing a TST in the future once a test that was properly performed and read is considered positive.<sup>30</sup>

**Medical evaluation**

This should include assessment of symptoms suggestive of possible active TB, risk factors for TB such as contact history or other medical illness and a chest X-ray. In the event of symptoms or an abnormal chest X-ray, sputum for acid-fast bacteria smear and culture should be taken. In persons with no evidence of TB disease, treatment of LTBI should be considered.

**Table 2.1: Categories of response to TSTs (Mantoux tests) based on individual's risk factor(s) for development of TB disease<sup>33</sup> †**

|   |   |
|---|---|
| <p><b>An induration of &gt;5mm is considered positive in:</b></p>                       | <ul style="list-style-type: none"> <li>• HIV-infected persons</li> <li>• A recent contact of a person with active TB disease</li> <li>• Persons with fibrotic changes on chest X-ray consistent with prior TB and no documented treatment</li> <li>• Persons with organ transplants and other immunosuppressed persons e.g. those taking the equivalent of <math>\geq 15\text{mg/day}</math> of prednisolone for one month or longer or taking TNF-alpha antagonists</li> <li>• Children aged &lt; 5 years (with no BCG) from a country with a high incidence of TB (<math>\geq 40/100,000</math> per year)</li> </ul>  |
| <p><b>An induration of <math>\geq 10\text{mm}</math> is considered positive in:</b></p> | <ul style="list-style-type: none"> <li>• Immigrants: Persons (aged 16 to 35 years) who have immigrated within the past 5 years from countries with a very high TB incidence (<math>&gt;500/100,000</math>) and children aged 5 to 15 years who have immigrated (within the past 5 years) from countries with TB incidence <math>\geq 40/100,000</math> per year</li> <li>• All children &lt;5 years of age or children/adolescents exposed to adults in high-risk categories*</li> <li>• Injecting drug users</li> <li>• Residents or employees of high risk congregate settings e.g. prisons, homeless shelters</li> <li>• Mycobacterial laboratory personnel</li> <li>• Persons with clinical conditions which place them at increased risk of progression to active TB e.g. silicosis, diabetes mellitus</li> <li>• HCWs from high incidence countries (<math>\geq 40</math> cases per 100,000 population per year)<sup>†</sup> ‡</li> </ul> |
| <p><b>An induration of <math>\geq 15\text{mm}</math> is considered positive in:</b></p> | <ul style="list-style-type: none"> <li>• Irish HCWs and HCWs from countries where the annual rate of TB is <math>&lt;40</math> per 100,000<sup>§</sup></li> <li>• All others i.e. any person including persons with no known risk for TB. However, targeted skin testing programmes should only be conducted among high risk groups.</li> </ul>   |

<sup>‡</sup> In the context of serial tuberculin skin testing an increase of >5mm represents conversion and recent exposure.

\* Recent converters, HIV-positive individuals, persons receiving immunosuppressive therapy i.e. tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) antagonist, persons with evidence of old healed TB lesions on chest X-ray i.e. fibronodular disease/non-calcified fibrotic lesions (if not previously treated or if treated, and not adequately treated), foreign-born persons from countries with high TB endemicity, homeless persons, IDUs and HCWs

<sup>†</sup> Such patients should generally be referred to a respiratory or infectious disease clinician for assessment. However, an occupational medicine consultant may wish to treat these patients if appropriate protocols, audit of care and resources are in place

<sup>‡</sup> HCWs from countries of high TB incidence have a higher risk of having TB, hence the lower cut-off point for considering LTBI

<sup>§</sup> Such patients should generally be referred to a respiratory or infectious disease clinician for assessment. However, an occupational medicine consultant may wish to treat these patients if appropriate protocols, audit of care and resources are in place

## 2.4 Factors Affecting the Result of the Tuberculin Skin Test

### False positive TST results

Although for persons with LTBI and normal immune responses the test sensitivity approaches 100%,<sup>34</sup> false positive results can occur because of the sensitising effect on the immune system of either prior BCG vaccination or NTM.

BCG and NTM have important effects on the predictive value of the TST when the expected prevalence of true LTBI is low such as in Western Europe or North America. In contrast, when the expected prevalence of tuberculous infection is high, such as close contacts of a smear positive pulmonary case or persons from high TB incidence countries, then the predictive value of a positive TST result is high. A study by Menzies *et al* in 1992 showed that BCG leading to a false positive TST was more common among participants from low-incidence countries compared to those from countries of high endemicity for TB.<sup>35</sup>

Menzies and Doherty<sup>36</sup> state that although all recipients of BCG will have positive tuberculin reactions within two months of vaccination with BCG, these reactions will wane over time. Studies by Menzies *et al* (1992, 1994) indicate that for those vaccinated with BCG in infancy, only 3-5% manifest a positive TST when tested 5 years after the vaccination.<sup>37;38</sup> This may reflect the relative immaturity of the immune system in infants although protective efficacy if anything is higher.<sup>39;40</sup> Of those vaccinated at an older age, tuberculin reactions are larger and wane more slowly. In this older cohort, on average 30-35% will have BCG-related positive TST results even after an interval of more than 10 to 15 years.<sup>37-39;41-43</sup> Post-BCG vaccination can account for up to 10mm of induration, and there is no published evidence to suggest that this sensitivity correlates with immunological protection.<sup>44-47</sup>

#### Note:

Care should be taken when attributing BCG vaccination as a cause of a positive TST if:<sup>30</sup>

- BCG vaccine was given in infancy and the person tested is now aged 10 years or older
- There is a high probability of TB infection i.e. close contacts of an infectious TB case or immigrants (including HCWs) from countries with high annual TB incidence (see table 2.1)
- There is a high risk of progression from TB infection to disease (see table 3.2)
- Any TST  $\geq 15$ mm induration should not be attributed to BCG vaccination.

#### False negative TST results

The reaction to tuberculin protein may be suppressed by the following:

- Cutaneous anergy (anergy is the inability to react to skin tests because of a weakened immune system)
- Recent TB infection (within eight to 10 weeks of exposure)
- Old TB infection
- Age: very young age (less than three months old) and the elderly
- Major viral infections e.g. varicella (chickenpox), measles, mumps, infectious mononucleosis
- Recent live viral vaccination e.g. measles, mumps, rubella, varicella and yellow fever (tuberculin testing should not be undertaken within four weeks of having received a live viral vaccine)
- Malnutrition, particularly when there has been recent weight loss<sup>48</sup>
- Extensive TB disease (pulmonary or miliary) can itself also temporarily depress immunity and can lead to a paradoxically negative TST<sup>49</sup>
- Other illnesses e.g. malignancies especially lymphoma, renal failure, sarcoidosis, diabetes mellitus
- Immunosuppression due to disease including HIV infection
- Immunosuppression due to treatment including cytotoxics, corticosteroid therapy ( $\geq 15$ mg prednisolone daily for four weeks or longer), transplant therapy and infliximab
- Incorrect method of TST administration.<sup>50</sup> This should be avoidable.
- Incorrect interpretation of the TST reaction
- Insufficient dose of PPD
- Inactive tuberculin PPD: tuberculin PPD vials must be used within 24 hours of opening.

Subjects who have a negative test but who may have had one of the major viral infections (excluding the common cold) outlined above at the time of testing or at the time of reading the test should be re-tested two to three weeks after clinical recovery before being given BCG.

## 2.5 Conversion and Boosting

A newly positive TST after an initial negative test result and an increase of  $> 5$ mm represents a true biological phenomenon in two consecutively performed TSTs. This could be due to conversion or boosting.

## Conversion

Conversion is defined as the development of new hypersensitivity to mycobacteria following exposure to new TB or NTM infection including BCG vaccination.<sup>36</sup> A conversion is presumptive evidence of new *M. tuberculosis* infection and poses an increased risk for progression to TB disease indicating a change from being uninfected to infected.<sup>51</sup>

Conversion is more likely in a previously tuberculin negative individual or in a situation of high risk of exposure to TB such as in a close contact of a sputum smear positive index case or in an outbreak investigation. If a person who has a documented negative TST result within the previous 12 months is exposed to an infectious TB case, then only one TST (Mantoux test) is necessary to detect conversion. Persons who demonstrate TST conversion should be investigated for active disease or LTBI.<sup>36</sup>

## Boosting

Boosting is defined as the recall of non-specific immunity in the absence of new infection and is mainly seen in adults and older persons.<sup>36</sup> When non-specific or remote sensitivity to tuberculin (PPD in the skin test) wanes or disappears with time, subsequent tuberculin skin tests can restore the sensitivity.<sup>51</sup> An initially limited reaction size is followed by a larger reaction size on a later test, which can be confused with a conversion or a recent *M. tuberculosis* infection. If an increase in reaction size is noted after one to three weeks and there has been little or no possibility of exposure then it is likely that the increase is due to boosting.<sup>51</sup> Boosting is best distinguished from conversion on clinical grounds.

## Two-step testing

Two-step testing is used to distinguish new infections from boosted reactions in infection control and prevention surveillance programmes. This method is not recommended for testing contacts of infectious TB cases. A contact whose second test result is positive after an initial negative result should be classified as recently infected.<sup>51</sup>

In persons who may be liable to boosting in whom it is important to establish a true baseline TST response, a second TST can be administered one to three weeks after the first. The second test should be done on the other arm; repeat testing at one site may alter the reactivity either by hypo- or more often hyper-sensitising the skin and a changed response may only reflect local changes in skin sensitivity. The result of the second boosted reaction is the correct result, that is the result which should be used for decision making and future comparison. This two-step approach can reduce the likelihood that a boosted reaction to a subsequent TST will be misinterpreted as recent infection.

Two-step testing is indicated in the following situations when the first TST (Mantoux test) in the two-step series is negative:

- (a) Where serial tuberculin tests are to be used as in HCWs; and
- (b) When tuberculin testing those with previous BCG vaccination, *this does not apply to contacts of infectious cases who will already have been re-sensitised when transmission has occurred.* <sup>33;52</sup>

If the second test is positive (table 2.1), it is recommended that the individual is referred for medical evaluation including a chest X-ray and they should not undergo further tuberculin testing. If the chest X-ray is normal and there are no associated factors that increase the risk of TB reactivation, then preventive therapy is not indicated.

The two-step test needs to be performed **once** only if properly performed and documented. It never needs to be repeated. Any subsequent TST can be one step regardless of how long it has been since the last TST.<sup>30</sup>

## 2.6 Interferon-Gamma Release Assays (IGRA)

In recent years in-vitro immunological assays called IGRA have been developed to diagnose TB infection. These assays involve a single blood test and operate on the basis that T-cells which have been in previous contact with TB antigens release high levels of the cytokine interferon gamma when they are re-exposed to the same mycobacterial antigens.<sup>53</sup> This reaction is specific to a small number of mycobacteria including *M. tuberculosis* but not to the BCG vaccine strain of *M. bovis* and consequently are less influenced by prior BCG vaccination than TSTs. The amount of interferon gamma or the number of *M. tuberculosis* sensitive T-cells in the blood is then estimated by the tests. T-cells which have not been in contact with the bacterium will not release cytokine.<sup>54</sup>

There are currently two IGRA assays commercially available for use: QuantiFERON-TB Gold® In –Tube (Cellestis Ltd., Australia) and T-SPOT.TB (Oxford Immunotec) (see chapter 4).

QuantiFERON-TB Gold® In –Tube assay measures the release of interferon gamma in whole blood in response to stimulation by ESAT 6 and CFP 10. In the T-SPOT.TB test, individual activated ESAT 6, CFP 10 and TB 7.7 specific T-cells are enumerated using the ELISPOT methodology. It has been suggested that the T-SPOT.TB test may be more sensitive than QuantiFERON-TB Gold® In –Tube in children under five years of age and in immunocompromised patients.<sup>55</sup>

### International guidelines on the use of IGRA

In 2005, CDC recommended that the Food and Drug Administration (FDA)-approved version of QuantiFERON-TB Gold® In –Tube assay may be used in place of the TST for all indications including contact tracing and serial testing of healthcare workers.<sup>56;57</sup> In 2007, an updated version QuantiFERON-TB Gold® In –Tube was approved for this function. In 2006, the UK National Institute for Health and Clinical Excellence (NICE) guidelines recommended a hybrid two-step approach for LTBI diagnosis; initial screening with TST and subsequent IGRA testing (if available) for those who are TST positive (or in whom TST may be unreliable) to confirm TST results.<sup>26</sup>

Evidence from international studies suggests that IGRA have a higher specificity than tuberculin skin tests and have less potential for false positive results.<sup>26;58;59</sup> Both IGRA are very specific (93% to 99%) and are unaffected by prior BCG. While several QuantiFeron studies have consistently shown very high specificity, data are limited on the specificity of the commercial T-SPOT.TB assay.<sup>60</sup> A number of systematic reviews have been published which support this view.<sup>54</sup> The results of a meta-analysis carried out in 2007 however, is not so clear cut. While both IGRA tests were more specific than TSTs when applied to all patients, the difference between IGRA and TST disappeared when patients known to have BCG vaccine were excluded. Both IGRA tests were more sensitive than TST with the T-SPOT.TB assay displaying higher sensitivity (~90%) compared to the QuantiFERON-TB Gold® (approximately 75% to 80%).<sup>60 61</sup>

Use of IGRA also showed little evidence of being affected by prior BCG vaccination and stronger correlation with exposure categories than did tuberculin skin tests. This was shown in low prevalence groups, in household contacts and in outbreak situations.<sup>62;63</sup> A recent study on the use of TST versus IGRA for the diagnosis of LTBI in a HCW population in Germany concluded that TST overestimates the prevalence of LTBI in HCWs and recommended that a positive TST result should be verified by IGRA. However, they also concluded that more studies are required in order to confirm that IGRA are more sensitive in diagnosing LTBI than the TST.<sup>64</sup> In conclusion, from the evidence, it is currently justifiable to assume that IGRA are at least as sensitive as TST and more specific in populations that include previously BCG vaccinated individuals.

The results of a limited number of studies, published to date, assessing the predictive value of IGRA are inconclusive. A recent German study found that 14.6% of IGRA positive individuals developed active TB compared to 5.6% of TST positive contacts.<sup>65</sup>

## Recommendations for the use of IGRA

IGRA use should be considered in conjunction with a clinical and public health risk assessment. If available, IGRA can be used for the diagnosis of LTBI in the following settings.

### Contact tracing (see chapter 8)

- The TST (Mantoux test) should be used as the first line test for the diagnosis of LTBI in contacts of infectious TB cases and others considered to be at high risk of LTBI. Those with positive TST results should be considered for IGRA testing, if available (see figures 8.1 & 8.2)
- IGRA may be considered on a case by case basis in adults and children as per the general recommendations in section 8.7.<sup>60</sup>

### Pre-placement screening of HCWs

In new HCWs who are asymptomatic for TB and have a low pre-test probability of LTBI, IGRA, if available, can be used to confirm a positive TST result. Persons with a positive IGRA should be considered for treatment of LTBI (see chapter 9).

### New entrant screening

Although the use of IGRA in screening new entrants has not clearly been demonstrated to date, the use of IGRA can be considered:

- As a confirmatory test in those individuals with a positive TST
- In screening new entrants with concomitant conditions that increase the individual's risk of reactivation of LTBI (chapter 9).

### For individuals commencing on immunosuppressive therapy, i.e. tumour necrosis factor- $\alpha$ (TNF- $\alpha$ ) antagonists.

- IGRA, if available, can be used as an adjunct to screening in addition to a medical history, chest X-ray and TST.

### IGRA, if available, can be considered as the sole test for LTBI in the situation outlined below:

- When screening large numbers of individuals as part of a public health investigation where logistic issues make repeated visits for sequential testing impractical.<sup>54</sup>

#### Recommendation:

For contact tracing, the TST (Mantoux test) should be used as the first line test for the diagnosis of LTBI in contacts of infectious TB cases and others considered to be at high risk of LTBI. Those with positive TST results should be considered for IGRA testing (see figures 8.1 & 8.2). IGRA may be considered on a case by case basis in adults and children as per the general recommendations in section 8.7.<sup>60</sup>

### IGRA performance in immunocompromised populations

There are few studies on the sensitivity and specificity of IGRA in immunocompromised populations. TST sensitivity is modest to poor in these populations. The sensitivity of T-SPOT.TB appears to be maintained in immunocompromised individuals and appears to have a higher rate of positivity than TST. QuantiFeron studies have not demonstrated this.<sup>60</sup> In the immunocompromised person (adult or child), the TST should be the initial test used to detect LTBI. If the TST is positive, the person should be considered to have LTBI. However, in light of the known problem of false negative TST results in immunocompromised populations, a clinician still concerned about the possibility of LTBI in an immunocompromised person with an initial negative TST result may perform an IGRA test. If the IGRA test is positive, the person might be considered to have LTBI. If the IGRA result is indeterminate, the test should be repeated to rule out laboratory error. If the second test is negative, the clinician should suspect anergy and rely on the person's history, clinical

features and other laboratory results to make a decision on the likelihood of LTBI. Either IGRA test may be used, however, there is evidence that the T-SPOT.TB assay may be more sensitive than the QuantiFERON test and this will be especially relevant for immunocompromised populations.<sup>60</sup>

While the approach of accepting either test result (TST or IGRA) as positive will improve the sensitivity of detecting LTBI in immunocompromised populations, there are no data supporting the efficacy of preventive therapy in TST negative but IGRA positive individuals. Thus the clinician must weigh the potential benefit of detecting more persons with positive test results against the lack of evidence for the benefit of preventive therapy in such persons.

### Potential boosting of IGRA by previous TST

Previous guidelines by CDC state that the results of IGRA are not influenced by previous TST.<sup>51</sup> Studies by Leyten *et al*<sup>66</sup> and Richeldi *et al*<sup>67</sup> report no boosting phenomenon following the evaluation of T-SPOT.TB assay. Some studies however, have reported boosting of the QuantiFERON-TB Gold® In-Tube assay results when taken 6 to 8 weeks after a TST.<sup>68;69</sup> Although these studies have limitations, there are animal studies suggesting that TST might boost subsequent measurements of interferon gamma.<sup>70;71</sup> This issue requires further investigation. Due to these concerns, it is recommended by both the HPA and the Public Health Agency of Canada that the IGRA test should be undertaken at the time of reading the Mantoux results.<sup>54;60</sup>

### Serial testing

There are insufficient data to inform recommendations on serial testing with IGRA. Studies of serial testing of individuals with either LTBI or TB disease do not show a clear pattern. In some studies, IGRA responses increased,<sup>72</sup> decreased<sup>73</sup> or showed no change.<sup>74</sup> Further studies are needed.

### Diagnosis of active TB disease

IGRA should not be used in the first instance for the diagnosis of active TB disease in either adults or children and should not replace the appropriate microbiological and molecular investigation.

Culture remains the gold standard for the diagnosis of TB disease as it provides a definitive diagnosis and permits the identification of drug resistance. IGRA have no benefits in known pulmonary TB cases with bacteriological/molecular confirmation.

#### **Recommendation:**

IGRA tests should not be used in the first instance for the diagnosis of active TB disease. Appropriate microbiological and molecular investigations remain the gold standard.

However, in some patients (adults and children) with TB, it is not possible to isolate *M. tuberculosis* from clinical specimens or to obtain clinical specimens, despite the individual having symptoms, signs and/or radiological changes consistent with the diagnosis of TB. In these circumstances, a positive IGRA may increase confidence in the diagnosis. In those with symptoms or signs compatible with but not indicative of the diagnosis of TB, a positive IGRA test may suggest more strongly the possibility of a TB diagnosis.<sup>54</sup> However, the final decision should be based on clinical judgment.<sup>54 60</sup> IGRA tests cannot distinguish between active TB and LTBI.<sup>60</sup>

#### *Advantages of IGRA tests*

- It only requires one visit from the patient compared to two visits for a TST
- IGRA demonstrate improved specificity over the TST i.e. the proportion identified as disease free and the reduced cross-reactivity with BCG vaccine and most NTM means that persons are less

likely to have unnecessary treatment for presumed LTBI if they are correctly identified as disease free

- IGRA are at least as sensitive as the TST.<sup>75</sup>

#### *Limitations of IGRA tests*

- Some patients may find a blood test less acceptable than an intradermal test
- The TST is cheaper than IGRA
- Logistical issues may arise, as the laboratory must receive the blood sample within 8 hours for the T-SPOT.TB test and within 16 hours for QuantiFERON-TB Gold® In-Tube assay.<sup>75</sup>

Recommendations on IGRA use are based on the best currently available scientific evidence and medical practice. Over time, if new evidence emerges in relation to IGRA, this will be reviewed by the committee and the recommendations revised if deemed appropriate.



## 2.7 Interpretation of TST and IGRA Results

Use of the following table (from the Public Health Agency of Canada)<sup>60</sup> is recommended for the interpretation of TST and IGRA results:

**Table 2.2: Interpretation of results when both TST and IGRA results are available**

| Risk of developing TB disease if infected with <i>M. tuberculosis</i> ** |                             |  |   |                             |                                     |   |
|--|-----------------------------|--|---|-----------------------------|-------------------------------------|---|
|  | High                        |  |   | Low                         |                                     |   |
|  | IGRA positive               | IGRA negative                                    | IGRA indeterminate                                    | IGRA positive               | IGRA negative                       | IGRA indeterminate                                    |
| TST +ve  | Consider treatment for LTBI |  |   | Consider treatment for LTBI | Treatment for LTBI is not necessary | Repeat IGRA test or base interpretation on TST result |
| TST -ve  | Consider treatment for LTBI | LTBI treatment not necessary if immuno-competent | Repeat IGRA test or base interpretation on TST result | Consult TB specialist       | Treatment for LTBI not necessary    |   |

Source: Updated recommendations on interferon gamma release assays for latent TB infection. Canada Communicable Disease Report, Public Health Agency of Canada (October 2008). Reproduced with the permission of the Minister of Public Works and Government Services Canada, 2009. Available at [www.phac-aspc.gc.ca/publicat/ccdr-rmtc/08pdf/acs-6.pdf](http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/08pdf/acs-6.pdf).

\*\* See table 3.3 in chapter 3 for risk factors for the development of active TB disease among persons with LTBI

### Note:

- This table is offered in the context of the IGRA recommendations above and is not meant to be a comprehensive guide to the management of LTBI. See chapter 3 for the management of LTBI and for groups at risk of developing active TB disease (table 3.3)
- IGRA are more specific in populations that include previously BCG vaccinated individuals and hence would be very useful in the Irish context as it would lead to a decrease in false positive results.

## 2.8 Chest X-Ray

### Chest X-Ray for the diagnosis of LTBI

Chest radiography is not usually considered a tool to diagnose LTBI. Its main role is in the diagnosis of TB disease. However, it is quite common that a chest X-ray is done for some other reason and radiographic abnormalities consistent with previous TB infection are detected. Individuals are considered to have inactive TB or LTBI when their chest X-ray shows certain abnormalities consistent with TB infection AND they have a positive TST result (table 2.1). These individuals have an increased risk for reactivation and may be considered for treatment of LTBI (chapter 3).

The following radiographic findings are commonly believed to represent latent/inactive TB. While some are associated with increased risk of reactivation of active TB disease in future, others are not.

- **Granulomas that may be calcified or not:** this doubles the risk of reactivation resulting in active TB disease
- **Calcified hilar lymph nodes:** if there are no parenchymal lesions, these individuals do not appear to have an increased risk relative to those who are TST positive and have normal chest X-rays
- **Costophrenic angle blunting:** this is due to past pleural effusion or pleurisy which may have many causes. The most common cause in individuals from countries with high TB incidence and other TB-endemic areas is previous exposure to *Mycobacteria tuberculosis*. Such individuals have an increased risk of reactivation
- **Apical pleural capping:** this is not considered to be related to TB infection and is a non-specific finding that is more common in older individuals
- **Apical fibronodular disease:** this is associated with increased risk of reactivation ranging from 6 to 19 times greater than those who are TST positive and have normal chest X-rays. Individuals with more extensive abnormalities have greater risk of disease.<sup>30</sup>

Source: Canadian Tuberculosis Standards, 6<sup>th</sup> Edition. Public Health Agency of Canada, 2007. Reproduced with the permission of the Minister of Public Works and Government Services, 2009. Available at [www.phac-aspc.gc.ca/tbpc-latb/pubs/pdf/tbstand07\\_e.pdf](http://www.phac-aspc.gc.ca/tbpc-latb/pubs/pdf/tbstand07_e.pdf)

### Chest X-ray for the diagnosis of TB disease

Chest radiography [posterior-anterior (PA)]<sup>76</sup> is the usual first step in the evaluation of an individual with pulmonary symptoms. Additional views may be ordered at the clinician's discretion. It is also recommended that patients suspected of having extrapulmonary TB have a chest X-ray to rule out pulmonary disease. In all instances, if the chest X-ray results are abnormal (including pleural TB), sputum samples should be collected on 2 to 3 separate days and tested for acid fast bacilli (AFB) (smears) as well as for culture and drug susceptibilities.

The radiological findings usually seen on chest X-ray for both immunocompetent and immunosuppressed adults are outlined below. However, it is important to be aware that chest X-ray has substantial limitations in the diagnosis of pulmonary TB disease.

#### Typical findings: a triad of classic findings are seen in immunocompetent adults

**Position-** apical-posterior segments of upper lobes or superior segment of lower lobes in 90%

**Volume loss-** this is a hallmark of TB disease as a result of its destructive and fibrotic nature

**Cavitation-** this is seen at a later stage and depends upon a vigorous immune response. Therefore, it may not be seen in severely immunocompromised individuals.

#### Atypical features:

These will be seen in patients with **immunocompromising conditions** such as HIV infection, diabetes, renal failure or corticosteroid use.

**Hilar and mediastinal lymphadenopathy**, particularly in HIV-infected individuals

**Non-cavitary infiltrates** and lower lobe involvement

**Radiographic signs of complications:**

**Endobronchial spread of disease.** TB may spread via airways to the ipsilateral and contralateral lower lobes. This results in irregular poorly defined small nodular shadows which represent acinar shadows. These will slowly enlarge and coalesce to form TB pneumonia, formerly known as "galloping consumption"

**Pleural effusion** can be seen concomitant with pulmonary disease and may represent TB empyema

**Pneumothorax** can rarely occur as a result of erosion of a caseous focus into a bronchus and simultaneously into the pleural space causing a bronchopleural fistula.

Source: Canadian Tuberculosis Standards, 6<sup>th</sup> Edition. Public Health Agency of Canada, 2007. Reproduced with the permission of the Minister of Public Works and Government Services, 2009. Available at [www.phac-aspc.gc.ca/tbpc-latb/pubs/pdf/tbstand07\\_e.pdf](http://www.phac-aspc.gc.ca/tbpc-latb/pubs/pdf/tbstand07_e.pdf)

**Limitations of chest radiography**

**Sensitivity:** chest radiography will have a sensitivity of only 70% to 80% for diagnosis of active TB based on the abnormalities listed above. If any abnormality is considered it will have more than 95% sensitivity. Approximately 10% of HIV-positive persons or close contacts with active pulmonary disease will have normal X-rays

**Specificity** is relatively poor, in the range of 60% to 70%. If the sensitivity were improved (any abnormality considered possible TB), then the specificity would be much lower

**Inter reader variability:** one of the greatest problems with chest X-ray reading is that the interpretation is highly variable. There is very poor agreement between readers regarding the presence of cavitation, hilar lymphadenopathy and the likelihood of active disease.<sup>30</sup>

Source: Canadian Tuberculosis Standards, 6<sup>th</sup> Edition. Public Health Agency of Canada, 2007. Reproduced with the permission of the Minister of Public Works and Government Services, 2009. Available at [www.phac-aspc.gc.ca/tbpc-latb/pubs/pdf/tbstand07\\_e.pdf](http://www.phac-aspc.gc.ca/tbpc-latb/pubs/pdf/tbstand07_e.pdf)

**Recommendation:**

Chest X-ray is not considered the gold standard for the diagnosis of pulmonary TB.

**Chest X-ray in pregnancy**

The decision to perform a chest X-ray on women undergoing evaluation for active TB disease during pregnancy should be made on a case-by-case basis following discussion between the respiratory physician/infectious disease consultant and the consultant radiologist. A lead shield should be used if a chest X-ray is performed.<sup>77</sup>

**Chest X-ray in children**

Chest X-ray is useful in the diagnosis of TB in children. Children should have an anterior-posterior chest X-ray which should be read by a radiologist experienced in paediatric radiology. A lateral chest X-ray is taken only in certain cases and generally after consultation with a radiologist. In the majority of cases, children with pulmonary TB have chest X-ray changes suggestive of TB. The most common finding is persistent opacification in the lung in conjunction with enlarged hilar or subcarinal lymph glands. A miliary pattern of opacification in HIV-uninfected children is highly suggestive of TB. Patients with persistent

opacification which does not improve after a course of antibiotics should be investigated for TB. More than half of children with radiological pulmonary disease are asymptomatic (identified through contact tracing). The chest X-ray is typically "sicker" than the child.<sup>77</sup>

### 3. Management of Latent TB Infection

An estimated one-third of the world's population is infected with *M. tuberculosis*. Some of these infections are latent TB infections (LTBI) i.e. when the bacteria remain inactive in the body, although they can be reactivated later. People with LTBI have no symptoms and are not infectious but they usually have a positive TST or IGRA and may develop active TB disease if not treated. Approximately 10-15% of those presumed infected may eventually develop the active disease at some point in their lives. Approximately 50% of those persons who develop clinical disease do so within five years of the initial infection, with the remaining 50% reactivating over ensuing years.<sup>26</sup>

If co-morbidity develops impairing the immune system e.g. HIV infection, this risk further increases. In cases where there is a long period documented between the exposure and the development of disease, dormant bacilli are thought to remain in either the lung or other sites, which can be 'reactivated' if favourable circumstances for the organism occur. However not everyone with LTBI will develop active TB disease. The majority of exposed persons will kill off the TB bacteria and will be left only with a positive skin test as a marker of exposure.

LTBI should be treated to prevent the development of active TB disease with its associated risk of the spread of TB and the development of outbreaks. Treatment of people with LTBI, including those with HIV co-infection, effectively reduces the risk of progression to active TB disease. However, there is no accurate tool to predict which individuals with LTBI are at greatest risk of developing active disease.

A person with LTBI usually has a positive TST or IGRA but no physical findings of TB disease and the chest X-ray is normal or only reveals evidence of healed infection i.e. granulomas or calcification in the lung, hilar lymph nodes or both. Persons with LTBI can develop TB disease later in life.

The following table outlines the difference between LTBI and active TB disease (table 3.1).

**Table 3.1: Differences between LTBI and active TB disease**

| A person with latent TB infection                  | A person with active TB disease  |
|--|--|
| No symptoms  | Has symptoms which may include <ul style="list-style-type: none"> <li>• Unexplained productive cough lasting 3 weeks or more</li> <li>• Chest pain</li> <li>• Productive cough/haemoptysis</li> <li>• Weakness or fatigue</li> <li>• Weight loss</li> <li>• Anorexia</li> <li>• Chills</li> <li>• Fever</li> <li>• Night sweats</li> </ul> |
| Usually have a positive skin test or blood test    | Usually have a positive skin test of blood test  |
| Sputum is TB smear and culture negative            | May have a positive sputum smear/culture   |
| Normal chest X-ray or evidence of healed infection | May have an abnormal chest X-ray   |
| Not infectious                                     | May be infectious  |

#### 3.1 Epidemiology of LTBI

In the USA, it is estimated that approximately 10 to 15 million persons have LTBI. Particularly high rates of infection are found among the urban poor such as intravenous drug users and homeless persons.<sup>78;79</sup> The elderly also have high rates of positive TST tests attributable to the much higher risk of TB infection during

their youth. Among the foreign-born, prevalence of infection is correlated with incidence of TB in their country of origin and the age of immigration.

The contacts of active TB cases also have a high prevalence of TB infection with the risk of infection being higher if the index case is pulmonary sputum smear positive or if the contact is close. However, absolute levels of risk have been estimated in relatively few of the studies that measured the prevalence of infection in non-contacts in the general population.<sup>36</sup>

In 2005, a study was undertaken in a large Dublin teaching hospital which reviewed the screening data for two groups of persons, namely new employees (n= 2,410) and a high-risk group of HIV positive patients attending the hospital (n= 331).<sup>80</sup> Cases with positive TSTs were offered chest X-rays and if clear of TB were categorised as LTBI. The study found that 31.7% of the HCWs had LTBI while 11% of the HIV positive group had LTBI.

There is little information in relation to the prevalence of LTBI in Ireland.

### Diagnosis of LTBI

There is no gold standard test for LTBI and therefore diagnosis of active or latent TB involves a number of tests. In asymptomatic persons, exposure to and potential infection with TB can be demonstrated by a positive TST or a positive IGRA. In practice, the TST is the standard method of determining whether a person is infected with *M. tuberculosis*. Reliable administration and reading of the TST requires standardisation of procedures, training, supervision and practice. Individuals with positive skin tests are regarded as having been infected with TB. Neither TST nor IGRA can distinguish active TB disease from LTBI. Further details on the diagnosis of LTBI i.e. TSTs, IGRA and chest X-rays are outlined in chapter 2.

## 3.2 Risk Factors for LTBI

TB may be transmitted from a person with active TB disease and is much more likely to be transmitted from an active respiratory TB case. However, some individuals are more likely than others to develop TB infection when exposed. The most important risk factors for developing TB infection are the extent of the exposure and the infectivity of the source case.<sup>52</sup> Risk factors for developing TB infection are outlined as follows:

- **Closeness of contact with a source case:** close contacts at greatest risk
- **Duration of exposure to a source case:** brief exposure carries low risk
- **Sputum status of source case:** sputum smear positive case carries greatest risk
- **Extent of pulmonary disease of source case:** cavitation and cough carry greatest risk
- **Laryngeal TB:** carries the highest transmission risk
- **Age:** prevalence increases with age but incidence is highest in young children. In young children, the risk of disease after infection is up to 40%<sup>81</sup>
- **Cough frequency of source case:** higher cough frequency results in higher risk. However, cough frequency is a less statistically significant indicator of infectivity than extent of disease or bacteriological status
- **Delay in diagnosis or appropriate treatment of source case:** effective chemotherapy of the source case progressively reduces infectiousness (and therefore risk to contacts)
- **Open skin TB abscess:** dressing or irrigation of an open abscess can lead to infection
- **Residence in institutions.**

### Risk factors for LTBI progressing to active TB disease

The risk of an individual with latent TB developing active TB varies depending on a number of factors (tables 3.2 and 3.3).<sup>52</sup>

**Table 3.2: Risk factors for developing active TB disease following LTBI**

| <b>Risk factor</b>  | <b>Comment</b>   |
|---|--|
| <b>Time since infection</b>   | Risk is highest in the first two years after infection   |
| <b>Age</b>  | Inverse association: Peaks in increased risk occur in the preschool years and adolescence/early childhood  |
| <b>Dose of infection</b>  | Risk higher if the source case is smear positive; less if smear negative/culture positive; minimal if culture negative   |
| <b>Size of tuberculin reaction</b>  | The larger the reaction the greater the risk of subsequent disease. However, there is a substantial degree of variation in the extent of increased risk associated with larger tuberculin reactions (table 2.1, chapter 2) <sup>82</sup>   |
| <b>Predisposing medical conditions</b>                                    | HIV is the strongest risk factor. Other risk factors include: chronic renal failure or receiving haemodialysis, diabetes, haematological malignancy, jejeunoileal bypass or gastrectomy, silicosis, alcoholism and drug addiction including injecting drug users and solid organ transplantation |
| <b>Immunosuppressive treatment</b>  | Current or recent oral steroids, some cancer therapy, immunosuppressive drugs, receiving Tumour Necrosis Factor- $\alpha$ (TNF- $\alpha$ ) antagonist treatment  |
| <b>Immigrants who have recently arrived from a high incidence country</b> | Risk is highest in the first two years <sup>83;84</sup>  |
| <b>Body weight</b>  | There is an increased risk associated with being underweight or malnourished   |

Reproduced with kind permission from *Guidelines for tuberculosis control in New Zealand*. New Zealand Ministry of Health (2003). Available at [www.moh.govt.nz/moh.nsf/pagesmh/2046?Open](http://www.moh.govt.nz/moh.nsf/pagesmh/2046?Open)

**Table 3.3 Risk factors for the development of active TB among persons infected with *M. tuberculosis*<sup>30</sup>**

| Risk Factor   | Estimated risk of TB relative to persons with no known risk factor |
|---|--|
| <b>High Risk</b>  |  |
| AIDS  | 110-170 <sup>85</sup>  |
| HIV infection   | 50-110 <sup>6</sup>  |
| Transplantation (related to immunosuppressant therapy)                                      | 20-74 <sup>86</sup>  |
| Silicosis   | 30 <sup>87</sup>   |
| Chronic renal failure requiring haemodialysis   | 10-25 <sup>88</sup>  |
| Carcinoma of head and neck  | 16 <sup>89</sup>   |
| Recent TB infection ( $\leq 2$ years)   | 15 <sup>90</sup>   |
| Abnormal chest X-ray – fibronodular disease   | 6-19 <sup>91</sup>   |
| <b>Increased risk</b>   |  |
| Treatment with glucocorticoids  | 4.9 <sup>92</sup>  |
| Tumour necrosis factor (TNF)- alpha inhibitors  | 1.5-4.0 <sup>93</sup>  |
| Diabetes mellitus (all types)   | 2.0-3.6 <sup>94</sup>  |
| Underweight (<90% ideal body weight; for most persons this is a body mass index $\leq 20$ ) | 2.0-3.0 <sup>95</sup>  |
| Young age when infected (0-4 years)   | 2.2-5.0 <sup>96</sup>  |
| Cigarette smoker (1 pack/day)   | 2.0-3.0 <sup>97</sup>  |
| Abnormal chest X-ray - granuloma  | 2.0 <sup>98</sup>  |
| <b>Low risk</b>   |  |
| Infected person, no known risk factor, normal chest X-ray (“low risk reactor”)              | 1.0 <sup>99</sup>  |

Source: Canadian Tuberculosis Standards, 6<sup>th</sup> Edition. Public Health Agency of Canada, 2007. Reproduced with the permission of the Minister of Public Works and Government Services, 2009. Available at [www.phac-aspc.gc.ca/tbpc-latb/pubs/pdf/tbstand07\\_e.pdf](http://www.phac-aspc.gc.ca/tbpc-latb/pubs/pdf/tbstand07_e.pdf)

Among persons with LTBI, dual infection with HIV is the most important risk factor for the development of TB disease.<sup>30</sup>

### 3.3 Selecting People for Treatment of LTBI

The rationale for the treatment of LTBI is to kill any residual dormant (inactive) bacilli, thus reducing or preventing the reactivation and development of TB disease. With treatment of LTBI, the number of persons who go on to have TB disease may be significantly diminished. This is an important part of TB control. If active TB has been excluded by chest X-ray and examination, then the decision to treat LTBI should be based on an assessment of the individual’s situation.

High-risk individuals fall into two categories:

1. Persons presumed to have been recently infected and
2. Persons whose underlying medical conditions substantially increase their risk of developing active TB.

A multidisciplinary team approach including the patient should be adopted in the treatment and management of persons with LTBI. The assessment criteria before deciding whether to treat or not include:

- How likely is it that a person has been infected?
- How likely is it that disease will develop? (table 3.3)
- What are the risks of an adverse reaction to treatment?
- What is the likely adherence to treatment?



It is recommended that all age groups in priority groups 1 to 5 listed below should be considered for treatment of LTBI. This is similar to the US strategy for treatment of LTBI which recommends no age limits as the risk of severe fatal hepatotoxicity from treatment with anti-TB drugs is considered low even in those aged over 35 years and if testing and treatment are targeted at these high risk groups then the risk: benefit ratio should be acceptable.<sup>100</sup> Recommendations for LTBI treatment in priority groups 6 to 9 are also listed below.

The following groups should be prioritised for the treatment of LTBI [see table 2.1 for TST (Mantoux) cut off points for treatment of LTBI in these groups]:

1. Recent converters
2. HIV positive individuals
3. Those aged less than five years
4. Persons receiving immunosuppressive therapy i.e. Tumour Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) antagonists
5. Persons with evidence of old healed TB lesions on chest X-ray i.e. fibronodular disease/non-calcified fibrotic lesions (if not previously treated or if treated, not adequately treated)<sup>30;77</sup>
6. Foreign-born persons from countries with high TB endemicity<sup>#</sup>
7. Homeless persons
8. Intravenous drug users
9. HCWs.

The risk of isoniazid toxicity has been shown to increase with age in particular in persons aged 55 years and older.<sup>77</sup>

#### **Recommendation:**

**Groups 1-5:** LTBI treatment should be offered to those in all age groups

**Groups 6-8:** LTBI treatment should be offered to all those aged  $\leq 55$  years if supervised treatment (DOT)<sup>††</sup> is available. Otherwise it should be offered to those aged  $\leq 35$  years. These groups should be closely monitored for isoniazid toxicity<sup>77</sup>

**Group 9:** The age limit for LTBI treatment should be assessed on a case-by-case basis i.e. treat all HCWs where the risk of progression from LTBI to TB disease is high regardless of age. Where the risk of progression is low, the upper age limit is  $\leq 35$  years (chapter 9)

**All others not mentioned above:** The upper age limit should be  $\leq 35$  years

**Care should be taken when prescribing LTBI therapy for those with co-morbidities which increase the likelihood of hepatotoxicity.**

#### **Management of Persons Exposed to Infectious TB after Previous LTBI Treatment**

Very high risk severely immunocompromised persons (e.g. those with HIV infection) who are re-exposed to TB infection, having already completed a satisfactory course of LTBI therapy should be considered for a repeat course of treatment for LTBI. If questions arise regarding risk of TB following repeat LTBI, referral to a respiratory physician or an infectious disease consultant is recommended.<sup>30</sup>

<sup>#</sup> Countries where the annual rate of TB disease is  $\geq 40$  cases/100,000 population

<sup>††</sup> A way of helping patients to take their medicine for TB. A person receiving DOT will meet with a healthcare worker everyday or several times a week at an agreed place e.g. the patient's home, the TB clinic or other convenient location. The healthcare worker will observe the patient taking their medication at this place helping to ensure that higher treatment completion rates are achieved. Sometimes someone in their family or a close friend will be able to help in a similar way to the healthcare worker. Further definitions are available in the glossary of terms.

### 3.4 Treatment of LTBI

The choice of treatment regimen for LTBI will depend on:

- The presence or absence of risk factors for progression to TB disease
- An assessment of the likely adherence level of the patient and the amount of time available for completion of the patient's treatment
- The antibiotic susceptibility of the presumed source case
- Drug tolerance of the patient.

Poor adherence is the most important reason for the failure of LTBI treatment. Many people with LTBI do not complete treatment as most are not sick and may not feel the urgency to complete the prolonged therapy. Directly observed therapy (DOT) for LTBI is an excellent method for promoting adherence to treatment.<sup>77</sup> Because of limited resources, DOT (supervised therapy) for LTBI cannot be offered to all persons on LTBI treatment, however, it should be provided to those in the priority groups 6, 7 and 8 mentioned above.

However, for all others receiving LTBI treatment, a great deal can be accomplished to improve adherence by developing a relationship based on trust and support between the healthcare worker and patient.<sup>30</sup> Barriers to adherence should be addressed and overcome (appendix 4)<sup>77</sup>

#### **Recommendation:**

Directly observed therapy (DOT) should be provided for those being treated for LTBI in groups 6, 7 and 8 above i.e. immigrants from areas of high TB endemicity, homeless persons and intravenous drug users.

#### **Recommendation:**

It is recommended that audits of compliance with LTBI therapy are undertaken.

#### **Treatment of LTBI in adults**

The effectiveness of isoniazid in preventing progression from LTBI to active TB disease was first reported in 1957 and has been confirmed by many studies since. Isoniazid is the most widely used anti-TB agent as it is relatively non-toxic, easily administered and inexpensive.

Similar treatment regimens for LTBI in adults are recommended by the UK<sup>26</sup> and New Zealand.<sup>52</sup>

The NICE guidelines<sup>26</sup> recommend that non HIV-infected adults are treated with either (i) six months of isoniazid or (ii) three months of rifampicin and isoniazid **or** six months of rifampicin for contacts of isoniazid resistant TB cases. This recommendation applies to persons aged 16-35 years and to persons older than 35 years for whom treatment of LTBI is recommended. These recommendations are based on a Cochrane review of randomised trials of isoniazid of at least six months duration which were placebo controlled with at least two years follow up.<sup>101</sup> This review states that the efficacy of treatment increased with the duration of treatment but that the efficacy of six months or 12 months did not vary significantly. In fact, the small advantage of 12 months over six months may not be worthwhile except in those individuals at high risk of developing TB.

The American Thoracic Society (ATS) 2000<sup>34</sup>, Canadian (2007)<sup>30</sup> and New York guidance (2008)<sup>77</sup> recommend similar treatment regimes of daily isoniazid for nine months. Alternatively, a regime of rifampicin for four months may be used if isoniazid is contraindicated due to a history of an isoniazid-

induced reaction or for a contact of an isoniazid resistant-TB case or if the patient may not be able to adhere to therapy for a six to nine month period.

ATS guidelines state that although nine months of isoniazid was the preferred regimen for the treatment of LTBI, a six month regimen also provides substantial protection and has been shown to be superior to placebo in both HIV negative and HIV positive persons. However, treatment for six months rather than nine months may provide more favourable outcomes from a cost effectiveness standpoint.<sup>34</sup>

The rationale for the ATS recommendations was based on evidence from randomised controlled clinical trials that assessed the benefits of isoniazid. These studies showed that isoniazid was effective in preventing TB disease. Most of the studies compared isoniazid for 12 months with placebo. However, one trial, conducted by the International Union Against Tuberculosis and Lung Disease (IUATLD), was designed to evaluate various durations of isoniazid and this indicated that a 12 month regimen provided a substantial reduction in risk compared with a six month regimen among compliant persons with small lesions.<sup>102</sup> A further reanalysis of data from community studies in Alaska indicated that the protection conferred by taking at least nine months of isoniazid was considered greater than taking six months but it was not likely that further protection was conferred by extending the duration of treatment from nine to 12 months.<sup>103</sup>

Based on a review of the evidence and guidance in the international literature and by consensus of the National TB Advisory Committee, the following are the recommended treatment regimens for LTBI in adults:

**Recommendation:**

The recommended treatment regimens for LTBI in adults are:

(i) Isoniazid for a minimum of six months with an optimum duration of nine months

or

(ii) Rifampicin for four months

or

(iii) A combination of rifampicin and isoniazid for a duration of at least three months with an optimum of four months.

**Treatment of LTBI in children**

The US Centers for Disease Prevention and Control (CDC) defines paediatric TB as occurring in persons aged less than 15 years.<sup>104</sup> LTBI in a child can be defined as a child or adolescent with a positive TST who has no evidence of TB disease.

Infants and young children under the age of five years with LTBI have been only recently infected and therefore are at a higher risk of progressing to active TB disease. The literature suggests that 40% of untreated infants will develop active TB disease although the risk of progression decreases throughout childhood.<sup>105</sup> These children are also more likely than older children and adults to develop life-threatening forms of TB disease in particular meningeal and disseminated disease. Among children the efficacy of treatment of LTBI with isoniazid approaches 100% with appropriate adherence to therapy. Hepatotoxicity from isoniazid in infants and children is rare and in general children tolerate the drug better than adults.<sup>106</sup>

*International recommendations for treatment of LTBI in children*

The American Academy of Pediatrics and CDC convened the Pediatric Tuberculosis Collaborative Group. This group produced a consensus document which stated that treatment is recommended for all children and adolescents diagnosed with LTBI because:<sup>105</sup>

- The drugs used are safe in the paediatric population
- Infection with *M. tuberculosis* is more likely to have been recent

- Young children are at a higher risk of progression to TB disease and
- The paediatric population has more years to potentially develop TB disease.

The Pediatric Tuberculosis Collaborative Group also recommended:

- TB disease should be excluded by chest X-ray and examination before initiating treatment for LTBI
- That the regimen for treatment of LTBI in children and adolescents should be isoniazid either daily or twice weekly for nine months and
- That if the source case is isoniazid resistant, rifampicin should be used daily for six months.

The collaborative group recommendations were based on clinical trials, which showed that treatment of LTBI in children with isoniazid therapy reduces the risk of progression to active disease.<sup>34</sup> The only published efficacy trials of treatment of LTBI in children are for isoniazid alone with a recommended regimen for treatment of LTBI in HIV non-infected children of a nine month course of isoniazid daily or twice weekly by DOT.

Based on a review of the evidence and guidance in the international literature and by consensus of the National TB Advisory Committee, the following are recommended treatment regimens for LTBI in children:

**Recommendation:**

The recommended treatment regimens for LTBI in children are:

(i) Isoniazid for a minimum of six months with an optimum duration of nine months

or

(ii) Rifampicin for six months

or

(iii) A combination of rifampicin and isoniazid for a duration of four months.

Physicians experienced in the management of children with LTBI should supervise treatment.

### 3.5 Treatment of Multidrug-Resistant or XDR LTBI

A source case can be sputum smear positive for MDR-TB or XDR-TB and therefore contacts have to be managed in the appropriate manner. The WHO recommends that close contacts of MDR-TB or XDR-TB patients should receive careful clinical follow-up for a period of at least two years. If active disease develops, prompt initiation of treatment with a regimen designed to treat MDR-TB or XDR-TB is recommended. On the basis of currently available evidence, WHO does not recommend the universal use of second-line drugs for chemoprophylaxis in MDR-TB or XDR-TB contacts.<sup>107</sup> It is also recommended that the management and follow-up of contacts aged <5 years is undertaken in consultation with a physician who has expertise in this area.

**Recommendation:**

Consultation with a respiratory physician or infectious disease consultant should be sought for the management of all persons with active TB or LTBI who have been exposed to patients with MDR-TB or XDR-TB.

For treatment of LTBI in HIV infected persons, see chapter 10.

### 3.6 Pre-treatment Evaluation

The pre-treatment evaluation (figure 3.1) of persons who are targeted for treatment of LTBI provides an opportunity for healthcare providers to:

- Establish a rapport with the patient
- Discuss details of the patient's risk of TB
- Emphasise the benefits of treatment and the importance of adherence to the drug regimen
- Review possible adverse effects of the regimen, including interactions with other drugs, and
- Establish an optimal follow up plan.

The evaluation should include an interview conducted in the patient's primary language with the assistance of qualified medical interpreters, if necessary.

