A study using molecular, epidemiological and sociological information to examine obstacles and opportunities to interrupt the transmission of *Mycobacterium tuberculosis* in the Greater Glasgow NHS Board area

Abaigeal Hopkins
B.A. (Mod)

Submitted in fulfilment of the requirements for the Degree of Doctor of Philosophy

University of Glasgow
Faculty of Medicine
Section of Public Health and Health Policy

March 2006

Summary

Introduction:

In centuries past, tuberculosis was a significant cause of morbidity and mortality. Throughout the twentieth century in the United Kingdom, there has been a general pattern of decline in case numbers. This decreasing trend is attributed to numerous factors including improved socio-economic conditions, the advent of chemotherapeutic drug therapies, and BCG vaccination. From 1987 onwards, tuberculosis notifications in Scotland have been relatively stable, with approximately 400 to 500 new cases diagnosed annually. In 2003, the incidence of tuberculosis stood at 7.2 cases per 100,000 population.

The vast majority of disease in low-incidence countries (defined by the World Health Organisation as countries with less than 10 cases per 100,000 population per annum) is thought to be due to the reactivation of latent infection, acquired many years in the past, rather than disease due to ongoing transmission of *Mycobacterium tuberculosis*. In Glasgow, an urban area of Scotland, which accounts for approximately 50% of annual notifications, recent outbreaks associated with public houses and nurseries indicate transmission of tuberculosis is ongoing. This contradicts classical medical thinking which postulates transmission of disease follows close, prolonged contact and usually occurs within the household and between family members.

In low-incidence countries, strategies to further reduce case notifications in low-incidence countries rely on strengthening current control practices. Such strategies are based on the principals of prompt case detection to reduce the period in which an infected individual can infect others, and completion of treatment, to prevent relapse and development of drug resistance. This research study sought to examine obstacles and opportunities to interrupting the transmission of *Mycobacterium tuberculosis* in the Greater Glasgow NHS Board area.

Methodology:

A novel methodology was developed, using molecular, epidemiological and sociological information. It was anticipated that the combination of such research techniques would provide a novel insight into TB transmission and control. Four sub-studies were devised. The first sought to describe the epidemiology of recently transmitted TB in Greater Glasgow, by analysing epidemiological data for culture positive cases (diagnosed January

2000 to 11th November 2003), for whom IS*6110* RFLP patterns were available. Epidemiological data were obtained from the Enhanced Surveillance of Mycobacterial Infection (ESMI) scheme managed by Health Protection Scotland, while genotyping information was made available by the Scottish Mycobacterial Reference Laboratory (SMRL). Secondly, the social network of cases clustered on the basis of sharing a genetically indistinguishable IS*6110* RFLP pattern (believed to represent recent transmission) was explored, to improve current understanding of the nature of epidemiological links between cases. This sub-study focussed initially on cases with a 15-banded IS*6110* RFLP pattern, diagnosed between January 2000 and 11th November 2003. To this end, epidemiological information was obtained from ESMI, and nurse and patient interviews were undertaken. The third sub-study sought to examine the understanding of TB transmission and causation and help seeking beliefs of cases included in the second sub-study. An evaluation of contract tracing was undertaken for the final sub-study, and cases diagnosed with pulmonary TB in Glasgow between 2000 and 2003 were included. Contact tracing information was obtained following a series of meetings with Greater Glasgow TB nurses.

Results:

Findings from sub-study one indicate that between 2000 and 2003, reactivation of latent infection is likely to play a significant role in disease causation. On the basis that 19.1% of cases were in genetically defined clusters (on the basis of IS*6110* RFLP typing and Spoligotyping) this study showed that transmission was also occurring, albeit to a lesser extent than observed in some low-incidence countries. Ninety cases (of 643 notified in Glasgow between January 2000 and 11th November 2003) were members of 17 distinct clusters, ranging in size from 2 to 23 cases. Risk factors for all IS*6110* RFLP clustered cases were analysed, and although factors were not indicated for just under half of the clustered case population (47.7%), alcohol misuse was frequently cited where risk information was provided (attributed to 41.5% of the 176 cases clustered on the basis of IS*6110* RFLP typing alone).

In the second sub-study, an investigation to identify epidemiological links between cases with a 15-banded IS*6110* RFLP pattern found that routinely recorded surveillance (ESMI) information indicated 25.9% of cases had associations with another cluster member, and contact with known TB cases was not indicated for any other cases. Following interviews with TB nurses and cluster cases (28 of 51 cluster cases, or next of kin where appropriate, participated in an interview), epidemiological links were identified for 56.3% of cluster

cases. Public houses and drinking dens were identified as putative sites of exposure. Just over two-thirds (67.3%) of cases had detectable links to cases and/or locations. Results from this analysis suggest clustering of cases on the basis of IS*6110* RFLP typing information within a defined observation period represents instances of ongoing transmission. While epidemiological associations were detected for some cluster cases, links were not identifiable for others, and it is possible the latter may indicate the reactivation of latent infection acquired many years previously. Clustering in Glasgow may represent the acquisition of disease by these concurrent methods because the genetic pool of *M. tuberculosis* present in Scotland is likely to be relatively static, as levels of disease imported by non-UK born individuals remains low at present.

Cultural factors contributing to the continued propagation of this 15-banded IS*6110* RFLP pattern were explored during patient interviews in sub-study three. Factors such as delayed patient presentation to medical services, which extends the period in which an undiagnosed case can infect others were identified. Patients fail to associate non-specific symptoms with this uncommon disease, and postpone seeking care in the hope symptoms will resolve. Patient beliefs about the way in which tuberculosis spreads differ from that of health professionals, and as a result the success of contact tracing may be challenged by appropriate identification of at risk contacts. Feelings of shame and embarrassment associated with a TB diagnosis, and the stigma associated with the disease conceivably hinder early case detection. Anecdotal information suggests that in a limited number of cases, doctors may delay the initiation of treatment for TB by initially misdiagnosing symptoms.

To determine whether current control strategies are effectively interrupting the transmission of *M. tuberculosis*, an evaluation of contact tracing outcomes was undertaken in sub-study 4. On average 6.9 contacts were screened per pulmonary case between 2000 and 2003. One in 56.8 screened contacts were diagnosed with tuberculosis, representing a yield of 1.8%. Sufficiently discriminatory IS*6110* RFLP typing and Spoligotyping information sourced for study pulmonary cases and respective infected contacts (n=17) revealed 76.5% of these case pairings (n=13) had genetically indistinct genotypes. The discharge of contacts from screening programmes, and their subsequent presentation to medical services up to two years later with symptoms of TB indicated opportunities for control were missed.

Conclusions:

The evaluation of contact tracing indicates that the current approach is relatively effective, particularly for early detection of disease in close contacts and unvaccinated children. However, molecularly defined clusters described in the first sub-study suggest that to some extent, transmission of *M. tuberculosis* appears to go undetected by contact tracing in Glasgow. The second sub-study shows that in addition to disease transmission between family and other close contacts, disease spreads between casual contacts, at high-risk of infection or progression to disease due to alcohol misuse. This high-risk population are hard to reach using the current stone-in-the-pond approach, which focuses on disease detection in close contacts.

Findings from this research study support the view that an updated approach to contact tracing is required to improve TB control. Such an approach will need to take into account the modern structure of disease networks, associated risk behaviours and potential sites of exposure. Outbreak investigations targetting groups of high risk of disease should be mindful of the nature of associations within such populations. A standardised approach to contact identification and screening may improve screening outcome and efforts to improve the recording of information pertaining to epidemiological linkage is required. Consideration should be given to utilising molecular typing information to identify disease clusters in routine practice and guide screening programmes. Efforts are required to reduce the period in which patients are symptomatic. By providing appropriately targeted information about TB transmission to the public (acknowledging differences highlighted during interviews between medical professionals and patients' beliefs), and improving awareness of this disease, this may contribute to earlier self-presentation to medical services.

Acknowledgements

I wish to thank the following individuals for their support, guidance, encouragement and enthusiasm over the past three years.

Firstly, my supervisors Dr Jim McMenamin at Health Protection Scotland, and Prof Margaret Reid at the Public Health and Health Policy Section, in the University of Glasgow.

Dr Peter Christie, Scottish Executive, who secured funding for this PhD studentship.

The Greater Glasgow NHS Board public health protection unit. Dr Syed Ahmed, Consultant in Public Health, TB liaison nurses: sisters Alice Bennett, Mary Waldemichael, Norma Brewster and Una Lees and TB surveillance data co-ordinators, Sarah McCullough and Anne McDonald.

Dr Louise Seagar, Dr Xavier Emmanuel and colleagues at the Scottish Mycobacterial Reference Laboratory, Edinburgh.

Dr Ken Forbes, Department of Microbiology, University of Aberdeen.

Fiona Johnston, Rebecca Flanagan, and my Immunisation & Respiratory team colleagues in Health Protection Scotland.

All medical and scientific staff at Health Protection Scotland and Public Health and Health Policy Section, University of Glasgow.

All individuals who took part in patient interviews.

Finally, thanks to Andrew, my parents John and Dolores, my family, the Jackson family & friends.

Table of contents

List of tables

List of figures

List of abbreviations

AAFB	Acid and Alcohol Fast Bacilli
BCG	Bacille-Guérin Calmette vaccine
Bp	Base pair
BTS	British Thoracic Society
CFP-10	Culture filtrate protein-10
CPHM	Consultant in Public Health Medicine
CPX	Chemoprophylaxis
DNA	Deoxy-ribonucleic acid
DOT	Direct observed therapy
DR	Direct repeat region
ESAT-6	Early secretory antigenic target-6
ESMI	Enhanced Surveillance of Mycobacterial Infections
HIV	Human Immunodeficiency Virus syndrome
HPA	Health Protection Agency
HPS	Health Protection Scotland (formerly SCIEH)
IFN-γ	Interferon gamma
ml	Millilitre
MDR-TB	Multi-drug resistant TB
MIRU	Mycobacterial interspersed repetitive units
MTBC	*Mycobacterium tuberculosis* complex
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NNS	Number needed to screen
NOIDS	Notification of Infectious Diseases scheme
PPD	Protein purified derivative (used in tuberculin skin testing)
IS*6110* RFLP pattern	IS*6110* Restriction Fragment Length Polymorphism pattern
SCIEH	Scottish Centre for infection and Environmental Health (now HPS)
SMRL	Scottish Mycobacteria Reference Laboratory
ST	Spoligotype
TB	Tuberculosis
TST	Tuberculin skin test
UK	United Kingdom
WHO	World Health Organisation
VNTR	Variable number tandem repeat

Chapter 1: Introduction

In April 1993, the World Health Organisation (WHO) declared tuberculosis (TB) a global health emergency in response to an observed resurgence in notified cases, following many years of steady decline. This communicable disease is recognised as an important threat to public health, killing more adults on an annual basis than any other (World Health Organization, 1994). One third of the world's population is infected with *Mycobacterium tuberculosis*, and are at risk of developing disease. Every year, 8 million new cases of disease develop, and about two million die (Dye *et al.*, 1999).

Tuberculosis has caused disease in humans throughout recorded history. The *M. tuberculosis* pathogen, which causes human tuberculosis, is thought to have evolved from *M. bovis*, acquired from domesticated cattle (Daniel *et al.*, 1994). It is believed tuberculosis became endemic in the human population about 10,000 years ago, as a result of humans beginning to live together in communal settings (McGrath, 1988). In Europe, the presence of *M. tuberculosis* complex DNA has been detected in skeletal and mummified material from prehistoric times. By the early 17th century, this disease had gained a foothold in Europe, as a result of increasing populations in cities (Dubos & Dubos, 1952).

1.1 Historical epidemiology of TB in the United Kingdom

Following Robert Koch's identification of the causative agent of tuberculosis (*M. tuberculosis*) in 1882, surveillance programmes were developed to accurately estimate the number of cases and deaths. However, deaths thought to be due to tuberculosis were recorded long before this, and in the United Kingdom in the mid-1800s, TB was one of the most common causes of death. In Scotland, a mortality rate of as high as 400 per 100,000 was reported in 1850 (Scottish Office Department of Health, 1998). Amongst other factors, poor nutrition, overcrowding, and sanitation contributed to these high rates.

Since the introduction of formal statutory notification for tuberculosis in Scotland in 1914, a general pattern of decline has been observed (figure 1), with the exception of increased rates during World Wars I and II, and a two-year period between 1957 and 1958. Although improved socio-economic conditions are thought to have contributed to the decrease in case notifications across the United Kingdom in the early 1900s, the introduction of chemotherapeutic treatment and Bacille-Guérin Calmette (BCG) vaccine in the 1950s accelerated this decline.

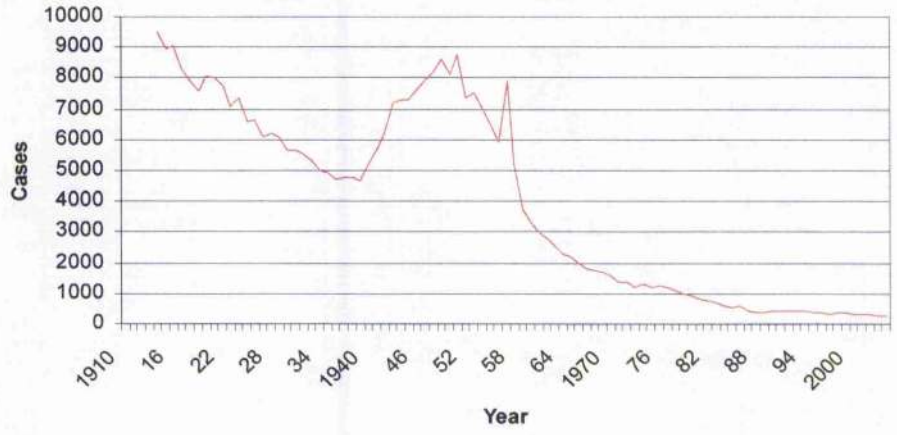

Figure 1: TB cases reported in Scotland since the introduction of statutory notification in 1914

Whereas the number of TB cases in Scotland increased considerably throughout the wartime period and for some time after, the increased trend observed in England and Wales at that time was less marked. In Glasgow for example, respiratory TB increased from 139 to 200 per 100,000 population over this period, and was believed to be due to overcrowded living conditions, as a large proportion of the population lived in one-roomed tenement apartments (Glasgow Corporation, 1957). In response to the dramatic rise in cases during this period, a two-year programme (1957 and 1958) known as the 'Mass Miniature Radiographic Screening' campaign was initiated in Scotland (MacGregor, 1961). The purpose of this programme was to identify and treat the maximum number of undetected infected cases, thus reducing the spread of infection so that the incidence of new disease would be reduced in the future. In Glasgow, a five-week campaign ensured 76% of the city's adults (700,000 people) were screened for TB by x-ray. In total, 2,200 cases of active TB were detected and treated (Glasgow Corporation, 1957). Similar initiatives were undertaken across Scotland, resulting in increased case notifications during 1957 and 1958 (figure 1).

Today, the incidence of tuberculosis in Scotland stands at 7.4 cases per 100,000 population (for 2003)[1], and according to WHO standards, Scotland is classified as a low-incidence country (<10 cases per 100,000 per annum) (World Health Organization *et al.*, 2002). This rate varies across Scottish National Health Service (NHS) Boards, and each year, approximately half of all cases are detected in the Greater Glasgow NHS Board area. In

[1] 373 cases were notified to the ESMI scheme in 2003 (as of August 2005). The General Register Office mid-year population estimates reported a total population of 5,057,400 in Scotland for 2003.

2003, Greater Glasgow reported an incidence rate of 19.4 per 100,000 population, and was the only NHS Board to exceed 10 cases per 100,000 population.

With regards to the United Kingdom as a whole, case notifications have generally declined throughout the twentieth century, reaching a nadir of just over 5,500 cases in 1987. Case rates subsequently increased and in 2003, 6,837 new cases were notified (French *et al.*, 2005). In England alone, a 25% increase in case notifications has been observed between 1992 and 2002 (Department of Health, 2004). This increase has been attributed in part to the increased contribution of cases born outside the United Kingdom to the overall burden of disease.

Despite an overall increase in United Kingdom case notifications, a distinct pattern of case notifications has prevailed in Scotland over the past twenty years. Since 1987, the number of TB cases has remained relatively stable or in slight decline, with approximately 400 to 500 new cases diagnosed annually. Whereas seventy percent of cases in England, Wales and Northern Ireland were born outside the United Kingdom in 2003, such cases represented only one quarter of cases in Scotland in 2002 (French *et al.*, 2005, McMenamin & Johnston, 2004). As is the case in many low-incidence countries, tuberculosis in Scotland tends to be more frequently diagnosed in the elderly population as a result of reactivated latent infection, acquired many years in the past (Harper, 1999), as well as in groups with high risk behaviours (e.g. the socio-economically deprived, and individuals who are homeless and/or misuse alcohol), where infection has been recently transmitted (Patel, 1985). Socio-economic factors continue to play an important role in the continued presentation of disease (Gandy & Zumla, 2002). Indeed, TB remains a disease which predominantly affects those in poorer socio-economic classes in Scotland (King, 2002).

1.2 Case detection

The vast majority of cases present to the health services with symptoms subsequently diagnosed as tuberculosis (passive case detection). Alternately, cases are diagnosed as a result of an active case detection strategy, which principally occurs as a result of contact tracing. As individuals in contact with an infected case are at greater risk of acquiring infection than a member of the general public, contacts of a newly diagnosed case are identified and offered screening.

Glasgow has a long history of actively screening for tuberculosis in the community, which can be traced back to mass miniature radiographic campaigns in the 1950s. Indeed, many historical texts document the conduct of such campaigns (Glasgow Corporation, 1957). Today, active case detection and completion of an appropriate treatment regimen remain key components of strategies to control tuberculosis in Scotland, as in other low-incidence countries. As tuberculosis is spread by the airborne transmission of mycobacteria when a pulmonary case coughs or sneezes, it spreads mainly during the period in which patients are symptomatic. Patients become non-infectious when symptoms resolve, usually within a couple of weeks of commencing treatment. Early diagnosis by active case finding is therefore important for reducing the period of time in which an infected individual can pass the infection to others (Styblo, 1984).

1.3 Study aim, sub-study aims and objectives

The aim of thesis was to examine some of the obstacles challenging the control of *M. tuberculosis* transmission in Glasgow and to identify potential opportunities for improving control.

To achieve this aim, four related sub-studies were devised. Each sub-study has a distinct sub-aim, which are described below and labelled number 1 to 4. The objectives for each sub-study are also outlined.

1 Describe the epidemiology of recently transmitted TB:

a link genotyping information for Greater Glasgow cases (notified between 2000 and 11th November 2003) to epidemiological information reported to the ESMI scheme

b compare the epidemiological profile of cases with available IS*6110* RFLP patterns, with the profile of cases without IS*6110* RFLP patterns over the study period

c compare the epidemiological profile of cases with IS*6110* RFLP patterns by clustered (i.e. 2 or more cases with same genotype) and non-clustered status, and identify risk factors associated with being a clustered case

d determine the proportion of clustered cases identified by contact tracing

e identify the epidemiological characteristics of each genetically defined cluster

f calculate the proportion of cases within the study population thought to be due to recent transmission

2 Describe the social network connection between cases clustered on the basis of infection with a genetically indistinguishable strain of *M. tuberculosis*, believed to represent recently transmitted disease:

a describe the epidemiology of the study cluster, consisting of cases with a 15-banded IS*6110* RFLP pattern diagnosed between 2000 and 11th November 2003

b compare the epidemiological profile of the study cluster with a population consisting of all other clustered cases diagnosed between 2000 and 11th November 2003

c describe epidemiological links between cases in the study cluster previously reported to the ESMI scheme

d undertake interviews with TB nurses and patients to identify and describe previously unrecognised epidemiological links

e describe the network in terms of the associations between cases, associations between cases and places frequented, and the degree of infectiousness of study cases.

f compare the characteristics of study cases with identifiable epidemiological links and those with no epidemiological links

3 Examine patient understanding of *M. tuberculosis* transmission and patient help seeking behaviour:

a undertake interviews with study cases (or case's next of kin where applicable) with a 15-banded IS*6110* RFLP pattern diagnosed between 2000 and 11th November 2003, and resident in the Greater Glasgow NHS Board area.

b examine interviewee's general knowledge of tuberculosis prior to diagnosis, perceived modes of transmission, beliefs regarding required duration of contact for transmission to occur, understanding of disease reactivation, personal factors thought to enhance the risk of infection, and beliefs regarding putative sources of infection.

c examine interviewee's recollection of recognising symptoms, decision making when seeking medical care, their response to a TB diagnosis, coping strategy and experience of having a TB diagnosis

4 **Evaluate the effectiveness of contact tracing:**

a gather contact tracing data from TB nurses for pulmonary TB cases diagnosed in Greater Glasgow between 2000 and 2003

b link contact tracing data to epidemiological information reported to the ESMI scheme

c describe epidemiology of study population and outcome measures from contact tracing i.e. yield of contacts diagnosed with TB as a result of contact tracing

d analyse outcome from contact tracing in terms of bacteriological status of study cases, associations between study cases and contact cases

e compare molecular typing information for index cases and respective contact cases

f identify and describe deficiencies in contact tracing service i.e. absence of contact investigations etc.

1.4 Study overview:

As indicated, each sub-study has a distinct aim, and the study population used for each are not necessarily the same. To clarify the structure of this research project, table 1 outlines the sub-study number, the objective, the study population and the chapter number where

results can be found (section 1.6 describes the thesis layout in more detail, while section 3.2 describes the study population selection).

Sub-study	Chapter	Objective	Population
1	5	To describe the epidemiology of recently transmitted TB	Culture positive cases diagnosed in Greater Glasgow NHS Board area between 2000 and 11th November 2003
2	6	To describe the social network connection between cases with a genetically indistinguishable genotype (IS*6110* RFLP pattern), believed to represent recently transmitted disease	Culture positive cases diagnosed in Scotland (Greater Glasgow and Western Isles) 2000 to 2004, with a 15 banded IS*6110* RFLP pattern
3	7 & 8	To examine patient understanding of M. tuberculosis transmission and help seeking behaviour	Culture positive cases diagnosed in Greater Glasgow NHS Board 2000 to 2004, with a 15 banded IS*6110* RFLP pattern
4	9	To evaluate the effectiveness of contact tracing	Pulmonary TB cases diagnosed in Greater Glasgow NHS Board, 2000-2003

Table 1: Structure of research project, consisting of 4 sub-studies, their respective chapters, aims and study populations

1.5 A novel study approach

To achieve the central study aim, an original study design was devised, which combined research tools from the traditions of epidemiology, molecular biology and medical sociology. Molecular epidemiological techniques have been used to study *M. tuberculosis* transmission since the early 1990s; however, social and cultural aspects contributing to disease transmission have been neglected in the wake of this emerging field of investigation. In this study, sociological information was integrated with molecular epidemiological information for experimental purposes, and it was hoped the combination of these traditions would allow additional insight into difficulties facing control strategies.

Contact tracing is one of the principal methods for interrupting the spread of *M. tuberculosis* in the United Kingdom, yet outbreaks of disease occur frequently within the household and community-based settings. From enhanced surveillance information in Scotland it is known that a small proportion of TB cases have indicated having had contact with a known TB case prior to diagnosis. Between 2000 and 2003, 23.1% of Greater Glasgow cases (157/680) indicated having had an association with a TB case. Despite the fact TB is spread via human-to-human transmission of airborne droplets and requires close prolonged contact, 37.2% of cases indicated having no known contacts, and for the remaining 39.7%, information was not available. Studies in low-incidence countries using molecular epidemiological information to evaluate the effectiveness of contact tracing procedures have found that just 10% of cases clustered on the basis of infection with a genetically indistinguishable strain (indicating recent transmission of infection) were identified as a result of contact tracing (Alland *et al.*, 1994, Bauer *et al.*, 1998, Small *et al.*, 1994, van Soolingen *et al.*, 1999). Together, this evidence suggests the current approach to contact tracing is failing, as transmission of disease continues.

To enhance our understanding of modern *M. tuberculosis* transmission patterns, interviews were conducted with TB nurses and patients, in order to detect previously unrecognised epidemiological links between cases infected with the same *M. tuberculosis* genotype. Importantly, this research study attempts to understand some of the reasons why such epidemiological links are not uncovered during routine contact tracing, and therefore why strategies for TB control are not more effective. It was felt that this research study should explore new ways in which the contact tracing service in Glasgow could be improved. To provide new insights into the apparent failure of contact tracing (as the majority of cases present to the health services of their own volition), patient interviews were undertaken to examine socio-cultural factors contributing to the continued propagation of single strain of *M. tuberculosis*.

In 2000, Health Protection Scotland (then known as Scottish Centre for Infection and Environmental Health – SCIEH) established the Enhanced Surveillance of Mycobacterial Infections (ESMI) scheme. This surveillance scheme was introduced to gather detailed information, thereby enhancing data gathered through the statutory Notification of Infectious Diseases (NOIDs) scheme, which has been in operation since 1914 in Scotland. For the first time, ESMI enabled information pertaining to identifiable risk factors, ethnicity, and putative sources of infection to be recorded.

Secondly, advances in molecular biology have resulted in the development of genotyping techniques to discern and differentiate between strains of *M. tuberculosis*. Since 1997, the Scottish Mycobacterial Reference Laboratory (SMRL) has undertaken IS*6110* RFLP typing, a highly discriminatory technique for strain identification, for all eligible (i.e. culture positive) patient isolates. Genotyping information has been used for public health purposes, specifically in instances where the occurrence of an outbreak requires confirmation. Where epidemiologically linked cases are diagnosed, *M. tuberculosis* strain genotyping verifies whether transmission is likely to have occurred, on the basis these individuals are infected with a genetically indistinguishable IS*6110* RFLP pattern (Alland *et al.*, 1994, Bauer *et al.*, 1998, Small *et al.*, 1994, van Soolingen *et al.*, 1999).

The integration of epidemiological and molecular genotyping information has greatly improved our understanding of TB transmission dynamics (van Soolingen *et al.*, 1999). In low-incidence countries it has demonstrated that more transmission is occurring than previously suspected, contradicting previous suspicions that the majority of cases were due to the reactivation of latent infection. Transmission of tuberculosis has been shown to follow casual or transient contact with an infected individual, and outbreaks have been occurring in the community and in institutions with increasing regularity (Klovdahl *et al.*, 2001). Also, active case detection appears to be inadequate for interrupting ongoing transmission, on the basis that 10-20% of cases in a genetically defined cluster (i.e. clustered on basis of having same IS*6110* RFLP typing pattern, suggesting cases are part of the same transmission pathway) were detected by contact tracing. In Scotland, aside from the selective use of molecular genotyping information as a confirmatory tool in outbreak situations, the utility of molecular epidemiological information in routine public health practices has not be fully explored.

Although *M. tuberculosis* genotyping techniques have provided great insights into TB transmission, these advances alone are insufficient to tackle the global resurgence of tuberculosis. Indeed, Rubel & Garro point out that the resolution of this problem by means of a "magic bullet" (i.e. molecular genotyping, a new drug therapy or vaccine) is an unrealistic prospect, particularly when the lack of education, poor motivation, poverty etc. continue to pose significant challenges for early case detection and compliance with treatment. It is interesting to note that despite recognising non-adherence to treatment and delay in seeking medical assistance as factors contributing to ongoing transmission, the influence of cultural and behavioural factors on early case detection has received little attention in the tradition of social science (Rubel & Garro, 1992).

In view of the fact tuberculosis is a social disease, this study approached the identification of obstacles and opportunities for interrupting tuberculosis transmission by integrating information from sociological and molecular epidemiological traditions. In effect, this study used research methodologies from both qualitative and quantitative research paradigms. It was anticipated this combined approach would provide a comprehensive overview of the biological and behavioural problems encountered in tuberculosis control.

1.6 Thesis overview

In this chapter (chapter 1), the epidemiology of TB in the United Kingdom, the rationale for undertaking research on TB transmission and control, and the study aim, sub-study aims and objectives have been described. Chapter 2 extends some discussions briefly outlined in chapter 1, reviewing current literature on TB transmission, and describing strategies for active case finding. Current understanding of the epidemiological profile and challenges to control of TB in Glasgow and Scotland are also discussed.

Chapters 3 and 4 outline the various methods used in this research project. As previously indicated, both quantitative and qualitative research methods are employed in this study. Chapter 3 considers the mixed method approach used in this study, and focuses on quantitative aspects, describing the sourcing of epidemiological, molecular and contact tracing information and the use of statistical tools. Chapter 4 describes the rationale for conducting nurse and patient interviews, the recruitment and interview of patient interviews, and the analysis of qualitative data.

As mentioned previously, the use of molecular typing information has been limited to providing confirmation of putative outbreaks, when epidemiologically linked cases are infected with identical *M. tuberculosis* genotypes. Therefore, the contribution of disease due to recently transmitted infection (as opposed to reactivated latent infection) is currently unknown. The first step towards identifying obstacles and opportunities for interrupting the transmission of *M. tuberculosis* requires determining how much disease is caused by recently transmitted infection. In chapter 5, clusters of cases, suggestive of recently transmitted infection are identified. Using IS*6110* RFLP typing, cases infected with a genetically indistinguishable genotype are grouped together, and characteristics of cases putatively involved in transmission pathways are described.

As the literature show, clustered cases do not always reflect recent transmission of infection, therefore epidemiological information is required to validate the interpretation of

clusters of cases as such (Braden *et al.*, 1997). Using patient and nurse interviews, epidemiological links between cases within a genetically defined cluster are elucidated, and a hypothesis describing the transmission pathway of a single strain of *M. tuberculosis* is proposed in chapter 6. It is intended that such an undertaking will provide an improved understanding of *M. tuberculosis* transmission dynamics in the Greater Glasgow NHS Board area.

Patient interviews also provide an opportunity to establish some reasons for the continued propagation of this single strain through Glasgow over an extended period of time, by exploring some of the cultural factors that may influence transmission. Patients understanding and perspective of TB transmission are examined in chapter 7 as it is recognised this influences patients behaviour when attempting to help seek medical assistance for symptoms. Patterns of help seeking behaviour are also described in chapter 8.

In the final results chapter, chapter 9, an evaluation of contact tracing is undertaken. In addition to conventionally measured outcomes such as the yield of contacts newly diagnosed with tuberculosis, molecular genotyping information is utilised to test the assumption contact tracing interrupts the transmission of *M. tuberculosis*, on the basis that epidemiologically linked cases are infected with the same strain.

Challenges facing the control of TB transmission that emerged as a result of this study are discussed in chapter ten. The limitations of current approaches to interrupting the transmission of *M. tuberculosis*, the value of the novel study approach and opportunities for utilising these techniques to improve TB control are considered. The main recommendations for improving TB control are proposed in chapter 11.

Chapter 2: Tuberculosis & control of tuberculosis

In chapter one, tuberculosis was described as a disease that generally declined in the United Kingdom throughout the twentieth century. Despite the development of a vaccine and therapeutic drugs, this disease began to re-emerge as a threat to public health towards the end of the century, and the global incidence of disease is estimated to be increasing at a rate of 1% per year (Dye *et al.*, 2005). This chapter provides an introduction to the aetiology and pathogenesis of disease, and the control strategies currently used to limit morbidity and morbidity caused by *Mycobacterium tuberculosis*. An overview of TB epidemiology in Scotland and Glasgow (where the research study took place), and a summary of current arrangements for active case detection strategy contact tracing is provided. Recently, molecular genotyping techniques have greatly enhanced our understanding of *M. tuberculosis* transmission, and insights into the spread of disease and current approaches to TB control are described. In reviewing current literature, this chapter aims to describe current understanding of TB transmission and control.

2.1 Tuberculosis: from case to cure

2.1.1 Transmission

Tuberculosis is an infectious disease caused by bacterium from the *M. tuberculosis* complex (*M. tuberculosis*, *M. bovis*, and other mycobacteria). *M. tuberculosis* bacilli are released in an aerosol by an infected individual when they cough or sneeze, and these small aerosolised particles, referred to as droplet nuclei (approximately 1 to 5 microns in diameter, containing 1 to 10 bacilli), are inhaled by another individual. The transmission of mycobacteria depends upon the volume of infectious material expelled by the infected individual (the degree of infectiousness), the environment in which this occurs, and the proximity and duration of exposure to the infected individual(s) (Centers for Disease Control and Prevention, 2000). Once inhaled, bacilli may become implanted in the alveoli (air sacs) of the lungs, where the focus of infection establishes (referred to as the Ghon focus). Bacilli are then transported to the lymph nodes by the lymphatic system where additional foci of infection develop. From these two sites of infection (together termed the primary complex), bacilli spread through the blood stream and lymphatic system to other parts of the body, where infection can occur.

2.1.2 Natural history of disease

Following inhalation of infectious droplet nuclei, the immune system will mediate the development of disease. Firstly, it is possible the infection may resolve spontaneously if the immune system destroys all invading pathogens. Secondly, the infection may be contained by the immune system, and over the individual's lifetime, there is a small risk the infection may become active (reactivation of latent infection) when the body's defences weaken. Individuals with latent infection have no clinically overt signs or symptoms of disease, and are incapable of propagating the spread of disease (The Interdepartmental Working Group on Tuberculosis, 1996). Finally, if the immune system is overpowered, the infection may progress to the active form of disease within a matter of weeks or months (primary disease). In the United Kingdom, only cases with active disease are statutorily notifiable.

Approximately 5% of infected individuals develop primary disease within two years of acquiring the infection (Enarson & Rouillon, 1998). In the remaining 95% of cases, the progression to disease is precluded by the immune system, by means of encasement of bacilli in caseous granulomas (an aggregation of macrophages) in the lymphatic system. Although tuberculous infection will never become active in the majority of such cases, 5% will develop disease within their lifetime. When the immune system weakens, the previously latent infection becomes active and the individual develops secondary disease (also referred to as endogenous reactivation). Typically, this is observed during old age. However, other concomitant illnesses/conditions impairing the body's defences e.g. poorly controlled diabetes, liver/renal disease, and human immunodeficiency virus (HIV) for example, may increase the risk of infection developing into disease (Joint Tuberculosis Committee of the British Thoracic Society, 1998). Whereas an otherwise healthy infected individual has a 1 in 10 chance of developing active disease over their lifetime (Murray, 1989), those co-infected with human immunodeficiency virus HIV have a 50% probability of developing disease (Selwyn *et al.*, 1989).

Finally, one episode of tuberculosis does not negate the possibility of developing disease on another occasion (Orme *et al.*, 2001). Disease can recur, and may be attributable to relapse with the same strain of *M. tuberculosis* causing the initial infection. Alternately, subsequent episodes of disease may occur following exogenous reinfection, i.e. once again acquiring tuberculosis from an infected individual. It is possible for this strain to be either the same or different to that responsible for the initial infection (Lambert *et al.*, 2003). In areas where the burden of disease is high, exogenous reinfection contributes considerably

to the overall TB burden (Sonnenberg *et al.*, 2001), whereas relapse is thought to be more common in countries where the incidence of disease is low (less than 10 cases per 100,000 population per annum) (de Boer *et al.*, 2000).

2.1.3 Screening for tuberculosis

Skin testing is the principal tool used to screen for TB in the United Kingdom[2]. This involves administration of purified protein derivative (PPD) tuberculin by intradermal injection to the forearm (Scottish Office Department of Health, 1998). After inhalation of mycobacteria, the body develops a hypersensitive (allergic) reaction and a specific cell-mediated immunity. Subsequent contact with mycobacteria through skin testing can cause a rapid allergic response from the previously primed lymphocytes, and is referred to as tuberculin positivity. This hypersensitivity to modified tuberculoprotein can be detected two to ten weeks after infection (Centers for Disease Control and Prevention, 2000). Two to three days after injection of PPD, a hard, raised formation may develop on the skin surrounding the site of injection. The result of the skin test is interpreted by measuring the diameter of the induration, along with information on the individual's BCG and immune status. A strongly positive reaction of 15mm or greater may indicate the presence of active disease, while a positive result (induration of 6-14 mm) may indicate past infection or previous BCG vaccination.

Despite being in use for nearly one hundred years after its development, the skin test is not a perfect screening tool. Firstly, infection with environmental mycobacteria and prior BCG vaccination may lead to a positive skin test result, although the individual may not be infected with *M. tuberculosis*. In addition to this false positive reaction, a negative skin test reaction may be detected in an individual infected with *M. tuberculosis*. One reason for this result is the disappearance or reduction of the delayed-type hypersensitivity response, a condition commonly referred to as anergy. Typically, this occurs in those with overwhelming disease, HIV and other viral infections, or those with other conditions that result in an immunocompromised state. Furthermore, skin test results can be influenced by a phenomenon known as "boosting". Individuals infected with *M. tuberculosis* many years in the past may have a negative initial skin test reaction as a consequence of a weakened hypersensitivity to tuberculoprotein. However, this initial skin test may stimulate their ability to react to tuberculin, and subsequent testing may result in a positive reaction. This

[2] Mantoux testing is the skin test recommended for use in the United Kingdom. Prior to May 2005, Heaf testing was also undertaken, however this method of skin testing ceased because of the discontinuation of tuberculin PPD production by Chiron Vaccines Evans (Scottish Executive Health Office, 2005b).

positive reaction to the second test indicates either past infection or prior BCG vaccination (Centers for Disease Control and Prevention, 2000). Boosting becomes more frequent with increasing age. Chest x-ray provides an alternative to tuberculin skin testing, and are often used to screen for TB where false positive or false negative skin test results are likely. On x-ray film, active tuberculosis disease can be detected by the presence of white nodules or cavitating lesions in the lungs, which are filled with bacilli.

Patients with pulmonary cavities are usually "smear positive", that is to say, when there are more than 5000 bacilli per millilitre of sputum, the presence of bacilli is detectable by microscopic examination of a sputum smear. On this basis, patients can rapidly be diagnosed with tuberculosis, although the gold-standard for confirming a case of tuberculosis is on the basis of culture, i.e. growing *M. tuberculosis* from a patient specimen (World Health Organization *et al.*, 2002).

2.1.4 Treatment

A multi-drug regimen comprising isoniazid, pyrazinamide, rifampicin and ethambutol for the first two months, and rifampicin and isoniazid for the following four is recommended for treating a standard pulmonary case of active tuberculosis in the United Kingdom (Joint Tuberculosis Committee of the British Thoracic Society, 1998). Quadruple drug therapy is recommended, as this lessens the opportunity for the development of drug resistance.

In addition to the provision of an appropriate drug regimen, compliance with treatment is critical to successful treatment outcome. TB treatment can be unsuccessful, largely as a consequence of the prolonged treatment period. The duration of treatment is between 6 and 24 months, and because individuals start to feel well very shortly after commencing treatment, there is a tendency to abdicate from treatment, long before the infection has been excluded from the body. In specific patient populations, particularly the homeless population and individuals with excessive alcohol consumption, compliance with treatment is a significant challenge. To this end, the WHO have advocated DOT (direct observed therapy) as a means of encouraging full adherence to treatment. This strategy requires health professionals to observe patients taking their medications (Joint Tuberculosis Committee of the British Thoracic Society, 1998).

Patients with latent infection can be offered chemoprophylactic (CPX) treatment, to prevent the progression of infection to active disease. Usually, CPX is offered to those under 16 years of age in the United Kingdom, and the regimen consists of isoniazid for six

months or isoniazid and rifampicin for three months (Joint Tuberculosis Committee of the British Thoracic Society, 1998). However, the value of chemoprophylactic therapy is contested, particularly as only 5% of individuals with latent infection will develop active disease, and drugs such as isoniazid are known to have hepatotoxic effects (Nolan *et al.*, 1999).

2.2 Patterns of disease

TB was declared a global emergency in 1993 in response to a marked reversal of a previously steady decline in case numbers. Targets were proposed to reduce the incidence of disease (World Health Organization, 1994), and reports monitoring global progress towards these goals have determined that the previously increasing incidence of TB has begun to slow, and between 1990 and 2003 a rate of increase of 1% per year was observed. If this trend was to continue, the number of individuals diagnosed is forecast to reach 10 million in the year 2015 (Dye *et al.*, 2005).

2.2.1 Recent global trends

The burden of disease disproportionately affects those in the developing countries as a consequence of prevailing social, economic and political conditions, and inequalities in access to healthcare (Nunn *et al.*, 2002). The disparity between the burden of disease in developed and developing countries is evident. With 659 cases diagnosed in every 100,000 of the Zimbabwe population, this country had the highest rate of TB incidence in the world in 2003 (World Health Organization, 2005b). This contrasts markedly with an incidence rate of 7.4 TB cases per 100,000 in Scotland in the same year.

Progress in reducing the incidence of disease across the globe has been variable. While decreases have been observed since 1990 in Central Europe and Latin America, incidence rates in Eastern and Southern Africa and Eastern Europe have been increasing (Dye *et al.*, 2005). Since 1990, case notifications have increased at a rate of 10% per year in Sub-Saharan Africa (Dye, 2000). The spread of human immunodeficient virus (HIV) has had a significant impact on this trend, as increasing rates of tuberculosis have been attributed to co-infection with HIV (Churchyard *et al.*, 1999, Raviglione *et al.*, 1997). In 1997, one-third of all TB cases in Africa were co-infected with HIV, and this is thought to have contributed to the rate high case fatality observed (34% of TB cases) (Dye *et al.*, 1999). Indeed, TB is the leading cause of death among HIV patients in Sub-Saharan Africa (Colebunders & Lambert, 2002).

In Europe, regional rates of incidence are diverse, with greater incidence of disease reported in Eastern Europe per year than in Western European countries[3] (Dye *et al.*, 1999). In Eastern Europe, particularly in countries of the former Soviet Union, the resurgence in tuberculosis has been associated with the development of drug resistance, which usually develops as a result of poor compliance with treatment, or poor clinical management (Horsburgh, 2000). Transmission of drug resistant strains of *M. tuberculosis*, particularly in prisons, has also been observed (Dye *et al.*, 2005). Transmission of multi-drug resistant tuberculosis (MDR TB) is particularly problematic in Kazakhstan, Estonia and Latvia, where an increasing proportion of multi-drug resistant cases are being detected (World Health Organization, 2005a). In contrast, the decline in annual case notifications has slowed in Western countries in recent years. It has been suggested this is due in part to a demographic shift of disease to the elderly population, who are more likely to suffer endogenous reactivation of a latent infection acquired in the past (Styblo, 1984). It is recognised that these low-burden countries are faced with importation of infection and disease from high prevalence countries (possibly resistant to anti-tuberculosis drugs), deteriorating TB control services, the loss of expertise as the disease become less common, and the emergence of high-risk populations e.g. HIV infected and homeless individuals for example (World Health Organization *et al.*, 2002). Just as TB is more prominent in developing than in developed counties due to poor socio-economic conditions, such conditions also mean the more deprived populations in low-incidence countries are at risk of disease (Moore-Gillon, 1998).

2.2.2 United Kingdom

Since formal statutory notification through the Notifications of Infectious Diseases (NOIDs) system commenced in England and Wales in 1912 (McCormick, 1993), and 1914 in Scotland (Scottish Office Department of Health, 1998), declining rates of mortality and morbidity have been generally been observed. A combination of improved socio-economic conditions (such as better housing and the reduction of overcrowding) and biological factors (e.g. improved nutrition, the introduction of chemotherapeutic drugs, BCG immunisation programme, and mass radiographic screening) were believed to accelerate the decline of TB in the latter half of the twentieth century (Evans, 1998).

However, this pattern of decline was reversed in the late 1980s. After the lowest figure of notifications was recorded in 1987 (5745 cases), the UK experienced a resurgence of TB.

[3] With the exception of Spain and Portugal.

In England, case numbers increased by 25% between 1992 and 2002 (Department of Health, 2004), while in London, case notifications increased by 71% between 1988 and 1998 (Rose *et al.*, 2001). This changing trend was characterised by declining case notifications in the indigenous population and the increasing incidence rates among ethnic groups (Rose *et al.*, 2001). In 2003, seventy percent of cases diagnosed in England, Wales and Northern Ireland were born outside the United Kingdom, of which individuals born in India, Pakistan, Bangladesh and Africa made a significant contribution. Just over one quarter of cases (26%) were of White ethnic origin (French *et al.*, 2005). By comparison, three quarters of cases in Scotland were of Caucasian ethnicity, and disease in non-UK born individuals comprised a far smaller proportion of the TB population (24%) in the same year (McMenamin & Johnston, 2004). Furthermore, in England, Wales and Northern Ireland, the increasing burden of non-UK born individuals is thought to have contributed to a rise in cases observed in the 15-34 year age cohort. Meanwhile, the incidence rate of TB per 100,000 in the indigenous population aged 60 and over has decreased.

In October 2004, the Department of Health for England, Wales and Northern Ireland published an action plan, which outlined measures to tackle the threat posed by TB to public health. The long-term goals of this national programme to control TB were based on the principles of reducing the risk of acquiring infection, the provision of appropriate and complete treatment, and maintaining low levels of resistance to anti-TB drugs (Department of Health, 2004). Strategies for the reduction of disease incidence control will be addressed in greater detail in section 2.4.

2.3 New insights into recent transmission of *M. tuberculosis*

In recent years, the development of molecular genotyping techniques has provided a new insight into the aetiology and transmission of disease, by means of discerning and differentiating between *M. tuberculosis* strains. This has proved useful in gaining an understanding of modern *M. tuberculosis* transmission dynamics, and evaluating current efforts to control tuberculosis.

2.3.1 IS*6110* RFLP typing

Prior to the availability of molecular typing techniques, bacteriophage typing and comparison of antibiotic susceptibility patterns were used in epidemiological investigation to understand transmission patterns, but had significant limitations (Gruft *et al.*, 1984). Strain differentiation was greatly enhanced when variable repetitive elements of DNA

were first detected on the single circular *M. tuberculosis* genome in 1988 (Eisenach *et al.*, 1988). One such DNA sequence, insertion sequence (IS) *6110*, was immediately recognised as being useful for strain differentiation. When applied to outbreak investigations (Daley *et al.*, 1992, van Soolingen *et al.*, 1991), IS*6110* was found to be sufficiently variable within a population of TB cases, yet was relatively stable over time, enabling strains with the same identity to be found in multiple individuals. In one study, the spread of infection between residents in a facility for HIV-infected individuals was supported by the fact individuals were infected with a single strain (Daley *et al.*, 1992). Methods of visualising IS*6110* were subsequently developed using restriction fragment length polymorphism (RFLP) typing (colloquially known as DNA fingerprinting). To ensure IS*6110* RFLP typing patterns from different patients were comparable, a standardised technique was developed (van Embden *et al.*, 1993).

M. tuberculosis DNA contains between 1 and 25 copies of IS*6110* (although no copies are occasionally observed), which vary in location along the genome (van Soolingen, 2001). Studies have estimated that the half-life of an IS*6110* pattern is three to four years, which infers that half of IS*6110* RFLP patterns observed over such a period of time will remain stable (i.e. not undergo evolutionary change) (de Boer *et al.*, 1999). On this basis, RFLP patterns with an identical number of IS*6110* copies, appearing at the same location along the *M. tuberculosis* genome are considered genetically indistinguishable. Epidemiologically linked cases with genetically indistinguishable IS*6110* RFLP patterns are thought to have derived from a single transmission pathway, with infection having been recently acquired from one another, or from a common ancestral source (recent transmission). Such cases are referred to as clustered cases.

During a period of observation, strains of *M. tuberculosis* can often only be detected once. Cases infected with such strains are considered to have unique IS*6110* RFLP patterns. As no other individual has the same IS*6110* RFLP pattern, it is unlikely the patient acquired disease from another individual within the observed study population. Instead, infection was probably acquired from an individual outwith the study population. Molecular epidemiological studies have suggested a proportion of such individuals represent instances of reactivated latent infection, which may have been acquired many years in the past[4]. A unique IS*6110* RFLP pattern detected in a individual entering the country for the

[4] Published studies have arbitrarily defined the time period in which recent transmission can occur as up to a maximum of five years. Transmission occurring over a more extended time frame is referred to as remote transmission (Cronin *et al.*, 2002, Jasmer *et al.*, 1999, Vynnycky & Fine, 1997).

first time may represent the introduction of a strain into the pool of indigenous *M. tuberculosis* strains (Godfrey-Faussett, 1998, van Soolingen, 2001).

However, there are important caveats to the interpretation of clustering on the basis of infection with genetically indistinguishable IS*6110* RFLP patterns. Firstly, the ability to predict the existence of an epidemiological association on the basis of clusters of cases sharing the same molecular genotyping may be imprecise. In a rural Arkansas population, despite identifying a cluster of cases infected with a genetically indistinguishable IS*6110* RFLP pattern, either no epidemiological links were detectable, or epidemiological links existed only in the distant past (Braden *et al.*, 1997). It was postulated that this cluster of cases did not represent the occurrence of recent transmission, rather cases acquired infection in the past, and progression to active disease happened to occur many years later, within the study observation period. This study highlighted the necessity to validate molecular typing information with epidemiological information (using conventional epidemiological methods) to determine associations on the basis of shared time, place or person (i.e. epidemiological links).

Secondly, accurate identification of clustered cases is based on the premise that a large proportion of the cases diagnosed in the period of observation are available for evaluation. This requires genotyping to be conducted for the vast majority of cases. Indeed, this can be problematic, as current genotyping techniques can only be undertaken for patients' whose specimens were successfully cultured. Also, the period of observation for molecular epidemiological studies need to be sufficiently extensive to allow time for disease to develop in newly infected individuals (Glynn *et al.*, 1999).

For many years, comparative analysis of IS*6110* RFLP patterns has been the gold-standard technique for strain differentiation. However, when RFLP patterns contain five or less IS*6110* copies (low IS*6110* copy number strains of *M. tuberculosis*), the discriminatory power of the comparative method is reduced. As such a comparative analysis will be based on fewer polymorphic regions of the genome, there is a reduced likelihood of detecting differences between RFLP patterns. In such instances, sub-typing techniques are employed, and in Scotland, Spoligotyping can be undertaken. This technique focuses on a different polymorphic region of the genome, and is more discriminatory for *M. tuberculosis* strains with low, rather than high IS*6110* copy numbers (RFLP patterns with 6 of more copied of IS*6110* are considered to have a high copy number pattern).

More recently, polymorphism in a number of tandem repeat sequences on the *M. tuberculosis* genome has led to the development of a new genotyping technique. Typing of such tandem repeat sequences at fifteen different loci, known as mycobacterial interspersed repetitive units (MIRU), is proving to be as discriminatory as IS*6110* RFLP typing. It is rapid and less labour intensive, and circumvents many of difficulties associated with the current typing technique (Hawkey *et al.*, 2003). In early 2006, MIRU-VNTR typing was phased into operation in the Scottish Mycobacterial Reference Laboratory (SMRL), replacing IS*6110* RFLP typing and Spoligotyping (personal communication, Dr F.X.S. Emmanuel, Director of the SMRL).

2.3.2 Modern *M. tuberculosis* transmission dynamics

Studies identifying clusters of cases thought to be representative of recently transmitted infection, have provided great insights into the aetiology and modern transmission dynamics of tuberculosis. Prior to the availability of molecular genotyping information, ninety percent of TB cases in developed countries were thought to be due to infection acquired many years in the past (reactivation of latent infection) (Styblo, 1984). However, population-based molecular epidemiological studies in low-incidence countries indicated recent transmission caused more disease than previously suspected. On the basis clustered cases represent the occurrence of recent transmission, studies have been conducted in urban areas of the United States and Europe, and have reported on average 43% of cases are found in clusters (Alland *et al.*, 1994, Bauer *et al.*, 1998, Small *et al.*, 1994, van Soolingen *et al.*, 1999). In other low-incidence settings such as London, the proportion of clustered isolates was found to be lower between 1995 and 1997, and here authors proposed that the reactivation of previous infection and importation of infection by new entrants played a more significant role in the aetiology of disease (Maguire *et al.*, 2003). In Scotland, the first nationwide comparative analysis of IS*6110* RFLP patterns is underway, and an estimate of disease due to recently transmitted infection will be determinable in due course (personal communication, Dr. K Forbes, Senior Lecturer, Dept of Microbiology, University of Aberdeen).

Secondly, molecular epidemiological investigations have highlighted that transmission between casual contacts is occurring with increasing frequency. The long-held belief that TB only spreads as a consequence of contact, typically between household and/or family members, is being challenged. Indeed, transmission has not only been documented in institutional settings such as hospitals, prisons and hostels for the homeless, but in the community, in social and workplace settings (Barnes *et al.*, 1997, Golub *et al.*, 2001). In a

Minneapolis public house, a highly infectious homeless index case frequented a bar, and the subsequent investigation determined 14% of screened contacts at that location had active TB (Kline *et al.*, 1995). Factors favouring transmission in these locations include overcrowding, lack of ventilation, the aggregation of susceptible individuals, sustained exposure to an infected case and the virulence of the infecting strain.

The environment in which mycobacteria are expelled influences rates of transmission, as does the clinical characteristics of the source case, the immunity of the contact and the virulence of the strain. Traditionally, medical thinking has contended close, prolonged contact, characteristic of family/household members as mentioned above, is required for transmission to occur. Indeed, transmission of *M. tuberculosis* during a eight-hour long-haul flight has been reported (Kenyon *et al.*, 1996). In the absence of standardised definitions for type, duration and closeness of contact in guidelines for contact tracing in Scotland, contact tracers work under the assumption that close contact involves spending a cumulative total of eight hours a day, on a regular basis, with an infected case (Scottish Office Department of Health, 1998). However, identification of clusters by molecular genotyping has instigated retrospective epidemiological investigations, which have resulted in the detection of previously unrecognised outbreaks between cases with limited contact (Barnes *et al.*, 1997, Fitzpatrick *et al.*, 2001, Valway *et al.*, 1998). In one Texas study, contact between clustered cases occurred in workplace settings, labour pools and public houses. Exposure to infected cases was so minimal that photographs were required to facilitate the identification of contacts, as full names of photographed cases often eluded study participants (Weis *et al.*, 2002). Identifying the social network of cases, by tracing social connections in the community, identifying high-risk contacts and potential sites of exposure has proved a useful way of determining epidemiological links between contacts that have had minimal exposure to a case (Klovdahl *et al.*, 2001).

M. tuberculosis is predominantly spread by pulmonary cases, and traditionally sputum smear negative (bacilli in sputum undetectable by microscopic examination) cases have been considered less infectious. However, a study in Vancouver revealed that sputum smear negative cases were the source of disease transmission for one in every six clustered cases (Hernandez-Garduno *et al.*, 2004). This supports earlier work conducted by Behr *et al.* (Behr *et al.*, 1999), which pointed out that although sputum smear positive contacts are more infectious than their smear negative counterparts, they should not be considered non-infectious. Of course it is quite possible that smear negative cases were smear positive earlier on in their disease, prior to diagnosis (Davies, 2004). Hernandez-Garduno *et al.* also proposed that non-pulmonary cases could have facilitated the spread of *M.*

tuberculosis, but it was not possible to determine whether disease was acquired from a non-pulmonary site, or whether pulmonary involvement had not been recognised. Furthermore, historical data suggests 20-25% of untreated pulmonary TB cases recover spontaneously, and transmission of *M. tuberculosis* before this occurs may also play a role (Davies, 2004).

2.4 Control of tuberculosis

Like many other low-incidence countries, active case finding within the general population has become impractical due to the large number of cases to be screened, and the low resulting yield makes this practice cost ineffective. Nowadays, active screening is performed in specific populations (clearly defined by national experts on the basis of local epidemiology) where the incidence of disease is found to be higher than that of the general population.

2.4.1 Contact tracing

Testing individuals in contact with a case of TB has proven to be an effective approach to active case detection. The yield of new tuberculosis cases from contact screening in the United Kingdom has historically averaged 1% (Ansari *et al.*, 1998, Irish *et al.*, 1997). Typically, 10% of all notified cases are diagnosed as a result of contact tracing, as opposed to self-presentation to the health services (Ormerod, 1992, Teale *et al.*, 1991).

The approach to prioritising contacts for screening is based on a concentric circle approach (also known as the stone in the pond principle), where consecutive theoretical concentric circles contain contacts, and radiate out from the index (or newly diagnosed) case (Veen, 1992). These circles represent the proximity and frequency of contact with the source case, allowing prioritisation of contacts for investigation. Close contacts of a newly diagnosed TB case would be present in the concentric circle immediately next to the index case.

As cases with pulmonary disease have the greatest potential to be infectious, contact tracing is mainly focussed on contacts of such individuals. The duration of symptoms provides an estimate of the period of infectiousness, which is used to restrict the contacts requiring screening to those in contact with the case in that time period. If unknown, contact investigations include those associating with the case within three months prior to diagnosis (Joint Tuberculosis Committee of the British Thoracic Society, 2000).

Secondly, the degree of infectivity determines whether screening should be offered to those in closest proximity to the patient, or is extended to less proximal contacts. Infectivity is likely to be at maximum when the patient is sputum smear positive (that is to say bacilli are detectable in a patient specimen on the basis of microscopy).

In the UK, contacts are designated close or casual contacts following consideration of their proximity to the TB case and the duration of the exposure. Traditionally, family members of those living in the same accommodation are deemed close contacts, whereas work or recreational associates are considered casual contacts. In accordance with UK guidance, close and casual contacts of a sputum smear positive case require screening, while screening is required for close contacts only of sputum smear negative cases, due to the reduced risk of infection (Joint Tuberculosis Committee of the British Thoracic Society, 2000). Generally, the decision to screen casual contacts is determined by the yield of disease in close contacts, and is guided by the prevalence of disease in the community and known susceptibility of the contacts (e.g. children or immunosuppressed adults would be prioritised for screening).

2.4.2 Contact tracing failures

Recently, molecular typing information has provided opportunities to evaluate the success of contact tracing in interrupting the transmission of *M. tuberculosis*. By comparing clusters of cases defined by IS*6110* RFLP typing information with findings from contact tracing identifying epidemiological linkage between cases, only a small proportion of cases clustered on the basis of molecular typing information were linked by epidemiological information. In the United States, 10% of cases with matching *M. tuberculosis* strains were also linked on the basis of contact tracing information (Alland *et al.*, 1994, Small *et al.*, 1994). As has been previously highlighted, unsuspected transmission has been occurring between casual contacts, and using current approaches to contact tracing, such associations cannot be detected.

Furthermore, studies have been undertaken to determine whether contact tracing is truly interrupting transmission pathways, by comparing IS*6110* RFLP patterns of epidemiologically linked cases (Behr *et al.*, 1998, Bennett *et al.*, 2002, Sun *et al.*, 2002). In a San Francisco study, in nearly one third of instances where contacts were diagnosed with TB as a result of contact tracing, they were infected with a different strain to that infecting the index case, i.e. the case for whom they were screened as a contact. This is possibly due to the fact the secondary case is a reactivation of latent infection, which

occurred during the period in which contact tracing was being undertaken, or the case recently acquired their infection from an unidentified source.

The finding that high proportions of TB cases in many low-incidence countries are due to recently transmitted disease indicates strategies to impede the transmission of *M. tuberculosis* are failing. It has been suggested that patient behaviour contributes to the continued transmission of tuberculosis. In particular, studies have described patient delay in presenting to medical services, and have shown contacts fail to be identified for the purposes of contact screening (Chin *et al.*, 2000, Cronin *et al.*, 2002). The contribution of patient behaviour to ongoing transmission of *M. tuberculosis* in Glasgow will be examined in this thesis. To this end, patient interviews are undertaken to explore the ways in which patients' understanding of disease transmission and experience of ill health can influence the outcome of contact tracing.

