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. canetii, 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.[1] 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.[2] To improve control, targets for TB control recommended by WHO's World Health Assembly[3] 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.[4;5]

Table 1.1: Indicators of progress towards Millennium Development Goals[5]

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.[4;6] 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.[7] 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.[8]

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.[9] 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.[10] 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.[10]

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.[11] 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.[12] 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.[13] 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).[14] 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%).[15] In 2004, an action plan entitled 'Stopping Tuberculosis in England'[16] 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[10] 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
Total all EU countries	17.0	na

(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[17] (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.[18] 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.[19] Mortality rates also declined, from 266 per 100,000 population in 1901[18] to 0.94 per 100,000 in 2006, and are now amongst the lowest reported in Western Europe.[10] The majority of deaths from TB now occur in those aged 65 years and older.

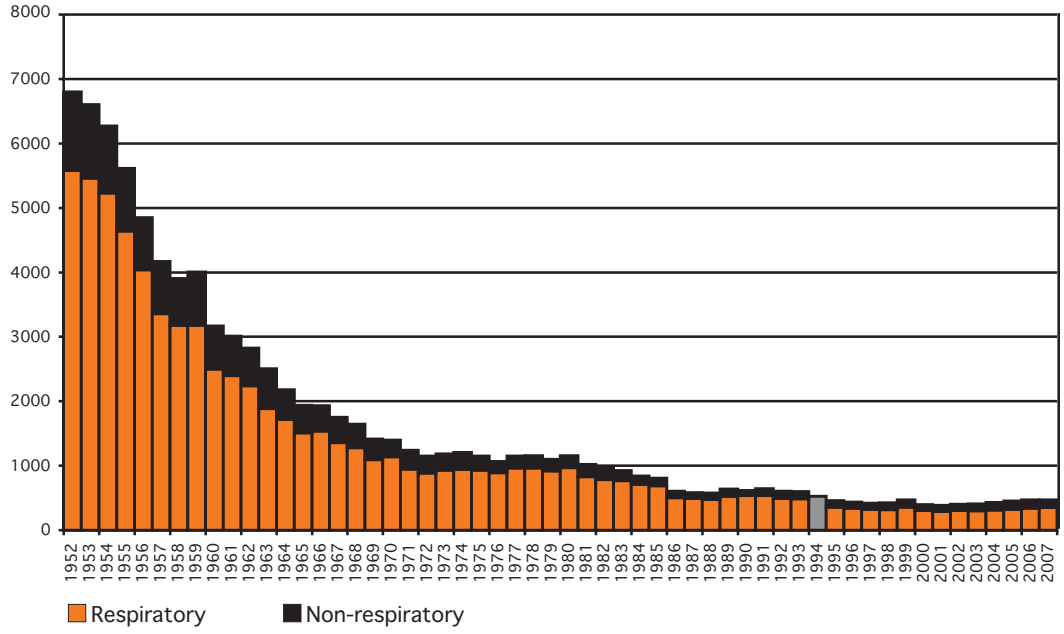

Figure 1.1: TB cases notified to the Department of Health and HPSC, 1952-2006 (breakdown by respiratory /non-respiratory not available for 1994)[19]

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.[18] In 2006, the largest number of notifications was reported by HSE East (193 notifications).[19]

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.[15]

Table 1.4: Crude TB incidence rates per 100,000 population by HSE area, 1992-2006[19]

	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.[19]

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.[19]

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.[19] In 2005, the first reported case of XDR-TB was detected in Ireland.[20]

1.4 Surveillance of TB

Clinical notification of TB was introduced in 1948[17] 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.[21] 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).[21]

The 2003 amendment also made reporting of outbreaks a mandatory requirement.[21] 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.[22] In April 2008, the above decision was amended (Decision No. 2008/426/EC) updating these case definitions.[23] The updated standardised European case definitions are used for notification of TB in Ireland (table 1.5).[23]

Table 1.5: EU standardised case definitions for notification of a TB case[23]

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/.

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.[24]

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).[25]

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.[25]

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/.

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.[21]

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,[10] 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/.

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*.[26] 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.[26]

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).[27]