The patient history should document:

- Risk factors for TB
- Prior treatment for TB or LTBI
- Pre-existing medical conditions that may be contraindications to treatment or are associated with an increased risk for adverse effects from treatment and
- Current and previous drug therapy, with particular attention to previous adverse reactions to drugs and to current drugs which may interact with LTBI treatment e.g.
  - o Isoniazid: interacts with antacids (decrease absorption of isoniazid)
  - o Phenytoin and carbamazepine (isoniazid decreases metabolism of these drugs hence leading to increased blood levels); and corticosteroids (concentration of isoniazid possibly reduced by corticosteroids)
  - o Rifampicin: causes reduced levels of many drugs including warfarin, methadone, oral contraceptive pill, oral hypoglycaemic agents, theophylline, ketoconazole, dapsone, PIs and NNRTIs (figure 3.1).<sup>77</sup>

#### Recommendation:

Clinicians may choose to undertake baseline liver function tests (LFTs) for all patients aged over 14 years at the start of treatment for LTBI. However, this is not universally obligatory.

However, baseline LFTs **should be done** on the following persons prior to commencing therapy for LTBI:

1. Everyone over the age of 35 years
2. All HIV-infected persons
3. Pregnant or post-partum women (up to 2-3 months postpartum)
4. Those with a history of hepatitis, liver disease or heavy alcohol ingestion
5. Injecting drug users
6. Those on treatment with other potential hepatotoxic agents.

All patients prescribed a rifampicin-containing regime should have a baseline full blood count and platelets.<sup>52;77</sup>

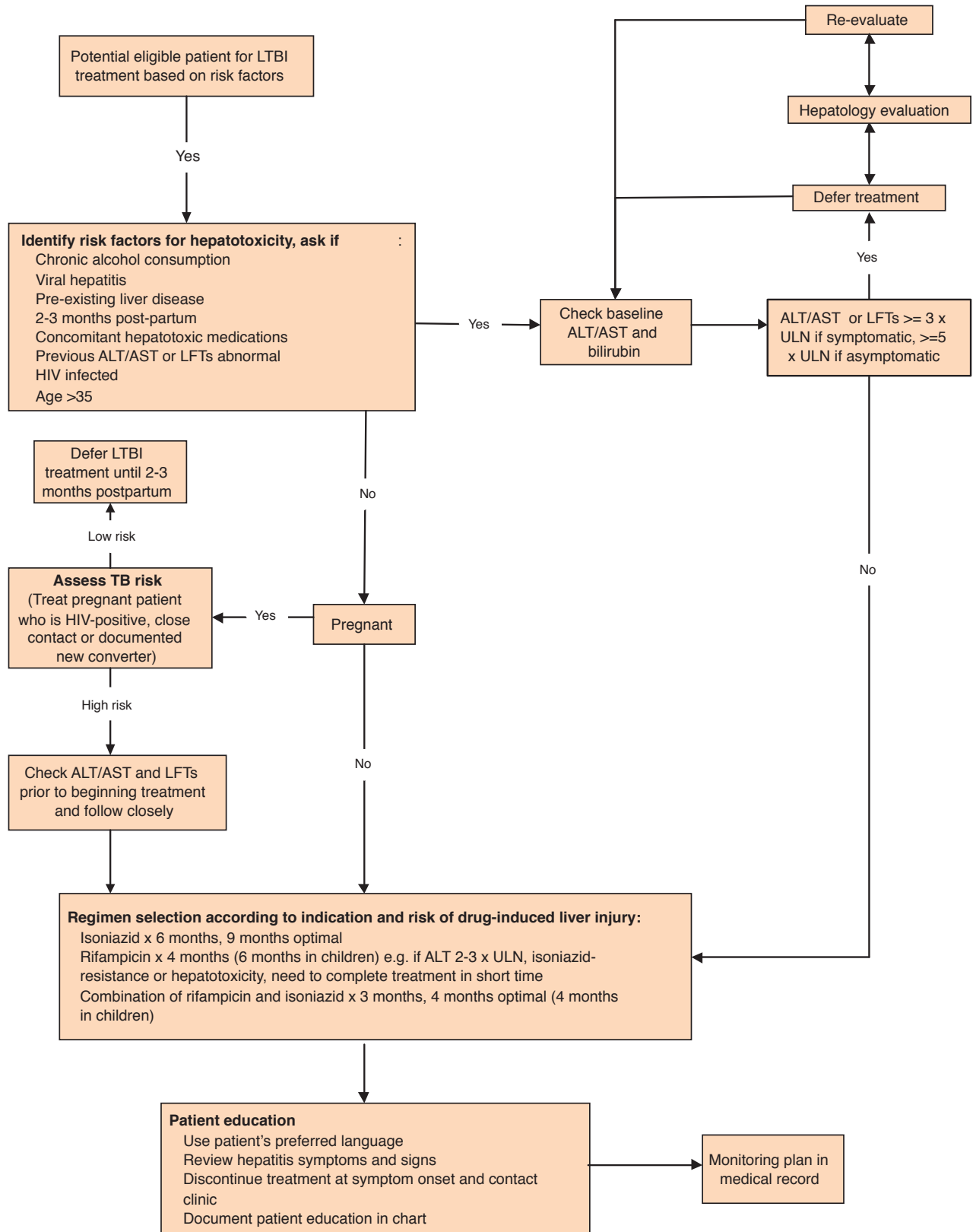
Patients with baseline transaminases of more than three times the upper limit of normal (ULN)<sup>‡‡</sup> should have the ALT and bilirubin retested. Screening for viral or other causes of hepatitis including alcohol and hepatotoxic drugs should also be undertaken. In this situation, the decision to treat LTBI or more likely to defer treatment should be carefully made on a case-by-case basis weighing the risk of progression to TB disease against the risk of isoniazid or rifampicin drug induced liver injury (DILI). Factors influencing the risk

<sup>‡‡</sup> The upper limit of normal (ULN) used should be that of the laboratory performing the assay.

of DILI include the degree of baseline ALT elevation, alcohol consumption, increasing age and evidence of active replication of the hepatitis virus.

If LTBI treatment is started, some experts recommend measuring the serum transaminases and bilirubin concentrations every 2 to 4 weeks for the first 2 to 3 months of treatment. The international normalised standard (INR) may be followed periodically as well in patients with severe hepatic impairment.<sup>108</sup>

**Figure 3.1: Latent tuberculosis infection (LTBI) pretreatment clinical evaluation and counselling\***



ALT = alanine aminotransferase; AST = aspartate aminotransferase; LFTs = liver function tests; ULN = upper limit of normal

\* Adapted from the New York City Department of Health and Mental Hygiene TB guidelines

### 3.7 Drug Regimens for LTBI

Isoniazid is used alone for preventive therapy for a minimum of six months with an optimum duration of nine months. The drug is given in a single daily dose of 5mg/kg (max dose: 300mg) per day for adults and 5-10mg/kg (max dose: 300mg daily) for children.<sup>77</sup> Ideally, anti-TB therapy for the treatment of LTBI should be dispensed in monthly allocations. However in some situations, if the clinician or public health doctor deems it appropriate it may be dispensed at less frequent intervals e.g. every two months. If isoniazid cannot be given daily, it can be given twice weekly in a dose of 15mg/kg (up to 900mg) for adults and 20-30mg/kg (up to 900mg) for children (see table 3.4).<sup>77;109</sup>

For persons intolerant to isoniazid or who are likely to be infected with isoniazid resistant organisms, rifampicin for four months may be used (see table 3.4).

Dosages for drugs commonly used for treatment of LTBI are outlined in table 3.4. For treatment with other drugs, referral to a clinician experienced in TB is advised, particularly for contacts of MDR-TB cases (section 3.5).

**Table 3.4: Drug Regimens for LTBI**

| Drug and duration  | Dosage   |   | Major adverse reactions   | Comments   |
|--|--|---|---|--|
|  | Daily  | Twice weekly  | Recommended monthly monitoring <sup>1</sup>   |  |
| <b>Isoniazid</b><br><br>Children: 6 months optimum<br><br>Adults: 9 months optimum | <b>Children:</b><br>5-10mg/kg<br>(max 300mg)<br><br><b>Adults:</b><br>5mg/kg<br>(max 300mg)<br><br><b>Completion Criteria:</b><br>270 doses within 12 months | <b>Children:</b><br>20-30mg/kg<br>(max 900mg)<br><br><b>Adults:</b><br>15mg/kg<br>(max 900mg)<br><br><b>Completion Criteria:</b><br>76 doses within 12 months | <b>Symptoms:</b> Unexplained anorexia, nausea, vomiting, dark urine, jaundice, persistent fatigue, weakness, abdominal tenderness (especially right upper quadrant discomfort), easy bruising or bleeding, rash, persistent paresthesias of the hands and feet, arthralgia<br><br><b>Signs:</b> Elevated LFTs, hepatitis, icterus, rash, peripheral neuropathy, increased phenytoin levels and possible interaction with disulfiram<br><br><b>Clinical evaluation:</b> LFTs (if baseline is abnormal or patient has risk factors for toxicity) <sup>2</sup> | <b>Preferred regimen for all individuals</b><br>Vitamin B6 (25mg/day) or pyridoxine may decrease peripheral and CNS effects, and should be used in patients who are: <ul style="list-style-type: none"> <li>- Abusing alcohol</li> <li>- Pregnant</li> <li>- Breastfeeding infants on isoniazid</li> <li>- Malnourished</li> </ul> Or who have <ul style="list-style-type: none"> <li>- HIV</li> <li>- Cancer</li> <li>- Chronic renal or liver disease</li> <li>- Diabetes</li> <li>- Pre-existing peripheral neuropathy</li> </ul><br><i>Note: aluminium-containing antacids reduce absorption</i> |

Table 3.4 contd.

| Drug and duration   | Dosage  |   | Major adverse reactions   | Comments   |
|---|---|---|---|--|
|   | Daily   | Twice weekly  | Recommended monthly monitoring <sup>1</sup>   |  |
| <b>Rifampicin</b><br><br>Children:<br>6 months<br><br>Adults:<br>4 months | <b>Children:</b><br>10-20mg/kg<br>(max 600mg)<br><br><b>Completion criteria:</b><br>182 doses<br>within 9 months<br><br><b>Adults:</b><br>600 mg<br>(range: 8-12<br>mg/kg)<br>(max: 600mg)<br><br><b>Completion criteria:</b><br>120 doses<br>within 6 months | <b>Children:</b><br>not recommended<br><br><br><b>Adults:<sup>3</sup></b><br>600mg<br>(range 8-12 mg/kg)<br>(max 600mg)<br><br><b>Completion criteria:</b><br>34 doses within 6<br>months | <b>Symptoms:</b> Nausea, vomiting, rash, fever or flu-like symptoms, easy bruising.<br><br><b>Signs:</b> Elevated LFTs, hepatitis, rash, thrombocytopenia<br>Reduced levels of many drugs including methadone, warfarin, hormonal contraception, oral hypoglycaemic agents, theophylline, dapsone, ketoconazole, PIs and NNRTIs<br><br><b>Clinical evaluation:</b><br>- LFTs (if baseline is abnormal or patient has risk factors for toxicity) <sup>2</sup><br>- Complete blood count, including platelets as needed | May be used to treat persons who have been exposed to isoniazid-resistant, rifampicin-susceptible TB, or who have severe toxicity to isoniazid, or who are unlikely to be available for more than 4-6 months.<br><br>Be aware that<br>- There will be orange discoloration of secretions, urine, tears and contact lenses<br>- Patients receiving methadone will need their methadone dosage increased by an average 50% to avoid opioid withdrawal<br>- Interactions with many drugs can lead to decreased levels of either or both<br>- Rifampicin may make glucose control more difficult in diabetics<br>- Rifampicin is contraindicated for patients taking most PIs and NNRTIs<br>- Patients should be advised to use barrier contraceptives while on rifampicin |

<sup>1</sup>Baseline LFTs should be done for everyone over the age of 35, all HIV-infected persons, pregnant and post-partum women (up to 2-3 months post-partum), those with history of hepatitis, liver disease or alcohol abuse, injection drugs users and those on treatment with other potential hepatotoxic agents. A baseline CBC with platelets should be done on anyone prescribed a rifampicin-containing regimen

<sup>2</sup>Monthly LFTs should be conducted for all HIV infected persons, pregnant and post-partum women (up to 2-3 months post-partum), those with history of hepatitis, liver disease or alcohol abuse, injection drugs users and those on treatment with other potential hepatotoxic agents. Those whose baseline LFTs were abnormal should be monitored monthly regardless of other conditions.

<sup>3</sup>There is very little data or clinical experience on the use of intermittent treatment of LTBI with rifampicin. This regimen should be used with caution.



## Pyridoxine

It is believed that isoniazid competes with pyridoxyl phosphate for the enzyme apotryptophanase, which may lead to symptoms of pyridoxine (vitamin B6) deficiency. Pyridoxine administration may decrease the peripheral and CNS effects complicating isoniazid use. If on isoniazid, pyridoxine 10mg daily (20mg daily may be used if 10mg tablets are not available) should be prescribed for:

- all adults, including pregnant women
- children who have poor nutrition and therefore are at risk of pyridoxine deficiency
- children who develop paraesthesia
- breastfeeding infants on isoniazid
- a fully breastfed infant if the mother is on isoniazid, regardless of whether the infant is on anti-TB treatment
- In particular, those with, pre-existing peripheral neuropathy, diabetes, chronic renal or liver disease, cancer, alcoholism, malnutrition, other immunosuppressive conditions or HIV.<sup>52 77</sup>

As there are no side effects to low dose pyridoxine, many centres routinely prescribe it to prevent the development of neuropathy.<sup>30</sup> However, it is not routinely prescribed in children except in the situations mentioned above.

## LTBI treatment: contraindications

### Isoniazid

- Previous history of an isoniazid-induced reaction including hepatic, skin or allergic reaction
- Close contact with a person who has isoniazid-resistant TB
- Pregnancy: unless the woman is HIV infected or has been recently infected i.e. is a close contact of an infectious TB case. In these cases, a risk assessment should be undertaken on a case-by-case basis and treatment deferred if possible until after the first trimester. Apart from the above situations, the small benefits of LTBI treatment in pregnancy are not thought to outweigh the small risks associated with taking the medications
  - o For all other pregnant women, treatment if indicated for LTBI (provided active TB disease is excluded) should be deferred until two to three months post-partum (figure 3.1)
  - o The need to treat active TB disease during pregnancy is unquestioned. Treatment of LTBI is more controversial since the possible risk of hepatotoxicity must be weighed against the risk of developing TB disease
  - o In pregnant women known or suspected to be infected with a TB strain resistant to at least isoniazid and rifampicin treatment for LTBI should be deferred until after delivery. This will avoid possible adverse effects of the medications on the developing foetus. <sup>30;34;77</sup>

An alternative regimen to isoniazid is to give patients (with or without HIV infection) four months of rifampicin for treatment of LTBI. This course is especially recommended if there are contraindications or resistance to isoniazid but not to rifampicin and if there may be adherence problems and the individual is unlikely to complete a six or nine month course of therapy.

### Rifampicin

- A history or rifampicin-induced reactions including skin and other allergic reactions, hepatitis or thrombocytopenia
- Pregnancy unless the woman is HIV infected, has been recently infected and is a close contact of an isoniazid-resistant case or is intolerant to isoniazid (see under isoniazid and figure 3.1)
- Current treatment with a protease inhibitor (PI) or certain non-nucleoside reverse transcriptase inhibitors (NNRTIs).<sup>77</sup>

### LTBI treatment: precautions

Persons with any of the conditions outlined below should be referred to a respiratory clinician or infectious disease consultant for treatment of LTBI:

- Acute or chronic liver disease of any aetiology
- Acute liver disease: If a person with acute liver disease has a high risk of progression to TB disease for example if the person is on immunosuppressive therapy and also had prolonged contact with a highly infectious TB case, then a risk assessment should be carried out to determine whether they should be treated for LTBI
- Receiving other drugs which may interact with anti-TB drugs
- History of heavy alcohol ingestion
- History of previous discontinuation of isoniazid because of possible, but not definite, related side effects e.g. headaches, dizziness, nausea
- Major concerns about adherence to treatment
- Major concerns about adherence to arrangements for biochemical or clinical monitoring
- Peripheral neuropathy or risk factors for its development e.g. insulin dependent or type II diabetes, alcoholism, chronic renal failure or malnutrition. Pyridoxine 10mg daily (or 20mg if 10mg not available) should be offered to these patients (see section on pyridoxine).

#### Recommendation:

A consultant with expertise in TB should always be consulted when treating a patient with LTBI with documented hepatotoxicity.

A risk-benefit approach on a case-by-case basis should be adapted to commencing treatment for LTBI on these patients. Treatment of patients with underlying liver disease should be undertaken in consultation with a consultant hepatologist.

#### Recommendation:

Breastfeeding is not a contraindication to LTBI therapy. Isoniazid or rifampicin are not secreted in sufficient quantities in breast milk to harm the baby.<sup>52;77</sup>

### Monitoring during treatment

Clinical monitoring is indicated for all patients and ideally involves monthly visits, or at the discretion of the physician, where patients are educated about the symptoms and signs that can result due to adverse effects of the drug(s) being prescribed and the need for prompt cessation of treatment and clinical evaluation should symptoms occur.

The symptoms of adverse affects include:<sup>34;52</sup>

- unexplained anorexia
- nausea
- vomiting
- dark urine
- jaundice
- rash
- persistent paresthesia of the hands and feet
- persistent fatigue

- weakness or fever lasting three or more days
- abdominal tenderness (especially right upper quadrant discomfort)
- easy bruising or bleeding and
- arthralgia.

The interval between commencing isoniazid and the appearance of hepatitis varies widely. Using a standardised proforma may facilitate monthly clinical monitoring (appendix 5). Appropriate educational materials (information leaflet) in the patient's language should be provided (appendix 6).

### Liver function tests (LFTs)

Monthly LFTs during treatment of LTBI are indicated for patients whose baseline liver function tests are abnormal and for all HIV-infected persons, pregnant and post-partum women (up to 2-3 months post-partum), those with a history of hepatitis, liver disease or heavy alcohol ingestion, injecting drug users and those on treatment with other potential hepatotoxic agents.<sup>77</sup>

Some experts recommend that healthy adults aged >35 years on LTBI treatment with isoniazid or isoniazid with rifampicin have eight weekly monitoring of LFTs or at one, three and six months for those on a nine month regimen. The frequency depends on the perceived hepatotoxicity risk and effectiveness of patient education.<sup>108</sup>

In addition, laboratory testing (e.g. liver function studies for patients with symptoms compatible with hepatotoxicity or a uric acid measurement to evaluate patients who develop acute arthritis) should be used to evaluate possible adverse effects that occur during the course of treatment.

### Interventions for hepatotoxicity during treatment for LTBI

If hepatic side-effects occur during treatment, expert advice should be sought from the treating physician. A hepatology evaluation should be undertaken and hepatology consultation is recommended for unusual or severe cases of hepatitis particularly those who become sufficiently ill to require hospitalisation.<sup>108</sup>

Isoniazid should be withheld if hepatic transaminases (ALT) are at least three times the ULN when the patient is symptomatic (jaundice or symptoms of hepatitis) or if at least five times the ULN when the patient is asymptomatic. An isoniazid rechallenge should be considered when the ALT is less than twice the ULN. This should be decided by the treating physician on a case-by-case basis.

A rapid increase in ALT may be an indication for more frequent monitoring i.e. every two weeks instead of monthly, particularly if one of the above treatment-limiting ALT thresholds is being approached or if the patient has previously identified risk factors for hepatotoxicity.

For the few patients who may begin isoniazid LTBI treatment with a baseline ALT >3 times the ULN, some experts recommend that in the absence of adequate clinical data that treatment should be discontinued if there is more than a two- to threefold increase above baseline or if there is a mental status change, jaundice or significant increase in bilirubin or INR.<sup>108</sup>

More detailed information on the hepatotoxicity of anti-TB therapy is available in the Official American Thoracic Society's Statement: Hepatotoxicity of Anti-TB Therapy.<sup>108</sup>

#### **Recommendation:**

Ideally monthly clinical monitoring (at the discretion of the clinician) is recommended for all patients receiving treatment for LTBI.

### Interruptions in therapy

Adherence to treatment regimens is recognised as a significant problem, especially in relation to the treatment of LTBI, with CDC stating that only 60% of patients who start treatment for LTBI complete at least six months of treatment.<sup>34</sup> The length and complexity of the regimen and the side effects of the medication influence adherence to treatment. Directly observed therapy (DOT) has been used to try to improve adherence to treatment regimens. Ideally, patients should receive medication on a regular dosing schedule until completion of the indicated course. However, in practice some doses may be missed, requiring the course to be lengthened.

If interruptions in therapy occur the person responsible for supervision must decide whether to restart a complete course of treatment or whether simply to continue as originally intended.

Completion of therapy is based on the total number of doses administered not on the duration of therapy alone. The nine month regimen of daily isoniazid should consist of a minimum of 270 doses administered within 12 months, which allows for minor interruptions in therapy. The six month regimen of isoniazid should consist of at least 180 doses administered within nine months.<sup>34</sup>

When therapy is restored after an interruption of more than two months, a medical examination to rule out active TB disease is indicated.

### 3.8 Risk of TB Associated with the Use of TNF- $\alpha$ Antagonists

TNF- $\alpha$  antagonists offer great promise to patients suffering a number of immune-mediated diseases and have been used safely in many patients worldwide. However, it is plausible that these agents may carry a risk of reactivation of LTBI or of new TB infection. Concern is supported by the finding of a possible increased risk of TB in peer-reviewed publications from a number of countries. While the design of these studies does not allow causality to be concluded, the consistency of the studies and the temporal association with the agents, together with the gravity of the consequence for individual patients and for the wider community suggest that a precautionary approach is appropriate. Manufacturers of TNF- $\alpha$  antagonists have indicated that TB is a possible side effect of treatment and a number of guidelines for management of this risk have been issued by professional organisations and individuals.

The following recommendations (summarised in figure 3.2) are taken from a briefing paper prepared by members of the National TB Advisory Committee in consultation with members of the Irish Society for Rheumatology. The full version of this document is available at: [www.hpsc.ie/hpsc/A-Z/VaccinePreventable/TuberculosisTB/Guidance/](http://www.hpsc.ie/hpsc/A-Z/VaccinePreventable/TuberculosisTB/Guidance/).

1. Prior to commencing TNF- $\alpha$  antagonists, patients should be thoroughly assessed for clinically active TB disease, including clinical history, physical examination and chest radiograph. If clinically active TB disease is diagnosed, it should be treated as per existing guidelines (chapter 5).
2. Patients without clinically active TB disease should be screened for LTBI with clinical history, assessment of risk factors (for example time spent living in a high incidence country, immunocompetence, etc.), physical examination, chest radiograph and TST.
  - IGRA testing may be a useful adjunct in screening where it is available.
3. Patients without radiographic evidence of TB but with a positive TST should be classified as a case of LTBI.
  - For the purpose of LTBI screening prior to commencing TNF- $\alpha$  antagonists, 2TU Mantoux testing is recommended. While reactions over 10mm should be interpreted as indicating TB infection, this cut off may not be reliable for some patients being considered for treatment with TNF- $\alpha$  antagonists since their disease and co-medications may lead to anergy. Therefore, the use of a 5mm cut-off may be more useful for patients who are considered to be immunocompromised. It

is recognised that on the basis of individual risk assessment, clinicians may prefer to use an even more conservative cut-off for individual patients. Although a negative TST (Mantoux test) reduces the probability of LTBI, a high clinical suspicion for LTBI should be maintained, since the reaction to tuberculin may be complicated by anergy.

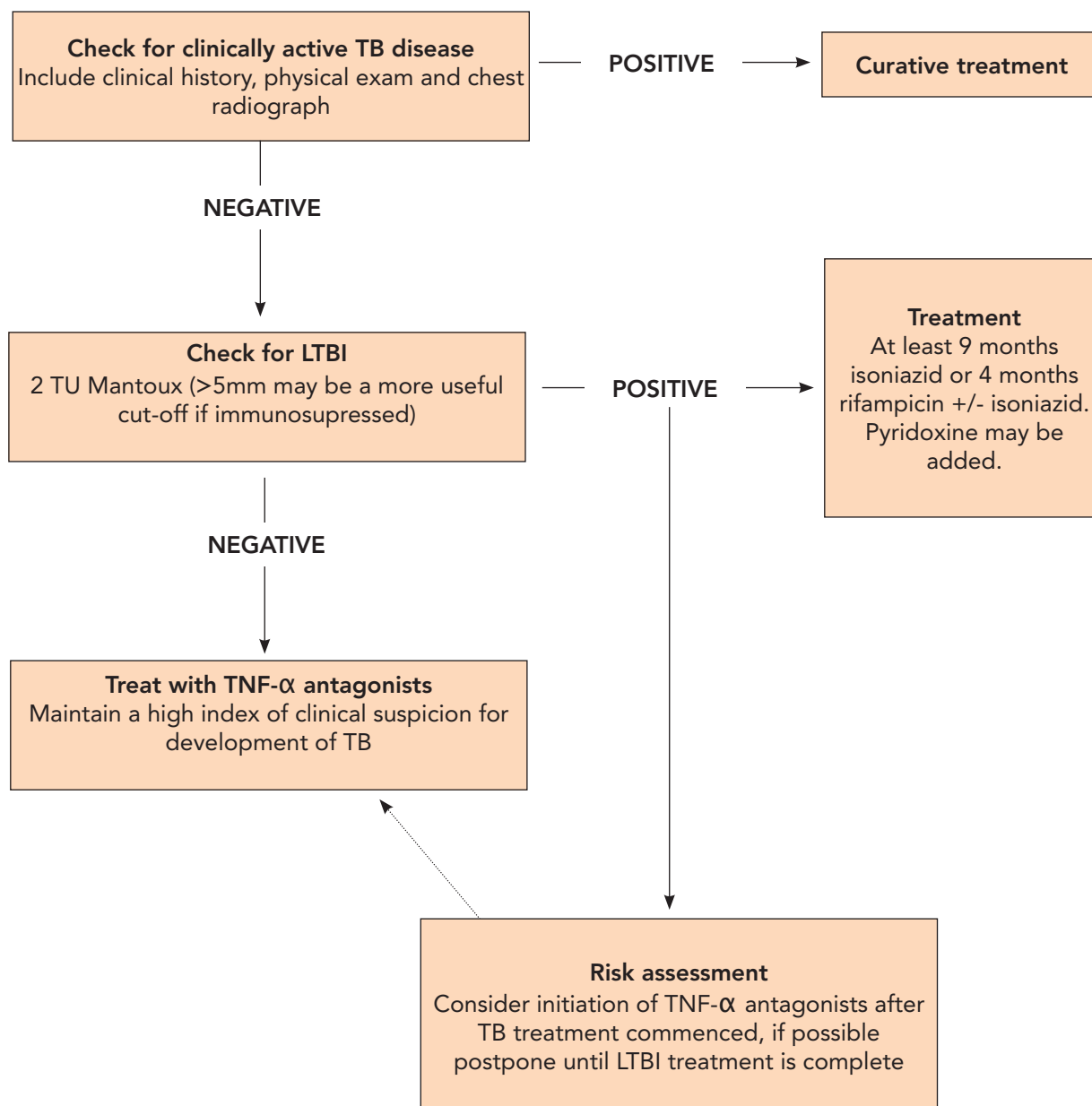
- It is recommended that the interpretation of Mantoux testing in the context of testing for LTBI prior to commencement of a TNF- $\alpha$  antagonist should not usually take account of the patient's BCG history.
4. It is recommended that patients diagnosed with LTBI should be treated. Options for treatment include at least nine months of isoniazid, which is associated with a lower risk of hepatotoxicity, or four months of rifampicin (R) +/- isoniazid, associated with a higher risk of hepatotoxicity but offers the advantage of shorter duration which may promote successful completion of treatment for some patients. Rifampicin for four months may also be used if isoniazid is contraindicated e.g. a past history of an isoniazid induced reaction. Pyridoxine may also be used in combination with these regimens.
  5. Optimal timing of initiation of TNF- $\alpha$  antagonists is challenging and in the absence of high-quality evidence to support specific recommendations in this regard, decisions on the treatment of individual patients need to be made collaboratively by patients and clinicians following a careful assessment of the risks of TB disease and the benefits of TNF- $\alpha$  antagonist treatment and discussion of individual preferences.
    - Initiation of TNF- $\alpha$  antagonists prior to commencement of treatment of clinically active TB disease or LTBI should be avoided
    - The risk associated with commencement or re-commencement of TNF- $\alpha$  antagonists in the setting of clinically active TB disease requires particularly careful assessment; where possible, it is recommended that TNF- $\alpha$  antagonists be postponed until curative treatment has been satisfactorily completed; in some cases, clinicians and patients may prefer to avoid TNF- $\alpha$  antagonists completely in this scenario
    - The risk associated with commencement or re-commencement of TNF- $\alpha$  antagonists in the setting of LTBI also requires careful assessment; again, where possible, it is recommended that TNF- $\alpha$  antagonists be postponed until LTBI treatment has been satisfactorily completed. However, clinicians and patients may, on balancing risks and benefits, prefer to initiate TNF- $\alpha$  antagonists during treatment for LTBI; while no specific duration of LTBI treatment prior to initiation of TNF- $\alpha$  antagonists can be recommended on the basis of currently available evidence, where possible, a longer duration of satisfactory LTBI treatment is suggested as good practice in managing the risk of initiation of TNF- $\alpha$  antagonists.
  6. Clinically active TB disease may still arise in patients treated with TNF- $\alpha$  antagonists despite a negative initial assessment or LTBI treatment. Therefore, it is recommended that a high index of clinical suspicion for development of TB is exercised in the setting of any clinical deterioration while patients are undergoing TNF- $\alpha$  blockade.
  7. Cooperation between clinicians initiating TNF- $\alpha$  antagonists and clinicians with expertise in TB is recommended in the assessment and management of patients.
  8. Clinicians are encouraged to report all adverse drug events associated with the use of TNF- $\alpha$  antagonists to the Irish Medicines Board (IMB).

It is suggested that these national recommendations provide a framework for the drafting of guidelines for use by individual professional societies, units and clinicians on the use of TNF- $\alpha$  antagonists in clinical guidance; it is recognised that such guidelines may have broader concerns than the management of the risk of TB (e.g. surveillance for other side effects) and may wish to include local good practice advice, however, guidelines should be made cognisant of these recommendations.

**Recommendation:**

Prior to commencing TNF- $\alpha$  antagonists, patients should be thoroughly assessed by the treating physician for clinically active TB disease and for LTBI.

**Figure 3.2: Algorithm for TB assessment prior to the use of TNF- $\alpha$  antagonists**



## 4. Laboratory Diagnosis of Tuberculosis

### 4.1 Role and Goals of the Modern TB Laboratory

The microbiology laboratory makes a key contribution to TB control in terms of diagnosis, infection prevention and control and management of the disease. The detection and isolation of mycobacteria, identification of the mycobacterial species or complex isolated and the determination of susceptibilities of the organism to anti-mycobacterial drugs are key functions of a modern TB laboratory.<sup>110</sup> The gold standard for diagnosing active disease is by microbiological identification of TB by culture. Molecular typing of isolates contributes significantly to understanding the epidemiology of TB. Population based molecular epidemiology studies have been used to evaluate TB control efforts, providing insights into transmission dynamics, enhancing contact tracing and aiding the detection of laboratory cross-contamination.<sup>111</sup> The role and importance of skilled and experienced staff cannot be over emphasised.<sup>112</sup>

In 1993, WHO declared TB a global emergency in response to an increase in cases after nearly a century of decline. Targets for achieving improved control were developed which involved diagnosing a minimum of 70% of individuals with sputum smear positive TB and curing at least 85%. In Ireland, important legislative changes have occurred since the publication of the 1996 TB guidelines.<sup>113</sup> In 2003, the Infectious Diseases Regulations 1981 were amended by the Infectious Disease (Amendment) (No. 3) Regulations 2003 (S.I. No. 707 of 2003), stating that a clinical director of a diagnostic laboratory shall have regard to the case definitions for notification of infectious diseases.<sup>21</sup> The DPH or designated medical officer should be notified of the identification of a TB case ideally within one working day.

#### Recommendation:

It is a mandatory requirement for clinical directors of diagnostic laboratories to notify cases of active TB disease to the medical officer of health (director of public health or designate).

Culture is necessary to achieve the "gold standard" for the diagnosis of active tuberculosis disease.

#### Levels of service

Before offering mycobacteriology services, each laboratory should assess the capacity and capability of the level of services performed. Clinical laboratories offering a mycobacteriology service are divided into three major categories of service (table 4.1). This follows recommendations by CDC and the American Thoracic Society (ATS) stating that laboratories interpreting acid fast stained smears should process at least 10-15 specimens per week to maintain proficiency and those processing specimens for culture should handle a minimum of approximately 20 specimens per week.<sup>114-117</sup> The majority of laboratories in Ireland are Level 2.

**Table 4.1: Levels of service for diagnostic microbiology laboratories**

| Laboratory service level |   |
|--------------------------|---|
| Level 1                  | Collection and transport of specimens; preparation and examination of smears for AFB.   |
| Level 2                  | Procedures of level 1, plus procedures for the isolation of <i>Mycobacterium</i> species. Identification of <i>M. tuberculosis</i> complex may or may not be performed.   |
| Level 3                  | All procedures in level 2, plus identification of all species of mycobacteria. The determination of drug susceptibility for all <i>Mycobacterium</i> species and typing of <i>M. tuberculosis</i> complex should be performed at level 3. |

**Recommendation:**

Microscopy and culture for TB should only be performed in those laboratories where there is sufficient throughput to ensure proficiency.

In 1993, Tenover,<sup>118</sup> Huebner<sup>119</sup> and subsequently CDC<sup>120</sup> and Styr<sup>121</sup> recommended by way of “goals” (not mandates or regulations) that a TB laboratory should report within certain time frames as shown in table 4.2.

**Table 4.2: TB laboratory service goals**

| Goals   | Time frame*      |
|---|------------------|
| Report results of acid fast stains  | Within 24 hours  |
| Detect growth of mycobacteria in liquid medium  | Within 10 days   |
| Identify <i>M. tuberculosis</i> complex by mycolic acid pattern, AccuProbe or Bactec NAP test | Within 3 weeks   |
| Determine and report susceptibilities of new <i>M. tuberculosis</i> isolates to primary drugs | Within 3-4 weeks |

\*Within receipt of specimen in the laboratory

**Recommendation:**

Laboratories should aim to meet the “goals” set down by CDC and others.

**The Irish Mycobacteria Reference Laboratory (IMRL)**

The IMRL was established in 2001 to provide a timely reference service in relation to the diagnosis and treatment of TB (see appendix 7 for contact details). Advice is available from a consultant microbiologist, a respiratory physician with expertise in the treatment of TB and senior laboratory scientists. The Department of Health and Children has set out the core functions that the reference laboratory service will be required to perform once it is fully developed. The IMRL functions include:

- Identification of mycobacterial isolates
- Sensitivity testing of isolates to anti-mycobacterial drugs
- Assistance with isolation of mycobacteria in difficult cases
- Provision of advice to clinicians and laboratories
- Provision of clinical advice on diagnosis, treatment and infection prevention and control
- Provision of a molecular diagnostic service for rapid identification
- Molecular typing of *M. tuberculosis*
- Training of medical/technical staff
- Research
- Provision of epidemiological information as required, subject to agreement with the HPSC.

Some of the above services are currently not available. As the IMRL is developed, all of the services outlined above will be provided.



**Recommendation:**

All mycobacterial isolates should be referred to the Irish Mycobacteria Reference Laboratory (IMRL) for identification and susceptibility testing once its new facility is opened.

**Recommendation:**

All *M. tuberculosis* complex isolates should be referred with immediate effect to the IMRL for molecular typing where typing is now offered.

**Recommendation:**

The results of all *M. tuberculosis* complex isolates which have already had identification, susceptibility and molecular typing performed should be forwarded to the IMRL for incorporation into a national repository of *M. tuberculosis* complex isolates.

## 4.2 Specimens

All specimens should be collected and submitted in sterile, clean, plastic, leak-proof, disposable, wide-mouthed, appropriately labelled, laboratory approved containers, without any fixative. Generally, transport media or preservatives are not needed owing to the robust nature of mycobacteria.<sup>122</sup> Swabs are not optimal for the recovery of AFB.<sup>122</sup> Ideally specimens should be procured before chemotherapy is initiated. Even a few days of therapy can obscure the diagnosis because of the failure to recover mycobacteria.<sup>123</sup> Specimens should be transported to the laboratory as soon as possible and refrigerated until processed. The transportation of infectious substances is subject to international legislation, to which laboratories are required to comply (section 4.7).

### Rejection of unsuitable specimens

The best mycobacteriological laboratory practices are frustrated if a poor or unsuitable specimen is presented for examination. Processing of inappropriate clinical specimens for mycobacteria can be wasteful, may be rejected and the clinician notified.

Examples of inappropriate specimens are as follows:

- Insufficient amount submitted
- Specimens consisting of saliva
- Dried swabs
- Pooled sputa or urine
- Broken sample containers
- Interval too long between specimen collection and processing<sup>124</sup>
- Analysis of urine specimens for the diagnosis of pulmonary TB.

**Recommendation:**

Reasonable efforts should be made to obtain the best quality sample possible depending on site of disease and to deliver it in a timely fashion to the analysing laboratory.

### Sputum specimens

A direct relationship between mucopurulent sputum and positive results has been demonstrated.<sup>125</sup> Therefore, patients should be instructed as to the proper method of sputum collection. Ideally a 5-10ml specimen<sup>122;126</sup> collected early in the morning<sup>§§</sup> on three consecutive days (with a minimum of one early morning specimen) prior to the commencement of treatment, if possible, is required (or failing that, within seven days of commencement of treatment).<sup>123;126;127</sup> Failure to isolate *M. tuberculosis* complex (MTC) from appropriately collected specimens from persons suspected of having a pulmonary diagnosis does not exclude a diagnosis of active TB. Depending on the clinical features and differential diagnosis, other diagnostic testing such as induced sputa, bronchoscopy lavage and biopsy should be considered before making a presumptive diagnosis of culture negative TB.<sup>128</sup>

### Bacteriological monitoring

Bacteriological monitoring after diagnosis may be required to assist with a decision to discontinue isolation. The period of time a patient on effective therapy takes to become non-infectious varies. Patients who have unrecognised or inadequately treated drug-resistant TB may remain infectious for weeks or months.<sup>129</sup> Laboratories can be overwhelmed with specimens obtained for the purposes of demonstrating smear conversion in smear positive patients. This can also contribute to an increase in false positive cases in the laboratory. It should be noted that beyond 12 weeks of treatment, 63% to 73% of patients with persistently positive smear results have negative culture results. In the absence of MDR-TB and XDR-TB, the persistence of AFB in smears at the end of therapy is not necessarily a treatment failure.<sup>130;131</sup> Laboratories should liaise with clinicians to develop a protocol for processing such specimens. Follow-up sputum specimens for smear and culture should be obtained monthly in patients with drug-susceptible pulmonary disease. For patients with isoniazid- and rifampicin-susceptible TB there is no need to examine sputum monthly once culture conversion is documented (i.e. two negative cultures taken at least 2 to 4 weeks apart).<sup>77</sup> It is recommended that identification and sensitivities are repeated in cases who are still culture positive at  $\geq$  two months. If the patient has isoniazid and/or rifampicin resistant TB, sputum cultures should be examined monthly until the end of treatment.<sup>77</sup> Bacteriological monitoring i.e. culture at the end of treatment is strictly recommended in confirmed cases of TB to assess precisely that the patient has been cured. Culture positive *Mycobacterium tuberculosis* complex (MTC) from each different site should undergo identification and sensitivity testing.

### Induced sputum and fiberoptic bronchoscopy

Hypertonic saline can be nebulised for induction of sputum. Bronchoscopy is the next best choice because this procedure provides additional material for study, washings, brushings and biopsy specimens. Induced sputum has been shown to be as sensitive<sup>132</sup> or more sensitive<sup>133;134</sup> than bronchoscopy and is also cheaper to perform. Sputum induction in children has been shown to be safe and useful for microbiological confirmation of TB in children and preferable to gastric lavage.<sup>135</sup> Where facilities permit it may be preferable to gastric lavage.<sup>135</sup>

The bronchoscopy procedure may cause the patient to continue producing sputum for several days. The use of bronchoscopy in evaluating children with TB is not routine but it can provide useful information in selected cases.<sup>136</sup> (See section 8.1. Chapter 8 for contact tracing) (See section 6.5. Chapter 6 for infection prevention and control). These samples should also be collected and examined.<sup>110</sup>

### Gastric washings

Gastric lavage may be necessary for those patients, particularly children, who cannot produce sputum even with aerosol inhalation. Fasting early morning specimens are recommended to obtain sputum swallowed during sleep.<sup>124</sup> These specimens should be processed within four hours or neutralised with sodium carbonate or another buffered salt to a pH of 7.0. It has been suggested that for these reasons gastric aspiration is best performed by experienced staff.<sup>137</sup> AFB smear testing is unreliable due to the high prevalence of atypical mycobacteria in gastric lavage. Culture should only be used for further clinical management.

### Urine

Urine is an inappropriate specimen for the diagnosis of pulmonary TB. The diagnosis of renal TB, disseminated TB or TB in severely immunocompromised persons can be aided by the culture of 3 early

§§ Early morning sputum: sputum from the first productive cough in the day (after waking)

morning mid-stream urines each with a volume of 40-50ml. Smears of urine are usually negative and may not be cost effective<sup>110</sup> or they may give unreliable results due to the presence of environmental mycobacteria that may be found in the lower urethra.<sup>127</sup> However, if examination of urine is restricted to those patients who are severely immunocompromised, suspected of having renal or disseminated TB, or when haematuria or sterile pyuria has been demonstrated, the value of performing smears may be improved.

### Faeces

Faecal specimens are largely used in the detection of *Mycobacterium avium* complex (MAC) from the intestinal tract of patients with HIV/AIDS, in conjunction with specimens from other sites. Interpretation may also be difficult due to the presence of saprophytic AFB frequently present in faeces samples.<sup>127</sup>

### Cerebrospinal fluid

Cerebrospinal fluid (CSF) should be examined for protein, glucose and white cell count and differential. Lymphocytosis together with a low glucose and high protein are typical of TB meningitis. The volume of CSF is critical and a minimum of 5ml<sup>110</sup> but up to 10ml is ideally required<sup>126;138</sup> provided it is medically safe to obtain this volume. Studies should be undertaken prior to the administration of anti-tuberculous chemotherapy. There is a low yield of approximately 40% and if feasible it may be worthwhile to perform repeat cultures.

### Blood culture

Infection with *Mycobacterium* species became increasingly common as the incidence of HIV infection and AIDS increased. Up to 63% of HIV/AIDS patients with active TB disease have positive blood cultures.<sup>139</sup> Blood culture should be the first step in the routine evaluation of HIV positive patients with suspected TB.<sup>140</sup>

### Tissue

When non-invasive procedures have failed to provide a diagnosis, invasive procedures to obtain specimens from lung, pericardium, lymph nodes, bones and joints, bowel, etc. should be considered.<sup>110</sup> **Specimens submitted in formalin are not suitable for microbiological smear and culture.** In patients with haematogenous or disseminated disease, bone marrow biopsy, lung biopsy and liver biopsy for histological examination and culture can be useful.<sup>110</sup> Tissue is preferable to necrotic material or pus, as the latter contain free fatty acids that are toxic to mycobacteria.<sup>127</sup> A caseous portion should be selected if possible as the majority of organisms will be found in the periphery of a caseous lesion.<sup>126</sup> Pleural biopsy shows granulomatous inflammation in approximately 60% of patients.<sup>110</sup> Minute amounts of biopsy material may be immersed in a small amount of sterile saline to stop them drying out.

### Body fluids

Pleural, peritoneal, synovial and pericardial fluids should be aseptically collected by aspiration or during surgical procedures and transported to the microbiology laboratory immediately. It should be noted that detection of AFB in smears of culture positive pleural fluids is extremely low at between 0 to 1%<sup>141</sup> and the sensitivity of nucleic acid amplification tests (NAAT) has been shown to be in the order of only 27 to 32% using fully commercially available methods (see section on nucleic acid amplification tests).<sup>142</sup>

## 4.3 Specimen Processing

### Microscopy

Acid-fast microscopy is "the microscopic examination of stained smears for the presence of organisms that retain the primary stain when the smear is decolourised with an acid alcohol solution". Fluorescence staining,<sup>143</sup> of clinical material using auramine-o or auramine-rhodamine is to be preferred over Ziehl-Neilson (ZN) staining because it is quicker and easier to read,<sup>124;144;145</sup> whilst the ZN is more appropriate in determining microscopic morphology of bacilli in positive TB cultures. Factors affecting the sensitivity of smears are many and include the staining technique, centrifugal force, decontamination technique used, the infecting species, reader experience and the prevalence of disease in the population being tested.<sup>110;145;146</sup>

#### Key points relating to microscopy:

- Results should be available within one working day
- Microscopy of clinical material (by either Auramine or Ziehl-Neilson (ZN)) is the easiest, most cost-effective and rapid procedure for detecting mycobacteria

- Both viable and non-viable organisms will stain acid fast
- Microscopy has a sensitivity of approximately 90% for the most infectious cases of presumed TB. It therefore provides information to support respiratory isolation of patients and other infection control measures that prevent transmission of disease.
- The grading of a smear can give some indication to the probability of a positive culture<sup>124;147</sup> (see table 4.3)
- The minimum number of bacilli necessary to produce a result has been estimated to be between 5,000 and 10,000 per millimetre of sputum. The incremental yield of AFB from serial smear examination has been shown to be 80-82% for the first, 10-14% for the second and 5-8% for the third specimen.<sup>124;147</sup>
- 50-80% of patients with pulmonary TB will have positive smears<sup>110</sup>
- It is a useful tool for initiating treatment and monitoring the progress of anti-TB drug therapy
- Fluorescence microscopy is more sensitive and as specific as conventional AFB microscopy<sup>148</sup>
- A minimum of 75 fields (250x) or 300 fields (1000x) should be examined by fluorescence and ZN respectively<sup>145</sup>
- Re-examination of negative smears from specimens with positive culture can dramatically decrease a laboratory's rate of false negative smears<sup>144</sup>
- Supervisory review of doubtful results in newly diagnosed patients can markedly decrease the incidence of false positive smears<sup>144;145</sup>
- Optimal results for sputum are obtained when auramine phenol stain is applied to a liquefied, concentrated sample and examined before the decontamination process<sup>149</sup>
- In laboratories with good expertise the predictive value of a positive smear can be as high as 90% and the predictive value of a negative smear 96% (based on good quality specimens)<sup>144</sup>
- The laboratory should participate in an external quality assurance scheme e.g. UK NEQAS AFB scheme.

**Table 4.3: Relationship of acid-fast smear and culture yield**

| Report           | No. of AFB seen by staining method and magnification |              |          |               | Estimated concentration of bacilli | Probability of a culture positive result |
|------------------|--|--------------|----------|---------------|------------------------------------|--|
|                  | ZN stain   | Fluorochrome |          |               |                                    |  |
|                  | X 1,000  | X 250        | X 450    |               |                                    |  |
| Doubtful; repeat | 1-2/300F   | 1-2/30F      | 1-2/70F  | 5,000-10,000  | 50%                                |  |
| 1+               | 1-9/100F   | 1-9/10F      | 2-18/50F | About 30,000  | 80%                                |  |
| 2+               | 1-9/10F  | 1-9/F        | 4-36/10F | About 50,000  | 90%                                |  |
| 3+               | 1-9/F  | 10-90/F      | 4-36/F   | About 100,000 | 96.2%                              |  |
| 4+               | > 9/F  | >90/F        | >36/F    | About 500,000 | 99.95%                             |  |

### Decontamination

Many of the specimens sent for the isolation of *Mycobacterium tuberculosis* are contaminated with commensal flora originating from the specimen site. This is particularly true of specimens from the respiratory and genitourinary tracts. Sodium hydroxide is the most common decontaminating agent used in mycobacteriology. A contamination rate of between 2% to 5% is deemed acceptable.<sup>115</sup> An incidence of less than 2% may suggest excessive decontamination and above 5% may suggest that cultures which might contain mycobacteria may be overgrown by commensal organisms.<sup>110</sup>

Samples from cystic fibrosis (CF) patients present a significant problem in that *Pseudomonas aeruginosa*, isolated from approximately 80% of CF patients can hinder and even prevent the recovery of

*Mycobacterium tuberculosis*.<sup>150</sup> A two-step approach is advised where samples are initially decontaminated with N-acetyl-L-cysteine NaOH (NALC/NaOH) and only those samples which remain contaminated are subjected to a second round of decontamination with NALC/NaOH and oxalic acid. Results suggest that this protocol could improve the recovery of mycobacteria from heavily contaminated specimens.<sup>151</sup>

### Culture

Culture is the bedrock and most reliable tool for the diagnosis of TB<sup>152</sup> and has a detection limit of 10<sup>1</sup> to 10<sup>2</sup> viable organisms.<sup>124</sup> It is essential so that isolates are available for susceptibility testing, the results of which are necessary for the proper management of the patient. A confirmed case of TB is a case with culture confirmed disease due to *M. tuberculosis* complex.<sup>23</sup>

Isolates are also necessary in genotyping studies which are required for epidemiological investigations and tracking laboratory cross-contamination.<sup>153</sup> *Mycobacterium tuberculosis* is a slow growing bacterium and special media and procedures, not required for the culture of other organisms, are necessary.<sup>127</sup> Agar based and egg based media, Middlebrook broths or solid media, the "traditional" methods of culture, have been superseded by the semi automated Bactec 460 and more recently by the continuous automated monitoring in liquid culture techniques (CAMLiC)<sup>154</sup> e.g. the Bactec MGIT960™, MB/BacT Alert 3D™ and the VersaTREK™ systems. These are now the basis of the "gold standard" in the isolation, culture and definitive diagnosis of mycobacterial disease.

Each of the Bactec 460TB and CAMLiC systems has advantages and disadvantages and the choice of system is often based on non-microbiological factors, e.g. size of equipment, quality of manufacturer's service and maintenance or in-built electronic data management systems. The microbiological factors include:

- Sensitivity of the detection system
- Performance in recovery of *Mycobacterium tuberculosis* complex (MTC) and non-tuberculous mycobacteria (NTM)
- Speed to positivity
- Ability to perform susceptibility tests to anti-mycobacterial drugs and
- Chemical agents, safety and cross-contamination.