2.4.3 The influence of cultural factors on TB control

Epidemiological analysis provides useful information about patterns of disease, and identifies associations between disease and attributes of infected individuals, or risk factors. However, it is recognised that a disparity exists in the way the public and medical professions interpret information about health risks. The difference between 'illness', as patients view their ill health, and 'disease' as viewed by the medical profession, have long been recognised (Helman, 1985). Whereas the medical definition of ill health is usually based on physical changes in the body's structure or function, and quantified by comparison to normal physiological measurements, the patient perspective involves understanding the social, cultural and psychological dimensions of ill health. It is the latter that shapes the meaning of ill health for the individual patient and those around him/her (Herzlich, 1973). Indeed, a wealth of literature exists that addresses doctor and patient perspectives of ill health, and which describes the differences between these beliefs, and attempts to identify ways to bridge these disparate perspectives in order to ensure effective communication between both parties.

A useful way of looking at the process of ill health is to understand the way in which patients interpret and treat their personal experiences of sickness. In a process of interpretation known as 'lay epidemiology', private and public experiences, observation, information from various sources (e.g. media, books) are used by patients to interpret illness and death (Frankel *et al.*, 1991). By examining experiences of ill health, it is possible to gain insights into the cultural factors that influence the way in which patients

assign meaning to these events. The importance of understanding this cultural component of ill health for disease prevention (and for tuberculosis, interruption of transmission) is clear. For example, studies enhancing our understanding of TB cases viewpoint and attitudes have enabled patient illness behaviour to be rationalised. This has led to the identification of barriers to rapid case detection, which are known to include delayed patient presentation to medical services and failure to identify contacts for contact tracing (Chin *et al.*, 2000, Cronin *et al.*, 2002).

Understanding cultural factors that influence patients understanding of infection and the route patients take to reach diagnosis is important for TB control. Although calls have been made for further research into social and cultural reasons for patient non-compliance for example (and therefore TB control), this area has received little attention. Literature searches indicate the existence of some published articles, however a small proportion of these relate to developed countries, or countries with a low incidence of tuberculosis.

In 1995, a study conducted by Singh-Bakhshi *et al.* provided baseline information pertaining to patients' attitude and knowledge of tuberculosis in the United Kingdom (Birmingham). It highlighted the complexity of patient beliefs and indicated a difference in baseline knowledge between Caucasian cases and cases of ethnic origin. An association was detected between knowledge and awareness of symptoms (how patients perceived the threat of disease, its frequency in the population, and the outcome from illness) and seeking medical assistance. The authors postulated that when tuberculosis is perceived as a common, predictable and non-threatening disease, individuals will be more likely to seek assistance. Although the authors believed that gaining an understanding of patient attitudes required addressing issues of social rejection and social stigma, these issues were not important in case management/contact tracing. These issues will be explored further in this research project.

2.5 Local epidemiology and TB control arrangements

In Scotland, cases of TB have been statutorily notifiable to the NOIDs scheme since 1914, and to the Enhanced Surveillance of Mycobacterial Infections (ESMI) scheme since 2000. Whereas the NOIDs scheme facilitates rapid feedback of a minimum dataset of information for use in outbreak investigations, the ESMI scheme gathers detailed

information to allow precise descriptions of trends in TB epidemiology over prolonged periods of time. To date, five full years of ESMI data have been accumulated[5].

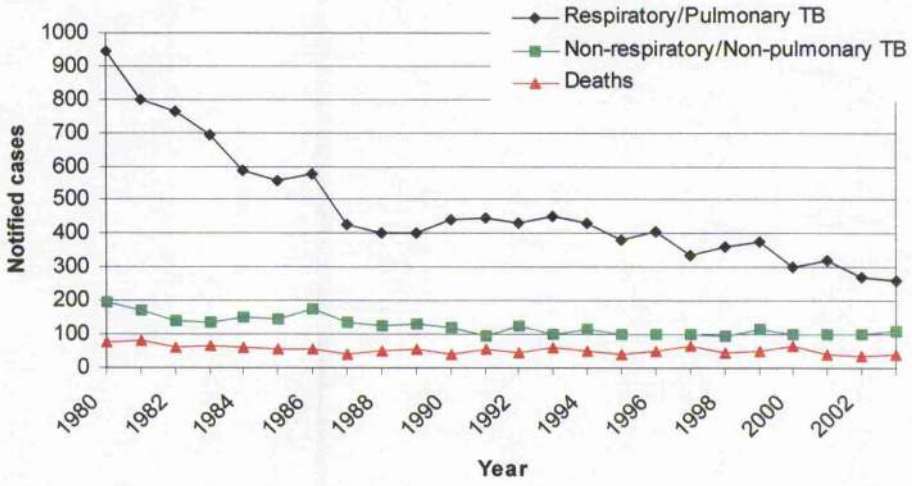

Figure 2: TB notifications in Scotland, 1980-2003*

Source: Information & Statistics Division (ISD) of the NHS: data for 1990-1999 from Statutory Notifications of Infectious Diseases (NOIDs). Health Protection Scotland: data from 2000-2003 sourced from ESMI. * 2003 ESMI figures are provisional.

At present, between 400 and 500 new cases of TB are diagnosed annually. Although tuberculosis in humans is primarily a pulmonary disease, mycobacteria can spread through the vascular and lymphatic system to other parts of the body, where they can cause infection in any body tissue. Approximately two thirds of TB cases in Scotland have pulmonary disease, with one third of cases affecting other parts of the body (McMenamin & Johnston, 2004). Classic symptoms include a cough (of 3 or more weeks duration), chest pain, and haemoptysis (production of bloodstained sputum). Disease in non-pulmonary sites tend to produce symptoms particular to the body system affected. Fever, chills, loss of appetite, weight loss, night sweats and fatigue are symptoms common to cases of pulmonary disease (Centers for Disease Control and Prevention, 2000). In Scotland, non-pulmonary TB is most commonly diagnosed in the lymph nodes and pleural cavity (McMenamin & Johnston, 2004).

Each year, tuberculosis is the cause of death for approximately 350 cases in the United Kingdom (Department of Health, 2004), while TB is the cause of, or contributes to death in about 40 cases in Scotland annually (McMenamin & Johnston, 2004).

[5] A detailed description of operational aspects of the ESMI scheme is provided in chapter 3.

The stability of case notifications in low-incidence European countries like Scotland is thought to be due to a rise in incidence in the elderly population since 1980 (Duffield *et al.*, 1996, Springett, 1991). While the proportion of respiratory cases in the over 65 age cohort increased, cases in all other age cohorts decreased or became static (Duffield *et al.*, 1996, Scottish Centre for Infection and Environmental Health, 2000). In 2002, over one quarter of cases in Scotland were aged over 65 years (McMenamin & Johnston, 2004).

The epidemiological profile of tuberculosis in Scotland differs in some respects to that observed in the rest of the United Kingdom. Whereas TB has been increasing in England, Wales and Northern Ireland since 1987, cases have plateaued or declined slightly in Scotland (see figure 2) (Scottish Office Department of Health, 1998). As previously indicated (see section 2.2.2), one such notable difference exists in the ethnicity and birthplace of the TB population. Whereas two-thirds of cases in England and Wales were born outside the United Kingdom, non-UK born individuals represent a smaller proportion of cases notified in Scotland (approximately 25 to 30%). It is thought this is not the case in Scotland because of relatively stable population dynamics (Duffield *et al.*, 1996).

In Scotland, cases are disproportionately distributed, with most cases detected in urban centres such as Glasgow. Despite the fact that notified cases in Scotland have decreased slightly over the years, the number of cases in Glasgow has remained static (between 150 and 200 cases annually). In effect, the annual contribution of Glasgow cases to the TB population in Scotland increased from 28% in 1993, to 50% in 2002 (figure 3). Higher proportions of cases are found in urban centres firstly because this is where impoverished areas are likely to be found, and also new entrants to the country often settle in central belt areas or major academic centres (Scottish Office Department of Health, 1998). The higher population density in urban areas is thought to support the ongoing transmission of disease, while tuberculosis in rural areas may be due predominantly to the reactivation of latent infection (King, 2002).

In low-incidence countries, the emergence of groups at high risk of infection and disease is a recognised threat to the control of TB. In Scotland, information gathered through the ESM1 scheme has provided valuable information about high-risk populations, indicating that alcohol misuse and homelessness are particularly important factors. Many of such cases reside in urban centres such as Glasgow, Lothian and Lanarkshire. Socio-economic deprivation is perhaps the greatest risk factor for infection in Scotland (Hadjichristodoulou *et al.*, 2001, Patel, 1985). A recent study determined the most deprived patients were

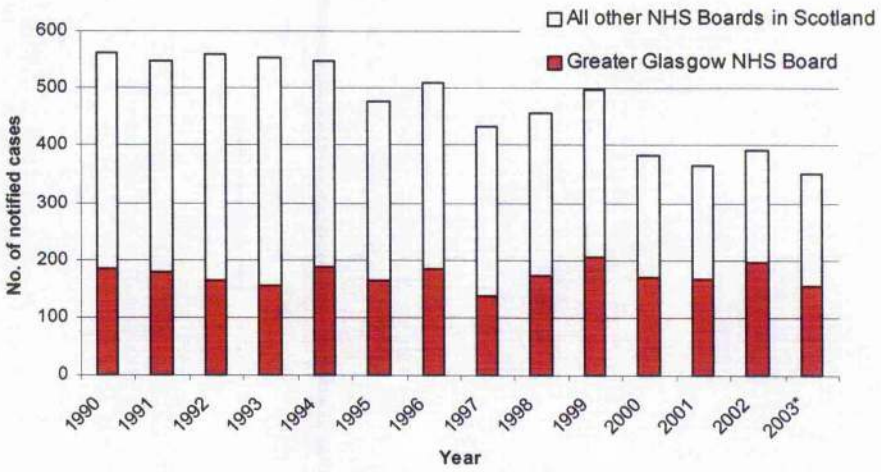

Figure 3: TB notifications in Greater Glasgow NHS Board and all other NHS Boards in Scotland, 1990 – 2003*

Source: Information & Statistics Division (ISD) of the NHS: data for 1990-1999 from Statutory Notifications of Infectious Diseases (NOIDs). Health Protection Scotland: data from 2000-2003 sourced from ESMI. * 2003 ESMI figures are provisional.

mostly located in the Glasgow area. A typical patient in this category was male, under 65, white-Caucasian, and born in the United Kingdom (King, 2002).

Although multi-drug resistance and HIV co-infection are recognised as a global threat, these factors currently have a limited impact on TB epidemiology in Scotland. Between 2000 and 2003, a maximum of three cases with multi-drug resistant tuberculosis were detected annually, and had been imported from high prevalence countries. Transmission of MDR-TB in Scotland has not yet been observed (personal communication, Dr J. McMenamin, Consultant Epidemiologist, Health Protection Scotland). In Scotland, HIV testing is not routinely undertaken for newly diagnosed TB cases, and the HIV status of cases is not required information for the ESMI surveillance scheme. A recent research project linking TB and anonymous HIV databases revealed that 2.7% of TB cases notified to the ESMI scheme between 2000 and 2002 were co-infected with HIV (Wilson, 2004).

2.5.1 Control of TB in Glasgow

The purpose of TB control is to "*reduce mortality, morbidity and transmission of the disease until it no longer poses a threat to public health*" (World Health Organization, 1994). The basis of TB control is prompt case identification, to reduce the period in which an infected individual can pass *M. tuberculosis* to others (Styblo, 1984), and treatment to cure, which minimises the risk of emerging drug-resistance that can occur as a result of

inadequate or inappropriate drug therapy (Weis *et al.*, 1994). Contact tracing, whereby contacts of a newly diagnosed case are identified and offered screening, is the principal TB control strategy in Scotland, as in other low-incidence countries. Its function is to detect new TB cases, those with TB infection, and those not infected but eligible for BCG vaccination (Joint Tuberculosis Committee of the British Thoracic Society, 2000).

In Glasgow, there has also been a long tradition of active case detection, and in the past this control strategy has taken the form of chest x-ray screening programmes. In the 1950's, a mass miniature radiographic campaign was launched to screen the general population (Glasgow Corporation, 1957). Today, chest x-rays remain an important tool and are often used in screening exercises in high-risk populations i.e. the homeless (Patel, 1985). However, as in the rest of the United Kingdom, the Mantoux test is currently the principal tool used to screen for TB in Scotland (see section 2.1.3). Currently in Glasgow, this is with the exception of TB contacts eligible for screening and aged 50 years and over. Such contacts are offered screening by chest x-ray. This action is taken to reduce the likelihood of a false negative result from a skin test, which increases with old age (personal communication, Dr S. Ahmed, Consultant Epidemiologist, Greater Glasgow NHS Board). In keeping with UK guidance, diagnoses of TB are confirmed bacteriologically wherever possible. In Scotland, local laboratories make diagnoses on microscopy and culture, while the Scottish Mycobacterial Reference Laboratory (SMRL) additionally undertake sensitivity testing and strain identification.

In Scotland, the majority of cases present to medical services when they experience symptoms. Between 2000 and 2003, 83% of cases were detected in this manner[6]. Contact tracing therefore detects a minority of TB cases, typically in the order of 10% per annum (the remainder of cases detected incidentally, or through BCG schools or immigrant screening programme). In Scotland, each NHS Board public health protection unit is responsible for providing a contact tracing service. In Glasgow, four TB liaison nurses ensure the provision of this service, in addition to other case management duties. With approximately 200 cases detected in Glasgow each year, each nurse manages on average 50 cases per annum. Once a case of TB is diagnosed, a case is referred to the relevant TB liaison nurse, who will ensure contacts are appropriately identified and invited to be screened. Screening is undertaken by nursing staff in accordance with current guidance. However, local protocols or standard operating procedures have not been developed to

[6] Data sourced from the Enhanced Surveillance of Mycobacterial Infections scheme, May 2005.

instruct contact tracing in Glasgow, therefore each nurse adapts guidelines according to the situation at hand and in keeping with their own previous experience.

Whole-blood assay tests for TB are now commercially available for diagnostic purposes. As they offer greater convenience, ease of administration and may be less expensive than conventional skin testing, they are likely to replace the tuberculin skin test in the future[7]. Two versions of the blood test are available, namely QuantiFERON TB-Gold (Cellestis Ltd, Carnegie Victoria, Australia) and the T SPOT-TB test (Oxford Immunotec, Oxford, England) (Whalen, 2005). Although the testing methods differ slightly, both are based on the premise that interferon-gamma (IFN-γ), a mediator of the immune response, is produced in response to *M. tuberculosis* antigens. Whereas tuberculin skin testing with PPD cross-reacts with antigens found in environmental bacteria and BCG (derived from *M. bovis*), whole-blood assays detect IFN-γ produced in response to antigens ESAT-6 and CFP-10 (early secretory antigenic target 6 and culture filtrate protein 10), which are unique to the *M. tuberculosis* genome. Although still undergoing rigorous testing, the high specificity and sensitivity of this technique make it a potentially useful tool for screening purposes.

Other active case detection strategies employed in Scotland include a programme to screen immigrants at ports of entry into the United Kingdom, the rationale for which is that infected individuals entering the UK are most likely to develop disease within five years of entry (Rose *et al.*, 2001). Until the schools BCG programme was replaced by a selective BCG vaccination policy in 2006[8], schoolchildren aged 10 to 13 years were skin tested prior to administration of BCG. However, screening prior to vaccination is still required for those aged six and over (except in children under six years who were born in/visited a high incidence country for more than a month) (The National Collaborating Centre for Chronic Conditions, 2006), and represents another opportunity to detect infection/disease. The third strategy involves the initiation of screening programmes on an ad-hoc basis within high-risk groups. As has been the case in Glasgow, in response to an unusually high number of infected homeless individuals residing in a given hostel presenting to medical

[7] Guidance published by the National Institute of Clinical Excellence (NICE) in March 2006 in England and Wales recommends use of Mantoux testing followed by IFN-gamma immunological testing for previously vaccinated contacts with a Mantoux induration of ≥15mm, and non-vaccinated contacts with ≥6mm induration (The National Collaborating Centre for Chronic Conditions, 2006)

[8] The selective BCG vaccination programme focuses resources on those at greatest risk of acquiring infection e.g. e.g. babies born into families with a history of TB in a close family member, babies who have lived for more than a month in a country with a high prevalence of TB (>40 cases per 100,000 population) or who have parents or close relatives who originate from such areas (Scottish Executive Health Office, 2005a).

services, a screening initiative was undertaken to reduce the spread of disease between members of this community.

In conclusion, the true extent of TB transmission and the effectiveness of case detection strategies in controlling the incidence of disease in the Greater Glasgow NHS Board area is unknown. This research study therefore seeks to examine barriers to controlling *M. tuberculosis* transmission in the Greater Glasgow NHS Board area. The next chapter (3) describes the methodology used in this investigation.

Chapter 3: Study design & quantitative methods

The selection of research methods for this study was pragmatic. Specific tools were chosen based on their perceived usefulness and appropriateness in answering the research question. Multiple methods were utilised, each with different philosophical and methodological considerations, which are considered here.

Both quantitative (epidemiological analysis) and qualitative methodologies (patient and nurse interviews) were employed in this research study, and as such the methodology is split into two chapters. In this chapter, the overall study design is elucidated, and the quantitative approach taken to analyse molecular epidemiological information and evaluate contact tracing outcomes is described. Interviews with TB nurses and patients were employed to identify the transmission pathway of a particular strain of *M. tuberculosis*, and to examine the cultural underpinnings of patient health beliefs and help seeking behaviours. The latter is described in chapter 4.

3.1 A mixed method approach

Research in social and natural sciences is underpinned by paradigms, which Guba and Lincoln defined as a:

> "basic belief system or worldview that guides the investigation, not only in choices of method but in ontologically and epistemologically fundamental ways" (Guba & Lincoln, 1994)

In this study, positivistic and naturalistic paradigms are combined. A positivistic approach is based on enumeration and cause and effect relationships between measurable variables. Typically associated with natural sciences, this research paradigm underpins quantitative enquiry. Positivistic approaches hold true that only a single reality exists, and that there is an independent relationship between the investigator and those under investigation.

The competing theory of the naturalistic paradigm believes there are multiple constructed realities. These realities are the subjective experience of individuals and can only be examined in that context using qualitative methods. Naturalism holds that the investigator and those under investigation are inseparable, and the investigator becomes part of that reality when they begin to collect data.

Whereas positivism benefits from objectivity and reliability (in that results should be reproducible), qualitative research is considered more of a subjective technique, achieving validity by tapping into people's perceptions of events or experiences. These approaches differ further in that the positivistic paradigm utilises research findings to verify hypotheses in a deductive manner, while the qualitative inductive approach allows the development of theories or concepts (Pope & Mays, 1995). For many years, these approaches were considered incompatible, and both disciplines argued their superiority, debating the strengths of the philosophical assumptions underpinning their research paradigms[9]. Towards the end of the twentieth century, pragmatism prevailed and propounded the integration of both methodologies in one study.

Many models of combined qualitative-quantitative research have been proposed (Tashakkori & Teddlie, 1998). These afford the investigator a more complex study design, and offer advantages of both research techniques for example, an investigator can achieve both valid and reliable results. Firstly, qualitative methods are effective when used as part of a preliminary investigation attempting to provide a description of a little known research topic, and can assist in defining further research questions. Secondly, bias introduced by method selection can be limited when other ways of sourcing data are sought. The combination of qualitative and quantitative research methods also adds depth to an investigation. It allows various aspects of the one topic to be examined, the concordance of results to be tested, and allows further exploration of contradictions or new perspectives that arise (Cresswell, 1994).

In this study, quantitative and qualitative phases were conducted separately, although the quantitative paradigm dominates in this study. To determine whether *M. tuberculosis* transmission is occurring in Glasgow and to describe the epidemiology of cases resulting from recently transmitted infection, characteristics of cases infected with genetically indistinguishable strains are enumerated and analysed using statistical methods (chapter 5). To understand the dynamics of disease transmission, the transmission pathway between cases with a genetically indistinguishable strain of *M. tuberculosis* is traced (a genetically defined cluster of cases is believed to represent recent transmission). Qualitative techniques are used to elicit detailed verbal accounts from infected individuals relating to acquaintances, socio-economic circumstances, and places or types of environment frequented prior to diagnosis, that could explain the continued transmission of this *M. tuberculosis* strain (chapter 6). Detection of epidemiological links using qualitative

[9] Readers are referred to Guba and Lincoln's 1994 text for a complete description of the paradigm wars.

approaches has proven effective in the field of sexually transmitted infection, by enabling investigators to focus on patients' life experience and social behaviour (Power, 2002). Reasons for the continued propagation of a particular strain of TB are examined by exploring patient knowledge, attitudes and perspectives of TB transmission and their experience of ill health (chapters 7 and 8). Again, qualitative techniques are utilised because they are more amenable to investigating meanings attributed to social events and behaviours through the means of contextual data (Pope & Mays, 1995). To complete this investigation of factors contributing to impaired TB control, the effectiveness of the principal strategy for interrupting the spread of disease, contact tracing, is evaluated by measuring the yield of newly identified cases of active TB (chapter 9).

Epidemiological information from the ESMI scheme (maintained by Health Protection Scotland), and molecular typing information from the Scottish Mycobacterial Reference Laboratory (SMRL) informed this research project. In chapter three, detailed descriptions of the epidemiological and molecular typing datasets are provided. The quantitative methodologies used to describe clusters, thought to represent recently transmitted tuberculosis and the evaluation of contact tracing is also described. Chapter four explores the rationale for utilising qualitative techniques, describes the methodology employed to trace the pathway of a recently transmitted strain of TB, and to explore lay epidemiology and patient help seeking behaviour.

3.2 Study population

Although the selection of study populations for each sub-study within this thesis differed (see table 1), all were focussed generally on cases residing within the Greater Glasgow NHS Board at time of diagnosis. Different study populations were used because the aim of each sub-study varied, and populations were appropriately selected to achieve those aims. The Greater Glasgow NHS Board is a district inclusive of the local authority areas of Glasgow City, part of North and South Lanarkshire, part of East Renfrewshire, West Dumbartonshire and part of East Dumbartonshire. In 2004, this NHS Board area had an estimated population of 867,083 (Registrar General for Scotland, 2005). This population was purposively selected due to the fact 46% of cases notified to the ESMI scheme between 2000 and 2003 were diagnosed while resident in this NHS Board area (figure 3, chapter 2). Findings from analyses would therefore be representative of a large proportion of Scotland's TB population. Also, at the beginning of this studentship, one study supervisor was a Consultant in Public Health Medicine (CPHM) in the Greater Glasgow

NHS Board. This ensured access to those providing TB services in that NHS Board, namely TB nurses.

Following the introduction of the ESMI scheme by Health Protection Scotland in January 2000, detailed epidemiological information began to be routinely collected for each notified case. With exceptions, epidemiological information for cases diagnosed from 2000 onwards was analysed in this study. Furthermore, an audit of surveillance information was piloted in the Greater Glasgow NHS Board area prior to this research study (see section 3.3.1). This ensured all known epidemiological information had been collected prior to analysis.

Study populations selected for each of the four sub-studies are described below.

3.2.1 Describing the epidemiology of recently transmitted TB (sub-study 1)

All cases notified and resident in the Greater Glasgow NHS Board area at time of diagnosis (between January 2000 and 11th November 2003) were eligible for inclusion in this sub-study. However, as IS*6110* RFLP typing can only be undertaken for cases with culture positive specimens, in essence culture positive cases were more likely to be included in this study. Estimates about recently transmitted infection could therefore only be made for a proportion of Glasgow cases, for whom IS*6110* RFLP patterns were available.

3.2.2 Describing the social network connection between cases with a genetically indistinguishable genotype (sub-study 2)

TB cases diagnosed in Scotland between January 2000 and 11th November 2003, with a 15 banded IS*6110* RFLP pattern were initially included in this sub-study. These cases were known to be living in the Greater Glasgow and Western Isles, and ethical approval was sought from a Glasgow research ethics committee to undertake patient interviews in this area, therefore Western Isles cases were not invited to interview. However, as the study progressed, previously unrecognised epidemiological links were detected with cases for whom molecular typing information was not always available. The population under investigation was extended to included those diagnosed from 1994 up to mid-2004. Cases diagnosed prior to 2000 were less likely to have genotyping undertaken, as the technique was being introduced to Scotland at that time.

3.2.3 Patient understanding of transmission and help seeking behaviour (sub-study 3)

Sub-study 3's population consisted of cases with the above 15-banded IS*6110* RFLP pattern. Only cases known to have this pattern were invited to participate in an interview, and such cases were diagnosed 2000 to 2004. As previously indicated, ethical approval was only sought from a Glasgow research ethics committee, therefore no Western Isles case was asked to participate in the study.

3.2.4 To evaluate the effectiveness of contact tracing (sub-study 4)

In keeping with guidance available for contact tracing used during the period 2000 to 2003, contact tracing was only required routinely for pulmonary TB cases (Joint Tuberculosis Committee of the British Thoracic Society, 2000). In this sub-study, pulmonary TB cases diagnosed in the Greater Glasgow NHS Board over (2000-2003) were included in this study.

3.3 Epidemiological data

As previously indicated, surveillance of newly diagnosed cases of active TB improved significantly in Scotland following the introduction of the ESMI scheme in 2000 by Health Protection Scotland (formerly known as the Scottish Centre for Infection and Environmental Health - SCIEH). The collection of more detailed information brought the minimum dataset collected in Scotland in line with that of other European countries striving to reduce the incidence of disease (Clancy *et al.*, 1991). Prior to the introduction of ESMI, cases were notified to the statutory Notification of Infectious Diseases (NOIDs) scheme, which gathered limited data relating to demographic and disease details. Although the supplanted surveillance scheme provided valuable information on disease incidence, morbidity and mortality of the disease, detailed information from the enhanced surveillance system allowed better definition of the health problem, as in-depth epidemiological information pertaining to demography, disease, treatment, laboratory, and epidemiology could be collected for each case as a matter of routine. Such information facilitated better description of outbreaks of disease, and populations at risk of infection/progression to disease. Furthermore, enhanced surveillance systems are useful in assisting evaluations of health interventions (e.g. contact tracing) and planning for future health requirements on the basis of current trends/patterns of disease (Centers for Disease

Control, 2001). Importantly, information from the ESMI scheme, particularly information on treatment outcome (see below), can be used to assess progress towards achieving WHO targets for control, which require a detection rate of 80% for sputum smear positive cases, and a cure rate of 70% (World Health Organization, 1994).

Figure 4 charts the flow of required information from individuals responsible for notifying the disease to Health Protection Scotland (HPS), where the national database is maintained. The ESMI scheme operates a paper-based system, whereby clinicians or nurses record required patient information on a set of three surveillance forms; form A, B and C. Form A is completed when a patient is suspected to have TB, and treatment commences.

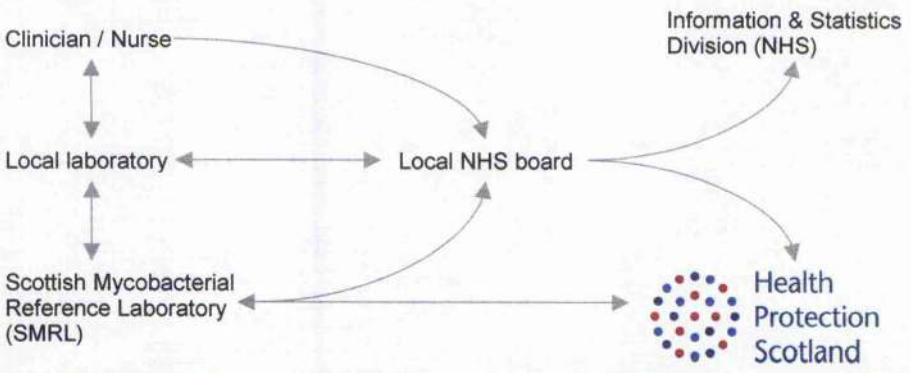

Figure 4: Flow of patient information through the Enhanced Surveillance of Mycobacterial Information (ESMI) scheme

(Adapted from the Scottish Office Control of Tuberculosis Guidelines, 1998)

Current guidance recommends early notification, which should not be delayed for bacteriological confirmation (Scottish Office Department of Health, 1998). The ESMI scheme can facilitate the denotification of erroneously notified cases[10] at a later stage. Form A requests demographic and disease information, and four months later a second form (form B) requests information pertaining to culture results, strain sensitivity, BCG status, previous TB history, occupation, ethnicity and place of birth, risk factors, potential sources of infection and known TB contacts. Finally, form C requests treatment outcome information, and is completed 12 months after the patient commenced treatment. The third form was introduced in 2003, and since then is required for all cases. Retrospective collection of data was initiated for cases diagnosed in 2001 and 2002; therefore outcome data are not available for those diagnosed in the first year of this scheme (2000).

[10] Erroneous notification can occur if another underlying cause of illness is diagnosed to explain the individual's symptoms, or if infection is caused by a non-tuberculous mycobacterium.

Surveillance forms completed by attending clinicians/nurses are forwarded to respective NHS Boards in the first instance. The delivery of form A fulfils statutory requirements to notify the Director of Public Health or relevant Consultant in Public Health Medicine in the local NHS Board area. Responsibility for notification also falls to the directors of local and/or national laboratories, and pathologists. Notifiable information is recorded at local NHS Board level, and original ESMI forms are forwarded to HPS, where information contained on surveillance forms is entered into the ESMI database, which operates a DATAEASE software package. Gathered information is formally disseminated on an annual basis, and reports are published in Health Protection Scotland's in-house publication, HPS Weekly Report (Christie & Johnston, 2002a, Christie & Johnston, 2002b, McMenamin & Johnston, 2004).

At this juncture, it is necessary to expand on terminology used on ESMI surveillance forms, as these variables will be used throughout this thesis. Sputum status is an indication of the volume of bacilli found in a patient's specimen, and therefore how infectious the patient is considered. The threshold for detecting bacilli on light microscopy is approximately 5,000 to 10,000 bacilli/mL of specimen, and a smear positive and negative status reflect the fact that the bacilli detected fall above or below this level respectively (Behr *et al.*, 1999). In this study, a patient identified as sputum smear positive had a minimum of one smear positive sample.

To facilitate comparison of TB notifications across Europe, the ESMI scheme replaced the historical respiratory/non-respiratory classification of tuberculosis with the pulmonary/non-pulmonary classification. Whereas respiratory TB involves infection of the lungs and pleura, pulmonary TB is defined as infection of the lungs and/or tracheobronchial tree. Individuals with pleural effusion, who would be considered respiratory cases in the past, are now considered non-pulmonary cases, as are those with infection in all other body sites.

For the purposes of this study, the definition of a paediatric case was a case aged fourteen years or under, mirroring the definition of paediatric case used in annual ESMI reports.

Eight pre-determined risk factors are available for selection on ESMI surveillance form B. These include alcohol misuse, homelessness, residence in a correctional facility or residential institution, refugee/asylum seeker, immunosuppression, health care worker and intravenous drug misuse. Selection of these risk factors is a subjective process, as nurses completing forms on behalf of newly diagnosed cases use their own criteria (no predefined

criteria are available) when deciding whether or not to select a risk category. This inevitably will lead to variability between those completing surveillance forms. Indeed, forms do not necessarily take into account a possible history of predisposing risk factors for infection (e.g. a patient who was homeless in the past, but when diagnosed with tuberculosis had been housed for some time).

In Scotland, HIV co-infection is not explicitly indicated as a risk factor on ESMI surveillance form B. Rather, cases positive for this syndrome would in theory be assigned to the immunosuppression risk category, as will cases suffering from other co-existing immunosuppressive conditions e.g. cancer. HIV testing is not routinely offered to those diagnosed with tuberculosis in Scotland, therefore the burden of tuberculosis in HIV infected individuals has been difficult to determine. Recent work undertaken in this respect has used date of birth, sex and postcode district to link notifications from the ESMI scheme to a database of results from HIV antibody testing in Scotland between 2000 and 2002. Results from this study indicated that the proportion of TB cases tested for HIV at or around the time of their TB diagnosis (2000 to 2002) was found to be small, at 2.7% (Wilson, 2004).

For the purposes of this analysis, data provided on ESMI forms A, B and C for all study cases were exported from the ESMI DATAEASE software programme by the ESMI database co-ordinator in HPS. The resulting file was imported into SPSS (version 12), where analysis was undertaken. For the purposes of acquiring additional information for cases from TB nurses (i.e. contact tracing information – see section 3.6), identifying information such as patient forename, surname and date of birth was required information. Data were either stored on the investigator's password protected personal computer in HPS (or a similarly protected laptop when travelling to site to acquire contact tracing information from TB nurses). Unique ESMI identifiers, consisting of a random eight-digit code, are assigned to each case when notified to the ESMI scheme. The anonymisation of patient information in this way is designed to maintain patient confidentiality, and wherever possible, anonymised data were used during analysis to remove potential bias. Identifying information was not used during the presentation of results.

Although the majority of cases included in this study were diagnosed from 2000 onwards, certain cases were diagnosed between 1994 and 1999, and were notified to the NOIDs scheme. As Health Protection Scotland did not collate this type of data from all NHS Boards at that time, Greater Glasgow NHS Board provided the required demographic and disease information for those cases.

3.3.1 Data completion exercise

The strength of inferences from research findings is dependent upon the quality and completeness of information collected through the ESMI scheme. With this in mind, the completeness of recorded surveillance information was optimised during an audit undertaken by this investigator, prior to commencing this research study. This task involved obtaining missing information from ESMI data fields for 560 (pulmonary and non-pulmonary) cases notified to the Greater Glasgow NHS Board between January 2000 and July 2003, for whom ESMI surveillance forms A and B had been returned to HPS. Missing information was requested from Greater Glasgow TB liaison nurses. Due to busy nursing schedules, seventeen meetings of one to two and a half hours' duration were conducted over a seven month period, to facilitate data retrieval. Data fields with poor completion rates (e.g. place of birth, risk factors, symptom duration) were targeted. This investigator furnished the ESMI data co-ordinator with any new information, and data was subsequently entered into the ESMI database.

Although many data fields were reasonably well completed in the first instance, the proportion of missing information for targeted fields was reduced on completion of the exercise. Improvements were most notable in the 'country of birth', 'symptom duration' and 'contact with a TB case' fields (see table 2). With the exception of the 'risk factor' category, where data fields remained blank after completion of this exercise, TB nurses had no knowledge of this information. With regards to the 'contact with a TB case' category, a high proportion (32.7%) of data fields remained blank indicating this information was not known because to patients' and nurses' knowledge, no friend, family member or other acquaintance had been diagnosed with tuberculosis. For the 'risk factor' field, one-third of notified cases selected a minimum of one risk factor e.g. alcohol misuse, homeless, immunosuppression etc. As a result of this audit, risk factors had been indicated for a nominal number of cases for the first time. This is believed to reflect the fact that the majority of notified cases did not have any of the predetermined risk factors on the ESMI form. Surveillance forms have since been amended to allow those completing the forms to indicate when a case does not have any of the pre-selected risk factors.

Data field completion	Pre-validation n=560	%	Post-validation n=560	%
Date of diagnosis				
Provided	545	97.3%	558	99.6%
No information provided	15	2.7%	2	0.4%
Duration of symptoms	*(n=471)*		*(n=481)*	
Provided	352	62.9%	412	85.7%
No information provided	119	25.3%	69	14.3%
Previous TB diagnosis				
Provided	550	98.2%	553	98.8%
No information provided	10	2.8%	7	0.2%
Country of birth				
Provided	398	71.7%	533	95.2%
No information provided	162	28.9%	27	4.8%
Risk factor				
Provided	193	34.5%	201	35.9%
No information provided	367	65.5%	359	64.1%
Contact with TB case				
Provided	308	55%	349	62.3%
No information provided	252	45%	211	32.7%

Table 2: Results from an audit of ESMI data fields for 560 Greater Glasgow NHS Board TB cases notified between 2000 and July 2003 (and for whom ESMI forms A and B had been returned to Health Protection Scotland)

3.4 Molecular typing data

In Scotland, the Scottish Mycobacteria Reference Laboratory (SMRL) undertakes routine molecular typing of culture positive *M. tuberculosis* complex (MTBC) isolates, principally using the standardised IS*6110* RFLP typing method (van Embden *et al.*, 1993). IS*6110* is an insertion sequence containing 1355bp, copies of which can be present zero to twenty-five times on the MTBC genome and which are integrated at various chromosomal locations. Where RFLP patterns contain five or less IS*6110* copies, a sub-typing technique known as Spoligotyping is employed to supplement the primary analysis. The methodologies of techniques used by SMRL have been previously described in published scientific papers (Fang *et al.*, 1999), and are briefly outlined here. Computer assisted comparative analysis of RFLP patterns was undertaken using GelComparII version 2.0 (Applied Maths).

3.4.1 IS*6110* RFLP typing

IS*6110* RFLP requires relatively large quantities of genomic DNA for analysis. Prior to DNA extraction, each isolate is grown on solid culture medium at 37° Celsius for approximately four to eight weeks, until colony growth becomes visible. DNA is extracted from a loopful of bacterial growth using the CTAB method (van Soolingen *et al.*, 1991) after the organism has been heat inactivated to render it non hazardous (Fang *et al.*, 2001).

A restriction endonuclease, *Pvu*I, is added to the MTBC chromosomal DNA. It cleaves the DNA into fragments when it recognises a specific short DNA sequence within IS*6110*. Since the DNA fragments are of variable lengths (0.5 to 25 kilobases) they are referred to as restriction fragments. These restriction fragments can be separated on the basis of size by agarose gel electrophoresis. Since DNA is negatively charged, it will migrate through a gel from the negative pole towards the positive pole (anode) when an electrical current is applied. The rate at which fragments migrate from the cathode is dependent upon the molecular weight of the DNA fragment, with smaller fragments moving most rapidly.

Following electrophoresis, the DNA is made single stranded (by denaturation) and immobilised onto a membrane by a technique called Southern blotting, which uses capillary action to draw DNA fragments from the gel onto the surface of a nylon membrane. The DNA is then fixed to the membrane by baking at 120° Celsius. A digoxigenin (DIG) labelled IS*6110* probe (245bp in length) then hybridises to IS*6110* DNA to the right of the *Pvu*II cleavage site. Detection of the bound probe is performed using the chemiluminescent alkaline phosphatase substrate CSPD® (Disodium 3-94-methoxyspiro{1,2'-(5'chloro)tricyclo{3.3.1.1.^{37}}decan}-4yl)phenlphosphate) (Roche Diagnostics Ltd., East Sussex, England) which produces a light signal that can be detected by exposing the membrane to x-ray film in a light-blocked cassette.

To allow comparative analysis of RFLP typing results from MTBC strains on different gels, internal markers are also incorporated into each gel lane. A comparison of the rate of migration of DNA fragments of a defined size can then be made across different gels. These internal markers are used to provide a reference system for GelComparII analysis, which allows standardisation of results from different gels through the normalization process. DIG-labelled ΦX*174-Hae*III DNA (Advanced Biotechnologies, London, United Kingdom), and a supercoiled DNA ladder (Gibco-BRL, Life Technologies Ltd. Paisley, United Kingdom) are used as internal markers in IS*6110* RFLP. In addition, *Pvu*II-digested DNA from the reference strain of *M. tuberculosis* MT14323 is loaded into one

well on each gel. MT14323 gives ten approximately evenly spaced bands of known size thus acts as a control to assess that *Pvu*II cleavage has occurred correctly.

3.4.2 Comparative analysis of RFLP patterns

Comparative analysis of IS*6110* RFLP patterns at SMRL was conducted using computer software GelComparII version 2.0 (Applied Maths, Ghent, Belgium) using the internal marker system. After scanning autoradiographs into the software package, the gel data were prepared for analysis through a process of lane definition, curve calculation, track normalisation and band assignment. Pairwise similarities of IS*6110* fingerprint patterns were calculated using the Dice coefficient of similarity with clustering by unweighted pair group method of averages (UPGMA). The position tolerance, the measure of the maximal shift (in percentage of the pattern length) between two bands allowed to consider bands as matching, was set at a level of 4% (usually 1-2% is sufficient). At SMRL, the position tolerance was increased to allow for some gel mis-alignment and/or weak RFLP fingerprint patterns contained in the SMRL GelComparII database. As a result, patterns that may not be considered clustered at 1-2% may be deemed clustered at 4%. Indeed, computer analysis of RFLP patterns remains a subjective process requiring skill to minimise potential errors.

Where individuals are found to be infected with genetically indistinguishable strains of *M. tuberculosis* (as indicated by identical IS*6110* RFLP patterns), it suggests transmission has occurred in the recent past. The *M. tuberculosis* genome and the *6110* insertion sequence in particular is not thought to undergo polymorphic change as frequently as other bacteria or viruses. IS*6110* is thought to have a half life of 3 years three to four years, which infers that half of IS*6110* RFLP patterns observed over such a period of time will remain stable (i.e. not undergo evolutionary change) (de Boer *et al.*, 1999). The definition of recent as opposed to remote (occurred in the past) transmission varies between studies, with some researchers describing it as the spread of disease over a 1, 2 or 5 year period (Cronin *et al.*, 2002, Jasmer *et al.*, 1999, Vynnycky & Fine, 1997). Individuals with 'unique' *M. tuberculosis* strains (detected only once in a given TB population within an observation period) are thought to represent reactivated latent infection. Alternately, the strain may have been recently imported from another country, if detected in an individual who arriving in the United Kingdom for the first time (Dale *et al.*, 2003).

In Scotland, IS*6110* RFLP typing of *M. tuberculosis* complex isolates is currently used to confirm the probability that recent transmission of infection has taken place, on the

premise that epidemiologically linked cases share the same RFLP pattern. RFLP analysis of clinical *M. tuberculosis* isolates belonging to epidemiologically-linked cases is undertaken by SMRL when requested by public health professionals to confirm the occurrence of putative transmission. When epidemiologically linked cases have disparate IS*6110* RFLP patterns, this indicates transmission did not occur between these individuals. Occasionally, epidemiologically linked cases are found to have RFLP patterns with IS*6110* copies that are essentially identical, but differ in only one or two copies of IS*6110*. In such instances, it is difficult to determine whether patterns reflect transmission of a strain that underwent a small genetic polymorphism, or whether this is due to infection with two closely related strains (Cave *et al.*, 1991).

Recently, a research team led by Dr Ken Forbes at the University of Aberdeen (affiliates of SMRL) was awarded funding to describe the molecular epidemiology of *M. tuberculosis* in Scotland. During this two-year project (2004-2005), RFLP patterns available for all patients diagnosed in Scotland between 1997 and November 2003 were sourced from SMRL and analysed. Clusters of cases with genetically indistinguishable IS*6110* RFLP patterns were then identified. For the purposes of this research study, both SMRL and the University of Aberdeen conducted IS*6110* RFLP analysis. While the University of Aberdeen provided information pertaining to the identity of clustered cases[11] (section 3.5), SMRL facilitated comparison of RFLP patterns belonging to epidemiologically linked cases (section 3.6),

3.4.3 Spoligotyping

Despite a high degree of stability, discrimination and reproducibility, IS*6110* RFLP cannot adequately discriminate between strains with low copy numbers (i.e. with five or fewer copies) of IS*6110* (Godfrey-Faussett, 1998, van Soolingen, 2001). Strains with few copies of IS*6110* are regarded as being naturally more homogenous in their DNA fingerprint pattern than their counterparts with many IS*6110* copies (Kamerbeek *et al.*, 1997). A higher level of differentiation between strains with five or less IS*6110* copies has been achieved at SMRL using a technique known as Spoligotyping (Kamerbeek *et al.*, 1997). This method exploits DNA polymorphisms at one particular chromosomal locus in the *M. tuberculosis* complex genome, known as the Direct Repeat (DR) region. This region is composed of directly repeated 36 base pair sequences interspersed with non-repetitive 37

[11] The University of Aberdeen made required information available to this investigator in March 2005. As the analysis undertaken by the University of Aberdeen was due for completion in July 2005, data provided for this investigator's analysis was considered provisional.

to 41 base pair sequences, referred to as spacers. Briefly, the technique detects the presence or absence of spacers of known sequence that occur between the directly repeated sequences. Following PCR amplification of the entire DR region, the PCR products are denatured then hybridised to a membrane containing 43 rows of oligonucleotides, each representing a known spacer DNA sequence (Isogen Biosciences BV, Maadsen, The Netherlands). Hybridised DNA is detected by the enhanced chemiluminescence method (Amersham Pharmacia Biotech) which generates a light signal that can be detected on x-ray film. A Spoligotype pattern is generated for each isolate, where the presence or absence of spacers is indicated by a 43 digit binary code (the presence of spacer is indicated by 1 and its absence by 0). An international database of Spoligotypes (SpolDB3.0), containing 11,708 patterns from isolates from more than 90 countries was available for comparative analysis (Sola *et al.*, 2001).

At SMRL, *M. tuberculosis* complex isolates received from 2000 onwards were randomly selected for Spoligotyping as part of an ongoing research study investigating the feasibility of this technique as a possible first-line typing strategy for DNA fingerprinting of Scottish *M. tuberculosis* isolates, with the aim of reducing turnaround times and improving the level of genetic discrimination for low IS*6110* copy number strains. Therefore, Spoligotyping information was not available for all low IS*6110* copy number isolates, but wherever available, this information was provided.

3.5 Describing the epidemiology of recently transmitted TB

In chapter five, results are provided of a descriptive analysis of clustered cases thought to represent recent transmission of infection in the Greater Glasgow NHS Board area between 2000 and (11th November) 2003. As previously indicated, the University of Aberdeen undertook a GelComparII analysis of IS*6110* RFLP patterns for these cases. Where patients' RFLP patterns contained 5 or less copies of IS*6110*, Spoligotyping information was sought from SMRL.

Clustering was defined as the detection of genetically indistinguishable RFLP patterns with 6 or more copies of IS*6110*, in two or more study cases within the four-year period of observation. Also, two or more cases with genetically indistinguishable RFLP patterns with 5 or less copies of IS*6110* and matching Spoligotypes within the study period were also deemed clustered. Alternatively, patients with unique IS*6110* RFLP banding patterns within the study period were deemed unique and therefore referred to as non-clustered cases.

The proportion of cases due to clustering was determined by the "n" method, which involved summing the number of cases in all clusters and dividing by the total number of study cases. To determine the rate of cases due to recent transmission, the "n-1" method was applied. It assumes one case in each cluster represents the source of infection (the index case), and all other cases acquired tuberculosis infection from that case (Glynn *et al.*, 1999). The proportion of cases due to recent transmission was determined by subtracting the total number of index cases from the number of clusters, and dividing this by the total number of cases under investigation.

As the study population in chapter 5 was restricted to those diagnosed within approximately a four-year period, estimates of cases caused by recently transmitted infection may be underestimated. It is probable some cases considered as non-clustered for the purposes of this study may in fact be part of a cluster, but were not noted during the period of observation. If the study period was expanded prospectively and retrospectively, a proportion of IS*6110* RFLP banding patterns infecting non-clustered cases may be incorporated into newly identified clusters. Similarly, this may occur if geographical boundaries were widened to incorporate other NHS Board areas. Further, the estimate of cases caused by recently transmitted infection does not reflect culture negative cases, as IS*6110* RFLP typing cannot be undertaken for such cases. Although limitations of this population-based study are discussed in the discussion section of chapter 5, readers are referred to Glynn's article for a detailed review of inherent limitations of population-based molecular epidemiology studies (Glynn *et al.*, 1999).

3.6 Contact tracing data

The second research objective was to examine the usefulness of contact tracing procedures in identifying and preventing new cases of tuberculosis in the Greater Glasgow NHS Board area. As TB is primarily transmitted by the expulsion of mycobacteria carried in the sputum of individuals with a pulmonary form of the infection, contact tracing is routinely undertaken for these patients[12]. Consequently, patients in Greater Glasgow with a diagnosis of pulmonary tuberculosis were eligible for inclusion in this study. Although 453 pulmonary cases were notified during the study period[13], 10 patients (2.2%) were

[12] In accordance with current guideline documents, contact tracing is not required for non-pulmonary patients. However, if used in a local setting as a strategy to access and screen high risk populations, or if close contacts of non-pulmonary patients are HIV-positive, a child, or has features suggestive of recent infection (e.g. erythema nodosum or meningitis), contact tracing is recommended.

[13] Data was exported from ESMI database in March 2004.

excluded from the study population because contact tracing nursing notes could not be located.

Required contact tracing information was sourced directly from members of the Greater Glasgow NHS Board TB nursing team. Since the decision was taken to discontinue the collection of contact tracing information by the Greater Glasgow NHS Board in 1997 (A. McDonald, TB database administrator, Greater Glasgow NHS Board, personal communication), documents detailing contact tracing information were retained at site only, in the care of the nurse responsible for the conduct of the screening event. For each TB case, contact tracing nursing records contain names of contacts requested to attend screening, attendance records, and the method and outcome of examination.

To ensure the efficient collection of required contact tracing information, the identity of the responsible TB nurse was determined from ESMI information, as this determined the storage location of contact tracing notes. Although the Greater Glasgow NHS Board TB nursing team consisted of four full-time nurses over the study period, and four patient sub-groups were anticipated, five were defined. Patients in this fifth sub-group had been assigned to a nurse who retired in late 2002 after 17 year's service on the TB liaison nursing team. Required information from contact tracing records for these individuals was therefore accessed and interpreted by the successor to that post. Where study cases' contacts resided within Scotland, but outwith Glasgow, respective NHS Boards were responsible for the completion of screening. Screening outcome was determined by this investigator contacting the relevant TB nurses/health visitor if information was not previously made available to the Glasgow TB nurse.

Individual meetings were arranged with nurses to facilitate the collection of data for study cases. These took place at each nurse's respective office, and were conducted over a seven-month period, from July 2003 to February 2004. This method of data collection was warranted because information did not exist in an electronic format. Furthermore, it ensured rapid clarification of complex or unclear issues or scenarios, e.g. screening in outbreak investigations that may involve many individuals, over prolonged periods of time. Information supplemental to that documented in nursing notes was obtained, such as reasons for the absence of contact tracing, the details of which are not usually explicitly recorded. All data gathered were recorded at site using Microsoft Excel (v2000) on a laptop computer.

Information requested for each study case included the number of contacts requiring screening, completing screening, the number diagnosed with TB, in receipt of chemoprophylactic treatment, and vaccinated. In addition, the number of patients requiring and attending a follow-up chest x-ray was recorded. As contact investigation is advised for all close contacts of pulmonary cases of tuberculosis, reasons for its absence were obtained when staff indicated no contacts were screened. Where contacts were in receipt of chemoprophylaxis, nurses were again asked to indicate whether this was a primary chemoprophylaxis for a child under the age of two, as the latter are often given chemoprophylactic therapy to prevent the acquisition of infection (as opposed to treatment of latent infection for those over two years of age (Joint Tuberculosis Committee of the British Thoracic Society, 2000). No identifiable information was sought for such cases. Finally, when a screened contact was found to have active TB, identifying information was sought for that individual so their epidemiological information could be sourced from the ESMI database[14]. As this analysis involved the use of existing contact tracing records, ethical approval from a research ethics committee was not deemed to be required.

Members of staff were asked to indicate the closeness of relationships between the patient and each screened individual by stating whether contact was close or casual. The status of close contact was assigned to associates considered to be the equivalent of a household contact, a very close associate e.g. a boyfriend/girlfriend, a close relative/family member, having spent at least a cumulative total of eight hours in the same room as a case of active TB. In situations where the index case infected more than 10% of his/her close contacts, casual acquaintances verging on the threshold of close contact were duly reassigned as close contacts, as suggested by the Scottish Office Department of Health Guidelines (1998). All other contacts, usually work colleagues, friends etc. were deemed casual contacts.

Where index cases are related or part of the same social network/outbreak, it is not unusual for contacts to be identified by more than one study case. This posed a problem during data collection, as there was a risk of unknowingly counting screened contacts more than once. In such situations, nursing staff assigned all common contacts to one of the index cases. Common contacts were consistently assigned to the index case with the earliest date of diagnosis, and should index cases share the same date of diagnosis, contacts were allocated to the sputum smear positive index case.

[14] Contacts found to have TB through contact tracing will have been notified, and therefore identifiable through the ESMI surveillance scheme. Notification of individuals receiving chemoprophylactic treatment is not required, therefore were not identified.

Epidemiological characteristics of the 443 study cases were compared with those of pulmonary cases diagnosed in the rest of Scotland between 2000 and 2003. Measured outcome variables were displayed in an algorithm, and were subsequently analysed in terms of the bacteriological status of the index case and by associations between index and identified contact cases. A score referred to as the number needed to screen (NNS) was devised to determine how many cases needed to be screened to find one case of active disease (Neely *et al.*, 2004). This score was calculated by dividing the number of screened contacts by the number of contacts with active disease.

Only guidelines exist to guide contact tracing, as no standard operating procedures or protocols have been developed for use in Glasgow. To evaluate contact tracing practices, only standards/benchmarks set out as best practice in guideline documents (Joint Tuberculosis Committee of the British Thoracic Society, 2000), or outcome measures used in peer-reviewed articles, presenting results from other audits of contact tracing practices in the UK were used in this study. This allowed a comparison between this Glasgow audit and other audits. However, differences in local epidemiology, study periods and service provision were recognised and meant a direct comparison between the Glasgow audit and others was not possible. In this study, the term 'index case' is used to identify the case for whom contact tracing was initiated. The individual found to have active disease as a result of contact tracing is herein defined as a 'contact case'. For the purposes of analysis, an index case and a contact case (the individual found to have TB as a result of contact tracing initiated for the index case) are considered an epidemiologically linked pairing, and are referred to as an 'index-contact case pair'. The assumption index and contact cases were infected with genetically indistinguishable IS*6110* RFLP pattern was tested. SMRL were provided with identifying information (name and date of birth) for each member of identified index-contact case pairs, and where *IS6110* RFLP patterns were available, comparative analyses were undertaken. Spoligotyping information was sought when RFLP patterns contained five or less IS*6110* copies.

3.7 Statistical analysis of epidemiological information

Data files were prepared in, and statistical tests conducted using SPSS version 12. Firstly, epidemiological data from the ESMI database (operating in DATAEASE) was exported into SPSS format. As contact tracing and molecular typing data were collected/provided in Microsoft Excel spreadsheets, cut and paste functions were used to insert these data into the new SPSS file, containing epidemiological information. Care was taken when merging

information to ensure molecular and/or contact tracing information was attributed to the correct case (row) and respective epidemiological information. Molecular typing and epidemiological data were first sorted by ESMI number (or surname, then forename for contact tracing data), and pasted into the new SPSS file on a case-by-case basis.

Frequencies and cross tabulation functions were used to calculate information for summary tables. The cut and paste function was used to transfer data into Microsoft Excel for presentation of summary tables, and to construct bar and line charts, as suitable graphing options were not provided by SPSS.

Data were converted to a numeric format to assist statistical analysis. Where original data fields contained string text, numeric code now existed (e.g. males and females were coded 0 and 1). Prior to χ^2 analysis, cells in which data were not known were coded as missing (denoted 99), and were therefore excluded from analysis.

Frequency analysis and mean comparison was undertaken to test the null hypothesis there was no difference between specific variables within two populations being compared. This was undertaken on the premise data were independent, that is to say the value of one variable was not dependent on the value of another variable. Where variables were categorical (e.g. sex), χ^2 independence tests were conducted to test for an association between the frequencies of a given variable in the two test populations. The χ^2 test does this by comparing the observed to expected values for the variable under investigation. When observed frequencies had a value of 1 or more, and a maximum of 20% of expected frequencies were below a value of 5, χ^2 independence tests were undertaken. Where these assumptions were not met, Fisher's exact tests were employed. P values were observed, and values below 0.05 were considered statistically significant, as this indicates there is less than a 5% chance of the association occurring by chance.

Where variables were continuous (i.e. age), the distribution of values was examined (e.g. clustered and non-clustered population). In all statistical analyses undertaken involving age, the values were not normally distributed (as indicated by a U-shaped curve on histograms), and the non-parametric Mann-Whitney U-test was conducted.

Multivariate logistic regression models were developed to investigate which combination of independent explanatory variables was associated with the dependent variable or outcome (e.g. within a TB population, being a clustered case). Multiple logistic regression models were developed because dichotomous values were being used (i.e. a population of

clustered and non-clustered cases). For example, the dependent variable was denoted 0 when the patient had a unique IS*6110* RFLP pattern, and 1 when the patient was part of a cluster, on the basis of being infected with a strain, genetically indistinguishable from that of another member of the study population.

Up to ten categorical variables were included in these models, and included sex, age-group, place of birth, ethnicity, BCG status, disease type, previous TB diagnosis, alcohol misuse, homelessness and a category denoted "other risk factors", which included all other predetermined risk factors on ESMI surveillance forms (immunosuppressed etc.).

For univariate and multivariate analysis, variables included in the analysis were coded in a similar way to that described for χ^2 independence tests. However, in this instance, missing variables were not identified as missing, rather were coded as additional category (typically assigned the "other" category). This ensured all cells were included in the analysis. Categories were aggregated as required to ensure cells contained a value equal to or greater than 5 (e.g. with regards to age, the values of categories 0-14 and 15-24 years were aggregated in chapter 5).

Parameters of the model are expressed as odds ratios, which are calculated by dividing the probability of the presence of the outcome by the absence of the outcome. Firstly, each variable was considered the only explanatory variable for the outcome, and unadjusted odds ratios were determined by entering one variable into the model at a time (see table 3). Statements about the effect of category (e.g. being male) on the outcome (e.g. being a clustered case) can only be made by comparison with another category (e.g. female). A reference category was assigned for each variable (e.g. male is the reference category in table 3). The category with the largest number of cases was usually selected as the

					95% Confidence interval (C.I.)	
	Unique IS*6110* RFLP pattern (n=295)	Clustered IS*6110* RFLP pattern (n=176)	TB population (n=471)	Univariate Odds Ratio	Lower C.I.	Upper C.I.
Male	170	128	298	Reference		
Female	125	48	173	0.51	0.34	0.76

Table 3: Example univariate analysis, with dependent variable 'type of IS*6110* RFLP pattern' (y axis) and independent variable 'sex' (x-axis))

reference category, with the exception of age group, where the 0-24 cohort was randomly assigned the reference category.

Odds ratios for each variable were then adjusted to account for the effect of multiple explanatory variables, and therefore all variables were entered into the model. This accounts for associations between the variables, which may have confounded results from the univariate analysis. Odds ratios and their respective standard deviations with a value of above 1 were considered to have a positive association with the dependent variable.

To evaluate the regression model and identify variables resulting in a model capable of making good predictions about the outcome, variables were tested using forwards and backwards conditional selection. Backwards selection starts with all variables in the regression model, and sequentially removes variables that are most likely to make poor predictions about the outcome, as indicated by small changes in the correlation coefficient R^2, at a significance level greater than 0.1. Forwards selection began with a model containing a constant, and variables most likely to make poor predictions about the dependent variable were added. Variables were entered into the model if they resulted in large change in R^2, at an observed significance level of 0.05. Variables remaining in the model following backwards selection and those excluded in a model developed using forward selection are those most likely to make a good prediction about the outcome, i.e. being a clustered case.

Chapter 4: Qualitative methods

This research study has a novel study design, utilising both quantitative and qualitative approaches to examine obstacles facing the control of *Mycobacterium tuberculosis* transmission. To complement conventional epidemiological analyses described in chapter 3, interviews were undertaken with nurses and patients to identify a network of disease transmission and to examine the influence of social and cultural factors on continued disease dissemination. Studies attempting to explain reasons for continued transmission of disease have classically approached this topic from an epidemiological perspective, thus the novelty of this research study lies in the combination of epidemiological and sociological approaches. In this chapter, the purpose, perceived value, and conduct of nurse and patient interviews are described.

4.1 Rationale for qualitative approach

To trace the transmission pathway of a given strain of *M. tuberculosis*, cases clustered on the basis of being infected with the same strain of *M. tuberculosis* were selected. As a genetically defined cluster of cases are believed to represent recently transmitted infection, cases were purposively selected so that inferences from the subsequent analysis could be made about cases thought to be involved in ongoing transmission of disease.

Interviews were undertaken with nurses and patients to augment surveillance information relating to epidemiological linkage between cases, thereby uncovering pathways of disease transmission. Greater Glasgow nursing staff use ESM1 surveillance forms to routinely record epidemiological information, but from this information it is known that only a small proportion of cases had contact with a known TB case prior to diagnosis. Between 2000 and 2003, 23.1% of Greater Glasgow cases (157/680) indicated having had an association with a TB case. Despite the fact TB is spread via human-to-human transmission of airborne droplets, 37.2% indicated having no known contacts, and for the remaining 39.7% of cases, information was not available. Nurse and patient interviews were deemed a suitable way to extend the capture of this information pertaining to epidemiological linkage, and in particular, obtain information about the identities of known TB contacts and the nature of associations, which are not necessarily recorded on surveillance forms.

Interviewing nursing staff was perceived to be a valuable contribution to this research study. As nursing staff have an aggregated knowledge of each cases' medical information,

social history and lifestyle, they were in a unique position to assist the detection of previously unrecognised epidemiological links between cases. This is a consequence of nursing staff involvement in the administration of drug treatment (DOT – direct observed therapy), and the completion of contact investigations. Information accumulated by nursing staff over the treatment period pertaining to patient lifestyle and social behaviour is likely to exceed that requested and captured by ESMI forms. Such information is requested towards the start of the treatment period, on ESMI notification form A and form B, which is completed up to four months after diagnosis. Form C, specifically requests information pertaining to treatment outcome, and the absence of requests for further epidemiological information may result in the failure to capture information that becomes available later on in the course of treatment.

One-to-one patient interviews were deemed important for tracing the transmission pathway of a single strain of *M. tuberculosis*, as this would allow patients to speak freely about their social behaviour and lifestyle. First-hand accounts could be obtained from patients, and patients could be questioned directly to query or clarify information that could assist in identifying previously unrecognised epidemiological links on the basis of sharing a common time, place or person with another infected individual. As the approach to identify TB contacts in this study differed from that used during routine contact tracing, it is possible previously unrecognised (or withheld) information pertaining to TB contacts, sites of exposure etc. could be identified. Finally, by conducting interviews with both TB nurses and patients, this ensured cases in the cluster under investigation were represented both collectively (by nursing staff) and individually. It was felt this would provide a more accurate description of disease transmission in this particular cluster.

In addition, interviews with patients provided a valuable opportunity to gain an insight into patients' understanding of disease transmission, attitude towards their illness, and experience of seeking medical assistance for ill health. It is acknowledged that culture plays an important role in shaping patients understanding of ill health, and consequently health beliefs and health seeking behaviour. Gaining an understanding of the social and cultural factors influencing patients experience of tuberculosis was therefore deemed critical to this study. The rationale for choosing semi-structured interviews is discussed in more detail in section 4.3.

4.2 Selection of a cluster of study cases

As part of a research project undertaken at SMRL, a cluster of predominantly Glasgow cases were identified as having identical Spoligotypes over an nine-year period (1997 to 2004). As of July 2004, 49 cases were found to have this Spoligotype, which belonged to the Beijing evolutionary lineage of *M. tuberculosis*. Identifying information (name and date of birth) for those cases was passed to this investigator for the purposes of this analysis.

In March 2005, provisional findings from a nationwide analysis of IS*6110* RFLP patterns (1997 to November 2003) conducted by the University of Aberdeen became available. As expected, one such cluster of cases corresponded with some of the cases identified on the basis of Spoligotyping by SMRL in the previous year. On comparison, many of the identities of cases included in the cluster identified by IS*6110* RFLP and Spoligotyping analysis were similar, however some disparities were detected. Two cases identified by the IS*6110* RFLP analysis had been omitted from the Spoligotyping analysis, as Spoligotyping had not been undertaken for those cases. Furthermore, 13 cases identified during Spoligotyping analysis were omitted from the analysis of IS*6110* RFLP patterns, due to the fact the final analysis undertaken by the University of Aberdeen excluded poor or weak banding patterns. All were included in this analysis.

In total, 51 study cases diagnosed between May 1997 and July 2004 with a genetically indistinguishable 15-banded *IS6110* RFLP pattern were included in the study population. Figure 5 shows a dendrogram displaying the similarities detected between IS*6110* RFLP patterns (courtesy of SMRL). The vertical line to the left of the dendrogram indicates a 100% similarity for the majority of patterns at a position tolerance of 2 to 4%. Patients' identities are indicated by a number or by pseudonym (the assignment of patient pseudo-identities is explained in section 4.4.3). Patient 11 and Andrew are 92% similar to the remaining clustered cases. As line copies rather than original autoradiograph results were used to create this dendrogram, appropriate adjustments could not be made to improve the percentage similarity. However, visual comparison suggests the IS*6110* RFLP patterns belonging to Patient 11 and Andrew are highly similar to those belonging to the remaining clustered cases.

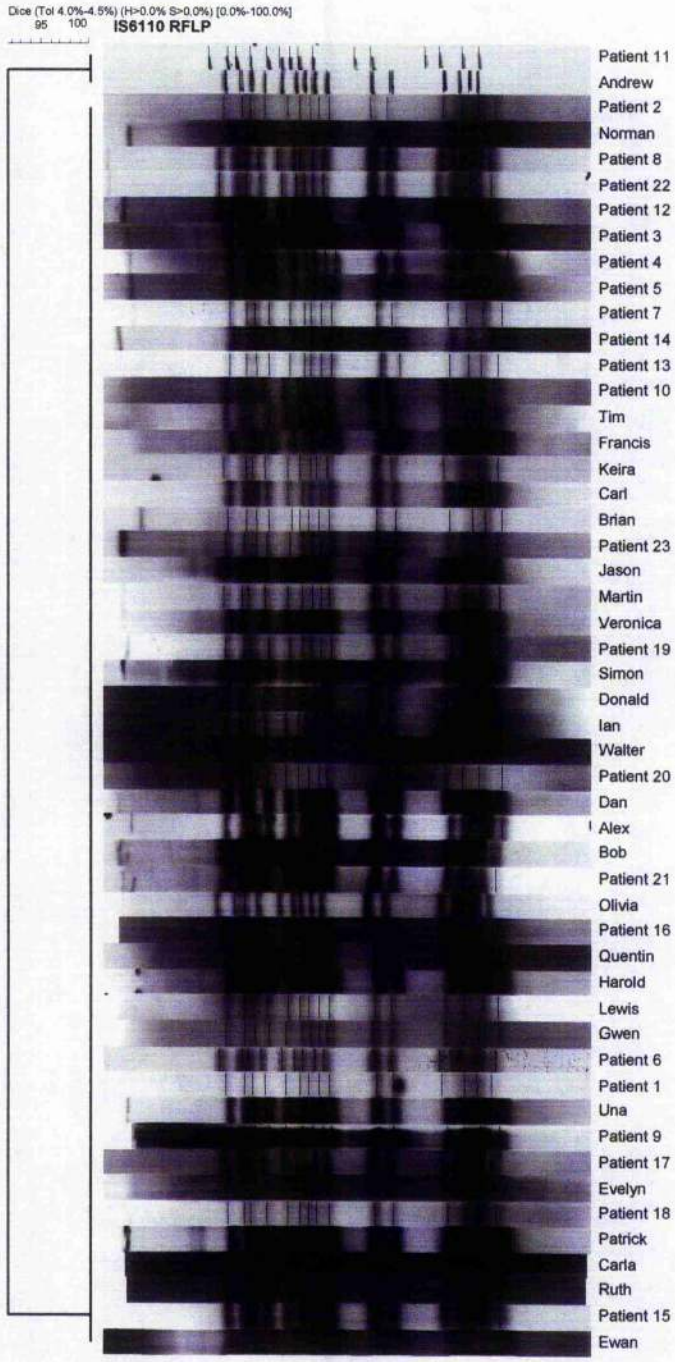

Figure 5: Dendrogram of genetically indistinguishable 15-banded IS*6110* RFLP patterns for 51 cases diagnosed with TB between 1997 and 2004. With the exception of 3 cases (notified to the Western Isles NHS Board), all cases were notified to Greater Glasgow NHS Board

All cases (with the exception of two cases), had 100% similarity on GelComparII analysis. All cases are identified using pseudonyms

4.3 Detection of transmission pathways

Experienced TB liaison nurses routinely conduct contact screening events to actively seek source cases or infected contacts. Despite extensive efforts at the time study cases were diagnosed, associations on the basis of time, place or person(s) were detectable for only a minority of cases.

4.3.1 Surveillance data

To determine epidemiological links between cases, the investigation first involved revisiting epidemiological information from surveillance databases to establish known epidemiological links. Information was sourced from the ESMI database for 37 cases diagnosed from 2000 onwards, and the NOIDs database for 14 cases diagnosed between 1997 and 1999. In contrast to the limited information available from the NOIDs scheme, the identities of known TB contacts, source cases detected as a result of contact tracing, and details of social behaviour were occasionally recorded on the ESMI database. Documented places of residence, employment or schooling were compared in an attempt to uncover ostensible location-based connections between cases. A search of free-form comment cells on ESMI surveillance forms was also undertaken.

4.3.2 Nurse interviews

As a result of case management duties, TB nurses acquire substantial knowledge about each individual's lifestyle, social and risk behaviours. Study cases were located largely within the northwest of the city (46 cases in total), and therefore in the care of the northwest district TB liaison nurse. A series of interviews were undertaken with this nurse to uncover additional contextual and lifestyle information for patients, which had not been documented on ESMI surveillance forms. In terms of recruitment and for the purposes of providing information to link study cases, this nurse's input proved critical in this investigation. Two east Glasgow cases were under the care of a TB liaison nurse, who retired from the post in 2002. The successor to that post reviewed contact tracing and case file notes in an attempt to identify possible associations with other known cases. Three Western Isles patients were also included in this cluster, and the CPHM in that NHS Board area provided required information.

Interviews with health professionals were informal and an interview schedule was not designed to guide these conversations. Instead, the nurse was made aware that the purpose

of the interview was to gather information about associations between cases clustered on the basis of having a genetically indistinguishable IS*6110* RFLP pattern. The topics covered during these conversations related to the individuals activities on a day-to–day basis, i.e. whether the individual was employed, or how the case spent their time if unemployed, or after work. Nurses were asked to identify places cases were known to frequent and whether, to their knowledge, the case had spent time with a known TB case (past or present case). The format of the interview was such that the above questions were posed for each cluster case in turn, as it enabled nurses to retrieve the appropriate case file notes, and provide information contained therein. This investigator felt it was important to ensure the format of the interview was flexible to allow interviewees to provide information about the nature of complex associations, which often involved several cases.

Interviews with health professionals were conducted either in person or by phone. While the northeast Glasgow district nurse and CPHM in the Western Isles were interviewed by phone, both methods were used to acquire information from the northwest Glasgow district TB nurse (due to the fact over 40 clustered cases had been in her care, more than one interview was required). Conversations were not tape recorded, rather notes were hand written by this investigator. In retrospect, tape recording conversations would have allowed the investigator to concentrate on probing the interviewee for more detail about the nature of associations (as done for patient interviews), rather than trying to ensure all information was recorded. Notes were subsequently typed up, and information was analysed as described in section 4.5.

4.4 Patient interviews

The objective of patient interviews was two-fold. Firstly, it was intended that such an approach would assist in eliciting information that could potentially link patients on the basis of time, place or person. Secondly, interviews provided an opportunity to explore patient's understanding of TB transmission, attitude towards their illness, and experiences of seeking help from medical services.

To this end, face-to-face, semi-structured interviews were conducted because they allow complex issues to be probed, immediate clarification of responses, and were considered suitable for the collection of personal, in-depth information. The NHS Greater Glasgow Primary Care Division Local Research Ethics Committee (Community and Mental Health) granted ethical approval for the conduct of patient interviews in March 2004 (Appendix 1).

4.4.1 Interview schedule

An interview schedule (or guide) was developed to assist patient interviews, and unlike a survey questionnaire, is a list of topics or areas of questioning (Appendix 2). These topics are not necessarily addressed in a specific order during the interview; rather the interview guide acts as a checklist to ensure all topics have been addressed, thus ensuring consistency between interviews. As the study population was diverse in terms of age and lifestyle, the flexible nature of this research tool would allow questions to be tailored to each individual's circumstances, thereby maximising the data obtained for analysis. Furthermore, the semi-structured format of the interview allows the interviewer to pursue issues and concepts raised by interviewees, not previously considered by the investigator (Rubin & Rubin, 1995).

The interview schedule was partially designed to explore themes around which an individual may have been at risk of acquiring tuberculosis. TB nurses regularly report that during contact investigations, patients forget or withhold information when asked to name contacts they have spent time with prior to their diagnosis. It was anticipated such difficulties could be overcome with broad, semi-structured interviews. Rather than ignoring the social context from which patients are trying to recall contact names, the interview guide asks patients to speak at length about this, as it was thought this would probe patients' memory of social activity and behaviour. This was perceived to be of key importance, as the period between acquiring tuberculosis and developing active disease could be in the order of years. Patients do not necessarily retain risky behaviours, which may have led to acquisition of TB in the first instance. Unlike contact tracing interviews, which typically focus on the symptomatic period (Joint Tuberculosis Committee of the British Thoracic Society, 2000), the interview schedule was designed to avoid restricting the conversation to this period in patients lives.

As little methodological instruction existed in the literature to assist the detection of epidemiological links, much effort was expended in developing and piloting this research tool. A set of guideline documents for contact tracing was initially used to identify areas of enquiry for the interview schedule (New Jersey Medical School National Tuberculosis Center, 2000). Routine questions asked by TB nurses during contact investigation interviews were also utilised because this information is not always recorded on ESMI surveillance forms. New areas of enquiry were designed to explore the potential common time/place and person characteristics that may link individuals. Prompts regarding locations of work/recreational pursuits, contacts with other cases of TB or undiagnosed

respiratory illness or unexplained deaths and a range of personal data (including interpersonal relationship, and alcohol/drug use etc.) formed the basis of the interview. Patients were also asked about knowingly having contact with another case of tuberculosis. The anonymity of other cluster members was maintained throughout, since the names of those individuals were not disclosed during the interview.

In addition to seeking to trace transmission pathways, the interview guide was developed to elicit information about patient beliefs and perceptions of TB transmission. For example, patients were asked about whether they had been aware of the disease before receiving their own diagnosis, how they thought tuberculosis could be spread and factors potentially putting them at risk of infection. These questions were designed to be open-ended to encourage interviewees to speak at length about their perceptions and experiences. The data were important for this study because it provided an insight into some of the social and cultural factors influencing the continued propagation of this particular strain of *M. tuberculosis*.

A preliminary interview schedule was piloted on eight patients identified by SMRL as having a genetically indistinguishable 5-banded IS*6110* RFLP pattern and identical Spoligotypes. Several revisions were made during the piloting process, the most significant of which related to the ordering of questions. When interviews commenced with questions pertaining to health beliefs, patients appeared more responsive. The elucidation of health beliefs and health seeking behaviour usually lasted twenty minutes, by which time rapport had been established, and interviewees had begun to feel at ease. Undoubtedly, this improved patient willingness to divulge personal information about issues relating to lifestyle and social behaviour, which took place in the latter part of the interview.

4.4.2 The interview

All interviews were conducted at the home address of the patient or next of kin to ensure cases would feel comfortable by being present in a relaxed atmosphere. Prior to commencing the interview, this investigator ensured the interviewee had received and read the study information sheet. Their involvement in the study was explained, and any questions the individual had were addressed at this point. A consent form was signed by participants, which stated they were participating of their own free will, and could opt to withdraw from the study at any time. The consent form also made a request to tape record the conversation, and declared personal information would remain confidential.

Occasionally, the interviewee had a family member or partner present during the interview, and often they participated in the conversation. Interpreting services were requested on one occasion to assist an interview with the mother of a case who spoke Urdu.

Questions raised by the interviewee during the interview were addressed after the interview had ended and the tape recording had stopped in order to limit bias that could be imposed by the investigator. The interview was drawn to a close by thanking the interviewee for participating in the study, answering any remaining questions, and by presenting their voucher. Interviewees were informed of a report that would be drawn up for their benefit, to detail some of the research findings, and were asked if they wished to receive a copy.

A digital tape recorder (Olympus DS-330 digital voice recorder) was used to record interviews, which varied in length from ten to seventy minutes. The digital file was subsequently uploaded into the software package (Olympus DSS player version 1.3.0) on the investigator's PC. This investigator transcribed all interviews. In the first instance, identifying information was not anonymised so putative epidemiological links could be detected. Following this analysis, names of places were anonymised, and patient's names were replaced with pseudonyms to protect their identities. The first interviewee was identified with a random pseudonym starting with the letter A, the second with the letter B and so on. Non-interviewed cases were randomly assigned a number between one and thirty-six.

4.4.3 Recruitment

To accurately trace the transmission pathway of this strain, it was important as many cases as possible agreed to be interviewed. However, certain cases were not eligible for interview. Firstly, ethical permission was not sought from the Western Isles Local Research Ethics Committee to involve the three Western Isles study cases. Surveillance information retrieved from the ESMI scheme contained details of epidemiological links between these cases, and relevant health authorities provided further assistance. Two Glasgow study cases were aged seven at the time of interview, and although unable to participate personally, their respective parents were interviewed on their behalf. A further two cases were not invited to interview. The first case had recently died, and it was deemed inappropriate to contact next of kin because his death was the subject of an investigation by the Procurator Fiscal. The second case's son was seriously ill, and it was considered inappropriate to approach her at that time (July-November 2004).

Twelve patients within this study cluster were known to have died, and the feasibility of interviewing next of kin was discussed with the TB nurse, on a case-by-case basis. The inclusion of next of kin in this investigation was imperative, as their absence may have contributed to the loss of useful information, and integral epidemiological links between cases may have been overlooked. Of course, individuals' wellbeing was a primary concern, and consideration was given to whether next of kins' participation was likely to cause distress. For a large proportion, no objections were envisaged, particularly as many had previously participated in contact investigations for their next of kin, and were likely to understand the public health significance of this investigation.

In certain instances, recruiting candidates from the eligible study population for interview posed a challenge. As some cases had been diagnosed four years previously, contact details (address, telephone number) were sometimes invalid and traditional recruitment methods such as telephone calls or letters were unlikely to yield a good response. Recruitment methods were therefore revised during the piloting process to allow a familiar TB nurse to assist the investigator in making contact with the candidate. This change proved critical in accessing the population.

Up-to-date contact details were obtained for all eligible study participants. Identifying information (e.g. name, date of birth, last known address) was forwarded to the Greater Glasgow NHS Board. A member of the Health Protection Unit accessed the Community Health Index (CHI)[15], and details of patients' registered last known address, as well as that of their General Practitioner were made available. This investigator was also notified if any study cases were registered as deceased.

Where patients were known to be alive, letters of invitation were posted to their last known address. Covering letters explained the reason they had been contacted was because when diagnosed with TB, they were found to have a particular strain of TB, and that other individuals with the same strain were also being invited to take part. Their involvement in the study was outlined, and the areas of inquiry to be addressed during an interview were described. It was also indicated a voucher to the value of ten pounds would be offered to reimburse them for their time and any inconvenience caused by participating in the study[16].

[15] CHI (community health index) is a register of patients within the NHS in Scotland, containing patient name, address, date of birth, gender and details of registered GP. It holds some historical data including previous GPs name and address, and can be used to track patient medical records.

[16] Much thought was given to choosing an appropriate incentive to boost participation. As many patients were known to use excessive amounts of alcohol, a voucher for a high street pharmacy was selected, as this could not be redeemed for alcoholic beverages.

The letter was co-signed by the patients' TB nurse in an effort to improve the response rate. Two information sheets were enclosed. One informed patients of the study aims, and included relevant study information. The second leaflet published by Health Protection Scotland explained how personal information is gathered and utilised by the organisation, and outlined their rights under the 1998 Data Protection Act. Finally, alongside a prepaid return envelope, an acceptance of invitation letter was enclosed. This required patients to provide a current telephone number, so this investigator could telephone them to schedule an appointment for interview.

Where patients did not respond to letters or letters were returned, the TB nurse and this investigator rang the phone numbers contained in the patient's old case note file, or used telephone directory enquiry services as required. Alternatively, this investigator spoke with staff at patient's GP practices to obtain current home and telephone details. In the event new contact information became available, the letter of invitation was resent and/or phone calls were made.

Following these initial recruitment attempts, several hours were spent conducting house-to-house enquiries (at patients last known address). Those approached by this investigator and the northwest district TB nurse included individuals who did not respond to letters, or for whom telephone numbers were unavailable or no longer operational. If there was no response, a note was left to notify the individual of the visit, and after three door-to-door enquiries on various days, the patient was excluded from the study. Finally, the northwest district TB nurse recruited two cases when they attended respiratory clinics for routine follow-up appointments.

4.5 Analysis of interview data

This section describes the analysis of data from nurse and patient interviews. Data from patient interviews were analysed in two ways. Firstly, in trying to determine epidemiological links between cases with a genetically indistinguishable strain, qualitative interview data were quantitized, or transformed into quantitative data (Tashakkori & Teddlie, 1998). To examine lay epidemiology and help seeking behaviour, an inductive thematic analysis was undertaken.

4.5.1 Detection of transmission pathways

Firstly, notes made during nurse interviews were reviewed to determine the identity of cluster cases with epidemiological links to known TB patients, and places frequented. Patient interview transcripts were also reviewed to determine known TB contacts, individuals identified as suspected TB cases, and places frequented. Although not always possible, patients provided identifying information (e.g. address) to enhance the likelihood of establishing the correct identity of individuals or places. A search of relevant databases (ESMI/NOIDs) were conducted to determine if individuals named during interviews had been diagnosed with TB in the past. If a match was found, a further search of the SMRL library of IS*6110* RFLP patterns was requested. Locations nominated were compiled for each interviewee and compared with others, and those nominated by two or more interviewees were included in the analysis.

A matrix was constructed using social network mapping software UCINET 6.0 (Borgatti *et al.*) to allow links between cases and between cases and locations identified during both nurse and patient interviews to be captured. Cases and locations were first anonymised (the anonymisation of cases was previously described in section 4.4.3, and locations were randomly assigned letters A to P). The pseudonyms of cases and locations were entered on both the horizontal and vertical axes of a spreadsheet, producing a matrix. Cells were completed using binary code to indicate the association between each case/location and each of the other cases/locations. The absence of an epidemiological link between cases/cases and locations was denoted 0, and its presence by 1. To assist the visualisation of the network in NetDraw (Borgatti), specifications were made for node shape, colour etc. Spreadsheets were developed that coded for year of diagnosis, using 0 to denote the year 1997, 1 for 1998 and so on (up to 2004). Files were developed for disease type (pulmonary and non-pulmonary) and bacteriological status (sputum smear positive, sputum smear negative, and bronchial alveolar lavage or tracheal aspirate smear positive). Finally, the detection of links at various stages of this investigation was also coded (e.g. information known prior to investigation, information determined after patient interview – see figures 15 to 18).

After importing the matrix of association into NetDraw, the network was automatically displayed in a default format. The network was manipulated using attribute files (e.g. year of diagnosis/disease type file etc.) to develop a more meaningful network diagram. Sputum smear positive (culture positive) pulmonary cases were represented by red squares, and all other pulmonary cases by blue squares. Where information on sputum status for

pulmonary cases was not available, square nodes were grey in colour. Non-pulmonary TB cases were represented by black diamonds. Locations are show as circular green nodes and were randomly assigned a position within outbreak networks. A time line from runs from 1997 on the left of networks diagrams to 2004 on the right. Cases are located within respective columns (representing years) based on their year of diagnosis, however, the location of cases within each year column was left to the discretion of the investigator, so the clarity of the diagrams could be improved.

As previously stated, pseudonyms or numbers were used to identify cases. Where no links were detectable between cases, identifying codes were excluded, again to enhance the clarity of the diagram. Six cases with the 15-banded pattern had two episodes of disease and the episode was denoted in brackets next to the case identifier.

Lines connecting cases represent epidemiological links. Connections between cases were non-directional, due to the inherent difficulties of accurately predicting which individual represents the true index and contact case. Despite the availability of dates of diagnosis, the latency of this infection can be variable prior to active disease, and leads to difficulties in determining the directionality of the spread of infection. The coloration of lines connecting cases are explained in the relevant sections of chapter 6.

Statistical analyses of epidemiological characteristics were undertaken. Risk factors associated with having this 15-banded IS*6110* RFLP pattern (n=51) were compared with those belonging to all other clustered cases (n=153), to assist the description of the study cases. Characteristics of cases within this cluster with and without identifiable links on completion of the investigation were also compared. Details of statistical analyses were addressed in section 3.7.

4.5.2 Qualitative analysis of patient interview

Interview data relating to lay epidemiology and help seeking behaviour were explored using inductive reasoning. Two interviews were excluded from content analysis, the first of which was a mother of a seven-year old patient (Carla) who declined having the conversation tape-recorded, and therefore only notes taken during the interview were available for analysis. The second interviewee's transcript (Lewis) was omitted because it appeared his mental health was impaired at the time of interview, and much of the conversation was unintelligible.

Firstly, transcripts were reviewed to identify topics that had emerged during patient interviews. Six transcripts were randomly selected and systematically examined for this purpose. Transcripts were reviewed a second time to establish distinctions, qualifications and contradictions between and within transcripts, for each identified theme. This required reviewing one transcript at a time, while keeping the other five transcripts in mind, a practice referred to as constant comparison. Sub-themes or categories within each theme were coded and a preliminary index of codes was developed. Coding categories were continually refined until no new categories were identified. The remaining transcripts were reviewed, and additions to established categories were made to reflect all nuances in the data. Early versions of index categories inevitably relied on *a priori* codes (themes that informed the research aim, and thus the development an interview schedule), but as the analysis progressed, concepts or topics not anticipated by the investigator (referred to as *in vivo* codes) emerged (Ritchie & Spencer, 1994).

Following content analysis, one supervisor reviewed transcripts to ensure themes identified in patient transcripts were valid, and that the final indexing category incorporated all identifiable themes. To facilitate the analysis of results, similarly coded text was cut from transcripts and pasted into a Microsoft Word document. Analysis was undertaken manually rather than using specialised software, to enable the investigator to grasp the similarities and discrepancies existing within specific coding categories, and the complexity of the analytical process.

Data in categories were used to develop hypotheses that were subsequently tested against formulated theories in a process of analytic induction. This process required moving between data and established theory, and assisted in the interpretation of how patients made sense of their own experiences of social phenomenon. Presentation of results in the final script was guided by the final index category, and is supported by quotations.

Chapter 5: Epidemiology of recently transmitted TB

In recent years, molecular epidemiological studies have shown *Mycobacterium tuberculosis* transmission is occurring more often than previously thought, outbreaks of disease are going unnoticed and conventional methods of interrupting disease transmission are failing. In this chapter, the epidemiology of cases thought to result from recent *Mycobacterium tuberculosis* infection in the Greater Glasgow NHS Board area is described. Subsequent chapters seek to enhance our current understanding of *M. tuberculosis* transmission patterns, thereby providing an opportunity to reflect on the challenges faced by current strategies for early case detection. Although molecular typing information is useful in identifying clusters of cases on the basis of having a genetically indistinct *M. tuberculosis* genotype, this does not necessarily reflect the existence of epidemiological linkage. Epidemiological analysis is required to identify the pathway of transmission by describing the nature of associations between cases, potential sites of exposure etc (chapter 6). A deeper understanding of social and cultural factors influencing patient behaviour can provide further insights into factors contributing to continued disease transmission (chapter 7 and 8). In view of the enhanced understanding of disease transmission and identification of socio-cultural factors influencing disease control, the final analysis seeks to explore the effectiveness of principal control strategy contact tracing (chapter 9).

In this chapter, putative causes of disease are determined using IS*6110* RFLP typing and sub-typing technique Spoligotyping. Cases are believed to result from recent transmission of infection on the basis cases share a genetically indistinguishable IS*6110* RFLP pattern, while cases of reactivated latent infection, acquired in the distant past, are thought to be represented by unique IS*6110* RFLP patterns[17].

5.1 Identification of clusters of genetically indistinguishable IS*6110* RFLP patterns

The Department of Microbiology at the University of Aberdeen undertook the comparative analysis of IS*6110* RFLP patterns. A search was undertaken on a database of IS*6110* RFLP patterns from TB patients diagnosed in Scotland between 1997 and the 11th November 2003. Eight hundred and forty-one IS*6110* RFLP patterns were identified as

[17] There are caveats to the interpretation of molecular genotyping information, and readers are directed to chapter 3, section 3.3.1 for further discussion

belonging to patients resident in the Greater Glasgow NHS Board area. Three hundred and fifty-four patterns were immediately excluded from analysis because they had not been assigned an ESMI number, indicating a date of diagnosis prior to the establishment of the scheme in 2000 (the study period for this analysis was January 2000 to 11th November 2003). Of the remaining 487 IS*6110* RFLP patterns, 65 had poor definition or banding patterns were weak on autoradiographs, and could not be included in the analysis. As a result of this search, 422 patterns were identified as belonging to cases diagnosed in Greater Glasgow between January 2000 and 11th November 2003.

Of these 422 IS*6110* RFLP patterns, 182 were unique, that is to say, appeared only once during the study period. The remaining 240 patterns were considered clustered (genetically indistinguishable from at least one other IS*6110* RFLP pattern during the study period). However, the detection of duplicate or triplicate entries for cases in the clustered population led to the removal of 46 IS*6110* RFLP patterns. Generally, these duplicate and/or triplicates were genetically indistinguishable from the pattern remaining in the clustered population. However, three cases had two genetically distinguishable IS*6110* RFLP patterns, and here all relevant IS*6110* RFLP patterns were excluded to investigate the possibility of laboratory contamination or data error.

Identifying information was subsequently provided for the remaining 194 clustered cases, and epidemiological information was sourced from the ESMI database at Health Protection Scotland. Such information indicated 7 of the 194 clustered cases were residing outwith the Greater Glasgow NHS Board area at diagnosis. Epidemiological information could not be obtained for a further 9 clustered cases, as identifying information provided by the University of Aberdeen did not match records held in the ESMI database. Patient identifying information held by either the University of Aberdeen or Health Protection Scotland (or both) was likely to be incorrect, and could have led to the inability to retrieve epidemiological records from the ESMI database. As the date of diagnosis and NHS Board could not be verified for these 9 cases, they were excluded from the clustered population. Two of these nine cases were members of distinct clusters, containing two cases each. On eliminating these cases, both clusters were left with one case. As clusters are comprised of a minimum of two cases with genetically indistinguishable IS6110 RFLP patterns, the remaining cluster cases were excluded from the clustered population. In total, 176 cases were considered clustered for the purposes of this analysis.

5.2 Notified cases with & without IS*6110* RFLP patterns

In the Greater Glasgow NHS Board, 665 cases notified to the ESMI scheme were diagnosed between January 2000 and 11th November 2003. Twenty-two were resident in other NHS Board areas at diagnosis (they attended Greater Glasgow hospitals, but did not reside within the Greater Glasgow area), and were excluded from further analysis. Of the

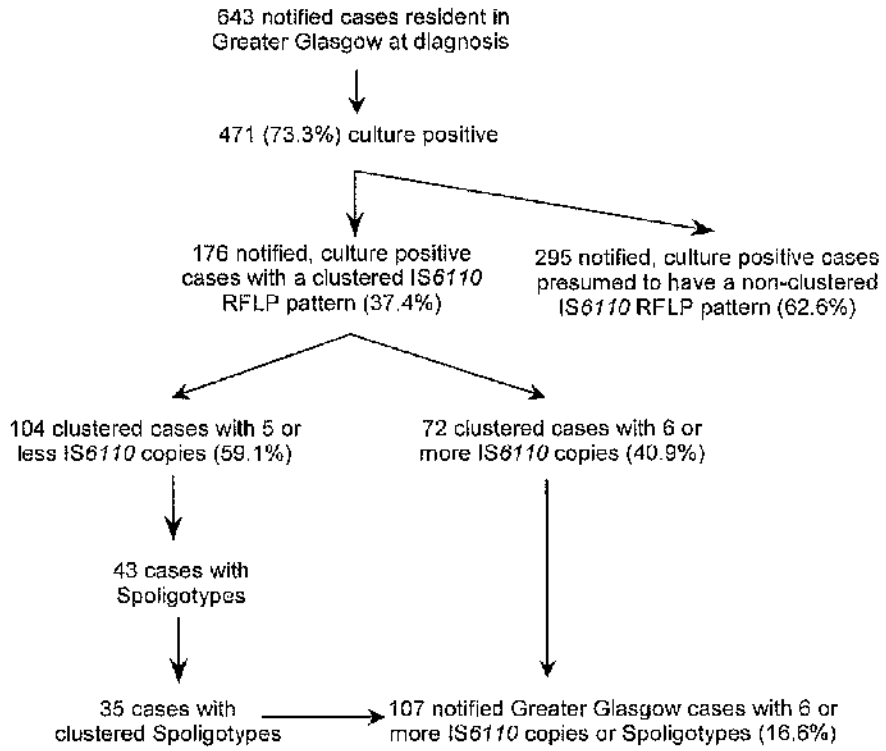

Figure 6: Algorithm summarising the derivation of clustered & non-clustered TB cases resident and notified to the Greater Glasgow NHS Board between 2000 and 11th November 2003, on the basis of IS*6110* RFLP typing and Spoligotyping

*** Diagnosed between January 2000 and 11th November 2003**

643 notified cases, there was approximately a 2:1 ratio of pulmonary (443) to non-pulmonary cases (200) TB cases. Isolates from 73.3% of cases were culture positive (471/643). Therefore, cases clustered on the basis of sharing genetically indistinguishable IS*6110* RFLP patterns represented 27.4% of all notified cases (176/643), or 37.4% of all culture positive cases (176/471). The derivation of clustered and non-clustered cases on the basis of IS*6110* RFLP typing is described here and displayed diagrammatically in figure 6.

Identifying information for cases with unique IS*6110* RFLP typing patterns was not available. Assuming RFLP typing had been completed for all culture positive cases, the remaining 62.6% of culture positive cases (295) were assigned the status of a "non-clustered" case, i.e. are likely to have a unique IS*6110* RFLP pattern within the study period. On this basis, it can be postulated that disease in 45.9% of notified cases (295/643) was a result of reactivated latent infection or the importation of new strains, probably from a high-incidence country.

However, in making this assumption, it is important to recognise that some clustered cases may have been assigned the status 'non-clustered' by default. First, culture positive cases with putatively clustered IS*6110* RFLP patterns may have been reclassified as non-clustered if the clarity of IS*6110* banding patterns was poor. Although the IS*6110* RFLP pattern would have been eliminated from the comparative analysis, the case was culture positive, and in line with the criteria for defining cases as non-clustered, were classified as such. It is also possible IS*6110* RFLP patterns for culture positive cases diagnosed near the study end date may not have been available for the University of Aberdeen analysis, as strain identification is a lengthy process, first requiring isolates to be cultured (which can take approximately 6 to 8 weeks). As all culture positive cases were presumed to have been included in the comparative RFLP analysis, such cases for whom IS*6110* RFLP patterns were not yet available were designated non-clustered. As a consequence, the proportion of culture positive clustered cases may be higher than is reported here.

Genotyping information was presumed to be absent for 172 non-culture positive cases[18], or 26.7% of the study population. As just less than three quarters of the Greater Glasgow population are included in subsequent analyses, it is important to determine whether conclusions can be extended to all cases diagnosed over the study period. Table 5 summarises results from a comparative analysis of culture positive TB cases, representative of cases deemed to be clustered and non-clustered on the basis of IS*6110* RFLP typing (471 cases), and all non-culture positive cases (172), for whom IS*6110* RFLP typing could not be undertaken.

Cases without IS*6110* RFLP patterns were significantly more likely to be younger (Mann-Whitney U-test = -3.775 $p<0.001$). This is entirely expected given the fact gastric washings are typically collected from paediatric cases and prove difficult to culture under

[18] Non-culture positive cases include cases for whom isolates returned a culture negative result and cases for whom no isolates were sent for culture.

Characteristics	Cases with IS*6110* RFLP patterns n=471		Cases without IS*6110* RFLP patterns n=172		Test	P value
Sex					χ^2 test	0.606
Male	298	63.3%	105	61%		
Female	173	36.7%	67	39%		
Age					Mann-Whitney U-test	p < 0.001
0-24	44	9.3%	49	28.5%		Z=-3.775
25-44	168	35.7%	46	26.7%		
45-64	143	30.4%	43	25%		
65+	116	24.6%	34	19.8%		
Mean age	49.2		40.8			
Standard deviation	19.28		24.19			
Country of birth					χ^2 test	0.595
United Kingdom	326	69.2%	107	62.2%		
Other country	120	25.5%	44	25.6%		
Not known	25	5.3%	21	12.2%		
Ethnicity					χ^2 test	0.034
Caucasian	333	70.7%	98	57%		
Non-Caucasian	133	28.2%	59	34.3%		
Not known	5	1.1%	15	8.7%		
BCG					χ^2 test	0.107
Yes	208	44.2%	64	37.2%		
No	134	28.5%	58	33.7%		
Not known	129	27.4%	50	29.1%		
Disease type					χ^2 test	<0.001
Sputum smear + pulmonary TB	240	51%	5	2.9%		
Other pulmonary TB	114	24.2%	86	50%		
Non-pulmonary TB	117	24.8%	81	47.1%		
Alcohol misuse					χ^2 test	<0.001
Yes	129	27.4%	19	11%		
No	342	72.2%	153	89%		
Homeless					χ^2 test	0.051
Yes	33	7%	5	2.9%		
No	438	93%	167	97.1%		
Other risk factors*					χ^2 test	0.170
Yes	69	14.6%	18	10.5%		
No	402	85.4%	154	89.5%		
Previous diagnosis					χ^2 test	0.549
Yes	43	9.1%	12	7%		
No	418	88.7%	143	83.1%		
Not known	10	2.1%	17	9.9%		
Method of identification					χ^2 test	<0.001
Contact tracing	28	5.9%	35	20.3%		
Illness subsequently diagnosed as TB	412	87.5%	120	69.8%		
Other	31	6.6%	17	9.9%		

Table 4: Characteristics of cases notified to Greater Glasgow NHS Board between 2000 and 11th November 2003 with and without IS*6110* RFLP patterns

*** Other risk factors include intravenous drug use, immunosuppression, residence in a correctional or other institution, health care worker and refugee/asylum seeker status.**
Indicates a statistical significance at p<0.05.

laboratory conditions. These isolates therefore cannot undergo IS*6110* RFLP typing. Cases without IS*6110* RFLP patterns were statistically more likely to be Caucasian (χ^2 test = 4.5, p<0.034) and identified as a result of contact tracing (χ^2 test = 33.294, p<0.0001). More cases with IS*6110* RFLP patterns had sputum smear positive pulmonary disease, while cases without IS*6110* RFLP patterns appeared to have more non-sputum smear positive pulmonary and non-pulmonary disease than expected (χ^2 test = 123.552, p<0.0001). Cases with IS*6110* RFLP patterns misused alcohol more frequently than was expected (χ^2 test = 18.989, p<0.0001).

As cases tended to be younger in the population without IS*6110* RFLP patterns, it is not unsurprising that other variables such as vaccination were found less frequently in this population. Children under the age of ten years are less likely to have been vaccinated (unless they had certain risk factors) through the schools BCG programme. Children are less likely to have infectious pulmonary disease (sputum smear positive TB), due to difficulties producing sputum. Furthermore, as will be shown in chapter 9, children are more commonly detected as a result of contact tracing initiated for close family contacts.

In conclusion, inferences about results from subsequent analyses will be largely representative of the TB population in Greater Glasgow between January 2000 and 11th November 2003. Predominantly, these cases were born in the United Kingdom, Caucasian, and had sputum smear positive pulmonary disease. Most are likely to have been diagnosed after seeking medical care of their own volition, and some will have alcohol misuse as a risk factor for infection/progression to disease. Younger cases will not be well represented due to difficulties associated with conducting molecular genotyping on specimens obtained from children.

While just over one quarter of all notified cases had no IS*6110* RFLP patterns for analysis, cases with non-clustered and clustered IS*6110* RFLP patterns represented 45.9% and 27.4% of notified cases respectively over the study period. This indicates tuberculosis resulted more frequently from reactivated latent infection or importation to infection from a high prevalence country over the observation period.

The contribution of known clustered cases (cases believed to be caused by recently acquired infection), presumed non-clustered cases (putative reactivation of latent infection or importation of infection/disease) and all other cases (cases not included in the IS*6110* RFLP comparative analysis) to the annual number of case notifications (with the exception of 2003, for which cases notified up to 11th November is provided) is shown in figure 7.

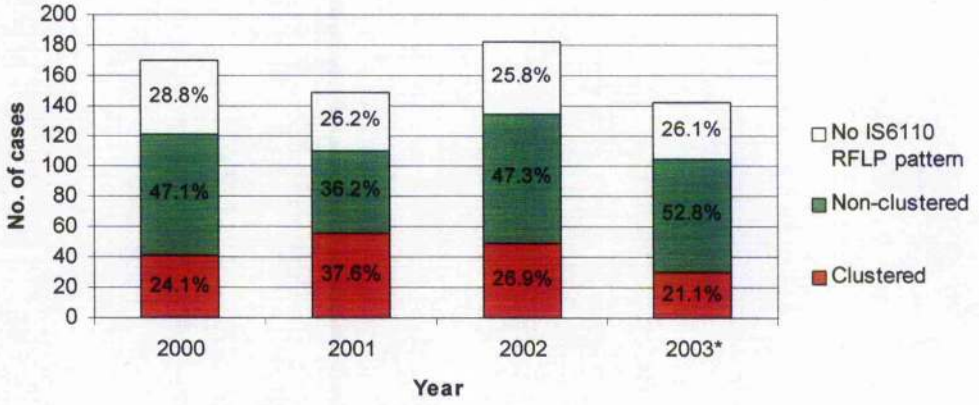

Figure 7: Clustered and non-clustered cases resident and notified to the Greater Glasgow NHS Board within the study period, by year

***IS*6110 RFLP typing and case notification information was determined to 11th November 2003.**

The proportion of notified cases without IS*6110* RFLP patterns remained relatively stable, fluctuating between 26.1% and 28.8% over the study period. At 37.6%, the largest proportion of notified clustered cases was observed in 2001. Indeed, the number of cases with clustered IS*6110* RFLP patterns exceeded those noted in other years, despite the fact a low number of cases were notified in that year. The lowest number of notified cases with clustered IS*6110* RFLP patterns was observed in 2003, as the number of clustered cases included in this analysis was likely to be incomplete, for reasons previously described.

Furthermore, 2001 proved an exceptional year with regards to the proportion of non-clustered notified cases, as it exceeded those of non-clustered cases. Coupled with the fact a large proportion of notified cases had clustered IS*6110* RFLP patterns, this suggests a greater amount of disease was due to ongoing transmission of infection in this year, as compared with other years in the observation period. Although analysis of epidemiological data could improve our understanding of the reasons for the large proportion of clustered cases found in 2001, this was outwith the scope of this study.

5.3 Clustered & non-clustered case characteristics

To describe the characteristics of cases thought to result from recently transmitted infection, characteristics of these 176 cases were compared to 295 cases with unique

Characteristics	Clustered cases n=176		Non-clustered cases n=295		Test	P value
Sex					χ^2 test	0.001
Male	128	72.7%	170	57.6%		
Female	48	27.3%	125	42.4%		
Age					Mann Whitney U-test	p = 0.491
0-24	15	8.5%	29	9.8%		Z = -0.688
25-44	60	34.1%	108	36.6%		
45-64	64	36.4%	79	26.8%		
65+	37	21%	79	26.8%		
Mean age	49.6		48.9			
Standard deviation	18		20.03			
Country of birth					χ^2 test	<0.001
United Kingdom	147	83.5%	179	60.7%		
Other country	20	11.4%	100	33.9%		
Not known	9	5.1%	16	5.4%		
Ethnicity					χ^2 test	<0.001
Caucasian	151	85.8%	182	61.7%		
Non-Caucasian	24	13.6%	109	36.9%		
Not known	1	0.6%	4	1.4%		
BCG					χ^2 test	0.494
Yes	79	44.9%	129	43.7%		
No	46	26.1%	88	29.8%		
Not known	51	29%	78	26.4%		
Disease type					χ^2 test	0.001
Sputum smear + pulmonary TB	105	59.7%	135	45.8%		
Other pulmonary TB	44	25%	73	24.7%		
Non-pulmonary TB	27	15.3%	87	29.5%		
Alcohol misuse					χ^2 test	<0.001
Yes	73	41.5%	56	19%		
No	103	58.5%	239	81%		
Homeless					χ^2 test	0.004
Yes	20	11.4%	13	4.4%		
No	156	88.6%	282	95.6%		
Other risk factors*					χ^2 test	0.198
Yes	21	11.9%	48	16.3%		
No	155	88.1%	247	83.7%		
Previous diagnosis					χ^2 test	0.115
Yes	21	11.9%	22	7.5%		
No	153	87%	266	89.8%		
Not known	2	1.1%	8	2.7%		
Method of identification					χ^2 test	0.108
Contact tracing	15	8.5%	13	4.4%		
Illness subsequently diagnosed as TB	147	83.5%	265	89.8%		
Other	14	8%	17	5.8%		

Table 5: Characteristics of clustered and non-clustered cases (on the basis of IS*6110* RFLP typing) resident and notified to the Greater Glasgow NHS Board between 2000 and 11th November 2003

*** Other risk factors include intravenous drug use, immunosuppression, residence in a correctional or other institution, health care worker and refugee/asylum seeker status.**

Indicates a statistical significance at p<0.05

IS*6110* RFLP patterns (table 6). Statistically significant differences between clustered and non-clustered cases were discernible with regards to sex, place of birth and ethnicity, disease type and risk factors alcohol misuse and homelessness.

Both clustered and non-clustered populations contained more male cases than females. More males were observed than expected in the clustered case cohort, as compared to the non-clustered category (χ^2 test = 10.816, $p < 0.001$). Both clustered and non-clustered populations had a similar mean age, and the smallest proportions of cases were found in the 0-24 age-group. This may reflect the fact that 52.7% (49/93) of cases notified to Greater Glasgow NHS Board aged 24 and under did not have IS*6110* RFLP patterns, and therefore could not be included in this analysis.

Clustered cases were significantly more likely to have a greater frequency of sputum smear positive pulmonary TB than cases with unique IS*6110* RFLP patterns, while nearly twice as many non-clustered cases had non-pulmonary disease (29.5%) than clustered cases (15.3%) (χ^2 test = 13.3, $p = 0.001$).

BCG status, previous TB diagnosis, method of identification and other risk factor variables were not found to differ significantly between clustered and non-clustered cases. In both clustered and non-clustered case populations, more cases were vaccinated than not, however, information was not available for a large proportion of these cases. The majority of cases in both populations were diagnosed after presenting to health professionals with symptoms subsequently diagnosed as TB, and had not been previously diagnosed with tuberculosis.

With regards to place of birth and ethnicity, a statistically significant difference was detected between clustered and non-clustered cases. Clustered cases were more often born in the United Kingdom (χ^2 test = 30.257 $p < 0.001$) and of Caucasian ethnicity (χ^2 test = 30.205, $p < 0.001$) as compared with non-clustered cases.

The age banding of Caucasian and non-Caucasian cases was then analysed by clustering status (figure 8). With regards to all non-clustered cases, an increasing number of cases are observed in each successive age cohort in the Caucasian population, with 69.8% of cases aged 45 years and older. This contrasts with the non-Caucasian, non-clustered case population, as over half (58.7%) of cases are aged 25 to 44 years. The difference in mean age of Caucasian and non-Caucasian non-clustered cases was found to be statistically significant (Mann-Whitney U-test = 5165.5, $p<0.001$). It is likely reactivation of latent

infection plays an important role in disease causation in the Caucasian population, while the observed peak of non-Caucasian non-clustered cases in the 25-44 year age group represents the importation of infection from high prevalence countries in the Indian Sub-Continent (or transmission of TB within non-Caucasian communities in Scotland).

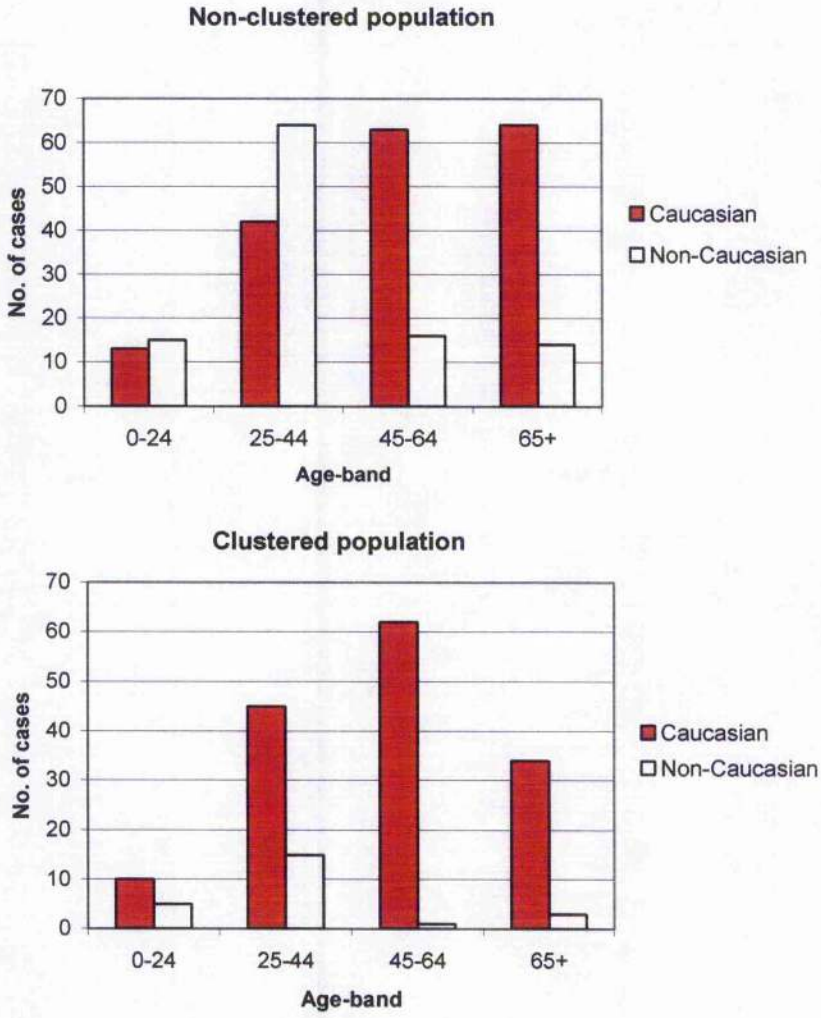

Figure 8: Age distribution of clustered and non-clustered cases resident and notified to the Greater Glasgow NHS Board between January 2000 and 11th November 2003, by ethnicity

The numbers of Caucasian and non-Caucasian cases with clustered IS*6110* RFLP patterns peak in the 45-64 and 25-44 age groups respectively. A statistically significant difference in age was detectable between Caucasian and non-Caucasian clustered cases (Mann-Whitney U-test= 799.9, $p<0.001$). In the Caucasian population, the increasing trend with respect to age banding of clustered cases is similar to that of non-clustered cases.

However, the number of clustered cases in the 65 and older age cohort declines, indicating transmission of infection plays a greater role in disease causation in younger Caucasian population. In the non-Caucasian population, far fewer cases are thought to be due to recent transmission than reactivation or importation of infection, particularly in cases aged 45 and older.

Returning to the findings displayed in table 6, significantly more clustered than non-clustered cases misused alcohol (χ^2 test = 28.047, $p < 0.001$) and were homeless (χ^2 test = 8.188, $p < 0.004$). Having such risk behaviours and being infectious are expected to enhance the potential for TB transmission to occur. Intravenous drug use, immunosuppression, residence in a correctional or other institution, health care worker, refugee/asylum seeker were included in the 'other risk' category, but for the vast majority of clustered (88.1%) and non-clustered (83.7%), these factors were not indicated.

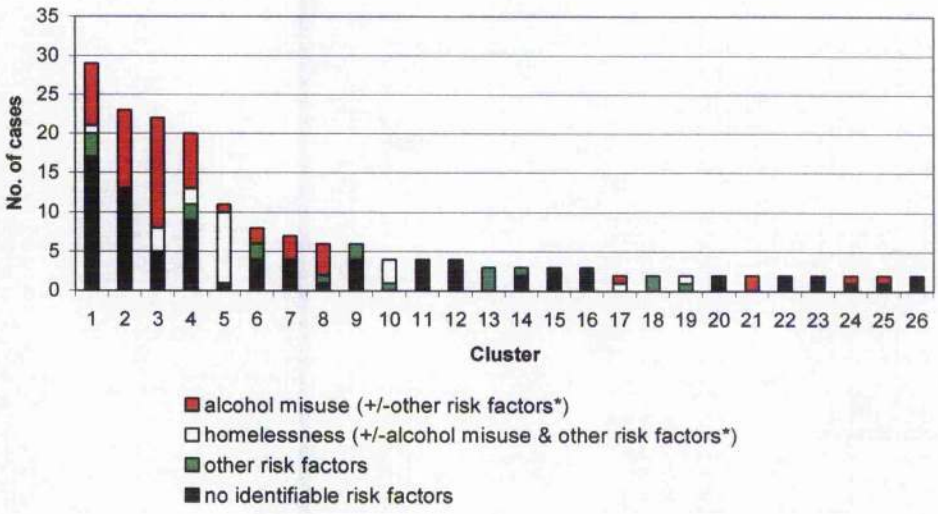

Figure 9: Risk factors attributed to clustered cases within 26 clusters identified on the basis of IS*6110* RFLP typing. Cases were resident in and notified to the Greater Glasgow NHS Board between 2000 and 11th November 2003

*** +/- other risk factors indicates other concurrent attributes, such as alcohol misuse, intravenous drug use, immunosuppression, residence in a correctional or other institution, health care worker, refugee/asylum seeker.**

Risk factors attributed to members of the 26 identified clusters are presented in figure 9. Just over half (52.3%) of clustered cases had identifiable risk factors. Eight clusters (clusters 11, 12, 15, 16, 20, 22, 23, 26) had no identifiable risk factors for any cluster member. Of all 176 clustered cases, twenty-three had multiple risk factors (indicated by

+/- alcohol misuse and/or other risk factors). Typically, this was indicated for homeless individuals who were known to have concurrent alcohol misuse issues.

Alcohol misuse was the most commonly cited risk factor and was attributed to 41.5% of the clustered case population,. This risk factor was indicated by a minimum of one case in 14 of the 26 clusters. Within the four largest clusters (clusters 1 to 4), the proportion of cases in each cluster indicated as having alcohol misuse issues ranged from between 27.6% to 63.6%. The majority of cases allocated to cluster 5 were known to be homeless, suggesting that a specific strain exhibiting a 7-banded IS*6110* RFLP pattern was circulating in this risk population. Indeed, seven were known to have resided in the same hostel in Glasgow. Homelessness also dominated in cluster 10, with cases exhibiting another seven-banded IS*6110* RFLP pattern. This pattern was genetically distinct from that in cluster 5, due to IS*6110* copy positioning on the *M. tuberculosis* genome. Other than being homeless and having alcohol misuse issues, surveillance information did not provide information to determine the nature of association between cluster 10 cases. Overall, homelessness was indicated by at least one case in seven distinct clusters over the study period.

Clusters 13 and 18 involved three and two cases respectively, with risk factors other than alcohol misuse or homelessness. Cluster 13 cases were nursing home residents with a 3-banded RFLP pattern. Two were resident in the same nursing home at the time of diagnosis, and information to epidemiologically link the third case had not been collected through the ESMI scheme. Cluster 18 comprised of two female Somalians, who arrived in the UK in 2001 and were diagnosed in 2002. There appeared to be no association between these two women. It is possible both women were infected with a strain prevalent in Somalia. Shortly after arriving in the United Kingdom, their infections may have reactivated. Alternatively, information to link these patients may have been withheld from nursing staff.

Furthermore, three cases spent time in correctional facilities, two of which were diagnosed with an 8-banded pattern (cluster 8). Surveillance data did not indicate whether they were imprisoned within the same institution, or had overlapping sentences.

Characteristics	Total cases n= 471	Clustered cases n=176 (% of total cases)		Odds Ratio Unadjusted	95% C.I. for O.R. Unadjusted	Odds Ratio Adjusted	95% C.I. for O.R. Adjusted
Sex							
Male	298	128	43%	1	-	1	-
Female	173	48	27.7%	0.510	(0.34, 0.764)	0.651	(0.414 1.025)
Age							
0-24	44	15	34.1%	1	-	1	-
25-44	168	60	35.7%	1.074	(0.534, 2.16)	0.893	(0.417, 1.91)
45-64	143	64	44.8%	1.566	(0.774, 3.17)	0.719	(0.325, 1.591)
65+	116	37	31.9%	0.905	(0.434, 1.889)	0.574	(0.255, 1.292)
Country of birth							
United Kingdom	326	147	45.1%	1	-	1	-
Other country	120	20	16.7%	0.244	(0.144, 0.413)	0.481	(0.158, 1.465)
Not known	25	9	36%	0.685	(0.294, 1.595)	0.844	(0.31, 2.302)
Ethnicity							
Caucasian	333	151	45.3%	1	-	1	-
Non-Caucasian	133	24	18%	0.265	(0.165, 0.434)	0.528	(0.176, 1.58)
Not known	5	1	20%	0.301	(0.033, 2.725	1.006	(0.039, 26.256)
BCG							
Yes	208	79	38%	1	-	1	-
No	134	46	34.3%	0.854	(0.542, 1.343)	0.797	(0.465, 1.368)
Not known	129	51	39.5%	1.068	(0.68,1.675)	0.993	(0.588, 1.674)
Disease type							
Sputum smear + pulmonary TB	240	105	43.8%	1	-	1	-
Other pulmonary TB	114	44	38.6%	0.775	(0.493, 1.219)	0.926	(0.509, 1.685)
Non-pulmonary TB	117	27	23.1%	0.399	(0.242, 0.659)	1.042	(0.833, 1.716)
Alcohol misuse							
No	342	103	30.1%	1	-	1	-
Yes	129	73	56.6%	3.025	(1.992, 4.594)	1.623	(0.963, 2.735)
Homeless							
No	438	156	35.6%	1	-	1	-
Yes	33	20	60.6%	2.781	(1.347, 5.743)	1.421	(0.627, 3.219)
Other risk factors*							
No	402	155	38.6%	1	-	1	-
Yes	69	21	30.4%	0.697	(0.402, 1.209)	1.027	(0.554, 1.904)
Previous diagnosis							
No	418	153	36.6%	1	-	1	-
Yes	43	21	48.8%	1.653	(0.88, 3.105)	1.4	(0.71, 2.761)
Not known	10	2	20%	0.433	(0.091, 2.065)	0.434	(0.44, 4.313)

Table 6: Univariate and multivariate logistic regression analysis on the likelihood of cases resident and notified to the Greater Glasgow NHS Board being a clustered case

*** +/- other risk facts indicates other concurrent attributes, such as alcohol misuse, intravenous drug use, immunosuppression, residence in a correctional or other institution, health care worker, refugee/asylum seeker.**

A multiple regression model was developed to investigate the effect of numerous epidemiological characteristics on the probability of being a clustered case (table 7). For this purpose, the odds of being a case with an IS*6110* RFLP pattern, genetically indistinguishable from at least one other during the study period (clustered case), was measured against that of being a case with a unique IS*6110* RFLP pattern (non-clustered case).