It is emphasised that in order to get optimal recovery of mycobacteria from clinical specimens using a CAMLiC system, a combination of liquid and solid media is essential especially in non-specialised laboratories with a low incidence of *M. tuberculosis*.<sup>155-157</sup>

#### Recommendation:

It is recommended that solid media be used in combination with a liquid culture system.

### Nucleic acid amplification tests (NAAT)

CDC has produced an updated algorithm which offers useful guidance on the use of nucleic acid amplification tests (NAAT)<sup>158</sup> directly on specimens. CDC now recommends that NAAT should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities such as contact tracing.<sup>158</sup>

#### Recommendation:

All those wishing to undertake NAAT on suspected cases of pulmonary TB should seek advice from the local consultant microbiologist. It is recommended that NAAT should be made available at the IMRL.

Clinicians need to be aware of the limitations of these tests particularly in relation to the types of specimens analysed, the commercial system in use and the quality assurance programmes in place.<sup>159-162</sup> Application of NAAT for the diagnosis of TB in sputa, CSF, and the detection of rifampicin and isoniazid resistance in primary and reference specimens should be provided only where there is an adequate infrastructure, primarily sufficient space for a unidirectional workflow and dedicated equipment.<sup>163</sup> Standardised methods with adequate and appropriate positive and negative controls should be used.<sup>112</sup>

A cost effective approach is to base these tests in laboratories in Ireland with expertise in molecular biology. For procedural and economic reasons, NAAT might be impractical for laboratories with a small volume of testing. Referral of samples for NAAT to high-volume laboratories might be preferable to improve cost-efficiency, proficiency and turnaround times.<sup>158</sup>

## 4.4 Processing of Positive Cultures

### Identification methods

#### Phenotypic methods

Microscopic and colonial morphology and other growth characteristics are useful in making a preliminary identification of an acid-fast bacillus. Colonies of the tubercle bacilli are described as being "rough, tough and buff" on solid media and colonies tend not to emulsify easily for making smears. MTC form serpentine chords in liquid media and are easily observed with ZN staining. These characteristics can lead to the most relevant tests being performed on each isolate to obtain identification.<sup>127</sup>

#### Probe techniques

Probe detection methods such as the AccuProbe, targeting ribosomal RNA gene, can identify the MTC, *M. avium*, *M. intracellulare*, *M. avium complex* (MAC), *M. goodii* and *M. kansasii*. The technique is relatively simple and the results are available within hours. The specificity has been shown to be 100% but the sensitivity can vary within the species or species complexes.<sup>124</sup>

#### PCR and restriction endonuclease analysis

In 1993, Telenti<sup>164</sup> modified the Polymerase Chain Reaction (PCR)-Restriction Endonuclease Analysis technique, subsequently known as the PRA method, to allow for the rapid identification of mycobacteria to the species level. The method has been used extensively for mycobacterial identification. The principal disadvantage is that it is not commercialised and does not have US Food and Drug Administration (FDA) approval or carry CE\* markings.

#### PCR and reverse hybridisation techniques

New molecular biology techniques based on PCR and reverse hybridisation procedures have recently been marketed for mycobacterial identification. The hybridisation technique is performed on nitrocellulose strips onto which probe lines are fixed in parallel. This format enables simultaneous detection and identification of different mycobacterial species. At present, two systems with this design are commercially available in Europe, the INNO-LiPA™ Mycobacteria v2 test, designed to amplify the mycobacterial 16S-23S rRNA spacer region, and the HAIN GenoType™ Mycobacteria assay, targeting the mycobacterial 23S rRNA.<sup>165</sup> Both methods can be completed within two working days and allow precise identification of the majority of mycobacteria usually isolated in clinical laboratories. They are expensive to perform but this can be offset by the reduction in turnaround and labour times. These methods are available in the United States as FDA-approved tests and bear the CE mark in the European Community.

#### DNA sequencing

The availability of DNA sequencing technologies constitutes a great benefit for mycobacterial identification, owing to the slow growth of these organisms. Recent improvements in automation of target amplification and sequence analysis have led to the practical implementation of DNA sequencing in some clinical laboratories.<sup>124</sup> The technique requires expensive equipment and is best reserved for reference laboratories.

\* The CE marking (also known as CE mark) is a mandatory conformity mark on many products placed on the single market in the European Economic Area (EEA).



### **Mycobacterium tuberculosis complex (MTC)**

The *Mycobacterium tuberculosis* complex now consists of the following strains; *M. tuberculosis* sensu stricto, *M. bovis*, *M. bovis* BCG, *M. africanum*<sup>166</sup>, *M. canettii*<sup>167</sup>, *M. bovis* subsp. *caprae*<sup>168;169</sup>, *M. microti*<sup>170</sup>, and *M. pinnipedii*.<sup>171</sup> All are known to cause infections in humans but they differ in their primary host, geographic range and pathogenicity. *M. microti* grows very slowly, often requiring up to 16 weeks incubation in liquid and solid culture media.

Various methods may be used in order to differentiate members of the MTC. Specific inhibitors can be added to a culture medium and growth or the lack of growth determined e.g. thiophen-2-carboxylic hydrazide (TCH). *M. tuberculosis* is resistant to TCH while the other members of the complex are sensitive. Similarly, susceptibility to pyrazinamide is useful in differentiating *M. bovis* from other members of the complex in the majority of cases.

More recently, a new commercially available DNA strip, GenoType MTBC, has been developed and evaluated.<sup>172;173</sup> Results demonstrated that the assay could unambiguously differentiate all of the MTC, with the exception of *M. tuberculosis*, *M. africanum* type II and *M. canettii*. The latter is considered to be a smooth variant of *M. tuberculosis*<sup>167</sup> and *M. africanum* II has not been successfully differentiated from *M. tuberculosis* using molecular techniques suggesting that it likely represents phenotypically atypical *M. tuberculosis* strains.<sup>174</sup>

The GenoType MTBC was found to:

- Enable a very rapid identification of the MTC
- Fit into the work flow of a routine laboratory and
- Be conducted in laboratories that do not carry out sophisticated biochemical tests for differentiation of the MTC.

The results of these studies challenge the use of biochemical characteristics for classifying these organisms in diagnostic laboratories.<sup>174</sup>

### **Susceptibility testing of *M. tuberculosis***

CDC has recommended that mycobacteriology laboratories work towards the goal of reporting first-line susceptibility results for MTC within three to four weeks of receipt of the initial diagnostic specimen. Ideally, susceptibility results should be available within seven to 14 days after isolation of an MTC isolate. *M. tuberculosis* complex resistance is defined as "a decrease in sensitivity of sufficient degree to be reasonably certain that the strain concerned is different from a sample of wild strains of human type that have never come into contact with the drug".<sup>175</sup> Methods of drug susceptibility are not designed merely to detect drug resistant mutants but are also to show that the great majority of bacilli in a culture are as susceptible to a given drug as one or more known susceptible strains. The object of susceptibility testing is therefore to determine whether an isolate is as likely to respond to standard therapy as one or more known susceptible strains.<sup>127</sup>

There are five methods in current use as outlined below:

1. The absolute concentration method which is popular in some parts of Europe
2. The proportional method also used in Europe and using Middlebrook 7H10 agar is the "gold standard" method in the USA
3. The disk diffusion method
4. The resistance ratio method is used in the UK and those countries that are influenced by UK practice and
5. Commercially available systems, including the FDA approved Bactec 460TB, Bactec MGIT 960 and the Versa TREK systems.

The first four methods rely on conventional media and thus have the great disadvantage that there is a long delay before results are available. In developed nations commercially available systems are used, so that results are made available more rapidly.<sup>127</sup> If resistance is detected the test may be repeated for confirmation purposes, however, a report of the initial result should not be delayed while the repeat testing is being performed. The report should indicate that the drug resistance findings are preliminary and confirmatory testing has been initiated.

The first isolate of MTC obtained from every patient should be tested but also each isolate recovered

from each different anatomical site in the same patient. Susceptibility tests should be repeated if there is clinical evidence of failure to respond to therapy or if cultures fail to convert to negative after two months of therapy. For patients with resistant isolates, including resistance to the lower, critical concentration of isoniazid, referral to or consultation with a specialist in TB treatment should be considered.<sup>175</sup>

The application of two commercially available DNA line probe assays, Genotype MTBDR™ and INNO-LiPA Rif™ to detect resistance to isoniazid and rifampicin (HAIN) or rifampicin alone (INNO LiPA) can be performed when there is a strong suspicion of MDR-TB. Neither is 100% sensitive and results must be confirmed by conventional testing.<sup>176</sup> In vitro susceptibility tests are very satisfactory for isoniazid, rifampicin and pyrazinamide and slightly less so for streptomycin. Results from ethambutol (E) and second line drugs may vary depending on the test method used.

### Monitoring of anti-mycobacterial drug serum levels

This may be occasionally required in suspected cases of non-compliance, malabsorption or toxicity. This service can be provided by prior arrangement with the Antimicrobial Reference Laboratory in Southmead Hospital, Bristol (see appendix 7 for contact details).

### Molecular typing of *M. tuberculosis*

There are currently three prominent methods for typing of *M. tuberculosis* strains. The current "gold standard" is the IS6110-based restriction fragment length polymorphism fingerprinting.<sup>177</sup> This technique is technically demanding and requires abundant amounts of growth of isolates. The remaining two methods are polymerase chain reaction (PCR)-based genotyping tests, mycobacterial interspersed repetitive units (MIRU) typing<sup>178</sup> and spoligotyping.<sup>179</sup> In combination, the latter two tests (MIRU typing and spoligotyping) provide a highly discriminatory method to identify strains and will be used in the CDC TB Genotyping Programme to enable rapid genotyping of isolates from every patient in the United States.<sup>180</sup> The IMRL intends to use MIRU typing in the first instance supported by spoligotyping.

Genotyping of isolates can assist in the clinical and public health management of patients in several situations:<sup>112</sup>

- Genotyping allows evaluation of isolates with different patterns of drug susceptibility. The original organism may develop drug resistance during or after anti-TB therapy or the patient may be re-infected with a different strain. The former may be due to non-adherence to therapy or reduced concentrations of anti-TB drugs as a result of malabsorption or drug interaction. The latter may be due to re-infection which would require further contact tracing investigations as a public health issue.
- Evaluation of an outbreak can be more clearly delineated or previously unrecognised contacts detected
- Genotyping can help to establish where resources might best be directed in a TB control programme
- On average 3% of patients from whom *M. tuberculosis* is apparently isolated in clinical laboratories do not have TB. These positive cultures are due to cross-contamination.<sup>181</sup>

## 4.5 False Positive Cultures

A review of reports of false positive cultures for *M. tuberculosis* showed that false positives were identified in 93% of studies that evaluated more than 100 patients.<sup>181</sup> The median false positive rate was 3.1%, with a range of 2.2% - 10.5%, and even higher rates (13.6%) have since been published.<sup>182</sup> The mechanism of false positive cultures can be many and include contamination of clinical equipment, clerical error and laboratory cross-contamination.

For the purposes of further investigation, the source laboratories should not delay the forwarding of possible false positive *M. tuberculosis* complex isolates to the IMRL. The IMRL should perform DNA fingerprinting on all positive *M. tuberculosis* isolates and not delay the reporting of test results back to the source laboratory. Confirmed false positives should be reported back to the clinicians as soon as possible. Clinicians should balance laboratory test results with their clinical judgement on whether or not a patient has TB and inform the laboratory of any doubts.



### Laboratory cross-contamination

Often the most significant laboratory feature is that the false positive culture is the only positive culture from a patient. However, single positive cultures also occur among patients who meet the clinical criteria for a diagnosis of TB. Prospective monitoring of single-positive cultures detected two outbreaks of laboratory cross-contamination that had not been recognised by clinicians or laboratory personnel.<sup>181</sup>

The quality assurance programme for mycobacteriology laboratories should include a plan for the identification and review of possible false positive cultures. Criteria that might prompt a review should include a patient with a single culture positive specimen, cultures with a very low colony count on solid media and isolates with unexpected drug resistance.

### Possible causes of laboratory cross contamination

The most common causes of laboratory cross-contamination include:<sup>183</sup>

- Contamination of multiple-use equipment for dispensing reagents
- Aerosols
- Splashing
- Sampling equipment
- Reprocessing of contaminated specimens and
- Mislabelling.

The general principle is to isolate each specimen completely so that there are no opportunities to transfer an inoculum from one sample to another via pipettes, the lips, caps of tubes, splashes or common reservoirs of reagents or containers used for discarded materials. Examples of good laboratory practice include the following:<sup>184</sup>

- Only bring the required numbers of items such as loops, swabs, pipettes, universal containers, etc. into the safety cabinet for each session of work
- When using pipettes to deliver reagents, use a separate pipette for each specimen and each time that the reagent bottle is entered
- Individually wrapped sterile plastic pipettes should be used
- Reagents, such as sodium hydroxide, should be supplied or prepared in individual sterile vials. Use a separate vial to add a reagent to each sample rather than dispensing it from a common container.
- Remove and replace the cap from each specimen tube sequentially during the addition of reagents to specimens, so that only one tube is open at a time and so that tube caps do not become interchanged
- Avoid spills and splashes when decanting supernatants
- Clean and disinfect the exposed surfaces of the safety cabinet after each session of work
- Where possible ensure that specimens are processed in the order of smear negative to smear positive specimens. This requires the keeping of an up-to-date list of known smear positive patients.
- Process positive culture vials only when all the work on specimens has been completed for the day
- At the end of the working day dispose of any used items in the cabinet and clean and disinfect the interior surfaces of the safety cabinet
- If possible, use a separate safety cabinet for specimens and all positive cultures, whether liquid or solid<sup>185</sup>
- Investigate for possible cross-contamination when specimens in proximity to one another become positive. Cross-contamination may not occur with all samples in sequence, such that negative cultures occasionally may be found between positive cultures<sup>183</sup>
- Ensure that written procedures for the processing of cultures include detailed instructions and that staff have a very good understanding of the rationale for all aspects of the procedure.

## 4.6 Interferon Gamma Release Assays (IGRA)

The TST is a long established test that uses a relatively crude mixture of antigens from *M. tuberculosis* to detect the immune response to infection with *M. tuberculosis* (past or present). As a result false positive reactions can occur because of previous BCG vaccination or sensitisation to non-tuberculous mycobacteria. It has many limitations and requires well-trained personnel to both administer and interpret the test (see chapter 2).

The immune response to infection with *M. tuberculosis* is predominantly a cell mediated immune (CMI) response. As part of this response, T-cells are sensitised to *M. tuberculosis* antigens. Activated effector T-cells produce a cytokine called Interferon gamma (IFN- $\gamma$ ) when stimulated by these antigens. Laboratory blood tests have been developed that detect this release of gamma interferon and are collectively known as interferon gamma release assays (IGRA). The use of selected antigens for the *M. tuberculosis* complex improves specificity by reducing cross-reactivity to the BCG vaccine and to many environmental mycobacteria.<sup>186</sup>

Two separate panels of antigens which simulate the well characterised proteins ESAT-6 and CFP10, are used to optimise the sensitivity of the T-SPOT.TB test, while the QuantiFERON-TB® Gold In-Tube (IT) method additionally incorporates a third antigen, TB7.7 (p4). The T-SPOT.TB and the QuantiFERON-TB Gold® IT are tests for *M. tuberculosis* complex infection (including disease) and are intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.

### T-SPOT.TB (Oxford Immunotec)

T-SPOT.TB is a simplified variant of the enzyme-linked immunospot (ELISPOT) assay technique. The assay is designed for the detection of effector T-cells that secrete the cytokine in response to stimulation by antigens specific for *M. tuberculosis*.<sup>187-190</sup>

### Limitations of the TSPOT.TB

According to the manufacturer:

- While ESAT-6 and CFP10 antigens are absent from BCG strains and from most environmental mycobacteria, it is possible that a positive result from the T-SPOT.TB assay may be due to infection with *M. kansasii*, *M. szulgai* or *M. marinum*. Alternative tests would be required if these infections are suspected
- Variation to the stated pipetting and washing techniques, incubation times and/or temperatures may influence the actual results obtained and should be avoided
- Blood must be collected and progressed into the assay within eight hours
- T-SPOT.TB should be used and interpreted only in the context of the overall clinical picture
- A negative test result does not exclude the possibility of exposure to or infection with *M. tuberculosis*
- Individual users should validate their procedures for collection of PBMCs, enumeration of PBMCs and choice of suitable media to support T-cell functionality during the primary incubation stage of the assay and
- Failure to adhere to the recommended incubation time may lead to an incorrect interpretation of the result.

### QuantiFERON-TB Gold®- In-Tube (IT)

QuantiFERON-TB Gold®- In-Tube (IT) (Cellestis, Victoria, Australia) is an in vitro diagnostic test using a peptide cocktail simulating ESAT-6, CFP-10 and TB7.7(p4) proteins to stimulate cells in heparinised whole blood. Detection of IFN- $\gamma$  by enzyme-linked immunosorbent assay (ELISA) is used to identify in vitro responses to these peptide antigens that are associated with *M. tuberculosis* complex infection.

### Limitations of the QuantiFERON-TB Gold® In-Tube (IT)

According to the manufacturer:

- The magnitude of the measured IFN- $\gamma$  level cannot be correlated to the stage or degree of infection, level of immune responsiveness or likelihood for progression to active disease
- A negative QuantiFERON-TB Gold® IT result does not preclude the possibility of *M. tuberculosis* infection or TB disease: false-negative results can be due to the stage of infection (e.g. specimen obtained prior to the development of cellular immune response), co-morbid conditions which affect immune functions, incorrect handling of the blood collection tubes following venepuncture, incorrect performance of the assay or other immunological variables
- A positive QuantiFERON-TB Gold® IT result should not be the sole or definitive basis for determining infection with *M. tuberculosis*. Incorrect performance of the assay may cause false positive responses. Diagnosing or excluding TB disease and assessing the probability of LTBI, requires a combination of epidemiological, historical, medical and diagnostic findings that should be taken into account when interpreting QuantiFERON-TB Gold® IT results

- A positive QuantiFERON-TB Gold® IT result should be followed by further medical evaluation and diagnostic evaluation for active TB disease (e.g. AFB smear and culture, chest X-ray)
- While ESAT-6, CFP-10 and TB7.7 (p4) are absent from all BCG strains and from most known non-tuberculous mycobacteria, it is possible that a positive QuantiFERON-TB Gold® IT result may be due to infection by *M. kansasii*, *M. szulgai* or *M. marinum*. If such infections are suspected, alternative tests should be investigated.

### Sensitivity and specificity of IGRA

The lack of a gold standard for the diagnosis of LTBI makes it difficult to estimate the sensitivity or specificity of IGRA or TST. Most studies use newly diagnosed active TB as a surrogate for LTBI but there is an inherent problem with this, in that the cell-mediated immune response being measured must have failed, to some extent, in any person with active disease. It has been well documented that in patients with active infection the cell-mediated immune response is often diminished and this possibly explains the finding that all three tests, but particularly TST, has sub-optimal sensitivity.<sup>61,191-193</sup> Of the three, the T-SPOT.TB was found to have the highest sensitivity and this correlates well with studies of immunocompromised patients that have shown T-SPOT.TB to have better sensitivity than TST.<sup>194-196</sup>

Other studies compared IGRA and TST among contacts categorised into clinically defined gradients of exposure and sought to measure the agreement or discordance between the three. However, this is limited by differences in the degree and categorisation of exposure. The prevalence of positives was found to be similar for the most exposed groups but the TST had a greater prevalence of positives in the least exposed groups. Discordance was shown to be higher in persons with BCG vaccination, especially those vaccinated at age two years or older.<sup>63,197,198</sup>

Despite the variability in studies to date the most consistent finding has been the high specificity of IGRA. This is most likely due to the fact that IGRA use antigens that are not found in BCG or most non-tuberculous mycobacteria. To date there have been insufficient studies of IGRA performance among children, immunocompromised persons and the elderly.

## 4.7 Laboratory Safety

### Levels of containment

The principal legal framework governing safety in relation to biological agents is contained in the following:

- The Safety, Health and Welfare at Work Act 2005
- The Safety, Health and Welfare at Work (General Application) Regulations 2007 (S.I. No. 299 of 2007)
- The Safety, Health and Welfare at Work (Biological Agents) Regulations, 1994 as amended in 1998 (S.I. No. 146, 1994, and S.I. No. 248 of 1998).

These give effect to the European Council, Biological Agents Directives.

Official copies of the legislation can be purchased from the Government Publications Sale Office, Sun Alliance House, Molesworth Street, Dublin 2. Tel. No: 01-6476000 or copies can be downloaded from [www.irishstatutebook.ie](http://www.irishstatutebook.ie).

The following containment measures in the Seventh Schedule (Safety Health and Welfare at Work (Biological Agents) regulations, S.I. No. 146, 1994) of the legal framework are compulsory:

- Extract air to the workplace are to be filtered using HEPA
- Access is to be restricted to nominated workers only
- There must be specified disinfection procedures
- Effective vector control e.g. rodents and insects
- Surfaces (bench and floor) impervious to water and easy to clean
- Surfaces resistant to acids, alkalis, solvents and disinfectants
- Safe storage of a biological agent and
- Infected material is to be handled in a safety cabinet (class 1 or class 2) or other suitable

containment.

Although the Seventh Schedule recommends the following points, the National TB Advisory Committee is proposing that these recommendations outlined below should be considered compulsory.

- The workplace is to be separated from any other activities in the same building
- The workplace is to be sealable to permit disinfection
- The workplace is to be maintained at an air pressure negative to atmosphere
- An observation window, or an alternative, is to be present, so that occupants can be seen and
- A laboratory is to contain its own equipment.

The decision to make this proposal has been influenced by looking at best international practice in relation to the items that are recommended. In the UK, the Control of Substances Hazardous to Health regulations 1994 (COSHH) implements the EC Biological Agents Directive. The Advisory Committee on Dangerous Pathogens (UK) (ACDP) originally published the *Categorisation of biological agents according to hazard and categories of containment (4<sup>th</sup> edition) 1995*.<sup>199</sup> This guidance has now been replaced by *The management, design and operation of microbiological containment laboratories, 2001*.<sup>200</sup> This publication complements the Health and Safety Commission's Health Service Advisory Committee's (HSAC) guidance on *Safe working and the prevention of infection in clinical laboratories and similar facilities*<sup>201</sup> and the ACDP publication *Biological agents: Managing the risks in laboratories and healthcare premises*.<sup>202</sup> Under this guidance the above recommendations are compulsory.

In the USA, laboratories performing functions at ATS level 2 or 3 must use Biosafety Level 3. Biosafety level 3 is very similar to Containment Level 3 (CL3) and the above recommendations are included as rules.<sup>114;203</sup> Finally, a CL3 Laboratory will fail to achieve accreditation with Clinical Pathology Accreditation (UK) Ltd if these recommendations are not in place.

#### Recommendation:

Recommendations in the Seventh Schedule of the S.I. No. 146/1994 Safety, Health and Welfare at Work (Biological Agents) Regulations 1994 should be interpreted as mandatory in relation to working with *M. tuberculosis* complex.

#### Transportation

The transport of infectious substances by road, rail, sea and air are each the subject of international regulation, whose whole description is beyond the remit of these guidelines. The relevant legislation in Ireland for transport by road is the "Carriage of Dangerous Goods by Road" Regulations 2007 Statutory Instrument No. 288 of 2007<sup>204</sup> and the 2007 ADR regulations.<sup>205</sup>

#### Specimens

Biological substances that have been correctly classified as UN No. 3373 which are packaged and marked in accordance with packaging instruction P650, are not subject to any other requirements of the 2007 ADR regulations. This implies that provided the correct packaging is used, there is no requirement for any ADR documentation or for the requirement to have specially marked and equipped vehicles or trained drivers. In summary, any method of transportation can be used to transport patient specimens by road once properly packaged and labelled.

#### Cultures

For transport purposes, pathogens are assigned to two categories, A and B. Category A includes the higher risk infectious microorganisms such as *M. tuberculosis* complex but only when it is present as a culture. Nevertheless, when cultures that are being transported by road are intended for **diagnostic** or **clinical** purposes (not research), they may be classified as infectious substances of Category B. Infectious substances in Category B shall be assigned to UN No. 3373 and the proper shipping name of *UN No. 3373*

is "BIOLOGICAL SUBSTANCE, CATEGORY B". These are transported in accordance with ADR packaging regulations P650.

However, at the time of publication of this document, when cultures of *M. tuberculosis* complex are being transported by air or sea they must follow the International Air Transport Association (IATA) and the International Maritime Dangerous Goods (IMDG) regulations, that currently assign *M. tuberculosis* to Category A and they must be transported as UN No. 2814 "INFECTIOUS SUBSTANCE AFFECTING HUMANS" and packaged in accordance with packing instruction P620.<sup>205</sup> This is most easily achieved by using an approved and licensed courier.

### ***M. tuberculosis* complex outside the CL3 laboratory**

It is worth noting that *M. tuberculosis* has been recovered from many body sites.<sup>206-209</sup> It follows therefore that appropriate risk assessments with regard to *M. tuberculosis* are carried out when processing samples for other pathogens in other parts of the laboratory. This is especially so when an extended incubation time is applied to recover fastidious pathogens. The observation that *M. tuberculosis* can be grown within six days on blood agar and that blood agar is at least as efficient as Lowenstein Jensen medium in recovering *M. tuberculosis* from respiratory and lymph node aspirates must be considered when performing risk assessment analysis for other procedures in the microbiology laboratory.<sup>210</sup> Respiratory specimens, in particular, may contain viable *M. tuberculosis* organisms and there are recommendations that these should be analysed in a CL3 facility.<sup>199;211</sup>

#### **Recommendation:**

All relevant legislation (national and international) for the transport and handling of specimens and cultures for tuberculosis should be strictly adhered to at all times.

### **Molecular testing**

Tests involving molecular methods do not require CL3 practices after the organism has been rendered non-viable. This is normally achieved through the application of heat. Some systems have been shown not to render the cultures completely unviable and therefore a laboratory must be able to definitively state and demonstrate over time that any protocol in use for extracting mycobacterial DNA/RNA has succeeded in rendering the sample non-infectious before its removal from a CL3 facility. Methods which have produced consistent killing of all mycobacterial species tested are those by which the tubes were fully immersed in boiling water or within a forced-hot-air oven set at 100°C.<sup>212-214</sup>

### **Audit**

There should be regular safety audits of the CL3 premises and processes.

## **4.8 Quality Assurance**

Modern laboratory practice necessitates participation in both an internal and an approved external quality assurance scheme e.g. United Kingdom National External Quality Assessment Service (NEQAS). Quality assurance is a system that monitors and improves the efficiency and reliability of the laboratory service by paying attention to detail at every step. There are three phases to the process as follows:

### **Pre-analytical activities**

- How the test is ordered
- Specimen collection procedures
- Transport to the laboratory
- Specimen handling and storage and
- Completeness of patient information.

**Analytical activities**

In the laboratory quality assurance procedures guide and monitor all related activities including:

- Instrument maintenance and operation
- Test reagents
- Personnel and
- Actual test performance.

**Post-analytical activities**

Work quality continues to be monitored in areas such as:

- Report sent to the appropriate party
- Timely reporting of data and
- Immediate reporting of positive results.

Essential components of a quality assurance programme are:

- Quality control
- Quality improvement
- Proficiency testing.

A quality control system is essential for the effective and systematic monitoring of the performance of bench work against established limits of acceptable performance. It ensures that the information generated by the laboratory is accurate, reliable and reproducible. Effective monitoring is carried out through regular audit at all levels in the process. Proficiency testing is essential and can be undertaken by participation in external quality control schemes such as NEQAS. Quality assurance is an essential component in achieving accreditation to ISO or CPA UK Ltd standards.

**Recommendation:**

Laboratories should participate in internal and external quality assurance schemes for all tests performed.



## 5. Clinical Management

The cornerstone of an effective TB control programme is prompt and accurate diagnosis, effective treatment and identification and appropriate management of contacts. The management of contacts is dealt with in chapter 8. This requires a multidisciplinary team approach involving clinicians, public health staff, the laboratory and pharmacists.

### 5.1 Diagnosis

General practitioners and all other medical staff should maintain a high index of suspicion in relation to TB. CDC recommends that patients in the following situations should be evaluated for TB:<sup>215</sup>

- Any patient with a cough of  $\geq 3$  weeks duration with at least one additional symptom, including fever, night sweats, weight loss or haemoptysis
- Any patient at high risk of TB<sup>Y</sup> with an unexplained illness, including respiratory symptoms of  $\geq 3$  weeks duration
- Any patient with HIV infection and unexplained cough and fever
- Any patient at high risk of TB with a diagnosis of community-acquired pneumonia who has not improved after seven days of treatment and
- Any patient at high risk for TB with incidental findings on chest X-ray suggestive of TB even if symptoms are minimal or absent.

#### Recommendation:

All persons with an otherwise unexplained productive cough lasting three or more weeks with at least one additional symptom, including fever, night sweats, weight loss, or haemoptysis should be evaluated for tuberculosis.<sup>25</sup> This will include clinical, radiological and bacteriological examinations.

#### Recommendation:

All cases of suspected active TB should be referred to a TB clinic and have a clinical assessment at the next available clinic.<sup>216</sup> If immediate evaluation is required, consult with the clinical team regarding the need for more urgent clinical assessment. The management of suspect TB cases can be undertaken in collaboration with the clinical team (respiratory or infectious diseases) who will advise on sputa collection and the clinical management (including commencement of therapy, if the sputa are positive for AFB), until the next clinic appointment.

Where pulmonary TB is suspected, a clinical evaluation including examination should be undertaken preferably by a respiratory physician or infectious disease consultant with appropriate training in the management and treatment of TB. The evaluation should include an interview conducted in the patient's primary language with the assistance of qualified medical interpreters, if necessary.

Diagnostic investigations should include chest X-ray, sputum smear microscopy and culture. All persons with chest X-ray findings suggestive of TB should have sputum specimens submitted for microbiological examination.<sup>25</sup> Culture for *M. tuberculosis* complex (MTC) is considered the gold standard for diagnosis. Specimens may need to be obtained by sputum induction, bronchoalveolar lavage (BAL) or gastric lavage particularly in children<sup>77</sup> (see chapter 4 on laboratory diagnosis).

<sup>Y</sup> Patients with one of the following characteristics: recent exposure to an infectious case; history of a positive test result for *mycobacterium tuberculosis* (MTB) infection; HIV infection; injection or non-injection drug use; foreign birth and immigration in  $\leq 5$  years from high endemic region (TB rate  $\geq 40/100,000$  per annum); residents and employees of high-risk congregate settings; membership of a medically underserved, low-income population; or a medical risk factor for TB e.g. diabetes, immunocompromised patients.

All patients (adults, adolescents and children who are capable of producing sputum) suspected of having pulmonary TB should ideally have three sputum specimens obtained for microscopic examination. When possible at least one early morning specimen should be obtained.<sup>25</sup> The recommendations in chapter 4 on laboratory diagnosis should be implemented in this regard.

A sputum smear positive patient has a minimum of one sputum specimen positive for AFB by microscopy.<sup>24</sup> The diagnosis of sputum smear negative pulmonary TB should be based on the following criteria:

- At least three negative sputum smears (including at least one early morning specimen)
- Chest X-ray findings consistent with TB and
- Lack of response to a trial of broad-spectrum antimicrobial agents.<sup>25</sup>

As fluoroquinolones are active against *M. tuberculosis* complex and thus cause transient improvement in persons with TB, they should be avoided. For such patients, if facilities for culture are available, sputum cultures should be obtained. In persons with known or suspected HIV infection, the diagnostic evaluation should be expedited.<sup>25</sup>

An assessment of the likelihood of drug resistance based on history of prior treatment, exposure to a possible source case having drug-resistant organisms and the community prevalence of drug resistance should be obtained from all patients.

In an era of increasing drug resistance every effort should be made to obtain bacteriological diagnosis in order to obtain drug susceptibility data. This is also critical for obtaining molecular typing data essential for contact tracing and TB control programmes. For patients in whom drug resistance is considered to be likely, culture and drug susceptibility testing for isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin should be performed promptly.<sup>25</sup>

Where extrapulmonary TB is suspected, specimens from the suspected sites of involvement should be obtained for microscopy, culture and histology.<sup>25</sup> The NICE guidelines suggest various site-specific investigations for the diagnosis of extrapulmonary TB (see table 5.1).<sup>26</sup>

CDC now recommends that NAAT should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established and for whom the test result would alter case management or TB control activities such as contact tracing.<sup>158</sup> All those wishing to undertake NAAT on suspected cases of pulmonary TB should seek advice from the local consultant microbiologist (see chapter 4 on laboratory diagnosis of TB).



**Table 5.1: Suggested site-specific investigations in the diagnosis of extrapulmonary TB<sup>26</sup>**

| Site               | Imaging                             | Biopsy                       | Culture  |
|--------------------|-------------------------------------|------------------------------|--|
| Lymph node         |                                     | Node                         | Node or aspirate   |
| Bone/joint         | Plain X-ray and CT scan<br>MRI      | Site of disease              | Biopsy or para-spinal abscess<br>Site or joint fluid             |
| Gastrointestinal   | Ultrasound<br>CT abdomen            | Omentum<br>Bowel             | Biopsy<br>Ascites  |
| Genitourinary      | Intravenous urography<br>Ultrasound | Site of disease              | Early morning urine<br>Site of disease<br>Endometrial curettings |
| Disseminated       | CT thorax<br>Ultrasound abdomen     | Lung<br>Liver<br>Bone marrow | Bronchial wash<br>Liver<br>Bone marrow<br>Blood                  |
| CNS                | CT scan<br>MRI                      | Tuberculoma                  | Cerebrospinal fluid (CSF)  |
| Skin               |                                     | Site of disease              | Site of disease  |
| Pericardium        | Echocardiogram/MRI                  | Pericardium                  | Pericardial fluid  |
| Cold/liver abscess | Ultrasound                          | Site of disease              | Site of disease  |

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## Children

The diagnosis of TB in children can be difficult because of non-specific symptoms and infrequent isolation of the organism. WHO recommends that diagnosis should be based on a careful history, clinical examination, and relevant investigations including tuberculin skin test, chest X-ray and sputum smear microscopy.<sup>217</sup> Caution should be used when interpreting chest X-ray changes in children (and particularly so in very young children), as changes are less specific than in adults. The approach to be taken should be discussed with the consultant radiologist.

The diagnosis of intrathoracic (i.e. pulmonary, pleural and mediastinal or hilar lymph node) TB in symptomatic children with negative sputum smears should be based on the finding of chest X-ray abnormalities consistent with TB and either a history of exposure to an infectious case or evidence of TB infection (positive TST). For such patients, if facilities for culture are available sputum specimens should be obtained (by expectoration, induced sputum or gastric washings) for culture (chapter 4).<sup>25</sup>

## 5.2 Supervision of TB Treatment

### Recommendation:

Treatment of TB should be directed by a consultant respiratory physician/consultant in infectious diseases with appropriate training in the management and treatment of TB.

## Drug-resistant TB

Treatment of patients with drug-resistant TB is complicated. The drugs used are toxic and expensive and the outcome is not always successful in inexperienced hands. Treatment should always be directed by a consultant respiratory physician/consultant in infectious disease with appropriate training in the

management and treatment of TB. Treatment should be in line with the International Standards for TB Care (ISTC) (appendix 8) and should be given for at least 18 months.<sup>25</sup>

### Children

Children with TB disease should be treated and managed by a consultant paediatrician with appropriate training in the management and treatment of TB in children. In areas where a consultant paediatrician with appropriate training is not available, the committee recommends joint supervision of such patients by a respiratory physician/consultant in infectious disease and the diagnosing consultant paediatrician.

## 5.3 Role of Public Health Staff in Clinical Management

Under the Infectious Disease Regulations 2003, all TB cases (confirmed or presumed) are statutorily notifiable to the medical officer of health (MOH).<sup>21</sup> The role of public health doctors includes the identification of contacts of TB cases and arrangement of appropriate investigations (symptom questionnaire, tuberculin testing, chest X-ray, sputum examination) and chemoprophylaxis. Contacts in receipt of chemoprophylaxis are reviewed on a monthly basis or more frequently if indicated.

When a TB case occurs in a healthcare setting, effective contact tracing requires liaison between public health services, hospital infection prevention and control and occupational health services. Coordination of contact tracing is most appropriately led by hospital infection prevention and control (vis. consultant microbiologist) in those healthcare settings where this is in place. This will include the initial alerting of public health and occupational health services. In all other healthcare settings, coordination should be undertaken by the public health service.

Compliance with treatment is one of the most important determinants of treatment outcome and a significant aspect of the work of public health staff (doctors and nurses) is to develop strategies to improve compliance. Public health doctors also work with treating clinicians, public health nursing staff and pharmacists in the management of patients who may require DOT. They also have a role in the ongoing education and training of other health professionals, both within the hospital setting and within the community.

#### Recommendation:

There should be active case management with a dedicated case manager or health care professional who liaises with and follows the patient during the entire treatment course to monitor and enhance adherence.

Combined clinics attended by both respiratory physicians and public health staff have operated as models of good practice throughout the country for the diagnosis and treatment of TB and the evaluation of contacts. Ideally all TB clinics should be based on this model. There is a need for the physician, public health staff and the pharmacist to have a strong working relationship for the successful management and treatment of TB.

#### Recommendation:

More widespread establishment of combined clinics attended by both respiratory physicians and public health doctors for the diagnosis and treatment of TB (and LTBI) and the evaluation of contacts is recommended. Such clinics should be appropriately staffed with medical, nursing, pharmacy, administrative staff and medically qualified interpreters and should be integrated with the hospital system.

### Role of the pharmacist in the management of TB

It is recommended that a pharmacist is a member of the clinical team and attends the combined clinics where they have an important role to play in: 1) dispensing of TB medications to patients and maintaining dispensing records; 2) providing appropriate written and verbal information to patients to enable them to understand and comply with their medication; 3) promoting and monitoring patient compliance with their medication regime; 4) screening for potential drug interactions, monitoring adverse drug reactions and advising on their management, particularly for patients with MDR-TB and HIV-TB co-infection; 5) maintaining links with community and hospital pharmacy services where appropriate and 6) participating in research and audit.

The committee also encourages the development and maintenance of regional collaborative TB committees throughout the country. These multidisciplinary committees can review regional epidemiology and local strategies for the prevention and control of TB.

## 5.4 Treatment of Tuberculosis

Effective chemotherapy taken over an adequate period of time is the guiding principle of treatment for all forms of TB (pulmonary and extrapulmonary). The objective of anti-TB therapy is to achieve a lifetime cure of the disease while preventing drug resistance.<sup>30</sup>

All patients (including those with HIV infection) who have not been treated previously for TB should receive an internationally accepted first-line treatment regimen using drugs of known bioavailability.<sup>25</sup>

### Recommendation:

Isoniazid (H) and rifampicin (R), with pyrazinamide (Z) and ethambutol (E) for the initial two months (intensive phase), followed by isoniazid and rifampicin for a further four months (continuation phase) is recommended in patients with sensitive strains of tuberculosis and where there are no contraindications.

As susceptibility results are not available at the start of treatment, regimens can be adjusted as these results become available. Under certain circumstances the continuation phase may be extended beyond four months.

Because of the difficulties with increased pill burden/medication volume and difficulty in monitoring for E toxicity an initial three-drug (HRZ) regimen is often acceptable in children, who generally have a low bacillary burden. For children for whom there are specific concerns regarding resistance or the presence of CNS involvement, and for adolescents, an initial four-drug regimen should be used.

**Recommendation:**

Six months of chemotherapy is usually adequate for drug-susceptible pulmonary TB (table 5.2). However, clinical trials have shown that selected patients have a higher rate of relapse with a six month regimen and may benefit from longer treatment.<sup>77;128;218;219</sup> Therapy should be extended to nine months in the following cases:

- Patients who have drug-susceptible pulmonary TB with initial cavitation on chest X-ray and whose sputum cultures remain positive after the intensive phase i.e. the first two months of therapy
- Other patients who are still culture positive at two months regardless of chest X-ray results
- Patients whose treatment regimen did not include pyrazinamide in the intensive phase or whose organism is resistant to pyrazinamide
- Patients being treated with once-weekly isoniazid and rifampicin whose sputum culture remains positive after the two month intensive phase of treatment.<sup>77</sup>

**Recommendation:**

Follow-up sputum specimens for smear and culture should be obtained monthly in patients with drug-susceptible pulmonary disease. Requests for more frequent testing should only be undertaken following discussion between the treating clinician and consultant microbiologist. For patients with isoniazid- and rifampicin-susceptible TB there is no need to examine sputum monthly once culture conversion is documented (i.e. two negative cultures taken at least two to four weeks apart).<sup>77</sup> It is recommended that identification and sensitivities are repeated in cases who are still culture positive at  $\geq$  two months.

Bacteriological monitoring i.e. culture at the end of treatment in confirmed cases is strictly recommended to assess precisely that the patient has been cured. A negative sputum culture at the end of treatment is the only conclusive evidence that the patient has been cured.<sup>77</sup>

EuroTB classifies treatment failures as patients who have culture or sputum microscopy remaining positive or becoming positive again at the fifth month or later during treatment.<sup>10</sup> Patients who fail treatment should be assessed by a consultant respiratory/infectious disease physician with appropriate training in the management and treatment of TB for possible drug resistance and have therapy modified accordingly.

In cases of extrapulmonary TB, the same regimens should apply, though in certain circumstances, treatment may need to be more prolonged e.g. TB meningitis, miliary/disseminated disease. In such cases, a longer course of therapy is suggested, especially in children, in whom 2 months of at least three drugs in the initial phase and 10 months of two or more drugs in the continuation phase are recommended, assuming that the initial isolate is fully drug sensitive.<sup>30</sup> In patients with extrapulmonary TB and in children, the response to treatment is best assessed clinically. Follow-up radiographic examinations are usually unnecessary and may be misleading.<sup>25</sup>

*M. bovis* is invariably resistant to pyrazinamide and a three-drug nine month regimen is indicated (RHE<sub>2</sub> + RH<sub>7</sub>).

Patients should be assessed monthly during the initiation phase and one to two monthly during the continuation phase of therapy, depending on their level of compliance, likelihood of treatment-related adverse events etc. (see appendix 5: TB therapy audit form).

A written record of clinical symptoms and examination, all medications given, adverse reactions, adherence to treatment and bacteriological response should be maintained on all patients.<sup>25</sup> The assessment should include an interview conducted in the patient's primary language with the assistance of qualified medical interpreters, if necessary.

The prompt recognition and appropriate management of adverse drug reactions is an essential part of the treatment programme and clinicians, nurses and pharmacists responsible for drug therapy need to be well acquainted with these reactions (table 5.2). Toxicity and hypersensitivity reactions require that the offending drug(s) be discontinued. However, this should be accompanied by careful evaluation of the reaction and identification of the offending drug(s) to avoid unnecessary cessation of a first-line drug.<sup>30</sup>

If a DOT programme is employed, a three-times-weekly regimen may be used if acceptable to the patient (table 5.2). Agents such as streptomycin, amikacin, quinolones, etc. should only be used under the supervision of a consultant respiratory physician or consultant in infectious disease with appropriate training in the management and treatment of TB. Advice on potential drug interactions and adverse effects should be sought from the pharmacist on the clinical team.

Table 5.2. Dosages for primary medications used in the treatment of tuberculosis

| Drug<br><i>Mode of action</i>                | Route of administration       | Daily dose [max]  | 3 Times a week dose [max]  | 2 Times a week dose [max]  | Major adverse reactions*   |
|--|-------------------------------|---|--|--|--|
| <b>Isoniazid</b><br><i>Bactericidal</i>      | Oral/<br>Intramuscular        | Children:<br>5-10mg/kg <sup>1</sup><br>Adults: 5mg/kg [300mg]   | Children:<br>20mg/kg<br>Adults:<br>10mg/kg<br>(range<br>8-12mg/kg)<br>[900mg]  | Children: 20mg/kg<br>Adults: 15mg/kg<br>(range 13-17mg/kg)<br>[900mg]  | Hepatic enzyme elevations, hepatitis, rash, peripheral neuropathy, CNS effects, increased phenytoin levels, possible interaction with disulfiram   |
| <b>Rifampicin</b><br><i>Bactericidal</i>     | Oral/<br>Intravenous          | Children: 10-20mg/kg <sup>2</sup><br>Adults: 600mg<br>(range<br>8-12mg/kg)<br>[600mg]                                 | Children: 10-20mg/kg<br>Adults:<br>600mg<br>(range<br>8-12mg/kg)<br>[600mg]  | Children: 10-20mg/kg<br>Adults: 600mg<br>(range 8-12mg/kg)<br>[600mg]  | Hepatic enzyme elevations, hepatitis, rash, fever, thrombocytopenia, influenza-like syndrome, reduced levels of many drugs (including methadone, warfarin, hormonal forms of contraception, oral hypoglycaemic agents, theophylline, dapsone, ketoconazole, PIs, and NNRTIs) |
| <b>Pyrazinamide</b><br><i>Bacteriostatic</i> | Oral                          | Children:<br>25mg/kg<br>(range 20-30mg/kg)<br>Adults: 25mg/kg<br>(range 20-30mg/kg)<br>[2.0g for adults and children] | Children:<br>35mg/kg<br>(range 30-40mg/kg)<br>Adults:<br>35mg/kg<br>(range 30-40mg/kg)<br>[3.0g for adults and children] | Children: 50mg/kg<br>(range 40-60mg/kg)<br>Adults: 50mg/kg<br>(range 40-60mg/kg)<br>[3.5g for adults and children] | Gastrointestinal (GI) upset, hepatotoxicity, hyperuricaemia, gout (rarely), arthralgias, rash  |
| <b>Ethambutol</b><br><i>Bacteriostatic</i>   | Oral                          | Children:<br>20mg/kg<br>(range 15-25mg/kg)<br>[1.5g]<br>Adults: 15-25mg/kg<br>[2.0g]                                  | Children:<br>30mg/kg<br>(range 25-35mg/kg)<br>Adults:<br>30mg/kg<br>(range 25-35mg/kg)<br>[2.8g]                         | Children: 40-50mg/kg<br>[2.5g]<br>Adults: 45mg/kg<br>(range 40-50mg/kg)<br>[3.6g]                                  | Decreased red-green colour discrimination, decreased visual acuity, skin rash  |
| <b>Streptomycin</b><br><i>Bactericidal</i>   | Intramuscular/<br>Intravenous | Children:<br>15-30mg/kg<br>Adults: 15mg/kg [1.0g]   | Children:<br>15mg/kg<br>Adults:<br>15mg/kg<br>[1.0g]   | Children: 15mg/kg<br>Adults: 15mg/kg<br>[1.0g]   | Auditory toxicity, renal toxicity, hypokalaemia, hypomagnesaemia   |

\*All toxicities are not listed here. Full prescribing information should be checked in the package insert or pharmacology texts.

Table 5.2. Contd.

| Drug                | Recommended regular monitoring   | Comments   |
|---------------------|--|--|
| <b>Isoniazid</b>    | <ul style="list-style-type: none"> <li>- Monthly clinical evaluation</li> <li>- Liver function tests<sup>3</sup></li> </ul>  | <ul style="list-style-type: none"> <li>- Vitamin B<sub>6</sub> (pyridoxine) 10mg/day may decrease peripheral neuritis and CNS effects and should be used in patients who are abusing alcohol, pregnant, breastfeeding infants on isoniazid, malnourished, or who have HIV infection, cancer, chronic renal or liver disease, diabetes, or pre-existing peripheral neuropathy</li> <li>- Aluminium-containing antacids reduce absorption</li> <li>- Drug interactions with several agents</li> </ul>  |
| <b>Rifampicin</b>   | <ul style="list-style-type: none"> <li>- Monthly clinical evaluation</li> <li>- Complete blood cell count including platelets and liver function tests as indicated<sup>3</sup></li> </ul> | <ul style="list-style-type: none"> <li>- Orange discolouration may occur in contact lenses and body secretions such as tears and urine</li> <li>- Patients receiving methadone will need their methadone dosage increased, by an average of 50%, to avoid opioid withdrawal</li> <li>- Interaction with many drugs leads to decreased levels of the co-administered drug</li> <li>- May make glucose control more difficult in people with diabetes.</li> <li>- Contraindicated for patients taking most PIs and NNRTIs</li> <li>- Patients should be advised to use barrier contraceptives while on rifampicin</li> </ul> |
| <b>Pyrazinamide</b> | <ul style="list-style-type: none"> <li>- Monthly clinical evaluation</li> <li>- Liver function tests as indicated<sup>3</sup></li> </ul>   | <ul style="list-style-type: none"> <li>- May complicate management of diabetes mellitus</li> <li>- Hyperuricaemia can be used as indicator of compliance</li> <li>- Treat increased uric acid only if symptomatic</li> <li>- Allopurinol increases level of pyrazinamide by inhibiting xanthine oxidase resulting in failure of allopurinol to lower serum uric acid</li> </ul>  |
| <b>Ethambutol</b>   | <ul style="list-style-type: none"> <li>- Monthly clinical evaluation</li> <li>- Check colour vision and visual acuity monthly</li> </ul>   | <ul style="list-style-type: none"> <li>- Optic neuritis may be unilateral; check each eye separately. If possible avoid in children too young to undergo vision testing.</li> <li>- If patient develops visual complaints, refer for prompt ophthalmologic evaluation. May need to discontinue ethambutol while awaiting evaluation.</li> </ul>  |
| <b>Streptomycin</b> | <ul style="list-style-type: none"> <li>- Monthly clinical evaluation</li> <li>- Audiometry, renal function, electrolytes, including magnesium</li> </ul>                                   | <ul style="list-style-type: none"> <li>- Ultrasound and warm compresses to injection site may reduce pain and induration</li> </ul>  |

<sup>1</sup>World Health Organization (WHO), International Union against TB and Lung Disease (IUATLD), and British Thoracic Society (BTS) recommend 5mg/kg in children; Centers for Disease Control and Prevention (CDC), American Thoracic Society (ATS), Infectious Disease Society of America (IDSA) and the American Academy of Paediatrics (AAP) recommend 10-20mg/kg

<sup>2</sup>WHO, IUATLD, and BTS recommend 10mg/kg in children; CDC/ATS and the AAP recommend 10-20mg/kg

<sup>3</sup>Liver function tests are indicated if baseline is abnormal or patient has risk factors for toxicity

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#### Recommendation:

To enhance compliance and to minimise potential problems from the development of drug resistance, it is strongly recommended that only combination tablets should be used.

Syrup/tablet dosage should be rounded up or down to facilitate the prescription of easily given volumes/tablets. All cases of TB placed on the above regimens for active disease should be notified to the local public health physicians. In addition, the committee recommends routine audit of both inpatient and outpatient care of TB.

Care should be taken in writing prescriptions so that rifadin (contains rifampicin only) is not confused with rifinah (contains rifampicin and isoniazid) and rifater (contains rifampicin, isoniazid and pyrazinamide).

## Pyridoxine

Pyridoxine is often used in conjunction with anti-TB drugs to prevent side effects in the peripheral and central nervous systems. It is recommended that pyridoxine 10mg daily (20mg daily may be used if 10mg tablets are not available) should be prescribed for:

- All adults, including pregnant women
- Children who have poor nutrition and therefore are at risk of pyridoxine deficiency
- Children who develop paraesthesia
- Breastfeeding infants on isoniazid
- A fully breastfed infant if the mother is on isoniazid, regardless of whether the infant is on anti-TB treatment
- In particular, those with pre-existing peripheral neuropathy diabetes, chronic renal or liver disease, cancer, alcoholism, malnutrition, other immunosuppressive disorders or HIV.<sup>52 77</sup>

As there are no side effects to low dose pyridoxine, many centres routinely prescribe it to prevent the development of neuropathy.<sup>30</sup> However, it is not routinely prescribed in children except in the situations mentioned above.

## Monitoring

Baseline LFTs and a complete blood count including platelets and biochemistry panel (including creatinine) should be obtained from all patients prior to commencing TB therapy. Monthly follow-up blood testing is not necessary if the baseline is normal unless a patient develops symptoms consistent with adverse drug reactions.

Other relevant laboratory tests should be obtained according to the medications used and side-effects present (see table 5.2). For example, renal function and hearing may be affected by the aminoglycosides and capreomycin; uric acid levels are affected by pyrazinamide. (Note: an increase in uric acid is not an indication to discontinue pyrazinamide as long as the patient remains asymptomatic). Thyroid function tests should be performed for patients on para-aminosalicylic acid or ethionamide.

## Management of adverse reactions: hepatotoxicity

Several anti-TB medications cause hepatotoxicity (see table 5.2). In addition, concomitant use of TB medications increases the risk of developing drug-induced liver damage. Despite these risks, the benefits of TB treatment to the individual far outweigh the risks. Concomitant use of other known hepatotoxic agents should be avoided if possible during anti-TB treatment especially in patients with underlying liver disease. **A consultant with expertise in TB should always be consulted when treating a patient with active TB disease with documented hepatotoxicity.**

## Follow-up

In most cases of TB, it is desirable to review the patient at six months after completing treatment as relapses, should they occur, tend to present within this time. Unless there is a specific cause for concern the patient may be discharged at this time.

## Anti-TB regimens in pregnancy

The risk of untreated TB to a pregnant woman and her foetus is far greater than the risk of the toxic effects from the drugs used in its treatment.<sup>220</sup> In a pregnant woman who has active TB disease as verified by a positive *M. tuberculosis* culture or who is highly suspected of having active TB it is essential that prompt effective treatment be administered. Very rarely, following risk assessment by and approval from the treating clinician, treatment for suspected TB may be deferred until the end of the first trimester. This may be done if the pregnant woman is very reluctant to take the treatment and meets all the following criteria:

- Sputum smear negative for AFB
- HIV-negative



- No risk factors for HIV infection
- Has no symptoms of TB i.e. cough, fever, weight loss or night sweats
- Has no cavitation on chest X-ray.<sup>77</sup>

The use of isoniazid, rifampicin and ethambutol have been well studied during pregnancy and their use is safe in this setting.<sup>221</sup> The use of aminoglycosides (streptomycin, amikacin and kanamycin) and the polypeptide capreomycin are contraindicated during pregnancy.<sup>30;77</sup> The effect of pyrazinamide on the foetus is not known. However, if treatment is started after the first trimester, pyrazinamide should be included in the initial treatment regimen for the following women:

- Women who are HIV positive
- Women with behavioural risk factors for HIV infection but decline HIV testing
- Women suspected of having MDR-TB.

Despite the lack of data on pyrazinamide, WHO recommends its use at all stages of pregnancy for all pregnant women.<sup>77</sup>

### **Standard regimen for pregnant women**

The initial treatment regimen in pregnancy should consist of isoniazid, rifampicin and ethambutol unless there are absolute contraindications.<sup>30</sup> Pyridoxine 10mg daily (20mg daily if 10mg tablets are not available) is recommended for pregnant and breastfeeding women (unless the patient is already on a prenatal vitamin supplement that contains the equivalent amount of pyridoxine).

### **Pregnant women suspected or known to have MDR-TB**

Unlike the treatment of drug-susceptible TB, it is not possible to develop standardised protocols for the treatment of known or suspected MDR-TB. As with all drug-resistant TB cases, expert consultation should be sought with a respiratory physician or infectious disease consultant.

### **Anti-tuberculosis medications in breastfeeding women**

The small concentrations of anti-TB drugs in breast milk are not toxic to the nursing newborn. Therefore, breastfeeding should not be discouraged for women who are HIV negative and who are planning to take or who are taking isoniazid or other anti-TB medications. Furthermore, the low concentration of anti-TB medications in breast milk should not be considered effective treatment for disease or for treatment of LTBI in a nursing infant. Women who are HIV positive should not breastfeed because of the risk of HIV transmission to the infant.<sup>77</sup>

## **5.5 Inpatient or Outpatient Management**

Many patients do not require admission to hospital either for investigation or initiation of treatment for TB. However, a minority will be acutely ill and will require admission to hospital. These include:

- Those with severe forms of TB such as: central nervous system (CNS) and meningeal TB, pericardial TB or disseminated or miliary TB
- Haemodynamic instability
- Severe haemoptysis
- Severe debilitation with weight loss, severe cough, high fevers and inability to care for themselves
- Advanced AIDS
- Co-morbid medical conditions that require treatment in hospital.<sup>77</sup>

Other indications for admission include:

- MDR-TB or XDR-TB
- Toxicity from medication
- Poor compliance

- Social reasons e.g. having no fixed abode, alcohol or drug abuse, not ambulatory and needing professional home care e.g. home help
- The need for isolation because of:
  - o particularly vulnerable (immunosuppressed or children under five years of age who have not been evaluated for LTBI and window period prophylaxis) household or other contacts or
  - o living in a congregate setting such as a nursing home.<sup>77</sup>

Others will require admission to clarify the diagnosis.

On a practical basis, young children will often require hospital admission to complete TB investigations.

#### **Recommendation:**

It is recommended that the supraregional TB centre at St. James's Hospital and a number of regional centres should have a small number of non-acute beds available to facilitate the inpatient care of patients who are non-compliant or have drug-resistant TB.

The beds should be on the campus of an acute general hospital and each unit should have adequate recreation and rehabilitation facilities. For patients who require inpatient supervision throughout the course of their treatment, 'stepdown' beds in a non-acute facility may be appropriate when the patient is clinically stable.

### **5.6 Adherence and Directly Observed Therapy (DOT)**

Treatment of TB is very effective. The International Standards for Tuberculosis Care state that any practitioner treating a patient for TB is assuming an important public health responsibility. To fulfil this responsibility, the clinician must not only prescribe an appropriate treatment regimen but must also be capable of assessing the adherence of the patient to the regimen and of addressing poor adherence when it occurs.<sup>25</sup> The responsibility for successful treatment lies with public health in cooperation with the treating physician.<sup>30</sup> However, patients should be involved in their treatment decisions from the onset and the importance of adherence should be emphasised.<sup>26</sup>

In this context, it is essential that patients take their medication as prescribed by the consultant respiratory physician/consultant in infectious disease. Treatment completion is a fundamental principle of TB control. Failure to complete treatment can result in patient relapse, a potential to infect contacts and an increased risk of drug resistance. The most important reason for failure is that patients do not take the prescribed drugs regularly or for long enough.<sup>222</sup> The importance of adherence is therefore central to establishing good cure rates for TB and preventing the emergence of drug resistance. As the patient improves and feels better, compliance may be more problematic.

To foster and assess adherence, a patient-centred approach to administration of drug treatment based on the patient's needs should be developed for all patients. A central element of the patient-centred strategy is the use of measures to assess and promote adherence to the treatment regimen and to address poor adherence when it occurs. Supervision and support should be gender-sensitive and age-specific. The measures should be tailored to the individual patient's circumstances.<sup>25</sup> In this regard, the committee recommends the appointment of a key worker/treatment supporter for each patient. TB services should

also provide medically qualified interpreters and patient information in the relevant language. The NICE guidelines recommend the following interventions if a patient defaults from treatment: reminder letters in the appropriate language, patient-centred interview and health education booklet; health education counselling; home visits; patient diary and random urine tests and other monitoring e.g. pill counts.<sup>26</sup>

### **Directly observed therapy (DOT)**

DOT is a way of helping patients to take their medicine for TB. A person receiving DOT will meet with a healthcare worker/key worker everyday or several times a week at an agreed place e.g. the patient's home, the TB clinic or other convenient location. The healthcare worker will observe the patient taking their medication at this place helping to ensure that higher treatment completion rates are achieved. Sometimes someone in their family or a close friend will be able to help in a similar way to the healthcare worker.

Blumberg *et al* have reported completion rates of between 85 and 90% using DOT. These compared with completion rates of 60% after self-administration of therapy.<sup>219</sup> In addition, the use of DOT has also been shown to reduce the rate of drug resistance and relapse when compared to self-administered therapy.<sup>223</sup>

The key worker will be actively involved in the administration of DOT and should actively monitor and ensure compliance. They should also be acceptable and accountable to the patient and to the health system.

However, the availability of DOT is currently limited and needs to be improved in the majority of HSE areas. Where universal provision of DOT is not feasible because of resource limitations, the following circumstances should be given priority:

- Suspected or proven drug-resistant organisms
- Treatment failure
- Documented re-treatment disease
- Injection drug users/homeless persons
- Suspected non-adherence or previous non-adherence
- HIV infection
- Children
- Psychopathology
- Too ill to self administer
- Smear positive for AFB<sup>30;77;224</sup>

Ormerod *et al* have shown that DOT may be selectively used when not all patients are being treated with DOT and at least 90% of patients complete treatment (no culture done at the end of treatment) or are cured (negative culture at the end of treatment).<sup>224</sup>

The establishment of a structured national DOT programme is vital for the effective management and control of TB and in particular, for effective control of TB among foreign-born cases.

#### **Recommendation:**

Prioritising the establishment of a structured national DOT programme is recommended for more effective management and control of TB.

This will require close coordination between the secondary care hospitals and the public health service.

Staff supervising DOT should be appropriately trained. The regimen should be determined by the treating physician in conjunction with the patient. In some cases, an intermittent regimen may be appropriate. In others, a daily regimen is more appropriate. See HSE South (Cork and Kerry) DOT referral form in appendix 9.

In addition, procedures for monitoring compliance such as pill counts need to be established early in the treatment of the disease. Blister packs labelled with each day's TB medication will also facilitate compliance. Pharmacists should be involved in monitoring compliance. In order to monitor and improve compliance, the patient should receive their anti-TB medications from the same pharmacy on a monthly basis. Electronic records of each dispensing should be maintained and ongoing liaison between the pharmacist and prescriber is recommended. Medication must be easily accessible for the patient and ideally should be available at the diagnosing clinic/hospital.

A directly observed therapy short-course strategy (DOTS strategy), the internationally recommended approach by WHO to TB control has been successfully implemented in many countries but requires careful institution and monitoring. This comprises five components as follows: (i) political commitment with increased and sustained financing; (ii) case detection through quality-assured bacteriology; (iii) standardised treatment with supervision and patient support; (iv) an effective drug supply and management system; and (v) a monitoring and evaluation system and impact measurement.<sup>5</sup> The committee recommends endorsement of the WHO DOTS strategy at the highest level.

#### **Use of DOT in MDR-TB and XDR-TB**

In all cases of MDR-TB and XDR-TB the use of DOT is recommended. A daily regimen is more appropriate.

#### **Use of DOT in children**

Three times weekly therapy is not generally recommended for children but twice or thrice weekly administration of rifampicin and isoniazid by DOT can be considered after completion of the initial two month period of treatment in selected circumstances.

## **5.7 Legislation**

Compliance with medication is core to TB control. In practice, a subset of patients are noted who are non-compliant with treatment and are resistant to any intervention in the community. Under Section 38 of the Health Act, 1947 the MOH may order the detention and isolation of an infectious person until that person is no longer a probable source of infection.<sup>225</sup> Section 35 of the Health Act, 1953 amends the 1947 Act, directing that the order must be signed by the MOH and another registered medical practitioner.<sup>226</sup>

This legislation dates back to the 1940s and 1950s (1947 and 1953). It gives the power to detain non-compliant patients but does not give the power to ensure that patients comply with treatment. Personal communication with HSE areas has highlighted a number of enforcement-related issues in recent times primarily with regard to treatment refusal, place of detention and personal rights. This legislation is currently being reviewed by a HSE committee.

## 6. Infection Prevention and Control

The extent and duration of measures required to prevent and control TB infection, depends upon the estimated degree of infectiousness of the patient, the response to treatment, the nature of the activities undertaken, and who will be exposed to the patient in the course of those activities.

### Risk factors for acquiring TB infection

The risk of acquiring TB is determined by a number of factors such as the degree of infectiousness of the source patient or the presence of predisposing medical conditions in contacts e.g. HIV infection, diabetes, alcoholism, drug addiction, immunosuppression and renal failure. The following features in the source case have been shown to increase the risk of infection:

- Close contact with the source case (section 8.5)
- Duration of contact (the longer the contact the greater the risk)
- Sputum smear positive
- Presence of a productive cough
- Delay in diagnosis
- Open TB lesions requiring irrigation
- Institutional contact with the source case (prisons, nursing homes, shelters, etc).

### 6.1 Classification of Risk of Procedures in Healthcare

HCWs are at risk of infection depending on their contact with patients and the clinical procedures undertaken during care. These procedures have been categorised into high, medium and low risk activities.

#### **High risk**

- Cough inducing procedures (including sputum induction and bronchoscopy)
- Autopsy
- Pathology examination
- Bronchoscopy
- Designated TB laboratory procedures especially handling cultures of TB

#### **Medium Risk**

Staff whose work entails regular contact with the patient (e.g. nursing, physiotherapy, nursing attendants, cleaning staff, catering staff)

#### **Low risk**

Staff with minimal patient contact (e.g. administration, maintenance).

### 6.2 Definition of an Infectious TB Case

Patients aged 10 years and over with suspected or confirmed pulmonary or laryngeal TB should be considered infectious if any of the following are present **and** if they are not receiving therapy, have just started therapy or have a poor response to therapy<sup>77;227-229</sup>

- Are coughing
- Are undergoing sputum inducing procedures
- Have cavitations on chest X-ray
- Are sputum AFB smear positive
- Have suspected laryngeal involvement (i.e. hoarseness)

BAL AFB smear positive **if** any of the following are present:

- Cavitations on chest X-ray
- Suspected or confirmed MDR-TB
- Admitted to a ward or living with immunosuppressed\*\*\* individuals.

The determination of infectivity of all other BAL smear positive patients should be considered on a case-by-case basis (clinical/microbiology/public health input).

Most children aged less than 10 years with suspected or confirmed TB are not infectious (chapter 8) however, they should be considered infectious if any of the following are present:<sup>77</sup>

- Cavitations on chest X-ray
- Sputum smear positive (not BAL or gastric washings positive)
- Suspected laryngeal involvement
- Extensive pulmonary infection
- Congenital TB and undergoing procedures involving oropharyngeal airway.

In addition, patients with extrapulmonary TB in an open abscess or lesion should be considered infectious when aerosolisation of drainage fluid occurs.

When a patient with suspected or confirmed infectious TB is receiving healthcare, appropriate infection, prevention and control must be followed to protect employees and other patients from infection.

The effective prevention and control of TB relies on:

**Administrative aspects**

**Implementation of Standard and Airborne Precautions.**

### 6.3 Administrative Aspects

Administrative aspects of the prevention and control of TB comprise early investigation, diagnosis and treatment by:

- A high level of suspicion amongst clinical teams and GPs
- Local procedures and guidelines for the management of TB in acute hospitals and community care areas
- Staff education and training on current guidelines and procedures
- Informing the infection prevention and control team promptly of all suspected and confirmed cases of TB
- Collaboration between laboratory, microbiological and clinical teams to ensure rapid testing of specimens for acid-fast bacilli (AFB).

### 6.4 Standard Precautions

Standard precautions are defined as follows:<sup>230</sup>

**Standard precautions are a set of work practices that require all HCWs to assume that all blood, body fluids (except sweat), excretions and secretions from all patients in all settings are potential sources of infection.**

\*\*\*Immunosuppressed is defined as either due to disease or therapies e.g. HIV, individuals receiving >15mg prednisone or equivalent for more than four week or other immunosuppressive agents for cancer, chemotherapeutic agents, anti-rejection drugs for organ transplantation and TNF- $\alpha$  antagonists or as defined by the attending consultant.

Implementation of standard precautions constitutes the primary strategy for the prevention of healthcare associated transmission of infectious agents among patients and healthcare personnel.<sup>230</sup> Full details of standard precautions are available in appendix 10.<sup>230</sup>

Standard precautions include the following work practices and measures:

- Occupational health programme
- Hand hygiene
- Personal protective equipment
- Management of spillages of blood and body fluids
- Appropriate patient placement
- Management of sharps
- Management of needle stick injuries and exposure to blood and body fluids
- Management of waste and laundry
- Safe injection practices
- Respiratory hygiene and cough etiquette
- Appropriate decontamination of reusable medical equipment
- Appropriate decontamination of the environment.

Certain transmissible infections require additional control measures to standard precautions to effectively prevent transmission. Infectious pulmonary and laryngeal TB require airborne precautions in addition to standard precautions.

## 6.5 Airborne Precautions

Full details of Airborne Precautions are available in appendix 10.<sup>230</sup>

The following section outlines the elements of Airborne Precautions and how they apply to the management of a suspected or confirmed infectious TB case.

### Patient placement

#### *Isolation rooms with ventilation*

Specially engineered rooms have been designed to limit the spread of certain transmissible infections that are transmitted via air such as TB. Two designs are suitable for Airborne Precautions:

1. **Negative pressure isolation room with an ante room.** This room has an air handling unit which ensures that the air in the room remains at negative pressure to the ante room and the hospital environment
2. **Neutral pressure design** as detailed in HBN 04 Supplement 1.<sup>231</sup>

#### *Air changes per room*

It is recommended that a minimum of six air changes per hour (ACH) is required for the protection of staff and visitors however, in new buildings 12 ACHs are advised.<sup>129; 232-234</sup>

Isolation rooms can be designed for negative pressure use only but some may have an air handling unit that can be switched from negative pressure to positive pressure depending on infection control requirements. These dual action rooms have been implicated in outbreaks when the incorrect air pressure was selected for a specific infection or patient. This design should not be used in new builds or refurbishments.

#### *Monitoring of ventilation system*

Airborne isolation rooms should be monitored continuously by the pressure differential between the room and the surrounding ward. The monitoring system should alert staff of any failure.<sup>235</sup>

There should be:

- Standard operating procedures (SOPs) in place for changing the air handling settings at ward level (if applicable)
- SOPs in place for documenting the daily checks on the monitoring system at ward level
- Regular engineering checks on the number of air changes and air direction (smoke tests) to ensure compliance with best practice<sup>234;235</sup>
- Regular training for staff in their use
- Changing of HEPA filters as directed by manufacturers' instructions (if applicable).



More detailed information regarding the operation of these rooms is available in the UK Department of Health's document on "*The prevention and control of tuberculosis in the United Kingdom: UK guidance on the prevention and control of transmission of 1. HIV-related tuberculosis 2. drug-resistant, including multiple drug-resistant, tuberculosis, 1998*", "*Hospital and community acquired infection and the built environment-design and testing of infection control rooms. Journal of Hospital Infection 2007* published by Walker et al and HBN 04 Supplement 1.<sup>231;234;235</sup>

The design of airborne isolation rooms planned for new buildings or major refurbishments should be based on the neutral pressure design, as detailed in HBN 04 Supplement 1 rather than a "switchable" negative/positive pressure design.<sup>236</sup>

It is important to note that no ventilation system will function correctly if the doors or windows are open.

### **Sputum induction and aerosol-generating procedures**

- **Sputum induction** is used to obtain sputum when patients are unable to expectorate a specimen. The procedure uses sterile water or hypertonic saline to irritate the airway, increase secretions, promote coughing, and produce a specimen. It is also recommended for children as a preferred option to gastric washings.<sup>26</sup> Sputum induction is classified as a high-risk procedure when performed on a person with suspected or known infectious TB.<sup>26;229</sup> There is a consensus in international best practice guidelines that sputum induction should only be performed in an airborne isolation room or if no such room is available a ventilated booth from which air is exhausted outside or HEPA filtered.<sup>30;229</sup> The committee agrees with this. These booths or local exhaust ventilation (LEV) systems must be maintained and regularly monitored to ensure they are working satisfactorily.
- **Aerosol-generating procedures** such as the administration of medications by nebuliser on suspected or confirmed cases of TB must be avoided in an open bay or in an unventilated area in all wards/departments. Treatment of an extrapulmonary TB open abscess or lesion where aerosolisation of drainage fluid may occur should only be undertaken in an airborne isolation room.

### **Current international guidelines**

There are differing recommendations in the current international best practice guidelines on the type of rooms suitable for patients with infectious TB. The CDC guidelines<sup>229</sup> recommend that all suspected and confirmed TB cases be treated in negative pressure rooms while the NICE guidelines<sup>26</sup> advise that a negative pressure room is only required for suspected or confirmed MDR-TB cases. The NICE guidelines further advise that while single rooms without specific ventilation systems can be used for non-MDR-TB patients no immunosuppressed patients should be on the ward.

#### **Recommendation:**

Patients with known or suspected pulmonary or laryngeal TB should be admitted to an airborne isolation room (negative pressure isolation room with an ante room or a neutral pressure design as outlined in HBN 04 supplement 1). Hospitals need to have a risk assessment process to ensure the appropriate provision of isolation facilities (see figure 6.1).

### **Availability of isolation rooms**

A study in 2003 reported that only 14% of Irish hospitals had an isolation room suitable for Airborne Precautions.<sup>237</sup> While the available number of rooms may have increased with recent new builds and refurbishments in Irish hospitals, it is likely that some hospitals have an insufficient number of isolation rooms with a ventilation system to isolate all known or suspected infectious TB cases.

Hospitals should prioritise the building of airborne isolation rooms. New buildings or major renovations in acute general hospitals should have a minimum of one airborne isolation room to 150 beds or one to 75 beds for regional/tertiary hospitals. Critical care and accident and emergency units should have at least one airborne isolation room.<sup>236</sup>



**Risk assessment for all confirmed or suspected pulmonary or laryngeal TB cases.** <sup>26</sup>**Recommendation:**

All patients with suspected or known pulmonary or laryngeal TB must have a risk assessment for MDR-TB.

**Risk factors for MDR-TB include the following:**

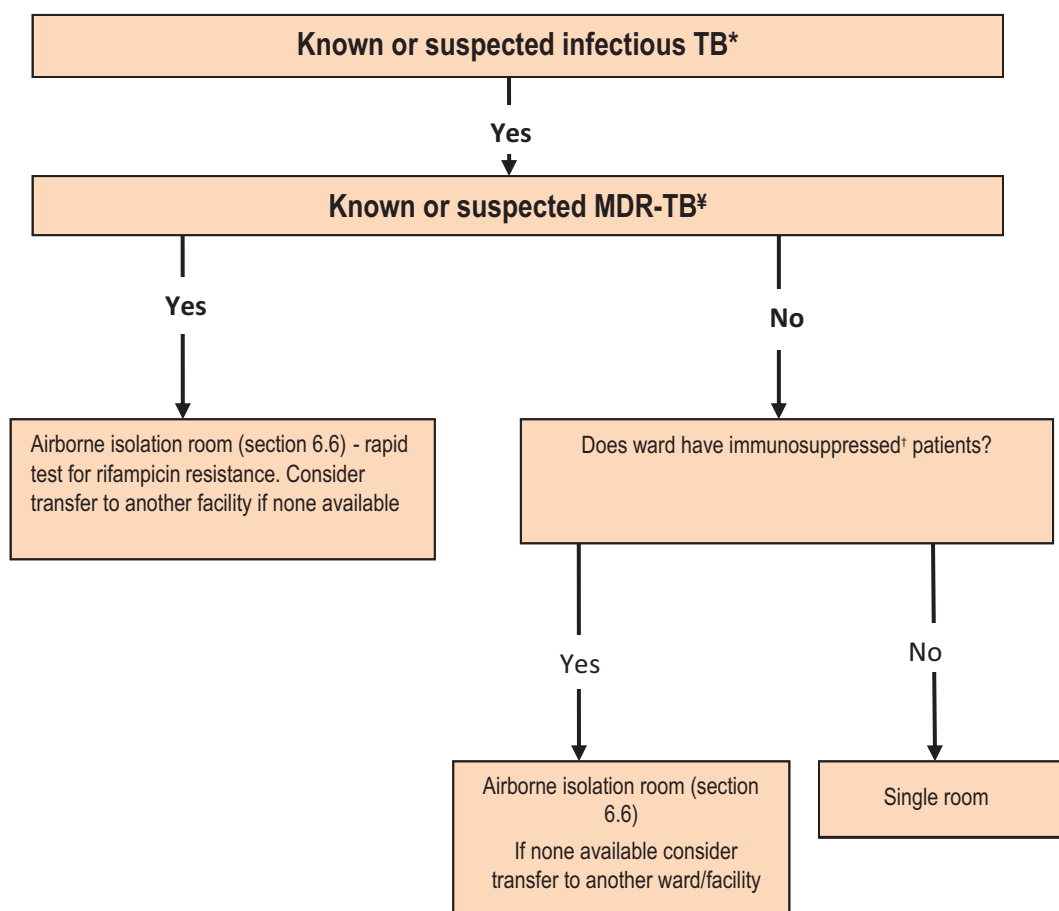
- A history of prior TB treatment (especially incomplete treatment) and/or prior TB treatment failure
- Contact with a known case of MDR-TB
- Birth in a foreign country, particular a high incidence country for MDR-TB (Lithuania, Estonia, Latvia, Uzbekistan, Kazakhstan, China ( Henan & Liaoning provinces) Tomsk Oblast (Russian Federation) and Ecuador) (refer to [www.who.int/tb/publications/mdr\\_surveillance/en/index.html](http://www.who.int/tb/publications/mdr_surveillance/en/index.html) for latest information on countries with high incidence of MDR-TB)
- HIV infection

**Recommendation:**

Patients with suspected or confirmed MDR-TB must be admitted to an airborne isolation room (negative pressure isolation room with an ante room or a neutral pressure design as outlined in HBN 04 supplement 1). (This may require transferring the patient to another institution where the facilities, together with a physician experienced in the management of complex drug-resistant cases are available).

See figure 6.1 for risk assessment for patient placement if a sufficient number of airborne isolation rooms are not available.

**Figure 6.1: Patient placement for pulmonary or laryngeal TB if a sufficient number of airborne isolation rooms (section 6.6) are not available**



**\*Definition of an infectious case**

**> 10 years of age**

Coughing, undergoing sputum inducing procedures, cavitations on CXR, sputum smear positive, suspected laryngeal involvement, extrapulmonary TB in an abscess or lesion if aerosolisation of drainage fluid occurs. Bal AFB positive if any of the following is present: Cavitations on CXR, suspected or confirmed MDR-TB, admitted to a ward or living with immunosuppressed individuals.

**< 10 years of age**

Cavitations on CXR, sputum smear positive (not BAL or gastric washings) suspected laryngeal involvement, extensive pulmonary infection, congenital TB & undergoing procedures involving oropharyngeal airway, extrapulmonary TB in an abscess or lesion if aerosolisation of drainage fluid occurs.

**\*Risk factors for MDR-TB**

A history of prior TB treatment (especially incomplete treatment) and/or prior TB treatment failure.

Contact with a known case. Birth in a foreign country, particular a high incidence country for MDR-TB (Lithuania, Estonia, Latvia, Uzbekistan, Kazakhstan, China (Henan & Liaoning provinces) Tomsk Oblast (Russian Federation) & Ecuador) (refer to [www.int/tb/publications/mdr\\_surveillance/en/index.html](http://www.int/tb/publications/mdr_surveillance/en/index.html) for latest information on countries with high incidence of MDR-TB).

†Immunosuppressed is defined as either due to disease or therapies e.g. HIV, individuals receiving >15mg prednisone or equivalent for more than four week or other immunosuppressive agents for cancer, chemotherapeutic agents, anti-rejection drugs for organ transplantation and TNF- $\alpha$  antagonists or as defined by the attending consultant.

**Patients with HIV**

A HIV positive patient with suspected or confirmed pulmonary or laryngeal TB must be placed in an airborne isolation room. HIV positive or other immunosuppressed individuals should not be exposed to possible or confirmed infectious TB cases. In wards with HIV positive patients all aerosol-producing procedures (e.g. sputum induction) regardless of whether a diagnosis of TB has been considered or not should be conducted in airborne isolation rooms.<sup>26</sup>

**Emergency departments**

Emergency departments (ED) without airborne isolation rooms must have a process in place to prioritise transfer of suspected or confirmed pulmonary or laryngeal TB cases to an appropriate room. ED with no single or isolation rooms should place a surgical mask on the patient and place him/her in an examination room while awaiting transfer. This room should be left vacant for at least one hour after the patient is transferred to allow for a full exchange of air.<sup>230</sup>

**Bronchoscopy departments**

Bronchoscopy should preferably be performed in an appropriate negative pressure suite with adequate ventilation. Unnecessary staff and other patients should be excluded during the procedure. If endoscopy rooms are without air handling equipment, a bronchoscopy procedure on a patient with suspected or confirmed laryngeal or pulmonary TB should be undertaken at the end of the list for the day, or in the patient's room. Avoid placement of recovering patients in a multi-bedded ward. Bronchoscopy for other clinical reasons on a confirmed TB case should be delayed if possible until the patient has had three sputum smear negative samples.

**Autopsy**

It has been estimated that the risk of TB in mortuary workers is 100-200 times more than the general population.<sup>238</sup> Recommendations to reduce the risk of infection are detailed in good practice guidelines from the Royal College of Pathology, 2003.<sup>239</sup>

**Laboratory**

See chapter 4 for infection control precautions in the laboratory.

**Use of personal protective equipment**

In addition to the use of personal protective equipment (PPE) as outlined in Standard Precautions (see appendix 10), respiratory protection is advised for HCWs when Airborne Precautions are applied.

**Health care workers**

Exposure of HCWs to TB should be minimised by reducing the number involved in the direct care of an infectious case. Recommendations for the use of respiratory protective equipment vary from country to country. The NICE guidelines<sup>26</sup> recommend that healthcare staff do not need to use respiratory protection unless MDR-TB is suspected or for cough-inducing procedures such as bronchoscopy and sputum induction. Where MDR-TB is suspected or known they recommend that staff and visitors use FFP3 masks or equivalent. The NICE guidelines also recommend that patients while infectious should wear a surgical mask when they are outside their room, for example visiting the X-ray department. In New Zealand and Canada, N95 (equivalent to European FFP2) masks are recommended when caring for patients with known or suspected infectious pulmonary TB.<sup>30;52</sup> In the USA, the N95 mask is recommended as the minimum standard for respiratory protection in areas where patients with suspected or confirmed infectious TB might be encountered. A higher level of protection should be considered where the risk for exposure to *M. tuberculosis* is especially high e.g. cough inducing procedures.<sup>230</sup>

Respiratory masks are only effective if there is a tight seal to the wearer's face. Fit testing is a method for checking that the mask matches the person's facial features and seals adequately to the wearer's face. A good seal is only possible when the wearer is clean shaven. Fit testing will also help to ensure that incorrectly fitting respiratory masks are not selected for use.<sup>240</sup>

A respiratory protection programme for staff advised to wear respiratory masks should be provided by each healthcare facility to ensure compliance with the following health and safety legislation and standard:

- Safety, Health and Welfare at Work Act, 2005
- Safety, Health and Welfare at Work (General Application) Regulations 2007 (S.I. No. 299 of 2007). Chapter 3 of Part 2: Personal Protective Equipment
- Safety, Health and Welfare at Work (Biological Agents) Regulations 1994 (S.I. No. 146 of 1994) (as amended by S.I. 248 of 1998)
- IS EN 529:2005 (Irish Standard on Respiratory Protective Devices).

The respiratory protection programme should include the following;

*Governance*

- Identify department responsible to deliver the respiratory protection programme
- Identify personnel responsible for the implementation of the respiratory protection programme
- Allocation of resources to deliver the programme
- Selection, purchase and supply of suitable masks to each healthcare facility
- Storage of equipment
- Maintenance of equipment
- Disposal of used equipment
- Record keeping.

*Theoretical information, training and instruction including:*

- Types of risk
- Knowledge and understanding of respiratory equipment including limitations
- Personal factors including medical conditions, improper fitting
- Fit testing and fit checking.

*Practical training*

- An initial fit test using qualitative method
- Ongoing check fitting to confirm the seal each time the mask is donned
- Donning, removing and disposing of masks.

FFP2 or FFP3 respiratory masks are unsuitable for HCWs with facial hair as it affects the seal between the mask and the face. Beards, sideburns or even a visible growth of stubble will affect the face seal of such masks which rely on close contact between the face and the mask.

For HCWs where the removal of facial hair is not possible, an employer must look at the provision of suitable respiratory equipment which does not rely on a good face seal for protection e.g. powered/air-supplied hoods. Otherwise, redeployment may be required as an employer cannot ensure the safety of personnel.

**Recommendation:**

A respiratory protection programme for staff advised to wear respiratory masks should be provided by each healthcare facility.

HCWs (including HCWs visiting a patient in their own home) should wear FFP2 masks when caring for patients with suspected or confirmed infectious TB where MDR-TB or XDR-TB is not suspected. These patients are usually non-infectious after a minimum of two weeks treatment. The supervising clinician should be consulted before the use of masks is discontinued (section 6.7).

HCWs should wear FFP3 masks when undertaking cough-inducing procedures on all patients (fully susceptible and resistant strains included) e.g. sputum induction, bronchoscopy, administration of aerosolised medications, airway suctioning, endotracheal intubation, caring for patients on mechanical ventilation and during treatment of lesions/abscesses when aerosolisation of drainage fluid is anticipated.

HCWs (including HCWs visiting a patient in their own home) should wear FFP3 masks when caring for patients with suspected or confirmed infectious MDR-TB or XDR-TB. The supervising clinician should be consulted before the use of masks is discontinued (section 6.7).

A respiratory protection programme should be provided for all HCWs who may be required to use respiratory masks during the course of their work. HCWs should be fit tested by a trained professional as part of this programme. All HCWs should fit check each time a mask is donned.

**Patients**

CDC and NICE guidelines advise that patients with suspected TB when not in an isolation room should wear surgical masks to reduce the expulsion of droplet nuclei into the air. Respirators masks (FFP2/3) are designed to filter the air before it is inhaled by the person wearing the mask. In addition, correctly wearing respiratory masks increases respiratory effort which can be difficult for a patient already compromised. In line with this, the recommendation of the National TB Advisory Committee is as follows:

**Recommendation:**

Patients should wear a surgical mask while they are infectious, when they are outside their room, for example visiting the X-ray/OPD department.

**Removal of PPE**

Remove PPE in the following sequence:

1. Gloves
2. Apron/gown
3. Decontaminate hands
4. Eye wear
5. Respiratory mask – (handle with the straps of the mask to avoid touching the front)
6. Decontaminate hands.

Gloves, apron/gown are removed in the room. Mask and eyewear are removed outside the room.

In addition:

- Discard PPE that is contaminated with blood or body fluids from patients with known or suspected infection in healthcare risk waste
- Discard respiratory masks in healthcare risk waste
- Gloves, aprons/gowns and eye wear are not required for Airborne Precautions but are required to be worn if contact with blood or body fluid is anticipated as per Standard Precautions (appendix 10).

### **Patient transportation**

Limit the movement and transport of the patient to essential purposes only. If transport or movement is necessary, staff should ensure that precautions are maintained to minimise the risk of transmission to other patients and the contamination of environmental surfaces or equipment.

### **Transfer of patients with suspected or confirmed infectious TB**

International best practice guidance on respiratory protection required for HCWs when transferring a patient with suspected or confirmed TB is not consistent. Guidance from the Public Health Agency of Canada and the Bureau of TB control in New York recommend that HCWs wear the equivalent of FFP2 masks during transfer.<sup>30 77</sup> CDC recommends that FFP2 or equivalent masks are only required for transfer if the patient is unable or unwilling to wear a surgical mask.<sup>230</sup> The newly published Scottish guidelines do not specifically address transfer however, do advise the use of FFP3 masks if intensive nursing is required leading to close contact (equivalent to household contact) for a cumulative total of eight hours or more.<sup>241</sup>

The following actions are recommended prior to patient transfer:

- The transferring facility should inform transport personnel (emergency medical technicians, porters) and the receiving department/facility of the need for Airborne Precautions
- Prior to accepting a patient with known or suspected TB, it is the responsibility of the receiving facility to ensure compliance with facilities as described above under patient placement
- Remove contaminated apron/gown/gloves (if worn) and mask and dispose prior to transporting patients. Staff do not need to wear FFP2/FFP3 mask during internal hospital transportation unless the patient is unable to wear a surgical mask (e.g. confused, respiratory distress)
- Ambulance staff should consider the use of FFP2 or FFP3 mask in the following situations: (a) the patient is unable or unwilling to wear a surgical mask; (b) it is anticipated that the duration of the journey will be  $\geq 8$  hours ( $\geq 4$  hours if HCW is immunocompromised) and (c) if the patient has either MDR-or XDR-TB (consult infection prevention and control team in this situation)
- Request the patient to wear a surgical mask which should be changed when heavily contaminated and/or wet or if torn. Educate on cough etiquette and ensure patient has a supply of tissues
- Don FFP2 or FFP3 mask prior to handling the patient at the transport destination (e.g. X-ray, bronchoscopy suite)
- Transport equipment (stretcher, bed, wheelchair) used to transport the patient should be cleaned and disinfected using a disinfectant with 1,000ppm of available chlorine if contaminated with sputum/respiratory secretions.

### **Patients and visitors**

To preserve privacy and confidentiality, restricting visiting to immediate family should be discussed with the patient.

Each hospital should have a system in place to alert visitors to check with ward nursing staff regarding hand hygiene and other requirements before and after visiting a patient with TB.

Patients with TB and their visitors/carers should be given information on the following;

- Preventing transmission of TB
- Medications used to treat TB and the importance of compliance with the treatment plan
- The range and need for appropriate infection prevention and control precautions
- Hand hygiene
- How to don/remove masks.

## 6.6 Discontinuation of Airborne Precautions

**Discontinue Airborne Precautions, if MDR-TB is not suspected or confirmed,** when all of the criteria (1-3) below are met:<sup>26,77</sup>

1. On standard multi-drug therapy for a minimum of two weeks
2. Clinical symptoms are improving
3. Three consecutive (properly performed) negative sputum smear examinations collected over 48 to 72 hours of which at least one should be an early morning sample. Patients unable to produce sputum i.e. no productive cough should be discussed with clinical and infection prevention and control teams.

See figure 6.2 for criteria for discharge from hospital.

Patients who are on standard multidrug therapy for TB and remain hospitalised after Airborne Precautions have been discontinued should have sputum tested for AFB smear every one to two weeks.<sup>77</sup>

**Discontinue Airborne Precautions for suspected or confirmed MDR-TB** when all of the following criteria (1-3) are met:<sup>30</sup>

1. Three consecutive sputum samples are smear and culture negative after six weeks incubation
2. Current treatment with anti-TB regimen to which the strain is known or likely to be susceptible
3. Clinical symptoms are improving/resolving.

See figure 6.2 for criteria for discharge from hospital.

**Discontinue Airborne Precautions for suspected or confirmed XDR-TB when:**

- Patients with XDR-TB should remain in airborne isolation for the duration of their hospital stay.<sup>30</sup> Such patients should not be discharged to home until three consecutive sputum samples are smear and culture negative after six weeks incubation.

**Discontinue Airborne Precautions for suspected cases when TB is ruled out if:**

- Three sputum samples are negative for AFB taken on separate days or an alternative diagnosis is made that accounts for respiratory symptoms (e.g. cancer, pneumonia).

If no alternative diagnosis is made such patients should not be admitted to an open ward with immunosuppressed patients until culture negative confirmed.

## 6.7 Discharging Patients with TB from Hospital

**MDR-TB not suspected or confirmed**

Patients who are confirmed with infectious TB (but MDR-TB is not suspected or confirmed) can be discharged home in most situations from hospital while still sputum AFB positive when the following criteria are met:

1. Commenced on standard multidrug anti-TB therapy
2. Clinical symptoms are improving
3. Can be discharged to a stable residence at a verified address
4. Is willing and able to observe risk reduction activities e.g. respiratory hygiene, cough etiquette and follow discharge instructions (see appendix 11)
5. Is willing and able to follow up with DOT if necessary (see appendix 9 for HSE South (Cork and Kerry) DOT referral form)
6. Arrangements are in place for outpatient clinic review.

**These patients should not be discharged to following situations unless they fulfill criteria 7 and 8 below in addition to criteria 1 to 6 above:**

- Congregate setting (nursing or care home, prison, etc.)
- Living with immunosuppressed\* individuals

\*Immunosuppressed is defined as either due to disease or therapies e.g. HIV, individuals receiving >15mg prednisone or equivalent for more than four week or other immunosuppressive agents for cancer, chemotherapeutic agents, anti-rejection drugs for organ transplantation and TNF- $\alpha$  antagonists or as defined by the attending consultant.

- Living with children < five years of age who have not been evaluated by a public health physician for window period prophylaxis for LTBI
  - Settings where the patient or a family member requires care from HCWs (home helps, nursing staff) for several hours a day
7. Completed at least two weeks of standard multi drug anti-TB treatment
  8. Three consecutive sputum AFB negative samples taken at least 24 hours apart with at least one early morning specimen (if patient cannot produce sputum i.e. non-productive cough discuss with clinical, public health and infection prevention and control teams).<sup>77</sup>

### **MDR-TB suspected or confirmed**

Patients who are confirmed or suspected with infectious MDR-TB should not be discharged home in most situations unless the following criteria (1-7) are met:

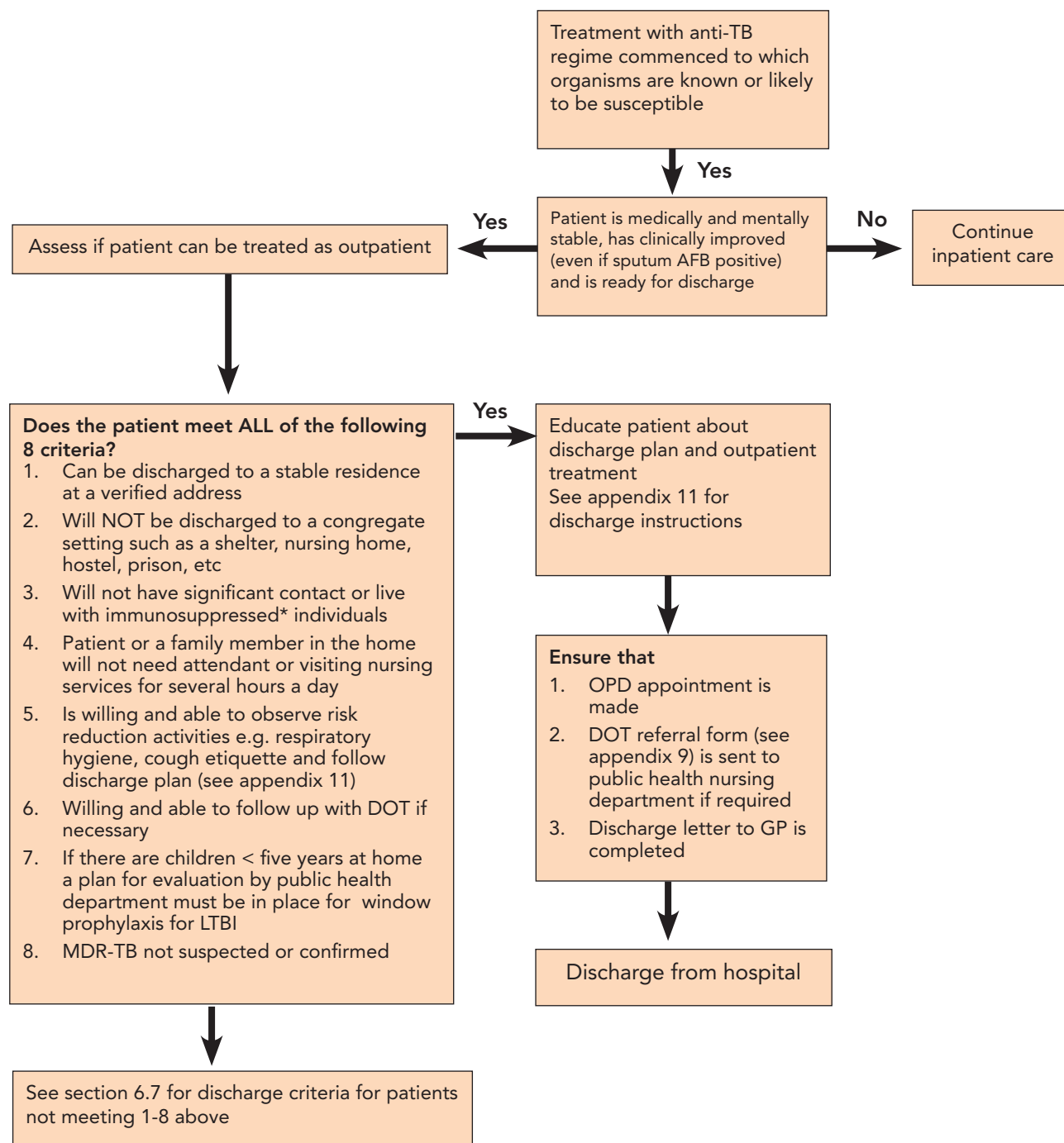
1. Clinical symptoms are improving
2. Current treatment with anti-TB regimen to which the strain is known or likely to be susceptible
3. Three consecutive sputum AFB negative samples taken at least 24 hours apart with at least one sample an early morning specimen (if patient cannot produce sputum i.e. no productive cough, discuss with clinical and infection prevention and control teams)
4. Can be discharged to a stable residence at a verified address
5. Is willing and able to observe risk reduction activities e.g. respiratory hygiene, cough etiquette and follow discharge instructions (see appendix 11)
6. Willing and able to follow up with DOT (see appendix 9)
7. Arrangements are in place for outpatient clinic review.

**These patients should not be discharged to the following situations unless they fulfil criterion 8 below in addition to criteria 1-7 above:**

- Congregate setting (hostel, nursing or care home, prison, etc.)
  - Living with immunosuppressed individuals
  - Living with children < five years of age who have not been evaluated by a public health physician for window period prophylaxis for LTBI
  - Settings where the patient or a family member requires care from health care workers (home help, nursing staff) for several hours a day<sup>77</sup>
8. Three consecutive sputum samples are smear and culture negative after six weeks incubation. If patient cannot produce sputum i.e. does not have a productive cough, discuss with clinical, public health and infection prevention and control teams<sup>30</sup>



Figure 6.2: Criteria for discharging patients with suspected or confirmed infectious TB from a hospital



Adapted with kind permission from *Tuberculosis, Clinical Policies and Protocols*. New York City Department of Health and Mental Hygiene (2008). Available from [www.nyc.gov/html/doh/downloads/pdf/tb/tb-protocol.pdf](http://www.nyc.gov/html/doh/downloads/pdf/tb/tb-protocol.pdf).

## 6.8 Education

### Healthcare workers

There should be an ongoing education programme for HCWs that includes the following:

- Signs and symptoms of TB
- Definition of infectious TB
- Local guidelines and protocols for the management of TB
- Local incidence of TB
- Management of dual action, negative pressure ventilated rooms or neutral pressure design rooms

\*Immunosuppressed is defined as either due to disease or therapies e.g. HIV, individuals receiving >15mg prednisone or equivalent for more than four week or other immunosuppressive agents for cancer, chemotherapeutic agents, anti-rejection drugs for organ transplantation and TNF- $\alpha$  antagonists or as defined by the attending consultant.

- Management of sputum induction to minimise risk to staff and other patients
- Reducing risk associated with immunosuppressed patients.

### **Education of patients/family/carers**

See appendices 6 and 11 for patient information leaflet and hospital discharge leaflet. Some patients who are infectious can remain at home in the household that has already been exposed, as it has been shown that the risk of additional transmission of infection in this setting is extremely low.<sup>52</sup>

The infectious patient must be instructed to take the following precautions until advised by their doctor to return to normal activities:

- Stay at home and not go to work, school, public places or any other locations where there will be previously unexposed people until advised to do so by the treating clinician
- No visits by previously unexposed people
- No visits by children (young children living at home will be assessed by public health doctors regarding the need for LTBI window prophylaxis)
- Avoid visits by relatives or friends who are immunosuppressed
- Cover their mouth and nose with a tissue when sneezing or coughing.

The infectious patient must be educated regarding:

- Safe disposal of tissues and the importance of hand washing after coughing/sneezing
- Disease transmission and disease control
- The importance of compliance with medication
- Side-effects of anti-TB medication
- Contact tracing.

## 7. BCG Vaccination

The Bacillus Calmette-Guerin (BCG) vaccine was derived by in-vitro attenuation of the bovine tubercle bacillus between the years 1908 and 1918 in France. WHO encouraged widespread use of the vaccine starting in the 1950s and as a result more than 70% of the world's children now receive BCG. However, the policies on BCG vaccination differ greatly both nationally and internationally, reflecting differences of expert opinion as to the mechanism of action and effectiveness of the vaccine.<sup>242</sup> The potential loss of the tuberculin test as an indicator of natural infection with tubercle bacilli when BCG is routinely used may be a disadvantage that has to be weighed against the benefits of the vaccine.