Unadjusted odds ratios were first determined from univariate analysis; therefore odds were not corrected for confounding by multiple variables. Compared to the reference category "male", being female was associated with lower odds of being a clustered case (0.51, 95% confidence interval 0.36 - 0.804). There was a statistically significant odds of being a non-clustered case if born outside the United Kingdom (0.144, 0.413), and if of non-Caucasian ethnic origin (0.165, 0.434). Having non-pulmonary TB was also independently associated with having lower odds of being a clustered case (0.242, 0.659). Compared with their respective reference categories, misuse of alcohol (1.992, 4.594) and homelessness (1.347, 5.743) were independently associated with higher odds of being a clustered case.

Statistically significant odds of being a clustered case were not detectable for any of the ten explanatory variables, once all were entered into a multiple regression model. That is to say, variables such as being female, non-UK born, of non-Caucasian ethnicity and having non-pulmonary TB, associated with lower odds of being a clustered case, and variables alcohol misuse and homelessness independently associated with a higher odds of being a non-clustered case, were not found to be statistically significant in a multivariate model.

Therefore, epidemiological characteristics used to develop this multivariate model were not found to have a significant influence on the outcome of being a clustered case. For example, although alcohol misuse and homelessness were independently associated with being clustered, in reality these variables often present together in a TB patient, and independent association with the outcome cannot be proven.

To identify variables capable of making good predictions about the outcome of being a clustered case, multivariate models were constructed by backwards and forwards selection methods. This technique is undertaken to identify characteristics that may prove useful in constructing improved multivariate models in future analyses. Both forwards selection and backwards elimination strategies were employed for this purpose, and both identified the variables alcohol misuse and country of birth (United Kingdom or outwith United Kingdom) as good predictors of the outcome of having a genetically indistinguishable

IS*6110* RFLP pattern. In addition, the variable sex was not eliminated during the development of the backwards conditional model, indicating that this factor may also prove to be a good predictor of the outcome.

5.4 Cluster characteristics

As shown in figure 6, 176 cases were found to have an RFLP pattern (with between 1 and 15 IS*6110* copies) that was genetically indistinguishable from at least one other one case. In total, 26 RFLP patterns were detected in two or more cases over the study period, therefore 26 clusters were identifiable. Clusters contained up to 29 cases, with a mean of 6.8 cases per cluster. For the purposes of describing this analysis, numbers were used to identify clusters, and were assigned in decreasing order, beginning with the cluster containing the greatest number of cases. The four largest clusters (cluster numbers one to four) contained 29, 23, 21 and 20 cases respectively, and together accounted for over half (52.8%) of clustered cases. In terms of IS*6110* RFLP patterns, the cases in these clusters had banding patterns containing 4, 15, 5 and 2 IS*6110* copies.

Indeed, half (13/26) of all clusters involved cases with RFLP patterns containing five or less copies of IS*6110* (figure 10). One cluster of cases (cluster 9) with a one-banded RFLP pattern (containing 6 cases), and one cluster of cases with a 2-banded pattern (cluster 4 - containing 20 cases) were detected. Three genetically distinct three-banded RFLP patterns were detected containing 7, 3 and 3 cases each (cluster 7, 13, 14). Four clusters with genetically indistinguishable four and five banded RFLP patterns, respectively, were identified (clusters 1, 22, 23 and clusters 3, 11, 25, 26 respectively) . Again, clusters with the same number of IS*6110* copies (e.g. four, four-banded RFLP patterns) were distinguished by differential location of insertion sequences on RFLP patterns.

It is recognised that supplementary typing techniques are required to improve the discriminatory power of comparative analysis of low-copy number RFLP patterns (RFLP patterns with 5 or less IS*6110* copies). Spoligotyping information was sought for the 104 clustered cases (59.1% of clustered case population) identified as having RFLP patterns with 5 or less IS*6110* copies. As Spoligotyping was undertaken on an ad-hoc basis during the study period, information was available for 43 of such cases (41.3% of cases with low IS*6110* copy numbers). Spoligotypes were assigned by the Scottish Mycobacterial Reference Laboratory (SMRL), in accordance with international classification (e.g. ST137), and are shown in figure 11.

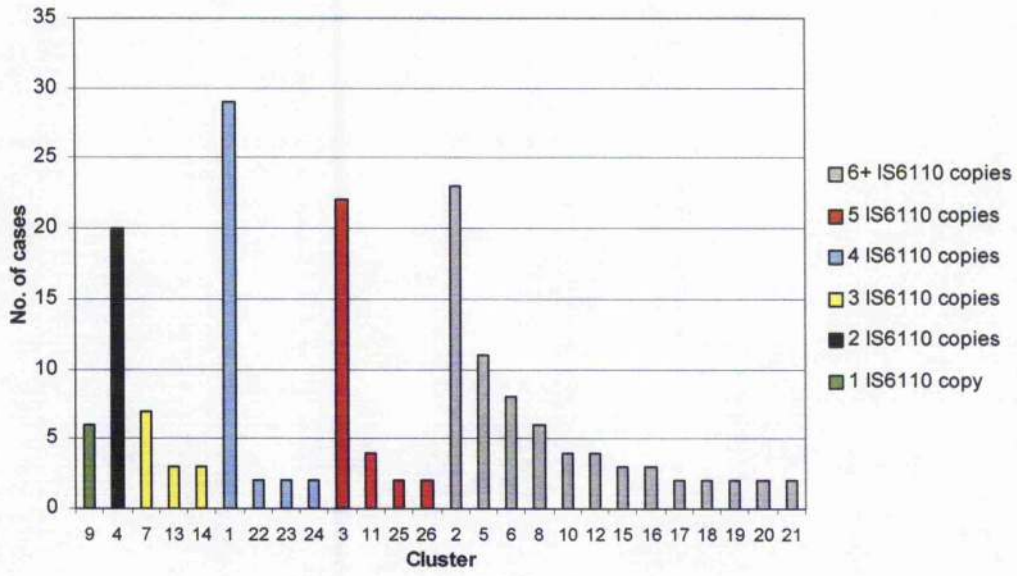

Figure 10: Distribution of RFLP patterns belonging to clustered cases resident in and notified to the Greater Glasgow NHS Board between 2000 and 11th November 2003, by IS*6110* copy number

Spoligotyping information was not available for any case within 5 of the 13 low-copy number clusters (clusters 7, 13, 22, 25, 26). In five of the eight remaining clusters, only one Spoligotype was detected (clusters 9, 11, 14, 23, 24). However, in clusters 1 and 4, four different Spoligotypes were identified, and in cluster 3, two Spoligotypes. This suggests each of these three clusters contain more than one *M. tuberculosis* genotype, and IS*6110* RFLP typing alone was not powerful enough to distinguish between these genotypes.

In total, eleven different Spoligotypes were identified across eight of the thirteen clusters with low-copy number IS*6110* RFLP patterns. Eight of these Spoligotypes were unique to a specific cluster. This is in contrast to the three remaining Spoligotypes (ST119, ST137, ST244), which were detectable in two or more genetically distinct clusters. For example, 13 cases in cluster 1 and 1 case in cluster 24 were found to have ST119.

Utilising both IS*6110* RFLP typing and Spoligotyping information, the proportion of cases attributed to clustering and recent transmission were recalculated. Of the 176 cases clustered on the basis of IS*6110* RFLP typing information, 104 cases had low-copy number IS*6110* RFLP patterns requiring further sub-typing to confirm their clustered status. The remaining 72 cases had RFLP patterns with 6 or more IS*6110* copies. Spoligotyping information was only available for 43 cases, therefore 61 low-copy number cases were excluded from the calculation. Eight of the 43 remaining cases had Spoligotypes that were

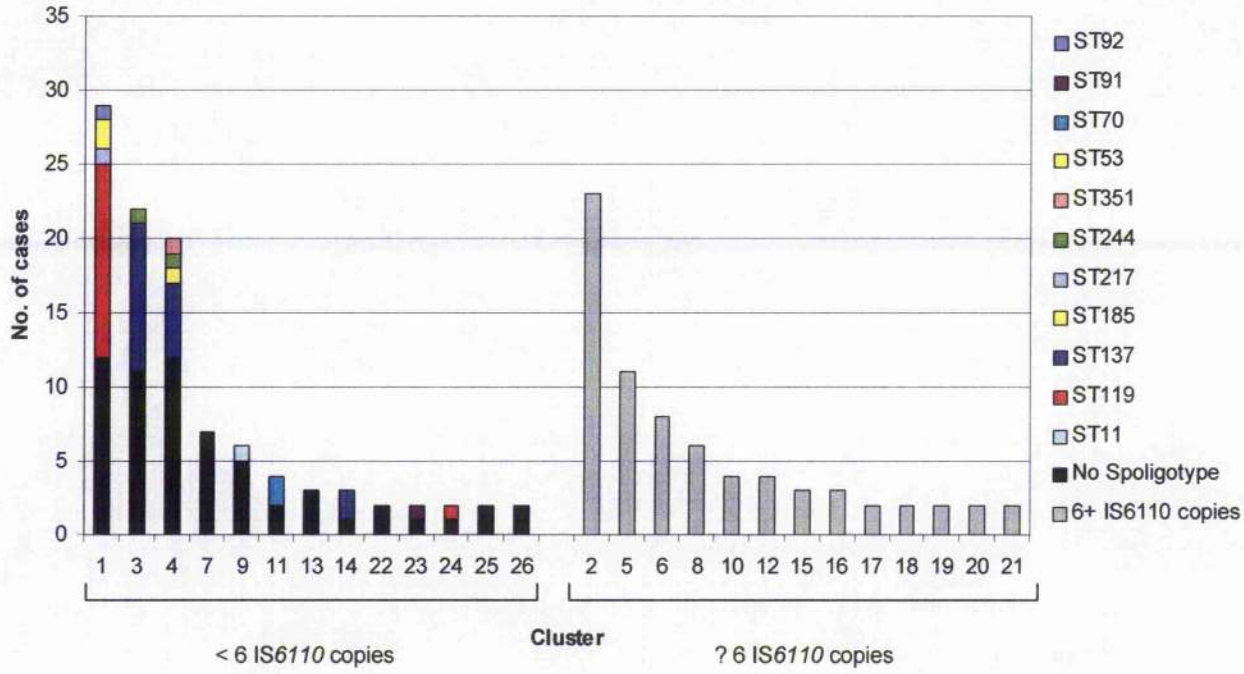

Figure 11: Distribution of RFLP patterns belonging to clustered cases resident in and notified to the Greater Glasgow NHS Board between 2000 and 11th November 2003, by IS*6110* copy number and Spoligotype

only detected once and were therefore excluded as a cluster by definition must include a minimum of 2 cases with the same genotype. Therefore, 35 cases with low IS*6110* copy number RFLP patterns and Spoligotyping information, and 72 cases with high IS*6110* copy number RFLP patterns were included in this calculation (107 clustered cases in total).

Between January 2000 and 11th November 2003, 22.7% of culture proven cases (107/471) were infected with strains of *M. tuberculosis* found in at least one other study case. By defining clusters strictly on the basis of having a high IS*6110* copy number RFLP pattern, or a low IS*6110* copy number RFLP pattern with corresponding Spoligotyping information, 17 clusters were identified. These clusters contained between 2 and 23 cases, and had a mean of 6.3 cases per cluster. By assuming one member of each cluster represents the source of infection for all other cluster members (107-17=90), the proportion of cases due to recently transmitted infection can be estimated. Using a denominator of all culture proven TB cases (n=471)[19], the proportion of cases due to recent infection was calculated as 19.1% (90/471).

The TB case presumed to be the index was excluded from each of the 17 clusters (index case was chosen based on earliest date of notification assigned to a case within each

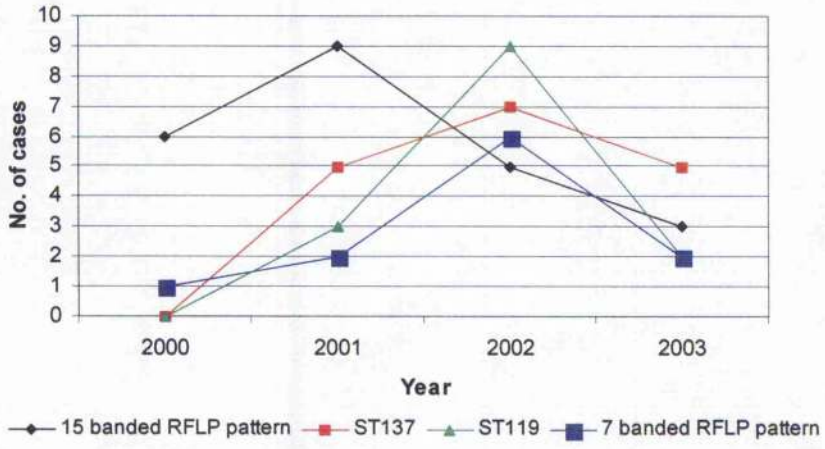

Figure 12: Four most frequently detected IS*6110* RFLP patterns/Spoligotypes in cases resident in and notified to the Greater Glasgow NHS Board between 2000 and 11th November 2003, by study year

[19] A clustering rate using a denominator consisting of all cases with high copy number IS*6110* RFLP patterns and low copy number patterns with available Spoligotyping information would have been preferred to calculate an accurate estimate (as opposed to culture proven cases only, which include low copy number patterns with no sub-typing information). However, banding numbers and Spoligotype information was only available from the University of Aberdeen analysis for clustered cases only (n=176) (not cases deemed to be unique, n=295 – see figure 6).

cluster). On this basis, 6 of the 90 remaining cases, presumed to have recently acquired TB, were identified as a result of contact tracing (6.7%).

The annual distribution of cases in the four most prevalent clusters over the study period, as defined by IS*6110* RFLP typing and Spoligotyping, is presented in figure 12. These clusters contain 23 (15-banded RFLP pattern), 17 (ST137), 14 (ST119) and 11 cases (7-banded RFLP pattern) respectively. Whereas the greatest number of cases with a 15-banded IS*6110* RFLP pattern were detected in 2001, the detection of this *M. tuberculosis* genotype declined in subsequent years. This contrasts with the observable trend in all other clusters, as the number of cases increased over the first three years of the study. Case numbers decreased in all four clusters in the final study year, as data for 2003 were unavoidably incomplete for that year.

The increased detection of cases in 2002 may be due to a number of reasons. An outbreak associated with a South Glasgow public house was known to have occurred in that year. Six of the seven cases with ST119 had known epidemiological associations with this public house and/or public house staff. With regards to the case cluster with a genetically indistinguishable 7-banded IS*6110* RFLP pattern, all six cases diagnosed in 2002 were homeless, and known to reside at the same hostel. When two individuals from this hostel presented to the health services with symptoms in 2002, they were diagnosed with tuberculosis, and an x-ray screening program was subsequently initiated in that hostel. This initiative diagnosed disease in a further 3 cases, one of which was identified by this RFLP analysis as having a genetically indistinguishable 7-banded strain.

Finally, factors contributing to the peak in case detection observed in 2002 for ST137 were not determinable from surveillance information, although some associations between cases had been determined during contact tracing. It is likely alcohol misuse placed these cases at risk of acquiring disease/progression from latent to active disease, as 11 of these 17 cases were known to misuse alcohol.

5.5 Discussion

In this analysis, IS*6110* RFLP and Spoligotyping information was used to identify clusters of cases, believed to represent the occurrence of ongoing transmission in Greater Glasgow over (approximately) a four-year period. One hundred and seventy six cases were clustered on the basis of IS*6110* RFLP typing alone, and were assigned to 26 clusters containing between 2 and 29 cases. A proportion of these cases (59.1%) had low-copy

numbers of IS*6110*, and Spoligotyping information was sought to increase the discriminatory power of the principal genotyping technique. Of the 643 cases notified over the study period, 107 cases (16.6%) were attributed to 17 clusters on the basis of IS*6110* RFLP typing and Spoligotyping. Twenty-two point seven percent of all culture proven cases were considered clustered, therefore on the basis one case in every cluster represents the source of infection, 19.1% of culture positive cases are believed to be due to ongoing transmission.

Whereas in the past, it was postulated that 10% of cases in low-incidence countries were attributable to recent transmission of infection, many molecular epidemiological studies have provided evidence to suggest recently transmitted infection makes a greater contribution to the overall burden of disease than previously thought. Such studies indicated that on average, 43% of disease is caused by recently transmitted infection (Alland *et al.*, 1994, Bauer *et al.*, 1998, Small *et al.*, 1994, van Soolingen *et al.*, 1999). Findings from this study suggest 19.1% of cases in this study population were thought to have acquired TB following recent transmission.

Although this figure is lower than determined in other molecular epidemiological studies, this finding needs to be interpreted with caution. In this analysis, molecular typing information was firstly unavailable for over a quarter (26.7%) of notified cases over the study period as patient isolates were culture negative, and sufficiently discriminatory molecular genotyping (Spoligotyping) information was unavailable for 34.7% of cases found to be clustered on the basis of having low copy number (<6 IS*6110* copies) RFLP patterns. Also, the disparity between study populations, periods under investigation and epidemiological profiles preclude direct comparison between results from molecular epidemiological studies.

Mindful of these caveats, it is worth considering findings from a population-based study in another urban area in the United Kingdom (London) between July 1995 and 1997. Here, a clustering rate of 22.7% was determined for cases with 5 or more IS*6110* copies (as opposed to 6 or more in this study), and 19.1% of study cases were thought to be due to recently transmitted infection (Maguire *et al.*, 2003). Although a similarly low rate of disease due to recent transmission was determined in Glasgow, the reasons attributed to these findings need further exploration, as the epidemiological profiles of London and Glasgow differ.

In London, multivariate statistical analysis showed that young age (0-19 years), being born in the United Kingdom, alcohol dependence and streptomycin resistance were independently associated with clustering. Importantly, 57.3% of the study population were born outwith the UK. Given that birth in the UK was associated with clustering, Maguire *et al.* postulated that those not born in the UK may have acquired disease before entering the country, and would not be observed in clusters detected within this study population. It was proposed that recent transmission played a small role in disease causation because of importation of infection by immigrants and also reactivation of previous infection.

In this study, multivariate analysis did not detect independent associations with an outcome of clustering. However, univariate analysis indicated that alcohol misuse and homelessness were associated with higher odds of being clustered, while being female, non-Caucasian, born outwith the UK and having non-pulmonary TB had a lower odds of being clustered. It is felt that variables such as being male, UK born, alcohol misuse and homelessness were confounded by association with one another; hence independent associations were not detected in a multivariate model.

These data suggests that like London, recent transmission of infection is responsible for a small proportion of disease. Despite this, interruption of ongoing transmission should continue to be the focus of strategies to control tuberculosis (World Health Organization *et al.*, 2002). In Glasgow, over two-thirds of the culture positive study population (n=471) were born in the UK. In contrast to London, importation of infection by immigrants is likely to play a lesser role, as non-UK born cases represent 33.9% of the non-clustered case population. The stable rate of immigration into Scotland may in part contribute to these low levels of recent transmission observed in Glasgow.

Of the culture positive study cases in this study, 62.6% were infected with a strain of *M. tuberculosis* detected only once over the four-year study period. A proportion of these cases are likely to result from the reactivation of latent infection and importation of strains found in high-prevalence countries. It is conceivable some may also have been clustered with cases failing to meet study inclusion criteria and are in fact part of clusters not observed in this study.

Like other low-incidence countries, increasing notifications of tuberculosis in the elderly population has been observed in Scotland (Harper, 1999). As the demographic profile has changed to one in which an increasing proportion of the population are elderly, reactivation of latent infection is likely to play an important role in TB epidemiology. This feature of

Glasgow's epidemiological profile was mirrored in this study, as the proportion of non-clustered Caucasian cases peaked in the 45 and older age group. By comparison, the proportion of clustered Caucasian cases peaked in the 45-64 year age group and declined in the 65 and older age group. For this reason, it is felt reactivation of latent or previous infection made a greater contribution than importation of infection to the non-clustered case population.

In London, the largest cluster detected was composed largely of individuals recently arrived from Somalia, and it is thought transmission may have occurred before arrival. Principally, clusters of cases were found amongst the indigenous population in Glasgow, and similar to other London clusters, alcohol misuse was also found to be a relatively common risk factor. Indeed, of the 176 cases clustered on the basis of IS*6110* RFLP typing, alcohol misuse had been indicated for 41.5%, and detected in at least one case in 14 of the 26 discernible clusters. Next to alcohol misuse, homelessness was the second most frequently noted risk factor, indicated for 11.4% of clustered cases. This suggests that efforts to control ongoing transmission might benefit from enhancing current efforts to tackle these problematic populations.

The proportion of cases resulting from recent infection fluctuated annually over the study period. Although little can be deduced from monitoring trends over this short time frame, other studies have used such an approach to evaluate the effectiveness of intensified contact tracing efforts by measuring the rate of new cases resulting from recent transmission (Jasmer *et al.*, 1999). Molecular typing has also been used to monitor the frequency of clustered cases and newly emerging strains within a community (Geng *et al.*, 2002, Munsiff *et al.*, 2002). Although outwith the scope of this investigation, the surveillance of strains in this manner offers an opportunity to determine the contribution of clustered and non-clustered cases to the static tuberculosis morbidity rate in Scotland. The possible uses of molecular genotyping in clinical management and public health activities require debate and discussion in Glasgow. Currently, molecular typing information is requested to confirm whether epidemiologically linked cases have genetically indistinguishable *M. tuberculosis* genotypes. It is recognised that IS*6110* RFLP typing has limited value in Glasgow, by virtue of the need to culture specimens, delaying strain identification by on average 6-8 weeks. Secondly, the high proportion of low-copy number RFLP patterns in the Glasgow TB population means the discriminatory power of comparative analysis of IS*6110* RFLP patterns is reduced. New alternatives are required, and are currently being evaluated at the Scottish Mycobacterial Reference Laboratory (personal communication, Director of SMRL, Dr X. Emmanuel).

As this study identified some previously unrecognised clusters of cases, thought to represent ongoing transmission of *M. tuberculosis* in Glasgow, this raises the question whether current strategies to interrupt disease dissemination are functioning effectively. In this study population, 90 of the 107 clustered cases were thought to be recently infected, of which 6 cases (6.7%) were identified as a result of contact tracing. This low rate of detection has been observed by other molecular epidemiological investigations (Small *et al.*, 1994). In view of these data, chapter 9 will examine whether contact tracing in Glasgow is operating effectively, by measuring outcomes such as the number of screened contacts diagnosed with tuberculosis. First, however, chapter 6 aims to gain further insights into the nature of disease transmission, by examining patient risk behaviour. As epidemiological enquiry overlooks the social and cultural factors that contribute to the ongoing dissemination of disease, chapters 7 and 8 continue to examine reasons for this, by exploring patients understanding of tuberculosis and help seeking behaviour.

Chapter 6: Identification of a previously undetected pathway of recently transmitted tuberculosis

In chapter 5, some previously unrecognised clusters of cases were identified on the basis of infection with a genetically indistinguishable IS*6110* RFLP patterns and matching Spoligotypes. The oversight of routine epidemiological investigation in identification of cases, putatively caused by recent transmission of infection, warrants further examination. First, it is recognised that clustering on the basis of infection with the same genotype is not always indicative of recently transmitted infection (Braden *et al.*, 1997). To determine whether a genetically defined cluster is truly representative of recently transmitted infection, epidemiological links between cluster cases should be established. Secondly, routine epidemiological techniques such as contact tracing interviews are used to identify infected contacts. In view of the previously unrecognised clusters detected in chapter five, it is important to examine reasons, which could explain the shortcomings of such an approach. To this end, one single genetically defined cluster of cases is the subject of further investigation in chapter six. The aim of this analysis is to describe the network of disease transmission between 51 patients with culture positive isolates, identified as having a genetically indistinguishable 15-banded IS*6110* RFLP typing pattern between January 1997 and September 2004.

6.1 Epidemiology of the cluster population

The first case confirmed as having this 15-banded IS*6110* RFLP pattern was a 61-year old male, diagnosed with sputum smear positive pulmonary tuberculosis in May 1997. Although just one other case was found to have the 15-banded IS*6110* RFLP pattern that year, the annual number of cases gradually increased until 2001, a year in which 11 cases were detected. From 2002 onwards, a decline in the number of cases was observed (figure 14).

With the exception of three cases, all were resident in the Greater Glasgow NHS Board area at the time of diagnosis. The three remaining cases were diagnosed in 2000 (two cases) and 2002 (one case) respectively, and were living in the Western Isles NHS Board area. Figure 13 shows the geographical distribution of cluster cases, using home address postcodes for the 48 patients diagnosed in Glasgow. Members of this cluster were predominantly resident in Northwest Glasgow.

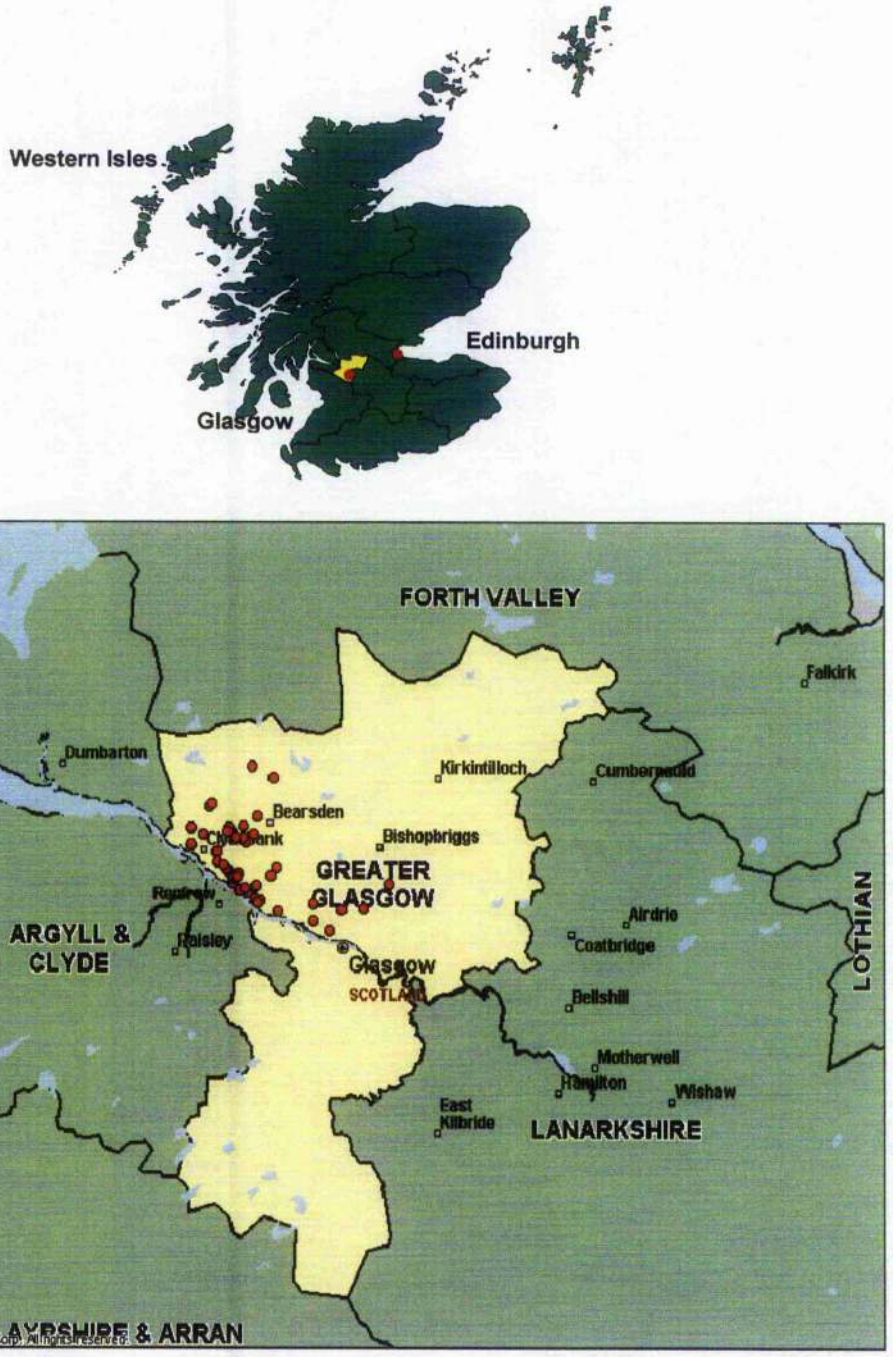

Figure 13: Distribution of 48 of the 51 cases notified between 1997 and 2004, with a genetically indistinguishable 15-banded IS*6110* RFLP pattern (three Western Isles cases not shown)

There was a 2:1 ratio of men to women in this cluster (table 8). Men had a higher proportion of sputum smear positive pulmonary TB disease (61.8%) than women (52.9%),

but a statistically significant difference was not detected when the frequency of disease type was compared on the basis of sex (data not shown).

Cluster cases were aged between 4 and 88 years of age, with a mean age of 44.7 years. Males had a mean age of 51.3 years (SD: 18-88), and women a mean age of 31.4 years (SD: 4-63). The difference in mean age between men and women was found to be statistically significant (Mann Whitney-U test: -3.469, p=0.001).

Figure 14 shows the age-banding of all cluster cases by year of diagnosis. Cases aged between 45 and 64 were detected during each year, accounting for the largest proportion (35.3%) of the cluster population. On the other hand, cases aged 65 years and over were observed only between 1998 and 2000, and cases under 25 years were diagnosed between 2000 and 2002. Although together these age cohorts represent 31.3% of the cluster population, it appears the years in which these cases were diagnosed loosely corresponds with peaks in the trend of annual case numbers.

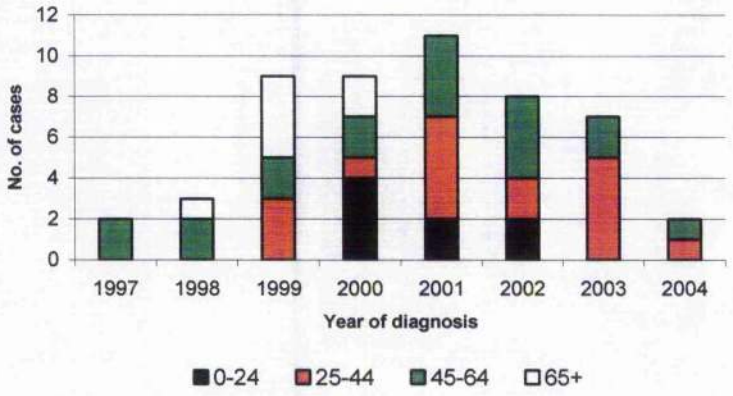

Figure 14: Annual distribution of cases found to have a genetically indistinguishable 15-banded IS*6110* RFLP pattern between 1997 and 2004, by age-band

Forty-seven cases had a pulmonary infection, 30 of which were sputum smear positive (58.8% of clustered cases). The remaining pulmonary cases were sputum smear negative (9 cases), had a positive bronchial alveolar or tracheal aspirate smear (4 cases), or specimens had not been tested/were not available (4 cases – empirical diagnosis). Four cases of non-pulmonary disease were diagnosed. The two female cases were under 24 years of age, while the male cases were 62 and 79 years old, respectively.

Although information relating to age, sex and disease type was available for all cases, information on country of birth, ethnicity, method of identification and symptoms was not

available for the 14 cases diagnosed prior to 2000 (table 8). This is due to the fact collection of detailed patient information only commenced in 2000, following the institution of the ESMI scheme.

Where information was available, cluster cases were predominantly Caucasian. Two cases were of Pakistani ethnicity, the first of which was a 7-year old female with non-pulmonary TB, and the other a Pakistani male (the only case born outwith the United Kingdom). There was no known association between these two cases. In terms of method of identification, 62.7% were identified after presenting to health care services with symptoms, 3 cases (5.9%) were detected as a result of contact tracing, and the remaining cases through a variety of other methods. Three quarters of cluster cases (38 cases) were known to have experienced symptoms prior to diagnosis. Of those 38 cases, 55.3% of cases experienced symptoms of 2 to 13 weeks duration, 21.1% had symptoms of 14 to 26 weeks duration, and one four year old female had symptoms of 34 weeks. Duration had not been defined for all other symptomatic cases (21.1%).

Finally, six cases were twice diagnosed with pulmonary tuberculosis, with three to four year intervals between first and second diagnoses. With one exception, all cases were known to misuse alcohol, and were sputum smear negative on the second episode of disease. All cases were of Caucasian ethnicity and born in the United Kingdom. Where IS*6110* RFLP typing had been undertaken on specimens obtained at both episodes of disease, each respective case's specimens were genetically indistinguishable. It is likely these cases had an endogenous reactivation of infection, or were reinfected from the same source (or different case with the same strain of *M. tuberculosis*).

Epidemiological information available for the 51 cluster cases was compared with that of clustered cases diagnosed in Glasgow between 2000 and 2003. In chapter five, this population included 176 cases, however, as 23 of these had the 15-banded IS*6110* RFLP pattern under investigation in this chapter, these were eliminated from the comparative population.

Few statistically significant differences were detected when the frequencies of variables (and mean of age) in the two populations were compared (table 8). A greater proportion of clustered cases diagnosed between 2000 and 2003 than cases with the genetically indistinguishable 15-banded IS*6110* RFLP pattern were homeless (Fisher's exact test,

Characteristics	Cases with 15-banded IS*6110* RFLP pattern 1997-2003 N=51	%	All other clustered cases 2000-11/11/2003 N=153	%	Test	P value
Sex					χ^2 test	0.478
Male	34	66.7%	110	71.9%		
Female	17	33.3%	43	28.1%		
Age						
0-24	8	15.7%	9	5.9%		
25-44	17	33.3%	52	34%		
45-64	19	37.3%	57	37.2%		
65+	7	13.7%	35	22.9%		
Mean age	44.6		50.8		Mann-Whitney	p = 0.057
Standard deviation	19.23		17.95		U-test	Z = 3206.5
Country of birth					Fisher's exact test	<0.001
United Kingdom	36	70.9%	126	82.4%		
Other country	1	2%	19	12.4%		
Not known	14	27.5%	8	5.2%		
Ethnicity					χ^2 test	0.107
Caucasian	36	70.6%	129	84.3%		
Non-Caucasian	2	3.9%	23	15%		
Not known	13	25.5%	1	0.7%		
BCG					χ^2 test	0.201
Yes	17	33.3%	70	45.8%		
No	5	9.8%	41	26.8%		
Not known	29	56.9%	42	27.4%		
Disease type					χ^2 test	0.147
Sputum smear + pulmonary TB	30	58.8%	92	60.1%		
Other pulmonary TB	4	7.8%	26	17%		
Non-pulmonary TB	17	33.3%	35	22.9%		
Alcohol misuse					χ^2 test	0.457
Yes	18	35.3%	63	41.2%		
No	33	64.7%	90	58.8%		
Homeless					Fisher's exact test	0.005
Yes	0	-	20	13.1%		
No	51	100%	133	86.9%		
Other risk factors*					Fisher's exact test	0.003
Yes	0	-	21	13.7%		
No	51	100%	132	86.3%		
Previous diagnosis					Fisher's exact test	0.386
Yes	6	11.8%	17	11.1%		
No	28	54.9%	134	87.6%		
Not known	17	33.3%	2	1.3%		

Table 7: Results of a comparison of characteristics between 51 cases with a genetically indistinguishable 15-banded IS*6110* RFLP pattern between 1997 and 2004 and 153 clustered cases in Glasgow between 2000 and 11th November 2003

*** Other risk factors include: intravenous drug use, immunosuppression, residence in a correctional or other institution, health care worker and refugee/asylum seeker status.**

Indicates statistical significance at p<0.05.

p=0.005) or had indicated risk factors such as intravenous drug use, immunosuppression, residence in a correctional or other institution, health care worker and/or refugee/asylum

seeker status (Fisher's exact test, p=0.005). Although similar proportions of cases were born in the United Kingdom, one of the 51 cluster cases were born outwith the UK. Twelve and a half percent of all other clustered cases were born outside the UK, a difference that was found to be statistically significant (Fisher's exact test, p<0.001). However, it is recognised that information was not known for one quarter of the 51 cluster cases, and this may have influenced the outcome of the statistical test.

6.2 Detection of epidemiological links

Outbreak networks diagrams are presented in figures 15 to 18, and show cases believed to be involved in the spread of this 15-banded IS*6110* RFLP pattern, and the epidemiological links between such cases. These diagrams present a hypothesis about the spread of this particular *M. tuberculosis* genotype, as transmission cannot be directly observed. Instead, information pertaining to epidemiological links was sourced from the ESMI database, patient and nurse interviews. Due to variability in the period of disease development, and latency of the disease, the sequence of infection cannot be exactly predicted. Therefore, directionality of disease transmission (in the form of arrows on lines between cases, representing epidemiological links) is omitted from outbreak network diagrams. Inferences, however, can be made on the basis of the infectiousness of epidemiologically linked cases. A summary of links detected at each phase of investigation (information from ESMI database, nurse and patient interviews) is described here, and a more detailed description of the putative transmission network is provided in section 6.3.

6.2.1 ESMI surveillance information

In addition to the fifty-one study cases with a genetically indistinguishable 15-banded IS*6110* RFLP pattern, three paediatric patients (patients 24, 25 and 26) were included in outbreak network diagrams. ESMI information recorded for Veronica indicated associations with patients 24, 25 and 26, while Martin was epidemiologically linked to patients 24 and 25. Gastric washings had been sent to the laboratory for culture to confirm a TB diagnosis for these supplementary cases, but *M. tuberculosis* could not be grown from these specimens (and consequently molecular typing information was absent). As contact with other cases of TB could not be detected, it is likely these three cases were infected with the 15-banded IS*6110* RFLP pattern under investigation. Martin was identified as a result of contact tracing for his daughters, patients 24 and 25, and together lived in the same multiple occupancy building as Veronica and patient 26. Patients 24, 25

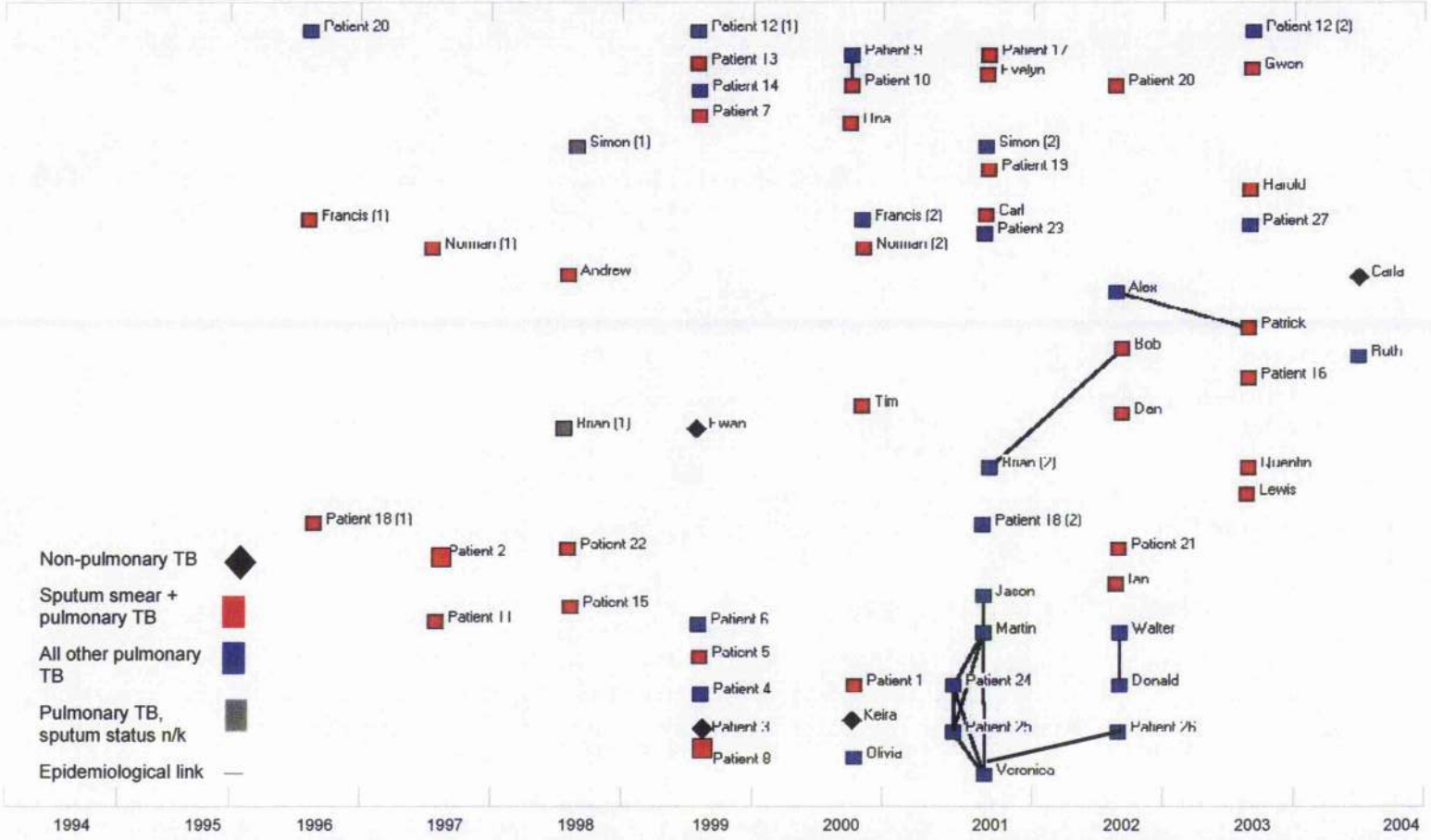

Figure 15: Epidemiological links between cases notified between 1997 and 2004 with a genetically indistinguishable 15-banded RFLP pattern. Epidemiological links were detected using epidemiological information from the ESMI database. (Numbers in parentheses record the first and second episodes of disease for six cases)

and 26 were identified as a result of contact tracing for Veronica. In total, 54 cases are included in the first outbreak network diagram (figure 15), showing epidemiological linkage information (represented by black lines) sourced from the ESMI scheme.

A total of twelve epidemiological links were identified, involving a total of fourteen cases. Seven of these epidemiological links were detected as a result of contact tracing, and the five remaining associations were identified for this study from information contained in free-text fields on ESMI surveillance forms. Of the 7 epidemiological links determined through contact tracing, three were classified as close, that is to say, involved parents (as index cases) and their children (as contact cases).

Outwith the cases included in figure 15, free-text field on ESMI surveillance forms indicated epidemiological links with undisclosed TB contacts for an additional eight cluster members. Associations for four cases were clarified during interviews with nursing staff, and following patient interviews (two cases). The identity of the final two TB contacts remained unknown (two cases).

6.2.2 Nurse interviews

Interviews with nursing staff also revealed further epidemiological associations between study cases and TB patients, for whom molecular typing information was not available. Patient 27, a 2 year old male was diagnosed in 2003 as a result of contact tracing for his father, Harold. Patient 28, diagnosed in 1996, was identified as the sister of patient 12 and patient 13. In total, 56 cases were included in the network diagram presented in figure 16.

Epidemiological links detected as a result of interviewing TB nurses are presented in red, in order to differentiate from epidemiological links determined from ESMI surveillance information. In figure 16, red lines were also drawn between nodes, with the same patient identifiers. Six cases in the study cluster had two episodes of disease, which are indicated on outbreak network diagrams by the number recorded in parentheses, beside the patient identifier. On completion of nurse interviews, the total number of identified associations increased from twelve to twenty-five (excluding links between cases with 2 episodes of disease), and involved 28 of the 56 study cases (50%).

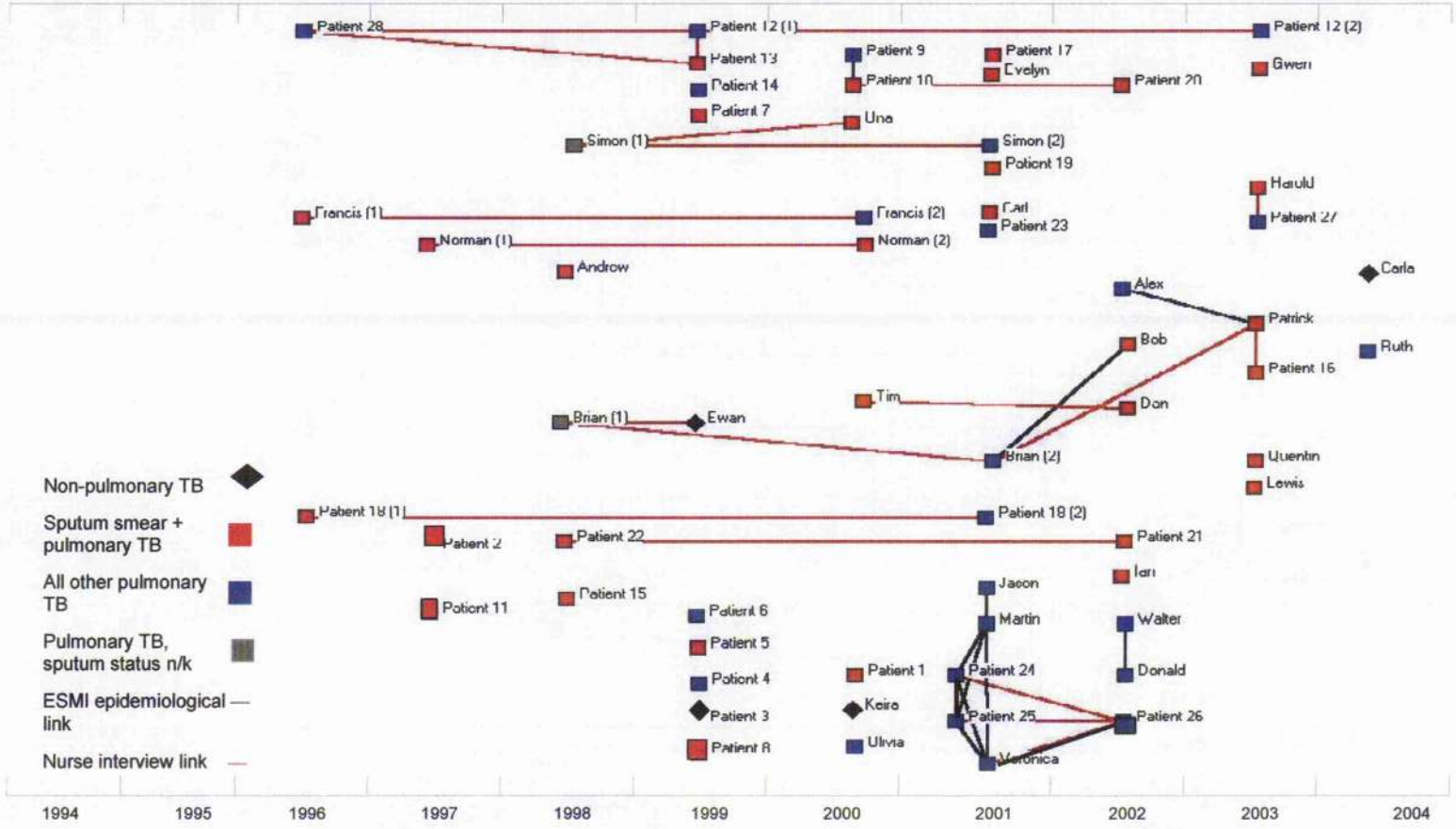

Figure 16: Epidemiological links between cases notified between 1997 and 2004 with a genetically indistinguishable 15-banded RFLP pattern. Epidemiological links were detected using epidemiological information from the ESMI database and TB nurse interviews

6.2.3 Patient interviews:

A number of patients invited to participate in an interview revealed previously unknown associations with past TB patients. These are identified in figure 17 as patients 29, 30, and 36, each of which were nominated by two cluster cases. Subsequent discussions with patients and nursing staff indicated these three cases were amongst others involved in an outbreak associated with one public house in Northwest Glasgow in the mid-nineteen nineties. As a result, all cases associated with this outbreak are included in the outbreak network diagram in figure 17 (patient 29, 30, 31, 32, 33, 34 and 36).

In addition, an eighth case was included in the outbreak network diagram shown in figure 17. Patient 35 was identified as a friend and drinking partner of Francis, and was known to have been diagnosed with pulmonary TB in 1994. Molecular typing information was unavailable for all 8 cases because this technique was not routinely undertaken at the time these cases were diagnosed. In total, sixty-four cases are included in figure 17. Forty-two associations involving 36 of the 64 patients (56.3%) were detected on completing all phases of the investigation. In figure 17, epidemiological links detected from ESMI surveillance information are shown in black, while associations determined as a result of nurse and patient interviews appear in red.

6.3 Epidemiological links

Fifty-six percent of the study population had a known association with another member of the cluster. Eight distinct network component (labelled I to VIII) or portion of a network where nodes (/cases) are connected by at least one association were identified. These ranged in size from 1 epidemiological link between 2 cases (components III, V, IV, VII), to the largest component consisting of 17 epidemiological links between 13 patients (component VI).

6.3.1 Case-case epidemiological linkage

Patient 28 was the earliest diagnosed case in the first component (I), and her sisters, patient 12 and patient 13 were diagnosed in 1999. Patient 12 was diagnosed a second time in 2003, perhaps due to endogenous reactivation of infection. Provided all contact with known TB cases was disclosed by patients 12 and 13, it is likely patient 28 represented the source of infection for her sisters, who were diagnosed three years later.

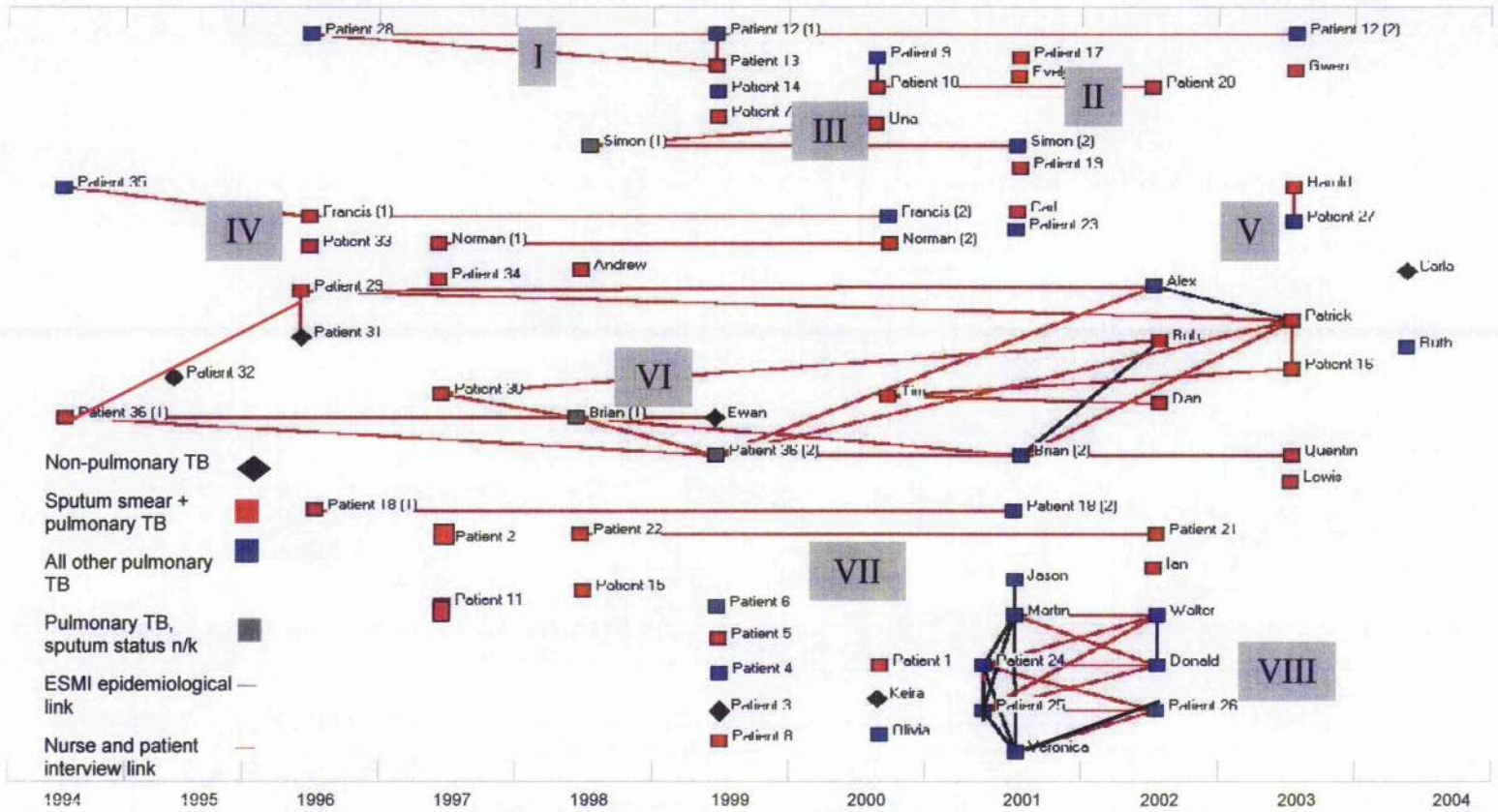

Figure 17: Epidemiological links between cases notified between 1997 and 2004 with a genetically indistinguishable 15-banded RFLP pattern. Epidemiological links were detected using epidemiological information from the ESMI database, TB nurse and patient interviews. (Roman numerals indicate components or portions of the network where two or more cases are linked)

In component II, patient 9, a nursing home assistant in the Western Isles, was diagnosed in 2000 with sputum smear positive, culture positive TB. The contact tracing event undertaken resulted in the patient's mother (patient 10) being diagnosed with sputum smear negative pulmonary TB. Patient 20 was a friend and second cousin of patient 9, and together they worked in a nursing home for the elderly. This individual had been examined during the original screening event, but was discharged when she was deemed to have no evidence of infection. Over two years later patient 20 presented to her GP with symptoms, and was diagnosed with sputum smear positive tuberculosis.

Component III comprised of a father and daughter. Simon was first diagnosed with TB in 1998, and Una, then aged 22, was not identified as a contact by her father. When Una was diagnosed with sputum smear positive TB in 2000, she also failed to identify her father as a contact, as they had lost contact following a dispute some years previous. Many months into her treatment, Una indicated her father had just recently received a diagnosis of tuberculosis (Simon was diagnosed for a second time 4 months after his daughter). During treatment for his first episode of disease in 1998, he failed to comply with treatment, and his second diagnosis was likely due to the recurrence of disease.

In component IV, Francis identified patient 35 as a friend he would often socialise with in various public houses in Northwest Glasgow. Both men were known to have alcohol misuse issues. Francis indicated he knew many other friends and acquaintances within the social scene in this area of Glasgow, who had previously received a diagnosis of TB. Unfortunately, Francis was unable to recall their names during interview.

As previously discussed, patient 27 was included in cluster diagrams despite an absence of molecular typing information (component V). This two-year old male was diagnosed following contact screening for his father (Harold), who was diagnosed with sputum smear positive TB in 2003. Harold's second son received chemoprophylactic therapy for latent infection.

Component VI was the largest component identified within this putative network of transmission, as it involved 13 of the 64 cases (20.3%). The putative source case was patient 36, first diagnosed with sputum smear negative pulmonary tuberculosis in 1994. During interviews with Alex, Patrick and Brian, all independently verified having associated with patient 36. Each case was familiar with patient 36 as a result of being part the same social scene, which involved drinking in the same public house. Patient 29 and 31 (diagnosed in 1996) were also known to socialise with one another at the same public

house. Patient 30 was a bar maid at that public house, but other than frequenting this location, confirmation of associations between these cases was not forthcoming. Only two cases, Bob and Brian, identified this barmaid as a known TB contact.

Brian had known associations with six TB contacts, diagnosed between 1994 and 2003. Two such associates, patient 30 and patient 36 were diagnosed prior to Brian's first episode of disease in 1998. Brian had become acquainted with both cases as a result of frequenting the public house involved in the outbreak in the mid-1990's. Ewan, Brian's father, was diagnosed with non-pulmonary disease a year after Brian was first diagnosed with sputum smear negative tuberculosis. He too was known to spend time drinking with his son in this public house. Quentin was also known to have a friendship with Brian, however, this association was only indicated by one party to the friendship, namely Quentin. Both Bob and Patrick (diagnosed 2002 and 2003 respectively) indicated that they knew Brian from drinking in the public house implicated in the outbreak in the mid-1990's. Neither Bob, Patrick nor Quentin were identified by Brian during his interview with this investigator, as he proved reluctant to identify any of his acquaintances by name.

Patrick was diagnosed with sputum smear positive TB in 2003, and information recorded on his ESMI surveillance indicated his brother, Alex, had been diagnosed with tuberculosis in the previous year. This information came to light many months after Patrick commenced therapy. When contact tracing was initiated following diagnosis, neither Patrick nor Alex identified each other as a close contact for the purposes of contact tracing. During an interview with Patrick, he revealed he had established a friendship with patient 29 as a result of drinking in the public house involved in the outbreak in the mid-1990s. He also indicated that he drank with patient 16, at the home of this individual, which was later described by the district TB nurse as a known drinking den. In total, Patrick had spent time with five TB contacts (Alex, Brian, patients 16, 29 and 36) over a ten-year period, before presenting to medical services with symptoms, and being diagnosed with TB in 2003.

In the same component, Tim indicated having one TB contact. Identified as patient 16, Tim had made the acquaintance of this case during time spent at his local public house. An interview with Dan also revealed he frequented this public house, often spending time in Tim's company. Tim, however, did not identify this association. This is likely to have due to the fact Tim was unaware of Dan's 2002 diagnosis, as Dan revealed he never informed his friends of his diagnosis. The underlying reasons for Dan's (and others) illness behaviour are explored in chapter eight.