### 7.1 Clinical Efficacy

The clinical efficacy of a vaccine is measured in terms of the percentage reduction in disease among vaccinated individuals that is attributed to vaccination i.e. the proportion of those vaccinated who gain protective immunity from the vaccine.<sup>243</sup> BCG vaccines are generally given to protect against TB. BCG vaccine does not give 100% protection but it does protect against the more serious forms of the disease, e.g. TB meningitis especially in the young. The NICE guidelines cite evidence from both randomised controlled trials and case control studies for the efficacy of BCG vaccination in infancy in preventing pulmonary TB infection, TB deaths, TB meningitis, laboratory-confirmed TB cases and disseminated TB.<sup>26</sup> BCG vaccine is probably most consistently effective against tuberculous meningitis and miliary TB with protection lasting approximately 15 years. It is universally agreed that BCG vaccine protects small children from severe forms of childhood TB especially in areas with a high risk of infection.<sup>244;245</sup> In such areas with high infection risk, WHO EPI programme reports a global coverage of BCG in children less than one year at around 85%.<sup>246</sup>

An extensive study by Tala *et al.* attempted to interpret variations in the efficacy of BCG vaccine. Factors considered to be important are age at administration, prior exposure to environmental non-tuberculous mycobacteria, efficacy of BCG vaccine including vaccine quality, host genetics and nutrition, infection incidence, the study design and the route of administration.<sup>247</sup> A meta-analysis of large numbers of BCG efficacy trials revealed a protection rate against pulmonary TB of 86% in randomised trials and 75% in case control studies despite extensive use of the vaccine.<sup>40</sup> Colditz *et al.* in a meta-analysis estimated the overall efficacy of BCG in preventing pulmonary TB to be approximately 50%. Against TB meningitis the efficacy was 64% and against TB deaths 71%.<sup>248</sup> In summary, there is overall agreement that the efficacy of BCG is at its best about 80%<sup>249</sup> and of 15-20 years duration.<sup>250</sup> Kritski *et al.* reported a protection rate of 69% against MDR-TB in a recent study in 1996.<sup>251</sup>

### 7.2 Criteria for Discontinuation of a Universal BCG Vaccination Programme

In 1994, the International Union against Tuberculosis and Lung Disease (IUATLD) expert group published criteria for discontinuing BCG vaccination programmes in countries with a low prevalence of TB.<sup>252</sup> These criteria are outlined as follows:

#### IUATLD criteria

Before consideration is given to whether a country stops or modifies its BCG programme, the following requirements must be met:

- There is a well functioning TB control programme
- There has been a reliable reporting system over the previous five or more years, enabling the estimation of the annual incidence of active TB by age and risk groups, with particular emphasis on TB meningitis and sputum smear positive pulmonary TB. In Ireland, national data enabling a detailed epidemiological analysis for the country, as a whole was first produced by HPSC in the 1998 National TB Report. The 2006 National TB Report is the ninth national TB report.
- Due consideration has been given to the possibility of an increase in the incidence of TB resulting from the epidemiological situation of AIDS in that country.

#### With one of the following

- The average annual notification rate of sputum smear positive pulmonary TB should be 5 per 100,000 or less during the previous three years

- or
- The average annual notification rate of TB meningitis in children under five years of age should be less than one case per ten million general population over the previous five years
- or
- The average annual risk of TB infection should be 0.1% or less. This is not applicable to Ireland.

The national rate for sputum smear positive pulmonary TB has been under 5 per 100,000 for the three years prior to 2006. In 2005 the rate was 3.3 per 100,000, while in 2004, 2003 and 2002, the rates were 3.5 per 100,000, 3.7 per 100,000 and 3.1 per 100,000 respectively. However, data from between 2001 and 2006 indicate that there were four cases of TB meningitis notified in children aged less than five years, of whom two were culture positive and three had not received BCG vaccine.<sup>20</sup>

When considering the importance of neonatal BCG vaccination, it is worth considering the practice in other European countries. For example, Sweden discontinued routine neonatal BCG vaccination in 1975 when they had a total notification rate of 20 per 100,000 population and an age-specific incidence rate for children aged 0-14 years of 0.3 per 100,000. While the national crude rate in Ireland is less than 20 per 100,000 population, the 2006 age-specific incidence rate for children 0-14 years was 2.4 per 100,000, eight times the rate recorded in Sweden when they discontinued neonatal BCG vaccination. In 2005, 2004, 2003, 2002, 2001 and 2000, the age-specific incidence rate for children aged 0-14 years was 3.0 per 100,000, 1.2 per 100,000, 2.9 per 100,000, 2.2 per 100,000, 1.9 per 100,000 and 1.9 per 100,000 respectively. In 1999, the age-specific incidence rate for children aged 0-14 years was 5.1 per 100,000 population, almost seventeen times the rate recorded in Sweden. In 1998, the corresponding figure was 3.5 per 100,000 population almost twelve times the rate recorded in Sweden when they discontinued BCG.<sup>20</sup>

It is also notable that Finland who moved from a universal newborn BCG vaccination programme to a targeted risk group programme in September 2006 had only five notified cases of TB in the 0-2 year olds between 1997 and 2001 and no cases of TB meningitis in the 0-14 year olds notified in this period. Since 1970, only two cases of TB meningitis have been notified nationally in Finland. The national incidence rate for TB is 11 per 100,000 and 65% of cases occur in those aged over 60 years. Foreign-born patients represent 6 to 9% of the total.<sup>253</sup>

When Canada discontinued universal BCG in 2002, the national TB notification rate was 5.2 per 100,000 and the notification rate was 1.6 per 100,000 in 0-14 year olds.<sup>254</sup>

Also, rates of TB notifications in 1998 in the following Nordic countries that have discontinued neonatal BCG programmes are much lower than in Ireland and among the best in the world as outlined below:

- Sweden = 5.0 per 100,000
- Norway = 5.0 per 100,000
- Denmark = 9.6 per 100,000
- Iceland = 5.8 per 100,000.

As well as the IUATLD criteria, there are additional considerations which should also be reviewed when deciding to modify or stop a universal BCG programme as outlined below:

- Costs
- Adverse reactions to BCG
- Risk groups: In the event of discontinuation of the BCG vaccination programme for the general population, it may be advisable to continue it in certain well-defined population groups with a known high notification rate of active TB.<sup>253</sup>

While Ireland meets the IUATLD criteria on the basis of overall smear positive pulmonary TB reporting rates, the number of TB meningitis cases in children and general rates of TB in children remain a concern. Also, the TB control programme is currently under review and it is likely that recommendations will be made for strengthening the programme. In light of these findings, the continuation of the universal programme of neonatal BCG vaccination is recommended in Ireland at this time.

**Recommendation:**

The continuation of a universal programme of neonatal BCG vaccination is recommended in Ireland at this time.

**7.3 Dose and Route of Administration**

BCG Vaccine Statens Serum Institut (SSI) is the only available licensed BCG vaccine in Ireland. It contains the Danish strain 1331. It does not contain thiomersal or any other preservatives. It may be given concurrently with another live vaccine, but if they are not given at the same time an interval of at least four weeks should be allowed between such vaccines. It can also be given at the same time as killed vaccines e.g. DTaP/IPV/Hib/Hepatitis B, PCV (pneumococcal conjugate vaccine) or Men C.

**Recommendation:**

When BCG is given to infants there is no need to delay the primary immunisations. No further immunisation should be given in the arm used for BCG immunisation for at least three months because of the risk of regional lymphadenitis.

Infants under 12 months of age

The recommended dose is 0.05ml by **intra**dermal injection of the reconstituted vaccine at one site over the middle of the deltoid muscle.

Adults and children 12 months and over

The recommended dose is 0.1ml by **intra**dermal injection of the reconstituted vaccine and given at one site over the middle of the deltoid muscle.

Although the protection afforded by BCG vaccine may wane with time, there is no evidence that repeat vaccination offers significant protection and repeat BCG is not recommended. If re-immunisation with BCG is being considered expert advice should be sought.

Detailed instructions including illustrations are available from the Immunisation Guidelines for Ireland prepared by the National Immunisation Advisory Committee.<sup>255</sup>

**7.4 Indications for BCG Vaccine****Recommendation:**

Training for health professionals in the correct administration of BCG vaccine is recommended. Those administering vaccine should be aware of indications, contraindications, immunisation and adverse reactions associated with BCG.

*Groups in whom BCG vaccine is indicated:*

1. Newborn babies
2. Unvaccinated children aged one to 15 years (i.e. those with no documented evidence of BCG or without a characteristic scar)
  - i. Children aged three months to less than six years who are not in an at-risk environment<sup>¶</sup> do

<sup>¶</sup> Children in at-risk environments include those who are contacts of a pulmonary TB case, who are from an area of high endemicity (annual TB rates of  $\geq 40/100,000$ ) or whose parents are from an area of high endemicity or who have household contacts who belong to an at-risk group for TB

- not need a TST (Mantoux test) prior to receiving BCG vaccine<sup>¶</sup>
- ii. Children in at-risk environments should have a TST (Mantoux test) prior to BCG.<sup>256</sup>
  3. Unvaccinated (that is without adequate documentation or a characteristic scar) Mantoux negative immigrants under 16 years of age who were born or who have lived for a prolonged period (at least three months) in a high incidence country\* OR aged 16-35 years from a sub-Saharan African country or country with a TB incidence of 500 per 100,000<sup>26</sup>
  4. Unvaccinated Mantoux negative contacts aged 35 years and under of cases with active pulmonary TB. Children under five years of age in contact with smear positive TB should be referred to a contact tracing clinic for investigation and then immunised with BCG as indicated.
  5. Members of special at-risk groups such as the travelling community due to the logistical difficulties of providing alternative control measures and follow up of contacts
  6. Unvaccinated Mantoux negative persons under 16 years of age intending to live or work with local people in high incidence countries for more than one month<sup>257</sup>
  7. BCG is indicated for unvaccinated healthcare workers (HCWs) aged <35 years who are TST negative and who will have contact with patients or with clinically contaminated materials. Not all HCWs are at equal risk of TB. A risk assessment should be carried out to see if BCG is indicated for unvaccinated HCWs aged 35 years and older who are TST negative, taking into account their country of origin and the nature of their work. For more details see page 114.
  8. Those more likely than the general population to come into contact with someone with infectious sputum smear positive TB. Unvaccinated Mantoux negative persons aged 35 years and under in the following occupations should be offered BCG vaccination:<sup>26</sup>
    - i. Veterinary laboratory staff who handle animal species known to be susceptible to TB and abattoir workers who handle animal species, carcasses and products known to be susceptible to TB
    - ii. Prison staff working directly with prisoners
    - iii. Staff of facilities for the elderly
    - iv. Staff of hostels for homeless people and facilities accommodating refugees and asylum seekers.

## 7.5 Contraindications

BCG vaccine should not be given to:

1. Neonates in a household where an active TB case is suspected or confirmed
2. Those with a past history of TB
3. Those receiving systemic corticosteroid therapy (other than as replacement) or other immunosuppressive treatment including x-irradiation. Inhaled steroids are not a contraindication.
4. Those suffering from blood dyscrasias, lymphoma, or malignant neoplasms involving bone marrow or the lymphoreticular system, or with gamma globulin deficiency or abnormality
5. Those with a family history of primary immunodeficiency e.g. inherited severe combined immunodeficiency (SCID), chronic granulomatous disease (CGD), etc. until evaluation is complete
6. BCG should not be given to adults or children known to be HIV positive (asymptomatic or symptomatic). However, lack of knowledge of maternal HIV status is not a reason to defer routine BCG inoculation in healthy newborns.
7. Those with pyrexia  $\geq 38^{\circ}\text{C}$
8. Those with generalised infected dermatosis. The effect of BCG vaccine may be exaggerated in these patients and a more generalised infection is possible. If the person has eczema, an immunisation site should be chosen that is free from skin lesions. Eczema is not a contraindication.
9. Those who are pregnant. Breast-feeding does not constitute a contraindication to BCG vaccine.
10. Those with positive tuberculin tests (or positive IGRA)
11. Those who have had a confirmed anaphylactic reaction to a component of the vaccine
12. Those who received a live vaccine e.g. MMR within the previous four weeks.

<sup>¶</sup> In extremely rare instances, an accelerated local response to BCG vaccine known as Koch's Phenomenon characterised by induration that is more than 5mm (within 24-48 hours), early pustule formation (within 3 to 5 days), an ulcer (at seven day) and a scab (within 10-15 days) can occur and indicates concurrent TB

\* High incidence refers to countries where the annual rate of TB is 40/100,000 or greater

## 7.6 Interactions

Administration of blood or plasma transfusions, hepatitis B vaccine, hepatitis B immunoglobulin and normal immunoglobulin are thought not to reduce the effectiveness of BCG vaccine.<sup>258-261</sup> A baby who has received blood or plasma transfusions can be subsequently immunised with BCG, after the observation period (24 hours) for transfusion reactions has ended. A baby who has received hepatitis B vaccine, hepatitis B immunoglobulin or normal human immunoglobulin can be subsequently immunised with BCG without delay.

## 7.7 Administration of BCG Vaccination

Detailed instructions are available in chapter 2 of the Immunisation Guidelines for Ireland available at [www.immunisation.ie](http://www.immunisation.ie) and also on the Staten Serum Institut (Denmark) website at [www.ssi.dk/sw4145.asp](http://www.ssi.dk/sw4145.asp).

## 7.8 Immunisation Reaction and Care of the Immunisation Site

The expected reaction to a successful BCG vaccination seen in 90-95% of recipients is induration at the injection site followed by a local lesion which starts as a papule two or more weeks after vaccination. It may ulcerate and then slowly subside over several weeks or months to heal leaving a small flat scar. It may also include enlargement of a regional lymph node to less than 1cm.

It is not necessary to protect the site from becoming wet during washing and bathing. The ulcer should be encouraged to dry and abrasion (for example by tight clothes) avoided. Should any oozing occur a temporary dry dressing may be used until a scab forms. It is essential that air is not excluded. If absolutely necessary (e.g. to allow swimming), an impervious dressing may be applied but only for a short period as it may delay healing and cause a larger scar.

Further observation after routine vaccination with BCG is not necessary, other than as part of monitoring of the quality of the programme, nor is further tuberculin testing recommended.

Severe injection site reactions, large discharging ulcers, abscesses and keloid scarring are most commonly caused by faulty injection technique, excessive dosage or vaccinating individuals who are tuberculin positive. It is essential that all healthcare professionals be properly trained in all aspects of the process involved in tuberculin skin tests and BCG vaccination.

## 7.9 Adverse Reactions

**Local:** Side effects include local induration, pain and occasionally ulceration, enlargement of a regional lymph node greater than 1cm, abscess formation, lupoid reaction and inflammatory and suppurative adenitis.<sup>109</sup>

**General:** Headache, fever and generalised lymphadenopathy can rarely occur (in less than one in 1,500 vaccinated). Anaphylactic reaction and disseminated BCG complications (such as osteitis, osteomyelitis or disseminated BCG infection) are also very rare. Disseminated BCG infection occurs in approximately two per one million persons, primarily in persons with severely impaired immune systems.<sup>109</sup>

### Management of adverse reactions

Local adverse reactions to BCG vaccine occur in 1-2% of immunisations. Severe local reactions (ulceration greater than 10mm, caseous lesions, abscesses or drainage at the injection site) or regional suppurative lymphadenitis with draining sinuses following BCG vaccination should be discussed with a respiratory physician or consultant paediatrician.<sup>255</sup>

Most experts do not recommend treatment of draining skin lesions or chronic suppurative lymphadenitis caused by BCG vaccine because spontaneous resolution occurs in most cases. Large needle aspiration of suppurative lymph nodes may hasten resolution. There is little evidence to support the use of either locally instilled anti-mycobacterial agents or systemic treatment of patients with severe persistent lesions.



Disseminated BCG infection should be referred to a respiratory or infectious disease consultant for specialist advice and will normally require systemic anti-tuberculous treatment and mandate a detailed immunological investigation.<sup>255</sup>

### 7.10 Tuberculin Testing prior to BCG Immunisation

BCG vaccine should not be administered to an individual with a positive tuberculin test. Those with strongly positive tests should be referred to a respiratory or infectious disease physician for assessment of the need for further investigation and treatment.

A TST (Mantoux test) is necessary prior to BCG vaccination for:

1. Children aged three months to aged under six years in at-risk environments<sup>¶</sup>
2. Persons aged six years and older
3. Infants and children under six years of age with a history of ever having lived or had a prolonged stay (more than one month) in a country of high endemicity (i.e. an annual TB rate of  $\geq 40/100,000$ )
4. Those who have had close contact with a person with known TB and
5. There is a history of TB in a household contact in the last five years.

**BCG can be given up to three months following a negative tuberculin test.**

The standard skin test for use in Ireland is the Mantoux 2TU/0.1ml tuberculin PPD (see chapter 2).

**Recommendation:**

BCG should not be administered to an individual with a positive tuberculin (or IGRA) test.

For further detail on BCG, see the Immunisation Guidelines for Ireland available at [www.immunisation.ie](http://www.immunisation.ie)

<sup>¶</sup> Children in at-risk environments include those who are contacts of a pulmonary TB case, who are from an area of high endemicity (annual TB rate  $\geq 40/100,000$ ) or whose parents are from an area of high endemicity or who have household contacts who belong to an at-risk group for TB.



## 8. Contact Tracing

Contact tracing is a systematic process with three main objectives:

- To identify and initiate treatment of secondary cases
- To identify TB infected contacts in order to offer treatment for LTBI
- To identify those not infected for whom BCG vaccination may be appropriate.

Contact tracing may also be undertaken to find a source of infection or any co-primary cases where there is evidence of recent infection, as indicated by infection in children.

Current Irish epidemiological data indicate that between 6 and 10% of TB cases are diagnosed by contact tracing.<sup>19;20;262</sup> UK studies from the 1990s have shown that up to 10% of TB cases are diagnosed by contact tracing, that disease is detectable in about 1% of all screened contacts,<sup>263-270</sup> and is normally found in non-BCG vaccinated close contacts of pulmonary smear positive cases during the initial round of investigation.<sup>263-267</sup>

Early case detection as a result of contact tracing reduces the period in which cases are infectious and the risk of infection being transmitted to others. Evaluation of highest risk contacts can infer recent transmission if infection or disease is detected. Evidence of recent infection supports the extension of the contact investigation to progressively lower-risk contacts. Screening should be concluded when levels of infection detected in the tiers of at risk contacts equate to those in the general community.

### Recommendation:

Contact tracing should be conducted according to the concentric circle approach,<sup>271</sup> whereby contacts with greatest exposure to the index case are prioritised for screening.

### 8.1 Factors Predicting TB Transmission

TB is spread by airborne droplet nuclei (approximately 1 to 5 microns in diameter, containing 1 to 10 bacilli) which are released in an aerosol from an individual with infected pulmonary sites when they cough, sneeze or sing. Sociability of the index patient may contribute to disease transmission because of the increased number of contacts and the intensity of exposure.<sup>51</sup> The amount of contact necessary for TB infection to be transmitted is variable. It depends on the infectiousness of the source case, the susceptibility of the person in contact with the case and the environment in which contact occurs. Factors that predict likely transmission of TB are outlined below and it is important to consider all these factors together when evaluating the infectiousness of a case.<sup>272</sup>

#### Infectiousness of the source case

##### *Anatomical site of disease*

Cases with TB in pulmonary and laryngeal sites primarily transmit infection.<sup>273;274</sup> In such cases, determining whether or not AFB are present on microscopic examination of sputum is an important factor in establishing infectiousness. Infectious pulmonary and laryngeal cases should be considered a priority for contact investigation.

Cases of extrapulmonary TB are typically non-infectious and contact investigations should be aimed at identifying a source of infection in those with greatest exposure to the case (especially where there is evidence of recent infection e.g. TB in a child). This is especially important if the case appears to have resulted from recent transmission e.g. meningeal TB in a child. Diseased tissues are not usual infection sources, although aerosol-producing procedures (e.g. autopsy, embalming and irrigation of a draining abscess) undertaken without infection control precautions are considered an infection risk.<sup>227;275-278</sup>

##### *Sputum bacteriology*

A case of TB whose sputum is smear positive, defined as a patient with minimum of one sputum specimen

positive for AFB by microscopy is thought to be six to 10 times more contagious than a smear negative case, while laryngeal TB cases are four to five times more contagious than smear positive pulmonary cases.<sup>30;279</sup>

**Table 8.1: Definition of an infectious TB case**

| Infectious TB case   | TB case presumed infectious for contact tracing purposes                      |
|--|---|
| <ul style="list-style-type: none"> <li>• Sputum smear positive pulmonary TB</li> <li>• Laryngeal TB</li> </ul> | <ul style="list-style-type: none"> <li>• BAL positive: (see below)</li> </ul> |

The relative infectiousness of positive bronchial washings or BAL is unknown but some consider such specimens equivalent to sputum.<sup>280</sup> The US approach is to consider all BAL positive patients as infectious as those who are sputum smear positive<sup>51</sup> (table 8.1). It is recommended that a precautionary approach should be taken with BAL smear positive cases.

#### Recommendation:

- Infectious pulmonary and laryngeal cases are priorities for contact investigation. A precautionary approach should be taken with BAL smear positive cases
- Those BAL smear positive cases with cavitation on chest X-ray, MDR-TB or XDR-TB or where contacts are immunosuppressed or are under 5 years of age should be presumed infectious for contact tracing purposes
- The determination of infectivity of all other BAL smear positive patients should be considered on a case-by-case basis (clinical/microbiology/public health input).

#### Radiographic findings

Patients who have lung cavities observed on a chest radiograph typically are more infectious than those with non-cavitary disease.<sup>278;281;282</sup> This is an independent predictor after bacteriological findings are taken into account.

#### Age

Children younger than 10 years of age with pulmonary TB are rarely contagious because their pulmonary lesions are small (paucibacillary disease), cough is not productive, and few or no bacilli are expelled.<sup>109</sup> Generally, contact tracing investigations involving young children should be geared towards identifying the source and co-primary cases. However, although unusual, transmission from young children has been recorded.<sup>283;284</sup>

#### Recommendation:

Young children under 10 years of age with pulmonary disease are rarely infectious. Such contact tracing investigations should be focused on finding a source and co-primary cases.

#### Susceptibility of Contacts

##### Age

Children under five years of age are more likely to develop disease following recent infection.<sup>110</sup> The incubation period is usually short, and severe forms of TB are common. Children under five years of age should be assigned a high priority for contact investigation.

**Immunosuppression**

Immunosuppressed individuals should be assigned a high priority for contact investigation. TB patients who are HIV-infected with low CD4 T-cell counts frequently have chest radiographic findings that are not typical of pulmonary TB. Atypical radiographic findings increase the potential for delayed diagnosis which increases transmission.

**Indoor environment**

Transmission is rarely thought to occur outdoors. Risk of transmission is greatest where there is prolonged, close contact with a case in an indoor environment; small volumes of shared indoor air, limited ventilation of the airspace with outdoor air and recirculation of air in closed circulation heating or air conditioning systems. Indoor environments that are poorly ventilated, dark or damp, can lead to increased concentration and survival of *M. tuberculosis*.<sup>285-287</sup>

**Duration of exposure** <sup>281;288-290</sup>

The likelihood of transmission of *M. tuberculosis* increases with the intensity, frequency and duration of exposure to a case. Usually it takes many hours or days to transmit an infectious dose, but casual/short exposures may lead to transmission if the case is infectious and environmental air conditions are favourable.<sup>291</sup> Exposure duration of less than eight hours is generally considered not to be significant. Current US and UK guidelines<sup>26;51</sup> cite cumulative contact of eight hours or more for contact investigation.

**8.2 Initiating the Contact Investigation**

Prompt notification of active TB cases is crucial, allowing for the early initiation of contact tracing (table 8.2). Rapid evaluation of close contacts allows timely identification of those who have active disease and, if active disease has been excluded, allows initiation of treatment of LTBI for newly infected contacts before disease occurs.

**Table 8.2: Timeframes for completing various stages of the contact investigation**

|   |  |
|---|--|
| <b>Case notification</b>                    | Case should be notified as soon as possible, and not later than one working day following diagnosis  |
| <b>Contact tracing interview</b>            | Should be conducted no later than: <ul style="list-style-type: none"> <li>o 1 working day after notification of an infectious/presumed infectious case</li> <li>o 3 working days after notification for all other pulmonary and extra-pulmonary cases</li> </ul>   |
| <b>Site investigation</b>                   | Should be conducted no later than 3 working days after the contact tracing interview if deemed appropriate following a risk assessment   |
| <b>First screening of priority contacts</b> | Should be conducted no later than: <ul style="list-style-type: none"> <li>o 7 working days for close contacts of an infectious/presumed infectious case</li> <li>o 14 working days for all other contacts (i.e. casual contacts of infectious cases/contacts of non-infectious cases) after the contact tracing interview</li> </ul> |

### 8.3 Investigating the Index Case

Comprehensive information regarding an index patient is the foundation of a contact investigation. When a case of TB is identified, detailed information about the index case should be collated and considered, so that priorities can be established for screening. Criteria for consideration are multiple and include:

- Anatomical site(s) of TB disease
- Symptoms and date of illness onset
- Chest X-ray results (and other results of diagnostic imaging studies)
- Diagnostic specimens that were sent for bacteriological or histological analysis
- Current bacteriological results
- Previous diagnosis/treatment for TB infection or disease
- Concomitant medical risk factors/conditions
- Relevant socio-demographic information
- Names of contacts and
- Exposure locations.

The MOH (in practice regional director of public health/designated medical officer) is responsible for conducting TB contact investigations. Local standard operating procedures for investigation improve the efficiency and uniformity of investigations. Timeframes for completion of specific stages of contact investigation are recommended in table 8.2.

#### Determining the infectious period

Determining the infectious period focuses the investigation on those contacts most likely to be at risk for infection and sets the timeframe for testing contacts. Cases of pulmonary TB are generally considered to become infectious at the time of onset of cough. If no cough is reported or if the duration is difficult to determine, the time of onset of other symptoms attributable to TB may be used to estimate the onset of infectiousness. In practice, however, it is often difficult to know with certainty when symptoms began. Because the start of the infectious period cannot be determined with precision by available methods, a practical estimation is necessary.

**For infectious/presumed infectious cases:** (see table 8.1) assessment of the period of exposure should extend to three months before symptom onset or first positive finding consistent with TB disease (e.g. abnormal chest X-ray), whichever is longer. This is consistent with recent guidelines published by the US Centers for Disease Control and Prevention<sup>51</sup> and Canada.<sup>30</sup>

**For cases other than infectious/presumed infectious cases:** assessment of the period of exposure should

extend to four weeks before the date that TB was suspected. Again, this is consistent with current CDC and Canadian guidelines.<sup>30, 51</sup>

The decision about the period of infectiousness, therefore, will need to be determined for each case according to these guidelines and to the clinical situation. Priority should always be given to contact tracing during the period when the TB patient was symptomatic. If the yield of contacts with active disease is found to be higher than expected from tuberculin testing, the period of potential exposure should be further extended.

The period of time in which a patient on effective therapy takes to become non-infectious varies. This can be established in infectious pulmonary patients by monitoring susceptibility to treatment (as demonstrated by smear negative sputum results on three consecutive days)<sup>30, 51, 52</sup> and diminished symptoms.<sup>51</sup> Respiratory TB patients are usually non-infectious after a minimum of two weeks of treatment.<sup>26</sup>

## 8.4 Prioritisation of Contacts

As the circumstances in each contact investigation are unique, and risk of infection and disease to individual contacts cannot be determined precisely, the classification of contacts into 'close' and 'casual' is recommended to guide the decision making process (see table 8.3). Contacts with a cumulative total exposure to an infectious TB case exceeding eight hours within a restricted area should be regarded as close contacts i.e. equivalent to household contacts. A reduced cumulative total exposure time of  $\geq 4$  hours should be considered for vulnerable contacts such as young children aged less than 5 years and immunocompromised contacts.

**Table 8.3: Classification of contacts for prioritising contact tracing**

| Contact classification | Description   |
|------------------------|---|
| <b>Close contacts</b>  | <ul style="list-style-type: none"> <li>• All household contacts (an individual sharing a bedroom, kitchen, bathroom, or sitting room)</li> <li>• All other immunocompetent adult contacts with a cumulative total exposure <math>\geq 8</math> hours in a restricted area equivalent to a domestic room (may include girlfriend, boyfriend, close friends, sexual partners, frequent visitors to the home, etc.)</li> <li>• A reduced cumulative total exposure time of <math>\geq 4</math> hours may need to be considered for vulnerable contacts exposed in a restricted area such as children aged <math>&lt; 5</math> years and immunocompromised individuals, immunocompromised either due to disease e.g. HIV or therapies, individuals receiving <math>&gt;15\text{mg}</math> prednisone or equivalent for more than four weeks, or other immunosuppressive agents for cancer, chemotherapeutic agents, anti-rejection drugs for organ transplantation and TNF-<math>\alpha</math> antagonists or as defined by the attending consultant.</li> <li>• Individuals exposed during medical procedures (e.g. bronchoscopy, sputum induction or autopsy) where no infection control practices were in place</li> </ul> |
| <b>Casual contacts</b> | <ul style="list-style-type: none"> <li>• Generally all other contacts such as work colleagues, team/club members, etc. (some such contacts may be assessed as being close contacts following risk assessment)</li> </ul>  |

**For infectious/presumed infectious cases** (see table 8.1): all close contacts should be screened initially. Screening should be extended if there is evidence of infection or disease in close contacts following screening i.e. evidence of transmission.

**For cases other than infectious/presumed infectious cases:** Screening should be limited to household members only unless there is evidence of recent infection (e.g. TB in child) and the source remains

unknown. In such circumstances, screening by chest X-ray should be considered for those adults in regular contact with the child (e.g. childminder, teachers).

### Expanding a contact investigation

Consideration should be given to extending screening if there is evidence of transmission based on any of the following:

- There is an unexpectedly high rate of infection or TB disease in close contacts (e.g. if  $\geq 10\%$  of close contacts have TB infection or active disease)<sup>51</sup>
- TB disease is identified in a casual contact or a contact with low screening priority
- Infection is identified in any contact (close/casual) under five years of age.

## 8.5 The Contact Tracing Interview

A newly diagnosed patient should be interviewed by a trained member of staff in the hospital, TB clinic, in the patient's home or anywhere that will ensure the patient's privacy. Interviews should be completed as soon as possible (see table 8.2). The interview provides an opportunity to exchange information, for the patient to acquire information about TB and its control, and for the health professional to learn to adapt treatment and education strategies to the patient's specific requirements. The Centers for Disease Control and Prevention (CDC) developed standard procedures for interviewing TB patients in 1999.<sup>292</sup> The following principles as proposed by CDC are recommended for use:

1. **Building rapport** with a case is an important part of contact tracing. This can be achieved by assuring patient privacy, helping the patient decide how to share information about their diagnosis to contacts, and allowing approximately one hour for exchange of information (depending on the patient's health and endurance).
2. **Exchanging information** should allow the interviewer to obtain missing information e.g. date of symptom onset, and the patient to improve their understanding of disease causation/transmission and clarify their treatment plan requirements.
3. **Transmission settings** i.e. places the case attended while infectious should be identified so contacts attending those venues can be identified and prioritised for screening based on time spent by the index case in those settings. Topics for discussion could include where the patients worked, spent their leisure/recreational time, where they visited, ate, spent nights, etc. The interviewer should ask specifically about time spent in congregate settings (e.g. schools, prisons, hospitals/healthcare settings, etc.)
4. **Lists of contacts** should be made for those attending each potential site of transmission, including name of contact, approximate types, frequency and duration of exposure. Recent illness among contacts should be discussed.
5. **Closure:** The interviewer should express appreciation for the patient's contribution, and indicate how screening will proceed, that site visits will be conducted and confidentiality respected.
6. **Follow-up interviews** should be scheduled if further information is required.

### Site investigation

Site visits may need to be undertaken to complement interviews. It is important that consideration is given to the index case's lifestyle so that places of intense contact other than the household may be determined (e.g. work or leisure sites). Site visits may add contacts to the list and are the most reliable source of information regarding transmission settings.<sup>288</sup> Physical conditions at each setting can contribute to transmission. At congregate settings, the size of the room(s), ventilation system and airflow patterns should be considered along with information about how long and how often the patient was in that setting. Failure to visit all potential sites of transmission has contributed to TB outbreaks.<sup>293;294</sup> Visiting the index patient's residence is especially helpful for finding children who are contacts. Certain sites (e.g. congregate settings) require special arrangements to visit. Communication and liaison with management in congregate settings is an essential component of site investigation. Maintaining confidentiality for an index patient can be difficult. The index case should be informed that information needs to be shared with management. Every effort should be taken to maintain patient confidentiality.

## 8.6 Screening Tools

The TST using the Mantoux technique (2TU) is the primary tool used in contact tracing<sup>295</sup> (chapter 2). IGRA testing is an additional diagnostic method for screening of LTBI.

Guides to evaluating contacts of active TB cases are shown in figures 8.1 (for contacts of active TB cases) and 8.2 (for children between four weeks and five years who are contacts of infectious TB cases). These guidelines do not fit every circumstance and additional considerations beyond those discussed in these guidelines may need to be taken into account for specific situations. It is important to monitor attendance, to identify those contacts who fail to attend and to ensure that the contact's GP is informed of repeated failures to attend.

In the future, the rapidly expanding evidence base will provide more reliable information on the sensitivity and specificity of IGRA tests and their comparability to the TST. Evidence gathered to date suggests that the IGRA tests are at least as sensitive as the TST in diagnosing LTBI and more specific in populations that include previously BCG vaccinated individuals. However, discordant results between IGRA and the TST have been observed, leading to difficulties interpreting the results.<sup>60</sup>

In theory, a two-step strategy, using TST (with its high sensitivity) followed by IGRA testing (with its high specificity) should be an optimal approach for screening an individual exposed to a TB case.<sup>26</sup> The chest X-ray is generally reserved as a means of confirming pulmonary disease following recent contact with TB or in the presence of suggestive symptoms.

Canadian guidelines<sup>60,296</sup> on IGRA published in 2007 and updated in 2008 summarised current evidence in the context of contacts of a case of infectious TB and IGRA use as follows:

- IGRA correlated with exposure better than TST in BCG vaccinated contacts. There were significantly fewer positive results in low-exposure groups with the IGRA than with the TST
- In the absence of BCG, the IGRA and TST appeared to have similar rates of positivity, although there were discordant results.

Those guidelines conclude that, given that several studies have found significant discordance between TST and IGRA results (both TST positive/IGRA negative and the reverse) and because the biological basis of this discordance is uncertain, the reliance on IGRA should depend on the clinical context.

The Canadian guidance with regard to IGRA use in contact tracing is recommended.

### **Canadian guidance on IGRA for adult and child contacts of a case of active infectious TB tuberculosis<sup>60</sup>**

IGRA may be used as a confirmatory test for a positive TST in contacts (adult or child) who on the basis of an assessment of the duration and degree of contact with an active infectious case are felt to have a low pre-test probability of recently acquired LTBI and who have no other high or increased risk factors for progression to active disease if infected.

For close contacts or those contacts who have high or increased risk of progression to active disease if infected, a TST (or both TST and IGRA) should be used and if either is positive the contact should be considered to have LTBI.

If both TST and IGRA testing will be used, it is recommended that blood be drawn for IGRA on or before the day when the TST is read.

### **Repeating TST in contact investigations**

The interval between acquisition of infection and tuberculin conversion is an important issue. This determines the interval between the first and second TST in contact investigations i.e. the so-called window period. Traditionally this had been considered to be 12 weeks but all available evidence from

BCG vaccination and natural infection points to a shorter interval. After inadvertent vaccination with *M. tuberculosis* (the Lubeck Disaster), children developed positive reactions in three to seven weeks. Other studies have shown clinical illness with a positive tuberculin test from 19-57 days after exposure with a mean of 37 days.<sup>297</sup>

There continues to be international variation in practice. The 2003 New Zealand TB Control guidelines lowered the window period for testing from twelve to eight weeks based on the findings of the studies outlined above.<sup>52</sup> Current US guidelines<sup>51</sup> cite eight to ten weeks, while the UK advises a six-week interval between tuberculin tests (a recommendation based on consensus opinion of clinicians and experts).<sup>26</sup>

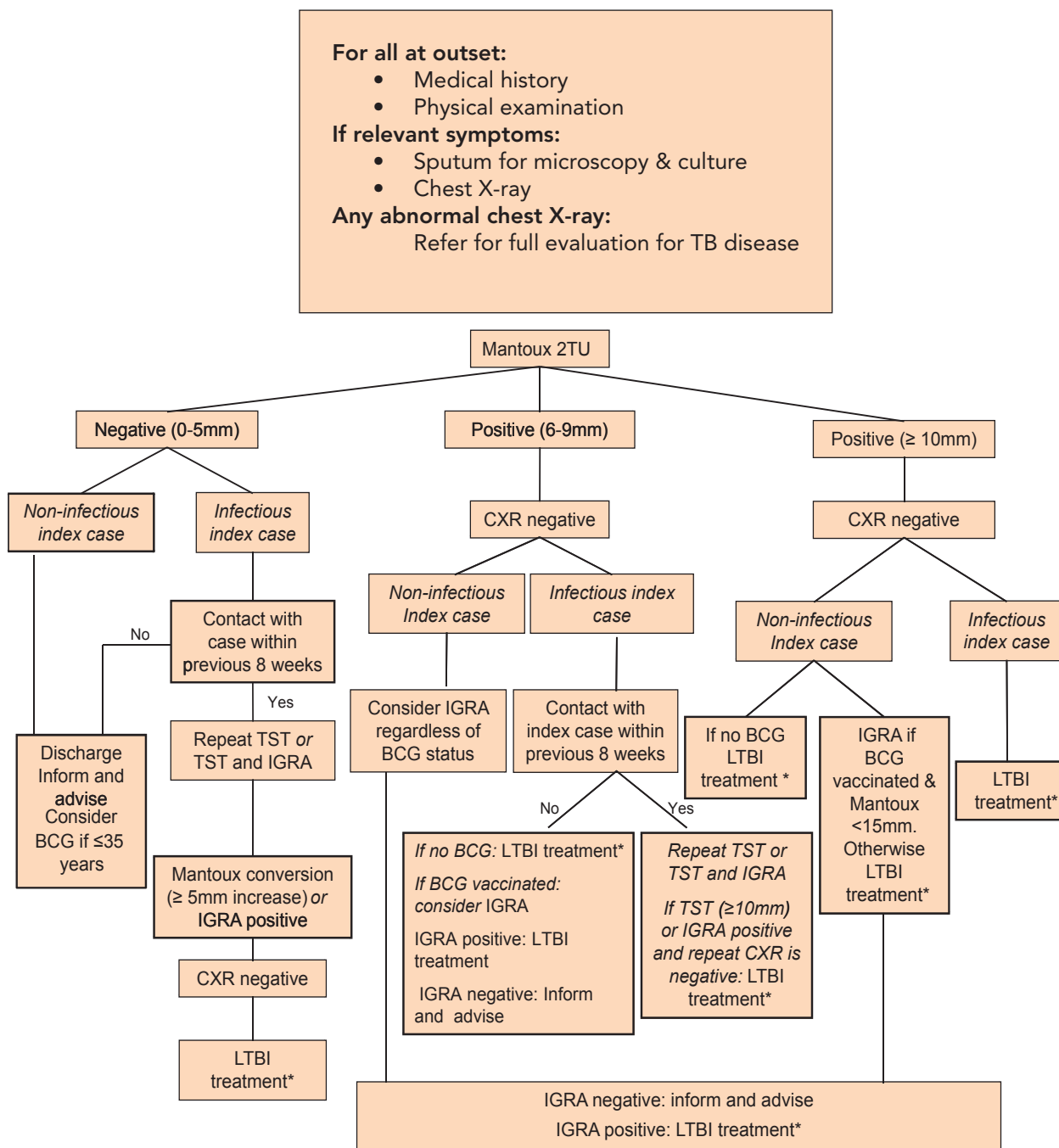
It is the view of this committee, based on available best evidence, that six-eight weeks constitutes a good timing interval as it is important to leave long enough for conversion to occur but not too long for a delayed diagnosis. Eight weeks is a good compromise and well within evidence for conversion times stated in the literature.

**Recommendation:**

The recommended interval between first and second screening rounds (TST ± IGRA) in contact investigations is eight weeks. If the last contact with the infectious case exceeded an eight-week period, one TST is sufficient.



**Figure 8.1: Algorithm for close contacts (adults and children ≥ 5 years) of all cases of infectious/presumed infectious TB**



The algorithm presented here is a guideline only and should be interpreted in accordance with the clinical context.

**Note:** At present, IGRA are not routinely recommended for children but may be considered in individual situations

\*If LTBI treatment is refused: Chest X-ray follow-up at three and 12 months

**Contact investigation for patients whose culture converts back to positive**

In some instances, a TB patient's culture may convert to negative and then become positive again. This may happen if a patient is lost to follow-up and discontinues medications before completing treatment or if treatment was not adequate because of multidrug resistance.

If the patient is located after a treatment lapse of three months or longer and if the patient's cultures have become positive again or if the patient relapses while on treatment after becoming culture negative, a second window period should be defined and the patient should be re-interviewed. Contacts identified during the initial investigation should be re-evaluated if they were exposed again. If new contacts are identified, they should be tested and evaluated.<sup>77</sup>

**Contact investigation among children and adolescents**

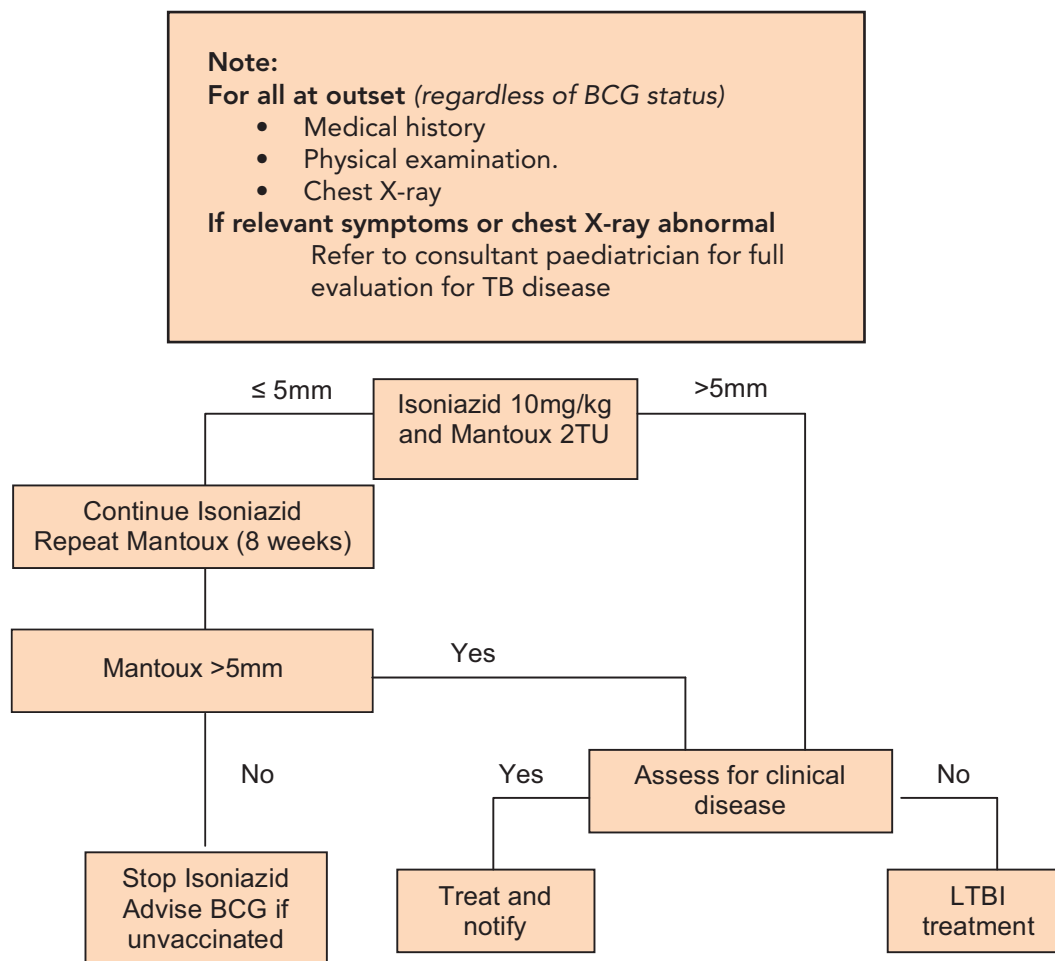
Contact investigations for children with suspected TB are generally conducted to identify the adult source-case. Because TB among infants and young children usually occurs within weeks to months of contracting infection with *M. tuberculosis*, having a child with disease is a marker of recent transmission from someone in the child's environment.<sup>51</sup> Children younger than 10 years with pulmonary TB are rarely contagious because their pulmonary lesions are small (paucibacillary disease), cough is not productive, and few or no bacilli are expelled.<sup>109</sup> However, children or adolescents of any age with characteristics of adult-type TB (i.e. productive cough and cavitary or extensive upper lobe lesions on chest X-ray) should be considered potentially infectious at the time of diagnosis.<sup>51</sup>

A negative TST does not exclude LTBI or TB disease. Approximately 10 to 15% of immunocompetent children with culture-documented disease do not react initially to a TST.<sup>109</sup> Host factors such as young age, poor nutrition, immunosuppression, other viral infections (especially measles, varicella and influenza), recent TB infection and disseminated TB disease can decrease TST reactivity. Many children and adults co-infected with HIV and *M. tuberculosis* do not react to a TST.

In the interpretation of a positive TST among child contacts of contagious TB cases, current US guidelines disregard previous BCG immunisation.<sup>109</sup>

**Young child contacts aged under five years of an infectious TB case**

Following exposure to a case of infectious/presumed infectious TB, children should have a TST and an evaluation for TB disease (chest X-ray and physical examination). Once active TB has been ruled out, children with positive skin tests should receive a full course of treatment for LTBI (chapter 3). Those who have negative skin test results should also receive treatment for presumed LTBI (chapter 3). This intervention is especially critical for infants and toddlers < 3 years but is recommended for all children aged < 5 years.<sup>51</sup> Those with a negative TST result should be retested eight weeks after exposure to infectious TB has ended. If the TST result is still negative in an immunocompetent individual, isoniazid can be discontinued (continue for further 7 months i.e. a total of 9 months if immunocompromised). If the second test is positive, treatment should be continued for a further 7 months i.e. a total of 9 months.<sup>51;109</sup>

**Figure 8.2: Algorithm for children aged between four weeks and five years who are close contacts\* of infectious/presumed infectious TB cases**

January 2014: The following amendment has been made to Figure 8.2: "Mantoux > 5mm AND increase on initial test > 5mm" changed to "Mantoux > 5mm".

The algorithm presented here is a guideline only and should be interpreted in accordance with the clinical context.

**Note:** IGRA may be considered on a case by case basis as per the general recommendations in section 2.6.

#### Management of newborn infant contact of TB<sup>109</sup>

Management of the newborn infant is based on categorisation of the maternal (or household contact) infection. Although protection of the infant from TB disease is of paramount importance, contact between infant and mother should be allowed when possible.

##### *Mother (or household contact) with TB disease*

Investigation of all household members should be conducted without delay. If the mother has TB disease, the infant should be evaluated for congenital TB. The mother (or household contact) and the infant should be separated until the mother (or household contact) has been evaluated and the mother (or household contact) and infant are receiving appropriate anti-TB therapy, the mother wears a mask, and the mother understands and is willing to adhere to infection control measures. Once the infant is receiving isoniazid, separation is not necessary unless the mother (or household contact) has possible MDR-TB or has poor adherence to treatment and DOT is not possible.

If congenital TB is excluded, it is recommended that isoniazid is given until the infant is three months of age, when a TST should be performed. If the TST result is positive, the infant should be reassessed for TB disease. If TB disease is excluded, isoniazid should be continued for a total of nine months. The infant

\* See Table 8.3 for definition of a close contact

should be evaluated at monthly intervals during treatment. If the TST result is negative and the mother (or household contact) has good adherence and response to treatment and is no longer contagious, isoniazid can be stopped. BCG vaccine should then be given provided there are no contraindications.

See chapter 5 for information on anti-TB medications in breastfeeding women.

## 8.7 TB Outbreaks

A TB outbreak indicates potential extensive transmission. An outbreak implies that the patient was contagious, that contacts were exposed for a substantial period and that the interval since exposure has been sufficient for infection to progress to disease (chapter 1). An outbreak investigation involves several overlapping contact investigations, with a surge in the need for public health resources.

### Outbreak definition

Definitions of TB outbreaks are relative to the local context. In general, two or more apparently related cases of TB constitute an outbreak until proved otherwise.<sup>298</sup> Outbreak cases can be distinguished from other cases only when certain associations in time, location, patient characteristics or *M. tuberculosis* attributes (e.g. drug resistance or genotype) become apparent. In low-incidence areas, any temporal cluster may be suggestive of an outbreak. In places where cases are more common, clusters can be obscured by the baseline incidence until suspicion is triggered by a noticeable increase, a sentinel event (e.g. paediatric cases) or genotypically-related *M. tuberculosis* isolates. Outbreaks of TB are statutorily notifiable under the Infectious Diseases (Amendment) (No.3) Regulations 2003 (S.I. No.707 of 2003).<sup>21</sup>

### Outbreak management

The primary objectives of outbreak management are to:

- Recognise the outbreak
- Define its epidemiological characteristics and aetiology
- Prevent its further spread and recurrence and
- Maintain satisfactory communications with appropriate external agencies and the general public.

For efficient and effective management of an outbreak, an outbreak management plan should be based on the principles that the director of public health/consultant in public health medicine has overall responsibility for investigation and control and for managing the outbreak and that individual members of the outbreak control team (OCT) have responsibility for managing clearly defined aspects of the outbreak. Suitably developed plans should be agreed between the relevant stakeholders in each HSE area.

### Outbreak control team

Appropriate representation on the OCT is crucial. In outbreaks affecting more than one area the chair should be agreed.

The main objectives of the OCT will include:

- To investigate the source/cause of the outbreak: epidemiological study including:
  - formulation of hypothesis to explain the most likely source, site and time of infection
  - case definition and
  - case finding (identifying numbers affected/exposed). Methods will vary according to numbers involved and the setting in which the outbreak has occurred. Molecular typing may be of assistance.
- To agree on the implementation of any measures necessary to control the outbreak including the identification and referral of cases, the screening of contacts and other measures as appropriate (e.g. chemoprophylaxis and referral). Potential resource implications will require estimation and addressing.
- To monitor the effectiveness of control measures
- To provide information to patients, patients' contacts, GPs, the general public, the media and appropriate staff
- To liaise with appropriate health bodies and statutory services
- To coordinate the investigation, evaluate the overall work of controlling the outbreak and implement the lessons learned and
- To produce interim reports as required and a final outbreak report at the conclusion of the outbreak.

## Communications

Communications often present an intensely challenging aspect of outbreak investigation and management. TB outbreak investigations can be complex and protracted. Communications may extend over lengthy periods. Apart from providing regular information to patients, contacts and their families, there are also regular professional and media aspects to be addressed. All media communications should be coordinated by the press officer. The setting up of a helpline to give specific advice and information may need to be considered.

## 8.8 Congregate Settings

Overall concerns associated with congregate settings include:

- The substantial numbers of contacts
- Incomplete information regarding contact names and locations
- Incomplete data for determining priorities
- Difficulty in maintaining confidentiality
- Collaboration with officials and administrators who are unfamiliar with TB
- Legal implications and
- Media coverage.<sup>51</sup>

Increased resources will be necessary when the scope or duration of an investigation is expected to disrupt other essential TB control functions.

Maintaining confidentiality for an index patient is particularly challenging if the patient was conspicuously ill or was absent from the setting while ill. Collaboration with officials at the setting is essential for obtaining access to employee and occupancy rosters, ascertaining contacts, performing on-site testing and offering education to associates (e.g. classmates, friends or co-workers) of the index patient. (see site investigation, section 8.5). For congregate settings, the types of information for designating priorities are site specific, and therefore a customised algorithm is required for each situation. The general concepts of source-case characteristics, duration and proximity of exposure, environmental factors that modify transmission, and susceptibility of contacts to TB should be included in the algorithm. The optimum approach for a setting-based investigation is to interview and test contacts on site. If this is not possible, then the contacts should be invited for evaluation at a designated health facility.

## 8.9 Workplaces

Many people spend the majority of their waking hours in their workplaces. Duration and proximity of exposure can be greater than for other settings. Details regarding employment, hours, working conditions and workplace contacts should be obtained during the initial interview with the index patient, and the workplace should be visited and examined after accounting for confidentiality and permission from workplace administrators or managers. Employee lists are helpful for selecting contacts, but certain employees might have left the workplace and thus have been omitted from current employee lists. Customers of a business workplace may also need to be considered.<sup>51</sup>

Workplace administrators or managers are likely to express concern regarding liability, lost productivity and media coverage. In addition, they might have limited obligations to protect patient confidentiality. All of these issues can be addressed during the planning phase of the investigation.

## 8.10 Hospitals and other Healthcare Settings

The primary TB risk to other patients and staff in hospitals/healthcare settings is the undiagnosed or unsuspected patient/staff member with infectious TB disease. The issue of potential exposure of patients, some of whom may have reduced immunity, may result in considerable resources being directed at identifying exposed patients many of whom are likely to be at minimal risk. Unnecessary screening of contacts with minimal risk should be avoided as yields from contact investigation in healthcare settings can be low.<sup>299-301</sup>

Healthcare-associated transmission of *M. tuberculosis* has been linked to close contact with persons

with TB disease during aerosol-generating or aerosol-producing procedures, including bronchoscopy, endotracheal intubation, suctioning, other respiratory procedures, open abscess irrigation, autopsy, sputum induction and aerosol treatments that induce coughing.<sup>229</sup>

Effective contact tracing requires liaison between public health services, hospital infection prevention and control and occupational health services. Coordination of contact tracing is most appropriately led by hospital infection prevention and control (vis. consultant microbiologist) in those healthcare settings where this is in place. This will include the initial alerting of public health and occupational health services. In all other healthcare settings, coordination should be undertaken by the public health service.

Contact tracing should be initiated where:<sup>229</sup>

- A person with infectious TB has been examined at a healthcare setting, and TB disease was not diagnosed and reported quickly, resulting in failure to apply recommended TB infection controls  
or
- Environmental controls or other infection control measures have malfunctioned while a person with infectious TB was in the setting  
or
- A HCW develops infectious TB and exposes other persons in the setting.

Contact tracing should be carried out only for patients for whom the risk is regarded as significant. No two episodes of this kind are likely to be identical in all respects, and narrowly drawn guidelines are thus inappropriate. A repeat risk assessment should also be made if investigation of the household contacts of the index case has an unusually high yield.

### **Guidance for contact tracing in hospitals and healthcare settings:**

#### **1. Infectious TB in a hospital inpatient**

- Following diagnosis of infectious TB in a hospital inpatient in an open ward, a risk assessment should be undertaken. This should take into account the degree of infectivity, the length of time before the infectious individual was isolated, the proximity of the contact, and whether other patients were unusually susceptible to infection
- In general, patients should be regarded as at risk of infection if they spent more than eight hours in the same section (rather than the whole ward) as an inpatient with infectious/presumed infectious TB (see table 8.1).<sup>302</sup> If patients were exposed to a patient with infectious/presumed infectious TB for long enough to be equivalent to household contacts (as determined by the risk assessment), or an exposed patient is known to be particularly susceptible to infection, they should be managed as equivalent to household contacts (see figure 8.1)<sup>26</sup>
- Where an inpatient has MDR-TB, or if exposed patients are immunocompromised, specialist expert advice should be sought
- Staff in casual contact with a case of smear positive TB should be reassured and reminded of the possible symptoms of TB to report. Staff who have undertaken mouth-to-mouth resuscitation without appropriate protection, prolonged care of a high dependency patient or repeated chest physiotherapy on a patient with undiagnosed respiratory TB should be managed as close contacts.<sup>302</sup>

#### **2. Infectious TB in a HCW**

- If the HCW has been at work while infectious, it will be necessary to identify patients, other staff and visitors who may have had significant contact and manage as per contact tracing procedures.

#### **Other healthcare settings**

Elderly people residing in nursing homes are almost twice as likely to acquire TB as those living in the community. Certain considerations for control of TB in hospitals apply also to such extended care facilities,<sup>229</sup> including maintaining a high index of suspicion for the disease, promptly detecting cases and diagnosing disease, isolating infectious persons and initiating standard therapy and identifying and evaluating contacts (contact investigation).

## 8.11 Schools

The notification of a case of TB in a school setting, whether a staff member or pupil, requires particular attention because of the potential for spread of infection and also because of the anxiety that can be generated among pupils, parents, staff and the wider public. The typical features of contact investigations in schools are the potentially substantial numbers of contacts and difficulties in assigning priorities to contacts who have undetermined durations and proximities of exposure.

If the index case is a staff member, the aim of contact tracing is generally to detect secondary cases in the school. This may also be the aim if the index is an infectious adolescent case. If the case is a younger child or a non-infectious adolescent, the main purpose is to detect a source case in addition to the possibility of detecting other secondary cases from a common source.

The NICE guidelines<sup>26</sup> attempted to establish whether contact tracing was effective in identifying latent and active TB in school contacts exposed to an index case of TB in the school setting. It found potential difficulties in making recommendations from the identified evidence base including the possibility of publication bias, the fact that the evidence base did not take into account the country of birth or ethnicity of pupils (likely to be a confounding factor), noting that many of the studies conducted outside the UK were carried out in non-BCG vaccinated populations, and that rates of disease were calculated on small denominators and were therefore imprecise. The guidelines here are broadly similar to those produced by the NICE guideline development group.

### Guidance following notification of a case of TB in a pupil or staff member:

- **Case risk assessment**
  - The case risk assessment should include an early visit to the school to check indoor spaces, observe general conditions and enquire about ventilation.
- **Communication**
  - Early meeting with school management to explain prevention and control measures
  - Early consideration of how to best communicate with the wider school population and how to keep updated
  - Early anticipation of, and planning for, media communication aspects. The presence of TB in schools often generates publicity. Ideally, the public health department should communicate with the school and parents (and guardians) before any media report a story.
- **School pupil with infectious/presumed infectious TB**
  - Screen class (if single class group) or year (who share classes)
  - Screen relevant staff members (class teachers/games/school bus/other)
  - Screen (by symptom enquiry and *single* chest X-ray) all other members of staff in the school if the index case of a school pupil's TB infection is not found. This is especially relevant if evidence of recent infection has been found in fellow pupils in order to exclude a potential index case among staff.
- **School pupil with non-infectious TB**
  - Consider screening by symptom enquiry and *single* chest X-ray all relevant members of staff (in order to exclude a potential index case among staff) in the school (relevant teaching/games/school bus/other) if the index case of a school pupil's TB infection is not found among household members or other immediate contacts outside of school.
- **Teacher with infectious/presumed infectious TB (i.e. including BAL positive)**
  - Screen, where in contact during preceding three months, relevant class pupils/games etc.
  - Screen staff member contacts.
- **Teacher with non-infectious TB**
  - Consider screening other adults in the school by symptom enquiry if the source (index case) is not found outside the school. Otherwise no contact tracing indicated in the school.
- **Screening extension**
  - Contact tracing may need to be extended to include children and teachers involved in extracurricular activities (e.g. sport, school bus travel, etc.) and non-teaching staff on the basis of degree of infectivity of index case/length of time the index case was in contact with others/whether contacts are unusually susceptible to infection/the proximity of contact. Outdoor activities would not normally pose a transmission risk, unless this involved confined spaces for prolonged time periods.



- **Secondary cases**
  - Any secondary cases of sputum smear positive TB should be treated as index cases for the purposes of contact tracing.
- **Further pupil case within 12 months**
  - Should a further case of TB occur in a child within a twelve month period, all adult staff in the school should be screened with a single chest X-ray (in order to exclude a potential index case among staff).

### Pre-schools

Children aged < five years who have been identified as contacts of cases of infectious TB should receive a clinical evaluation, including a TST and chest X-ray, to rule out active TB. TB disease in children aged < five years typically indicates that the infection must be recent. For this reason, it is a sentinel public health event. Young children usually do not transmit TB to others and their contacts are unlikely to be infected because of exposure to them.<sup>51</sup> In a source case investigation of a child aged < five years in a pre-school setting, all adults in the facility should be included if the source case has not been found in the family or household.

- **Child < five years with TB**
  - Screen all adults in the pre-school setting by symptom enquiry and single chest X-ray if the source case has not been found in family/household.
- **Adult with infectious/presumed infectious TB**
  - Screen all children (see figure 8.2)
  - Screen all adults as close contacts (see figure 8.1).
- **Adult with non-infectious TB**
  - No contact tracing indicated in the school **or** consider screening by symptom enquiry and single chest X-ray all relevant members of staff (in order to exclude a potential index case among staff) in the school if the index case of the teacher's TB infection is not found among household members or other immediate contacts outside of school
  - Contact tracing of children is not indicated.

## 8.12 Transportation

Prolonged journeys (i.e. eight hours or longer) in a confined space and recirculation of air on various modes of transport may increase the risk of transmission of *M. tuberculosis*. Although the risk of exposure relative to the frequency and duration of journeys and modes of transport has not been demonstrated, this risk is likely to be similar to that in other circumstances where people are together in confined spaces.

WHO have published guidelines for preventing and controlling TB transmission on aircraft in 2008, which are available at: [www.who.int/tb/features\\_archive/aviation\\_guidelines/en/](http://www.who.int/tb/features_archive/aviation_guidelines/en/).<sup>303</sup> Between 1992 and 1994, CDC conducted seven contact investigations, six of which were undertaken for passengers, and one for an infectious cabin crew member. Evidence of TB transmission (as indicated by the detection of latent infection) was determined in only two investigations: one from a cabin crew member to other crew members with a minimum of 12 hours' exposure, and the other from a passenger to other passengers seated in the same section of the aircraft, on a flight lasting more than eight hours.<sup>304;305</sup> To date, no case of clinical or bacteriologically confirmed TB disease has been identified as a result of exposure on a commercial aircraft.

The risk of exposure to a case of MDR-TB or XDR-TB during a flight causes considerable concern among travellers, health authorities, airline companies and the media. At present, little evidence exists to suggest that drug-resistant strains of TB would be more easily transmitted during air travel. In other settings drug-resistant TB has been found to be more transmissible than drug sensitive strains.<sup>306</sup> However, the consequences of infection with drug-resistant strains are more complex, the outcomes are not as good as for drug-susceptible TB, and therefore the consequences for exposed contacts are also more important. On these occasions, medical authorities, airline representatives and members of the public are advised to seek guidance from the DoHC and HPSC.

To prevent exposure on flights, WHO recommends that infectious TB cases should not travel by public air transportation until at least two weeks of adequate treatment have been completed or until the person is



sputum smear negative. Patients with MDR-TB or XDR-TB should not travel until they have been proved to be non-infectious (i.e. culture-negative). Health authorities and/or physician(s) should conduct a risk assessment of the potential infectivity, potential drug resistance, duration of the proposed flight, and the possible consequences of transmission to other passengers when a TB case wishes to travel. The public health authority and/or physician must give clear advice or instruction on whether or not to travel. Patients intending to travel against this advice should be reported to the MOH of the relevant HSE area for any necessary action.<sup>303</sup>

1. Contact tracing of infectious or potentially infectious TB cases on aircraft should be limited to flights which were  $\geq 8$  hours duration and took place during the previous three months. All cases of respiratory TB who are sputum smear positive and culture positive (if culture available) are deemed infectious. All cases of respiratory TB who are sputum smear negative and culture positive are deemed potentially infectious. The following criteria should also be used when determining the infectiousness of a case at the time of travel: (i) presence of cavitations on chest X-ray, (ii) presence of symptoms at the time of the flight and (iii) documented transmission to close contacts.
2. If the index case is a passenger, obtain contact details of passengers sitting in the same row and the two rows ahead and behind (from one side of the aircraft to the other because of ventilation patterns) the index patient. Inform contacts of possible exposure and advise screening of these flight contacts and cabin crew who serviced the section in which the TB case was seated.
3. If the index case is an aircraft crew member, contact tracing of passengers should not routinely take place. Contact tracing of other members of staff is appropriate, in accordance with the usual principles for screening workplace colleagues.

**Table 8.4: WHO recommendations for contact tracing of infectious TB cases on air flights  $\geq 8$  hours<sup>303</sup>**

Clinicians should immediately inform the MOH in the relevant HSE area of any patients with infectious pulmonary or laryngeal TB who have a history of air travel  $\geq 8$  hours.

The MOH should then inform HPSC of the case. Case and air flight details should also be forwarded to HPSC. HPSC will then verify with the airline(s) that:

1. The patient was on the flight
2. The flight time ( $\geq 8$  hours) and
3.  $\leq$  three months have elapsed since the flight.

If the TB patient travelled on more than one airline, HPSC will contact each airline on which the patient travelled on a flight for  $\geq 8$  hours total flight duration.

Once this is verified, HPSC (as country where the case was reported) will then inform the counterpart public health authorities in all countries where the flight(s) departed and landed. HPSC will then request from the airline(s) the list of relevant flight contacts outlined in figure 8.3 and will also inform the public health authorities of the countries of residence of the identified contacts and advise them of the situation. In countries of residence of the contacts, the public health authorities should follow national policy for TB contact investigation. In some circumstances such cases (as outlined in the WHO TB and Air Travel Guidance) may need to be reported to WHO under the International Health Regulations (IHR).<sup>303</sup>

Recommendations on the prevention and control of TB transmission on aircraft is based on best currently available scientific evidence and medical practice. Over time, if new evidence emerges in relation to this, it will be reviewed by the committee and the recommendations revised if deemed appropriate.

### 8.13 Prisons

Prisons are a significant reservoir of infection.<sup>307</sup> Infected inmates can spread TB both within the prison and in the community after release. A 2002 survey of the WHO European region found a mean notification rate

of 232 new cases per 100,000 prisoners (range: 0-17,808). Highest rates were observed in countries of the former Soviet Union, and have been attributed to overcrowding, poor hygiene and ventilation.<sup>308</sup>

Outbreaks of TB have been reported in prisons in the US and UK.<sup>15;309</sup> Although TB in prisons was not thought to be a problem in England and Wales in the 1980s,<sup>310</sup> routine surveillance has recently shown an increase in cases in this setting. Prisons in London have been associated with a large outbreak of isoniazid-resistant TB since 2001.<sup>311</sup> In the US, outbreaks have involved MDR-TB in HIV-infected individuals.<sup>309</sup>

Maintaining control of TB in prisons is challenging because of difficulties with practicalities such as prompt diagnosis of cases, identification of contacts, screening and compliance with prophylaxis and treatment. Contact tracing is typically complex in prison settings due to short stays and mobility of inmates. A multidisciplinary team, led by the local public health department (who will undertake the contact tracing), should be convened to manage the intervention.<sup>26;312</sup> In addition to key prison staff and prison medical services, the team may include other staff who have regular contact with prisoners such as social worker/education worker/probation officer representatives. CDC guidelines highlight the important role of correctional information systems (e.g. an inmate medical record system and inmate tracking system) in efficient contact tracing.<sup>312</sup> Any contacts who are HIV positive or immunosuppressed should be among those receiving the highest priority evaluation for infection.<sup>312</sup>

If a suspect infectious TB case is encountered on contact tracing there should be prompt transfer out of the facility for diagnostic evaluation if airborne infection-isolation rooms are not available. If the process is delayed, a substantial number of persons might be exposed as a result of the congregate living arrangements that characterise correctional facilities.

Continuity of care following transfer between prisons and release into the community is seen as a major barrier to treatment completion. For this reason, DOT is recommended for all prisoners receiving treatment for LTBI and active disease. Prison medical services in liaison with local public health departments are encouraged to make arrangements to facilitate treatment completion.<sup>26</sup>

#### **Recommendation:**

A multidisciplinary team approach to effectively manage TB contact tracing in prisons is required. This team should be led by the local public health department who will undertake contact tracing.

DOT is recommended for all prisoners receiving treatment for active disease and should be considered for those receiving treatment for LTBI.

### **8.14 Other High Risk Settings**

Homeless shelters are important sites for transmission of *M. tuberculosis* and an important cause of the continuing high incidence of TB among the homeless population.<sup>313</sup> Contact investigations may be wide-ranging. Genotyping may help with the rapid identification of clustered cases and sites of transmission.

In addition, epidemiological investigations prompted by an increase in the incidence of TB in a community or by the identification of clusters of cases with identical *M. tuberculosis* genotype patterns have detected transmission in such venues as bars.<sup>314</sup> Transmission has been identified with social activities including among persons who drink together in multiple drinking establishments.<sup>315</sup>

### **8.15 Incorporating New Approaches to Contact Tracing**

DNA fingerprinting can be used to confirm or disprove suspected linkages between cases. Genotyping also helps to identify case clusters that would otherwise not be recognised.<sup>111</sup> The Massachusetts Department of Public Health evaluated the impact of DNA fingerprinting on their practice and reported that

genotyping identified enough unexpected links and sites not considered by the concentric circle method to justify consideration of more casual contacts.<sup>316</sup> Genotyping allows earlier recognition of clusters for timely investigation and institution of control measures. All culture positive isolates are eligible for genotyping at the Irish Mycobacterial Reference Laboratory.

### 8.16 Evaluation of Contact Tracing

The evaluation of outcomes from contact tracing is important for evaluating the TB control programme, determining the appropriateness of decisions made regarding the contact investigation and future planning. The results of the investigation of each circle of contacts should be evaluated to determine the risk of transmission, attack rates, etc. The following information should be collected:<sup>317</sup>

- The number of contacts identified (particularly close contacts)
- The number of contacts who underwent a full evaluation
- The number of contacts diagnosed with active disease
- The number eligible for preventive therapy and
- The number who accepted and completed preventive therapy.

#### **Recommendation:**

Evaluation of all contact tracing activities is recommended. The following information should be collected: (a) number of contacts identified, (b) number of cases of active disease and LTBI and (c) the number of persons who accepted and completed preventive therapy.

### 8.17 *Mycobacterium bovis*

*M. bovis* is not frequently isolated from clinical specimens provided by suspected TB patients. Due to milk pasteurisation, the risk of disease from *M. bovis* infection is negligible. Four to five cases of *M. bovis* are reported to the National TB Surveillance System (NTBSS) annually (2002-2006). The mean age of cases over this time period was 62.3 years (range 32 – 86 years).

There is little evidence of cattle-to-human or human-to-human transmission of *M. bovis* in the UK and Ireland. The NICE guidelines have advised using diagnostic tests for LTBI in previously unvaccinated individuals under 16 years of age who have regularly drunk unpasteurised milk from animals with TB udder lesions. Treatment of LTBI should be offered to those with positive results. All individuals in contact with TB-diseased animals should be informed and advised of the signs and symptoms of TB disease.

## 9. Screening in Special Situations

Screening is the practice of identifying a condition or illness, which could benefit from early diagnosis, preventative or curative intervention.<sup>318</sup> Screening should only be undertaken where an illness is sufficiently prevalent, has a known natural history and appropriate and agreed diagnostic techniques and treatment(s) are available. Illnesses being screened for may not cause symptoms that would lead a patient to seek medical care of his/her own volition. In addition, there should be an agreed policy on whom to treat and the cost of screening should be economically balanced.

Screening for TB should be focused ('targeted screening') on groups or individuals with a greater risk or incidence of TB than the general population, and should be undertaken with the following aims:

- To detect and treat active disease, thereby reducing the possibility of transmission to susceptible individuals
- To identify those with LTBI and offer treatment and counselling as appropriate
- To obtain baseline data on TST status for comparison with data from routine surveillance to facilitate reassessment of levels of risk in high-risk groups.

Targeted screening should be conducted depending on local epidemiology and resource availability. It is important to be aware that high risk groups for screening may change over time. The committee agreed that in Ireland, priority groups for screening at this time include:

- HCWs
- New entrants to Ireland
- Prisoners
- Homeless individuals and
- Persons with HIV infection (chapter 10).

### 9.1 Healthcare Workers

Estimates of the risk of infection in HCWs vary according to time, geographical location, exposure intensity and duration (depending on type of hospital and job category).<sup>319-321</sup> In low-incidence countries, active disease among HCWs is often associated with non-occupational exposures.<sup>322</sup> Two UK studies reported that the risk of active disease in HCWs was two to three times higher than in the general population when matched for employment and socioeconomic status.<sup>323,324</sup> A questionnaire-survey of incidents involving potential transmission from HCWs found 105 incidents occurred in 2005, which mainly included non-UK born doctors and nurses, despite occupational screening at employment. Infection is thought to have been acquired in the past in their country of origin.<sup>325</sup> In 2006, HCWs were found to comprise 5% of all notified cases of TB in the United Kingdom, and were more likely to be non-UK born (89%) and female (67%).<sup>14</sup> In Ireland, the proportion of annual TB cases reported in HCWs has increased slightly from 5.7% in 2002 to 7.3% in 2006 (personal communication, HPSC). Between 2002 and 2006, 68.4% of HCW cases were aged between 20 and 40 years of age. Forty-two percent were Irish born individuals with the majority of non-Irish born HCWs originating from India (34.6%), Pakistan (15.4%) and the Philippines (12.8%).

#### Recommendation:

A pre-placement screen is recommended for all clinical staff working with patients or clinical specimens (this may also be applicable to ancillary staff as determined by a risk assessment).

#### Health questionnaire

All new HCWs should initially complete a pre-placement health declaration undertaken by occupational health which includes screening questions for active TB, details of previous immune status investigations and BCG status.

The following information should be recorded:

- Suggestive symptoms
- History of BCG (scar check by health professional or documentary evidence of date or age administered)
- Previous history of TB disease (dates or age, duration and type of treatment, name and address of treating physician) including family history
- Previous TST and result within the previous 5 years if available (documentary evidence of date/age, type of test and result, name and address of treating physician) and
- History and details of contact with known cases of TB (date/age, relationship to the case/s, degree of infectivity of the case).<sup>326</sup>

#### Recommendation:

If an employee has unexplained and suggestive symptoms such as cough lasting three or more weeks that is unresponsive to usual interventions and weight loss or fever, a chest X-ray and sputum examination should be carried out. Such employees should not start work. If an employee has no suspicious symptoms, completion of the pre-placement questionnaire should be followed by an appropriate medical evaluation.

#### Medical evaluation

In the US, CDC recommend that baseline testing for TB is performed for all new healthcare workers, regardless of their occupational risk of exposure to TB.<sup>229</sup> It is the view of this committee that in Ireland, screening of new employees (undertaken by occupational medicine) by TST (2TU Mantoux) should be prioritised as follows:

- **High priority\*\*\*\***  
HCWs arriving in Ireland (or returning to Ireland) from countries with a high incidence of TB ( $\geq 40/100,000$  TB cases notified per year). Such individuals require a chest X-ray (provided they are not pregnant) to rule out active TB in addition to a TST (2TU Mantoux test) to detect LTBI regardless of BCG vaccination status (section 9.2).<sup>326</sup>
- **Intermediate priority††††‡‡‡‡**  
HCWs (regardless of BCG status and not in the high priority group ) working in units managing and treating patients with MDR-TB or XDR-TB and patients who are immunocompromised, physiotherapists, laboratory,<sup>327</sup> mortuary,<sup>275</sup> endoscopy and bronchoscopy staff <sup>229,278,328</sup> should all have a TST (2TU Mantoux test) to rule out LTBI or active TB.
- **Low priority**  
In this group, TST is only offered to those who have no (or inconclusive) evidence of prior BCG vaccine.<sup>326</sup> This group constitutes the vast majority of HCWs. The Mantoux test is undertaken in this situation to obtain a baseline in case of future exposure in the healthcare setting and to offer BCG vaccine if necessary.

\*\*\*\*This prioritisation is based both on the increased likelihood of the HCW having TB due to country of origin and because of this the increased risk of transmission to patients if TB is undetected.

††††This prioritisation is based on both the procedures undertaken by the HCW which increases their risk of contracting TB and also on the risk of transmission to immunocompromised patients if the HCW has TB.

‡‡‡‡Healthcare associated transmission of *M. tuberculosis* has been linked to close contact with persons with TB disease during aerosol-generating or aerosol-producing procedures including bronchoscopy, autopsy, sputum induction, endotracheal intubation and open abscess irrigation.

## HCWs-Tuberculin Skin Testing

### Recommendation:

HCWs from countries of high TB incidence ( $\geq 40$  cases of TB per 100,000 per year) with a positive TST (Mantoux test) defined as  $\geq 10$ mm (table 2.1) should be referred to a respiratory or infectious disease clinician (with a chest X-ray) for a medical assessment to rule out TB disease or LTBI. However, an occupational medicine consultant may wish to treat these patients if appropriate protocols, audit of care and resources are in place.

Irish HCWs or HCWs from low incidence countries ( $< 40$  cases of TB per 100,000 per year) with a positive TST (Mantoux test) defined as  $\geq 15$ mm (table 2.1) should be referred to a respiratory or infectious disease clinician (with a chest X-ray) for a medical assessment to rule out TB disease or LTBI. However, an occupational medicine consultant may wish to treat these patients if appropriate protocols, audit of care and resources are in place.

Treatment for active TB should be considered in HCWs with a positive TST (as outlined above) if the chest X-ray is abnormal, and treatment for LTBI if the chest X-ray is normal and signs and symptoms of disease are absent. IGRA testing may be used as a confirmatory test in those individuals with a positive TST.

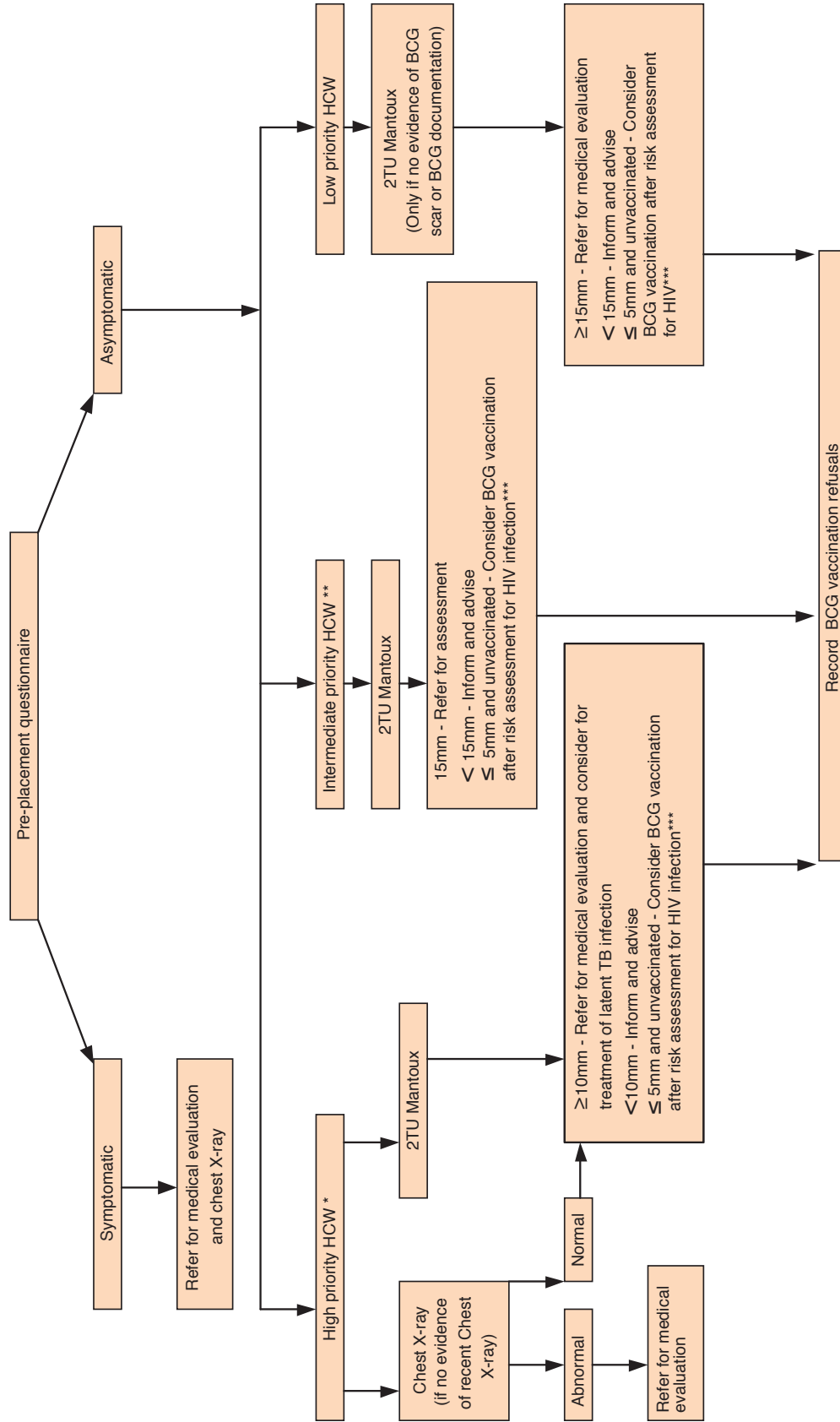
HCWs with active TB should not work while infectious (chapter 6). They will be advised in this regard and when to return to work following joint discussion between the treating physician and the occupational medicine consultant. The employer will need to consider each case individually taking account of employment and health and safety obligations.<sup>329</sup>

If HCWs with LTBI refuse treatment, the risk of developing TB disease should be explained to them including health and safety issues and the oral explanation supplemented by written advice (see information leaflet in appendix 6). In addition, they should be advised to report promptly to the occupational health department if they become symptomatic. All HCWs should complete an annual health questionnaire and be given an annual reminder of the signs and symptoms of TB disease and actions required if they become symptomatic (appendix 6).

The following groups should be informed of the signs and symptoms of TB and advised to seek prompt medical attention if they develop these symptoms (see figure 9.1):

- Employees from high incidence countries ( $\geq 40$  cases per 100,000 per year) with a TST result  $\leq 10$ mm
- All other employees with a TST result  $\leq 15$ mm.

Figure 9.1: Algorithm for screening new health care workers (HCWs)



\* All HCWs from countries with annual TB rates  $\geq 40$  per 100,000 population as described in section 9.1

\*\* All indigenous HCWs and HCWs from countries with annual TB rates  $< 40$  per 100,000 population who are working in high risk areas as described in section 9.1

\*\*\* BCG is indicated for unvaccinated healthcare workers (HCWs) aged  $< 35$  years who are TST negative and who will have contact with patients or with clinically contaminated materials. Not all HCWs are at equal risk of TB. A risk assessment should be carried out to see if BCG is indicated for unvaccinated HCWs aged 35 years and older who are TST negative, taking into account their country of origin and the nature of their work. For more details see page 114.



BCG is indicated for unvaccinated healthcare workers (HCWs) aged <35 years who are TST negative and who will have contact with patients or with clinically contaminated materials.

Not all HCWs are at equal risk of TB. A risk assessment should be carried out to see if BCG is indicated for unvaccinated HCWs aged 35 years and older who are TST negative, taking into account their country of origin and the nature of their work. For more details see page 114.

BCG should only be offered to such individuals if deemed appropriate following a risk assessment for HIV (chapter 7). If an employee declines BCG vaccination, the risks should be explained and supplemented by written advice. It is not advisable that such individuals work where there is a high risk of exposure, however judgements should be made on a case-by-case basis taking account of employment and health and safety obligations.<sup>329</sup> Individuals who decline and are classified as high or intermediate priority HCWs should be offered an annual TST (Mantoux test). Previously vaccinated TST negative employees should not receive a second BCG vaccination.

HCWs arriving in Ireland to work for one to two years from low- and medium-incidence countries without programmes of HCW BCG vaccination (Australia, New Zealand and North America) should all receive a baseline TST. If the TST is negative, they should be informed and advised of the symptoms of TB and of the need to be assessed if they are exposed to TB in the future. However, HCWs from these countries intending to work in high-risk locations e.g. units specialising in the care and treatment of MDR-TB or XDR-TB and immunocompromised patients should be offered BCG vaccination. An annual TST should be offered to those HCWs who belong to the high and intermediate priority categories who decline BCG vaccine.

### **Employees from countries with a high incidence of tuberculosis**

Often HCWs from high incidence countries supply results of TB screening performed in their country of origin. The quality and authenticity of these results should be considered. Chest X-rays should contain the individual's name, date of birth, passport number and be co-signed by the radiographer and the healthcare worker and performed within the previous three months. Chest X-rays that do not meet Irish standards should be repeated. Employees with abnormal chest X-rays and/or signs or symptoms of TB should be referred to a TB clinic.

### **Follow-up**

The professional code of practice from regulatory bodies in the UK and Ireland requires HCWs exposed to a communicable disease to promptly seek and follow professional advice about testing and treatment. This reduces the need for repeat testing. It is recommended that annual reminders of the signs and symptoms of TB are circulated in healthcare settings or a one-off reminder provided following a TB incident on a ward. Those working in high risk facilities or wards should maintain an increased awareness of TB.

Issues of compliance with screening, vaccination and treatment are some factors likely to affect outcomes from occupational screening programmes.<sup>330</sup>

## **9.2 New Entrants to Ireland**

The incidence of TB in immigrants has been rising in some previously low-incidence countries. Patients born outside the UK represented 72% of all TB cases in England, Wales and Northern Ireland in 2007.<sup>15</sup> A much lower rate was observed in Ireland, with approximately one third of annual notifications in 2006 born outside Ireland.<sup>19</sup> In the same year, the crude TB rate in the indigenous population in Ireland was 8.3/100,000 and 26.3/100,000 in the foreign-born population, with the majority from Asia (36.6%) and Africa (36%) and a smaller proportion from Europe (21%).<sup>19</sup> In addition, the percentage of all TB cases in the foreign-born has risen from 16.5% of cases in 2001 to 34.6% in 2006.<sup>19</sup> The incidence of disease in immigrant groups is high particularly within the first few years following arrival, principally due to reactivation of latent infection. Infected individuals entering the UK are most likely to develop TB disease within five years of entry.<sup>331</sup> Immigrants are often at increased risk of disease as they can originate from countries with a high incidence of TB and HIV.

All new entrants to Ireland who originate from a country with a high incidence of TB should be provided with an opportunity to be screened for TB. Every effort should be made to identify candidates either at



reception centres for asylum seekers or by immigration authorities who would in turn notify the relevant HSE areas. Ideally, GPs should refer newly arrived individuals to a combined public health/TB clinic for screening. New entrants are defined as those who have recently arrived or returned from a country with an incidence of TB of  $\geq 40$  cases per 100,000 population per year and will be spending at least three months in Ireland.

**Recommendation:**

All new entrants to Ireland who originate from a country with a high incidence of tuberculosis ( $\geq 40$  cases per 100,000 population per year) and will be spending at least three months in Ireland should be provided with an opportunity to be screened for TB.

Improved access to care for new entrants and especially illegal migrants is important for TB control. A good follow-up system is very important to maximise the yield from entry screening. Proper follow-up is needed to minimise withdrawals during screening and to maximise coverage of the target group as well as treatment adherence. Screening for active TB disease can only be beneficial for public health if treatment success rates are high. A continuum of TB diagnosis, care and support needs to be offered to new entrants at high risk for TB. It should also be recognised that TB prevention and control is not the only service that new entrants need. Specific TB care should be offered in the context of a holistic approach to ensure the health and well being of new entrants.

**HIV infection**

TB is the most common opportunistic infection in HIV-infected individuals. HIV infection acts by weakening the immune system, thereby heightening susceptibility to infection and progression to active TB. It is not known how many new entrants with TB are tested for HIV. WHO initiated their ProTEST initiative (Promote HIV voluntary counselling and testing) in 1997 to campaign for improved collaboration between TB and HIV programmes. This initiative was aimed at promoting voluntary testing for HIV as a means of ensuring a more inclusive approach to dealing with TB in areas with a high prevalence of HIV.

Screening for HIV should be accompanied by culturally sensitive counselling and support (chapter 10).

**Recommendation:**

An expanded programme of screening for TB including voluntary screening for HIV in new entrants should be established. The committee believes that this should be part of a broader health screening programme to improve the health of new entrants to Ireland.

The 2004 DoHC<sup>332</sup> guidance on '*Communicable Disease Screening for Asylum Seekers*' recommended that all new entrants to the Irish health care system undergo screening for TB. This is important as new entrants are most likely to develop disease within five years of entry and in particular, within the first two years of arrival.<sup>331</sup> TB screening for active disease and LTBI should be encouraged.

*Health questionnaire*

A health questionnaire should be undertaken for all new entrants, and enquire into past history of TB and BCG status, current symptoms, and recent contact with a TB case. All new entrants should complete a health screening questionnaire and those with symptoms should be urgently referred to a TB clinic for further clinical assessment (chest X-ray and sputum smear direct examination).

<sup>333</sup> These countries include Botswana, Cambodia, Djibouti, Lesotho, Namibia, Sierra Leone, South Africa, Swaziland, Timor-Lest, Zambia and Zimbabwe.

### *Chest X-ray*

Chest X-rays should be offered to all new entrants aged  $\geq 16$  years (provided they are not pregnant). All those with abnormal chest X-ray results suggestive of active disease or of inactive TB (chapter 2) should be referred for medical evaluation. Treatment of LTBI should be considered in those with radiological evidence of inactive TB. Asymptomatic individuals with a normal chest X-ray in a selected group i.e. those aged 16 to 35 years from sub-Saharan Africa or a country with a TB incidence greater than 500 per 100,000<sup>§§§§</sup> should be offered a TST (2TU Mantoux test) regardless of BCG vaccination status.

### *TST (Mantoux test)*

#### Individuals $\geq 16$ years

Asymptomatic individuals with a normal chest X-ray in a selected group i.e. those aged 16 to 35 years from sub-Saharan Africa or a country with a TB incidence greater than 500 per 100,000<sup>§§§§</sup> should be offered a TST (2TU Mantoux test) regardless of BCG vaccination status. Pregnant females (no chest X-ray, see above) should also have a TST (2TU Mantoux test), regardless of BCG vaccination status. A risk assessment for HIV should be undertaken for all individuals having a TST or receiving BCG vaccination which takes into account the HIV rates in the individual's country of origin.

Those with TST results  $\geq 10$ mm should be referred for further medical evaluation and considered for LTBI treatment. Individuals with TST results  $< 10$ mm should be informed and advised of the signs and symptoms of TB disease and asked to seek medical care if they experience these symptoms. Consider BCG vaccination for all those aged  $\leq 35$  years with TST results  $\leq 5$ mm who are previously unvaccinated (figure 9.2 - see page 120).

While all age groups should be considered for treatment of LTBI, care should be taken when prescribing LTBI therapy for those with co-morbidities which increase the likelihood of hepatotoxicity. The use of DOT should also be considered in this population (chapter 3).

#### Individuals $< 16$ years

##### 1. Unvaccinated (BCG)

New entrants aged 0 to 15 years should be screened initially by health questionnaire and TST (2TU Mantoux test). All those under 16 years of age with a negative TST result ( $\leq 5$ mm) should be offered BCG vaccination after consideration has been given to the individual's HIV status.

Unvaccinated children under five years of age with a Mantoux reading of 6-9 mm should be referred to a TB clinic where treatment for LTBI should be considered if the chest X-ray is normal. Unvaccinated children aged five to 15 years with a Mantoux reading of 6-9mm and without a history of recent contact with a TB case should be advised of the signs and symptoms of TB. All unvaccinated children (aged 0 to 15 years) with a Mantoux reading of  $\geq 10$ mm should be referred to the TB clinic where chemoprophylaxis should be considered if the chest X-ray is normal (figure 9.2 - see page 120).

##### 2. Vaccinated with BCG

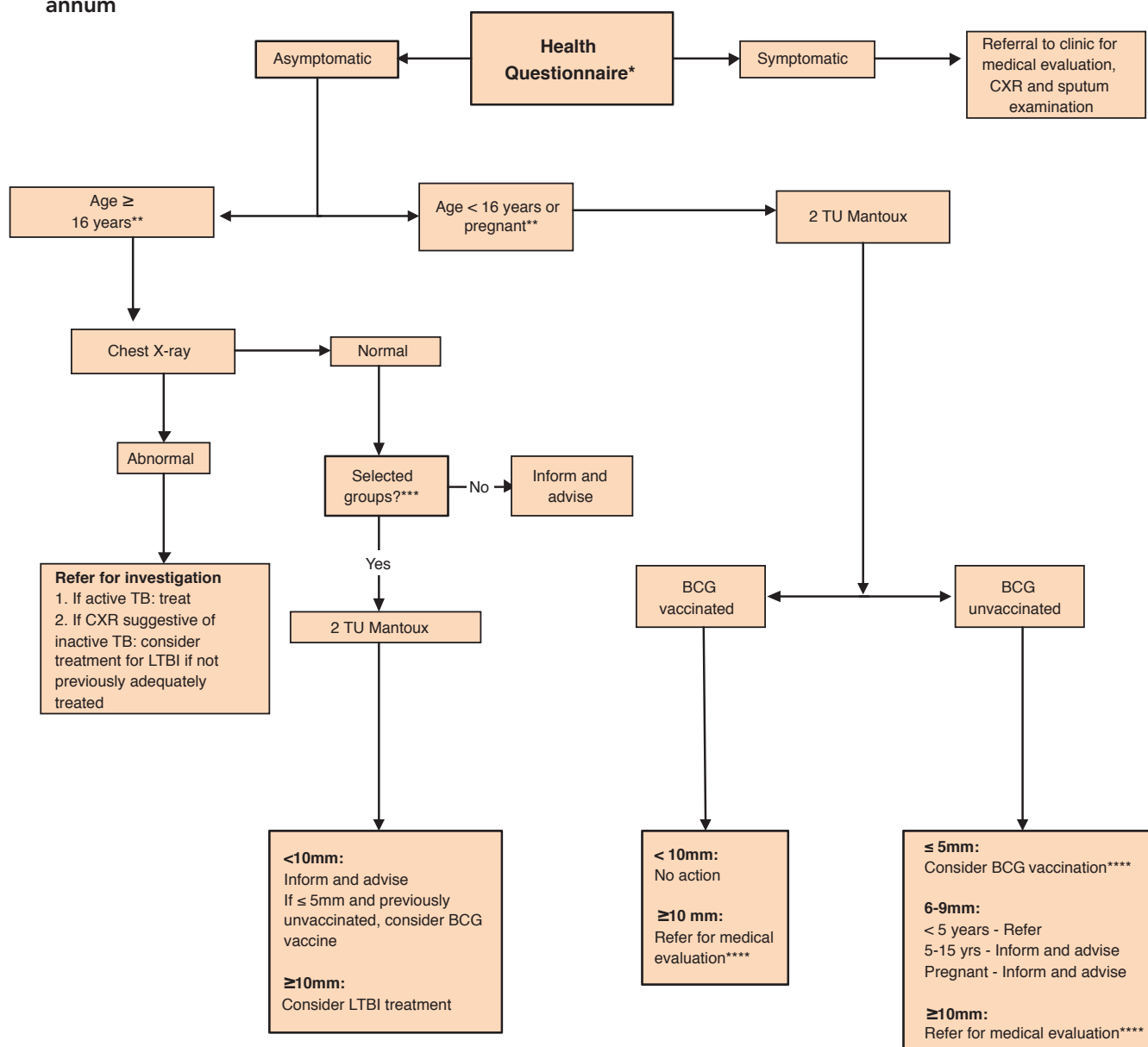
Vaccinated children should be referred for a chest X-ray and chemoprophylaxis considered if the Mantoux reading is  $\geq 10$ mm. If the result is  $< 10$ mm, no further action is required.

### *IGRA testing*

Foreign-born individuals can have a higher incidence of LTBI and may be more likely to have clinical conditions such as HIV infection that increase the likelihood of reactivation of LTBI.<sup>296</sup> False-negative TST results have been observed in such individuals.<sup>296</sup> Although the use of IGRA in screening new entrants has not clearly been demonstrated to date, the use of IGRA can be considered:

- As a confirmatory test in those individuals with a positive TST
- In screening new entrants with concomitant conditions that increase the individual's risk of reactivation of LTBI.

<sup>§§§§</sup> These countries include Botswana, Cambodia, Djibouti, Lesotho, Namibia, Sierra Leone, South Africa, Swaziland, Timor-Lest, Zambia and Zimbabwe.

**Figure 9.2: Algorithm for screening new entrants from countries with  $\geq 40$  cases of TB per 100,000 per annum**

\*If history of recent contact with an infectious TB case, follow algorithms 8.1 and 8.2, Chapter 8.

\*\* All persons from countries with annual TB notifications  $\geq 40/100,000$

\*\*\*Age 16-35 years from sub-Saharan Africa or a country with TB incidence  $> 500/100,000$

\*\*\*\* Timing of X-ray and BCG may be dependent on pregnancy status

### 9.3 Prisons, Remand and Detention Centres

High TB incidence rates<sup>308</sup> and outbreaks associated with multidrug-resistance and HIV co-infection<sup>309;311</sup> have been observed in prison populations in recent decades. High rates have been attributed to a disproportionate number of prisoners being of low socioeconomic status, at risk of disease due to alcohol, substance misuse, HIV infection and having recently arrived from areas of high endemicity (the risk of disease development is greatest within five years or arrival).<sup>331</sup> Prison facilities can often be over-crowded, poorly ventilated, with prisoners living in close proximity.<sup>333-336</sup> Short stays and movement between and within prison facilities increase the likelihood of exposure to TB patients and enhance the potential for transmission. This mobility also creates difficulties for the implementation of control strategies. Despite this, the congregation of many disadvantaged individuals in this setting provides an opportunity to improve the health of those who may not otherwise receive medical care.

### Screening in prisons

TB screening in prisoners should be provided as part of a routine health professional-led health screening exercise on entry to prison. The 1996 TB guidelines recommended routine use of a simple questionnaire on entry to prison, followed by chest X-ray to investigate only those with signs and symptoms.<sup>113</sup> Ideally, inmate screening should be undertaken at the beginning of every prison sentence in order to identify active cases of disease and latent infection and to initiate treatment before individuals join the main prison population.<sup>312</sup>

At a minimum, all prisoners should be screened for symptoms using a health questionnaire at entry. Symptomatic inmates should have a chest X-ray, three sputum samples (at least one of which is a morning sample), and should be isolated from the main prison population until microscopy results can verify the individual's sputum smear status.<sup>26</sup> Symptom screening alone is unsatisfactory in facilities where TB has been detected and where factors for increased risk of TB exist (e.g. prisoners with a condition/factor that increases the risk of TB, environmental factors).<sup>312</sup> Ideally, HIV testing should be offered as part of routine health screening for prisoners starting every prison sentence (assists interpretation of TST, also HIV infection is a contraindication for BCG vaccination).<sup>312</sup>

A risk assessment should be undertaken to establish an increased risk for TB transmission. Facilities at increased risk of transmission include the following:

- Documented cases of infectious TB have occurred in the facility in the last year
- The facility houses substantial numbers of inmates with risk factors for TB (e.g. HIV infection and injection-drug use) and
- The facility houses substantial numbers of new immigrants (i.e. persons arriving in Ireland within the previous 5 years from countries where the annual TB notification rate is  $\geq 40$  cases per 100,000).<sup>312</sup>

If the facility is deemed high risk, then individuals should be screened with a TST (2TU Mantoux test) and if this is positive, a chest X-ray will be required.<sup>312</sup>

Prisoners with a positive TST result or abnormal chest X-ray should be referred to a TB clinic. In congregate settings, a TST induration of 10mm<sup>312</sup> or greater is considered a positive result (for both prisoners and prison workers) (see table 2.1). An induration of greater than 5mm is positive in:

- Persons who are recent contacts of patients with TB disease
- Persons with fibrotic changes on their chest radiograph consistent with previous disease
- Organ transplant recipients
- Immunocompromised individuals (including persons with HIV) and
- Persons suspected of having TB disease.

Prisoners with a TST result of  $\geq 10$ mm and normal chest X-ray findings should be considered for LTBI treatment. Treatment of LTBI should be administered under medical supervision designated by the prison service. If prisoners decline LTBI treatment, a questionnaire screening for symptoms of TB should be completed annually. Chest X-ray follow-up at three and 12 months is also recommended.

HIV-infected or other immunosuppressed inmates (or those with other clinical conditions that render individuals at greater risk of latent infection) should have a TST and an IGRA test (which may be considered in light of false-negative TST results in immunocompromised individuals) to detect LTBI in addition to a chest X-ray to rule out active TB disease.<sup>312</sup>

A multidisciplinary approach to treating a case of active TB disease or LTBI is advised. The decision to refer an infectious case to a tertiary facility should be considered by the treating physician, consultant microbiologist, public health and the prison services. Individuals admitted for inpatient care in tertiary medical facilities should only be discharged back to the prison facility when the patient is deemed non-infectious (as defined in chapter 6).