In component VII, patient 21 and 22 were known contacts. The detail of this friendship was disclosed during a conversation between the district TB nurse and the wife of patient 21, shortly after his death. Patient 21's wife had worked as a barmaid in a public house in the past, and recalled during that time, her husband and patient 22 spent much time sitting together in each other's company at this location.

With regards to component VIII, Jason was the first case diagnosed, and was found to have sputum smear negative tuberculosis in July 2001. Contact tracing was undertaken, but his nephew, Martin, was not identified as a close contact at this point. In December 2001, Veronica was diagnosed with tuberculosis after experiencing symptoms over thirty-four weeks. Contact tracing was initiated at Veronica's nursery, and led to the detection of disease in two new cases, namely patients 24 and 25 (these cases were sisters). These three cases were friends, and often spent time playing together within each other's homes, as they resided in the same multiple-occupancy building. Screening was extended to this location and Martin, the father of patient 24 and 25, was diagnosed in addition to patient 27, a five-year old boy, who also lived in the same building. The degree of contact between the three female cases and patient 27 was unlikely to be close, as the boy attended a different nursery and had limited contact with these girls while at home. Patient 27 had no known contact with any other known TB case. The three girls spent significant amounts of time in each other's company, both at the nursery and at each other's homes. It is reasonable to assume Veronica had contact with Martin, particularly as he was the principal care-giver for his daughters.

During his interview, Martin indicated his uncle, Jason, had been diagnosed with TB five months prior to his own diagnosis. Although Martin claimed to having spent lengthy periods of time living in his uncle's home, Jason did not speak about these living arrangements, although he did identify Martin as a known TB contact. Martin also revealed that the uncle of a friend had died some months previous, and TB had contributed to his death. Using information provided by Martin during his interview, this patient was identified as Donald, and the friend as Walter. However, Martin was not aware that Walter had been diagnosed with TB, as a result of contact tracing undertaken for his uncle and flatmate, Donald (these friends had lost touch shortly after Donald's death). Martin indicated these friends would spend much time in each other's homes, often using illicit drugs and consuming alcohol. Occasionally Walter and Donald would stay overnight in Martin's home. As a result of this level of contact, patients 24, 25 and perhaps to a lesser extent, Veronica, would have spent time in Walter and Donald's company. Indeed, Walter confirmed having an association with Martins daughters.

It is reasonable to assume that sputum smear positive cases are more likely to represent sources of infection than other cases. In this cluster, it is difficult to determine the source of infection for cases included in component VIII, as no patient was found to be sputum smear positive. However, Martin is likely to have been integral to the spread of infection, as he had associations with six of the eight cases.

6.3.2 Case-location linkage

During interviews, patients were asked to identify places they frequented before they were diagnosed with tuberculosis. Places of residence, employment and education were mentioned, and were usually unique to each individual. Many indicated spending time in public houses, as they either worked or frequented these locations for recreational purposes. With the exception of one case, when enquiring about locations frequented, the investigator did not specify the location type. That is to say, although public houses were nominated frequently by cases, this was done so of cases own volition. Wherever public houses were discussed in this context, the investigator prompted cases to reveal the identity of the public houses.

In this analysis, places named by two or more individuals were included in figure 18. The names of sixteen locations were noted, 11 of which were pubs in the Northwest of Glasgow (A to L, excluding I)[20]. Location I represents a number of unnamed pubs, all of which are located on one road in a district of West Glasgow. Location M is a house in multiple-occupancy building, and home to four cases. Location N is a flat shared by cases prior to diagnosis, location O a known drinking den and location P, a nursing home in the Western Isles. Locations are presented in figure 18 as circular green nodes, and are positioned randomly to enhance the clarity of the diagram. Red lines represent all epidemiological links between cases, whether detected using information from ESMI, nurse or patient interviews. Black lines connect cases to locations, indicating the individual was known to frequent that location.

6.3.3 Network characteristics

To determine the relative importance of each node (cases and locations) in this network, the number of connections to each node was quantified. In total, 102 epidemiological links

[20] Outbreaks of tuberculosis associated with public houses have received much media attention in Glasgow in recent years. The most recent outbreak occurred in South Glasgow, but the locations referred to in this analysis did not include this particular public house

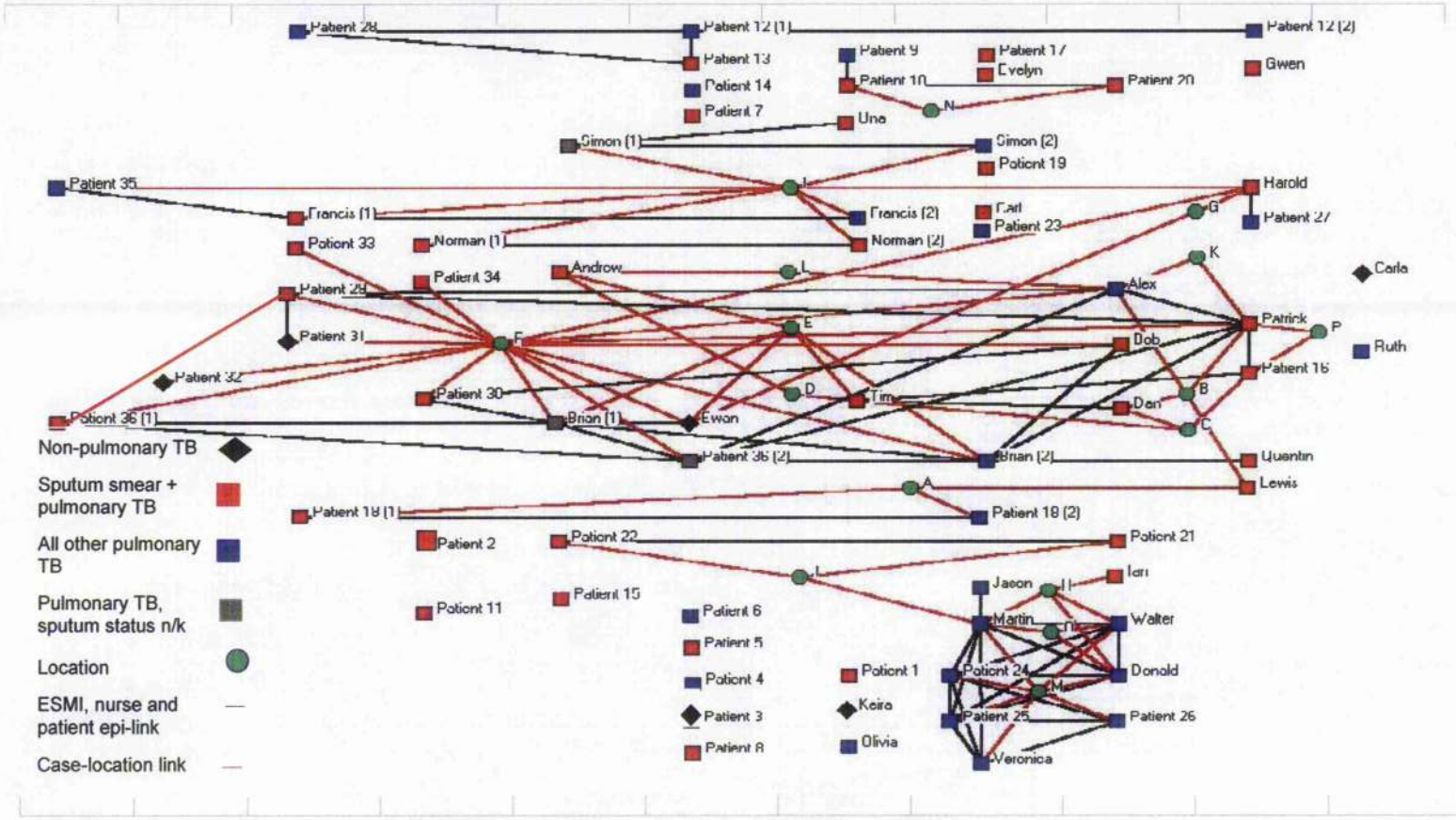

Figure 18: Epidemiological links between cases notified between 1997 and 2004 with a genetically indistinguishable 15-banded RFLP pattern. Epi-links between cluster cases and between cases and locations, were detected using the ESMI database, TB nurse and patient interviews

were detected, and are shown in figure 18, 42 between cases, and 60 between cases and locations. The number of epidemiological links identified for any one case ranged from zero (no epidemiological links) to six links.

Brian was identified as the case with the greatest number of epidemiological links to another clustered case (epidemiologically linked to six other cases), despite having sputum smear negative TB (less infectious than sputum smear positive TB)[21]. However, Martin and Patrick had the highest number of detectable epidemiological links to clustered cases and locations combined. Both cases had nine epidemiological links (table 9A), five to cases and four to locations. All three cases (Brian, Martin and Patrick) were important for the spread of disease as each had large numbers of associations with other cluster cases. With regards to locations nominated by cases, a maximum of four places was nominated by any one case (Alex, Martin, Patrick). Such individuals are likely to have played an

Case name	Disease type	No. of links to cases/locations
Martin	Sputum smear negative TB	9
Patrick	Sputum smear positive TB	9
Brian	Sputum smear negative TB	8
Alex	Bronchoalveolar lavage smear positive TB	7
Donald	Tracheal aspirate smear positive TB	7

Table A

Case/location name	Disease type	No. of links to cases/locations
F	-	13
Martin	Sputum smear negative TB	9
Patrick	Sputum smear positive TB	9
Brian	Sputum smear negative TB	8
Alex	Bronchoalveolar lavage smear positive TB	7

Table B

Table 8: Quantification of epidemiological links between cases with a genetically indistinguishable 15-banded RFLP pattern and associations between cases and locations

Table A shows five highest-ranking cases with epidemiological links to other nodes (cases and locations). Table B shows the five nodes (cases/locations) with greatest number of epidemiological links to other nodes.

[21] Where bacteriological status is referred to, all cases are culture positive, as inclusion in this cluster required cases to be culture positive for genotyping to be undertaken.

important role in carrying tuberculosis between different locations, where pools of susceptible individuals were to be found.

Of the sixteen locations named by cases during interviews, the public house at the centre of the mid-nineties outbreak (location F) was nominated most frequently, with 13 cases indicating having spent time there. As shown in table 9B, of all nodes represented (locations or cases), the node with the greatest number of epidemiological links was location F, followed by four cluster cases. Martin and Patrick shared second position, while Brian and Alex took third and fourth position, with 8 and 7 links respectively. Only one of these nodes (Patrick) was sputum smear positive at diagnosis. Risk factors for infection of disease included use of recreational drugs (Martin) and alcohol misuse for the three remaining cases.

6.4 Cases with no identifiable epidemiological links

Epidemiological links to a case or location were not detectable for 28 of the 64 cases finally included in the cluster, despite the fact all were considered to have the same genetically indistinguishable 15-banded IS*6110* RFLP pattern (13 of which were presumed to have this *M. tuberculosis* genotype in the absence of molecular genotyping information). Statistical analysis was undertaken for the 51 cases with available epidemiological information to establish whether characteristics of cases with links to other cases or locations (linked cases) differed from cases with no detectable links (non-linked cases) (table 10).

No significant differences were detectable between the two populations in terms of place of birth, ethnicity, disease type, BCG status or previous diagnosis. The mean age of linked and non-linked was 41.1 years (S.D.13.93) and 49.8 years (S.D. 24.41) respectively, but again, the difference in mean age between the two populations was not statistically significant. However, greater proportions of cases aged 65 and over were detected in the non-linked (as opposed to linked) case population, while greater proportions of cases aged 25-44 and 45-64 years were found in the linked case population. A statistically significant difference was detected between the frequency of cases with alcohol misuse issues between the linked and non-linked case populations (χ^2 test = 14.573, $p < 0.001$). Over half of linked cases (56.7%) indicated alcohol misuse in contrast to 4.8% of non-linked cases.

Characteristics	Linked cases N=30	%	Non-linked cases N=21	%	Test	P value
Sex					χ^2 test	0.227
Male	22	73.3%	12	57.1%		
Female	8	26.7%	9	42.9%		
Age						
0-24	5	16.6%	4	19%		
25-44	12	40%	5	23.8%		
45-64	12	40%	6	28.6%		
65+	1	3.3%	6	28.6%		
Mean age	41.1		49.8		Mann-Whitney U-test	Z= 249.5
Standard deviation	13.93		24.41			p= 0.21
Country of birth					Fisher's exact test	0.289
United Kingdom	27	90%	10	47.6%		
Other country	0	-	1	4.8%		
Not known	3	10%	10	47.6%		
Ethnicity					Fisher's exact test	0.078
Caucasian	27	90%	9	42.9%		
Non-Caucasian	0	-	2	9.5%		
Not known	3	10%	10	47.6%		
BCG					Fisher's exact test	1.0
Yes	10	33.3%	7	33.3%		
No	3	10%	2	9.5%		
Not known	17	56.7%	12	57.1%		
Disease type					χ^2 test	0.807
Sputum smear + pulmonary TB	17	56.66%	13	61.9%		
Other pulmonary TB	11	36.66%	6	28.6%		
Non-pulmonary TB	2	6.66%	2	9.5%		
Alcohol misuse					χ^2 test	≤0.001
Yes	17	56.7%	1	4.8%		
No	13	43.3%	20	95.2%		
Previous diagnosis					Fisher's exact test	0.069
Yes	6	20%	0	-		
No	16	53.3%	12	57.1%		
Not known	8	26.7%	9	42.9%		

Table 9: Results of a comparison between cases with a genetically indistinguishable 15-banded IS*6110* RFLP pattern with detectable epidemiological links (non-linked cases) and those without detectable epidemiological links (linked cases)

Indicates statistical significance at p<0.05

Table 11 presents summary information pertaining to the infectiousness of all 64 cases included in the final outbreak network model. Of the 37 cases with epidemiological links to a minimum of one other cluster case, 48.6% had sputum smear positive pulmonary TB. A greater proportion of cases with no epidemiological links (n=27) had sputum smear positive pulmonary disease (63%). This is unexpected, as contact tracing is more extensive for sputum smear positive cases (both close and casual contacts screened). As

screening for non-pulmonary disease is not routinely undertaken, and only close contacts are screened for non-smear positive pulmonary TB cases, one would have anticipated the majority of non-linked cases would have been attributed to these disease type categories. Furthermore, in the linked case population, similar proportions of cases had sputum smear positive TB (48.6%) and all other types of pulmonary disease (45.9%). Here, one would have expected the majority of cases to be attributed to the sputum smear positive category.

	Total cases	Linked cases		Non-linked cases	
Sputum smear + pulmonary TB	35	18	(48.6%)	17	(63%)
All other pulmonary TB	23	17	(45.9%)	6	(22.2%)
Non-pulmonary TB	6	2	(5.4%)	4	(14.8%)
Total	**64**	**37**		**27**	

Table 10: Cluster cases with and without detectable epidemiological links by disease type

6.5 Discussion

At present in Scotland, molecular genotyping is used to confirm epidemiologically linked cases identified through contact tracing or outbreak investigation. Those cases are infected with the same strain of *M. tuberculosis*, suggesting recent transmission has occurred. Surveillance of prevalent genetically indistinguishable strains and newly emerging strains is not undertaken as a matter of routine. Rather than detecting this temporal outbreak on the basis of epidemiological evidence, the identification of this study cluster was made possible by a recent analysis of IS*6110* RFLP patterns undertaken by the University of Aberdeen. In this study, routine ESMI surveillance data and information learnt as a result of nurse and patient interviews assisted the elucidation of a transmission pathway (predominantly) between cases infected with a strain of *M. tuberculosis* identified as having a genetically distinct 15-banded IS*6110* RFLP pattern.

At the outset of this investigation, information recorded in the ESMI database indicated 26% of study cases (14/54) were epidemiologically linked. Six of the 54 (11.1%) study cases had been identified as a result of contact tracing, indicating current strategies for active case detection failed to identify the majority of cases in this cluster. On completion of nurse and patient interviews, cases with known epidemiological links to at least one other case increased to 56.3% (36/64 study cases). Cases with detectable connections to cases and/or identifiable locations rose to 67.2% (43/64 study cases).

Individuals completing ESMI surveillance forms are required to indicate (if known) where the patient may have sourced the disease e.g. from a close/household contact, in a workplace setting etc. However, the identity of new cases' TB contacts, potential sources of infection and possible sites of disease acquisition is not required information. Interviews conducted with nursing staff responsible for managing cases in this study were highly valuable, as they resulted in the identification of many previously unrecognised associations. While some of this information was recalled from memory, much was abstracted from contact tracing nursing records, prepared while the contact tracing event was underway. The increased number of associations determined as a result of nurse interviews suggests these individuals play a key role in identifying epidemiologically linked cases, indicating outbreaks of disease, and understanding the behaviours that may put cases at risk of acquiring infection. TB control may be improved by making optimal use of information recorded and known by TB liaison nurses in Glasgow with respect to outbreak investigation and contact tracing. This may involve making improvements to the way in which this information is routinely recorded, and sharing this information with other health professionals (e.g. sharing information within and beyond Glasgow).

The absence of epidemiological linkage information (detected during nurse interviews) from ESMI surveillance forms was informally discussed with TB nurses, and can be attributed to a number of factors. Contact between cases was sometimes determined after completion of surveillance forms. Either cases withheld information pertaining to known TB contacts at the contact screening interview, or details of casual associations emerged circuitously at a later date, perhaps through other sources (a member of the patient's family for example). In a small number of instances, those responsible for completion of ESMI forms failed to indicate the patient had contact with a known TB case prior to diagnosis.

Patient interviews also proved useful in detecting epidemiological links between cluster members, and between cluster members and TB cases diagnosed many years previous. Routine genotyping of clinical isolates in Scotland commenced in 1997, therefore the *M. tuberculosis* strain infecting cases prior to 19997 could not be determined. Therefore, the assumption cases were infected with an identical strain could not be tested. In the study, four male cluster cases confirmed having been in contact with three individuals, diagnosed with tuberculosis between 1994 and 1997, who were known to be involved in a pub-related outbreak in West Glasgow. The reasons why the cluster cases failed to identify these putative sources of infection during contact tracing interviews were unclear. One can speculate that as these associations were casual, and cases' TB contacts were diagnosed up to five years beforehand (in some instances associations existed for a finite period of time

in the past), poor memory recall could have been a contributory factor. Other associations detected during patient interviews possibly went unrecognised because associates were unaware of each other's TB diagnosis. When asked to identify TB contacts during contact tracing interviews, individuals may have unknowingly indicated they had no previous contact.

Locations frequented by patients prior to diagnosis were recorded both during nurse and patient interviews. Although this information may be requested during contact investigation interviews, the identity of these locations is not required information on ESM1 surveillance forms. Named sites of putative exposure suspected by nursing staff were recorded for this first time in this study. In total, sixteen locations were nominated by at least two study cases, eleven of which were named public houses in Glasgow. Whether cases actually acquired tuberculosis on the premises of these locations cannot be ascertained, but in this study, the identification of locations frequented by cases provided a degree of insight into patient's social behaviour and social network.

Location F was a public house nominated by 6 cases with a genetically indistinguishable 15-banded IS*6110* RFLP pattern, and was known to be central to an outbreak involving seven TB cases diagnosed between 1994 and 1997. Provided these historical cases and recent cases were infected with a genetically indistinguishable 15-banded IS*6110* RFLP pattern, this investigation has monitored the dynamics of disease transmission in the aftermath of a small location-based outbreak in a Glasgow community. The network diagrams presented in this chapter have shown the after effects of an outbreak on a community, and indicate that this strain continues to propagate within a network of males with alcohol misuse issues. This suggests outbreaks associated with locations are key events, which require every effort to be made to detect all infected cases. As this strain was detected in cases frequenting public house 'F' up to ten years after the outbreak appeared to be contained, this raises an issue about the effectiveness of procedures for screening contacts frequenting non-household locations (i.e. a public house), that were in place at that time. An evaluation of contact tracing practices used in location-based outbreak investigations, which utilises molecular typing information, may provide important insights.

In this study, the node within the outbreak network diagram with the greatest number of associations was a location rather than a case, suggesting that as an adjunct to contact screening, location-based screening (e.g. public houses) may be a useful early case detection technique. In Glasgow, ad-hoc location-based screening events have been

undertaken at public houses and hostels for the homeless. These outcomes from these events may be improved by developing guidance for best practice, as current guidance focuses on screening household/close contacts.

As cases with epidemiological links to other cluster cases were more frequently reported as having alcohol misuse issues than their non-linked counterparts (χ^2 test = 14.573, $p < 0.001$), screening amongst this high-risk population may be worthwhile. This association may be explained by the fact cases who misuse alcohol may be at greater risk of infection due to increased exposure to tuberculosis while in public houses/drinking dens. Biological factors may also play a role, as those who misuse alcohol are known to have a greater susceptibility to infection, and a higher probability that infection will develop into active disease (Brown & Campbell, 1961, Feingold, 1976, Olin & Grzybowski, 1966).

It was interesting to note that of the four case nodes with the highest-ranking numbers of epidemiological links (table 9), just one case had sputum smear positive tuberculosis. In addition, 63% of the non-linked case population (n=27) were sputum smear positive, as compared with 48.6% of the population with epidemiological links to a minimum of one other case (n=37). In the linked case population, similar proportions of cases were attributed to sputum smear positive pulmonary TB cases (48.6%) and all other pulmonary TB cases (45.9%). Provided all epidemiological links were detected as a result of this investigation, these results appear to conflict with conventional wisdom that sputum smear positive cases will be the cause of infection for more contacts than less infectious cases. One would have expected to find those cases with the greatest number of epidemiological links to other cases to have been highly infectious. This study cannot definitely prove whether the risk behaviours of frequenting public houses and alcohol misuse have enhanced the capacity of this strain to propagate in Glasgow, particularly in the absence of a high proportion of sputum smear positive cases. Further research is required to tease out this association, the outcome of which may have important implications for the way screening is undertaken in high risk populations.

Outbreak network diagrams were utilised to present a hypothesis of the transmission pathway between study cases. Rather than detecting one single ongoing pathway of transmission, a number of components within this network were identified and characterised. For example, links between three Western Isles cases with familial relations were determined, however no links to the remaining Glasgow cluster cases were established. The largest network component spanned a ten-year period, and incorporated cases involved in a pub-related outbreak in the mid-nineteen nineties. The existence of

several components within this molecularly identified cluster may signify that not all epidemiological links were detected during this investigation. First, a proportion of cases infected with this strain, but with culture negative specimens, will have been excluded from this study. Epidemiological information for, or interviews with these patients may have led to the detection of other previously unrecognised epidemiological links in this cluster. Approximately 40% of cases (21/51) in this cluster did not have links to any other cases or locations, and this rate may have improved if more study cases agreed to participate. In total, interviews were undertaken with 28 of the 51 cases (54.9%) known to have the genetically indistinguishable 15-banded IS*6110* RFLP pattern. Whereas under a third of cases with links to other cases were not interviewed, nearly two-thirds of non-linked cases were not interviewed. In terms of characteristics of linked and non-linked case populations, the latter cases were significantly less likely to have alcohol misuse as a risk factor for tuberculosis (χ^2 test = 14.573, $p < 0.001$). A larger proportion of cases in the youngest and older age cohorts were observed in the non-linked population of cases than in the linked cases population. One can speculate that younger cases acquired their infection as a result of very brief contact and hence were unable to identify any known TB case. Older cases on the other hand may have suffered reactivation of a latent infection.

Secondly, the existence of components within this genetically defined cluster may be an indication that the strain under investigation has been in circulation (predominantly in Glasgow) for many years, and could therefore be described as an endemic strain. This might explain the co-existence of pockets of ongoing transmission, and cases with no epidemiological links, representing the cases with reactivated latent infection.

Inferences about the direction of the spread of infection were omitted from outbreak network diagrams. Cases were positioned within the network based on dates of diagnoses, but as rates of progression from infection to active, symptomatic disease are variable between cases, it was not possible to accurately determine respective source and secondary cases. As alluded to previously, this became increasingly difficult when suspected sources of infection were not necessarily highly infectious (i.e. sputum smear positive pulmonary cases). For example, epidemiological links were detected between eight cases in one component of the network (component VIII), none of which were sputum smear positive at diagnosis.

A further caveat to the outbreak network hypothesis presented here is that the importance of epidemiological links to named places and cases may have been overestimated. Places may have been nominated because of the ease of stating where patients spent time, rather

than recalling who they were with. Indeed the inability to recall such information, particularly for alcoholic individuals, was addressed in chapter 4. However, the introduction of bias by this investigator during patient interviews was examined by searching interview transcripts. Although patients were asked to indicate the types of places they frequented prior to diagnosis, this investigator did not prompt the nomination of public houses.

On the other hand, the significance of particular cases or locations may have been underestimated because of the absence of information from culture negative cases and non-interviewed individuals. Also epidemiological links may exist between study cases and individuals who may have been infected, but have not yet presented with symptoms. Immunocompetent individuals have a 5% chance of developing disease within the first 5 years of infection, and a probability of 5% over the remaining years of their life (Enarson & Rouillon, 1998).

Finally, the closeness of association between cases was not always clear, as the amount of time spent with a known TB contact could not be quantified. Familiarity with and the ability to name the contact in question constituted an epidemiological link in this study. Additionally, associations between epidemiologically linked cases were not always verified by both parties, as all linked study cases did not agree to participate in an interview.

In conclusion, it is this investigator's view that this cluster (defined on the basis of cases having a genetically indistinguishable IS*6110* RFLP pattern) is composed of cases who acquired disease as a result of recent transmission and reactivation of latent infection, acquired some years before. In Scotland, the genetic pool of *M. tuberculosis* is relatively stable, due in part to the low rates of importation of infection (approximately one quarter of cases in Scotland are detected in non-UK born individuals in comparison to two-thirds of cases in England and Wales for example). This information, together with the fact some cluster cases in this study are thought to have acquired disease from reactivated infections suggest that this strain of *M. tuberculosis* may have been present in Glasgow for at least eleven years, possibly longer. Should this particular strain of *M. tuberculosis* be one of a number of long-standing, endemic strains in Scotland, this may explain why both instances of recent transmission and possible reactivation of infection were observed within the study period. Where epidemiological links were detected, transmission was shown to occur not only between familial/close contacts, but also between casual contacts. In this

study, many of the casual associations involved individuals who knew one another from the social scene in their local public houses.

Chapter 7: Lay health beliefs

Early case detection by contact tracing is one of the principal strategies for control of *M. tuberculosis* transmission in Scotland. However, as shown in previous chapters, a considerable proportion of clustered cases fail to be detected in this manner. Rather, cases present to the health services of their own volition, when they experience symptoms. The failure of cases to present or be detected quickly is conceivably contributing to the ongoing transmission of this strain. Here, some clustered cases involved in the analysis of the previous chapter were interviewed; to explore the beliefs and attitudes of cases believed to be involved in a network of transmission (by virtue of sharing a genetically indistinguishable 15-banded IS*6110* RFLP pattern).

Individuals' perspectives of ill health are shaped by meanings they attach to their experiences (of symptoms for example), and do not necessarily mirror the beliefs of the medical profession, which dominate in Western society (Helman, 1985). Studies have highlighted the value of examining patients' experience of ill health, and gaining an insight into the cultural factors influencing their illness behaviour. Indeed, social and cultural reasons for continued morbidity and mortality have a role to play in TB control. Recent studies have identified delayed patient presentation to medical services and failure to identify contacts for contact tracing as barriers to early case detection. Illness behaviour can be rationalised by understanding the viewpoint and attitudes of TB cases (Frankel *et al.*, 1991), and in this chapter, patients' beliefs about illness causation and infection are explored.

This chapter begins by describing the outcome from the recruitment process, then describes patient's health beliefs, and finishes with a description of some practical issues encountered during the interview process.

7.1 Recruitment

Of the forty-six cases or suitable next of kin eligible for interview, 18 (39.1%) did not take part. Twenty-three face-to-face interviews were conducted with individuals who had the 15-banded IS*6110* RFLP pattern. Two interviewees acted in the capacity of next of kin for their deceased uncle and father respectively, who were also members of the cluster. Three further interviews were conducted; two with the mothers of girls aged seven at the time of interview, and one with a sister of a deceased patient. Patients were interviewed a

	Interviewee	Age at diagnosis	Age at interview	Occupation at diagnosis	Alcohol misuse
1	Alex	41	43	Unemployed	√
2	Andrew (c/o sister)	40	-	Unemployed	√
3	Bob	59	60	Carpet Fitter	√
4	Brian	33	36	Unemployed	√
5	Carl	18	22	Student	
6	Carla (c/o mother)	7	7	Schoolchild	
7	Dan	56	58	Unemployed	
8	Donald (c/o Walter)	39	-	School cleaner	
9	Ewan (c/o Brian)	62	-	Unemployed	√
10	Evelyn	45	49	Finance Officer	
11	Francis	51	55	Unemployed	√
12	Gwen	25	26	Unemployed	
13	Harold	37	39	Unemployed	√
14	Ian	50	53	Taxi Driver	√
15	Jason	45	48	Unemployed	
16	Keira	19	23	Unemployed	
17	Lewis	45	46	Unemployed	√
18	Martin	25	28	Unemployed	
19	Norman	69	73	Retired	√
20	Olivia	16	19	Student	
21	Patrick	40	41	Unemployed	√
22	Quentin	42	43	Unemployed	√
23	Ruth	42	44	Cleaning Supervisor	
24	Simon	44	48	Unemployed	√
25	Tim	50	54	Unemployed	√
26	Una	24	28	Confectioner	
27	Veronica (c/o mother)	4	7	Schoolchild	
28	Walter	22	24	Unemployed	

Table 11: Characteristics of individuals with a genetically indistinguishable IS*6110* RFLP pattern, who participated in an interview (/those for whom next of kin participated)

Pseudonyms have been assigned to protect patient identity

minimum of eight months to a maximum of four years after their date of diagnosis[22]. Table 4 provides information on age at diagnosis and interview, occupation and risk factor alcohol misuse as indicated by ESMI surveillance information.

7.2 General knowledge

The majority of patients indicated the term tuberculosis was not entirely novel, but patients felt the extent of their knowledge was limited. When asked what they knew about TB before being diagnosed, most patients initially claimed they "*.. didn't really know what TB was at the time...*" (Quentin). Comments from a small number of patients indicated that an understanding of disease pathogenesis and an awareness of typical TB symptoms appeared to be the two main criteria respondents used to assess their knowledge.

> "I didnae really know anything, whether it was, what it actually was, or what the symptoms were." (Olivia)

Despite insisting they knew very little, patients knowledge was investigated further using probing questions. The majority of patients indicated the disease was associated with the respiratory system by identifying the lungs as the affected organ, or by describing that it caused one to cough or have breathing problems. However, one patient failed to recognise tuberculosis was an infectious disease associated primarily with the lungs.

> "I thought maybe it was just a fever or cold" (Bob)

One interviewee indicated that prior to her diagnosis, she had not realised TB was mainly associated with the lungs. She explained this misconception arose because the only other individual she knew to have had TB, was diagnosed with non-pulmonary TB. She said:

> "Em, my whole family's had it, my mum and her dad, and all his family. Em, but, they didn't have, uh, TB of the lungs, they had TB of the bones, and it makes your bones rot. That's what my mum had, em, so I just knew, to me it was, your bones rotted, I never knew you could get one in your lungs, I never knew that" (Gwen)

Other respondents commented on the morbidity and mortality associated with tuberculosis. For example, Jason was mindful that the disease caused prolonged periods of ill health.

AH What kinds of things did you, had you known about it?

[22] The estimate was calculated using the date of diagnosis, which was sourced from the ESMI surveillance database, and the date the interview took place, and does not include patients who participated by proxy.

Jason That it can be a killer in, in certain circumstances, or in certain strains or something like that, and, or it can make you very ill for quite a long time.

Jason was one of a number of mainly male interviewees who used the term "killer" in an attempt to communicate a potentially fatal outcome from the disease. Patients tended to qualify that death was probable when certain conditions prevailed. In Jason's case, he asserted that there were different strains of TB, some of which were strongly correlated with an outcome of death. In contrast, Dan felt TB could cause death if the illness was allowed to progress to an advanced stage, probably in the absence of adequate treatment.

"Just that I knew it was a killer disease if it went too far..." (Dan)

Patients commented on the difference between current and historical trends. Una described how she thought tuberculosis was prevalent in the past, but virtually unheard of nowadays. Her father, Simon, commented that in the past a significant proportion of mortality had been attributed to TB, but this was no longer the case. (Simon was possibly referring to the introduction of chemotherapeutic therapies in the mid-twentieth century).

Ten respondents indicated a family member or friend had previously received a TB diagnosis. Although one might have anticipated these individuals had an enhanced understanding of the disease, this was not the case. All interviewees appeared to have a similar knowledge of disease causation, symptoms and pathogenesis. However, patients with known TB contacts were unique in that many had acquired knowledge about tuberculosis therapies. One patient sourced much of his knowledge from his in-laws, who themselves received treatment for tuberculosis in a Glasgow sanatorium in the 1950s.

"My wife never had it you know what I mean. But her 2 sisters and her brother, they had it. But like I say, they were in Robroyston (Glasgow TB sanatorium) for I think it was about 6 or 8 months at a time, away back when eh, it was just, it was just airs and things like that. Air, all they gave you was fresh air I think, you know." (Dan)

Although social and family networks proved the most popular way of gaining knowledge about the disease, the BCG schools programme mainly introduced the disease to individuals with no known TB contacts. Jason, a forty-five year old pulmonary patient recalled learning of tuberculosis during a modern history lesson. Like other interviewees, he commented that he had retained very little of this information, and postulated the reason for this was because he did not perceive it to be important or useful.

> "There was actually some mention about it, but it never stuck, you know so I said oh, I'll need to remember that sort of thing, you know it's not something you say to yourself you say got to remember, but I'd heard about it vaguely sorta thing you know." (Jason)

Only a small number of males cited television documentaries and books as sources of information. On the other hand, women spoke of actively seeking information from the Internet, in an attempt to alleviate their anxiety about symptoms they were experiencing. Following a six-month period of weight loss and sweats, Evelyn accessed the Internet to try find an explanation for her malaise.

> "Eh, yeah, I had started looking up the Internet and stuff like that, 'cos I was really worried and I thought oh, first you think its cancer and the weight was just coming off, I just didn't feel well at all." (Evelyn)

7.3 Modes of transmission

In a 1977 review of studies involving individuals from many populations, Chrisman postulated lay theories of illness causation (Chrisman, 1977). Like Chrisman, explanations for ill health in this study were mainly patient centred. Indeed, patients thought illness was caused by the invasion of a germ, by being run-down (degeneration) and because of a failure to maintain a balanced life, by not eating a balanced diet or lack of sleep.

The majority of interviewees had previously indicated tuberculosis was a communicable disease, and some realised a germ or bacterium was the causative agent for the illness. Respondents thought this was carried in the spit, sputum, or on the breath of individuals infected with TB. One patient thought a virus was responsible for causing the disease, and was joined by one other interviewee in describing the mode of transmission as "viral".

Jason ..its like a viral, eh distribution in certain cases...

AH How do you mean viral?

Jason As in, like passed through the air or close, close up, up contact with other people...

It can be speculated this term was used to indicate a mode of transmission that involved the airborne communication of the disease. Similarly, Ian described the spread of tuberculosis as viral, and indicated that he felt the illness was spread in the same way as other common illnesses such as a cold or influenza.

> "I thought it was spread, well, by the fact that people who have TB cough or, you know a lot, then its, its spread by, sputum spray or whatever it would be, same as a lot of diseases are.". (Ian)

It appears this respondent did not recognise the difference between the types of pathogens causing tuberculosis and other common illnesses. This example illustrates how the medical profession and lay population can attribute different meanings to the same term.

All interviewees were confident that the source of infection was an infected individual, and that TB was passed between people (person-to-person contact). Patients indicating TB was spread from person to person often postulated they acquired their illness from a known TB contact. Dan provided a clear indication of how he thought he caught TB from a friend, with whom he drank at his local public house.

> "I was thinking if it was [Tim] I caught it offa, when he'd speak to us all, so maybe it was off his breath…maybe, [Tim]'s spittle or something when he was speaking, but eh, you know, if he was drunk and maybe spitting…" (Dan)

Patients with no TB contacts indicated that they probably had unknowingly spent time with a person who had been infected with TB. Moreover, patients were surprised when contact tracing revealed none of their contacts had tuberculosis. Evelyn thought "*..when they started testing the people closest to me, I thought one of them is bound to have it. Somebody must, and its just been spread, but it came back negative to everyone.*"

When asked how they thought the infectious TB agent spread, competing methods of transmission were noted. Initially, patients referred to the airborne transmission of tuberculosis, and alluded to the release of the infectious agent using terms such as "*coughing*", "*spitting*", "*speaking*". The exchange of bodily fluids, and sharing with a TB case were also nominated as modes of transmission, and it was not uncommon for several modes to be mentioned by respondents. Patients drew on their life circumstances and personal experience when proposing these theories. Firstly, six patients thought tuberculosis could be acquired by sharing with an individual infected with tuberculosis. Reusing a TB patient's drinking vessel, dish or cutlery were proposed routes of transmission, particularly when utensils were not adequately cleaned. Mainly older males, who regularly frequented public houses, upheld this view.

> "Ah well, you know yourself, you just get, you get a pint, you finish your pint and you put it back behind the bar, they wash it and its supposed to be washed and its not washed you know." (Dan)

A further five interviewees discussed the possibility TB could be acquired from bodily fluids such as sweat, saliva, or following physical or sexual contact with an infected individual. One patient discounted the fact TB could be spread through the air, and thought physical contact with an infected individual was the only way TB could be contracted.

> "..it was a kind of a contact thing, it wasnae something that went through the air, you know." (Tim)

Three respondents nominated contaminated food and water as a reservoir for the infectious TB agent. Gwen worked as a chef in a public house, and enquired whether TB could be spread in food because following her diagnosis, she was not permitted to return to work for an extensive period of time. She commented that her workplace health and safety manual appeared to imply that if she had been diagnosed with AIDS, she could have continued to work. This perplexed Gwen, as she considered AIDS and TB equally serious infectious diseases. She thought the reason for this disparity might be because TB, rather than AIDS, could be spread in food.

> "I don't understand that, I'm a chef, and one thing I actually seen ... the health and safety is that if I have TB I can't work. So, there must be something somewhere, that, I don't know, its actually listed, it says other illnesses, cuts whatever, or tuberculosis, you can't work (laughs). And I'm like ok (laughs). If you have AIDS you can work, but if you have tuber, tuberculosis you can't. And I thought, I wouldn't have thought one was harder, that was more high profile, but there you go" (Gwen)

7.4 Duration of contact required for transmission

Medical thinking has proposed close, prolonged contact with an infected individual is required before TB can be transferred to a susceptible individual (Joint Tuberculosis Committee of the British Thoracic Society, 2000). For this reason, family members or contacts of a similar association are considered to be at an increased risk for acquiring TB. In this study, interviewees were asked about the duration of contact required with an infected individual, before one became infected.

Although respondents were aware the medical community viewed close contact for lengthy periods of time as necessary for transmission to take place, they reported this conflicted with their own opinion. Reflecting on their personal experiences, patients began to explain why they thought this was untrue.

AH So do you think it's a long time you would need to spend with somebody ..?

Evelyn Well, it can't be 'cos I hadn't been a long time in anybody else's company, apart from my own family. And yet, the bits I'd read that said it would be like people coughing and droplets in the air and stuff like that, but if that is how caught it, why did nobody else in my family have it?

The above excerpt from Evelyn's interview illustrates that respondents assessed their own situations, to see if their own close contacts had become infected. Patients' determined lengthy periods of contact were not required, because they would have expected to infect their own close contacts, and this was not the case. Similarly, Olivia found it difficult to understand why her close school friend did not have TB. As these friends claimed to rarely spend time apart from each other, Olivia concluded that she must have acquired her TB rapidly, otherwise her friend would also have been infected.

Interviewees agreed TB could be passed within a relatively short period of time. In trying to establish the length of time required, Dan surmised it could happen almost instantaneously.

"..all it takes is a, a dribble of spittle or something you know." (Dan)

Norman was also of this opinion, and explained how he felt hospital practices had reinforced this belief. When diagnosed with sputum smear positive TB, patients are located in a negative-pressure isolation room on a hospital ward, as a matter of routine, where they are treated until they are no longer considered infectious. Norman felt these measures were taken because he was highly contagious. He said:

"someone with TB, even go near them you can catch it. Certain TBs as far as I'm concerned, not all TBs...well I suppose that's why when I was up in [Glasgow hospital] they put me in a room, away from everybody else. So I told them, well I'm (mumbles), if somebody comes in here and doesn't know the score and sits and talks to me for ten minutes, they could walk away and in a few months time, they have TB." (Norman)

Only two patients stated that they believed the acquisition of TB required lengthy periods of time in the company of a TB patient. Walter thought TB was comparable to a cold, in the sense that the more time you spent around individuals with a cold, the more likely you are to contract the illness. Ruth maintained that usually close, prolonged contact was necessary, and when asked to explain how she interpreted this, she responded:

"..to me, prolonged daily contact would mean over a period of time, wouldn't it? And, I don't know whether they mean prolonged as a couple of days. I'm

> thinking prolonged as weeks or longer. So its kind of people like your colleagues that you're working with every day and so on." (Ruth)

Although Ruth indicates this level of contact means weeks rather than days, it is interesting that she gives work colleagues as an example of high-risk individuals. Current policy documents providing guidance for contact tracing assign work associates as lower priority for screening (Joint Tuberculosis Committee of the British Thoracic Society, 2000).

Furthermore, patients criticised the provision of conflicting advice and information in relation to the duration of contact required to facilitate TB transmission. Ian complained that different doctors held different opinions about the possibility that he could have acquired the disease from a passenger in his taxi. He queried whether there was any communication between these experts. He also felt that until experts in this field were clear about it, patients would remain unsure.

> "To me the answer, to me the answer is, they don't know and neither do I..." (Ian)

Similarly, Gwen commented that some family members were advised by their GP not to visit her, as they would be at risk of contracting the infection. However, she was being cared for by a pregnant nurse, and Gwen would have considered this individual at greater risk of infection that her family members.

> "one GP told my brother in law not to visit me in hospital in case he got it before his wedding...I was told that was, there's no way you could catch it in one visit, otherwise the nurses wouldn't come in. I had a pregnant nurse when I was in the [ward name], and if it was that dangerous, she wouldn't have come in to see me." (Gwen)

7.5 Reactivation of latent infection

Very few patients (of their own volition) stated that they could have suffered from a reactivation of a latent infection. When prompted, patients confirmed they had considered this possibility when their TB nurse or doctor originally introduced the concept to them.

> "..one of the doctors said to me you could have contacted this 30 years ago and now your systems low and its like the TB bug hibernates and it waits there, the conditions are not right for it to come out..." (Carl)

Many found it difficult to estimate how long the infection had been lying dormant in their bodies, primarily because they could not identify a period in their life when the risk of

acquiring TB was enhanced. On the other hand, patients who had known TB contacts were able to speculate about the duration of the latency period. Dan and Tim were part of the same social circle, and were diagnosed nine months apart. Dan thought that if he had acquired tuberculosis from Tim, tuberculosis could have been dormant for that period of time.

> "...if it was off [Tim] like I say going back again, that was about 6 to 9 months after it, the way it appeared in me." (Dan)

Other respondents felt this period of time could have been considerably longer. Brothers Alex and Patrick believed their late father, who was diagnosed with TB when they were children, could have been a source of infection. Norman, aged 69 at diagnosis, also felt he could have acquired TB a long time ago. During his youth, he drank excessively and lived "rough" in London, and believed at that point in his life, he was at greatest risk of infection.

Reasons for the reactivation of infection were sought from patients. Being run down or having a compromised immune system were the most commonly identified themes. Patients believed the disease flourished after lying dormant because factors such as poor diet and alcohol excess impaired their body's defences, allowing the disease to become active. All patients discussed the concept of wellbeing and immunity in detail, and an analysis of this topic will continue in the section below.

Although the reactivation of tuberculosis was mainly attributed to a weakening immune system, two respondents thought differently. Olivia indicated that prior to having invasive investigations at the hospital, she had been experiencing mild symptoms. On her return home she became very unwell, and thought the tests were responsible for reactivating the latent infection. Evelyn also recognised her symptoms worsened after a similar procedure, and said "*..after they did that tube down my throat I was coughing like nothing on earth.*". However, Olivia was alone in surmising the test caused her TB to become active.

> "when they did that test, it disturbed it because I was, it went through being ok with just the noise and the discomfort to really severely ill." (Olivia)

Secondly, Jason thought different strains of tuberculosis could reactivate at different rates. He believed that strains varied in their virulence, and that he had been diagnosed with a mild version of the disease. He considered milder strains to take longer to reactivate than "*stronger*" strains which were found in developing countries, and which progressed rapidly to active disease.

7.6 Susceptibility to illness

The majority of patients felt they were in part responsible for acquiring tuberculosis, as bodily defences were mediated by their behaviour and lifestyle. Herzlich proposed patients believed illness was caused by factors external to the body, and that their health was an internal reserve, maintained by their physical strength and resistance to illness (reserve of health theory) (Herzlich, 1973). Other researchers report that vulnerability to illness is considered to lie within the body and are under the control of the individual, however the acceptance of responsibility for health determining behaviour appears to vary between groups (Blaxter & Paterson, 1980). The extent to which individuals feel morally accountable for their illness is associated with socio-economic status (Pill & Stott, 1982), but it was not possible to examine this association within this study, as the study population largely had the same deprivation category score, and comparative analysis of different deprivation categories would not be possible.

Patients recognised the immune system as their primary defence against ill health, and once impaired, left them "*susceptible*", "*vulnerable*" and "*prone*" to invasion by the TB pathogen. Older males tended to describe this state as a "*weakness*", and although patients' explanation of this term was vague, it appears it was used to either refer to a genetic predisposition or an imposed environmental factor. Two patients believed the acquisition of TB was out of their control, because they considered certain individuals to be predisposed by virtue of their genetic-up.

> "..perhaps some people are naturally more vulnerable, em, different , em, resistances to different things". (Carl)

Simon, a recovering alcoholic thought similarly. Rather than identifying his social behaviour as a reason for ill health, he believed his relapses of TB were out of his control because TB was an illness his body was not equipped to fight.

> "And having it three times, and its reoccurred, and reoccurred and reoccurred. Eh, so I don't know if I got a weakness to it, or my immune system is weak to it, I don't know. But having it three times, I suppose am I?" (Simon)

As noted by Chrisman, respondents in this study felt bodily defences were mediated by factors such as a poor diet and excessive alcohol intake (Chrisman, 1977). Many male patients admitted they had not been eating balanced meals, and felt because they were inadequately nourished, they were at increased risk of becoming sick.

> "I'm not saying I wasnae eating, but I wasnae eating what I should have been eating, you know… So gradually, it takes its toll I think. I just let myself, my body go that far I think, just, I was just susceptible to anything at the time." (Tim)

Similarly, Martin, aged twenty-five, thought that by taking amphetamines and ecstasy, his body was unable to defend against infection. He was not aware of any other adult being diagnosed with the disease, and deduced his drug-taking behaviour rendered him susceptible to tuberculosis.

> "'Cos I used to drink a lot, take drugs, my immune system was phew (gestures), was gone (laughs). Even a, even a common cold I used to get really bad, you know what I mean, so that's how, I reckon, I reckon that's how I got it, 'cos I think my immune system was so low, I gave it such a battering, and it couldnae do anything about it, do you know what I mean?" (Martin)

A number of female respondents stated they had been run down before they became sick with TB (Chrisman's theory of degeneration). For example, Gwen attributed her illness to the fact she had just given birth to her second child, was suffering from post-natal depression, was having difficulties sleeping, and not eating "properly". Additionally, Evelyn reported that before she was diagnosed, her husband, grandson and father had been hospitalised, and she was exhausted doing her full-time job and visiting each individual daily.

One patient felt that having another illness would have put them at risk of getting TB. By initially weakening their immune system, this could have allowed easy passage of tuberculosis into their bodies. Ruth described how she thought TB entered the body when the immune system was weakened or compromised from fighting another illness.

> "..they [doctors] advised me that they, they generally deal with it as a secondary disease nowadays. In this country, mainly alcoholics, they find that they've got a lot of alcoholics they would be treating, people who live in the streets, and that's a, you can understand that 'cos they drink and don't eat.." (Ruth)

Herzlich pointed out that when speaking about health beliefs, patients provide an insight into moral dimension of illness causation. With one exception (Simon), it is evident patients generally took responsibility for their ill health, in the sense they believed they were to blame for not taking better care of their internal reserve of health (Herzlich, 1973). However, some male patients felt that becoming infected with the disease was a lottery even when their actions rendered them vulnerable to ill health. Quentin felt it was a matter of being at "*..the wrong place at the wrong time.*". Others supported this view because

they knew people who had been in contact with known TB cases, but had avoided infection.

> "..he didn't get it, yet he was staying with an uncle that died from it, do you know what I mean, so. It's a lottery innit?" (Martin)

Ian thought he hadn't put himself at any risk of getting TB, and did not think he had any control of acquiring the illness. In explaining the situation to his elderly mother he said

> "..its not something which you get because you shouldn't do it or you deserve it, its, it just, it comes from people passing on you know, like the flu or whatever it would be." (Ian)

7.7 Putative sources of infection

Blaming others for one's ill health is not uncommon, and often leads patients to give disease an aetiology that involves the social world, for example, giving/catching a cold from somebody (Helman, 1985). In this study, some patients blamed their illness on social interactions, and nominated instances of social mixing when contact with a TB case and subsequent transmission of infection may have occurred. Putative locations and individuals involved in the transmission of tuberculosis were proposed. It is likely environmentalist or social explanations feature prominently in health beliefs because populations close to scientific sources of information are likely to report views similar to those held in medicine (Blaxter & Paterson, 1980).

The majority of patients tended to focus on instances of social mixing with the general public when trying to identify situations where they could have been at risk of acquiring tuberculosis. Indeed, many highlighted the distinct lack of contact they had with the public or their communities, stating they were always at home and fellow household members did not have TB.

> "I don't use public transport, I drive, and I don't go out at weekends or anything, I don't socialise, I'm in the house all the time, I'm in with the same lot of people most of the time as well. So, I couldn't, couldn't understand how I had contacted it in the first place." (Evelyn)

Individuals providing a public service perceived themselves to be at heightened risk of acquiring TB, as the job required meeting many people. Both Ian, a taxi driver, and Quentin, a barman, explained that by virtue of meeting and speaking with so many people on a daily basis, their chances of catching TB were increased.

> "Eh, its maybe people who's maybe like myself, that's working in the pub all the time, maybe meeting all different people every day, you know what I mean? Eh (pauses) I think that's just, I think that's probably how I got it, you know what I mean, through, through the pub." (Quentin)

Respondents introduced the concept that environmental factors influenced the probability of becoming infected by a member of the public. For example, spending time in a confined space with a TB patient was understood to increase the risk of acquiring TB. Una described how she felt transmission could occur on a bus, as this was the main location she was in contact with the public, and possibly an unknown TB case. It was also a confined space, with little air movement. Ian understood the movement of air to be important in decreasing the risk of airborne TB transmission, as it has the potential to prevent the inhalation of infectious airborne particles.

> "..any place where you're out in the open air, em, there's less chance of it, well, the fact its, the airs moving would cut down your chances of it anybody coughed it coming towards you...". (Ian)

The spread of TB was also thought to be assisted by crowding, and public houses were nominated as locations were this often occurred. This was a popular choice amongst individuals who frequented these locations on a regular basis, or who were known to drink excessively. Respondents with this lifestyle felt assured they acquired TB while spending time in public houses or drinking dens, because they had spent time in the company of known TB patients, and had shared drinking vessels.

However, one patient described how the concepts of crowding and confinement were in conflict in her mind. Gwen described that before being diagnosed, the only time she had been in contact with the public was at a car boot sale, which she had attended on a number of occasions. She described the location as being crowded, but open air, and found it difficult to conclude whether she had been at greater risk of getting TB in that location. Finally, two previously homeless interviewees suggested they acquired their infection while living in hostels for the homeless.

> "..I stayed in a lot of guesthouses there [London] you know, and I never stayed long in one because they were rough places, you know, and most of them were drug addicts, alcoholics and you've got mental illnesses, and all the rest of it was in, you know so. Och, I look back and I could have dug that up somewhere along that line." (Norman)

Lay theories of illness causation not only include beliefs about the causes of illness, but stereotypes of people likely to get the illness (Chrisman, 1977). The view that homeless

individuals are likely to get TB was reflected in interviews with individuals who were not homeless.

> "..I just thought it was like...winos...like, down and outs, kind of thing.." (Veronica's mother)

Having spent many years working in a bookmaker, Ruth thought her clients were possible sources of infection, as she described them as "*jakey*" or "*tramp*" types. Poor and/or unhygienic types of individuals were often associated with tuberculosis by female respondents. (A discussion of the stigma associated with TB will be discussed further in chapter 8).

A minority of patients felt spending time in impoverished Glasgow areas could increase the risk of catching the infection. Jason explained he felt this was because infectious diseases were more prevalent in these areas, as opposed to wealthier areas, because they differed with regards to the amount of community interaction.

> "[in poorer areas] kids play about outside whereas more affluent places, they don't sorta seem to play about outside whereas younger kids and that, they always seem to be out, they're out and about all the time sort of thing so maybe they pick up things up that way, you know" (Jason)

Asylum seekers and immigrants were also perceived to be likely sources of infection. Some individuals understood that there had been a resurgence of tuberculosis in recent years, and thought immigration had played a significant role in this event. Although many interviewees introduced the idea of acquiring imported infection, all discounted the fact they personally acquired TB from this population, as these individuals reported having limited contact with immigrants.

> "And one of the things I had read was saying that was how it was starting up again with immigrants coming into the country. I can't say I'd been in touch with many of them either." (Evelyn)

Simon was an exception, as he felt he had been exposed to infection while spending lengthy periods of time waiting in TB clinics, predominantly in the company of immigrants.

7.8 Practical considerations

Prior to conducting patient interviews, this investigator held some concerns about issues of safety while undertaking such field work, and therefore a member of staff at Health Protection Scotland accompanied the investigator to each interview. This individual was present during the interview, but did not become involved in the conversation while the interview was being conducted.

At the outset of this research study, this investigator's BCG status was determined by tuberculin skin testing, and BCG vaccine was subsequently administered. This was undertaken to ensure both the investigator and those in contact with this investigator during the course of the research study were afforded as best protection as possible from inadvertent exposure to TB from any infected individuals they came into contact with.

Difficulties were encountered during the recruitment process. Of the 46 patients (or next of kin) eligible for interview, 39.1% (18) did not participate. It is recognised this could cause the investigation to miss a number of important epidemiological links. Five cases were not invited to participate in the study (three Western isles, 2 deemed unsuitable for interview), six did not wish to participate, and five did not respond despite many attempts to contact with them. A further three were not at their last known address and four cases had no known next of kin suitable for interview.

The quality of patient recall during interviews was variable, because some cases were interviewed four years after their diagnosis. Many interviewees commented that they would have difficulties recounting experiences and daily routines prior to their diagnosis because their memory was failing. Norman, aged 73 explains:

> "But I mean there's a lot of things that's happened in my life, my memory is not strong enough to pick it up again, its, its gone forever sort of, you know."
> (Norman)

Old age is likely to have affected interviewees ability to recollect specific details. In some instances, prolonged alcohol misuse may have contributed, as alcohol psychoses such as Korsakoff's psychosis and Wernickes encephalopathy have cognitive, behavioural and physiological symptoms, resulting in memory-loss and confabulation. Interviews with known alcoholics or heavy drinkers were sometimes conducted with a partner or next of kin present. In some instances, these individuals corrected the interviewee if providing incorrect information, or provided information on their behalf. Equally, it is possible

interviewees did not provide true accounts of their social behaviours because they were accompanied during the interview by partners/mothers. Many interviewees failed to recall names of friends or "drinking buddies" when requested to do so. On other occasions, they admitted only knowing nicknames, or called them by names interviewees admitted were not their own. This would make the detection of associations between cases more difficult.

> "If somebody come to me, see you call him Paddy? Aye. Well why don't you call him by his first name? 'Cos I don't know his first name. Its funny that, that's it. If you get a name of Joe or Paddy it sticks, and you've known guys for years, and you say hello Paddy, hello Joe...." (Norman)

Interviews with two known alcoholic men revealed an unwillingness to divulge contact information. The investigator confirmed that all information provided would be held in confidence and the public health importance of the study was reinforced. The following excerpt reveals a mistrust of the interviewee.

> "Ah well, I don't really want to give you any names, you know what I mean, I don't know, I don't know where this interview's going, you know what I mean?" (Brian)

Despite encountering these problems on occasion, interviews revealed much information about patients lifestyle and behaviours.

More mundane difficulties were encountered during the majority of interviews. These involved disruptions, for example, interviewees accepted phone calls during interviews, attended to children and pets, and in one instance a disturbance outside the interviewees home meant the interviewee left the room for some time to deal with vandals[23]. Also, despite scheduling an appointment with interviewees, they were not present when this interviewer arrived for the interview. Several trips were made to these individuals before an interview was conducted.

Many interviewees indicated that although they were provided with a voucher to reimburse them for any inconvenience caused, they initially tended to refuse it. Many indicated they were simply pleased to be assisting the investigation, as they perceived this research as important, as it could assist in preventing other individuals from getting the disease. However, offering a voucher as an incentive was clearly the motivating force for some individuals. In this excerpt, Una refers to her father who was interviewed a few days prior to her own interview. As this investigator had run out of vouchers at the time her father

[23] It transpired children were throwing stones at windows in the interviewees apartment block.

was interviewed, he indicated he would be happy for his daughter to receive his, after her interview, which was scheduled a few days later.

"He says, make sure you get my Boots voucher (*laughs*)." (Una)

7.9 Discussion

In this chapter, attitudes and beliefs held by TB patients believed to be involved in a network of transmission were explored. (These beliefs dictate patterns of behaviour, which will be explored in chapter 8.) Findings from this study support the view that individuals have complex ways of thinking about the causes of illness that do not necessarily mirror those held by the medical profession. 'Lay' beliefs are part of wider cultural concepts concerning the structure and function of the body, beliefs about misfortune in general, and are influenced by inherited folklore and medical concepts, and are used when trying to make sense of the bodily changes (Chrisman, 1977). It was clear that interviewees' beliefs were influenced by medical concepts disseminated by the medical profession during contact tracing/BCG programmes for example, but also by individuals within their lay referral system, i.e. patients supportive social network comprising of family/friends.

First, patients' explanatory model of modes of illness both mirrored and contradicted that of the medical profession. Patients referred to the airborne transmission of tuberculosis, however, in addition, many suggested the disease could be transmitted by contact with bodily fluids. For example, many male respondents known to regularly frequent public houses believed TB could be acquired by drinking from tumblers, which were contaminated with saliva from a TB infected individual.