Prison medical services should have liaison and handover arrangements to ensure continuity of care before any prisoner on TB treatment is transferred between prisons.<sup>26</sup>

**Recommendation:**

A programme of screening for TB in prisoners should be provided.

Prisoners should receive chemotherapeutic treatment for active disease or LTBI by DOT, as high rates of treatment failure have been observed in this population.<sup>337</sup> Patients undergoing any form of TB treatment should be assigned a key worker (a health professional) to promote compliance, monitor treatment effectiveness and the occurrence of adverse events.<sup>26</sup>

Prison medical services should liaise with community TB services to ensure the continuation of DOT after release from prison.

**Prison staff**

New staff should receive pre-placement screening which is equivalent to screening undertaken for new HCWs.<sup>26</sup> BCG should be offered to prison workers aged 35 years and under<sup>26;255;257</sup> if they are previously unvaccinated and tuberculin negative ( $\leq 5\text{mm}$ ) (chapter 7).

A high index of suspicion for TB should be maintained in all prisons and prison HCWs should raise awareness of TB symptoms among prisoners and staff. It is important that prison officers are educated to recognise the signs and symptoms of TB, the need to seek an early diagnosis by referral, methods of diagnosis and the effectiveness of treatment, the importance of compliance with TB treatment and monitoring for adverse events.

**9.4 Homeless Individuals**

Elevated rates of TB have been found in homeless individuals in low incidence countries.<sup>338, 339</sup> Many have concomitant risk factors for TB such as substance misuse, immunosuppression and malnutrition. High levels of infectious and drug resistant TB have been observed and poor adherence to treatment regimens and loss to follow up care in this population pose a challenge to TB control.<sup>340</sup> Providing health services to this high risk group is problematic, as they are often mobile and hard-to-reach through conventional channels. Therefore, screening in this population should focus on the detection of active disease.

**Recommendation:**

An opportunistic active case finding strategy is advised among homeless individuals. Screening by chest X-ray is recommended. TST and IGRA are believed to be less useful, as people may move before test reading/results are available.<sup>26</sup>

Screening on an opportunistic basis and/or symptomatic basis is advised, as is the use of incentives (hot drinks/snacks).<sup>26</sup> A recommendation on the frequency of screening was not made by the NICE guideline development committee due to an absence of evidence, whilst in other European countries, e.g. the Netherlands, illicit drug users and homeless individuals are screened twice per year by digital chest X-ray for two years (this is already used for screening prisoners and asylum seekers).<sup>341</sup> Although routine screening of homeless individuals is a preferred strategy for detecting disease in this high risk population, it is recognised that this is not always possible. Therefore, screening of homeless individuals in accordance with UK guidance is recommended.<sup>26</sup> As homeless individuals are at risk of failing to complete treatment, appropriate steps should be taken to encourage compliance.

**Recommendation:**

Nomination of a key worker for homeless patients receiving treatment and the provision of DOT are considered an optimal strategy for treatment completion.

In addition, statutory and voluntary organisations working with homeless individuals should be educated about TB and referral pathways, as this can aid early detection of disease.

## 10. TB and HIV Infection

The management of patients with TB and HIV infection is complex, requiring management by a multidisciplinary team which includes physicians with expertise in the treatment of both TB and HIV. This chapter provides a broad overview of the management and treatment of HIV-infected individuals with confirmed or suspected TB or LTBI. Readers are advised to refer to this document together with current international guidelines from the CDC,<sup>342;343</sup> WHO<sup>344</sup> and the British HIV Association (BHIVA).<sup>345</sup>

### Recommendation:

Cases of TB/HIV should always be managed by physicians with expertise in treating both TB and HIV.

### 10.1 Epidemiology and Surveillance of TB Infection

TB can occur at any point in the course of progression of HIV infection. It is the commonest opportunistic infection in HIV-infected individuals and is reported as the cause of death for 11% of all AIDS patients.<sup>2</sup> HIV infection acts by lowering the host's immune response to mycobacteria, heightening susceptibility to infection and progression to active disease. HIV is recognised as the single greatest risk factor for development of active TB disease.<sup>6;346;347</sup> The lifetime risk of a HIV and *M. tuberculosis*-infected individual developing active TB is 50%, ten times greater than a non-infected individual. It is therefore important that a high index of suspicion for TB should be maintained in HIV-infected individuals.<sup>344</sup> It is notable that 63% of AIDS patients with active TB infection have positive blood cultures.<sup>139</sup> Blood cultures should be the first step in the routine evaluation of HIV positive patients with suspected TB.<sup>140</sup>

Globally, the number of HIV positive TB cases continues to grow.<sup>1</sup> HIV infection has had a significant impact on the incidence of TB, particularly in areas where rates are highest e.g. Sub-Saharan Africa. WHO estimates that 9% of all TB cases are co-infected with HIV. Rates are believed to range from 1.1% in the Western Pacific, to 5.9% in the Americas, and to 31% in Africa.<sup>346</sup> In countries with a low incidence of disease, sub-populations with both infections are recognisable. In the United States, particular ethnic groups are disproportionately affected, while injecting drug use is a factor in other countries.<sup>348</sup> In Ireland, the incidence of TB in HIV-infected individuals is uncertain. This is due to a combination of factors, including the absence of routine HIV screening in TB patients, incomplete reporting of HIV as a risk factor for TB, and non-statutory notification of HIV. TB surveillance data indicate that between 2 and 19 cases were known to be infected with HIV per annum (2001-2006) (personal communication, HPSC). However, these figures are an under-estimate due to the factors outlined above.

### Recommendation:

A high index of suspicion should be maintained for TB in all HIV-infected individuals.

### 10.2 Pathophysiology

HIV infection destroys CD4 lymphocytes and affects monocyte function, rendering them unable to destroy certain invading microorganisms. HIV produces a progressively deficient immune response and as the infection develops, CD4 lymphocytes are depleted and immunity to *M. tuberculosis* is reduced. CD4 lymphocyte counts are a useful indicator of the degree of immunodeficiency and clinical features of TB in HIV-infected individuals have been found to correlate with CD4 counts.<sup>349</sup>

The tubercle bacillus begins its infection in the alveolar macrophage where it multiplies in activated



macrophages and leads to cell necrosis. Bacteraemia and secondary spread occurs when the macrophage cannot contain the bacilli. A T-cell mediated delayed hypersensitivity reaction may limit further spread of bacteria by granuloma formation at initial or regional sites of infection. The destruction of mycobacteria depends on increases in metabolic and enzymatic activity which is largely dependent on inhibitory mechanisms primed by CD4 lymphocytes.

HIV viral replication increases in alveolar macrophages and peripheral lymphocytes when exposed to *M. tuberculosis* antigens,<sup>350-352</sup> and inflammatory cytokines tumour necrosis factor alpha (TNF-alpha) and interleukin-1 (IL-1) are mediators of this enhanced replication. HIV acts by destroying lymphocytes and inhibiting the release of lymphokines from CD4 cells which are responsible for recruiting and enhancing macrophage resistance to mycobacterial replication. The result of the progression of CD4 lymphocyte destruction and consequent effect on macrophages results in poorly formed granulomas and the inability to kill ingested mycobacteria and the spread of infection. The results are seen in clinical TB as poorly formed granuloma, large organism load and blood stream invasion.

### 10.3 Diagnosis of TB in HIV-infected Cases

The diagnosis of TB in a HIV-infected individual may be difficult. The clinical, radiological and histopathological presentation of HIV-related TB disease can be atypical and is influenced by the degree of immunodeficiency.<sup>349,353</sup> Clinical presentation may mimic or co-exist with other opportunistic infections such as *M. avium* or *Pneumocystis carinii*.

Evaluation of a suspected HIV-infected TB case should always include a chest X-ray and sputum should be obtained for smear and culture. However, results become less sensitive with increasing immunodeficiency.

#### Bacteriological and histological findings

As with all TB cases, obtaining appropriate specimens is important for diagnosing HIV-related TB disease. The yield from sputum smear and culture is similar to that in immunocompetent individuals when HIV-infected individuals have high CD4 counts. However, in severely immunocompromised individuals, culture positive sputum is more likely to be smear negative.<sup>354</sup>

The likelihood of obtaining a positive culture from infected extra-pulmonary sites is greater in patients with advanced HIV than in HIV-uninfected cases.<sup>355-357</sup> Smear positive specimens from those sites may have a large burden of bacilli due to an impaired immune response.

Histological findings range from typical granulomatous inflammation in individuals with CD4 counts above 200 cells/ $\mu$ l, to poorly formed/absent granulomas in those with decreasing immunocompetence, particularly in individuals with CD4 counts below 100/ $\mu$ l. In those circumstances, AFB are more likely to be observed microscopically.

#### Radiological findings

The spectrum of clinical features associated with TB/HIV positive persons is influenced by the degree of immunosuppression. Chest X-ray findings of cases with CD4 lymphocyte counts above 350 cells/ $\mu$ l,<sup>342</sup> appear like those of non-HIV infected cases,<sup>343</sup> with disease confined to the lungs with upper lobe fibronodular infiltrates and with/without cavitation. Pleural effusions are more common in persons with CD4 counts of > 200 cells/ $\mu$ l. During advanced stages of HIV infection, pulmonary disease may present with unilateral or diffuse shadowing in lower and middle lobes or miliary infiltrates on X-ray. Cavitation is uncommon. TB may present as a systemic disease with high fever and sepsis.

At CD4 counts lower than 50 cells/ $\mu$ l, extra pulmonary disease (pleuritis, pericarditis, meningitis) becomes increasingly common (with or without pulmonary involvement).<sup>342</sup> Extrapulmonary disease is detected with greater frequency in HIV-infected than non HIV- infected individuals, however, the clinical presentation of extrapulmonary disease does not differ according to HIV status.

In patients with severe immunodeficiency, it is not uncommon to have normal chest X-rays and culture and smear positive sputum specimens.<sup>25</sup>



## 10.4 Diagnosis of HIV in TB Cases

It is recognised that currently HIV testing may not be undertaken routinely for all TB cases in Ireland. An optimal strategy for HIV screening in TB patients would involve all TB patients, regardless of the perceived risk of HIV infection, being offered HIV testing as part of their TB assessment.<sup>358</sup> In countries with a low-incidence of TB, studies have shown that cases of TB/HIV infection have been missed because heterosexual transmission was not considered as an important risk factor for HIV infection.<sup>359</sup>

### Recommendation:

All TB cases should be offered HIV testing.

## 10.5 Screening for LTBI

Individuals with symptoms of TB should have a chest X-ray and clinical evaluation as soon as possible, regardless of the TST result. Asymptomatic HIV-infected cases should have a TST (Mantoux test), an IGRA (if available) and chest X-ray to investigate the possibility that the patient has active disease. HIV positive individuals with an induration of >5mm and no chest X-ray findings are eligible for treatment of latent infection.

A baseline chest X-ray should be taken when a HIV diagnosis is confirmed,<sup>360</sup> and this committee recommends that screening by chest X-ray should be undertaken every two to three years thereafter, to determine any changes. CDC suggests annual repeat testing for those TST negative on initial testing and who belong to a population at substantial risk of exposure. Furthermore, hepatitis C screening should also be considered, particularly for HIV-infected cases with a history of injecting drug use.

### Tuberculin skin testing

The prevalence of positive TSTs decreases progressively with declining CD4 count,<sup>361</sup> therefore the TST has limited diagnostic value among patients with severe immunodeficiency.<sup>34</sup> The proportion of cases reacting to PPD declines from 50-90% for cases with a CD4 count of  $\geq 500$  cells/ $\mu$ l, to 0-20% for cases with a CD4 count of  $\leq 200$  cells/ $\mu$ l.<sup>345</sup> Tuberculin reactivity tends to be lost because increasing immunodeficiency results in a weakened delayed-type hypersensitivity response to mycobacterial antigens. HAART (Highly Active Antiretroviral Therapy) may improve the immune response to TB but patients most likely to go from a negative to a positive TST result are those whose CD4 rises by  $> 200$  cells/ $\mu$ l.<sup>345</sup>

In the UK, BHIVA do not recommend tuberculin skin testing in patients with CD4 counts  $< 400$  cells/ $\mu$ l,<sup>345</sup> while CDC guidance indicates that TSTs are positive in the majority of patients with pulmonary disease and CD4+ T lymphocyte count  $> 200$  cells/ $\mu$ l. The view of this committee is that a TST should be undertaken regardless of CD4+ T lymphocyte count, with the proviso that the result may be unreliable in an individual with lower CD4 counts. TST indurations of  $>5$ mm should be considered positive regardless of BCG status, and evaluation and treatment of latent infection should be considered. Previous BCG vaccination in a HIV-infected individual does not infer immunity.

### Interferon gamma release assays (IGRA)

The use of interferon gamma release assay for diagnosing latent and active TB has been addressed elsewhere in these guidelines (chapter 2). Despite being an immunological assay, studies suggest it may be more useful for diagnosing LTBI in HIV-infected individuals than the tuberculin skin test.<sup>34,362</sup> However, further studies are required to correlate IGRA results with CD4 counts and to test the reproducibility of the test in this population.<sup>345</sup> The lack of evidence concerning the utility of an IGRA in this population makes it difficult to devise recommendations.

It is recommended that the TST should be used initially to detect LTBI and a person with a positive result should be considered to have LTBI.<sup>30</sup> False negative results are not uncommon in immunodeficient individuals; therefore if a clinician is concerned about the possibility of such a TST result, an IGRA can be conducted. LTBI can be considered if an IGRA test is positive, while indeterminate results should be

repeated. Indeterminate results may indicate laboratory error or anergy, therefore a person's history, clinical features and laboratory findings must be taken into account when diagnosing LTBI using an IGRA.

### Diagnosis in children

A high index of suspicion is required for TB in HIV infected children, as those under two years of age are at risk of disseminated disease causing miliary TB or TB meningitis. It is advised therefore, that HIV infected children are screened annually for TB, beginning at age three to 12 months.<sup>217</sup>

Diagnosis of TB can be complicated by failure to detect *M. tuberculosis* in gastric washings, pre-existence or coincidental fever, pulmonary symptoms and chest X-ray abnormalities.<sup>343</sup> Cervical lymph nodes are commonly involved in extra-pulmonary cases. In children, lymphoid interstitial pneumonitis (LIP) is often associated with persistent generalised lymphadenopathy (PGL), a feature of HIV infection. It can be confused with TB as chronic symptoms are common. Lymphadenopathy due to LIP is generalised, symmetrical, mobile, non-tender, firm and non-fluctuant. Further information is available from the WHO's guidelines for clinical management of TB/HIV.<sup>344</sup> ([www.who.int/tb/hiv/en/](http://www.who.int/tb/hiv/en/)).

#### Recommendation:

In HIV-infected individuals, routine screening for TB is advisable. HIV-infected children should be screened annually for TB, beginning at age three to 12 months.

## 10.6 Treatment of Active Disease

The standard treatment regimen for adult TB/HIV- infected persons is the same as for non HIV- infected TB cases. It is recommended that physicians with appropriate expertise should be consulted prior to the initiation of treatment, due to the complexity of co-administration of anti-TB and antiretroviral therapies.

### Treatment of TB/HIV infected children

In children aged less than five years, treatment should commence as soon as possible to avoid dissemination of disease. As with adults, the initial phase of treatment should involve a four drug treatment regimen. Ethionamide can be used instead of ethambutol where TB meningitis is indicated, as it penetrates the CNS more effectively. For HIV-infected children with active pulmonary disease, treatment duration should be nine months and 12 months for extrapulmonary TB.

## 10.7 Treatment of LTBI in HIV-Positive Individuals

Treatment of LTBI has been proven efficacious in HIV-infected individuals.<sup>363-365</sup> The optimal treatment regimen for LTBI in HIV-infected persons of all ages is isoniazid for nine months or rifampicin and isoniazid for four months, once medical evaluation has ruled out active TB disease. However, six months treatment may be realistic and easier to enforce. These recommended regimens are based on a review of the evidence and guidance in the international literature and by consensus of the National TB Advisory Committee. Pyridoxine should also be administered to those in receipt of isoniazid to reduce the risk of peripheral neuropathy (chapter 3). Antiretroviral therapy can be delayed until LTBI treatment is completed.

#### Recommendation:

The recommended treatment regimens for LTBI in adults who are HIV positive are:

- (i) Isoniazid for an optimum duration of nine months or
- (ii) Rifampicin for four months or
- (iii) A combination of rifampicin and isoniazid for four months.

### Treatment of LTBI in HIV-positive children

For exposed contacts with impaired immunity i.e. with HIV infection and for all contacts younger than five years of age, isoniazid therapy should be initiated, even if the TST result is negative, once TB disease is excluded.

#### Recommendation:

The recommended treatment regimens for LTBI in children who are HIV positive are:

- (i) Isoniazid for a minimum of six months with an optimum duration of nine months or
- (ii) Rifampicin for six months or
- (iii) A combination of rifampicin and isoniazid for four months.

As there is significant potential for an interaction between rifampicin and antiretroviral agents it is important that treatment of LTBI in HIV positive children be undertaken by a specialist both in TB and HIV.

### Directly observed therapy (DOT)

During the 1990s, the United States experienced a resurgence in TB because of immigration, a failing public health infrastructure and due to the emerging HIV epidemic. In New York, case notifications tripled and the proportion of drug-resistant isolates more than doubled between 1978 and 1992. To tackle this growing problem, the programme of supervised medication taking was expanded. Improved rates of treatment completion and decreasing case numbers were observed, giving credence to the concept of directly observed therapy (DOT).<sup>366-368</sup> CDC and WHO advocate the use of DOT for HIV-positive individuals in receipt of a multiple TB drug regimen, due to the severity of the disease in immunodeficient persons.<sup>369</sup>

It is recommended that all TB/HIV patients should receive daily TB therapy. However, TB treatment may be given five days a week by directly observed therapy.<sup>345</sup> Indications for intermittent therapy are the same for HIV-infected and non HIV-infected patients. Thrice-weekly administration of a modified dose of treatment can be used, particularly after daily administration during the initiation phase of treatment (first two months). However, certain alternative regimens (once weekly isoniazid-rifampentine in the continuation phase, and twice weekly isoniazid-rifampicin/rifabutin in any HIV patient with CD4 count < 100 cells/ul) have been associated with the acquisition of rifampicin resistance and should be avoided.<sup>345</sup> Guidelines for managing treatment and interruptions to treatment are provided in the BHIVA guidelines ([www.bhiva.org/](http://www.bhiva.org/)).

#### Recommendation:

Directly observed therapy (DOT) is recommended for treatment of all HIV-infected TB cases.

## 10.8 Evaluation of a TB/HIV Case

### Baseline evaluation

The BHIVA guidelines recommend that the following baseline measurements are made:<sup>345</sup>

1. Absolute CD4 count and percentage
2. Measure LFTs, i.e. serum aminotransferases (AST, ALT), bilirubin and alkaline phosphatase. LFTs should be retested at one to two weeks if asymptomatic
3. Serum creatinine and a platelet count
4. Serological testing for hepatitis B and C
5. Visual acuity with Snellen charts when ethambutol is to be used
6. A repeat smear and culture should be done after two months of treatment in a pulmonary TB patient who still has a productive cough
7. Chest X-ray if progress is unsatisfactory after two months. For patients with pulmonary TB, baseline and 'completion of treatment' chest X-rays are necessary and
8. Other evaluations e.g. additional chest X-rays, ultrasound or CT scans may be indicated depending on the clinical need.

### Follow up evaluation

A clinical evaluation should be performed monthly to assess medication intolerance and adherence in TB/HIV-infected individuals. Treatment effectiveness should be monitored throughout the treatment period. In pulmonary TB/HIV patients, a minimum of one sputum specimen should be examined microscopically each month, until two consecutive specimens are negative on culture. Drug susceptibility should be re-evaluated in patients with culture positive specimens after three months of treatment. The ease of monitoring treatment effectiveness will be determined by the site of infection in extrapulmonary cases. More frequent monitoring is required for patients with underlying liver disease including hepatitis C.

The risk of relapse is believed to be the same in HIV-infected and non-infected TB cases receiving rifampicin for a minimum of six months. HAART has been shown to reduce the risk of relapse.<sup>370-372</sup>

### Commencement of HAART

The International Standards for TB Care<sup>25</sup> propose that all patients with TB/HIV co-infection should be evaluated to determine if antiretroviral therapy is indicated during the course of TB treatment. The use of co-trimoxazole in TB/HIV-infected individuals as prophylaxis against other infections should also be evaluated.

While initiation of TB treatment should not be delayed, there is no international agreement on the optimal time to start HAART in TB/HIV patients. Case-by-case assessments are made in an attempt to balance the risk of progression of HIV against that of having to interrupt/discontinue therapies due to toxicities, side effects, drug interactions, etc. Delaying antiretroviral therapy can simplify patient management, limit adverse events, drug interactions and immune restoration reactions. Furthermore, studies have shown deaths due to TB are more common in the first month of TB treatment, while deaths occurring later on may be due to HIV disease progression.<sup>373-375</sup> BHIVA recommend the following start times of antiretroviral therapy in TB/HIV-infected patients.

**Table 10.1: Recommended HAART starting times (adapted from BHIVA guidelines)**

| CD4 cells/ $\mu$ L | Commencement of HAART                                   |
|--------------------|---|
| <100               | Case-by-case assessment (possibly delay up to 2 months) |
| 100-200            | After 2 months of TB treatment                          |
| >200               | After completing 6 months of TB treatment <sup>®</sup>  |

<sup>®</sup> CD4 count monitoring should be performed every 6-8 weeks. If CD4 count falls, patient may need to start HAART.

The initiation of HAART within two to four weeks of anti-tuberculous therapy has been associated with decreased HIV-1 progression (CDC) but a high incidence of adverse events and paradoxical reactions (see below). By delaying HAART by a minimum of four to eight weeks after initiation of TB therapy, specific causes can be assigned to drug side effects and the severity of a paradoxical reaction can be reduced. Optimal timing for starting HAART should be based on an individual's initial response to treatment, side effects and acceptance of antiretroviral treatment.<sup>342</sup>

TB treatment should only be modified when a patient has developed intolerance to, or severe toxicity from, HIV drugs or has evidence of genotypic resistance to specific HIV drugs thus limiting HAART therapy to agents which are likely to interact with anti-TB therapy. These factors may require the duration of TB treatment to be extended.<sup>345</sup>

### Factors complicating the treatment of TB/HIV<sup>344;345</sup>

Adverse pharmacological interactions occur between rifampicin and antiretroviral drugs used in the treatment of HIV disease due to shared routes of metabolism. Due to these complexities of treatment, it is important that the use of both HAART and anti-TB treatment is managed by those with relevant expertise. Here we provide an overview of the complexities of concomitant treatment of HIV and TB.

Rifampicin induces an enzyme in the hepatic cytochrome P-450 (CYP) system which is involved in the metabolism of protease inhibitors (PIs) and non-nucleoside reverse inhibitors (NNRTI). Rifampicin can accelerate clearance of PIs and NNRTIs metabolised by the liver, resulting in sub-therapeutic levels of the

drugs. Clinically important drug interactions can become evident after two weeks of treatment when the inducing effect is maximised and can persist for two weeks after rifampicin has been withdrawn from the treatment regimen. Furthermore, rifampicin can enhance the activity that results in the elimination of PIs from the body. Despite these interactions, rifampicin should not normally be excluded from the standard treatment regimen for TB/HIV cases receiving antiretroviral therapy.

An immune reconstitution inflammation syndrome (IRIS) or a paradoxical reaction is a temporary exacerbation of TB symptoms or radiographic findings after beginning anti-TB treatment. It has been described in non HIV-infected individuals but is more common in HIV positive cases. It occurs because of reconstitution of immune responsiveness due to HIV or TB treatment which leads to an abnormal immune response to TB antigens released by dead/dying bacilli and is accompanied by a high fever, increased size and inflammation of lymph nodes, new lymphadenopathy, expanding CNS lesions, worsening of lung parenchymal infiltrations and pleural effusions. Management of a non-severe paradoxical reaction involves treatment of symptoms with non-steroidal anti-inflammatory agents. Some studies have shown that more severe reactions involving high fever, airway compromise by enlarging lymph nodes, enlarging serosal fluid collections and sepsis syndrome can be treated with prednisone or methylprednisolone. IRIS can be transient, yet last for many months. Most cases experiencing IRIS are at an advanced stage of immunodeficiency. Patients commenced on HAART within the first two months of TB treatment are at greater risk of IRIS.

Overlapping toxicity profiles also occur in individuals receiving concomitant treatment for HIV and TB. NNRTIs and co-trimoxazole, and rifampicin, isoniazid and pyrazinamide used to treat TB are all associated with side effects of fever, rash, peripheral neuropathy and other neurological events, gastrointestinal intolerance and hepatitis. Side effects are most common in the first two months of treatment.

### **Dispensing of HIV and anti-TB therapy**

Given the complex drug interactions that can occur between HIV and anti-TB medications, and the need to be able to monitor compliance, patients receiving therapy for both HIV and TB or LTBI should receive their HIV and TB medications from the same pharmacy, from a pharmacist experienced in the use of these medications. The pharmacist should keep records of TB and HIV medications dispensed to each patient and advise patients on the importance of compliance with their treatment and on potential adverse drug reactions and interactions. Pharmacists should also be part of the multidisciplinary team looking after patients with TB/HIV infection. They have an important role in the provision of advice on dosages for anti-TB and HIV medications, on therapeutic drug monitoring for patients who are receiving treatment with drugs such as amikacin and in monitoring the patient for adverse drug reactions e.g. hepatotoxicity.

## **10.9 Prevention and Control**

Cases of TB in HIV positive individuals should be notified and contact tracing undertaken as recommended for non-HIV infected TB cases (chapter 8).

HIV positive cases are not considered to be more infectious to their contacts than HIV negative individuals.<sup>376;377</sup> On the contrary, it has even been suggested that the likelihood of transmission is reduced because bacillary loads are lower and cavitory disease is less common than in non-HIV infected TB cases. However, this has not been proven on an individual case basis, and procedures for contact tracing and infection control measures should be applied in the same manner as for non-HIV infectious TB cases.

HIV infection does lead to a greater likelihood of TB infection progressing to active disease and a high proportion of infections in this population result in disease with a short time frame between exposure and the development of symptoms.

### **BCG**

There is international agreement that BCG is contraindicated in HIV positive individuals.<sup>26;52;369</sup> In countries where the risk of TB is low, it is recommended that BCG should be withheld from all individuals known or suspected to be HIV positive.<sup>26</sup> Infants born to known HIV positive women should have BCG deferred until after the second HIV PCR proves negative (usually at/after 6 weeks of age).<sup>332</sup> The benefit of vaccinating HIV-infected individuals to prevent the development of TB is as yet unproven,<sup>378</sup> and adverse events

relating to complications from BCG e.g. ulceration, regional lymphadenopathy and dissemination have been reported.<sup>255, 257</sup>

**Infection prevention and control (see chapter 6)**

Hospital management of a HIV-TB case should include single room accommodation for a pulmonary case, preferably with negative pressure ventilation. HIV positive or other immunosuppressed individuals should not be exposed to possible or confirmed infectious cases.<sup>379</sup> Aerosol-producing procedures should be conducted in isolation rooms with sufficient ventilation to ensure airborne particles are removed between each patient's use. Furthermore, exposure to HCWs should be minimised by reducing the number of workers involved in direct care, e.g. using a named-nurse system/primary nursing. Individual assessments should be made with regards to risks for visitors.

## 11. Education, Research and Information

### 11.1 Education

The increased rates of TB in Ireland over the last seven years demand better education of our medical, nursing and pharmacy personnel about this important disease. Our public health priorities include such issues as dealing with LTBI in at-risk populations, TB disease prevention and treatment in immigrants and multiple drug-resistant TB disease. The small amount of time invested in TB education of Irish HCWs leaves them poorly prepared to address these emerging challenges.

**Recommendation:**

Given the increased importance of LTBI and TB diagnosis and treatment, TB education in the undergraduate and postgraduate medical/nursing disciplines needs to be strengthened.

### 11.2 Research

Research into TB has progressed apace, since the publication of the last national TB guidelines,<sup>113</sup> with new drug options, and new tests that seek to address resistant TB and difficult to diagnose TB disease. In this regard, a diarylquinoline anti-TB drug is under development,<sup>380</sup> and the IGRA blood tests have become a mainstream option to diagnose LTBI.<sup>57</sup> IGRA on pleural fluid and bronchoscopy washings are also under study.<sup>381</sup> Meanwhile, basic research has improved our understanding of the host response to TB and allowed new vaccine designs that may improve on BCG.<sup>382</sup> Finally, our understanding of the host response has allowed us predict and prevent reactivation of TB in patients taking specific cytokine blockers which make these immunosuppressants safer.<sup>93</sup>

A number of researchers in TB have relocated to Ireland and they are collaborating with immunologists, epidemiologists and scientists with an interest in bovine TB. Such work will inform better treatment, tests and vaccine design. It is noted however, that we specifically lack any data on LTBI prevalence and also on the use of IGRA in the diagnosis of LTBI in the Irish population.

In contrast to other diseases, TB research often lacks industry sponsorship. We therefore encourage continued research funding of this neglected disease by our governmental funding agencies. Research fellows willing to undertake TB research should be fostered and given seed money to try and promote such activity. The challenge falls to us to encourage our brightest investigators into the field of TB research.

The development of the IGRA blood tests for LTBI, the development of immunotherapies to treat multiple drug-resistant TB cases and the advances in vaccinology makes the TB field a scientifically exciting one to pursue. A number of worldwide consortia have been established to investigate TB (e.g. TBNET), and it is encouraged that Irish investigators should join such consortia to deliver answers to important questions that require a large number of patients (e.g. MDR-TB or XDR-TB treatment regimen development).

**Recommendation:**

Research that seeks to improve our understanding of the pathobiology of tuberculosis as well as the nature of the disease in our own country is to be encouraged; research funding agencies should foster such activity, which has the potential to improve the treatment of the disease both locally and internationally.

Studies to determine the prevalence rate of LTBI should be initiated and supported.

### 11.3 Information

Even as we see the deterioration of the general level of TB knowledge amongst our healthcare workers, it is important that we address this trend through specific information and research centred events. This document will help this process, however, it should be supported with publications and articles in the medical journals and medical literature as well. A formal annual TB meeting might serve as a focus point for this activity. Where possible, members of this committee should be available to provide a balanced and informed view of the disease when called upon by television, radio and/or public newspapers.



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## List of Appendices

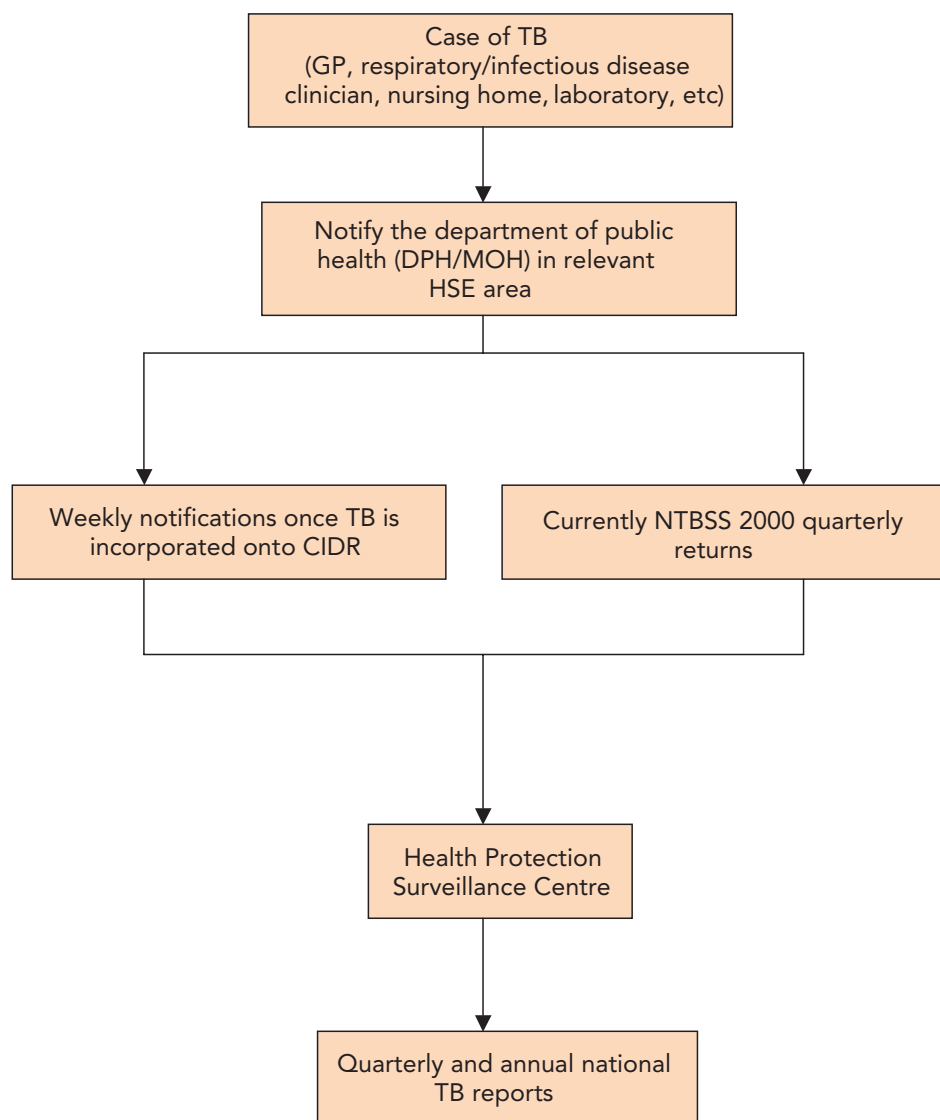
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## Appendix 1: List of groups who were consulted

The following is a list of those to whom a draft of the document was sent for consultation as well as those who made submissions. The document was also posted on the HPSC website. We would like to thank those who made submissions for their invaluable contribution to this document.

Academy of Medical Laboratory Science  
Claire Keane, Senior Pharmacist, St. Vincent's University Hospital, Elm Park, Dublin 4  
Consultants in Public Health Medicine  
Directors of Public Health  
Directors of Public Health Nursing in HSE areas  
Dr Eibhlin Connolly, Deputy Chief Medical Officer, Department of Health and Children  
Dr Karoline de La Hoz, European Centre for Disease Prevention and Control  
Dr Enda Dooley, Medical Director, Department of Justice, Equality and Law Reform  
Dr Pat Doorley, National Director of Population Health  
Dr Kevin Kelleher, Assistant National Director of Health Protection  
Dr Jim Kiely, Chief Medical Officer, Department of Health and Children  
Dr Tom O Connell, Chief Medical Officer, Occupational Health Department, Civil Service  
Emergency Medicine Association  
Faculty of Occupational Medicine, Royal College of Physicians of Ireland  
Faculty of Paediatrics, Royal College of Physicians of Ireland  
Faculty of Pathology, Royal College of Physicians of Ireland  
Faculty of Public Health Medicine, Royal College of Physicians of Ireland  
Faculty of Radiology, Royal College of Surgeons of Ireland  
Geraldine O Connell Public Health Nurse, South Lee Public Health Nursing Department  
Imelda O Connor, Public Health Nurse, HSE-Midwest  
Irish College of General Practitioners  
Irish Infection Society  
Infection Prevention Society  
Irish Medicines Board  
Irish Society of Clinical Microbiologists  
Irish Society of Gastroenterology  
Irish Society of Physicians in Geriatric Medicine  
Irish Society of Rheumatology  
Irish Thoracic Society  
Maeve Moran, Senior Pharmacist, St. Vincent's University Hospital, Elm Park, Dublin 4  
Mairead Lane, Occupational Health Department, Mid-Western Regional Hospital, Limerick,  
Marie Philbin, Chair of Irish Antimicrobial Pharmacists Group  
National Immunisation Advisory Committee, Royal College of Physicians of Ireland  
National Immunisation Office  
Principal Medical Officers, HSE  
Public Health Medicine Communicable Disease Group  
Royal College of Physicians of Ireland  
School of Pharmacy, Royal College of Surgeons, Ireland  
Stella Sheehan, Senior Medical Laboratory Technician, Cork University Hospital  
Surveillance Scientists Association  
The Federation of Irish Nursing Homes

## Appendix 2: Notification pathway for a case of TB



TB is a notifiable disease. A case of TB should be notified to the department of public health in the relevant HSE area. Currently, the department of public health in turn notifies HPSC through the enhanced TB surveillance system each quarter. Once TB is incorporated onto CIDR, TB cases will be notified to HPSC in "real-time"/ weekly basis. HPSC produces quarterly and annual national TB reports.





## Appendix 4: Ways to assess and promote adherence to LTBI treatment

### Ways to assess and promote adherence to LTBI treatment

1. Use directly observed therapy (DOT) for LTBI when available especially for foreign-born persons from countries with an annual TB notification rate  $\geq 40$  cases per 100,000, homeless persons and intravenous drug users
2. Provide written information about the potential adverse effects of the medications at the start of treatment
3. Send reminder letters or call patients before appointments
4. Follow up promptly on missed appointments to prevent interruption or cessation of treatment
5. Minimise wait time at clinics
6. Ask patients at monthly visits about the number of missed pills in the past week
7. Remind patients to bring in their medication bottle (s) and monitor pill counts (but not in their presence)
8. During each monthly visit, stress the importance of adherence and educate patients about the potential adverse effects of medication.

Adapted with kind permission from Tuberculosis, Clinical Policies and Protocols. New York City Department of Health and Mental Hygiene (2008). Available from [www.nyc.gov/html/doh/downloads/pdf/tb/tb-protocol.pdf](http://www.nyc.gov/html/doh/downloads/pdf/tb/tb-protocol.pdf).





## Appendix 6: Questions and Answers about Tuberculosis



Feidhmeannacht na Seirbhíse Sláinte  
Health Service Executive



### What is Tuberculosis?

Tuberculosis or "TB" is a disease caused by a bacterium (germ) called *Mycobacterium tuberculosis*. TB usually affects the lungs but it can also affect other parts of the body, including the glands, the bones and rarely the brain.

Tuberculosis used to be more common in Ireland. There were nearly 7,000 cases a year in the early 1950s. The incidence of TB has declined steadily since then. In 2006, there were 465 cases notified in Ireland. Doctors are obliged to notify each case of TB to the local departments of public health in the Health Service Executive.

TB disease is preventable and curable.

### What are the symptoms of TB?

Symptoms of TB can include any of the following:

- Fever and night sweats
- Cough (generally lasting more than 3 weeks)
- Weight loss
- Blood in the sputum (phlegm) at any time.

A person with any of these symptoms should visit their family doctor for advice.

### How is TB spread?

TB is usually spread in the air from another person who has TB of the lungs. It is spread by that person coughing, sneezing or spitting. People with TB in the lungs or throat can be infectious. This means that the bacteria can be spread to other people. Even then close and prolonged contact with such a person (i.e. family, friends, childminder, co-worker) is needed to become infected. Most cases of infectious TB stop being infectious after a few weeks of treatment. TB in other parts of the body such as the kidney or spine is usually not infectious.

Another type of TB called *Mycobacterium bovis* can arise from drinking contaminated milk. This form of TB is now rare as pasteurisation of milk removes the risk.

The following people have a greater chance of becoming ill with TB, if exposed to it:

- Those in very close contact with infectious people
- Children
- Elderly people
- Diabetics
- People on steroids
- People on other drugs affecting the body's defence system
- People who are HIV positive
- People in overcrowded, poor housing
- People dependent on drugs or alcohol
- People with chronic poor health.

### What happens when a person is found to have infectious TB?

- Treatment for TB is started
- Public health doctors talk to the infected patient to see if other people need to be checked for TB.

### What is the difference between latent tuberculosis infection and active tuberculosis disease?

Infection with the TB bacterium may not develop into TB disease. Most people who are exposed to TB are

able to overcome the bacteria. The bacteria become inactive but they remain dormant in the body and can become active later. This is called latent TB infection (LTBI).

People with LTBI:

- Have no symptoms
- Don't feel sick
- Can't spread TB to others
- Usually have a positive skin test reaction
- Can develop TB disease later in life.

Most people who have LTBI never develop active TB disease. In these people, the TB bacteria remain inactive for a lifetime without causing disease. But in other people, who have weak immune systems, the bacteria can become active and cause TB disease.

### The difference between latent TB infection and active TB disease

| A person with Latent TB Infection   | A person with Active TB Disease   |
|---|---|
| <ul style="list-style-type: none"> <li>• Has no symptoms</li> <li>• Does not feel sick</li> <li>• Usually has a positive skin test or blood test</li> <li>• Has a normal chest X-ray and sputum test</li> </ul> | <ul style="list-style-type: none"> <li>• Has symptoms which may include:               <ul style="list-style-type: none"> <li>A bad cough which lasts three weeks or longer</li> <li>Pain in the chest</li> <li>Coughing up sputum (phlegm) or blood</li> <li>Weakness or fatigue</li> <li>Weight loss</li> <li>No appetite</li> <li>Chills</li> <li>Fever</li> <li>Night sweats</li> </ul> </li> <li>• May spread TB to others</li> <li>• Usually has a positive skin test or positive blood test</li> <li>• May have an abnormal chest X-ray or positive sputum-smear or culture</li> </ul> |

### How is TB diagnosed?

There are a number of tests that can be done to check for TB:

- A skin test
- A chest X-ray
- A test of the sputum (phlegm)
- A blood or urine test.

### How is TB treated?

Yes, today TB is potentially completely curable, if the responsible organism is fully sensitive to the antibiotics being used and the patient takes his or her medication as prescribed.

TB is treated with tablets which must be taken for at least six months. Without treatment, many people used to die from TB. It is essential to take the treatment regularly and to complete the course as prescribed.

The most common medicines used to treat TB are: isoniazid, rifampicin, ethambutol and pyrazinamide. A vitamin B6 tablet called pyridoxine is also prescribed to help prevent some of the side effects that may be caused by isoniazid. Your doctor will decide which TB drugs are best for you.

If you have infectious TB (TB disease of the lungs or throat), you will need to stay at home from work or school so that you don't spread the TB bacteria to other people. After taking your medicines for a few weeks, you will feel better and will no longer be infectious to others. Your doctor will tell you when you can return to work or school or visit friends.

### **What are the side effects of TB medicines?**

If you are taking medicines for TB, you should take them as directed by your doctor or nurse. The medicines may cause side effects but everyone can react differently and not everyone will have side effects. **It is important to report any side effects to your doctor even if they are not listed below.** Side effects include:

- No appetite
- Nausea (feeling sick in the stomach) and/or vomiting
- Abdominal pain (tummy pain)
- Yellowish skin or eyes
- Dark-coloured urine
- Fever for 3 or more days
- Skin rash
- Itching
- Tingling of fingers or toes or around the mouth
- Easy bleeding and/or bruising
- Blurred or changed vision
- Ringing in the ears
- Hearing loss
- Dizziness
- Aching joints.

*The following side effects are caused by rifampicin. If you have any of these side effects you can continue your medications (your doctor will advise you of these before starting treatment for TB):*

Rifampicin can:

- Turn your urine, saliva (spit) or tears orange. The doctor or nurse will advise you not to wear contact lenses as they may get stained.
- Make your skin more sensitive to the sun. This means you should use a good sunscreen and cover exposed areas so that they don't burn.
- Make birth control pills and implants less effective. Women who take rifampicin should use another form of birth control.

### **How important is treatment?**

Treatment is very important. If you have TB disease or if you have been infected with the TB bacterium but have not yet become unwell i.e. have LTBI, you must take the treatment as directed. It is very important to complete the full course of treatment as it will stop you being infectious (spreading the disease to others) and it will remove the risk of you developing drug-resistant TB. It is important to remember that TB used to kill people before we had modern treatments.

### **Can I drink alcohol with my medication?**

It is always best to avoid alcohol while you are taking TB medicines. This is because drinking any alcohol can increase the chances of having problems with your liver when taking the medications.

### **What precautions need to be taken to prevent TB spreading in the home?**

Some patients who are infectious (with TB) can remain at home in the household that has already been exposed. However, the following precautions should be taken:

- Use tissues when sneezing or coughing and place into a household bin immediately after use
- Wash hands after disposing of the tissues
- Stay at home and do not go to places where there will be previously unexposed people (e.g. pubs, clubs, cinemas)
- Attend all outpatient visits
- No visits by previously unexposed people

- Children who do not live at home should not visit until your doctor allows
- Relatives or friends who have weakened immune systems should not visit until your doctor allows
- You can go for a walk outside but you should avoid close contact with previously unexposed people.

Most people are no longer infectious when they have completed a few weeks of TB tablets and are feeling better and their cough is gone or improving. However your doctor will advise you when the above precautions are no longer necessary. It is also very important that you continue your medications until the doctor tells you to stop.

### **What should I do if I have been in contact with someone with TB?**

Discuss this with your family doctor. Only close contacts are at risk of catching TB. You may be asked to attend a chest clinic and to have a skin test and/or a chest X-ray. Sometimes a doctor or nurse will contact you first (they will have a list of close contacts of the person who has TB). This does not necessarily mean that you have TB but is a chance to check for it, so it is very important to attend if you are asked to.

### **Can TB be prevented?**

Yes it can, in several ways:

- Treating all people with active TB disease promptly. After two weeks of treatment, most patients are no longer infectious to other people.
- Ensuring that all close contacts of people with TB are seen promptly in the chest clinic. Those found to have LTBI or those at high risk of developing TB after close contact may be offered a course of preventive therapy (chemoprophylaxis) once active TB has been ruled out.
- Vaccination: In Ireland the BCG vaccination (vaccine against TB) is recommended for newborn babies. BCG is also given to adults who are considered to be at risk of developing TB where potential contact with the disease could occur or has occurred. BCG vaccine is very effective, particularly in preventing childhood TB and the more severe forms of TB.

### **What are multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB)**

#### **Multidrug-resistant TB (MDR-TB)**

MDR-TB is a specific form of TB which is resistant to at least isoniazid and rifampicin, two of the main first line drugs used in the treatment of TB. MDR-TB therefore is much more difficult to treat. It takes longer to treat with second line drugs which are more expensive and have more side-effects.

#### **Extensively drug-resistant TB (XDR-TB)**

XDR-TB is a rare type of MDR-TB which is also resistant to any of a group of drugs called fluoroquinolones and at least one of three injectable second line anti-TB drugs (capreomycin, kanamycin or amikacin). Because XDR-TB is resistant to first line and second line drugs, treatment options are more limited. Further information on XDR-TB can be found on the WHO website at [www.who.int/tb/challenges/xdr/en/index.html](http://www.who.int/tb/challenges/xdr/en/index.html)

Information on TB in Ireland can be found on the Health Protection Surveillance Centre website at [www.hpsc.ie/hpsc/A-Z/VaccinePreventable/TuberculosisTB/](http://www.hpsc.ie/hpsc/A-Z/VaccinePreventable/TuberculosisTB/).

## Appendix 7: Contact details for clinical and laboratory TB advice

### Respiratory Physicians

Dr Tim McDonnell, St Vincent's University Hospital, Dublin  
Dr Brendan Keogh, Mater Misericordiae Hospital, Dublin  
Dr Terry O Connor, Mercy University Hospital, Cork  
Dr JJ Gilmartin, University College Hospital, Galway

### Infectious disease Physicians

Dr C. Fleming, University College Hospital, Galway  
Dr Karina Butler, Our Lady's Hospital, Crumlin, Dublin

### Consultant Microbiologists

Dr Margaret Hannan, Mater Misericordiae Hospital, Dublin  
Dr Bartley Cryan, Cork University Hospital

### Irish Mycobacteria Reference Laboratory

Mr Noel Gibbons, Chief Medical Scientist, (01) 416 2963, [ngibbons@stjames.ie](mailto:ngibbons@stjames.ie)  
Prof T Rogers, Clinical Director, (01) 896 2131, [rodgerstr@tcd.ie](mailto:rodgerstr@tcd.ie)  
Dr J Keane, Consultant Respiratory Physician, (01) 410 3920, [jkeane@stjames.ie](mailto:jkeane@stjames.ie)

Webpage: [www.stjames.ie/Departments/DepartmentsA-Z/I/IMRL/DepartmentOverview/](http://www.stjames.ie/Departments/DepartmentsA-Z/I/IMRL/DepartmentOverview/)  
or go to [www.stjames.ie](http://www.stjames.ie) choose Lab services and then Irish Mycobacteria Reference Laboratory

### Antimicrobial Reference Laboratory,

Department of Medical Microbiology,  
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The Antimicrobial Reference Laboratory user manual may be found at [www.bris.ac.uk/bcare/AssayBooklet.doc](http://www.bris.ac.uk/bcare/AssayBooklet.doc)

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## Appendix 8: International Standards for Tuberculosis Care

In 2006 the “International Standards for Tuberculosis Care” were published to describe a widely accepted level of care that all practitioners, public and private should seek to achieve in managing patients who have or are suspected of having tuberculosis. The standards are outlined below. The full document is available at [www.who.int/tb/publications/2006/istc\\_report.pdf](http://www.who.int/tb/publications/2006/istc_report.pdf).

### Standards for Diagnosis

**Standard 1.** All persons with otherwise unexplained productive cough lasting two to three weeks or more should be evaluated for tuberculosis.

**Standard 2.** All patients (adults, adolescents, and children who are capable of producing sputum) suspected of having pulmonary tuberculosis should have at least two and preferably three, sputum specimens obtained for microscopic examination. When possible, at least one early morning specimen should be obtained.

**Standard 3.** For all patients (adults, adolescents, and children) suspected of having extrapulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microscopy and, where facilities and resources are available, for culture and histopathological examination.

**Standard 4.** All persons with chest radiographic findings suggestive of tuberculosis should have sputum specimens submitted for microbiological examination.

**Standard 5.** The diagnosis of sputum smear-negative pulmonary tuberculosis should be based on the following criteria: at least three negative sputum smears (including at least one early morning specimen), chest radiography findings consistent with tuberculosis and lack of response to a trial of broad spectrum antimicrobial agents. (**Note:** Because the fluoroquinolones are active against *M. tuberculosis complex* and thus may cause transient improvement in persons with tuberculosis, they should be avoided.) For such patients, if facilities for culture are available, sputum cultures should be obtained. In persons with known or suspected HIV infection, the diagnostic evaluation should be expedited.

### Standards for Treatment

**Standard 6.** The diagnosis of intrathoracic (i.e. pulmonary, pleural, and mediastinal or hilar lymph node) tuberculosis in symptomatic children with negative sputum smears should be based on the finding of chest radiographic abnormalities consistent with tuberculosis and either a history of exposure to an infectious case or evidence of tuberculosis infection (positive TST or interferon gamma release assay). For such patients, if facilities for culture are available, sputum specimens should be obtained (by expectoration, gastric washings, or induced sputum) for culture.

**Standard 7.** Any practitioner treating a patient for tuberculosis is assuming an important public health responsibility. To fulfill this responsibility the practitioner must not only prescribe an appropriate regimen but, also, be capable of assessing the adherence of the patient to the regimen and addressing poor adherence when it occurs. By so doing, the provider will be able to ensure adherence to the regimen until treatment is completed.

**Standard 8.** All patients (including those with HIV infection) who have not been treated previously should receive an internationally accepted first-line treatment regimen using drugs of known bioavailability. The initial phase should consist of two months of isoniazid, rifampicin, pyrazinamide, and ethambutol. The preferred continuation phase consists of isoniazid and rifampicin given for four months. Isoniazid and ethambutol given for six months is an alternative continuation phase regimen that may be used when adherence cannot be assessed, but it is associated with a higher rate of failure and

relapse, especially in patients with HIV infection. The doses of antituberculosis drugs used should conform to international recommendations. Fixed-dose combinations of two (isoniazid and rifampicin), three (isoniazid, rifampicin, and pyrazinamide), and four (isoniazid, rifampicin, pyrazinamide, and ethambutol) drugs are highly recommended, especially when medication ingestion is not observed.

**Standard 9.** To foster and assess adherence, a patient-centered approach to administration of drug treatment, based on the patient's needs and mutual respect between the patient and the provider, should be developed for all patients. Supervision and support should be gender-sensitive and age-specific and should draw on the full range of recommended interventions and available support services, including patient counselling and education. A central element of the patient-centered strategy is the use of measures to assess and promote adherence to the treatment regimen and to address poor adherence when it occurs. These measures should be tailored to the individual patient's circumstances and be mutually acceptable to the patient and the provider. Such measures may include direct observation of medication ingestion (directly observed therapy, DOT) by a treatment supporter who is acceptable and accountable to the patient and to the health system.

**Standard 10.** All patients should be monitored for response to therapy, best judged in patients with pulmonary tuberculosis by follow-up sputum microscopy (two specimens) at least at the time of completion of the initial phase of treatment (two months), at five months, and at the end of treatment. Patients who have positive smears during the fifth month of treatment should be considered as treatment failures and have therapy modified appropriately (see Standards 14 and 15). In patients with extrapulmonary tuberculosis and in children, the response to treatment is best assessed clinically. Follow-up radiographic examinations are usually unnecessary and may be misleading.

**Standard 11.** A written record of all medications given, bacteriologic response, and adverse reactions should be maintained for all patients.

**Standard 12.** In areas with a high prevalence of HIV infection in the general population and where tuberculosis and HIV infection are likely to co-exist, HIV counselling and testing is indicated for all tuberculosis patients as part of their routine management. In areas with lower prevalence rates of HIV, HIV counselling and testing is indicated for tuberculosis patients with symptoms and/or signs of HIV-related conditions and in tuberculosis patients having a history suggestive of high risk of HIV exposure.

**Standard 13.** All patients with tuberculosis and HIV infection should be evaluated to determine if antiretroviral therapy is indicated during the course of treatment for tuberculosis. Appropriate arrangements for access to antiretroviral drugs should be made for patients who meet indications for treatment. Given the complexity of co-administration of antituberculosis treatment and antiretroviral therapy, consultation with a physician who is expert in this area is recommended before initiation of concurrent treatment for tuberculosis and HIV infection, regardless of which disease appeared first. However, initiation of treatment for tuberculosis should not be delayed. Patients with tuberculosis and HIV infection should also receive cotrimoxazole as prophylaxis for other infections.

**Standard 14.** An assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance, should be obtained for all patients. Patients who fail treatment and chronic cases should always be assessed for possible drug resistance. For patients in whom drug resistance is considered to be likely, culture and drug susceptibility testing for isoniazid, rifampicin and ethambutol should be performed promptly.

**Standard 15.** Patients with tuberculosis caused by drug-resistant (especially multiple drug-resistant [MDR]) organisms should be treated with specialised regimens containing second-line antituberculosis drugs. At least four drugs to which the organisms are known or presumed to be susceptible should be used and treatment should be given for at least 18 months. Patient centered measures are required to ensure adherence. Consultation with a provider experienced in treatment of patients with MDR-tuberculosis should be obtained.



**Standards for Public Health Responsibilities**

**Standard 16.** All providers of care for patients with tuberculosis should ensure that persons (especially children under 5 years of age and persons with HIV infection) who are in close contact with patients who have infectious tuberculosis are evaluated and managed in line with international recommendations. Children under 5 years of age and persons with HIV infection who have been in contact with an infectious case should be evaluated for both latent infection with *M. tuberculosis* and for active tuberculosis.

**Standard 17.** All providers must report both new and retreatment tuberculosis cases and their treatment outcomes to local public health authorities, in conformance with applicable legal requirements and policies.

## Appendix 9: DOT referral form-HSE South (Cork and Kerry)

Hosp Logo  
Address

**TO/ DIRECTOR OF PUBLIC HEALTH NURSING**

North Lee  South Lee   
 North Cork  West Cork   
 Kerry

**REFERRAL REQUEST FOR DIRECTLY OBSERVED THERAPY  
(TUBERCULOSIS MEDICATION)**

Name \_\_\_\_\_ D.O.B. \_\_\_\_\_  
 Home Address \_\_\_\_\_ Current Address (if different) \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

Contact Number \_\_\_\_\_  
 Hospital \_\_\_\_\_  
 Treating Consultant \_\_\_\_\_ GP \_\_\_\_\_  
 Diagnosis \_\_\_\_\_

Date of commencement of TB therapy \_\_\_\_\_

Most recent sputum: Date \_\_\_\_\_ Result \_\_\_\_\_

Case Currently Infectious? Yes  No  Mask wearing recommended? Yes  No   
 (If yes, for how long? \_\_\_\_\_)

Reason/s for DOT Request?

|                     |                              |  |
|---------------------|------------------------------|--|
| Poor/Non compliance | Yes <input type="checkbox"/> | No <input type="checkbox"/>                  |
| MDR-TB              | Yes <input type="checkbox"/> | No <input type="checkbox"/>                  |
| TB Relapse          | Yes <input type="checkbox"/> | No <input type="checkbox"/>                  |
| Homeless            | Yes <input type="checkbox"/> | No <input type="checkbox"/>                  |
| Other               | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Specify: _____) |

Date Next OPD Appointment \_\_\_\_\_

Patient informed of DOT Request? Yes  No

**TB Medication** \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

*(Prescription faxed)*

Signed: \_\_\_\_\_ Date \_\_\_\_\_  
 Referring Medical Consultant.

- c.c. Senior Medical Officer, Cork. Fax No. 021 4927370
- c.c. Senior Medical Officer, Kerry. Fax No. 066 7184542

## Appendix 10: Standard and Airborne Precautions

Standard Precautions to be used by all HCWs for all patients in all settings at all times

and Airborne Precautions, in addition to Standard Precautions, should be instituted when caring for a suspected or confirmed case of infectious pulmonary or laryngeal TB

See chapter 6 for definition of infectious case

See chapter 6 for criteria for discontinuation of Airborne Precautions

Standard Precautions must be continued for all patients once Airborne Precautions are discontinued

|  | STANDARD PRECAUTIONS   | AIRBORNE PRECAUTIONS   |
|--|--|--|
| <p><b>Clinical Work Practice</b></p> <p><b>Occupational Health Programme</b></p> | <p>All HCWs should be assessed by an occupational health team prior to commencing work. This assessment should include:</p> <ul style="list-style-type: none"> <li>• Immunisations (Irish guidelines on immunisations required for HCWs are available at <a href="http://www.hpsc.ie/hpsc/A-Z/VaccinePreventable/Vaccination/Guidance/">www.hpsc.ie/hpsc/A-Z/VaccinePreventable/Vaccination/Guidance/</a>)</li> <li>• Screening HCWs who perform exposure prone procedures for blood borne viruses. DoHC guidelines available at <a href="http://www.dohc.ie/publications/transmission_of_blood_borne_diseases_2006.html">www.dohc.ie/publications/transmission_of_blood_borne_diseases_2006.html</a></li> </ul> |  |
| <p><b>Patient Placement</b></p>  | <p>HCWs should include the potential for transmission of infectious agents in patient placement decisions</p> <p>Where possible, place patients who contaminate the environment or cannot maintain appropriate hygiene in isolation rooms with en suite toilet facilities and ante room</p>  | <p>Place all patients with suspected or confirmed pulmonary or laryngeal TB in one the following airborne isolation rooms. Refer to figure 6.1 for risk assessment algorithm if an airborne isolation room is not available. Refer to section 6.5 for engineering standards</p> <ol style="list-style-type: none"> <li>1. Negative pressure isolation room with a hand wash sink, an ante room and en-suite</li> <li>2. A neutral pressure design room, as detailed in HBN 04 Supplement 1</li> </ol> <p>Patients with <b>known or suspected multi drug-resistant TB (MDR-TB) must be placed in an airborne isolation room</b> which may require transfer of the patient to another facility</p> <p>A notice should be placed on the door of the isolation room advising those entering to report to the nurse in charge before entering</p> <p>Patients should be educated regarding the reason/indication for Airborne Precautions and requested not to leave the room unless absolutely necessary</p> |

|   | STANDARD PRECAUTIONS  | AIRBORNE PRECAUTIONS   |
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| <p><b>Clinical Work Practice</b></p> <p><b>Patient Placement (cont)</b></p> | <p>HCWs should include the potential for transmission of infectious agents in patient placement decisions</p> <p>Where possible, place patients who contaminate the environment or cannot maintain appropriate hygiene in isolation rooms with en suite toilet facilities and ante room</p> | <p>Emergency departments (ED) without an airborne isolation room must have a process in place to prioritise transfer of patients with suspected or confirmed TB to an appropriate room. ED departments without any airborne isolation rooms should place a surgical mask on the patient and place him/her in an examination room or single room while awaiting transfer. This room should be left vacant for 1 hour once the patient is transferred to allow for a full exchange of air.</p> <p>Aerosol-generating procedures such as sputum induction and the administration of medications by nebuliser must be avoided while a patient with suspected or confirmed TB is in an open bay or an unventilated area in any ward</p> <p>Bronchoscopy should preferably be performed in an appropriate negative pressure suite with adequate ventilation. Unnecessary staff and other patients should be excluded during the procedure. If endoscopy rooms are without air handling equipment, the procedure should be done at the end of the list for the day, or in the patient's room. Avoid placement of recovering patients in a multi-bedded ward post procedure.</p> <p>Procedures on an extrapulmonary TB open abscess or lesion where aerosolisation of drainage fluid may occur should only be undertaken in an airborne isolation room</p> |

|   | STANDARD PRECAUTIONS  | AIRBORNE PRECAUTIONS  |
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| <p><b>Clinical Work Practice</b></p> <p><b>Hand Hygiene</b></p> | <p><b>Hand hygiene is recommended;</b></p> <ul style="list-style-type: none"> <li>• Before and after each episode of patient contact</li> <li>• Between individual patient contacts</li> <li>• After contact with blood, body fluids, secretions or excretions, whether or not gloves are worn</li> <li>• After handling soiled/contaminated equipment, materials or the environment</li> <li>• Immediately before glove application</li> <li>• Immediately after removing gloves or other protective clothing</li> </ul> <p>Hands should be decontaminated using soap and water or alcohol gel if physically clean. Antiseptic soap should be used prior to aseptic procedures.</p> <p>Patients should wash their hands after toileting and before meals. HCWs should assist those patients unable to perform hand hygiene independently.</p> <p>Visitors should be educated on the importance of hand decontamination before and after visiting.</p> <p>(SARI) Guidelines on Hand Hygiene are available at <a href="http://www.hpsc.ie/hpsc/A-Z/Gastroenteric/Handwashing/">www.hpsc.ie/hpsc/A-Z/Gastroenteric/Handwashing/</a></p> | <p>Antiseptic soap or alcohol gel if hands are physically clean before and after patient care</p> |

| Clinical Work Practice        | STANDARD PRECAUTIONS               | AIRBORNE PRECAUTIONS  |
|-------------------------------|------------------------------------|---|
| Patient Movement and Transfer | No special precautions recommended | <p><b>Limit movement and transport of patient to essential purposes only</b><br/>Prior to patient transfer</p> <ul style="list-style-type: none"> <li>• Prior to accepting a patient with known or suspected infectious TB it is the responsibility of the receiving facility to ensure compliance with isolation room requirements as described above under patient placement. It is the responsibility of the facility transferring the patient to provide the information.</li> <li>• Inform transport personnel (emergency medical technicians, porters) and the receiving department of the need for Airborne Precautions</li> <li>• Request patient to wear a surgical mask which should be changed when heavily contaminated with respiratory secretions and/or wet or if torn.</li> <li>• Instruct patient on respiratory hygiene and cough etiquette and ensure the patient has a supply of tissues.</li> <li>• HCWs should remove contaminated apron/gown/gloves (if worn) and mask and dispose prior to transporting patients. Staff do not need to wear masks during internal transportation unless patient is unable to wear a surgical mask (e.g. confused, respiratory distress).</li> <li>• Ambulance staff should consider the use of FFP2 or FFP3 masks in the following situations: (a) the patient is unable to wear a surgical mask; (b) it is anticipated that the duration of the journey will be <math>\geq</math> 4 hours if HCW is immunocompromised); (c) if the patient has either MDR- or XDR-TB (consult infection prevention and control team in this situation).</li> <li>• Don FFP2/3 mask prior to handling patient at the transport destination (e.g. X-ray, bronchoscopy suite)</li> <li>• Transport equipment (stretcher, bed wheelchair) used to transport patient must be cleaned and disinfected with a detergent and 1,000ppm of available chlorine before use on another patient</li> </ul> |

|   | STANDARD PRECAUTIONS  | AIRBORNE PRECAUTIONS                    |
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| <p><b>Clinical Work Practice</b></p> <p><b>Respiratory Etiquette/<br/>Cough Etiquette</b></p> | <p><b>Administrative</b></p> <ul style="list-style-type: none"> <li>Educate HCWs on the importance of control measures to contain respiratory secretions to prevent droplet and contact transmission of respiratory pathogens, especially during seasonal outbreaks of viral respiratory tract infections (e.g. influenza, RSV, etc) in the community</li> <li>Ensure that supplies of tissues, foot operating waste bins and hand hygiene facilities are available in all departments including waiting areas throughout the facility</li> </ul> <p><b>Information for patients/visitors/public</b></p> <p>Educate patients/visitors/carers on respiratory etiquette and cough hygiene using some or all of the following:</p> <ul style="list-style-type: none"> <li>Patient information leaflets</li> <li>Welcome packs</li> <li>Posters in all departments especially waiting areas</li> </ul> <p><b>Additional precautions during times of increased prevalence of respiratory infections</b></p> <ul style="list-style-type: none"> <li>During periods of increased prevalence of respiratory infections in the community, offer masks to coughing patients and other symptomatic persons (e.g. persons who accompany ill patients) upon entry into the facility and encourage them to maintain special separation, ideally a distance of at least 3 feet, from others in common waiting areas</li> <li>Some facilities may find it logistically easier to institute this recommendation year-round as a standard of practice</li> </ul> <p>See appendix 14 for sample poster for respiratory etiquette/cough etiquette</p> | <p>No extra precautions recommended</p> |



|   | STANDARD PRECAUTIONS   | AIRBORNE PRECAUTIONS   |
|---|--|--|
| <p>Clinical Work Practice</p> <p>Use of Personal Protective Equipment (PPE)</p> | <p><b>Type and selection of PPE</b></p> <p><b>PPE</b> consists of:</p> <ul style="list-style-type: none"> <li>• Gloves,</li> <li>• Aprons/gowns</li> <li>• Eye, nasal and mouth protection</li> </ul> <p>Each HCW should make a risk assessment of the planned procedure and select PPE depending on:</p> <ul style="list-style-type: none"> <li>• The nature of the procedure</li> <li>• The risk of exposure to blood and body fluids</li> <li>• The risk of contamination</li> </ul> <p><b>Gloves</b></p> <p>Gloves should be single use items and should conform to European Community Standards</p> <p><b>Gloves are recommended;</b></p> <ul style="list-style-type: none"> <li>• For all activities that carry a risk of exposure to blood, body fluids, secretions or excretions, sharps or contaminated instruments</li> <li>• When touching mucous membranes and non-intact skin</li> <li>• When handling contaminated equipment</li> </ul> <p><b>Gloves should be;</b></p> <ul style="list-style-type: none"> <li>• Single use only</li> <li>• Sterile if contact anticipated with sterile body site</li> <li>• Put on immediately before an episode of patient contact and remove as soon as the activity is completed</li> <li>• Changed when caring for different patients and between different care activities on the same patient</li> <li>• Disposed of as health care risk waste if contaminated with blood or body fluids from patients with suspected or known infection.</li> </ul> <p>Hand hygiene should be performed before donning and immediately following removal of gloves</p> | <p>Additional respiratory protection required (see facial protection section)</p> <p><b>No extra precautions recommended</b></p> |

|   | STANDARD PRECAUTIONS  | AIRBORNE PRECAUTIONS   |
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| <p><b>Clinical Work Practice</b></p> <p><b>Use of Personal Protective Equipment (PPE)</b></p> | <p><b>Face protection</b></p> <p>Face protection should be worn where:</p> <ul style="list-style-type: none"> <li>• There is a risk of blood, body fluids, secretions or excretions splashing into the face or eyes</li> <li>• When placing a catheter or injecting into the spinal or epidural space.</li> </ul> <p>Face protection consists of one of the following:</p> <ul style="list-style-type: none"> <li>• Fluid repellent mask with separate goggles</li> <li>• Respiratory mask (FFP2/3)</li> <li>• Face shield</li> <li>• Fluid repellent mask with eye shield.</li> </ul> <p>Face protection should be:</p> <ul style="list-style-type: none"> <li>• Single use or single person use (face shields and goggles can be reused by the same HCW but they must be adequately cleaned and disinfected as per manufacturer's instructions after each use.</li> </ul> | <p>In addition to eye protection as required for Standard Precautions</p> <p>HCWs and visitors should don correctly fitted:</p> <ul style="list-style-type: none"> <li>• FFP2 masks before entering the isolation room of a suspected or confirmed infectious TB case where MDR-TB not suspected</li> <li>• FFP3 mask during high risk procedures for all patients where TB is suspected or confirmed (susceptible or MDR) such as:                             <ul style="list-style-type: none"> <li>o Sputum induction</li> <li>o Cough producing procedures (e.g. administering aerosolised medications, bronchoscopy, airway suctioning, endotracheal intubation)</li> <li>o Procedures where aerosolisation of drainage fluid from an abscess/ lesions may occur</li> </ul> </li> <li>• FFP3 masks before entering the isolation room of a suspected or known case of MDR-TB or XDR-TB</li> </ul> <p>To preserve privacy and confidentiality restricting visiting to immediate family should be discussed with the patient</p> <p>All HCWs who may be required to use respiratory masks (FFP2 &amp; FFP3) during the course of their work should be fit tested by a trained professional within each organisation</p> <p>HCWs should fit check the mask each time it is worn to check the seal</p> <p>HCWs visiting a patient in their own home should wear a FFP2 or FFP3 mask while the patient is infectious (see chapter 6 on Infection Prevention and Control for discontinuation of Airborne Precautions). Patient privacy must be maintained if mask is worn in the home.</p> <p>All masks should be removed in the ante room or immediately outside the single room if there is no ante room</p> <p>Discard mask into healthcare risk waste</p> <p>Decontaminate hands immediately after removing mask</p> |

|   | STANDARD PRECAUTIONS   |  | AIRBORNE PRECAUTIONS  |
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| <p>Clinical Work Practice</p> <p>Use of Personal Protective Equipment (PPE)</p> | <p>Aprons or gowns</p> | <p>Disposable aprons should be worn where there is a risk that the front of uniform/clothing may become exposed to blood, body fluids, excretions or secretions</p> <p>Long sleeved fluid repellent gowns may be required if there is a risk that uniform/clothing and skin may be exposed to blood, body fluids, excretions or secretions</p>   | <p>No extra precautions recommended</p>                         |
|   | <p>Removal of PPE</p>  | <p>Remove PPE when procedure is complete. PPE should be removed in the following order and disposed of into healthcare risk waste if contaminated with blood and/or body fluids</p> <ul style="list-style-type: none"> <li>• Gloves</li> <li>• Apron/gown</li> <li>• Decontaminate hands</li> <li>• Eye wear</li> <li>• Mask (handle by the mask straps to avoid touching the front)</li> <li>• Decontaminate hands</li> </ul> | <p>All masks should be discarded into healthcare risk waste</p> |

| Clinical Work Practice  | STANDARD PRECAUTIONS   | AIRBORNE PRECAUTIONS   |
|---|--|--|
| <p><b>Environmental Decontamination</b></p>                                   | <p>Routine environmental cleaning is required to minimise the number of micro-organisms in the environment.</p> <p>Particular attention should be given to frequently touched surfaces and those most likely to be contaminated with blood or body fluids e.g. bedrails, mattress, bedside tables, commodes, doorknobs, sinks, surfaces and equipment close to the patient</p> <p>Chemical disinfectants are not recommended for routine environmental cleaning</p> <p>When using disinfectants, staff should follow the manufacturer’s instructions for dilution and contact times</p> <p><b>Refer to National Hospital Office Cleaning Manual 2006</b></p>   | <p>Patient care environment be cleaned and disinfected with a detergent and 1000ppm of available chlorine daily before use on another patient if contaminated with respiratory secretions. PPE should be worn for all cleaning procedures as per page 180-182.</p> <p>Room should remain vacant for one hour with windows open before re-use</p> |
| <p><b>Patient Care Equipment &amp; Decontamination of Medical Devices</b></p> | <p>Medical devices designated as “Single Use Only” must not be reprocessed or reused under any circumstances (MDA DB 2000), (MDD) 93/42/EEC</p> <p><b>Non-critical equipment</b><br/>                     Non-critical equipment refers to equipment that is either not in contact with a patient or in contact with healthy skin. Such equipment should be:</p> <ul style="list-style-type: none"> <li>• In a state of good repair in order to facilitate effective cleaning</li> <li>• Must be thoroughly cleaned prior to use on another patient/resident. If soiled with blood or body fluids, disinfect using a chlorine-releasing solution of 1000ppm, or equivalent according to manufacturer’s instructions, rinse and dry.</li> </ul> <p><b>Reusable invasive medical devices (RIMD)</b><br/>                     RIMD refers to equipment that is classified as semi-critical or critical. RIMDs are in contact with sterile body sites, mucous membranes and breaks in the skin. HCWs must ensure that RIMDs are not used for another patient until they have been cleaned and reprocessed appropriately.</p> <p>(HSE Code of Practice for Decontamination of Reusable Invasive Medical Devices 2007)</p> <p><a href="http://www.hse.ie/eng/Publications/Hospitals/Code_of_Practice_for_Decontamination_of_Reusable_Invasive_Medical_Devices_.html">www.hse.ie/eng/Publications/Hospitals/Code_of_Practice_for_Decontamination_of_Reusable_Invasive_Medical_Devices_.html</a></p> <p><a href="http://www.hpsc.ie/hpsc/A-Z/MicrobiologyAntimicrobialResistance/CJD/Guidance/">www.hpsc.ie/hpsc/A-Z/MicrobiologyAntimicrobialResistance/CJD/Guidance/</a></p> | <p><b>No extra precautions recommended</b></p>   |

|   | STANDARD PRECAUTIONS   | AIRBORNE PRECAUTIONS   |
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| <p><b>Clinical Work Practice</b></p> <p><b>Management of Health Care Risk Waste</b></p>   | <p>Dispose of healthcare risk waste in accordance with the Department of Health &amp; Children's (DoHC) Guidelines for Waste Disposal, which outlines the categorisation and segregation of healthcare waste.</p> <p><b>Disposal of sharps;</b></p> <ul style="list-style-type: none"> <li>• Syringes and needles should be disposed of as a single unit</li> <li>• Used sharps should be carefully discarded into designated sharps bin at the point of use</li> <li>• Sharps bin should be securely stored out of reach of clients, visitors and children</li> <li>• Needles should not be re-capped, bent, broken or disassembled</li> <li>• Sharps should not be passed from person-to-person by hand</li> </ul> <p><b>DoHC Guidelines on Disposal of Healthcare Risk Waste are available at</b></p> <p><a href="http://www.dohc.ie/publications/segregation_packaging.html">www.dohc.ie/publications/segregation_packaging.html</a></p> | <p>Waste contaminated with sputum from a suspected or known TB patient should be disposed of as healthcare risk waste within a healthcare facility</p> <p>Respiratory masks should be disposed of into Healthcare risk waste</p> |
| <p><b>Management of needle stick injuries (NSI) and blood and body fluid exposure</b></p> | <p>All facilities must have a local guideline on the management of needle stick injuries and blood and body fluid exposure. This guideline should include;</p> <ul style="list-style-type: none"> <li>• First aid</li> <li>• Risk assessment and screening of source patient (if known)</li> <li>• Risk assessment for chemoprophylaxis</li> <li>• Counselling and follow up testing</li> </ul> <p>Further information from <a href="http://www.dohc.ie/publications/transmission_of_blood_borne_diseases_2006.html">www.dohc.ie/publications/transmission_of_blood_borne_diseases_2006.html</a></p>   | <p><b>No extra precautions recommended</b></p>   |

|  | STANDARD PRECAUTIONS  | AIRBORNE PRECAUTIONS                           |
|--|---|--|
| <b>Clinical Work Practice</b><br><br><b>Laundry care</b> | <p>Laundry should be handled and transported in a manner that prevents transmission of micro-organisms to other patients, HCWs or the environment</p> <p>Staff handling soiled linen should wear gloves and a disposable plastic apron</p> <p>Segregation and transportation of used laundry should be in accordance with the guidelines from the Society of Linen Services and Laundry Managers (2008)</p> <p>Staff should not manually sluice or soak soiled or infected linen/clothing</p> <p>Linen should be heat disinfected during the wash process by raising the temperature to either 65°C for not less than 10 minutes or preferably 71°C for not less than 3 minutes. Disinfection of heat labile materials (according to manufacturer instructions) can be achieved at low temperatures by introducing 150ppm of chlorine into the penultimate rinse.</p> | <p><b>No extra precautions recommended</b></p> |

|   | STANDARD PRECAUTIONS   | AIRBORNE PRECAUTIONS                           |
|---|--|--|
| <b>Clinical Work Practice</b><br><br><b>Spillages</b> | <p>Spillages of blood, urine, faeces or vomit should be dealt with immediately wearing protective clothing</p> <p>For spillages of body fluid (e.g. urine, faeces or vomit);</p> <ul style="list-style-type: none"> <li>• Soak up as much of the visible material as possible with disposable paper towels</li> <li>• Dispose of the soiled paper towels according to national guidelines</li> <li>• Clean the area using warm water and general purpose neutral detergent</li> <li>• Disinfect using a chlorine-releasing solution of 1,000ppm, rinse and dry</li> <li>• Discard gloves and apron according to national guidelines</li> <li>• Decontaminate hands</li> <li>• Do not apply chlorine-based disinfectants directly onto spillages of urine as it may result in the release of chlorine vapour</li> </ul> <p><b>For blood spillages;</b></p> <ul style="list-style-type: none"> <li>• Decontaminate all blood spills with a chlorine based disinfectant (e.g. powder, granules or liquid containing 10,000ppm available chlorine) or suitable alternative, in line with the manufacturer's instructions and local policy</li> <li>• Wipe up the spillage with disposable paper towels and discard into a yellow healthcare risk bag or rigid container</li> <li>• Wash the area with a general purpose neutral detergent and water</li> <li>• Discard gloves and apron into healthcare risk bag</li> <li>• Decontaminate hands</li> </ul> | <p><b>No extra precautions recommended</b></p> |

| Clinical Work Practice                                 | STANDARD PRECAUTIONS  | AIRBORNE PRECAUTIONS                       |
|--|---|--|
| <p><b>Safe Injection Practices</b></p>                 | <p><b>Administration</b><br/>Educate all HCWs who administer injections on the importance of safe injection practices<br/>All facilities should have a guideline on the use of multi-dose vials.</p> <p><b>Preparation of Injections</b><br/>All injections should be prepared in a clean area. This area must not be used for disposing of used needles and syringes, handling blood samples or any material contaminated with blood or body fluids<br/>An aseptic technique must be used when drawing up injections<br/>Needles, syringes and cannulae are sterile, single use items; they must not be reused for another patient nor to access a medication or solution that might be used for a subsequent patient<br/>Use single dose vials wherever possible<br/>Do not use single dose vials for multiple patients<br/>Do not combine leftovers for later use</p> <p><b>Multi-dose vials</b><br/>Multi-dose vials should only be used when absolutely necessary<br/>Restrict wherever possible the use of multi-dose vials to a single patient<br/>Label vial with patient's name and date opened<br/>Discard if sterility is compromised or questionable<br/>Do not leave multi-dose vials at a patient's bedside<br/>Use a sterile syringe and needle every time a medication vial is accessed even if it is a 2<sup>nd</sup> dose of the same drug for the same patient.</p> <p><b>Infusions and intravenous sets</b><br/>Do not use bags or bottles of intravenous fluids as a common source of supply for multiple patients<br/>Intravenous fluids and intravenous sets are single use sterile items for use by a single patient<br/>Consider a syringe or needle/cannula contaminated once it has been used to enter or connect to a patient's intravenous infusion bag or administration set.</p> | <p>No additional precautions necessary</p> |
| <p><b>Practices for lumbar puncture procedures</b></p> | <p>When inserting a catheter, injecting material/chemotherapy into the spinal canal or subdural space, healthcare workers should wear a surgical mask and adhere to aseptic technique.</p>  | <p>No additional precautions necessary</p> |



## Appendix 11: Discharge instructions for patients with potentially infectious TB

You have been placed on medication to treat TB. You are now being discharged home from hospital. However, your TB may remain infectious (contagious) for some time longer. A number of general instructions and temporary restrictions are therefore being advised until it is certain that you are no longer infectious to others. These restrictions will help reduce any possibility of spread of TB germs to other people. You should follow them carefully until you are advised otherwise by the doctor who is treating your TB.

### General instructions:

- Take your TB medications as instructed by your doctor
- You should always cover your nose and mouth with a tissue when coughing or sneezing
- Dispose of used tissues in a bin immediately after use and wash your hands
- It is ok to share eating utensils (spoons, forks, cups or glasses) and other household items
- Keep your doctor's or clinic appointment so that you complete your treatment.

### Temporary restrictions after hospital discharge

- Do not go to work or school and you should avoid going to any public areas (e.g. cinema, pubs or clubs, using public transport) until the doctor who is treating your TB says it is ok for you to do so.
- **If there are others living at home you should**
  - limit the time you spend in common household areas (e.g. kitchen or living room) and keep your bedroom door closed
  - If advised by your doctor to wear a surgical mask (as a temporary measure) that covers your nose and mouth (as explained to you in hospital) when you are around other people, follow the instructions given. This will reduce the number of TB germs that you put into the air when you cough or talk.
- You should not be around babies, young children or, to the best of your knowledge, people who have weakened immune systems such as people with HIV/AIDS. (If there are young children at home, you may still be discharged home if the children have been tested for TB infection and are being followed up by the local public health department).

These temporary restrictions will be removed once your doctor decides that you are no longer infectious. However, your TB treatment will continue until the course is completed.

If you have any questions about your treatment, please call .....

Adapted with kind permission from Tuberculosis, Clinical Policies and Protocols. New York City Department of Health and Mental Hygiene (2008). Available from [www.nyc.gov/html/doh/downloads/pdf/tb/tb-protocol.pdf](http://www.nyc.gov/html/doh/downloads/pdf/tb/tb-protocol.pdf).

## Appendix 12: List of Tuberculosis-related websites and resources

### National TB Websites

**Health Protection Surveillance Centre**

[www.hpsc.ie/hpsc/A-Z/VaccinePreventable/TuberculosisTB/](http://www.hpsc.ie/hpsc/A-Z/VaccinePreventable/TuberculosisTB/)

**Irish Thoracic Society**

[www.irishthoracicsociety.com/](http://www.irishthoracicsociety.com/)

**Immunisation Guidelines of Ireland**

[www.hpsc.ie/hpsc/A-Z/VaccinePreventable/Vaccination/Guidance/](http://www.hpsc.ie/hpsc/A-Z/VaccinePreventable/Vaccination/Guidance/)

### International TB Websites

**Centers for Disease Control and Prevention, USA, Division of TB Elimination**

[www.cdc.gov/tb/](http://www.cdc.gov/tb/)

**Health Protection Agency, UK**

[www.hpa.org.uk/webw/HPAweb&Page&HPAwebAutoListName/Page/1191942150134?p=1191942150134](http://www.hpa.org.uk/webw/HPAweb&Page&HPAwebAutoListName/Page/1191942150134?p=1191942150134)

**The Public Health Agency of Canada**

[www.phac-aspc.gc.ca/tbpc-latb/index.html](http://www.phac-aspc.gc.ca/tbpc-latb/index.html)

**European Centre for Disease Prevention and Control**

[www.ecdc.europa.eu/Health\\_topics/Tuberculosis/Tuberculosis.html](http://www.ecdc.europa.eu/Health_topics/Tuberculosis/Tuberculosis.html)

**EuroTB: Surveillance of TB in Europe**

[www.eurotb.org/](http://www.eurotb.org/)

**WHO-Geneva Tuberculosis Homepage**

[www.who.int/tb/en/](http://www.who.int/tb/en/)

**WHO-Euro Tuberculosis Site**

[www.euro.who.int/tuberculosis](http://www.euro.who.int/tuberculosis)

**The Global Plan to Stop TB**

[www.stoptb.org/globalplan/](http://www.stoptb.org/globalplan/)

**WHO Stop TB Department**

[www.who.int/tb/about/en/index.html](http://www.who.int/tb/about/en/index.html)

**Stop TB Partnership**

[www.stoptb.org/](http://www.stoptb.org/)

**The International Union against TB and Lung Disease**

[www.ariatld.org/](http://www.ariatld.org/)

**NICE: TB information for the Public**

[www.nice.org.uk/nicemedia/pdf/CG033publicinfo.pdf](http://www.nice.org.uk/nicemedia/pdf/CG033publicinfo.pdf)

**TB Alert**

[www.tbalert.org/](http://www.tbalert.org/)

## Tuberculosis Guidance

### UK

#### NICE Tuberculosis Clinical Guidance

[www.nice.org.uk/search/guidancesearchresults.jsp?keywords=TUBERCULOSIS&searchType=guidance](http://www.nice.org.uk/search/guidancesearchresults.jsp?keywords=TUBERCULOSIS&searchType=guidance)

#### Control and prevention of tuberculosis in the United Kingdom: Code of Practice 2000. Joint Tuberculosis Committee of the British Thoracic Society. *Thorax* 2000. Vol. 55, 11: 887-901

[www.thorax.bmj.com/cgi/reprint/55/11/887](http://www.thorax.bmj.com/cgi/reprint/55/11/887)

### USA

#### Centers for Disease Control and Prevention (CDC) TB Guidelines (listed by category or by date)

[http://www.cdc.gov/tb/pubs/mmwr/maj\\_guide.htm](http://www.cdc.gov/tb/pubs/mmwr/maj_guide.htm)

### Canada

#### Canadian Tuberculosis Standards 6th Edition, 2007

[www.phac-aspc.gc.ca/tbpc-latb/pubs/pdf/tbstand07\\_e.pdf](http://www.phac-aspc.gc.ca/tbpc-latb/pubs/pdf/tbstand07_e.pdf)

### New Zealand

#### New Zealand TB Guidelines, 2003

[www.moh.govt.nz/moh.nsf/0/4760df3580a6f5b5cc256c86006ed394?OpenDocument](http://www.moh.govt.nz/moh.nsf/0/4760df3580a6f5b5cc256c86006ed394?OpenDocument)

### World Health Organization

#### Tuberculosis and Airlight (WHO)

[www.who.int/docstore/gtb/publications/aircraft/PDF/98\\_256.pdf](http://www.who.int/docstore/gtb/publications/aircraft/PDF/98_256.pdf)

#### WHO Guidelines for the programmatic management of resistant TB

[www.who.int/docstore/gtb/publications/2006/9241546956\\_eng.pdf](http://www.who.int/docstore/gtb/publications/2006/9241546956_eng.pdf)

#### Treatment Guidelines for National Programmes – WHO Global Tuberculosis Programme, Geneva

[www.who.int/docstore/gtb/publications/ttgnp/](http://www.who.int/docstore/gtb/publications/ttgnp/)

#### Guidelines for the prevention of tuberculosis in health care facilities in resource limited settings – WHO Global Tuberculosis Programme, Geneva

[www.who.int/docstore/gtb/publications/healthcare](http://www.who.int/docstore/gtb/publications/healthcare)

#### What is DOTS? - Guide to the WHO recommended TB control strategy

[www.who.int/docstore/gtb/publications/whatisdots](http://www.who.int/docstore/gtb/publications/whatisdots)

### Scientific Resources

#### MEDLINEplus Tuberculosis

[www.nlm.nih.gov/medlineplus/tuberculosis.html](http://www.nlm.nih.gov/medlineplus/tuberculosis.html)

#### Francis J. Curry National Tuberculosis Center

[www.nationaltbcenter.edu/](http://www.nationaltbcenter.edu/)

#### New Jersey Medical School Global Tuberculosis Institute

[www.umdnj.edu/globaltb/home.htm](http://www.umdnj.edu/globaltb/home.htm)

#### Stanford Center for Tuberculosis Research<sup>12</sup>

[www.stanford.edu/group/molepi/index.html](http://www.stanford.edu/group/molepi/index.html)

#### Brown University TB/HIV Research Laboratory

[www.brown.edu/Research/TB-HIV\\_Lab/](http://www.brown.edu/Research/TB-HIV_Lab/)

#### The Public Health Research Institute (PHRI) Tuberculosis Center

[www.phri.org/programs/program\\_tbcenter.asp](http://www.phri.org/programs/program_tbcenter.asp)

#### Aeras Global TB Vaccine Foundation

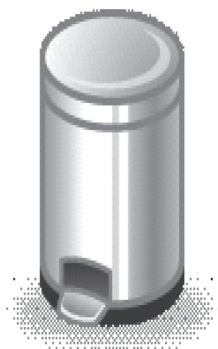
[www.aeras.org/](http://www.aeras.org/)

## Appendix 13: Respiratory hygiene and cough etiquette

These 3 steps will help prevent the spread of respiratory infections



When coughing or sneezing use a tissue or cover your nose and mouth



Dispose of the tissues afterwards in a waste bin



Decontaminate your hands after discarding tissue using soap and water or alcohol gel

## Glossary of Terms

**Acid-fast Bacilli:** Bacteria which having been stained with a dye, retain their colour in acid alcohol. Used as a technique for microscopic detection of mycobacteria. The relative concentration of AFB per unit area on a slide (the smear grade) is associated with infectiousness. A positive culture is required for laboratory confirmation of *M. tuberculosis complex*.

**Active TB:** Infection with mycobacteria of the *M. tuberculosis complex*, where mycobacteria are growing and causing symptoms and signs of disease. This is distinct from LTBI where mycobacteria are present but are inactive and not causing symptoms of disease. The diagnosis of active TB is made most often on the basis of positive bacteriology but in approximately 15%-25% of cases on the basis of appropriate clinical and/or radiological and/or pathological presentation as well as treatment response.

**Adherence:** This refers to the patient's ability or choice to adhere to a treatment regimen

**Aerosol:** Small droplets of moisture that are exhaled or coughed up. In a patient with pulmonary tuberculosis they may contain *Mycobacterium tuberculosis* bacteria that are suspended in the air and lead to the spread of infection. Generation of infectious aerosols is greatest with laryngeal and cavitary pulmonary disease.

**Air changes per hour (ACH):** The number of air changes per hour in a room; one air change being a volume of air equal to the room volume

**Airborne isolation:** The conditions into which a patient with suspected or proven active tuberculosis may be placed for purposes of preventing transmission to other persons. In most institutional settings airborne isolation is provided by a combination of increased ventilation (e.g. in the room occupied by the patient) and the use, by staff or visitors, of personal protective wear (respirators that filter 95% of particles of 1 micron or larger and have less than 10% leak).

**Anergy:** A condition wherein a person has diminished ability to mount a delayed T-cell hypersensitivity response to antigens because of a condition or situation resulting in altered immune function e.g. HIV infection. When referring to an inability to react to a skin test, the correct term is "cutaneous anergy".

**Bacille Calmette-Guerin (BCG) vaccine:** A live attenuated vaccine derived from *Mycobacterium bovis* used to prevent tuberculosis disease

**BAL:** Bronchoalveolar lavage. This is a diagnostic procedure in which small amounts of physiological solution (sterile saline solution) are injected through a fiberoptic bronchoscope into a specific area of the lung, while the rest of the lung is sequestered by an inflated balloon. The fluid is then aspirated and inspected for pathogens, malignant cells, and mineral bodies. BAL is typically performed to diagnose lung disease.

**Booster phenomenon:** The presence of an initially negative TST response followed by a positive response when the test is repeated at any time from 1 week to 1 year later. The phenomenon often occurs many years after infection, most notably in the elderly. The initial negative response is based on the subject's initial failure to "recall" immunologically, prior infection. To avoid inadvertent labelling of a positive response as due to TST conversion, especially when serial skin testing is planned, initial two-step skin testing may be recommended.

**Cavitary disease:** This is a radiological-pathological label referring to evidence of lung destruction, i.e. evidence on chest X-ray or pathology of cavities or cystic areas that communicate with a bronchus. Cavities generally harbour large numbers of bacteria and, as a result, patients with cavitary disease tend to be highly infectious.

**Chemoprophylaxis:** Treatment of LTBI. The administration of anti-tuberculosis drug (s) to prevent the acquisition of LTBI or progression of LTBI to active TB disease.

**Chemotherapy:** The multidrug antibiotic treatment regimens used to treat active TB

**Compliance:** see adherence

**Contact:** A person identified as having come in contact with an active case of TB disease. The degree of contact is usually further defined as close and casual. The level and duration of contact usually suggests the risk of becoming infected.

**Contact tracing:** The identification of contacts to find associated cases of TB disease, to detect people with LTBI and to identify those not infected but for whom BCG vaccination might be appropriate.

**Conversion:** A change in the result of a test for *Mycobacterium tuberculosis* infection that is interpreted to indicate a change from being uninfected to infected.

**Culture:** The process of growing TB bacteria from sputum or other samples for identification and diagnosis

**Culture positive disease:** The isolation of *Mycobacterium tuberculosis* complex (excluding BCG strain) from sputum, body secretions or tissue

**Cure and completion rate:** The proportion of people receiving treatment for active TB who either have negative culture results during the continuation phase of treatment or who complete treatment without documented culture status

**Directly observed therapy (DOT):** A way of helping patients to take their medicine for TB. A person receiving DOT will meet with a healthcare worker everyday or several times a week at an agreed place e.g. the patient's home, the TB clinic or other convenient location. The healthcare worker will observe the patient taking their medication at this place helping to ensure that higher treatment completion rates are achieved. Sometimes someone in their family or a close friend will be able to help in a similar way to the healthcare worker.

**Directly observed prophylaxis (DOP):** The process whereby a health care worker or other responsible adult e.g. family member or close friend watches the patient swallow each dose of medication for latent tuberculosis infection, helping to ensure higher treatment completion rates. DOP is also known as directly observed preventive therapy (DOPT). This definition is used in the Canadian Tuberculosis Standards, 6<sup>th</sup> edition (2007).

**Directly observed therapy short-course (DOTS):** The internationally recommended approach to TB control, which forms the core of the World Health Organization (WHO) Stop TB Strategy (2006). The five components of DOTS are: political commitment with increased and sustained financing; case detection through quality-assured bacteriology; standardised treatment with supervision and patient support; an effective drug supply and management system and a monitoring and evaluation system and impact measurement

**Early morning specimen/sputum:** Sputum from the first productive cough of the day (after waking)

**Elimination:** The elimination of tuberculosis as a global public health problem, defined by the WHO Stop TB Partnership (see [www.stoptb.org/globalplan/](http://www.stoptb.org/globalplan/)) as an incidence of tuberculosis disease of less than 1 case per million population

**Extensively drug-resistant TB (XDR-TB):** is resistance to at least isoniazid and rifampicin (i.e. MDR-TB), plus resistance to any fluoroquinolone, and any one of the following second line anti-TB injectable drugs (capreomycin, amikacin or kanamycin)

**Gamma-interferon test (interferon-gamma or IGRA):** A blood test to diagnose LTBI (which may be used as an alternative or an addition to tuberculin skin tests) based on detecting the response of white blood cells to TB antigens

**Gastric washings:** Some patients (particularly children) with suspected TB are unable to cough up any sputum. As an alternative, in a gastric lavage, saline solution is introduced into the stomach through a tube, the contents are pumped out and are examined for *M. tuberculosis* complex bacteria.

**High incidence country:** Any country with an incidence of TB  $\geq$  40 cases per 100,000 population per year

**Histology:** Microscopic examination of cells and clinical samples

**Index case:** The initial person found to have TB whose contacts are traced. Consequently the source of their infection may be found, but the initial presenting patient is regarded as the index case.

**Induration:** The soft tissue swelling that is measured when determining the TST response to purified protein derivative (PPD) tuberculin. It is to be distinguished from erythema, which is not measured, i.e. does not constitute a measurable reaction to the antigen.

**Infectious:** The condition whereby the patient can transmit infection to others by virtue of the production of infectious aerosols. Those with smear-positive cavitory and laryngeal disease are usually the most infectious.

**Inform and advise information:** Information provided to patients so that they are able to recognise the symptoms of TB and be aware of the action they should take if these symptoms arise.

**Latent TB Infection:** A person with LTBI usually has a positive TST or interferon gamma test but no physical findings of TB disease and the chest X-ray is normal or only reveals evidence of healed infection i.e. granulomas or calcification in the lung, hilar lymph nodes or both. Persons with LTBI are asymptomatic and are not infectious.

**Mantoux test:** A type of TST in which tuberculin is injected intradermally. The injection site is examined for signs of an immune response after 2-3 days. A negative Mantoux test is  $\leq$  5mm. The reaction to a TST is classified according to the individual's risk factors (table 2.1, chapter 2).

**Meta-analysis:** A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than individual trials

***Mycobacterium tuberculosis* complex:** The related mycobacterial species (*M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, *M. canettii*, *M. caprae* or *M. pinnipedii*) which cause tuberculosis in humans

**Multidrug-resistant TB (MDR-TB):** TB bacilli resistant to at least isoniazid and rifampicin with or without resistance to ethambutol and streptomycin

**Non-tuberculous mycobacteria (NTM):** All mycobacterial species except those that cause tuberculosis (*Mycobacterium tuberculosis* [including subspecies *M. canettii*], *M. bovis*, *M. africanum*, *M. caprae*, *M. microti* and *M. pinnipedii*) and those that cause leprosy (*M. leprae*). These mycobacteria are ubiquitous, often found in soil and water and are usually more clinically significant in the immunocompromised patient. They are also described as atypical mycobacteria.

**Nucleic acid amplification test:** A test to detect fragments of nucleic acid allowing rapid and specific diagnosis of *M. tuberculosis* directly from a range of clinical samples

**New entrant:** Anyone coming to work or settle in Ireland. This will include immigrants, refugees, asylum seekers, students and people on work permits. This group may also include Irish born persons or Irish citizens re-entering the country after a prolonged stay in a high incidence country.

**Polymerase chain reaction (PCR):** The process whereby genetic material is amplified and subsequently evaluated for the presence of DNA material to identify various mycobacterial species



**Reactivation:** The advancement of old LTBI (whether previously detected or not) into active TB

**Short-course treatment:** Modern 6 month treatment regimens for active TB (previously treatment had been for at least 12 months)

**Smear:** A laboratory technique for preparing a specimen so that bacteria can be visualised microscopically. The results for sputum acid-fast bacteria (AFB) smears typically are reported as numbers of AFB per high-powered microscopy field, or else as a graded result from no AFB to 4+ AFB. The quantity of stained organisms is associated with the degree of infectiousness.

**Sputum:** Mucous expelled from the bronchi and lungs by coughing (or retrieved from gastric washings, see above). Sputum is examined for TB bacteria by microscopic examination of stained smear; part of the sputum can also be used for culture.

**Sputum smear negative TB Case:**

A sputum smear negative TB case has:

- o At least three negative sputum smears (including at least one early morning specimen)
- o Chest X-ray findings consistent with tuberculosis and
- o Lack of response to a trial of broad-spectrum antimicrobial agents (**Note:** because the fluoroquinolones are active against *M. tuberculosis complex* and thus may cause transient improvement in persons with tuberculosis, they should be avoided)

It should be noted that in making a diagnosis based on the above three criteria, a clinician who decides to treat with a full course of antituberculosis chemotherapy should report this as a case of sputum smear-negative pulmonary tuberculosis to the MOH.

**Sputum smear positive TB case:** The revised WHO definition of a new sputum smear positive pulmonary TB case is based on the presence of at least one acid fast bacilli (AFB+) in at least one sputum sample in countries with a well functioning external quality assurance (EQA) system

**Treatment failure:** Failure of the prescribed drug regimen to eliminate the TB bacteria from the body. This is demonstrated by a lack of clinical improvement or by positive culture after the end of the fourth month of treatment

**Tuberculosis:** Active TB; disease due to infection with *M. tuberculosis complex*

**Tuberculin skin test:** A test which involves the injection of tuberculin (purified protein derivative, PPD) into the skin. An immune reaction can be assessed after a few days according to the size of induration at the injection site. The test can demonstrate acquired immunity to TB, lack of immunity or possible current infection (a strong response) but are confounded by immunosuppression, prior BCG vaccine, serial TST and prior exposure to atypical mycobacteria. The results are generally referred to as positive or negative.

