Secondly, patient perspectives regarding the duration of contact required for transmission to occur departed from medical thinking, which suggests a minimum of eight hours daily contact with a TB case is required for infection to occur. Furthermore, the requirement for close, prolonged contact was dismissed. Instead, transmission was thought to occur within a much shorter time frame, and in confined spaces where mixing with members of the public took place (e.g. buses). It appears conflict arose because patients had difficulties making sense of expert advice regarding the impact of risk behaviour in terms of the workings of their body and personal experience. When expert advice is given it is sometimes couched in statistical terms drawn from a population level, which individuals find difficult to apply to themselves and their own situations (Helman, 1985). From this study, it is clear many patients felt even after they completed their course of treatment,

they remained unclear about the aetiology of disease and the duration of contact required to acquire the infection, particularly as their experiences departed from the information provided by medical staff. It is important these issues are addressed because these cases are members of a community, and are likely to be members of other individuals lay referral systems. The feedback of inaccurate information to such networks may continue to fuel myths and stigma that surround the disease. Findings from this study may therefore contribute to baseline information used to develop health education programmes.

The conflict between lay and medical models of thinking has important implications, because if patients and health professionals understanding of disease transmission differ, then the current method of contact tracing is inherently flawed. Contact tracing relies on newly diagnosed patients identifying individuals who have been at-risk of acquiring infection during the period in which the patient was symptomatic. As TB patients do not hold the same beliefs about TB transmission as medical professionals, patients may not identify the same at-risk contacts that contact tracers would, if the latter were privy to an insight into the patients social behaviour and network of contacts. Theoretically, this may result in the failure to identify all at-risk and potentially infected contacts during contact tracing. This difficulty is likely to be pronounced in casual contacts of infected cases, as such associations fail to be uncovered during routine epidemiological investigation, as was demonstrated in chapter 6.

In a 1995 study of TB case beliefs and attitudes in Birmingham (Singh Bakhshi & Ali, 1995), disease management and contact tracing was found to be associated with a lack of knowledge and awareness of symptoms. Results from this study reaffirm this finding, as patients had little prior awareness of the disease and its symptoms, and this could have delayed their presentation to medical services. However, Singh Bakhshi *et al.* also postulated no association existed between social stigma/rejection and delayed case presentation, and this point will be taken up in the discussion section of chapter 8.

Respondents had mixed feelings as regards their own culpability for acquiring the infection. With one exception, all interviewees felt responsible for acquiring tuberculosis because they had allowed themselves to become susceptible to the illness by failing to maintain good health. Males were generally in agreement with this statement, however, a number believed that it was essentially a matter of luck, as one may or may not acquire TB once their immunity had been weakened through poor diet, excessive alcohol intake etc.

The selection of study cases, all of whom had a genetically indistinguishable IS*6110* RFLP pattern, was of key importance in this study. To complement the improved understanding of disease transmission dynamics presented in chapter 6, this sub-study explored the cultural factors which contribute to the transmission of this specific strain. This sampling frame was presumed to represent cases, all of whom were thought to have acquired TB recently. However, as discussed in chapter 6, interviewees may have acquired infection in the recent past, and suffered reactivation of latent infection more recently.

In conclusion, patients generally believed that in order to become ill, they had to acquire the infection from another individual. Although interviewees realised that the classical medical belief is that close contacts are at greatest risk of infection, interviewees felt they may have acquired infection from a casual contact as a result of a brief social encounter (indeed the acquisition of TB following a short period of exposure is not impossible). Often locations outside the traditional household setting were suggested as sites of potential exposure. This contradicts the classical belief that for the most part, transmission requires close prolonged contact. The different beliefs held by patient and health professional about the level of contact required for TB to spread may influence the identification of at risk contacts. Contact tracing practices may benefit from maintaining an awareness of the differing beliefs held by patients nominating contacts for screening.

Chapter 8: Help seeking behaviour

In chapter 7, a baseline description of patients attitudes and beliefs about the aetiology, acquisition and transmission of TB was provided. As health beliefs dictate illness (and health) behaviours, this chapter seeks to building on information from the previous chapter by improving our understanding of patient illness behaviour, and in particular, the rationale used by patients when seeking help for symptoms. It is known that delayed presentation of cases to medical services and failure to identify contacts for contact tracing for example have an adverse effect on the control of disease (Chin *et al.*, 2000, Cronin *et al.*, 2002). This chapter therefore seeks to identify barriers to early case detection and therefore TB control.

8.1 Recognition of symptoms

Interviewees described how they became aware of feeling unwell, and how they came to seek assistance from the medical profession. With one exception, where the patient did not experience any symptoms, and was diagnosed following a contact investigation initiated for his uncle, all patients described symptoms they experienced. Symptoms of cough and weight-loss were most frequently reported, and Tim described the point at which he realised he had lost a significant amount of weight.

> "..you're washing or shaving and I look kind of...gaunt...and then the next thing you know your watch is slipping down your wrist, you know you're losing weight, you know." (Tim)

Chest pain, haemoptysis, lethargy, loss of appetite, nausea and night sweats were some other common symptoms discussed by patients. Loss of breath and exhaustion were reported following mild activity, as Olivia described: "*I couldnae really walk or anything, I was so out of breath and knackered.*". Five patients had symptoms that were initially non-specific, and it was confirmed these were akin to feeling run-down, while others said they felt "flu-like". Although patients recognised they were feeling unwell, they found it difficult to clearly describe their symptoms.

> "I started feeling not a hundred percent, nothing specific, but just not a hundred percent. I've always been really strong and healthy." (Ruth)

Veronica's mother commented her daughter had become so ill she had become a "*shadow*". Although the meaning of this was not pursued, it is possible this encapsulates

her weight loss, her inactivity and inability to interact with others. Her mother indicated her social development was affected, and nursery nurses commented on how introvert she had become.

8.2 Decision-making in health seeking

It is recognised the decision to seek help is influenced by socio-cultural factors, and not necessarily the severity of symptoms experienced (Zola, 1966). In 1966, Zola identified types of incidents responsible for triggering the decision to seek medical care. Although proposed over thirty years ago, these are still valid, and were reported by patients in this study. Amongst those noted were perceived interference (with social or personal relations), sanctioning (others put pressures on the individuals to seek help), interference with vocational or physical activity, and temporising of signs and symptoms, where patients have specific ideas about how long symptoms should continue.

Patients in this study actively sought medical attention when symptoms deteriorated. Anticipating her cough would improve, Gwen decided to ignore her symptoms. After some time her cough had worsened and she had developed additional symptoms. In this quotation, Gwen speaks about becoming so lethargic she felt incapable of work, and eventually decided to resign from her job.

> "And em, I gave up, I just left the job and everything, I didn't want to do anything…I wanted to lie on my bed all day." (Gwen)

Other patients appeared to ignore their symptoms, and often attributed them to other minor illness. It is interesting to note that no interviewee, even those with TB contacts, indicated they suspected tuberculosis. Some months before Ruth received her TB diagnosis, she received treatment for what she described as pleuritic pains. Although it provided relief from pain, she said "*..I just didn't feel back to normal afterwards.*". She described the persistence of these flu-like symptoms, and explained she thought she had acquired a virus and her body was taking time to fight it. She said "*I had just felt flu-like, you know, I kept on telling myself it was a virus that I couldn't shake.*". Reflecting on the three-month period she experienced these symptoms, she decided perhaps her illness was more serious than a virus. By attributing her symptoms to another illness, and thinking it would resolve itself, Ruth postponed seeking further medical care.

> "..I went on well after Christmas, into January until I started to think like, its not just a virus, 'cos I just don't get stuff like that and come on, you're gonna have to go." (Ruth)

Persistence of symptoms prompted some individuals to seek medical assistance. For example, Evelyn stated her chest pain motivated her to seek the advice of her GP, as it "*..[the chest pain] just wouldn't go away*". Similarly, Carl had felt tired and run-down, and had originally attributed it to having recently started in university. His health failed to improve, so "*..after maybe 3 weeks or something, and its not, not getting better, so em, went to doctor*". In this example, Carl tried to interpret his symptoms in the context in which they occurred, a process called normalisation. This example highlights the fact patients tried to normalise their symptoms, in other words, tried using theories of causation from lay culture to explain their condition. Generalisations about types of circumstances and types of people likely to suffer these symptoms are used by patients to explain disturbances to their body. If considered normal, patients will accept their symptoms fatalistically. Only when their understanding of the physical experience departs from this interpretive framework, patients tend to seek care (Zola, 1966).

Respondents commented that their symptoms interfered with their day-to-day living, and many employed interviewees indicated they struggled to continue to work. Inevitably, this would have imposed a significant financial burden on some patients, although patients did not mention this explicitly. Those performing physical tasks found it increasingly taxing, for example, Simon constructed scaffolding for a living and found this proved difficult as his health deteriorated. While painting his house, Ian found that he "*..didn't have the strength that I had...*".

Five patients in this study indicated they received treatment directly as a result of advice from a family member or friend, as they either encouraged them or actively sought medical assistance on their behalf. Particularly as patients' symptoms worsened, family members intervened out of concern for their health and wellbeing and either requested a home visit, or encouraged patients to make an appointment to meet their General Practitioner (GP). Bob indicated his sister phoned for a GP when she "*..saw I was in my bed and I was just wasnae getting up, you know, she was worried about me, she just decided to call the doctor, you know.*". Similarly, Ruth's work colleagues insisted she sought medical attention because she had felt ill for a prolonged period.

> "..my colleagues had been saying to me as well, you've got to go, you've got to go, there's something not right, and I went." (Ruth)

Such decisions to seek medical aid reflect another of 'Zola's triggers' known as 'sanctioning', whereby one individual takes responsibility for seeking medical assistance on behalf of the case (Zola, 1966).

8.3 Misdiagnoses

Evidence from patient interviews indicates delays in diagnosis were encountered even after patients chose to consult with medical practitioners. It appears patients with non-specific symptoms, with no known contact with a TB case, and those who did not fit the stereotypical image of a TB patient (as described in section 7.6) appeared to delay diagnosis for some interviewees. Evelyn was finally given a diagnosis of tuberculosis six months after she first contacted her GP, and felt that the absence of traditional symptoms such as a cough and sputum was responsible for the delay. As the period in which she was attending her general practitioner was prolonged, she feared her doctor was starting to consider her a nuisance and question whether she was truly ill.

> "I felt as if the doctor was starting to say what is she doing back here again, you know 'cos I just, I couldn't say what it was, I just knew there was something wrong. But because I didn't have the cough, I, the spit of anything, but after they did that tube down my throat I was coughing like nothing on earth" (Evelyn)

On the other hand, Gwen was suffering from post-natal depression following the birth of her second child. Each time she visited her GP the dosage of anti-depressant medication was increased, and Gwen described how she perceived this as a lack of understanding on the part of her GP. She describes feeling frustrated and hopeless.

> "..it was like you get fed up, you're so tired your fed up ... they put my anti-depressants up and everything, but I knew it wasn't that, I knew I wasn't depressed, I knew I was just sick and tired inside, it was a horrible feeling." (Gwen)

Similarly, Olivia reported the doctors she consulted with dismissed the development of new symptoms, and stated they "*..were just putting it down to my asthma.*".

After many months of experiencing symptoms, a number of patients were dissatisfied with the treatment they received and reported insisting on further investigations, in the hope of determining the cause of his/her illness. Olivia's mother felt strongly that if she hadn't spoken out, the physicians treating her daughter might not have diagnosed her as quickly. Similarly, a nineteen-year old miliary TB patient was diagnosed after an eight-month

period where she experienced loss of appetite, rapid weight loss, night sweats, nausea and hair loss. In that period she completed a total of seven courses of broad-spectrum antibiotics. Keira indicated that when she started to sleep sixteen hours a day, her mother demanded to see a specialist. She describes how after eight months of symptoms she felt her illness was finally being acknowledged, and became hopeful she would be cured.

> "Em, he sat me down and his words to me were, em (pauses) I know that you've got something seriously wrong with you, but its not critical, its not life-threatening, and it will be em, curable." (Keira)

Another interviewee spoke of her dissatisfaction with how long it took doctors to diagnose her daughter. Despite attending numerous clinics, her daughter was diagnosed with minor ailments, such as urinary infections, despite the continued deterioration of her health.

> "I hated the fact that it took so long for them to diagnose it,...the doctor in the hospital was saying this, if we hadnae, if I hadnae of pushed for them to do that test, she would have been away as well ... the GPs should be more, like alerted to it, than what it is... 'Cos she had like every symptom under the sun... belonging to it [TB], and he still put it down as a urine infection...that kind of makes you angry." (Veronica's mother)

Andrew's sister spoke about the death of her brother. Although she did not appear to be resentful, it was clear she wondered whether his death could have been avoided if immediate action was taken by medical staff.

> "We knew that his TB was coming back ... 'cos I actually had taken him to hospital and they wouldn't keep him in, and then it was like a couple of days after it or something, he got rushed back in again and actually died on the bed. So I think if they'd kept him in and gave him the x-ray that we asked to give him, 'cos I explained that he had TB and all that 'cos he was coughing up blood and all that and eh, no, they just put him back out again anyway, so."
> (Andrew's sister)

The issue of quality of healthcare provision was an emotive subject for many interviewees. In particular, females appeared critical of the health care they and their families received, whereas men did not appear to question the advice or information provided by health professionals. Further investigations would clarify whether barriers to seeking treatment differ according to gender.

8.4 Responses to a TB diagnosis

In the past, tuberculosis was a prevalent disease, one that was regarded with fear and dread because the cause of disease was unknown, and when treatment initially became available, it was not completely effective. It has been suggested that in today's society, cancer now fills this role (Sontag, 1977), as TB is now a relatively rare disease, with approximately 7.2 new cases per 100,000 population detected in Scotland in 2003. This comes across in this study, as many recall a great sense of relief that their diagnosis was not one of cancer or pneumonia. Evelyn recalled how she felt distressed when she couldn't explain what was wrong with her, and she began to expect the worst.

> "Eh, yeah I had started looking up the Internet and stuff like that 'cos I was really worried and I thought, oh, first you think its cancer…". (Evelyn)

Tim was convinced the weight loss he was experiencing was indicative of cancer, particularly as he had just recently lost his wife to the same disease.

> "So you start to think to yourself you know, losing that kind of weight, you start thinking cancer. You know, 'cos cancer's pretty prevalent in, prevalent in my family. So, I went to the doctor, you know, and I'd a sore throat as well, so I was kind of, made an excuse to go hoping that they'd find something more, than the sore throat so." (Tim)

Ruth was "*floored*" when she received her diagnosis because the symptoms she experienced were not symptoms she recognised as being traditionally associated with TB. Similarly, other respondents were surprised at the diagnosis, because they thought it was a disease which belonged in the past. Veronica's mother remembered thinking it was "*..an old-fashioned disease...*", and that it "*..was all done away with...*".

Even before being diagnosed, patients reported feeling frightened of invasive diagnostic procedures (e.g. bronchoscopy), which would assist physicians in diagnosing their illness. The prospect of hospitalisation concerned others, as Una said "*Oh I was in a state.*" Many individuals impressed the time it took to reach a diagnosis served to prolong their anxiety.

> "The most frightening thing probably was because they didn't know what it was, and I had to go back and forward to [Glasgow hospital] all the time. Taking x-rays, I think I was up in the x-ray about 8 or 9 times." (Alex)

Walter, a twenty-two year old male was found to have TB as a result of a screening program initiated for his uncle. During the interview, Walter used the words

"*downhearted*" and "*sad*" when he spoke about his diagnosis, and indicated that he had resigned himself to the fact he too would deteriorate and eventually pass away, in the way his uncle had.

Two patients reported thinking the only possible outcome from this disease was death. Ian mentioned his very first thought was

> "My initial reaction was do you die from it?" (Ian)

Olivia recalled with embarrassment that before becoming ill, she had been following a television soap opera, in which a character died from tuberculosis. When she received her diagnosis of TB, she thought she too would suffer the same fate, however, her physician was quick to reassure her it was treatable. Ian also commented that he felt less anxious about his diagnosis after his doctor said "*.. its curable, just like that, and I knew that when he said it like that, 'cos he passed it off, you know its curable, its not eh, life-threatening, or if its treated, its not life-threatening.*".

Patients who were aware tuberculosis was not necessarily life-threatening, stated they felt relieved when their diagnosis was confirmed. When Dan received his diagnosis, he said

> ".. [I] was over the moon that I'd TB, you know what I mean, it wasnae cancer (laughs). It sounds, it sounds daft but, when the doctor phoned me to confirm that it was TB, I said thanks very much, you know (laughs)." (Dan)

Many patients failed to understand how they had acquired the disease, and this led to a difficulty in coming to terms with the diagnosis. Evelyn found it difficult to comprehend how she got TB, as she claimed to have spent most of her time at home, with her family, and knew no one with a similar diagnosis. Jason also could not comprehend how he acquired his infection and said:

> "No, I don't know, I don't know, I haven't a clue because I don't know anybody else that has, had it. That's the one thing about it, 'cos I can, you know I picked it up if I knew somebody else had it or said they had it a wee while ago or something like that, then I could sorta feel relaxed, that's my connection. But, just don't know of any connection at all." (Jason)

This was also apparent when patients remarked they had received the BCG as a child, and thought this would have provided adequate protection. Olivia said "*.. 'cos I was like how come I got TB jags and I still caught it?*".

8.5 Coping with tuberculosis

Having a diagnosis of tuberculosis affected patients to varying extents. Males often indicated that their symptoms did not interfere with their lives, and this sentiment was articulated by Harold when said he just "*..got on with it...*". Jason cared for his wife, and after being discharged from hospital, he continued with this task. However, Jason appeared to understand that he had simply acquired "*..this small, sorta dose of it sorta thing compared to what full blown TB was...*", and because of this he was not concerned about his illness.

> "I got better and that was that, as far as I was concerned that was over and done with you know, so I didn't even thought about it that much after it. Then I don't even think much during it because as far as I was concerned I was getting the medication so, that was dealing with it, you know." (Jason)

One male reported having no concerns about his illness. It appears he did not have much interest in his health, as he failed to comply with treatment for his first episode of TB. He admitted he was a recovering alcoholic and in the past, tended to drink in "*..a lot of dingy places*" where he thought he could have acquired the disease. He understood that nowadays, a full recovery can be made, and because of this he did not think it necessary to worry.

Simon ...But, it didnae worry me, nothing bothered me anyway.

AH Why is that?

Simon It's just the way I am. I, I would just, I've got angina now, but it doesnae bother me. Its, I'm just one of these guys that takes life a day at a time, constantly. ... So, it basically, you know, it doesnae, I wasnae frightened or anything like that. Just, got up and got on with it.

Others were more concerned about their diagnosis. At the time Olivia was diagnosed with tuberculosis, she was to starting to study for her Higher examinations, and was worried she would be unable to catch up with her lessons, following a period of absence from school while she was recuperating. While experiencing symptoms, Keira was excluded from socialising with her friends, and was annoyed that she could not lead a normal life like those individuals. In addition, she felt she had always lived a hygienic and clean life, and felt it was unfair that she had gotten the disease.

> "..I was so young and everyone else was out clubbing and doing, and you're like, you're stuck in a hospital not knowing what's wrong with you..."
> (Keira)

Similarly, Ruth described how her illness had interfered with job prospects. Some years previous she changed career and accepted a post with less responsibility and a reduced salary. In this new career, she was starting to win promotions, and felt she was slowly building confidence. She spoke with much disappointment about the fact she had to withdraw her application from a post she felt sure she would have won. She spoke of the injustice of the situation.

> "So, I just felt fairly confident for the first time in a few years about, this is going to be a stepping stone, I'm going to get to move on here and, and you know, move, move my money back up and move my future back up again. And it was the irony of it. I just thought, what have I done to deserve this, as I'm sure most people do, you know, it's a natural human reaction, why me?"
> (Ruth)

Gwen commented on recent media coverage of the diagnosis of a pub manageress in Glasgow with TB. Gwen, herself a barmaid, spoke about how she worried her TB would return and she too would face being exposed by the media and stigmatised by her community. Indeed, when attending a recent check-up, she informed friends and colleagues she was going for a thyroid check.

> ".. I was going for a check 4 weeks ago, I wasn't telling anybody, 'cos if anybody tells anybody, its in the paper, my pubs going to suffer. So I'm not saying a word. If it came to it, I'd obviously have to deal with it, but until I know, people just panic and that thing in the paper, that is just (laughs)."
> (Gwen)

For others, a diagnosis of TB meant difficulties in obtaining services from community care workers. This had serious implication for Patrick, who had become blind as a consequence of a heredity eye condition, and was confined to his home. Although he had just completed a course of treatment for TB, he developed a cough, and his care worker refused to visit until his symptoms were investigated, and a relapse had been ruled out.

Although not a pre-defined area of questioning, the issue of medication was raised. Some interviewees asserted taking a regimen of twenty-two tablets a day was the greatest burden of all. Jason maintained that if he could have taken his medication in some other form, he would have found the treatment less problematic.

> "it was just an inconvenience of having to take so many pills because I'm not a pill taker, you know. So maybe if it was a liquid form or something like that I might have sorta just, just taken them without even thinking twice about it. Because there was so many daily, it sorta put me off.." (Jason)

Olivia on the other hand found adherence to the strict medication schedule a burden, and occasionally would forget to take them. This caused concern as she worried this would cause a relapse:

> "..a couple of times I forgot, and I pure panicked about it in case, like, it would just kick it off and ... all the other tablets I took wouldn't even work 'cos I missed one..." (Olivia)

The side effect of one of the medications (Rifampicin) was a shock to some patients, as they noted the colour of their urine changed to orange/red. Simon complained of other side effects. An alcoholic at the time he was first treated for TB, he spoke of how he had nausea and diarrhoea, and blamed this in part for his failure to complete a course of treatment. He explained he didn't take his medication because:

> "'Cos by the time I got through half of them, I was vomiting. I'd diarrhoea, so, I would take them and then I would go on a bender on the booze and then I wouldnae take 'em, and it'd take longer to cure it, and longer. And it came back." (Simon)

Despite having successfully completed treatment, many interviewees mentioned they have ongoing concerns. Evelyn spoke of her concern that cold or flu-like symptoms were an indication her TB was returning. This was evident when she said "*And I think the frightening thing since I've had it is every cough you get ... I was told there's a good possibility it would come back.*" She also worried that her husband, who had Non-Hodgkin's lymphoma, would develop symptoms.

8.6 'Stigma' of tuberculosis

The term 'stigma' originates from the Greeks, who used the word to refer to a sign on the body, which signifies something unusual or bad about the moral status of that individual (Goffman, 1963). Today, to possess a stigma means to have an attribute that makes the bearer different (in a negative way) from what is expected, or considered normal. In chapter 7, interviewees spoke about how, prior to diagnosis, they perceived the social identity (attributes assigned on first impressions) of individuals with tuberculosis. During interviews, tuberculosis was described as a discrediting condition, one which interviewees

associated with '*jakeys*' or '*tramps*' (Ruth). Here, interviewees described their experiences of having a stigmatising condition, and in particular, during instances of social interaction.

Health beliefs, such as patients feeling they were to blame for allowing themselves to become susceptible to the disease, provide an insight into moral dimensions associated with acquiring tuberculosis. By accepting the burden of a TB diagnosis, individuals can acquire associated feelings of guilt and shame. Four respondents reported feeling guilty because of the ramifications their illness had for their family and close contacts. On reflection, Ruth stated that for her, this was one of the worst parts of being diagnosed with TB, as she had been putting others at risk of getting TB. After the initial shock of being diagnosed, and eventually accepting the diagnosis, she realised it didn't only affect her, and that her contacts needed to be tested.

> "So once you've got kind of right, TB for God's sake, how the hell did I get that, you know, and then you think, oh God, I feel like a leper, you feel like a leper because cancer is a singular thing, you're dealing with it, you're, its only you its affecting, but suddenly you've got all these people to inform, you know, you know what I mean and your, your initial scare, the initial kind of shock of you having that and it being a serious illness, and then the next thought is, oh my God, I've got people, people are going to have to go and get tested, and that's, that's one of the worst bits about it too I think." (Ruth)

Quentin also spoke about being concerned he had passed the illness onto other individuals, however, he stated he was unwilling to inform them.

Evelyn's new-born grandson was given chemoprophylaxis as a precautionary measure, as he had been born prematurely and had been at risk of acquiring the disease from her. She spoke of her remorse, as this added to his health problems.

> "And then I felt awful when they said [grandson's name] had to go on the medication because of the TB. Again that's, that'll be all my fault after everything he'd come through already." (Evelyn)

Una admitted she felt ashamed when a screening exercise was initiated in her work place. She said: "*I felt terrible. I felt as if it was as if it was my fault, and what them people going to think of me and, and I mean there was a few people in work that I knew spoke about me, and went oh, imagine her and TB and, so.*" Una had previously described how she associated the disease with "*dirty people*", and now worried her work colleagues would think of her in this way.

The association of tuberculosis with homeless or alcoholic individuals caused shame and embarrassment for a number of individuals. Veronica's mother summed up this sentiment succinctly when she said "*I was absolutely disgusted because I thought it was an old jakey disease*". Three young females spoke about how they immediately thought it was a "*dirty thing*", because they perceived TB as a disease afflicting unclean and unhygienic people. Olivia was reluctant to inform anybody about her illness because in a similar way to Una, she thought friends would perceive the disease in the same way she did, and would isolate her as a consequence.

> "No, well I must have got it, it was like a dirty thing, 'cos I didn't want people to know about it. So I must have thought it was like that, I just, not really clean people or something, or ill people that would pass it to me...and old people. I didnae want people to think, oh well stay away from her, 'cos she's got TB sort of thing, so if I thought that about myself, then I must have thought I got it offa somebody like that..." (Olivia)

Goffman identified strategies employed by individuals to cope with a stigmatising condition during social encounters. Passing, where the patient attempts to conceal or deny their diagnosis, and covering, where patients try to reduce significance of the stigmatising condition, were particularly evident in this study (Goffman, 1963).

In this study, patients perceived their communities to react in one of two ways when informed of their diagnosis. Ruth and Keira felt they had been so ill in the lead up to their diagnosis, and friends had been genuinely concerned for their health, so they perceived individuals were accepting of their illness. Ruth in particular found younger individuals knew little of the disease, and were interested to learn more about it.

Three males known to misuse alcohol at the time of diagnosis stated that they thought their friends had no issues with their diagnosis, and felt they were not treated differently. However, Dan's insight into his friend Tim's situation suggests people within the same social circle can interpret events or situations in different ways. Although Tim felt people were comfortable in his company once he informed them he was not contagious, Dan said:

> "Its, I mean it was the same when [Tim] got it. Everybody was avoiding him, you know I mean everybody was staying out of his road." (Dan)

Gwen noted a range of responses. Where people knew little or nothing of the disease, they tended to accept her explanation, and did not react adversely. On the other hand, those who had heard anecdotes from older family members about the disease were less comfortable in her company.

> "..some people I've told didn't know what it was, and accepted when I told them its not dangerous, but some people who'd heard stories or their dad had it or their, and they had to get this thing, this poultice on their chest and all that, they've all these stories, they would, some people won't, like as I said took a step back from me, physically when I told them (laughs)." (Gwen)

Gwen proceeded to describe how her neighbour refused to let their children play together. Although she found this very hurtful, she felt this was because her neighbour was ignorant about the disease. Martin too experienced the effects of ignorance, because a number of children in his apartment block had been diagnosed with TB. The father of one of the children expressed his anger towards Martin, because as the only adult in the building with TB, he was a likely source of infection for the children. Martin's two children had also been diagnosed, and rather than feeling angry or upset, he empathised with this man, as he understood the motivations for his neighbours outburst.

> "Well it wasnae, it was nothing serious, it was just people shouting their mouths off, you know obviously worried because they didnae have a clue, they didnae know anything about TB..." (Martin)

The fear of social exclusion was a major concern particularly for the younger women in this study population. Respondents feared they would be stigmatised by friends and colleagues. Only one male spoke at length about this issue. He had declined to inform his friends about his illness, after witnessing how his friend, Tim, had been treated when diagnosed nine months previously.

Dan ...I tell you what, it was a panic in my case. I was panic-stricken I'll be honest with you...about having TB, you know to me it was a sorta stigma, you know what I mean. I thought it was, at first it was a kinda, a sorta dirty, sorta disease or something you know. Because what, from what I could make out it was the likes of maybe alcoholics and down and outs that got it you know...it wasn't that people were talking about it. Its, I mean it was the same when [Tim] got it. Everybody was avoiding him, you know I mean everybody was staying out of his road. He even, when eh, the period was up that he could catch anything you know...

AH Did you experience a similar kind of reaction from people?

Dan I never told anybody. I just never mentioned it, you know what I mean? I just got on with taking my drugs or whatever. And that was it.

AH Why do you think you didn't tell anybody?

Dan I was kinda ashamed actually, you know I mean yeah. It was frightening.

8.7 Discussion

This study examined patterns of behaviours exhibited by patients when seeking help for symptoms. No one pattern of resort was identified, and it appeared that complex social and cultural factors influence help-seeking behaviour.

Many interviewees indicated that they sought medical assistance after a period of time in which they tried to make sense of their symptoms. During this time, patients attributed symptoms to benign conditions such as influenza, or tried to 'normalise' or interpret symptoms in the context of events in their lives. Some interviewees only sought help when their symptoms interfered with jobs or activities, or as a result of sanctioning, while others adopted a wait and see approach. Clearly, this caused patients to delay seeking medical assistance for symptoms. This is an important finding because most transmission of *M. tuberculosis* occurs before patients are diagnosed, and strategies to interrupt the spread of disease aim to limit the symptomatic period. During interviews, patients revealed having very little prior knowledge of disease symptomatology, and this lack of knowledge arguably contributed to this behaviour (Singh Bakhshi & Ali, 1995).

Many studies investigating the contribution of patient behaviour to the delay in seeking treatment have overlooked the possibility that diagnosing physicians also play an important role (Asch *et al.*, 1998). Patients in this study indicated GPs failed to diagnose their illness immediately, and sometimes diagnoses were confirmed after multiple consultations. Some (mainly female) respondents vented their frustration with the quality of the service they or their children received, and commented that they had insisted on further diagnostic tests to determine the cause of illness. Although delay on the part of medical staff could not be verified, anecdotal evidence suggests further investigation into the existence of barriers for obtaining treatment is warranted. In particular, it would be worthwhile determining whether disparities are correlated with gender, or the presence or absence of known risk factors (e.g. alcohol misuse/homelessness) because generally, female interviewees with no identifiable risk factors reported delays in diagnosis.

Respondents reported a variety of responses when their diagnosis of tuberculosis was confirmed. While some were frightened they could die, some recognised it was not necessarily a life-threatening disease such as cancer, and were relieved. Others were surprised because they thought the disease belonged in the past, and stated nowadays, they anticipated this illness was present only in homeless or alcoholic male populations. The former statement affirms the belief that tuberculosis is perceived by the lay population as a

rare or uncommon disease. This is in agreement with Singh Bahkshi *et al.* hypothesis that the more common the disease, the more familiar the public would be with the illness, therefore leading individuals to seek medical assistance earlier (Singh Bakhshi & Ali, 1995).

As many patients knew no other individual with TB, and failed to see how they acquired the disease, some respondents initially found it difficult to come to terms with their diagnosis. Descriptions of how a TB diagnosis interfered with daily activities were provided, however some male respondents, with alcohol misuse issues at the time of diagnosis, claimed they continued life as normal. Other interviewees, however, reported feeling stigmatised by the illness, and feelings of guilt and shame emerged.

Interviewees reported experiences of social rejection because of the public's perception that tuberculosis was a highly infectious disease. In chapter 7, patients spoke of how they believed TB could be transmitted within a short period of time (in contrast to medical thinking which suggests close, prolonged contact is required), and the potential for transmission was enhanced in confined or crowded settings. For fear of becoming infected, some patients reported others avoided contact with them or their (non-infected) family members. By contrast, other patients reported no adverse treatment by others; indeed individuals were interested to learn more about the illness. Respondents associated tuberculosis with poor hygiene, alcoholism and homelessness, and feared they in turn would be associated with having these attributes. Fear of isolation from society was a principal concern, particularly for female interviewees (Zola, 1966).

Little research has been conducted to address the issue of stigma in low-incidence countries, whereas in developing countries, studies have shown stigma is associated with rejection of a diagnosis and failure to comply with treatment (Liefooghe *et al.*, 1995). Although issues of compliance were not investigated in this study, it was recognised that social rejection and stigma had an effect on how patients coped with their diagnosis. However, results from this study indicated that interviewees expressed an unwillingness to inform others of their diagnosis, due to the stigma associated with this illness. One can speculate that this has a negative outcome on the conduct of contact tracing because patients may not inform social contacts of their illness, for fear of social exclusion, and embarrassment may lead newly diagnosed cases to withhold the identities of at-risk contacts from contact tracing staff who may require to screen those individuals. This finding is in contrast to Singh Bakhshi *et. al*'s 1995 study, where the authors proposed that stigma does not adversely impact contact tracing.

Findings from this research project indicate disease transmission is ongoing in the Greater Glasgow area (chapter 6), and in part can by explained by an oversight in identifying epidemiological links between at-risk contacts during the contact investigation process. Failure to detect epidemiological links may in part due to patients unwillingness to share information about TB contacts and identify at-risk individuals. On the other hand, it is important to determine whether health professionals are playing their part in detecting infected TB contacts, and thereby contributing to the interruption of disease transmission. To this end, an evaluation of contact tracing will be undertaken in chapter 9 to determine whether contact tracing practices are operating effectively, and ensuring all nominated at-risk contacts are being appropriately screened.

Chapter 9: An evaluation of contact tracing outcomes

In previous chapters, the occurrence of ongoing transmission in Glasgow, the failure of control strategies and reasons for control strategy shortcomings were discussed. Here, the effectiveness of active case detection strategy, contact tracing, is examined using indicators such as the proportion of new TB cases detected. Variations in outcomes are analysed by study and contact case characteristics. Molecular typing information is employed to confirm the putative occurrence of recent transmission between epidemiologically linked cases detected by contact tracing, on the premise that linked cases are infected with a genetically indistinguishable strain.

9.1 The study population

Four hundred and forty-three Greater Glasgow NHS Board pulmonary TB patients, notified to the ESMI scheme between January 2000 and December 2003, were included in this analysis of contact tracing outcomes. Four patients were diagnosed and notified to the ESMI scheme twice within the study period, with a mean of 17.75 months between dates of diagnoses (range: 15-21 months). Each episode is considered independently in this analysis, therefore epidemiological information provided at each episode of disease is included in the study population. Select epidemiological characteristics for the 443 study cases are presented in table 12 alongside those of all remaining pulmonary cases in Scotland over the study period. As described in chapter 3, a data completion exercise was piloted in Glasgow during the study period, therefore data for non-Glasgow cases may not be as complete, which may influence the significance of statistical tests.

More males than female pulmonary cases were detected in both Glasgow and non-Glasgow case populations. Glasgow pulmonary cases had a mean age 46.9 years, as compared with a mean age of 51.3 years for the non-Glasgow case population, and difference found to be statistically significant (Mann-Whitney U-test: -3.227, p=0.001). Glasgow cases were also found to have significantly more cases that were UK-born (χ^2 test; 4.382, p=0.036), and experienced symptoms prior to diagnosis (χ^2 test; 36.521, p<0.001). Again, these results are most likely influenced by the incomplete data held for non-Glasgow cases.

Symptoms were experienced by 86.2% of the 443 study cases prior to diagnosis. Where duration of symptoms was indicated (382 cases), the majority (56.2%) reported symptoms lasting between one and thirteen weeks before being diagnosed. Symptom duration was

not found to differ significantly between men and women. As data for BCG status, disease type, method of case identification and risk factors alcohol misuse and homelessness were

Characteristics	Glasgow pulmonary cases n=443	%	Rest of Scotland pulmonary cases n=593	%	Test	P-value
Sex						
Male	288	65%	356	60%	χ^2 test	0.102
Female	155	35%	237	40%		
Age					Mann-Whitney U-test	p=0.001 Z= -3.227
0-24	67	15.1%	65	11%		
25-44	130	29.3%	166	28%		
45-64	145	32.7%	177	29.8%		
65+	101	22.8%	185	31.2%		
Mean age	46.87		51.26			
Standard deviation	21.05		21.81			
Presence of symptoms					χ^2 test	0.011
Yes	382	86.2%	448	75.5%		
No	46	10.4%	88	14.8%		
Not known	15	3.4%	57	9.6%		
Country of birth					χ^2 test	0.036
United Kingdom	335	75.6%	227	38.3%		
Other country	73	16.5%	73	12.3%		
Not known	35	7.9%	293	49.4%		
Ethnicity					χ^2 test	0.712
Caucasian	347	78.3%	415	70%		
Non-Caucasian	81	18.3%	91	15.3%		
Not known	15	3.4%	87	14.7%		
BCG						
Yes	185	41.76%	N/A			
No	150	33.86%	N/A			
Not known	108	24.37%	N/A			
Pulmonary disease type						
Sputum smear + culture +	237	53.5%	N/A			
All other pulmonary TB	206	46.5%	N/A			
Method of case identification						
Illness diagnosed as TB	357	80.6%	N/A			
Contact tracing	51	11.5%	N/A			
Other	35	7.9%	N/A			
Alcohol misuse	133	30%	N/A			
Homelessness	36	8.1%	N/A			

Table 12: Comparison of characteristics of pulmonary TB cases notified to the Greater Glasgow NHS Board with pulmonary cases notified to all other NHS Boards in Scotland between 2000 and 2003

Indicates statistical significance at p<0.05. N/A indicates data were not available.

not available at the time of data extraction from the ESMI database (an audit of these data was incomplete for ESMI form B information) for non-Glasgow cases, comparative analysis of these populations could not be undertaken.

Over the same four-year study period, 223 non-pulmonary cases were diagnosed in the Greater Glasgow NHS Board area, of which symptom duration was indicated for 153 cases (68.6%). Whereas the lengthiest symptomatic period for pulmonary cases was 52 weeks, symptoms experienced by members of the non-pulmonary population lasted up to 78 weeks before diagnosis. A statistically significant difference in symptom duration was not detected between these two populations (figure 19).

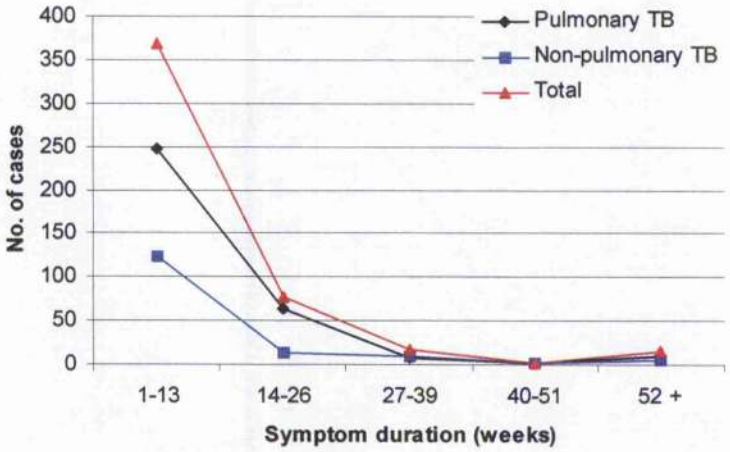

Figure 15: Symptom duration of pulmonary TB cases notified to Greater Glasgow NHS Board between 2000 and 2003, by disease type

Eighty-one study cases (18.3% of the study population) were of non-Caucasian ethnicity (see table 12), of which 12 were born in the United Kingdom and 69 were born outwith the UK. In Scotland, non-pulmonary TB is more often diagnosed in ethnic minority groups than in Caucasians (Rubilar *et al.*, 1995). Indeed, within Glasgow over the four-year study period, 57.4% of all non-Caucasian cases (n=190) were diagnosed with non-pulmonary disease, in comparison to 18.5% of Caucasian TB cases. A statistically significant difference in the proportions of pulmonary and non-pulmonary disease was detected between Caucasian and non-Caucasian populations in Glasgow (χ^2 test; 93.398, $p<0.001$). The distribution of disease type by ethnicity is shown in figure 20.

A total of seventy-three study cases (16.5%) were born outwith the United Kingdom, of which 69 were from ethnic minority groups (as indicated in the previous paragraph) and four were Caucasian individuals, three from Ireland and one case from Zimbabwe. Of those born abroad, 57.5% (42/73) had been diagnosed within 2 years of entering the United Kingdom for the first time.

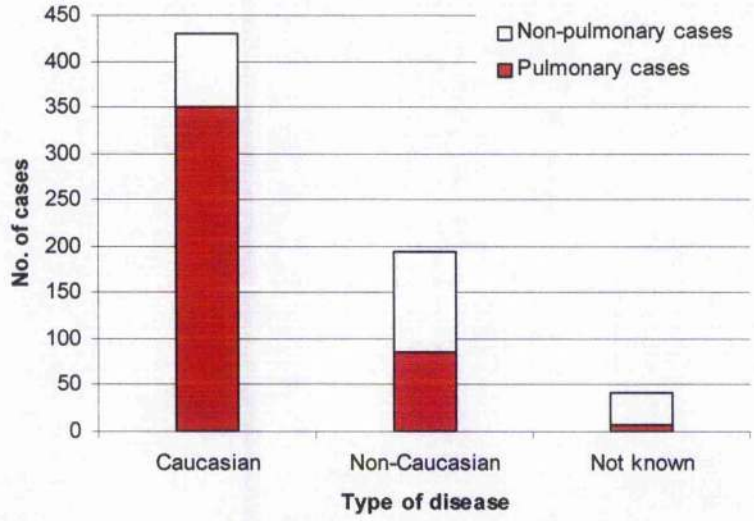

Figure 16: Pulmonary TB cases notified to Greater Glasgow NHS Board between 2000 and 2003 by ethnicity and disease type

Just over forty percent of the study population were reported as having previously received BCG vaccination, while one third had not received vaccination.

Predominantly, cases were detected after presenting to medical services with an illness subsequently diagnosed as TB. Fifty-one of the 443 study cases (11.5%) were detected as a result of contact tracing (see table 12). Twenty five of those 51 cases identified by contact tracing were under fifteen years of age.

Within the study population of 443 cases, 33 were aged under fifteen years. Therefore, 75.8% of paediatric study cases (25/33) were identified by contact tracing. (By contrast, 8 of the 410 adult study cases (2%) in the study population were identified by the same method.) Of the eight remaining paediatric study cases, six were identified when they presented to medical services with symptoms, one was detected as a result of the schools BCG programme, and one through the United Kingdom immigration screening programme.

Risk factors for tuberculosis were not indicated for 57.7% of pulmonary study cases (256). This is less than figures of 72.7% and 68.7% reported for all notified cases in Scotland in 2001 and 2002 respectively (Christie & Johnston, 2002b, McMenamin & Johnston, 2004). ESMI surveillance forms offer a selection of risk categories, such as "immunosuppressed", "in corrective facility", "alcohol misuse" etc, but until recently, individuals completing forms did not have the opportunity to indicate the patient had no identifiable risk factor(s).

This tick box option has now been made available on surveillance forms, and it is anticipated completion rates for this data field will improve.

At least one pre-selected risk factor was recorded for 187 study patients (42.2%). Of these cases, forty patients selected two or more risk categories. The frequency of selection of reported risk factors are presented by sex in figure 21. ESMI information indicated that significantly more men than women misused alcohol (χ^2 test; 41.205, $p<0.001$) and were homeless (χ^2 test; 17.873, $p<0.001$).

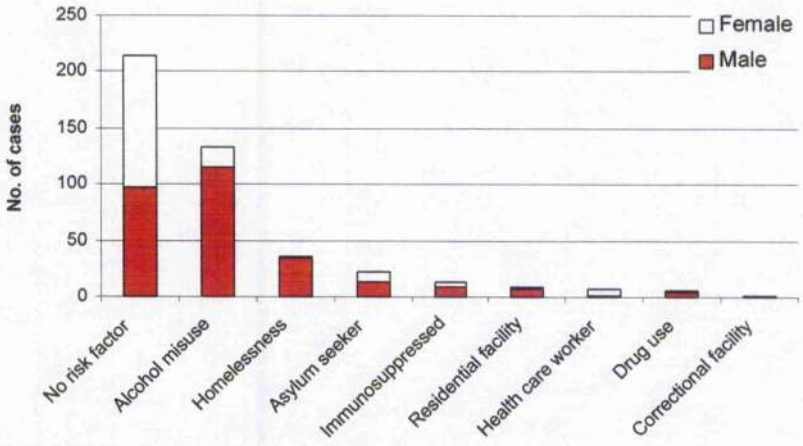

Figure 17: Frequency of risk factors reported by pulmonary TB cases notified to Greater Glasgow NHS Board between 2000 and 2003

Of the 443 study cases, at minimum of one risk factor was selected by 187 cases. Forty of the 187 cases selected two or more risk factors.

9.2 Outcome from contact tracing

Outcome data were obtained from TB liaison nurses for 443 pulmonary study cases, and findings from the subsequent analysis are presented here. An algorithm summarising these results is displayed in figure 22.

Of the 443 Greater Glasgow NHS Board pulmonary cases included in this analysis, 290 (65.5%) had at least one contact examined. Indeed, a total of 3378 of those patients' contacts were deemed to require examination. As 313 did not attend screening, a total of 3065 contacts were screened for TB (reasons for which will be discussed in section 9.4). Of the 443 study cases, a mean of 6.9 (SD 16.56) and a median of 3 (range: 1-152) contacts were screened. However, as contact tracing was not undertaken for 153 cases, a mean of 10.6 (SD 19.56) and a median of 6 contacts (range: 1-152) were screened for the

290 patients, for whom contact tracing was undertaken. In excess of one hundred contacts were screened during six distinct contact investigations, some of which took place in a maternity unit, a nursing home and children's nurseries.

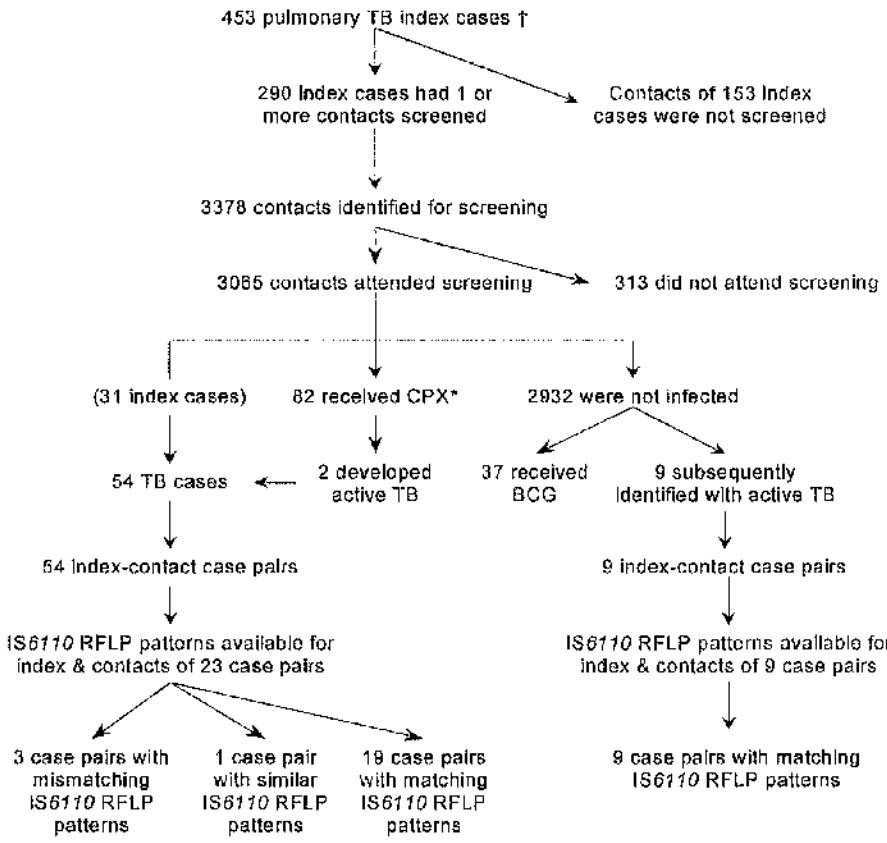

Figure 18: A summary of outcomes from contact investigations undertaken for pulmonary TB cases notified to Greater Glasgow NHS Board area between 2000 and 2003

† Contact tracing records were available for 443 study cases. *CPX: chemoprophylactic therapy

Of the 3065 contacts examined, 95.6% were not infected with tuberculosis. Before being discharged, at least 37 of these received BCG vaccination. Eighty contacts were given chemoprophylaxis for a latent tuberculosis infection (2.6% of screened contacts). On the

basis of x-ray changes and bacteriological findings respectively, two cases initially in receipt chemoprophylaxis developed active tuberculosis, within the period of evaluation. These paediatric cases were unvaccinated, and had been in close contact with sputum smear and culture positive cases. In total, fifty-four contacts (1.8% of screened contacts) were identified with active tuberculosis as a result of contact tracing.

	Cases with 1 or more infected contacts		Cases with no infected contacts		Test	P-value
	n=31	(%)	n=412	(%)		
Sex						
Male	22	71%	266	64.6%	χ^2 test	0.471
Female	9	29%	146	35.4%		
Age					Mann-Whitney U-test	Z = 5097 p =0.061
0-24	4	12.9%	63	15.3%		
26-44	14	45.16%	116	28.2%		
45-64	11	35.48%	134	32.5%		
65+	2	6.45%	99	24%		
Mean age	40.81		47.32			
Standard deviation	15.39		21.37			
Pulmonary disease type					χ^2 test	0.006
Sputum smear + culture +	24	77.4%	213	51.7%		
All other pulmonary TB	7	22.6%	199	48.3%		
Country of birth					χ^2 test	0.262
United Kingdom	26	83.87%	314	76.2%		
Other country	3	9.67%	72	17.5%		
Not known	2	6.45	26	6.3%		
Ethnicity					χ^2 test	0.152
Caucasian	28	90.3%	323	78.4%		
Non-Caucasian	3	9.7%	82	19.9%		
Not known	-		7	1.7%		
BCG					χ^2 test	0.5
Yes	16	51.6%	169	41%		
No	10	32.3%	140	34%		
Not known	5	16.1%	103	25%		
Method of case identification					χ^2 test	0.165
Illness diagnosed as TB	29	93.5%	328	79.6%		
Contact tracing	1	3.2%	50	12.1%		
Other	1	3.2%	34	8.3%		
Alcohol misuse	13	41.9%	120	29.1%	χ^2 test	0.133
Homelessness	5	16.1%	31	7.5%	χ^2 test	0.091

Table 13: Characteristics of pulmonary TB cases notified to Greater Glasgow NHS Board between 2000 and 2003, by yield from contact tracing

Indicates statistical significance at p<0.05

Screening events were undertaken for 290 cases, 259 of which (89.3%) did not detect disease in screened contacts. At least one contact was found to have active disease as a

result of 31 contact tracing events[24]. A statistical analysis was undertaken to identify variations in demographic and epidemiological characteristics between study cases with and without positive outcomes from contact tracing, that is to say, individuals for whom contact tracing identified at least one contact with tuberculosis (31), and those for whom no new cases were detected (412) (see table 13). A statistically significant difference was detected for disease type. More sputum smear positive, culture positive cases were observed than expected in the former population, while more cases with all remaining types of pulmonary disease (i.e. other than sputum smear positive culture negative TB) were observed in the latter (χ^2 test; 7.667, $p<0.006$).

Thirty-one screening events identified fifty-four contacts with active disease. Sixty-five percent of these contact investigations identified one contact with TB (20/31), and a maximum of six cases were detected during one screening event. The variation in yield from contact tracing will be now described in the context of the bacteriological status of study cases, the type of association between study and contact cases, and the interval (i.e. scheduled examination) at which contacts were diagnosed with disease.

9.2.1 Outcome by bacteriological status of index cases

Specimens from 415 study cases (93.7%) were available for bacteriological examination. Culturing techniques were used to confirm that 351 (84.6%) were infected with *M. tuberculosis* (table 14). Infection with tuberculosis was confirmed for 2.7% of the study population (12 cases) on the basis of histological findings. Sixteen cases did not have specimens sent for bacteriological examination, either because samples could not be provided by patients, or because patients had been diagnosed elsewhere, and had commenced treatment. Fifty-four cases (12.2%) were diagnosed on the basis of a combination of symptoms, skin test results and chest x-ray changes, in the absence of bacteriological evidence (*M. tuberculosis* was not detected in samples provided).

Just under 80% of all screened contacts (2417/3065) were associated with sputum smear and culture positive study cases. Three quarters of contacts (40 cases) found to have TB, and 87% of contacts in receipt of chemoprophylaxis (62 cases) as a result of contact tracing, were identified as contacts of sputum smear and culture positive study cases.

[24] 31 contact investigations were undertaken for thirty individuals. One patient had contact tracing in 2000 and 2002, and his son and daughter were identified as having tuberculosis at the first and second events, respectively. The patient was sputum culture and smear positive on both occasions.

Method of disease confirmation	No. of index cases (%)	No. of contacts	Contacts per index case	Contacts with TB	Case yield (%)	Contacts receiving CPX	CPX yield (%)	Contacts receiving BCG (%)	BCG yield (%)	NNS
Sputum smear + culture + *	246 (55.5%)	2417	9.8	40	1.7%	62	2.6%	32	1.3%	60.4
Bronchial/tracheal aspirate smear + culture + †	34 (7.7%)	183	5.4	3	1.6%	6	3.3%	3	1.6%	61
Sputum smear - culture +	53 (12%)	81	1.5	7	8.6%	5	6.2%	0	-	11.6
All other culture + specimens ‡	28 (6.3%)	165	5.9	3	1.8%	1	0.6%	1	0.6%	55
Histological findings	12 (2.7%)	7	0.6	1	14.3%	0	-	0	-	7
No bacteriological findings	54 (12.2%)	189	3.0	0	-	3	1.6%	1	0.5%	>189
No specimens sent	16 (3.6%)	23	1.4	0	-	3	13%	0	-	> 23
Total	443 (100%)	3065	6.9	54	1.8%	80	2.6%	37	1.2%	56.8

Table 14: Yield from contact tracing undertaken for pulmonary TB cases notified to Greater Glasgow NHS Board between 2000 and 2003, by bacteriological status of index cases

***Of the 246 sputum smear positive study cases, all but 7 were culture positive. † Of the 34 bronchial washing/tracheal aspirate smear positive cases, all but 3 were culture positive. ‡ Other culture positive specimens include all other culture positive pulmonary and non-pulmonary specimens. NNS: number of contacts needed to be screened to detect one new case of TB.**

A score developed by Neely *et al.* was utilised to provide an indication of the number of contacts needed to be screened, in order to detect one contact infected with tuberculosis (Neely *et al.*, 2004). On average, 56.8 contacts needed to be screened to find one contact with TB. Taking into account the bacteriological status of a study case, it appears 60.4 contacts of sputum smear and culture positive cases need to be screened to find one new case of TB. However, certain caveats do apply to the number needed to screen (NSS) score presented in table 14, and these will now be discussed.

During data collection, the 54 new contact cases detected as a result of contact tracing were linked to their respective study cases (the individual for whom the investigation was initiated). All study cases were assumed sources of infection, however, further investigation revealed some may not represent true sources of infection. Children for example have difficulties in producing sputum, thus rendering them unlikely candidates for the dissemination of the disease. Despite this, two children were considered index cases in this study, as true source cases were unfortunately unidentifiable.

Secondly, contact tracing conducted for a sputum smear negative, culture positive man of Pakistani ethnicity resulted in the detection of active disease in his six children. All but one was diagnosed with non-pulmonary TB. Such a high yield from a case of limited infectiousness appeared unusual, and enquiries by the TB liaison nurse revealed a household contact (grandmother) was suspected of having TB in the past, therefore another putative case of TB may have represented the source of infection for all cases. Four contact cases associated with a homeless sputum smear and culture positive study cases, may have been acquired infection from an undetected source. In response to the presentation of two individuals from the same hostel for the homeless to the health services within a matter of weeks of one another, a four-month screening programme was undertaken at this location. For the purposes of this study, the four contact cases identified were assigned to one of the original cases presenting to medical services.

A 16-year old female was considered the source of infection for her three siblings. These children had been screened two years previously during a contact investigation initiated for their mother. At that time, no disease was detected in any of the mother's four children. It is possible the mother or an undisclosed contact was the true source of infection for these children.

In light of such evidence, number needed to screen (NNS) scores were revised, and are presented in table 15. With adjustments, 76.6 contacts needed to be screened to find 1 case

of tuberculosis, on average. Sputum culture and smear positive cases require less contacts to be screened on average to find one new case. The NNS for sputum culture positive, smear negative, and other cases appears to have lower than the mean overall score. This is likely to be a reflection of the low population size in various bacteriological groupings.

Method of Disease Confirmation	No. of index cases (%)	No. of contacts	Contacts with TB (%)	NNS
Sputum smear + culture +	244 (55.7%)	2345	33 (89.2%)	71.1
Bronchial/tracheal aspirate smear + culture +	33 (7.5%)	160	2 (5.4%)	80
Sputum smear - culture +	52 (11.8%)	67	1 (2.7%)	67
All other culture + specimens	27 (6.2%)	143	-	>43
Histological findings	12 (2.7%)	7	1 (2.7%)	7
No bacteriological findings	54 (12.3%)	189	0	>189
No specimens sent	16 (3.7%)	23	0	> 23
Total	438	2834	37	76.6

Table 14: Adjusted scores for number of contacts needed to screen (NNS) to detect one case of tuberculosis

9.2.2 Outcome by proximity of association

During data collection, TB nurses were requested to indicate whether contacts were deemed to be close or casual associates, in accordance with definitions prescribed by the Scottish Office guidance documents (Scottish Office Department of Health, 1998). Forty-six percent of screened contacts were designated close (1414 cases), 48 of which were diagnosed with TB (3.4%). Of the 1651 casual contacts, six were diagnosed with active TB at their initial examination (0.4%), and half were contacts of sputum culture, smear positive index cases. Five of these six casual contacts were paediatric cases.

Of the 1414 close contacts in this study, 4.7% (62 individuals) received chemoprophylaxis. Sixty percent of all cases receiving chemoprophylaxis were in close contact with a sputum and culture positive study case (table 16).

9.2.3 Outcome by time of disease detection

All contact cases were detected at initial examinations[25], with the exception of five close contacts. One of the latter cases was a four-year-old unvaccinated male. He was initially skin tested and found to be negative when his smear positive mother was diagnosed with TB. Three weeks before he was due to attend a scheduled repeat skin test, symptoms

Method of Disease Confirmation	No. of index cases (%)	No. of contacts	Contacts with TB (%)	Contacts receiving CPX (%)
Sputum smear + culture +	246 (55.5%)			
Close contacts		1171	37 68.5%	48 60%
Casual contacts		1246	3 5.5%	14 17.5%
Bronchial/tracheal aspirate smear + culture +	34 (7.7%)			
Close contacts		64	3 5.5%	3 3.75%
Casual contacts		113	0	3 3.75%
Sputum smear - culture +	53 (12%)			
Close contacts		59	7 13%	5 6.25%
Casual contacts		22	0	0
All other culture + specimens	28 (6.3%)			
Close contacts		30	0	0
Casual contacts		135	3 5.5%	1 1.25%
Histological findings	12 (2.7%)			
Close contacts		7	1 1.9%	-
Casual contacts		0	0	-
No bacteriological findings	54 (12.2%)			
Close contacts		61	-	3 3.75%
Casual contacts		128	-	0
No specimens sent	16 (3.6%)			
Close contacts		16	-	3 3.75%
Casual contacts		7	-	-
Total	**443**	**3065**	**54**	**80**

Table 15: Yield from contact tracing undertaken for pulmonary TB cases notified to Greater Glasgow NHS Board 2000-2003, by proximity of case-contact association

developed, and a diagnosis of pulmonary tuberculosis was confirmed by chest x-ray. Two other vaccinated close contacts were identified by chest x-ray at scheduled 3-month follow-up appointments. Initial examinations for both individuals involved Mantoux skin

[25] Although 49 contacts were diagnosed at initial examinations, some examinations were conducted later than the recommended time for screening. This issue will be discussed in section 9.4

tests, and indurations of 18mm were recorded. A chest x-ray was additionally performed for the one contact of Pakistani origin, whose five siblings and father (index case) had been diagnosed. No abnormalities were detected until her 3-month follow-up chest x-ray.

Two contacts were diagnosed at 6-month follow-up appointments. The first was a vaccinated close contact of a sputum culture and smear positive work colleague. A 25mm induration was recorded at his initial Heaf test, and no cavities were detected on his chest x-ray. His TB diagnosis was confirmed following the isolation of *M. tuberculosis* from pleural fluid. The other contact, a vaccinated 17-year old of Pakistani origin was originally screened when his father was diagnosed. The results from his Heaf test were noted to have shifted between the initial and repeat test (an indication that tuberculin conversion had taken place), and he was requested to attend follow-up appointments. A chest x-ray conducted at his three-month appointment did not reveal abnormalities. This patient's diagnosis was confirmed at a six-month follow-up by x-ray findings and the detection of AAFBs in his sputum.

9.3 Epidemiologically linked index-contact case pairs

This section explores the characteristics of epidemiologically linked case pairs, of which fifty-four were identified as a result of contact tracing in Glasgow between 2000 and 2003. For the purposes of this analysis, the study case will be referred to as the putative index case, i.e. the individual for whom contact tracing was initiated. Each contact case and their respective index case form a pairing or single unit, referred to as an index-contact case pair. This section begins by considering, in turn, the characteristics of the thirty-one index cases and fifty-four contact cases. The relationships of index-contact case pairs are then described, and finally molecular typing information is used to examine the occurrence of recent transmission between linked cases.

9.3.1 Characteristics of index and contact cases

For comparative purposes, the characteristics of the contact and index population are presented alongside one another in table 17. The index population appear to be predominantly Caucasian, male, aged between fifteen and sixty-four, and sputum smear and culture positive. Just under half of all adult index cases identified alcohol misuse as a risk factor (13/28). On the other hand, paediatric cases are a prominent feature of the contact population. Considerably less contact cases than index cases experienced symptoms, and were sputum smear and culture positive, as might be expected with a

control strategy aiming for early case detection. Of all study index cases experiencing symptoms of 14 to 52 weeks duration (83 cases), 13.3% (11 cases) had a contact diagnosed with active TB. This is in comparison to 6.8% (11/83) of those experiencing symptoms of 1 to 13 weeks. As would be expected, contacts are more likely to be infected if index cases have longer symptomatic periods.

Characteristics	Index Cases n=31	%	Contact Cases n=54	%
Sex				
Male	22	71%	34	63%
Female	9	29%	20	37%
Age-group				
≤ 14	2	6.45%	25	46.3%
15 – 64	27	87.1%	25	46.3%
≥ 65	2	6.45%	4	7.4%
Ethnicity				
White	28	90.3%	45	83.3%
Pakistani/Indian	3	9.7%	8	14.8%
Chinese	-		1	1.9%
Symptoms				
Not known	1	3.2%	2	3.7%
No symptoms	1	3.2%	17	31.5%
Duration not known	1	3.2%	4	7.4%
1-13 weeks duration	17	54.9%	21	38.9%
14-52 weeks duration	11	35.5%	10	18.5%
Vaccination Status				
Vaccinated	16	51.6%	24	44.4%
Not vaccinated	10	32.3%	25	46.3%
Not known	5	16.1%	5	9.3%
Bacteriological Status				
Sputum smear + culture +	24	77.4%	10	18.5%
Sputum smear - culture +	2	6.5%	7	13%
Other	5	16.1%	37	68.5%
Risk factors				
Alcohol misuse	8	25.8%	7	13%
Homelessness & alcohol misuse	5	16.1%	4	7.4%
None identified	15	58.1%	43	79.6%

Table 16: Characteristics of 31 index (pulmonary) cases for whom contact tracing was undertaken and characteristics of 54 contacts found to have TB as a result of screening for those 31 index cases

9.3.2 Index-contact case pair associations

Table 18 summarises the type of associations between index and contact cases. A large majority of index-contact case pairs involved a parent and son/daughter (48.1%). Indeed, of the twenty-five paediatric contact cases detected, 76% (16 cases) named a parent as a putative source of infection, while the remainder identified a sibling (3), a grandparent (3) or a nursery playmate (3). Contact tracing within six families detected TB in fourteen paediatric contacts. Within the adult contact case population, associations were between a parent and their adult child (10), partners/spouses (6), homeless contacts (5), workplace contacts (4), housemates (2), a nephew and uncle (1) and a pair of friends (1).

TB nurses indicated forty-eight of 54 contacts had a close relationship with their index case. Thirty-six of these index-contact case pairs (75%) shared the same household. The other twelve involved associations within the workplace (5), between homeless individuals (4), grandparents and grandchildren (2) and a parent and child (1). The remaining six index-contact case pairs had casual associations outside the household. Three involved playmates (paediatric case pairs), two paediatric contacts were linked to their father, and the final linked cases were friends.

Type of association	n=54	%
Parent and child ≤ 14	16	29.6%
Parent and child > 14	10	18.5%
Spouses	6	11.1%
Workplace	4	7.4%
Homeless	5	.3%
Playmates	3	5.6%
Grandparent-grandchild	3	5.6%
Siblings	3	5.6%
Housemates	2	3.7%
Friends	1	1.9%
Uncle-nephew	1	1.9%

Table 17: Nature of associations for 54 index-contact case pairs identified as a result of contact tracing undertaken for pulmonary TB cases notified to the Greater Glasgow NHS Board 2000-2003

9.3.3 Comparison of index-contact case pair IS*6110* RFLP patterns

Comparative analyses of index and contact IS*6110* RFLP patterns could not be conducted for 31 case pairs (table 19). Either index or contact (or both) specimens were culture negative for 20 case pairs in total. Nearly four fifths (77.8%) of case pairs with culture

negative contact cases involved contact cases under nine years of age (14/18 case pairs). Of those fourteen case pairs with contacts age under nine years, 11 had gastric washings sent for culture. Eight contacts specimens were not sent to the national reference laboratory, where molecular typing is routinely conducted, and three were lost in transit.

One case pairing was deemed to have a highly similar DNA fingerprint pattern. The positioning of 14 IS*6110* bands for the index and contact case (father and daughter) were identical, except an extra hybridisation band was detected on one fingerprint. This could reflect the fact a polymorphic change in the structure of the *M. tuberculosis* DNA occurred between the time the father and daughter acquired the infection. Alternatively, this could indicate the female's infection was caused by a different strain (and therefore was acquired from a different source), which just so happens to share many of the genetic features found in the *M. tuberculosis* strain belonging to her father.

Unconfirmed index-contact case pairs	No. of case pairs n=31	
Contact specimen culture negative	18	33.3%
Index specimen culture negative	1	1.9%
Both index and contact specimen culture negative	1	1.9%
Contact specimen not sent for culture	8	14.8%
Contact specimen lost in transit to SMRL	3	5.6%

Table 18: Index-contact case pairs identified as a result of contact tracing undertaken for pulmonary TB cases notified to the Greater Glasgow NHS Board 2000-2003, and for whom comparisons of IS*6110* RFLP patterns could not be conducted

Three case pairs were found to have different IS*6110* RFLP patterns. The first mismatching case-pair involved a homeless index and contact case identified through a screening initiative in a Greater Glasgow hostel. Both reported alcohol misuse as a risk factor, and had 7-banded RFLP patterns. However, the positioning of the seven *6110* insertion sequences did not correspond, and the contact case had an isoniazid resistant strain of TB[26]. In the year prior to this screening initiative, another index-contact case pairing of alcoholic, homeless males was identified. Molecular typing conducted on both candidates' cultured sputum specimens indicated that strain types were mismatching, as the index and contact cases' DNA fingerprints contained seven and five IS*6110* bands respectively. The final index-contact case pairing involved workplace contacts. A screening programme initiated at the 42-year old index case's workplace detected disease

[26] Three other TB patients were detected during this screening initiative in a Glasgow hostel for the homeless. Two had the same strain as the index case, and the third did not have a specimen sent for culture

in a 18-year old male at a three-month x-ray follow-up examination, however, index and contact cases IS*6110* RFLP patterns were found to differ[27].

Cultured isolates for both the index and contact cases were available for 23 case pairs. Nineteen case pairs were deemed to have genetically indistinguishable IS*6110* RFLP patterns. Eight case pairs were found to have matching seven (3), nine (3), twelve (1) and fifteen banded (1) IS*6110* RFLP patterns. Eleven case pairs had matching fingerprints with less than six IS*6110* bands, with matching two (3), four (5), and five-banded RFLP patterns (3). However, it is recognised that RFLP typing is not a highly discriminatory technique for comparing genotypes with five or less IS*6110* bands. The sub-typing technique Spoligotyping was undertaken by SMRL, and five of these case pairs were confirmed to have been infected with genetically indistinguishable *M. tuberculosis* genotypes. Matching Spoligotypes were detected for two case pairs with a four-banded, and three with a five-banded RFLP pattern.

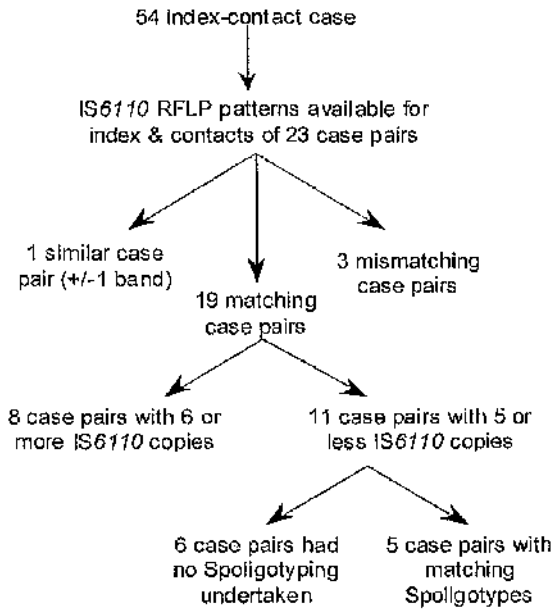

Figure 19: Algorithm summarising results from a comparative analysis of IS*6110* RFLP patterns for index-contact case pairs identified as a result of contact tracing investigations undertaken for pulmonary TB cases notified to the Greater Glasgow NHS Board between 2000 and 2003

[27] A second work colleague examined during the same screening programme was diagnosed with TB at a six-month follow-up. Molecular typing has indicated this case and the index case, for whom screening was initiated had genetically indistinguishable 9-banded RFLP patterns.

9.4 Missed opportunities for control

Returning to the algorithm in figure 22, it is evident some contacts either did not enter the screening programme, or failed to complete screening. These and other missed opportunities for controlling the spread of tuberculosis are discussed here.

9.4.1 Reasons for an absence of contact tracing

Contact tracing was not conducted for 34.5% of the study population (n=443). Reasons for an absence of contact tracing were established (table 20). For 39 index cases (8.8%), contacts were assigned to another index case to ensure contacts common to multiple index cases were accounted for only once during data collection. Screening was considered unnecessary when the index case posed a low risk of infection (23.5% of study cases), or because difficulties were encountered when screening contacts (34%), for example, if cases failed to identify close contacts, or if identified contacts refused screening. Sufficiently detailed information was not available for 17 patients, as cases were managed by a retired member of the nursing staff.

Reason for absence of contact tracing	Study Cases n=153	%
Contacts were assigned to another index case in the study	39	25.5%
No screening required on the basis of index cases' diagnoses	36	23.5%
Treated empirically due of a lack of bacteriological evidence	13	
Diagnosed on histological findings	11	
Diagnosed on chest x-ray findings	7	
Diagnosed on culture positive pleural fluid	3	
Diagnosed on culture positive faeces or gastric washings	2	
Index cases' contacts were not screened	52	40%
Index case deemed non-infectious & no close contacts	16	
Contacts located out with Scotland	15	
Contacts called for screening DNA/declined screening	11	
Index case did not identify any contacts	8	
Index case left country before contacts identification	2	
Information not available	17	11.1%
Diagnosed and commenced treatment in another country	9	5.9%

Table 19: Reasons for absence of contact tracing for pulmonary TB cases notified to the Greater Glasgow NHS Board 2000-2003

9.4.2 Contacts not attending screening

Of the 3378 contacts required to attend screening, 313 did not attend (9.3%). In the absence of computerised contact tracing records, nurses were questioned explicitly to find out whether any of these cases had subsequently been diagnosed with tuberculosis. To their knowledge, none had been subsequently found to have TB (as of completion of data collection in 2004). Unfortunately, reasons for failing to attend were not determined, as this was outside the scope of this analysis. This would be a useful endeavour for future investigations, as this could assist in improving contact tracing completion rates.

9.4.3 Delay of initial examinations

Tuberculosis was detected at the initial examinations of 49 contacts. However, it was noted that 13 contacts' illnesses were notified at least 2 months after their index cases' dates of diagnoses. The circumstances surrounding delay in case detection are discussed here.

In the first instance, two young boys had been screened immediately, were thought to have latent infection, for which they were prescribed chemoprophylactic therapy. Despite this intervention, both developed active TB and were notified four months after their respective index cases.

Secondly, a 50-year old male of Pakistani origin presented to healthcare services with a pleural effusion. Pleural fluid was found to be culture positive, but sputum samples were initially negative, therefore pulmonary infection was not suspected, and contact tracing was not required. After three months of drug therapy, *M. tuberculosis* was cultured from the patient's sputum. Close contacts were screened at that point, and five of his children were found to have active TB of the lungs, pleura or intrathoracic lymph nodes. (At a three-month follow up, some 6 months after the index case's original diagnosis, changes were detected on his sixth child's chest x-ray, and a diagnosis of pleural tuberculosis was confirmed by culture.)

Four homeless men were diagnosed during screening exercise at a hostel accommodating homeless individuals in Glasgow. One of these contacts was diagnosed one month after the designated index case, while four months elapsed before the other three cases were detected. This can be explained by the fact that this extensive screening program was undertaken over a four-month period. Also, screening in the homeless population is

especially challenging, as patients are unwilling to be screened, despite the offer of incentives, and tremendous effort on the part of the TB liaison nursing team to engage these individuals in the screening program.

Finally, on two separate occasions, index cases did not disclose the names of TB positive close contacts until approximately six months after their diagnosis. TB was identified in an ex-partner and close friend of two index cases after being brought to the attention of the TB liaison nursing team.

9.4.4 Screened contacts subsequently diagnosed with tuberculosis

Of the 2932 screened contacts deemed not to be infected, 9 subsequently presented to healthcare services with an illness that was diagnosed as TB. This occurred within

Characteristics	Index cases		Contact cases	
	n=7	%	n=9	%
Sex				
Male	5	71.4%	7	77.8%
Female	2	28.6%	2	22.2%
Age-group				
15 - 64	6	85.7%	9	100%
65+	1	14.3%	-	
Ethnicity				
Caucasian	7	100%	9	100%
Symptoms				
Duration not known	1	14.3%	-	
1-13 weeks	4	57.1%	9	100%
17-52 weeks	2	28.6%	-	
Vaccination status				
Vaccinated	3	43%	7	77.8%
Not vaccinated	3	43%	1	11.1%
Not known	1	14.3%	1	11.1%
Bacteriological status				
Sputum smear + culture +	6	85.7%	7	77.8%
Sputum smear - culture +	1	14.3%	2	22.2%
Risk factors				
Alcohol misuse	2	28.6%	3	33.3%
Homeless & alcohol misuse	2	28.6%	2	22.2%

Table 20: Characteristics of contacts diagnosed with TB after discharge from a contact screening programme and respective index (pulmonary) cases for whom contact tracing was initiated between 2000 and 2003 in the Greater Glasgow NHS Board area

approximately 2 to 24 months after the date of diagnosis of their respective index case, for whom they underwent screening. All index and contacts were adult Caucasian cases. Four of the six index cases misused alcohol, as did five of the nine contact cases (table 21).

When originally examined, one contact case was skin tested and x-rayed. This 54 year-old homeless man had a history of alcohol abuse, and did not have a BCG scar or documentation to suggest he had been vaccinated. He had a positive response to a tuberculin skin test, but abnormalities were not detected on his chest x-ray at that time.

Five contacts aged between 24 and 48 years had tuberculin skin tests. The first two cases had previously been vaccinated, and were partners of their respective sputum smear positive and sputum culture positive index cases. Three were associates (a husband, daughter and social contact) of a sputum smear positive index case at the centre of outbreak in Glasgow in 2002, in which approximately 147 people were screened. During the initial rounds of contact tracing, 6 contacts were found to have active TB. The daughter and social contact (unvaccinated) had been skin tested twice before being discharged. The index case's husband was skin tested initially, and examined again at 22 months by skin test and x-ray when the daughter (one of the 9 subsequently diagnosed cases) was diagnosed, and again, no abnormalities were detected.

Three men with histories of alcohol misuse (2 of which had BCG scars) were originally screened by x-ray alone, and no abnormalities were observed at that point. They were identified 4, 14 and 17 months after their respective sputum smear positive index cases were diagnosed.

All nine index-contact case pairs had genetically indistinguishable RFLP patterns. The 3 cases linked to the public house outbreak had the same 4-banded RFLP pattern and Spoligotype as the barmaid index case. This same RFLP pattern and Spoligotype was detected in another index-contact case pair, involving a father and son. One pair of homeless index–contact cases were found to have the same 7-banded pattern. This particular *M. tuberculosis* genotype had been detected in 30 other cases over a number of years, and an earlier epidemiological investigation had determined this outbreak was associated with a homeless hostel in Glasgow. Of the four remaining case pairings, three had genetically indistinguishable seven, eight and ten-banded RFLP patterns. The remaining case pair had a genetically indistinguishable five-banded pattern and matching Spoligotypes.

Finally, three of the seven index cases had contacts diagnosed during initial rounds of screening. Two of these index cases were homeless individuals, and the third was involved in the afore-mentioned outbreak.

9.5 Discussion

For the first time in Scotland, contact tracing practices have been evaluated using detailed epidemiological data from the ESMI scheme (established in 2000), in combination with molecular typing information from the national reference laboratory. This has allowed a detailed analysis of contact tracing outcomes in Glasgow. Its findings reaffirm the long-held belief that contact tracing in Scotland is highly valuable in detecting new cases of tuberculosis (Capewell & Leitch, 1984, Rubilar *et al.*, 1995). Just under two percent (1.8%) of contacts screened as a result of contact tracing (54/3065) were found to have active disease. This is greater than the historical rate of 1% in the United Kingdom, determined from contact tracing clinic audits, where disease was traditionally found at initial examinations in unvaccinated close contacts of smear positive index cases (Joint Tuberculosis Committee of the British Thoracic Society, 2000). The detection rate of 1.8% also mirrors past detection rates in Scotland of 1.4% (1995) and 1.8% (1984)[28].

Previous audits in Scotland found approximately half of all contacts with active disease were in the youngest age cohort of zero to fifteen years. This analysis determined twenty-five contact cases were aged fourteen years or under (46%), and of those paediatric contacts cases, 19 had been in contact with sputum smear and culture positive adult index cases (76%), and 21 had not been previously vaccinated (84%). This provides evidence screening is of particular importance for unvaccinated children in contact with sputum smear and culture positive index cases (Capewell & Leitch, 1984, Rubilar *et al.*, 1995).

Tuberculosis in children is indicative of ongoing transmission, and therefore the identification of source cases is imperative to interrupt the spread of infection. However, in this study, sources of infection were not identified for one quarter of paediatric cases (8

[28] In contrast to the present study population, previous audits in Scotland included both pulmonary and non-pulmonary cases in their analysis. This prevented the direct comparison of results from this and previous studies of contact tracing in Scotland.

cases). Contact tracing was undertaken for five of these cases, but no index cases were found. Screening events were not initiated for the three remaining paediatric cases[29].

A proportion of the eighty candidates identified by contact tracing and prescribed chemoprophylactic therapy were under fifteen years of age (34 cases). This reflects current guidance, which recommends provision of six weeks chemoprophylaxis for children, who have been in close contact with a case of sputum smear positive TB, and are two or under (Joint Tuberculosis Committee of the British Thoracic Society, 2000). Screened contacts notified to the ESMI scheme were considered cases of active tuberculosis, and patients in receipt of chemoprophylaxis were considered representative of cases with latent infection in this study. It is possible all individuals eligible for chemoprophylaxis did not receive it, because they may have refused it, or instead were requested to attend appointments for follow-up chest x-rays (Joint Tuberculosis Committee of the British Thoracic Society, 2000). Records for such individuals are maintained, but were not collected for this analysis. The yield of cases with latent infection detected during this analysis may not be complete, and in the absence of skin test results for such cases, means these findings are not directly comparable to other study results.

BCG vaccination is recommended only for contacts under 16 years of age, who are previously unvaccinated and are persistently tuberculin negative, or older contacts at occupational, ethnic or travel risk. Thirty-seven contacts were vaccinated as a result of contact investigations, and this appears less than in previous studies. Indeed, in 1991 a study in Newcastle determined 23.8% of 781 screened contacts under 16 years of age and with a negative Mantoux test, were given BCG (Esmonde & Petheram, 1991). The lower figure reported in this analysis can be explained to some extent by the failure of many screened contacts to meet current recommendations for the provision of BCG. Within the study period, interruptions were experienced to the supply of BCG and PPD in Scotland. Firstly, BCG vaccines were recalled because batches did not meet specifications for potency (Department of Health Medicines Control Agency, August 2002), and were unavailable for a period of four months. Secondly, BCG vaccine and PPD supplies used in skin tests were in short supply for an 18 month period, before being resolved in July 2001 (Scottish Centre for Infection and Environmental Health, 2001). Unfortunately, it is difficult to estimate the impact of these shortages and withdrawals over the study period,

[29] Two cases did not have contact tracing undertaken because diagnoses were made in the absence of bacteriological findings. The third case had recently arrived in the United Kingdom from Iraq, where his index case was thought to reside.

however, it is anticipated this resulted in minor decreases in the number of contacts screened and given BCG.

In 2002, 24% of TB cases in Scotland (Health Protection Agency, 2004), in comparison to 63% of cases diagnosed in England, Wales and Northern Ireland, were born outside the United Kingdom (McMenamin & Johnston, 2004). It is thought the contribution of immigrants to the TB population in Scotland has remained small and static over the years (Duffield *et al.*, 1996), and it is suspected infection in these individuals is imported from high-prevalence countries. To establish the effectiveness of contact tracing within ethnic minority groups in Scotland, molecular typing information may in the future be used to determine whether imported strains of TB are being transmitted to susceptible individuals, once introduced into Scotland. Secondly, it will be important to identify whether the immigrant screening programme or contact tracing is more effectively detecting new cases of TB (Underwood *et al.*, 2003). Findings from the present study suggest contact tracing is equally yielding in Caucasian and non-Caucasian populations, with 1.78% and 1.84% (respectively) of screened contacts found to have TB.

The evaluation of epidemiological links between paediatric contacts and index cases using molecular typing information could not be undertaken in many instances because gastric washings (which are usually obtained from children) are difficult to culture under laboratory conditions. In this study, the comparison of IS*6110* RFLP patterns could not be conducted for 21 of the 25 index contact case pairs involving a paediatric case (out of a total of 54 case pairs) because IS*6110* RFLP typing could not be undertaken. Of the four remaining case pairs (involving paediatric cases), IS*6110* RFLP patterns were available for comparison for three. However, these case pairs had low-copy number IS*6110* RFLP patterns, and Spoligotyping information was unavailable, therefore a definitive comparison of genotypes could not be conducted. Finally, the fourth case pairing had a genetically indistinguishable 9-banded IS*6110* RFLP pattern. In conclusion, the value of IS*6110* RFLP typing is therefore limited in this study by the high proportion of paediatric cases included in index-contact case pairs.

Screening within family or household settings has been shown to be successful in Glasgow. Half of all epidemiologically linked cases detected by contact tracing (26/54) involved associations between parents and children. Seventy percent (38/54) of case pairs involved household contacts. Where IS*6110* RFLP analysis of index-contact case pairs was undertaken for family and household contacts, genetically indistinguishable strains were detected, as would be expected.

The comparison of molecular genotyping information was undertaken for 42.6% of case pairs (23/54), however, conclusive results were only available for fourteen because Spoligotyping information was required, but not available for some case pairs. Of these fourteen case pairs with discernible IS*6110* RFLP patterns, ten were matching, and one had similar fingerprints that differed by one band. Three had mismatching DNA fingerprints, which had been detected during screening programmes for two homeless index case-pairs, and one during a screening event in a workplace setting. This indicates contact cases may have acquired infection from an undisclosed or unknown source of infection, or they may have had a reactivation of latent infection.

Five index-contact case pairings were identified within the homeless community in this study, and as already indicated, mismatching IS*6110* RFLP patterns were detected in two of the four instances where RFLP analysis was undertaken. Identifying contacts and conducting screening within this transient population presents a unique challenge (Patel, 1985). Future contact investigations in high-prevalence populations may benefit from using IS*6110* RFLP typing information as an adjunct to conventional epidemiological analysis, to guide the extensions of screening programmes.

The importance of screening highly infectious index cases is underscored by the fact 74.1% of contacts (40 cases) were sputum smear positive (Marks *et al.*, 2000, Reichler *et al.*, 2002). In recent years, evidence has been presented to suggest transmission from smear negative cases accounts for a sizeable proportion of new cases caused by recent transmission (Behr *et al.*, 1999, Hernandez-Garduno *et al.*, 2004). However, it was not possible to provide confirmation of transmission from a smear negative index case in this study, as it was not certain putative index cases represented true sources of infection. This of course conflicts with the evidence in chapter 6, which suggests that non-sputum smear positive pulmonary cases may play a greater role in disease transmission, particularly in a high risk population. While findings from this evaluation support the view that screening close contacts of a highly infectious case is a productive exercise, the hypothesis of disease transmission in chapter 6 suggests current practices are failing to detect disease in high-risk groups, and where index cases do not have sputum smear positive pulmonary disease.

Traditionally, screening of casual contacts has been found to be a largely unrewarding exercise, as the number of casual contacts screened outweighs close contacts and few, if any, casual contact cases are detected (Hussain *et al.*, 1992b, Rubilar *et al.*, 1995). In comparison to the 0.4% of casual contacts (6 cases) receiving a TB diagnosis, 3.4% of close contacts in this study were diagnosed with TB (48/1414). However, publications

describing outbreaks in casual contacts have usually involved unvaccinated children (Lalvani *et al.*, 2001, Wales *et al.*, 1985) and this was true for the majority (5/6) of casual contacts in this study. Therefore, findings from this study fail to discount the value of current methods for screening contacts with casual associations to the index case, particularly where casual paediatric contacts are involved.

Most disease (90.7%) was identified in contacts at initial examinations (Ansari *et al.*, 1998, Capewell & Leitch, 1984), and no new cases were identified after the 6-month scheduled follow-up (Rubilar *et al.*, 1995). Results from earlier audits of United Kingdom contact tracing practices found contacts diagnosed at 3 and 12-month follow-ups were frequently non-infectious and related to non-infectious index cases (Ormerod, 1992, Rubilar *et al.*, 1995, Teale *et al.*, 1991). It has also been postulated contacts diagnosed after initial examinations may have been infected by another source. This issue was investigated for the five index-contact case pairs detected after initial examinations in this study. Molecular typing information was available for 4 case pairings, two of which were found to have genetically indistinguishable IS*6110* RFLP patterns. One case pair had genetically similar (differing by one band) patterns, and the fourth pairing had mismatching genotypes (work place contacts).

Nine contacts had completed screening, but presented to the health services between two and 24 months after their index case's date of diagnosis with an illness subsequently diagnosed with TB. This finding begs the question, would these patients have been detected earlier, possibly before they became sputum smear positive (7 cases), if they had been required to attend follow-up appointments? Would improved screening tools have assisted earlier case detection? IS*6110* RFLP typing information indicated these contacts were infected with the same *M. tuberculosis* genotype, therefore the likelihood of being infected by another source case would have been somewhat reduced.

It is important to highlight that individuals identified as contacts by index cases, and who did not complete screening, did not present with disease over the study period. However, as discussed in chapter 7, difficulties associated with the identification of at risk contacts may hinder the effectiveness of contact tracing practices in Glasgow. As shown in this study, two index cases brought diseased contacts to the attention of nursing staff six months into their treatment. Improved methods are required to ensure at-risk contacts are promptly identified and screened. This issue was also raised in chapter 6, as a proportion of previously unrecognised associations between cases in a genetically defined cluster were detected.

In summary, contact tracing appears to have limited effectiveness in actively detecting new TB cases in Glasgow. Screening along family lines is particularly useful in detecting tuberculosis in unvaccinated paediatric cases, and half of all associations involved parents and children (young and adult). Contact tracing undertaken in non-traditional settings such as nurseries, hostels for the homeless and workplaces yielded new cases. Close contacts of sputum smear positive index cases were most frequently diagnosed with TB, while screening of casual contacts proved effective in outbreak situations involving unvaccinated children. IS*6110* RFLP typing and Spoligotyping information indicated many index-contact case pairs were genetically indistinguishable. Mismatching fingerprints were observed in three of the 17 index-contact case pairs comparable by IS*6110* RFLP typing (17.6%), and were detected during contact investigations in a workplace setting and between two case pairings of homeless individuals. One other important missed opportunity for TB control involved TB diagnoses in 9 close contacts of study cases, screened during contact tracing, but discharged as having no indications of disease. These cases presented to health care services and were subsequently diagnosed with TB.

Chapter 10: General discussion

Although the rate of decline of tuberculosis case notifications in Scotland has remained stable over the past twenty years, the relative contribution of Glasgow cases to the overall burden has been steadily increasing. Together with incidents of TB outbreaks associated with public houses and nurseries, this has raised concerns about the effectiveness of current strategies to control the incidence of disease. This research study sought to examine the occurrence of ongoing *M. tuberculosis* transmission in Glasgow and to identify challenges facing control strategies aiming to interrupt the dissemination of disease.

To achieve study objectives, an experimental methodology was devised, which combined molecular genotyping, epidemiological and sociological information. Within their respective disciplines, molecular epidemiology and sociological analysis have provided valuable insights into the control of *M. tuberculosis*. Molecular genotyping, in combination with epidemiological information, has enhanced our understanding of *M. tuberculosis* transmission, by providing evidence of outbreaks of disease, and indicating disease is caused by recently transmitted infection more often than previously suspected (Alland *et al.*, 1994, Klovdahl *et al.*, 2001). Similarly, sociological techniques have provided an insight into social and cultural factors that influence patients' behaviour and attitude towards their illness, often in the context of compliance with drug therapy (Farmer, 1997). In this study, these approaches were combined to examine obstacles facing early case detection strategies for the control of TB. Factors contributing to the ongoing transmission of *M. tuberculosis* were identified by taking the unusual step of exploring patients' social behaviour, health beliefs and help seeking behaviour.

Advances in molecular biology in recent years have focussed much attention on the elucidation of transmission patterns. Commentators have argued the introduction of these new tools has had a detrimental effect, as the valuable insight into disease transmission obtained by understanding behavioural and socio-cultural factors has been overshadowed (Day *et al.*, 1993). This study supports the view that molecular genotyping is a useful tool for highlighting a social problem, but cannot explain or describe the complex nature of relationships between cases with a genetically indistinguishable IS*6110* RFLP pattern, suggestive of recent transmission. Routine surveillance information was available for these cases, but was insufficient, as it failed to disclose information about the nature of many associations. To this end, nurse and patient interviews proved beneficial, as they

were capable of eliciting information to epidemiologically link such cases on the basis of time, place or person.

However, the reasons for continued propagation of the disease can only be partially explained by describing the social network of disease for a given *M. tuberculosis* strain. Completion of drug therapy and early case detection are central to controlling TB, however failure to comply with treatment and delayed presentation to the health services pose significant challenges (Chin *et al.*, 2000, Cronin *et al.*, 2002). Understanding the social and cultural context in which patients experience and make sense of their illness is an important step in rationalising these behaviours (Frankel *et al.*, 1991). The viewpoints and attitudes of these individuals towards their illness were determined during patient interviews.

Moreover, research on socio-cultural factors influencing TB control has focused primarily on the role of treatment compliance, while factors influencing case detection have received little attention (Rubel & Garro, 1992). The selection of study cases (i.e. a cluster of cases thought to be part of the same transmission pathway) provided a unique insight into the role of such factors in the continued propagation of *M. tuberculosis*. This study was novel in its selection of study cases, using molecular typing information to identify cases putatively caused by recently transmitted infection.

As a result of findings from these analyses, the effectiveness of contact tracing was brought into question, and this research project concluded with an evaluation of contact tracing outcomes. Current contact tracing practices were found to have been successful in detecting disease in close contacts of newly diagnosed cases, especially when the case for whom contact investigation is initiated has sputum smear positive pulmonary TB. Many contacts diagnosed with tuberculosis as a result of contact tracing over the study period (2000-2003), were fourteen years of age or less. Despite the apparent value of contact tracing, when these findings were placed in context of those from other analyses, it appeared current practices were unable to address *M. tuberculosis* transmission between less conventional, high-risk groups in a particular area of Glasgow.

The integration of disparate research paradigms resulted in a broader and more insightful perspective of obstacles facing early case detection strategies, and therefore TB control. In identifying that patients delay seeking medical assistance, fail to identify all known contacts during contact tracing, some GPs apparently fail to consider a diagnosis of tuberculosis for some time, and the contact tracing service itself has programmatic failures,

this unusual approach to examining TB control proved a success. In this chapter, the value of integrating molecular, epidemiological and sociological data are discussed in the context of the additional insight into TB control and transmission in Glasgow. Chapter 11 considers possible ways in which strategies for TB control could be improved.

10.1 Identification of previously unrecognised outbreaks

The ability to discern and differentiate between *M. tuberculosis* strains using molecular genotyping information has created the opportunity to verify previously held assumptions about the aetiology of disease. Like other low-incidence countries, increasing notifications of tuberculosis in the elderly population have been observed in Scotland. As the demographic profile has changed to one in which an increasing proportion of the population are elderly, reactivation of latent infection is likely to play an important role in TB epidemiology (Harper, 1999). Although a maximum of 81.9% of culture positive cases in this study were thought to be due to the reactivation of latent infection on the basis of having unique IS*6110* RFLP patterns (some of these cases are likely to have imported disease from a high-prevalence country), transmission of TB in Glasgow is ongoing, and its interruption should continue to be a principal strategy for controlling TB (World Health Organization *et al.*, 2002).

On the basis that two or more cases with a genetically indistinguishable IS*6110* RFLP pattern or Spoligotype represent recent transmission of infection, 17 distinct TB outbreaks (involving between two to 23 cases) were identified over the study period. This is despite an apparently effective contact tracing programme for pulmonary TB cases. An evaluation of contact tracing was undertaken, utilising a conventional measure, yield of infected contacts, as an indicator of program success. Audits of contact tracing conducted in the United Kingdom over the past two decades have reported a yield of 1% of screened contacts were found to have active TB. In this study, 1.8% of screened contacts were diagnosed with active tuberculosis, thereby suggesting the yield from contact tracing in Glasgow is above average. Secondly, 81% of pairs of index cases and their respective infected contacts (for whom genotyping was undertaken) had matching IS*6110* RFLP patterns, suggesting contact tracing is detecting the spread of infection between cases in a chain of transmission. The opportunity for infected contact cases to pass TB to others was limited, as the majority were not sputum smear positive at diagnosis (10 of the 54 contacts cases - 18.5%, were sputum smear positive). Furthermore, as 46% of infected contacts

were children (under 15 years), the spread of *M. tuberculosis* was unlikely to continue due to the fact children have difficulty producing sputum, which contains the TB pathogen.

The disparity between molecular typing information, suggesting transmission is ongoing, and the apparent success of contact tracing over the same period, is a curious finding. It is important to verify whether the identification of clusters of cases (groups of cases, where each case in a group has a genetically indistinguishable IS*6110* RFLP pattern) truly reflects the occurrence of recently transmitted infection. As clustering is not always a surrogate of recently transmitted infection, it is important genotyping data are interpreted together with epidemiological information (Braden *et al.*, 1997, McNabb *et al.*, 2002). An analysis of epidemiological links between a single large cluster suggests that in Glasgow, clustering may be largely representative of recently transmitted infection (67.2%).

However, the absence of information to epidemiologically link cases in each molecularly defined cluster meant the assumption that clusters of cases represent recently transmitted infection could not easily be verified. Often records held in the ESMI system indicated clustered cases had no known association with a TB cases prior to diagnosis. Information pertaining to the method of detection indicated that of the 90 study cases presumed to have acquired disease as a result of recent transmission, 6.7% were found as a result of contact tracing for an infected case. The absence of information from the ESMI database can be interpreted in two ways.

First, molecular genotyping information may be falsely indicating the occurrence of recent transmission. In a rural Arkansas study, a molecularly defined cluster was found to reflect simultaneous reactivation of latent infection in elderly cases, who had contact with one another only in their youth (Braden *et al.*, 1997). However, in this study, recent epidemiological links between cases in a single, large molecularly defined cluster were identified. Prior to commencing the investigation, epidemiological links could be established for 22% (14/64 cases) of cluster cases. On completion of nurse and patients interviews, links to at least one other case in the cluster had been established for an additional 34% of cases (i.e. 44% of all study cases could not be linked). Epidemiological links could not be established for the remaining cluster cases. With regards to the latter cases, it is possible infection was transmitted transiently, which would prove almost impossible to trace by conventional means. Secondly, this *M. tuberculosis* strain may have been present in this Glasgow community for some time. As cluster members have generally lived in the area for most of their lives, they may have acquired the infection many years ago and their latent infection reactivated within the observed study period. It is

this investigator's belief a combination of reactivation of latent infection and transient transmission explain the inability to detect epidemiological linkage for such cases.

As 56.3% of cases in the study cluster (chapter 6) had detectable epidemiological links to another cluster case, it is probable a considerable proportion of clustering reflects the occurrence of recent transmission. Therefore, the failure to capture information to epidemiologically link cases on the basis of shared time, place or person detected during this retrospective analysis highlights a weakness in the current surveillance system. This is an important finding, as one of the principal functions of an enhanced surveillance system is to assist the prospective detection of outbreaks.

Prior to commencing this research study, an audit of the ESMI database revealed poor completion of particular data fields. As incomplete information may lead to imprecise epidemiological descriptions, data for select cases was strengthened by collection of all available missing information. In particular, notable improvements in completion rates were detected for ethnicity, country of birth and method of case identification data fields. Despite being targeted during this exercise, the proportion of cases with missing data fields for identifiable risk factors remained static at 25%. ESMI surveillance forms require to know whether patients misuse alcohol, are homeless, immunocompromised etc; as such factors place individuals at high risk of acquiring infection, developing active disease, or both. This information can be used to appropriately target public health interventions to relevant high-risk populations. The poor completion of this data field was thought to be due to the fact that cases simply did not fall into these predetermined categories. Indeed, this selection of high-risk groups was proposed by an expert committee based on knowledge of local epidemiology. It is possible only a small proportion of Glasgow cases were found to have a predetermined risk factor because no alternative options were offered.

Authors in the field of HIV have suggested that rather than categorising cases by risk group, we should be discussing risk in terms of behaviour (De Bruyn, 1992). This may partially explain why epidemiological linkage was not detectable using information from the ESMI surveillance scheme. Although risk groups are proxies of risk factors that may be biological and behavioural (Smith, 1995), my audit of data completion fields highlighted the fact that predetermined risk groups on ESMI forms do not capture complete information on risk behaviour. For example, on interviewing nurses and patients, it emerged patients who drank heavily were not necessarily considered to be misusing alcohol, and therefore nurses did not select this risk category on surveillance forms.

(Criteria for selection of risk factors to assist the completion of surveillance forms are not provided.) Furthermore, although no risk group may have been selected for a case, this does not preclude the fact that a case may have had one of the pre-selected risk factors in the past. This is common amongst individuals who are currently in residence, but who stayed in hostels for the homeless in the past. Also, individuals may have had consumed excessive quantities of alcohol in the past, but had ceased this behaviour long before they developed active disease. The value of collecting a history of information pertaining to patient behaviour and social activities was demonstrated in this study, as it led to the detection of epidemiological links with cases associated with an outbreak in a public house, which occurred ten years previously. The transmission of this *M. tuberculosis* strain persisted predominantly through social networks in Glasgow, and it is possible this temporal outbreak may have been recognised sooner if cases' social behaviour had been documented, and followed-up with the appropriate action.

However, whether clustered TB cases can be detected earlier remains to be seen. A 2004 study in the Amsterdam area found that although clustering was largely represented of recently transmitted TB (86% of study cases had detectable epidemiological links), opportunities for early case detection using contact tracing were limited. The only risk factors independently associated with being detected at an earlier stage (as opposed to epidemiological links detected through second round interviews) was being male. This insight is not sufficient to allow appropriate action to be targeted, to allow improvements to be made to the contact tracing service (van Deutekom, *et al.*, 2004)

Currently, epidemiological linkage is indicated on ESMI surveillance forms when the notified case was detected as a result of contact tracing. Identifying information for the individual, for whom contact tracing was initiated, is requested. Data providers can also use free-text areas provided on surveillance forms to comment on associations with known TB cases. However, during the course of nurse interviews it became apparent that all epidemiological links between cases are not always recorded on ESMI surveillance forms. Although reasons for this oversight were not explicitly sought, a number of factors are likely to be involved. Firstly, ESMI surveillance forms enquire whether the patient had known contact with a TB case prior to diagnosis, however, the year of contact and not patient identifying information is required. It is quite possible those completing surveillance forms perceive this information to be of little value, and do not provide it in free-text comment fields. Secondly, information may not have been completed on ESMI surveillance forms because it was not known at that time. The patient may have revealed the information late on in treatment, or the discovery of the epidemiological link was

fortuitous. If this was the case, there may have been little opportunity to provide this information once paper surveillance forms were completed and passed to the relevant NHS Board. The retrospective nature of the cluster investigation in detecting links for an additional 34% of cluster cases is likely to have contributed to the success of the study.

Furthermore, data collected in contact tracing nursing notes record contacts' personal details, screening attendance and outcome as a matter of routine. Occasionally, notes include more descriptive information pertaining about the index case's lifestyle (the individual for whom contact tracing was undertaken). Interviews with nursing staff during the cluster investigation often led nurses to provide information about epidemiological links that were recorded in contact tracing nursing notes, but not on ESMI forms, or absent from both. The failure to routinely collect information about patients' lifestyles and social habits has resulted in the omission of information that could potentially link these individuals to an outbreak. The capture of this information is made all the more difficult by the fact such information in Glasgow is relatively inaccessible, as data were not recorded electronically over the study period and paper contact tracing nursing records are not routinely collated and analysed. Contact tracing notes have the potential to be used far more effectively if their information could be accessed for the purposes of contributing to the early detection and description of outbreaks.

Data providers may be failing to indicate information about associations on contact tracing nursing notes or ESMI forms, whether it is known at the time, or determined at a later point. However, this is essential for understanding the transmission dynamics of the disease and for the detection of outbreaks. Although reasons were not investigated in this study, it would be useful to explore the perceived usefulness of, and obstacles/problems associated with recording/providing this information, from the viewpoint of individuals completing forms, i.e. TB nursing staff. As indicated in a review of control services in Scotland in 2002, issues facing nursing staff include the absence of training and directives for the completion of ESMI surveillance forms and contact tracing nursing records (Hamlet, 2001).

10.2 A social network approach

In attempting to understand the socio-cultural factors contributing to the ongoing spread of disease, this research project centred on an investigation to examine the transmission pathway of a single strain of *M. tuberculosis* in a predominantly Glasgow population. Routine ESMI surveillance and contact tracing information contained limited information

about epidemiological linkage between cases, and nurse and patient interviews boosted the number of cluster cases with known epidemiological links from 22% to 56.3%.

Although many of the associations identified as a result of nurse and patient interviews were between family members and other associates without identifiable risk factors, a proportion of epidemiologically links were detected between individuals, traditionally referred to as casual contacts i.e., work and recreational acquaintances. This study has added to our understanding of TB transmission dynamics firstly by identifying the risk behaviour shared by many of these casual contacts. Frequenting public houses in West Glasgow was important in facilitating the spread of disease in this cluster, as it brought individuals who were infected, and those who were susceptible, in contact with one another. In some instances, adults frequenting these venues became sources of infection for their close contacts i.e. other adult members of their family/children. Although the purpose of this study was not to quantify the duration of contact required, it was apparent patients spent prolonged and often lengthy periods of time in identified public houses. One could argue the proximity and duration of contact between many of these cases could be deemed similar to that in a conventional close contact situation e.g. household environment.

Secondly, in tracing the social network of disease transmission, many potential sites of exposure were identifiable i.e. public house or patients' homes. Whereas in the past, tuberculosis was principally spread between individuals within the same household, this study identified non-traditional settings for disease transmission. This is significant, as conventional contact tracing measures were developed when transmission occurred mainly within the family, suggesting the current contact tracing approach may need to be updated (Weis, 2002). In this study, cases could not always be linked on the basis of sharing a common contact, rather by virtue of frequenting a common location. Indeed, 23.4% of cases (15 of 64 cases) in this single cluster were known to frequent one public house in West Glasgow, over a prolonged period. Many authors have proposed case detection can be improved by identification of non-household locations. As they play an important role in facilitating the spread of disease, they could prove useful in case detection strategies to improve TB control.

The concentric circle approach to contact tracing prioritises contacts for screening on the basis those in closest proximity, and lengthy duration of contact are likely to be infected. Thus, wasteful use of resources is limited and the cost effectiveness of contact tracing is maximised. However, in using this approach to focus on those at greatest risk, this study

has shown some infected individuals, usually casual associates of infected cases, avoided identification during contact tracing. Although the current method for early case detection appears to be highly effective in diagnosing disease in close contacts, more appropriate methods are required to extend screening to at-risk casual contacts. As contacts outside the home can often spend sufficiently extensive periods of time with a case of TB to be considered close contacts, the prioritising of contacts outside the home needs to be reassessed. Currently, recommendations for extending screening outside the traditional household setting is ambiguous.

Guidance for contact tracing also recommends screening of close and casual contacts for highly infectious sputum smear positive cases, and the screening of close contacts for all other bacteriologically confirmed cases. However, in tracing the transmission pathway of a single *M. tuberculosis* strain, casual associations were identified between less infectious sputum smear negative culture positive cases and their respective contacts. These associations may have failed to be identified during contact tracing because current guidance indicates extending screening to casual contacts in such instances is not required.

In eliciting social histories from nurses and patients, this study has shown that unlike contact tracing where individual chains of transmission are identified, a social network approach provides a broader understanding of how TB spreads through a community. While the failure of current contact tracing to establish all known epidemiological links was highlighted, the value of using patient and nurse interviews to establish social behaviour has proven a useful way of establishing epidemiological links between cases in a transmission pathway, at least in a retrospective study. Whether this approach can assist in improving prospective case detection strategies will be considered in chapter 11.

10.3 The influence of socio-cultural factors on TB control

Programmes to control the incidence of tuberculosis are based on early case detection, as this should limit the period of time in which a case can pass the infection to other individuals. Indeed, the most likely explanation for the ongoing spread of TB is that transmission is occurring prior to the initiation of drug treatment. Interviews with patients provided an insight into some social and cultural factors contributing to the continued propagation of a single strain of *M. tuberculosis* in the Glasgow area.

Delayed diagnosis has long been recognised as a contributory factor in community outbreaks. When patients were asked about their experiences of ill health, and how they

came to seek medical help, they indicated they had recognised they were unwell, but did not perceive symptoms as serious. Instead symptoms were attributed to minor illnesses, or patients simply felt they were run down. Interviewees often commented they thought they had cancer, and even those with known TB contacts did not consider the possibility of having tuberculosis. Generally patients adopted a wait-and-see approach, in the hope symptoms would resolve of their own accord. Triggers for seeking care were identified as the worsening or persistence of symptoms, interference with day-to-day life, and on occasion, friends/family encouraged the patient to seek help, or sought help on their behalf. It has been suggested that the failure to associate symptoms with tuberculosis due to the fact it is a relatively uncommon disease, resulted in patients delay in seeking help from medical services (Singh Bakhshi & Ali, 1995). In this study, patients attitudes towards their ill health resulted in the extension of symptomatic periods, during which time cases could have infected others, thereby contributing to the continued outbreak of this strain of *M. tuberculosis*.

In low-incidence countries, decreasing expertise in tuberculosis is recognised as an obstacle in reducing the incidence of TB (Brockmans, 1991). As case notifications dwindle, so too does experience in diagnosing and managing TB cases, so it is not altogether unsurprising when the responsibility for delayed diagnosis is partially imputed to physicians. During interviews, some patients reported that between contacting the health services and receipt of diagnosis, prolonged periods of time had elapsed. Often interviewees indicated they had received alternative diagnoses for their illnesses, before a conclusive diagnosis of tuberculosis was reached. More often, individuals without classic symptoms or identifiable risk factors such as alcohol misuse or homelessness commented on this. Such anecdotal information from patient interviews pertaining to doctor delay raises important questions about the quality of care received by patients. Generalising the characteristics of a patient likely to be infected with tuberculosis is perhaps a useful index for raising clinical suspicion of tuberculosis, however it is important to recognise that all cases do not fulfil these stereotypes or fit the stereotypical image of a TB patient. More useful ways of identifying potentially infected cases are required. Further research into risk behaviour and identification of potential sites of exposure may provide a better understanding of how seemingly low-risk individuals, or individuals with no identifiable epidemiological links, acquire TB.

In tracing the spread of a single strain of *M. tuberculosis*, many patients revealed social connections with other cluster members that were not identified during contact tracing. The identification of infected casual contacts for the purposes of contact tracing has proven

particularly problematic. Patients' failure to nominate contacts for screening may stem from their failure to completely grasp the concept that tuberculosis is an airborne droplet spread communicable disease, and infection usually occurs as a consequence of close, prolonged contact. Many thought disease was spread through sharing utensils or exchange of bodily fluids during sexual contact. Those who understood the disease to be airborne droplet spread thought it possible to acquire the infection after a very short period of time in contact with an infected contact. As shown during interviews, Glasgow patients often have different beliefs about TB transmission to the medical profession, and as a consequence, the contact tracer's perception of an at-risk contact may differ from that of the individual, for whom contact tracing is being undertaken. Interviewees even held disparate views about the definition of high-risk casual contacts, as the identification of an association between a case and his/her infected contact was not always reciprocated during contact tracing or study interviews.

Additionally, the stigma of tuberculosis as a dirty disease, one typically acquired by alcoholic, homeless males, meant a TB diagnosis usually incited feelings of shame and embarrassment for the newly diagnosed individual. Feelings of guilt for causing concern and worry among friends and family were also reported by interviewees, as contacts required to be screened for the purposes of contact tracing. Many interviewees indicated that they withheld the fact they had been diagnosed with TB from some friends and acquaintances. It is conceivable that such factors hinder the identification of contacts.

Previously, the role of cultural and behavioural factors in the failure to control TB has only been explored in the context of treatment compliance. Factors promoting ongoing transmission of *M. tuberculosis* were identified, as a result of conducting semi-structured interviews with patients believed to be part of the same transmission pathway. Its quite possible that current contact tracing approaches are inadequate for the detection of disease because they are not sufficiently sensitive to the social and cultural context in which patients experience their illness. A complex interplay of social and cultural factors influence patients' understanding and beliefs about their illness and their participation in contact identification during contact tracing. Raising contact tracers awareness of such issues may improve contact tracing outcome. Furthermore, by gaining an understanding how patients make sense of their illness, it may be possible to encourage infected individuals to present to medical services sooner, rather than later. This information may also assist physicians in making a prompt diagnosis.

Conducting semi-structured patient interviews to retrospectively identify TB contacts was a worthwhile undertaking, on the basis that the proportion of cases in a genetically identifiable cluster with identifiable epidemiological links increased, thereby enhancing our understanding of TB transmission. However, in the context of real-time contact investigation, such an approach is likely to prove time consuming. Interviews undertaken as part of this research study were, on occasion, in excess of one hour and given that contact tracing is one of the principle duties of TB nursing staff in Glasgow, such an approach to contact identification may not be entirely practical.

Some interviewees revealed fresh information during interviews which had not previously been provided to the TB nurses during contact tracing interviews. This may have been due in part to the different line of questioning used in this research study. In addition, the fact patients were being interviewed for a second time (first time was the contact tracing interview, and the second interview as part of this study) may also have enhanced the detection of epidemiological links between clustered cases. In the Netherlands, a second contact tracing interview is undertaken specifically with patients identified as being part of a cluster, on the basis of molecular typing information (personal communication, Dr Maruschka Sebek, KNCV). It is unclear whether the semi-structured nature of the interview (and the lengthy period of time spent building rapport with patients and elucidating information) or the fact that patients were being reinterviewed, and had time since their contact tracing interview to reconsider potential TB contacts and sources of disease resulted in the detection of an increased proportion of epidemiological links.

10.4 Study limitations

When epidemiological, molecular and sociological information was brought together in this study, the triangulation of methodological approaches minimised the limitations of each approach to understanding the transmission of *M. tuberculosis* and maximised the usefulness of each.

In this study, obstacles facing effective TB control were identified by evaluating outcomes from contact tracing and by examining patients' experience of ill health. Interviews were not conducted with health professionals providing health services to TB patients (e.g. TB nurses/contact tracers), yet the identification of obstacles perceived by such individuals to achieving effective TB control would have provided another useful insight into the problem of interrupting TB transmission. Although outcome measures from contact tracing provided an indirect view of the challenges involved in providing a health service

e.g. contact tracing, the focus of this study was not on the provision or quality of the service itself. However, practical and policy issues facing the provision of control services was the focus of a review of control services in Scotland in 2002 (Hamlet, 2001).

As highlighted in chapter 4, interviews undertaken with nurses were limited by the absence of an interview schedule, and the use of tape recording equipment. The use of an interview schedule would have improved consistency in terms of the line of questioning across nurse interviews. The use of tape recording equipment would have ensured information pertaining to epidemiological links was captured, and could be revisited as required during analysis. Unfortunately, attempts to involve nursing staff in face-to-face interviews were hampered by difficulties in scheduling interviews, as a result of nurses' heavy workloads.

The evaluation of effectiveness of current control strategies is hindered by the inconsistent approach to defining contacts as close and casual for contact tracing across the Greater Glasgow NHS Board, and Scotland. Guidelines exist to direct best practice, but a standardised protocol for contact tracing has not been developed in Glasgow. A standardised contact tracing interview questionnaire does not exist, therefore the elucidation of contacts relies on the experience and skill of TB nurses. There is also a lack of unambiguous definitions for close and casual contacts to enable prioritisation of screening. Both are detrimental to the outcome of contact tracing. The ability to analyse recorded contact tracing data is limited when definitions and approaches to data collection vary across districts (Marks *et al.*, 2000, Reichler *et al.*, 2002). This is recognised as a significant limitation of the evaluation of Glasgow contact tracing outcomes. Yet, the collection of data is essential for program management and evaluation. Finally, the true extent of the effectiveness of contact tracing cannot be completely determined without being able to identify cases who avoided becoming infected as a consequence of this intervention.

Greater Glasgow cases account for approximately 50% of new cases diagnosed annually, but does this mean the obstacles and opportunities for TB control identified in this study are applicable to the remaining NHS Boards? Given that the epidemiology of TB in Glasgow is similar to that of other urban areas across the central belt of Scotland (e.g. Lothian and Lanarkshire), it is possible the findings are broadly indicative of the situations in those districts. However, Scotland is unusual in comparison to other low-incidence countries, in that a large proportion of its population are dispersed over rural areas, where services and healthcare practices may differ. Indeed, TB-specific services do not necessarily exist, and health visitors undertake tasks such as contact tracing. In such

settings, difficulties associated with service provision are likely to hinder strategies to control TB. Therefore, conclusions from this study are likely to be representative of tuberculosis in urban areas of Scotland.

10.5 General comments on TB control in Scotland

Although Scotland has been fortunate in experiencing relatively low and stable case rates over the past twenty years, it is likely that challenges to the control of TB will emerge in the future. As is observed in England & Wales, a sizeable proportion of cases are attributed to individuals recently arrived in the United Kingdom (imported infection). In Scotland, approximately a quarter of cases per annum are born outwith the United Kingdom. Should this epidemiological profile change, this will require current control efforts to be refocused. Drug-resistance and HIV co-infection will continue to pose a threat, however are currently at low levels in Scotland. As highlighted in previous work by Hamlet (2001), Scotland faces challenges in providing a TB service because of the diverse structure and function in local TB services, due to the relative rarity of the disease (an incidence of less than 10 per 100,000 per annum), and the geographical spread of those cases. Despite the fact a relatively small number of cases are detected each year in Scotland (approximately 400 per annum), it will be important to be aware of differences that exist across Scotland when looking to the future, both in terms of service provision and the development of policies, both for the United Kingdom and Scotland specifically.

Indeed, the loss of expertise and downsizing of control services in the latter decades of the twentieth century in response to declining case rates has played an integral role in the resurgence of TB in many previously low-incidence locations (e.g. New York in the later 1980s/early 1990s). Many commentators warn of a return to increasing trends in case rates if service planners fail to learn from those mistakes.

This study focussed on just one aspect of TB control (early case detection), however, this investigator recognises the complex interplay of a multitude of factors involved in TB control. It is against this backdrop that this work is presented. The ability to provide TB services is due to the presence of an infrastructure across Scotland, which includes a network of professionals to detect and treat cases, supported by a laboratory capacity to assist diagnostic efforts. Additionally, the appropriate legislation needs to be in place in instances where highly infectious patients require isolation, thereby offering the public a degree of protection from that source of infection. Surveillance is required to monitor trends in disease and the feedback of such information can contribute to the development

of better targeted, and therefore more effective control efforts such as contact screening. To face challenges likely to emerge in Scotland in the future it is important these components of the TB service remain in place, so that the tremendous efforts made by service providers can continue.

Chapter 11: Conclusions & recommendations

In Glasgow, transmission of *M. tuberculosis* is ongoing and current methods of active case detection, which aim to interrupt transmission pathways, have limited effectiveness. In particular, casual contacts of infected individuals are failing to be identified by the conventional approach to contact tracing. Transmission between casual contacts appears to involve individuals at high-risk of infection or progression to disease due to alcohol misuse, and public houses have been identified as putative sites of exposure for casual contacts. One of the largest clusters of cases, believed to represent recent transmission of infection, is thought to be a long-standing strain, endemic to Glasgow. Reasons for the continued propagation of this strain include delayed patient presentation to medical services, which extends the period in which an undiagnosed case can infect others. Patients fail to associate non-specific symptoms with this uncommon disease, and postpone seeking care in the hope symptoms will resolve. Contact tracing outcome is impaired because infected contacts are not identified. Patient beliefs about the way in which tuberculosis spreads, the feelings of shame and embarrassment associated with this diagnosis, and the stigma of TB being a dirty disease conceivably hinder early case detection. Furthermore, anecdotal information suggests doctors may delay the initiation of treatment for TB by initially misdiagnosing symptoms.

The integration of molecular, epidemiological and sociological information has offered a novel insight into the occurrence of *M. tuberculosis* transmission. At this juncture, it is important firstly to ponder how our enhanced understanding of transmission and challenges facing control can lead to improvements in early case detection strategies in Greater Glasgow. Secondly, could tools utilised in this study be incorporated into routine control practices to interrupt *M. tuberculosis* transmission, and if so, what function would they have?

11.1 Contact tracing: an improved approach

Findings from this study have shown contact tracing fails to interrupt transmission because an outdated concentric circle approach is inadequate at detecting disease in casual contacts at high-risk of TB. The primary obstacle to obtaining a good yield from contact tracing casual contacts is the absence of detailed guidelines and standard operating procedures, which would advise on the most efficient and effective method of evaluating contacts at

highest risk of infection and disease. A standardised approach to screening is required in Greater Glasgow, to ensure the provision of a quality contact tracing service.

Currently, priority for screening is established by identifying contacts as close or casual on the basis of proximity and duration of contact, however definitions for each in current guidance documents are ambiguous. Although screening of contacts denoted as close yields a considerable number of newly diagnosed cases, this is not the situation for casual contacts. More useful ways of prioritising contacts at high risk of disease with casual ties to the index cases are required. An understanding of index cases' risk behaviour and identifying contacts at high risk of disease within patients' social network can assist this process. In some parts of Scotland, in the absence of guidance, this type of approach has already been adopted. In Lanarkshire for example, casual contacts are prioritised for screening by the contact tracing team, by conducting a risk assessment for each, thereby establishing the contacts' likelihood of acquiring infection/disease. High-risk casual contacts typically include children, immunocompromised individuals, and those who are homeless and/or misuse alcohol (personal communication, Dr Jim Miller).

At present, screening is extended to casual contacts in subsequent concentric circles around the index if the index case is sputum smear positive, or if 10% of close contacts have been infected. However, in the cluster investigation (chapter 6), many previously unrecognised putative epidemiological links were between index cases with a low degree of infectiousness (sputum smear negative), and their casual associates, many of which were known to misuse alcohol. This is a blind spot in the current approach to contact tracing. New criteria for extending screening, which embrace the concept of epidemiologically linked case pairs being part of a larger network of disease, need to be developed and evaluated. Molecular genotyping information can be of use here. To interrupt the transmission of disease, it will be important to decide whether more extensive screening is warranted in the event a newly diagnosed case is infected with a strain of *M. tuberculosis*, known to be circulating in a high-risk population such as alcohol-misusing individuals (as was demonstrated in chapter 6). Screening lower priority contacts may be entirely appropriate if the index case misuses alcohol, and/or socialises with similarly high-risk contacts.

Furthermore, although screening close contacts of sputum smear positive index cases was found to be an apparently effective strategy during an evaluation of contact tracing, perhaps screening of lower priority contacts in the above situation is warranted, regardless of the newly diagnosed case's sputum smear status. In essence, rather than extending

contact tracing on the basis of infectiousness, precedence should perhaps be awarded on the basis of knowledge pertaining to the nature of social network in which the identified strain circulates. Of course, background knowledge of the strains in circulation and an understanding of the transmission dynamics within clusters would be essential for this strategy.

Rapid molecular genotyping techniques (which are currently in development at SMRL) present the opportunity to assist decision-making in contact tracing and outbreak investigation. As demonstrated in chapter 9, secondary cases detected as a result of contact tracing are not necessarily infected with the same *M. tuberculosis* strain, as their respective index case. If this was found to be the case in an outbreak situation, the potentially wasteful use of resources required in extending screening could be avoided. Perhaps in the future, the detection of a unique *M. tuberculosis* strain in a newly diagnosed patient specimen will indicate limited contact tracing is required. Where such a strain is found in an elderly member of the indigenous population, it is likely the individual has suffered the reactivation of a latent infection, and sources of infection will prove difficult to detect. On the other hand, if a newly diagnosed case was infected with a clustered strain, this might warrant more extensive screening to interrupt the continuing transmission of that strain.

No standard procedures have been developed to assist the identification, screening and tracking of contacts in Scotland. In Greater Glasgow, TB nurses rely on instinct and experience when attempting to elicit names from newly diagnosed cases for contact tracing. Indeed, the absence of a standardised approach has been associated with poor outcome from contact tracing (Reichler *et al.*, 2002). To ensure contact tracing services are of high quality, a consistent approach across all NHS Boards is required.

The contact tracing interview provides an opportunity to acquire information about newly diagnosed patients' behaviour and to identify opportunities when they may have passed the disease to others. Typically, patients are asked to nominate individuals who they have been in contact with in a defined period, prior to their diagnosis. Interviews with patients in this study have highlighted that patients may not necessarily identify at-risk contacts at this point due to difficulties in recalling this information, or because they do not perceive certain acquaintances to be at-risk of infection. Patients' explanatory models for disease transmission were in conflict with those held by the medical profession, therefore it is conceivable this discrepancy will lead to the omission of potentially infected contacts from contact tracing. It is important that contact tracing staff are aware of this conflict, so that

contact tracers approach to eliciting information about contacts can be adapted appropriately.

During retrospective patient interviews, rather than simply collating a list of names, the line of questioning provided an opportunity to understand patients' behaviour and to get a sense of where they may have acquired disease, and passed TB to others. Patients spoke about their social behaviour, where they spent their time, how they knew their friends etc. By discussing their activities in the context of their every-day life, this approach proved effective in identifying previously unrecognised contacts. Perhaps rather than relying on the accuracy of patient recall, prospective contact tracing interviews would elicit the identities of more infected contacts if patients were encouraged to talk about everyday activities. This type of approach to may be worth evaluating in prospective contact tracing investigations, as it resulted in the detection of many previously unrecognised associations in this study. The form of sociological enquiry (semi-structured interviews) used in this study is time consuming and as the method of collecting data is not standardised, and as such, it may not be entirely suitable. However, a contact tracing interview that utilises a standardised questionnaire, with appropriately worded (open-ended) questions to elicit the maximum amount of information from the patient, may prove beneficial.

Furthermore, conducting a contact tracing interview as soon as possible with a newly diagnosed case is important for limiting the spread of disease. Indeed, the majority of infected contacts in Glasgow were detected at initial examination. However, from the patient's perspective, it is unlikely this is the most appropriate time. Often patients are trying to come to terms with their diagnosis, are inundated with new information, are trying to cope with the implications of this diagnosis for themselves and their friends and family, and the embarrassment of contacts knowing about their diagnosis in advance of undergoing screening. It may be appropriate to consider re-interviewing patients at a later time, particularly in instances where cases are known to be members of a cluster. Whereas a standardised questionnaire may be most convenient to use during an initial contact tracing interview, it may be appropriate to interview clustered cases in more detail about their social histories. This approach has been used in the Netherlands for some time. When IS*6110* RFLP typing information becomes available 6 to 8 weeks after diagnosis, cases with non-unique strains are re-interviewed. This approach is favoured because the transmission dynamics in given clusters can be monitored, and interventions to protect public health can be appropriately targeted e.g. screening programmes can be initiated (personal communication, Dr Maruschka Sebek, KNCV). Most recently, this involved screening thousands of individuals frequenting a supermarket in Zeist (Koster *et al.*, 2005).

Of course, gathering such information will only prove useful if it is documented consistently, collated routinely, analysed, and finally, if it can be put to good use for improving current strategies for protecting public health. Contact tracing information has not been routinely gathered in Greater Glasgow for nearly ten years, and re-establishing the collation of information needs to be considered. This process is currently hindered by the fact contact tracing nursing notes are recorded on paper documents, and are filed together with an individual case's file notes. Access to this information could be improved by introducing an electronic data management system. Collating contact tracing information will enable regular evaluation of the programme to be undertaken, which is important for maintaining an effective control strategy, and management of effective resource utilisation.

11.2 Screening in high-risk groups using a social network approach

Since clusters of cases with a genetically indistinguishable strain are (for the most part) believed to represent recently transmitted infection, how can this information be used to detect cases at greater risk of acquiring/developing disease, earlier than they would otherwise present to the health services? Combining molecular information with corresponding epidemiological information from the ESMI scheme, and enhanced information determined through contact tracing pertaining to epidemiological linkage and risk behaviour could prove useful. More accurate descriptions of transmission dynamics, social behaviour and identification of at-risk populations can be used to improve strategies to actively detect infected individuals. In addition to improved contact tracing procedures, at risk populations such as homeless and alcohol misusing individuals can be clearly defined by uncovering social networks, and this information may be used to appropriately target at-risk populations through ad-hoc screening events. This is not entirely novel, as screening initiatives have been previously undertaken in hostels for the homeless in Glasgow, the most recent of which took place in 2002. This was a relatively successful undertaking, however not all newly detected cases were infected with the same *M. tuberculosis* genotype.

In Scotland, the absence of screening initiatives in high-risk groups has been criticised before (Hamlet, 2001), and molecular and epidemiological evidence now provide evidence to warrant consideration of such schemes by NHS Boards, and ensure they are adequately targeted to ensure cost effectiveness. Of course, screening special high-risk populations poses unique challenges, and innovative new ways of overcoming these difficulties are

required. For example, in homeless populations, incentives are used to encourage individuals to participate in screening events. With enhanced epidemiological information, previously unrecognised sites of exposure, e.g. public houses/drinking dens could be targeted. In addition, old solutions are being used to assist new problems, in as much as mobile screening units are being used to identify infection in casual contacts of index cases, by virtue of parking vans with digital x-ray equipment at the site of a TB outbreak. Such an undertaking would bring Scotland in line with countries in the rest of Europe.

11.3 Maintaining an awareness of patient health beliefs

This research study focussed on patient health beliefs and help seeking behaviour, and shed some light on one small component of the highly complex relationship that exists between a patient and their doctor/the health services. Findings from patient interviews are important because the selection of study cases allows the exploration of a relatively new area, which is the health beliefs and help seeking behaviour of TB patients involved in a single TB network (on the basis of having a genetically indistinguishable IS*6110* RFLP pattern).

Cases predominantly presented to medical services of their own volition, and delay in seeking help is known to result in transmission of disease to susceptible individuals. To reduce the period in which disease can spread, awareness raising is likely to be of value. Education about the symptoms of disease, the way in which it can be acquired and the risk factors predisposing individuals to infection is required, not only for contacts of an infected case (should contacts develop symptoms some years later), but also for the general public. It is important that myths surrounding the spread of disease are dispelled (e.g. sharing of contaminated drinking vessels), and also that only high-risk individuals are at risk of tuberculosis. Attitudes and stigma associated with the disease need to be reduced to improve contact identification, and also the uptake of screening by those identified as contacts, and their willingness to return for follow-up appointments. Contact tracing and location based screening events present opportunities to improve knowledge and awareness of the disease. Baseline information from this and other studies could contribute to strengthening of such campaigns.

Further research is required to determine whether doctor delay contributes to delay in initiation of drug therapy, particularly for cases without recognisable risk factors for disease. If this were to prove to be the case, appropriate training and support should be made available as required. The difficulty remains that many individuals have no

identifiable risk factors, and again, further research is required to understand how clustered cases with no known TB contacts acquire disease.

Given that findings from this study suggest screening through social networks of high-risk individuals may prove beneficial, it is important that the health beliefs of such individuals are the subject of further investigation. Do this group hold the same beliefs about disease acquisition and risk as the elderly TB population for example, and if not, are these differences catered for when undertaking contact identification?

11.4 Integration of epidemiological & molecular genotyping information

Since 1997, all culture positive samples received at the Scottish Mycobacterial Reference Laboratory (SMRL) have undergone molecular genotyping. Presently in Scotland, comparative analysis of genotypes can only be undertaken for cases with suspected epidemiological links, to indicate whether cases are likely to have acquired disease from one another. Unfortunately, it is not possible at this time to determine whether a newly diagnosed case is a member of a cluster, by virtue of being infected with a strain genetically indistinguishable from that infecting other individuals. This is due to the fact this would involve comparing the IS*6110* RFLP pattern of the newly diagnosed case with all other patterns identified since 1997. Currently SMRL are not equipped with sufficient resources to undertake such a task.

The most significant drawback of IS*6110* RFLP typing is that it is a very labour-intensive process, and typically six to eight week elapse before DNA can be isolated from culture, for genotyping to commence. Furthermore, although this technique has been enhanced by the development of a standardised IS*6110* RFLP typing methodology, the use of internal and external marker systems and computer software to strengthen analysis, it remains a subjective analysis, whereby the positioning of IS*6110* copies on an RFLP pattern is assessed by eye.

In 2006, a new *M. tuberculosis* genotyping technique, Variable Number Tandem Repeat - Mycobacterial Interspersed Repetitive Units (VNTR-MIRU) typing will be phased into operation at SMRL, replacing IS*6110* RFLP typing and sub-typing technique Spoligotyping (personal communication, Dr F.X.S. Emmanuel). This multi-locus sequence typing technique is a PCR-based method, therefore can rapidly type genomic

material from cultured isolates. It offers many advantages over IS*6110* RFLP typing; the most important of which is its potential to assist in public health interventions, as results can be made available within a matter of days or weeks. This technique has been proven to be as discriminatory as IS*6110* RFLP typing (Hawkey *et al.*, 2003), but benefits from having strain types identified as a fifteen-digit code. This will mean that using the MIRU-typing technique, the identification of clusters can be done with relative ease, as matching 15-digit codes indicate cases are likely to be part of the same transmission pathway. As the prevalence of low copy number RFLP patterns was high in Glasgow, this new typing method should allow the extent of disease due to recent transmission to be more clearly defined, by inclusion of cases with low copy number IS*6110* RFLP patterns and perhaps those for whom only small amounts of genomic DNA were available (MIRU does not require as much genomic DNA as IS6110 RFLP typing). It is hoped this technique will improve the capacity to compare strain types across Scotland. As part of an UK-wide initiative, SMRL together with other United Kingdom reference laboratories are working towards a shared database of MIRU typing data. It is anticipated this will facilitate the identification of clusters across UK borders (personal communication, Dr F.X.S. Emmanuel, Director, SMRL).

To make genotyping information available for public health purposes, it will be important to develop a link between epidemiological information for patients notified to the ESMI scheme (maintained at HPS) and molecular genotyping information held at SMRL. Indeed, the use of unique ESMI identifiers to link datasets has already been piloted during the retrospective analysis of IS*6110* RFLP patterns by the University of Aberdeen, and should be considered for the prospective development of links between datasets (see chapter 3). Options for undertaking such a process on a routine basis will need to be worked through and formalised before this information can be linked.

Responsibility for disseminating information on detectable clusters to NHS Boards will need to be negotiated, as will the action required to be taken by NHS Boards on the back of this information. This study has indicated that ongoing transmission of *M. tuberculosis* in Glasgow involves principally the indigenous population, and strains involved are likely to be endemic. Despite this, the threat of increasing incidence is ever-present, particularly in the event of an increased contribution from the immigrant (as has been observed in England) and HIV co-infected populations. The adoption of a surveillance scheme, which could provide alerts when new strain types emerge, or when excessive numbers of case due to recent transmission are detected within a given time frame, needs to be given further consideration (in particular, would this information be of value to CPHMs in each NHS

Board, and what action would be taken?). In Scotland, respiratory illnesses such as influenza operate similar early warning schemes by monitoring virus sub-types in circulation. This provides an opportunity to implement interventions earlier than would otherwise be possible using epidemiological information alone.

Epidemiological information is required to validate findings of clusters, suggestive of recently transmitted TB in the population. If molecular genotyping information is to be fully utilised, improved access to quality data pertaining to epidemiological linkage is required. As HPS will act as a co-ordinating body, linking molecular and epidemiological data, improved reporting of epidemiological linkage is required through the ESMI scheme, and/or access to contact tracing records and social histories will be required. One option for improving epidemiological linkage involves making revisions to ESMI surveillance forms, in order to explicitly request identifying information for known TB cases. Secondly, contact tracing information could be made available by NHS Boards to assist tracing the spread of disease, particularly when strains move between different geographic areas. Third, the electronic submission of data to assist reporting of epidemiological links determined after completion of the contact tracing interview, may warrant consideration.

Along with the development of links between molecular and epidemiological datasets, it is most important that a consensus view is reached about the utility of such information in routine public health practice. Currently, molecular typing information is sought to confirm whether epidemiologically linked cases have the same genetic fingerprint, and discussions are required to identify how we can extend the utility of molecular epidemiological information, who should have access to the information (CPHM's, chest physicians?) and the perceived value of this information.

11.5 Summary of recommendations

In summary, opportunities to enhance the control of transmission of *M. tuberculosis* include improving current approaches to active case detection by enhancing the detection of casual contacts, and lessening the period of time cases experience symptoms before presenting to medical services. This may be achieved by focussing on the following areas:

- The identification and screening of at-risk individuals during contact tracing needs to be standardised. This may be achieved by developing guidelines at a national level, and adopting standard operating procedures/a protocol at local NHS Board level.

Contact tracing information should be recorded to allow the evaluation of contact tracing practices and policies/standard operating procedures.

- The elucidation and recording of information pertaining to epidemiological linkage needs to be improved if transmission dynamics are to be better understood, and if screening strategies are to be appropriately targeted to high-risk populations.

- High-risk populations for recently transmitted infection should be targeted. Location-based screening approaches should be considered as part of outbreak investigations, perhaps utilising mobile screening units.

- Public and professional awareness raising of tuberculosis is required to reduce the period in which infected cases can spread TB to others.

- Molecular genotyping offers great potential to assist in interrupting the transmission of *M. tuberculosis*. For example, surveillance of *M. tuberculosis* strain types could be used to monitor newly emerging strains and exceedences in cases due to recent transmission, caused by outbreaks of TB. Prompt feedback of such information to public health authorities is required to trigger follow-up action for cluster investigation.

11.6 Future directions

This section outlines some steps that could be taken to address recommendations proposed in the above section.

At the end of March 2006, the National Institute for Clinical Guidance (NICE) for England and Wales published updated guidance on the 'clinical diagnosis and management of TB and measures for its prevention and control'. To improve current approaches to contact tracing, it will be important to reflect on recommendations made in this document, identify whether current practice/policy differs from that currently in place, consider the evidence for the change if any has been suggested, and assess whether these changes are appropriate, given differing epidemiological profiles for Scotland and England and Wales. Resultant changes should be reflected in policy adopted at both national and local level.

As the burden of disease and provision of TB services varies across Scotland, it may be useful if each NHS Board develops a protocol/standard operating procedure or update existing policies to reflect new NICE guidance and when it becomes available some

months from now, Scottish guidance. As this may provide opportunities for NHS Boards to diversify in screening protocol, it may be useful if a single organisation co-ordinated a review of local policy documents to ensure a broadly consistent approach to TB control as possible across the country.

To address the issue of standardisation of contact tracing practices, further discussions could explore the value of a consistent approach and the challenges and shortcoming of taking such an approach. Evidence-based findings from this and other studies could be used to support the development of an agreed strategy. It may prove beneficial to involve the group of health professionals predominantly completing these questionnaires, namely TB nurses, from an early stage. The development of a training course/programme to provide instruction on the completion of questionnaires may assist the introduction of standardised contact tracing practices.

The latter would also provide an opportunity to provide guidance on the completion of ESMI forms, which may lead to improved completion of information pertaining to epidemiological associations between known TB cases. Given that in this study, nurse interviews revealed associations between cases not previously documented on ESMI surveillance forms, it will be important that efforts are made to minimise the failure to capture such information. This may be addressed by engaging those completing ESMI forms in discussions about the challenges faced in providing such information. As a result of such discussions, it may be appropriate to revisit the information sought on each of the three surveillance forms (ESMI form A, B and C), and revise the format accordingly. For example, it may be deemed appropriate that the identity of contacts known to have TB are recorded. The ESMI scheme has been in operation for six years, without any formal audit to establish whether the objectives laid out at its inception are being achieved. Furthermore, it may be worth considering the development of a web-based reporting platform to assist timeous and complete reporting of epidemiological information, and allow contributors to gain immediate access to automated reports. A similar system is currently in development in England, and would bring Scotland in line with such developments. It may therefore be timely to reconvene the working group involved in the development of the ESMI scheme prior to 2000, and canvas for new members as suggested above.

The merits and difficulties associated with conducting location-based screening events in high risk populations need to be debated. Current guidance (Scottish Office Department of Health, 1998) addresses screening in locations such as schools and hostels for the

homeless. However, the rationale for extending screening to lower risk contacts within a group exposed by virtue of spending time in the same location is unclear, and fails to address screening in public houses. When available, results from screening initiatives undertaken using mobile units across Europe should be examined, and an assessment made as to whether the convenience of attending screening at the place of exposure is an effective way of increasing screening uptake, particularly for screening events targeting hard-to-reach populations. This issue could be tabled for discussion at a TB guidelines working group meeting in the first instance.

To increase knowledge and awareness of tuberculosis, it is important that the correct information is made freely available to patients, health professionals and the general public. This can be done by using World TB day (March 24th) to highlight the signs and symptoms of disease to the general public, and to circulate information to health professionals. More often that not, tuberculosis captures the public's attention when an outbreak is reported, and this can be used positively, as an opportunity to raise awareness. To improve health professionals awareness of patient health beliefs, it will be important to continue to disseminate results from this study. In the United Kingdom, and across low-incidence countries, literature relating to TB patient health beliefs is scant, although health professionals are acutely aware of patients misconceptions and the stigma associated with the illness. It is important that further research is undertaken to address patient and health professionals understanding of disease, and that this is made available to assist efforts to better target TB control strategies.

Finally, opportunities to maximise the use of molecular epidemiological information in routine practice requires further discussion. A consensus view should be sought in this regard, and options for achieving the routine linkage of these databases considered. To this effect, discussions are scheduled to take place shortly between HPS and SMRL, and it may be useful to extend these discussions to a group of TB experts, namely the TB guidelines working group. A protocol for utilising molecular epidemiological information should then be developed to assist those who would want to use the information for public health action.

Bibliography

Alland, D. Kalkut, G. E. Moss, A. R. McAdam, R. A. Hahn, J. A. Bosworth, W. Drucker, E. & Bloom, B. R. (1994) Transmission of tuberculosis in New York City. An analysis by DNA fingerprinting and conventional epidemiologic methods. The New England Journal of Medicine, **330,** 1710-1716.

Ansari, S. Thomas, S. Campbell, I. A. Furness, L. & Evans, M. R. (1998) Refined tuberculosis contact tracing in a low incidence area. Respiratory Medicine, **92,** 1127-1131.

Applied Maths GelComparII version 2.0. Kortrijk, Belgium.

Asch, S. Leake, B. Anderson, R. & Gelber, L. (1998) Why do symptomatic patients delay obtaining care for tuberculosis? American Journal of Respiratory Critical Care Medicine, **157,** 1244-1248.

Barnes, P. F. Yang, Z. Preston-Martin, S. Pogoda, J. M. Jones, B. E. Otaya, M. Eisenach, K. D. Knowles, L. Harvey, S. & Cave, M. D. (1997) Patterns of tuberculosis transmission in central Los Angeles. Journal of the Americal Medical Association, **278,** 1159-1163.

Bauer, J. Yang, Z. Poulsen, S. & Andersen, A. B. (1998) Results from 5 years of nationwide DNA fingerprinting of *Mycobacterium tuberculosis* complex isolates in a country with a low incidence of *M. tuberculosis* infection. Journal of Clinical Microbiology, **36,** 305-308.

Behr, M. A. Hopewell, P. C. Anatonio Paz, E. Masae Kawamura, L. Schecter, G. F. & Small, P. M. (1998) Predictive value of contact investigation for identifying recent transmission of *Mycobacterium tuberculosis*. American Journal of Respiratory and Critical Care Medicine, **158,** 465-469.

Behr, M. A. Warren, S. A. Salamon, H. Hopewell, P. C. Ponce de Leon, A. Daley, C. L. & Small, P. M. (1999) Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. The Lancet, **353,** 444-449.

Bennett, D. E. Onorato, I. M. Ellise, B. A. Crawford, J. T. B., S. Byers, R. Kammerer, J. A. & Braden, C. R. (2002) DNA fingerprinting of *Mycobacterium tuberculosis* isolates from epidemiologically linked case pairs. Emerging Infectious Disease, **8,** 1224-1229.

Blaxter, M. & Paterson, E. (1980) Attitudes to health and use of health services in two generations of women in social classes 4 and 5. Report to DHSS/SSRC Joint Working Party on Transmitted Deprivation,

Borgatti, S. P. NetDraw: Graph Visualisation Software 1.0. Harvard: Analytic Technologies.

Borgatti, S. P. Everett, M. G. & Freeman, L. C. UCINET 6.0. Harvard: Analytic Technologies.

Braden, C. R. Templeton, G. L. Cave, M. D. Valway, S. Onorato, I. M. Castro, K. G. Moers, D. Yang, Z. Stead, W. S. & Bates, J. H. (1997) Interpretation of restriction fragment length polymorphism analysis of *Mycobacterium tuberculosis* isolates from a state with a large rural population. Journal of Infectious Diseases, **175,** 1446-1452.

Broekmans, J. F. (1991) The point of view of a low prevalence country: the Netherlands. Bulletin of the International Union of Tuberculosis and Lung Disease, **66,** 179-183.

Brown, K. E. & Campbell, A. H. (1961) Tobacco, alcohol and tuberculosis. British Journal of Diseases of the Chest, **55,** 150-158.

Capewell, S. & Leitch, A. G. (1984) The value of contact procedures for tuberculosis in Edinburgh. British Journal of Diseases of the Chest, **78,** 319-329.

Cave, M. D. Eisenach, K. D. McDermott, P. F. Bates, J. H. & Crawford, J. T. (1991) IS*6110*: conservation of sequence in the *Mycobacterium tuberculosis* complex and its utilizations in DNA fingerprinting. Molecular and Cellular Probes, 73-80.

Centers for Disease Control (2001) Updated guidelines for evaluating public health surveillance systems. Morbidity & Mortality Weekly Report, **50,** 1-35.

Centers for Disease Control and Prevention (2000) Core curriculum on tuberculosis. 1-139.

Chin, D. P. Crane, C. M. Ya Diul, M. Sun, S. J. Agraz, R. Taylor, S. Desmond, E. & Wise, F. (2000) Spread of *Mycobacterium tuberculosis* in a community implementing recommended elements of tuberculosis control. Journal of the American Medical Association, **283,** 2968-2974.

Chrisman, N. J. (1977) The health seeking process: an approach to the natural history of illness. Culture, Medicine and Psychiatry, **1,** 351-377.

Christie, P. & Johnston, F. (2002a) Enhanced Surveillance of Mycobacterial Infections (ESMI) in Scotland: annual report 2000. SCIEH Weekly Report, **36,** 80-83.

Christie, P. & Johnston, F. (2002b) Enhanced Surveillance of Mycobacterial Infections (ESMI) in Scotland: summary for the year 2001. SCIEH Weekly Report, **36,** 306-308.

Churchyard, G. J. Kleinschmidt, I. Corbett, E. L. Mulder, D. & De Cock, K. M. (1999) Mycobacterial disease in South African gold miners in the era of HIV infection. International Journal of Tuberculosis and Lung Disease, **3,** 791-798.

Clancy, L. Rieder, H. L. Enarson, D. A. & Spinaci, S. (1991) Tuberculosis elimination in the countries of Europe and other industrialized countries. European Respiratory Journal, **4,** 1288-1295.

Colebunders, R. & Lambert, M. L. (2002) Management of co-infection with HIV and TB. British Medical Journal, **324,** 802-803.

Cresswell, J. W. (1994) Research design. Qualitative and quantitative approaches. London: Sage Publications.

Cronin, W. A. Golub, J. E. Lathan, M. J. Mukasa, L. N. Hooper, N. Razeq, J. H. Baruch, N. G. Mulachy, D. Benjamin, W. H. Magder, L. S. Strickland, G. T. & Bishai, W. R. (2002) Molecular epidemiology of tuberculosis in a low to moderate incidence state: are contact investigations enough? Emerging Infectious Diseases, **8,** 1271-1279.

Dale, J. W. Al-Ghusein, H. Al-Hashmi, S. Butcher, P. Dickens, A. L. Drobniewski, F. Forbes, K. J. Gillespie, S. H. Lamprecht, D. McHugh, T. D. Pitman, R. Rastogi, N. Smith, A. T. Sola, C. & Yesilkaya, H. (2003) Evolutionary relationships among strains of *Mycobacterium tuberculosis* with few copies of IS*6110*. Journal of Bacteriology, **185,** 2555-2562.

Daley, C. L. Small, P. M. Schecter, G. F. Schoolnik, G. K. McAdam, R. A. Jacobs, W. R. & Hopewell, P. C. (1992) An outbreak of tuberculosis with accelerated progression among persons infected with the human immunnodeficiency virus: an analysis using restriction fragment length polymorphism. New England Journal of Medicine, **326,** 6231-235.

Daniel, T. M. Bates, J. H. & Downes, K. H. (1994) History of tuberculosis. In Tuberculosis: pathogenesis, protection, control, (ed. Bloom, B. R.) Washington, D.C.: ASM Press.

Davies, P. D. O. (2004) Molecular epidemiology unmasks the tubercle bacillus: new techniques reveal new aspects of virulence. Thorax, **59,** 273-274.

Day, S. Ison, C. Ward, H. & Weber, J. (1993) Genetic techniques and surveillance of tuberculosis. The Lancet, **342,** 1559-1560.

de Boer, A. S. Borgdorff, M. W. de Haas, P. E. W. Nagelkerke, N. J. D. van Embden, J. D. A. & D., V. S. (1999) Analysis of rate of change of IS*6110* RFLP patterns of *Mycobacterium tuberculosis* based on serial patient isolates. Journal of Infectious Diseases, **180,** 1238-1244.

de Boer, A. S. van Soolingen, D. & Borgdorff, M. W. (2000) Recurrent tuberculosis due to exogenous reinfection. New England Journal of Medicine, **342,** 1050-1051.

De Bruyn, M. (1992) Women and AIDS in developing countries. Social Science and Medicine, **34,** 249-262.

Department of Health (2004) Stopping tuberculosis in England. An action plan from the Chief Medical Officer.

Department of Health Medicines Control Agency (August 2002) Drug Alert: Class 2 Medicines Recall of Evans Vaccines Ltd. Intradermal, Percutaneous & Intradermal Isoniazid Resistant BCG Vaccine. London.

Dubos, R. & Dubos, J. (1952) Tuberculosis, man and society: the white plague. Boston: Little, Brown and Co.

Duffield, J. Adams, W. Anderson, M. & Leitch, A. (1996) Increasing incidence of tuberculosis in the young and the elderly in Scotland. Thorax, **51,** 140-142.

Dye, C. (2000) Tuberculosis 2000-2010: Control, but not elimination. International Journal of Tuberculosis and Lung Disease, **4,** 146-152.

Dye, C. Scheele, S. Dolin, P. Pathania, V. & Raviglione, M. C. (1999) Global burden of tuberculosis: estimated incidence, prevalence and mortality by country. Journal of the American Medical Association, **282,** 677-686.

Dye, C. Watt, C. J. Bleed, D. M. Mehran Hosseini, S. & Raviglione, M. C. (2005) Evolution of tuberculosis control and prospects for reducing tuberculosis incidence, prevalence and deaths globally. Journal of the American Medical Association, **293,** 2767-2775.

Eisenach, K. D. Crawford, J. T. & Bates, J. H. (1988) Repetitive DNA sequences as probes for *Mycobacterium tuberculosis*. Journal of Clinical Microbiology, **26,** 2240-2245.

Enarson, D. A. & Rouillon, A. (1998) The epidemiological basis of tuberculosis control. In Clinical Tuberculosis, (ed. Davies, P. D. O.) London: Chapman & Hall.

Esmonde, T. F. G. & Petheram, I. S. (1991) Audit of tuberculosis contact tracing procedures in South Gwent. Respiratory Medicine, **85,** 421-424.

Evans, C. C. (1998) Historical background. In Clinical Tuberculosis, (ed. Davies, P. D. O.) London: Chapman & Hall.

Fang, Z. Doig, C. Rayner, A. Kenna, D. T. Watt, B. & Forbes, K. J. (1999) Molecular evidence for heterogeneity of the multiple-drug-resistant *Mycobacterium tuberculosis* population in Scotland (1990 to 1997). Journal of Clinical Microbiology, **37,** 998-1003.

Fang, Z. Kenna, D. T. Doig, C. Smittipat, D. N. Palittapongarnpim, P. Watt, B. & Forbes, K. J. (2001) Molecular evidence for independent occurrence of IS*6110* insertions at the same sites of the genome of *Mycobacterium tuberculosis* in different clinical isolates. Journal of Bacteriology, **183,** 5279-5284.

Farmer, P. (1997) Social scientists and the new tuberculosis. Social Science and Medicine, **44,** 347-358.

Feingold, A. O. (1976) Association of tuberculosis with alcoholism. Southern Medical Journal, **69,** 1336-1337.

Fitzpatrick, L. K. Hardacker, J. A. Heirendt, W. Agerton, T. Streicher, T. Melnyk, H. Ridzon, R. Valway, S. & Onorato, I. (2001) A preventable outbreak of tuberculosis investigated through an intricate social network. Clinical Infectious Diseases, **33,** 1801-1806.

Frankel, S. Davison, C. & Davey Smith, G. (1991) Lay epidemiology and the rationality of responses to health education. British Journal of Medical Practice, **41,** 428-430.

French, C. Croft, J. & Abubakar, I. (2005) Annual report on tuberculosis cases reported in England, Wales and Northern Ireland in 2003.

Gandy, M. & Zumla, A. (2002) The resurgence of disease: social and historical perspectives on the "new" tuberculosis. Social Science and Medicine, **55,** 385-396.

Geng, E. Kreisworth, B. Driver, C. Li, J. Burzynski, J. DellaLatta, P. LaPaz, A. & Schluger, N. W. (2002) Changes in the transmission of tuberculosis in New York City from 1990 to 1999. New England Journal of Medicine, **346,** 1453-1458.

Glasgow Corporation (1957) Glasgow's x-ray campaign against tuberculosis 11th March - 12th April, 1957. Glasgow.

Glynn, J. R. Vynnycky, E. & Fine, P. E. (1999) Influence of sampling on estimates of clustering and recent transmission of *Mycobacterium tuberculosis* derived from DNA fingerprinting techniques. American Journal of Epidemiology, **149,** 366-371.

Godfrey-Faussett, P. (1998) The use of DNA fingerprinting in the epidemiology of tuberculosis. In Clinical Tuberculosis, (ed. Davies, P. D. O.) London: Chapman & Hall.

Goffman, E. (1963) Stigma: notes on the management of spoiled identity. New Jersey: Prentice-Hall Inc.

Golub, J. E. Cronin, W. A. Obasanjo, O. O. Coggin, W. B. S. Moore, K. Pope, D. S. Thompson, D. Sterling, T. R. Harrington, S. Bishai, W. R. & Chaisson, R. E. (2001) Transmission of *Mycobacterium tuberculosis* through casual contact with an infectious case. Archives of Internal Medicine, **161,** 2254-2258.

Gruft, H. Johnson, R. Claflin, R. & Loder, A. (1984) Phage-typing and drug-resistance patterns as tools in mycobacterial epidemiology. American Review of Respiratory Diseases, **130,** 96-97.

Guba, E. G. & Lincoln, N. K. (1994) Competing paradigms in qualitative research. In Handbook of qualitative research, (Eds. Denzin, N. K. and Lincoln, Y. S.) Thousand Oaks, California: Sage.

Hadjichristodoulou, C. Christie, P. & O'Brien, S. (2001) Pulmonary tuberculosis and deprivation in hospitalised patients in Scotland. European Journal of Epidemiology, **17,** 85-87.

Hamlet, N. (2001) A focussed review of tuberculosis control services in Scotland. Glasgow: University of Glasgow.

Harper, J. R. (1999) An old infection: the importance of pulmonary tuberculosis in elderly people in Scotland. Scottish Medical Journal, **44,** 134-136.

Hawkey, P. M. Grace Smith, E. Evans, J. T. Monk, P. Bryan, G. Mohamed, H. H. Bardhan, M. & Pugh, R. N. (2003) Mycobacterial interspersed repetitive unit typing of *Mycobacterium tuberculosis* to IS*6110*-based restriction fragment length polymorphism analysis for investigation of apparently clustered cases of tuberculosis. Journal of Clinical Microbiology, **41,** 3514-3520.

Health Protection Agency (2004) Preliminary Annual Report on Tuberculosis Cases Reported in 2002 in England, Wales, and Northern Ireland. 16

Helman, C. (1985) Culture, Health and Illness. England: John Wright & Sons Ltd.

Hernandez-Garduno, E. Cook, V. Kunimoto, D. Elwood, R. K. Black, W. A. & Fitzgerald, J. M. (2004) Transmission of tuberculosis from smear negative patients: a molecular epidemiology study. Thorax, **59,** 286-290.

Herzlich, C. (1973) Health and illness: a social psychological analysis. London: Academic Press.

Horsburgh, C. R. (2000) The Global Problem of Multi-Drug Resistant Tuberculosis. The Journal of the American Medical Association, **283,** 2575.

Hussain, S. F. Watura, R. Cashman, B. Campbell, I. A. & Evans, M. R. (1992b) Tuberculosis contact tracing: are the British Thoracic Guidelines still appropriate? Thorax, **47,** 984-985.

Irish, C. Baker, T. & Moore-Gillon, J. (1997) Contact tracing smear negative and non-pulmonary tuberculosis in a high-incidence area. Thorax, **52,** A34.

Jasmer, R. M. Hahn, J. A. Small, P. M. Daley, C. L. Behr, M. A. Moss, A. R. Creasman, J. M. Schecter, G. F. Paz, E. A. & Hopewell, P. C. (1999) A molecular epidemiologic analysis of tuberculosis trends in San Francisco, 1991-1997. Annals of Internal Medicine, **130,** 971-978.

Joint Tuberculosis Committee of the British Thoracic Society (1998) Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Thorax, **53,** 536-548.

Joint Tuberculosis Committee of the British Thoracic Society (2000) Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. Thorax, **55,** 887-901.

Kamerbeek, J. Schouls, L. Kolk, A. van Agterveld, M. van Soolingen, D. Kuijper, S. Bunschoten, A. Molhuizen, H. Shaw, P. Goyal, M. & van Embden, J. (1997) Simultaneous detection and strain differentiation of *Mycobacterium tuberculosis* for diagnosis and epidemiology. Journal of Clinical Microbiology, **35,** 907-914.

Kenyon, T. A. Valway, S. E. Ihle, W. W. Onorato, I. M. & Castro, K. G. (1996) Transmission of multi-drug resistant *Mycobacterim tuberculosis* during a long airplane flight. New England Journal of Medicine, **334,** 933-938.

King, L. A. (2002) Epidemiology of tuberculosis in Scotland. University of Edinburgh.

Kline, S. E. Hedemark, L. L. & Davies, S. F. (1995) Outbreak of tuberculosis among regular patrons of a neighbourhood bar. The New England Journal of Medicine, **333,** 222-227.

Klovdahl, A. S. Graviss, E. A. Yaganehdoost, A. Ross, M. W. Wanger, A. Adams, G. J. & Musser, J. M. (2001) Networks and tuberculosis: an undetected community outbreak involving public places. Social Science and Medicine, **52,** 681-694.

Koster, B. Borgen, K. Meijer, H. van der Plas, S. & Kuyvenhoven, V. (2005) Large scale contact tracing after a case of open tuberculosis in a supermarket, the Netherlands, January - February 2005. Eurosurveillance weekly, **10, 1.**

Lalvani, A. Pathan, A. A. McShane, H. Wilkinson, R. J. Latif, M. Conlon, C. P. Pasvol, G. & Hill, A. V. S. (2001) Rapid detection of *Mycobacterium tuberculosis* infection by enumeration of antigen-specific T cells. American Journal of Respiratory and Critical Care Medicine, **163,** 824-828.

Lambert, M. L. Hasker, E. Van Deun, A. Roberfroid, D. Boelaert, M. & Van der Stuyft, P. (2003) Recurrence in tuberculosis: relapse or reinfection. The Lancet Infectious Diseases, **3,** 282-287.

Liefooghe, R. Michiels, N. Habib, S. Moran, M. B. & De Muynck, A. (1995) Perception and social consequences of tuberculosis: a focus group study of tuberculosis patients in Sialkot, Pakistan. Social Science and Medicine, **12,** 1685-1692.

MacGregor, I. M. (1961) The two-year mass radiography campaign in Scotland, 1957-1958 : a study of tuberculosis case-finding by community action. Edinburgh: Her Majesty's Stationery Office.

Maguire, H. Dale, J. W. McHugh, T. D. Butcher, P. D. Gillespie, S. H. Costetsos, S. Al-Ghusein, H. Dickens, A. Marston, L. Wilson, P. Pitman, R. Strachan, D. Drobniewski, F. A. & Banerjee, D. K. (2003) Molecular epidemiology of tuberculosis in London 1995-1997 showing low rate of active transmission. Molecular Pathology, **56,** 121-126.

Marks, S. M. Taylor, Z. Qualls, N. L. Shrestha-Kuwahara, R. J. Wilce, M. A. & Nguyen, C. H. (2000) Outcomes of contact investigations of infectious tuberculosis patients. American Journal Respiratory Critical Care Medicine, **162,** 2033-2038.

McCormick, A. (1993) The notification of infectious disease in England and Wales. Communicable Disease and Public Health, **3,** R19-25.

McGrath, J. W. (1988) Social networks of disease spread in lower Illinois valley: a simulation approach. American journal of physiological anthropology, **77,** 483-196.

McMenamin, J. & Johnston, F. (2004) Enhanced Surveillance of Mycobacterial Infections (ESMI) in Scotland: summary for the year 2002. SCIEH Weekly Report, **38,** 54-56.

McNabb, S. J. N. Braden, C. R. & Navin, T. R. (2002) DNA fingerprinting of *Mycobacterium tuberculosis*: lessons learned and implications for the future. Emerging Infectious Diseases, **8,** 1314-13119.

Moore-Gillon, J. C. (1998) Tuberculosis and poverty in the developed world. In Clinical Tuberculosis, (ed. Davies, P. D. O.) London: Chapman & Hall.

Munsiff, S. S. Bassoff, T. Nivin, B. Li, J. Sharma, A. Bifani, P. Mathema, B. Driscoll, J. & Kreiswirth, B. J. (2002) Molecular epidemiology of multi-drug resistant tuberculosis, New York 1995-1997. Emerging Infectious Diseases, **8,** 1230-1238.

Murray, J. F. (1989) The White Plague: down and out, or up and coming? American Review of Respiratory Diseases, **140,** 1788-1795.

Neely, F. Le Brun, F. O. Davies, A. Yates, S. & Maguire, H. (2004) Contact tracing study for the isoniazid mono-resistant tuberculosis outbreak in North London. Health Protection Agency.

New Jersey Medical School National Tuberculosis Center (2000) TB interviewing for contact investigation: a practical resource for the healthcare worker. New Jersey.

Nolan, C. M. Goldberg, S. V. & Buskin, S. E. (1999) Hepatoxicity associated with isoniazid preventive therapy. Journal of American Medical Association, **281,** 1014-1018.

Nunn, P. Harries, A. Godfrey-Faussett, P. Gupta, R. Maher, D. & Raviglione, M. (2002) The research agenda for improving health policy, systems, performance, and service delivery for tuberculosis control: a WHO perspective. Bulletin of the World Health Organisation, **80,** 471-476.

Olin, J. S. & Grzybowski, S. (1966) Tuberculosis and alcoholism. Canadian Medical Association, **94,** 999-1001.

O'Reilly, L. M. & Daborn, C. J. (1995) The epidemiology of *Mycobacterium bovis* infections in animals and man: a review. Tuber Lung Dis, **76 (Suppl 1),** 1-46.

Orme, I. M. McMurray, D. N. & Belisle, J. T. (2001) Tuberculosis vaccine development. Trends in Microbiology, **9,** 115-118.

Ormerod, L. P. (1992) Results of tuberculosis contact tracing: Blackburn 1982-90. Respiratory Medicine, **87.**

Patel, K. R. (1985) Pulmonary tuberculosis in residents of lodging houses, night shelters and common hostels in Glasgow: a 5-year prospective survey. British Journal of Diseases of the Chest, **79,** 60-66.

Pill, R. & Stott, N. C. H. (1982) Concepts of illness causation and responsibility: some preliminary dat from a sample of working class mothers. Social Science and Medicine, **16,** 43-52.

Pope, C. & Mays, N. (1995) Qualitative research: reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. British Medical Journal, **311,** 42-45.

Power, R. (2002) The application of qualitative research methods to the study of sexually transmitted disease. Sexually Transmitted Infection, **78,** 87-89.

Raviglione, M. C. Harries, A. D. Msiska, R. Wilkinson, D. & P., N. (1997) Tuberculosis and HIV: current status in Africa. AIDS, **11,** S115-S123.

Registrar General for Scotland (2005) Mid-2004 population estimates Scotland. http://www.gro-scotland.gov.uk/files/04mypc-cahb-booklet.pdf.

Reichler, M. R. Reves, R. Bur, S. Thompson, V. Mangura, B. T. Ford, J. Valway, S. E. & Onorato, I. M. (2002) Evaluation of investigations conducted to detect and prevent transmission of tuberculosis. Journal of the American Medical Association, **287,** 991-995.

Ritchie, J. & Spencer, L. (1994) Qualitative data analysis for applied policy research. In Analyzing qualitative research, (Eds. Bryman, A. and Burgess, R. G.) London: Rutledge.

Rose, A. M. C. Watson, J. M. Graham, C. Nunn, A. J. Drobniewski, F. Ormerod, L. P. Darbyshire, J. H. & Leese, J. (2001) Tuberculosis at the end of the 20th century in England and Wales: results of a national survey in 1998. Thorax, **56,** 173-179.

Rubel, A. J. & Garro, L. C. (1992) Social and cultural factors in the successful control of tuberculosis. Public Health Reports, **107,** 626-637.

Rubilar, M. Brochwicz-Lewinski, M. J. Anderson, M. & Leitch, A. G. (1995) The outcome of contact procedures for tuberculosis in Edinburgh, Scotland 1982-1991. Respiratory Medicine, **89,** 113-120.

Rubin, H. J. & Rubin, I. S. (1995) Qualitative interviewing: the art of hearing data. London: SAGE Publications.

Scottish Centre for Infection and Environmental Health (2000) Respiratory infections and meningitis. In Review of Communicable Disease in Scotland 1999, Glasgow: Scottish Centre for Infection and Environmental Health.

Scottish Centre for Infection and Environmental Health (2001) BCG and PPD supplies. SCIEH Weekly Report, **35,** 196.

Scottish Executive Health Office (2005a) Chief Medical Officer Letter: Changes to the BCG vaccination programme. Edinburgh.

Scottish Executive Health Office (2005b) Chief Medical Officer Letter: Supplies of tuberculin for heaf and mantoux testing.

Scottish Office Department of Health (1998) The Control of Tuberculosis in Scotland.

Selwyn, P. A. Hartel, D. Lewis, V. A. Schoenbaum, E. E. Ermund, S. H. Klein, R. S. Walker, A. T. & Friedland, G. H. (1989) A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. New England Journal of Medicine, **320,** 545-550.

Singh Bakhshi, S. & Ali, S. (1995) Knowledge, attitude and behaviour of TB patients. Journal of Public Health Medicine, **17,** 343-348.

Small, P. M. Hopewell, P. C. Singh, S. P. Paz, A. Parsonnet, J. Ruston, D. C. Schecter, G. F. Daley, C. L. & Schoolnik, G. K. (1994) The epidemiology of tuberculosis in San Francisco - a population-based study using conventional and molecular methods. The New England Journal of Medicine, **330,** 1703-1709.

Smith, I. (1995) Define high risk behaviours, not high risk groups. British Medical Journal, **311,** 187a-187.

Sola, C. Filliol, I. Guttierez, C. M. Mokrousov, I. Vincent, V. & Rastogi, N. (2001) Spoligotype database of *Mycobacterium tuberculosis*: biogeographic distribution of shared types and epidemiologic and phylogenetic perspectives. Emerging Infectious Disease, **7,** 390-396.

Sonnenberg, P. Murray, J. Glynn, J. R. Shearer, S. Kambashi, B. & Godfrey-Faussett, P. (2001) HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. Lancet, **358,** 1687-1693.

Sontag, S. (1977) Illness as a metaphor. New York: Allen Lane.

Springett, V. H. (1991) Tuberculosis notification rates in the elderly. Communicable Disease Report, **1,** 149-150.

Styblo, K. (1984) Epidemiology of tuberculosis. In Infections Krankenheit und Ihre Erreger, Mykobakteria und Mykobakteriellen Krankenheiten, (ed. Meissner, G. e. a.): VEB Gustav Fischer Verlag Jena.

Sun, S. J. Bennett, D. E. Flood, J. Loeffler, A. M. Kammerer, S. & Ellis, B. A. (2002) Identifying the sources of tuberculosis in young children: a multistate investigation. Emerging Infectious Disease, **8,** 1216-1223.

Tashakkori, A. & Teddlie, C. (1998) Mixed methodology. Combining qualitative and quantitative approaches. London: Sage Publications.

Teale, C. Cundall, D. B. & Pearson, S. B. (1991) Time development of tuberculosis in contacts. Respiratory Medicine, **85,** 475-477.

The Interdepartmental Working Group on Tuberculosis (1996) The prevention and control of tuberculosis in the United Kingdom: recommendations for the prevention of tuberculosis at local level. 1-40

The National Collaborating Centre for Chronic Conditions (2006) Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. London: Royal College of Physicians.

Underwood, B. R. White, V. L. C. Baker, T. Law, M. & Moore-Gillon, J. C. (2003) Contact tracing and population screening for tuberculosis - who should be assessed? Journal of Public Health Medicine, **25,** 59-61.

Valway, S. E. Sanchez, M. P. C. Shinnick, T. F. Orme, I. Agerton, T. Hoy, D. Scott Jones, J. Westmoreland, H. & Onorato, I. M. (1998) An outbreak involving extensive transmission of a virulent strain of *Mycobacterium tuberculosis*. The New England Journal of Medicine, **338,** 633-639.

van Deutekom,H. Hoijng, S.P. de Haas, P.E.W. Langendam, M.W. Horsman, A. van Soolingen, D. Coutinho, R.A. (2004) Clustered Tuberculosis Cases: Do They Represent Recent Transmission and Can They Be Detected Earlier? American Journal of Critical Care Medicine, **169**, 806-810.

van Embden, J. Cave, M. Crawford, J. Dale, J. Eisenach, K. Gicquel, B. Hermans, P. Martin, C. McAdam, R. & Shinnick, T. (1993) Strain identification of *Mycobacterium tuberculosis* by DNA fingerprinting: recommendations for a standardized methodology. Journal of Clinical Microbiology, **31,** 406-409.

van Soolingen, D. (2001) Molecular epidemiology of tuberculosis and other mycobacterial infections: main methodologies and achievements. Journal of Internal Medicine, **249, 1**-26.

van Soolingen, D. Borgdorff, M. W. de Haas, P. E. Sebek, M. M. G. G. Veen, J. Dessens, M. Kremer, K. & van Embden, J. D. A. (1999) Molecular epidemiology of tuberculosis in the Netherlands: a nationwide study from 1993 through 1997. The Journal of Infectious Diseases, **180,** 726-736.

van Soolingen, D. Hermans, P. W. M. de Haas, P. E. W. & van Embden, J. D. A. (1991) The occurrence and stability of insertion sequences in *Mycobacterium tuberculosis* complex strains: evaluation of an insertion sequence-dependent DNA polymorphism as a tool in the epidemiology of tuberculosis. Journal of Clinical Microbiology, **29,** 2578-2586.

Veen, J. (1992) Microepidemics of tuberculosis: the stone-in-the-pond principle. Tubercle and Lung Disease, **73,** 73-6.

Vynnycky, E. & Fine, P. E. M. (1997) The natural history of tuberculosis: the role of age-dependent risks of disease and the role of reinfection. Epidemiology of Infection, **119,** 183-201.

Wales, J. M. Buchan, A. R. Cookson, J. B. Jones, D. A. & Marshall, B. S. M. (1985) Tuberculosis in a primary school: the Uppingham outbreak. British Medical Journal, **291,** 1039-1040.

Weis, S. (2002) Contact investigations: how do they need to be designed for the 21st century? American Journal of Respiratory and Critical Care Medicine, **166,** 1016-1017.

Weis, S. E. Pogoda, J. M. Yang, Z. Cave, M. D. Wallace, C. Kelley, M. & Barnes, P. F. (2002) Transmission dynamics of tuberculosis in Tarrant County, Texas. American Journal of Respiratory and Critical Care Medicine, **166,** 36-42.

Weis, S. E. Slocum, P. C. Blais, F. X. King, B. Nunn, M. Matney, G. B. Gomez, E. & Foresman, B. H. (1994) The effect of direct observed therapy on the rates of drug resistance and relapse in tuberculosis. New England Journal of Medicine, **330,** 1179-1184.

Whalen, C. C. (2005) Diagnosis of latent tuberculosis infection. Journal of the American Medical Association, **293,** 2785-2787.

Wilson, L. E. (2004) Testing patients with tuberculosis for human immunodeficiency virus infection. Glasgow: University of Glasgow.

World Health Organization (1994) Global tuberculosis programme: framework for effective tuberculosis control. Document WHO/TB/94.179, 1-7.

World Health Organization (2005a) Antituberculosis drug resistance in the world, report number 3.

World Health Organization (2005b) Global tuberculosis control: surveillance planning, financing. WHO report 2005.

World Health Organization International Union Against Tuberculosis and Lung Disease & Royal Netherlands Tuberculosis Association (2002) European framework for tuberculosis control and elimination in countries with a low incidence. European Respiratory Journal, **19,** 765-775.

Zola, I. K. (1966) Culture and symptoms: an analysis of patients' presenting complaints. American sociological review, **31,** 615-630.

Appendix 1

Letter of ethical approval from the Greater Glasgow Primary Care Trust Local Research Ethics Committee, 17th March 2004.

Greater Glasgow Primary Care NHS Trust

Trust Headquarters
Gartnavel Royal Hospital
1055 Great Western Road
GLASGOW G12 0XH
Telephone 0141 211 3600
www.show.scot.nhs.uk/ggpct/

NHS
Greater
Glasgow

Miss A Hopkins
Scottish Centre for Infection and
Environmental Health
Clifton House
Clifton Place
Glasgow
G3 7LN

Date 12 March 2004
Your Ref 03/A/103
Our Ref AMcM/03A103

Direct Line 0141 211 3824
Fax 0141 211 3814
Email anne.mcmahon@
gartnavel.glacomen.scot.nhs.uk

Dear Miss A Hopkins

Research Protocol

Protocol Number: 03/A/103	***Title: An investigation to identify epidemiological links between individuals with a genetically identical strain of mycobacterium tuberculosis (Tuberculosis).***

The Chair of the Greater Glasgow Primary Care NHS Trust Research Ethics Committee (Community & Mental Health) has considered the amendments submitted in response to the Committee's earlier review of your application on Thursday 08 January 2004 as set out in our letter dated 13 January 2004. The documents considered were as follows:

Considered at meeting on Thursday 11 March 2004:

- External advice

The Chair, acting under delegated authority, is satisfied that these accord with the decision of the Committee and has agreed that there is no objection on ethical grounds to the proposed study. I am, therefore, happy to give you the favourable ethical opinion of the Committee on the understanding that you will follow the conditions set out below:

- You do not recruit any research subjects within a research site unless favourable opinion has been obtained from the Committee.

- You do not undertake this research in an NHS organisation until the relevant NHS management approval has been obtained as set out in the Framework for Research

Governance for Health and Community Care. In our Trust this responsibility has been delegated to the Research & Development Directorate.

- You do not deviate from, or make changes to, the protocol without prior written approval of the Committee, except where this is necessary to eliminate immediate hazards to research participants or when the change involves only logistical or administrative aspects of the research. In such cases the Committee should be informed within seven days of the implementation of the change.

- You complete and return the standard progress report form to the Committee one-year from the date of this letter and thereafter on an annual basis. This form should also be used to notify the Committee when your research is completed. In this case the form should be sent to the Committee within three months of completion of the research.

- If you decide to terminate this research prematurely you must send a report to the Committee within 15 days, indicating the reason for the early termination.

- You must advise the Committee of any unusual or unexpected results that raise questions about the safety of the research.

- This favourable ethical opinion encompasses all the "sites/hospitals" within the GGNHS Board area. However, you are requested to send a copy of this letter, along with a Greater Glasgow locality form, to the Ethics Committee of any other Trust, within the GGNHSB area, in which you intend carrying out your research. You are also required to obtain management approval from any other Trust within the GGNHSB area in which you intend carrying out your research.

The project must be started within three years of the date on which the Research Ethics Committee approval is given.

The Greater Glasgow Primary Care – Community & Mental Health Research Ethics Committee is fully compliant with the International Committee on Harmonisation/Good Clinical Practice (ICH) Guidelines for the Conduct of Trials Involving the Participation of Human Subjects as they relate to the responsibilities, composition, function, operations and records of an Independent Ethics Committee/Independent Review Board. To this end it undertakes to adhere as far as is consistent with its Constitution, to the relevant clauses of the ICH Harmonised Tripartite Guideline for Good Clinical Practice, adopted by the Commission of the European Union on 17 January 1997.

May I wish you every success with your study, '***An investigation to identify epidemiological links between individuals with a genetically identical strain of mycobacterium tuberculosis (Tuberculosis)***'.

Yours sincerely

AP **Anne W McMahon**
Research Ethics Coordinator

Appendix 2

INTERVIEW GUIDE

1. To start off with, could you tell me how you came to find out you had TB?
   - How were you feeling?

2. Had you heard of TB before?

3. Have you thought about how you got TB?

4. Do you think you can have TB lying in your system for a while before you start to feel unwell?
   - Have you thought about when you could have picked it up?

5. Do you think there are some places it's easier to catch TB?

6. Have you thought about how long you need to spend with someone to catch TB from them?

7. Were you working (around the time you think you got TB/before you started to feel unwell)?
   - Can you tell me about your job?
   - Have you been/were you doing that job long?
   - Did you have a group of friends from work?

8. Can you talk me through an average day before you had TB?
   - What did you do in the evenings?

9. When you were not working, how did you fill an average day?

10. Have you stayed here long?
    - Who stays here with you?
    - Have you any friends living nearby?
    - Are you friendly with any of your neighbours?

11. Did you have people in to visit you before you had TB?
    - Did you have any family stopping by?

12. Have you ever know anybody with TB?
    - Have you ever known anybody who had a cough or who used to spit up blood?