Tuberculosis in the United Kingdom: epidemiology, immigration and control

Thesis submitted for degree of Doctor of Philosophy

Imperial College London

Manish Pareek

Supervisors:

Professor Ajit Lalvani

Professor Geoffrey P. Garnett

Dr. Peter J. White

Declaration

I hereby declare that the work in this thesis, submitted for examination for the

Doctor of Philosophy degree, is my own work.

Manish Pareek

Abstract

Tuberculosis (TB) continues to be a public health concern in high-income countries, such as the UK, with disease notifications primarily, and disproportionately, occurring in foreign-born immigrants who have a higher TB incidence than the local-born population. Underlying this epidemiology is the synergy of migration from high TB burden regions and the reactivation of imported latent TB infection (LTBI) in the initial years after migration which has refocused attention on immigrant screening for TB. In addition, amongst foreign-born individuals, TB disease primarily manifests as an extrapulmonary phenotype although the relative importance of demographic, host, mycobacterial lineage and environmental factors remains unclear.

International, and national (UK-specific), surveys of the current systems in place for immigrant screening were undertaken. Using empirical UK immigrant screening data obtained from a multi-centre assessment of single-step IGRA testing and a prospective, community-based evaluation of different screening modalities, estimates for LTBI prevalence, yields for screening and the relative performance of different screening methods were computed. Decision-analysis models were constructed, with the data obtained from these empirical studies, to assess the cost-effectiveness of screening for LTBI at different incidence thresholds with different screening tools with and without port-of-arrival chest radiography to enable specific policy recommendations to be made. To assess demographic, mycobacterial lineage and environmental factors associated with specific clinical phenotypes, data from three independent Northern hemisphere TB databases (Birmingham, UK; US CDC and London, UK) were analysed.

High-income countries prioritised screening for active TB but LTBI screening, paradoxically, was limited and those countries that did screen for LTBI varied significantly in whom they targeted and how they screened. Similar patterns were seen in the UK with heterogeneity particularly evident in the incidence threshold at which screening was instigated and the screening tools used. Moreover, screening for LTBI was inversely related to TB burden in the responding area. Data from the empirical studies of immigrant screening revealed that LTBI prevalence varied from 17-30% (depending on screening tool)

and that prevalence was independently associated with increasing TB incidence in country of origin. The proportion of latently infected individuals identified (with LTBI) decreased as the TB incidence screening threshold increased. Health economic analyses revealed that the most cost-effective screening model would be to dispense with port-of-arrival chest radiographic screening and screen for LTBI at an intermediate screening threshold (250 or 150/100000) using single-step IGRA testing (with the QuantiFERON Gold in-tube).

Data on the association of demographic and mycobacterial lineage factors revealed that, on multivariate analysis, extrapulmonary disease was most strongly associated (and more strongly than lineage) with non-White ethnicity. Mycobacterial lineages were geo-ethnically restricted and certain lineages (Euro-American and East African Indian) were preferentially associated with pulmonary disease whilst others, such as the East Asian lineage, were associated with extrapulmonary disease.

In a separate assessment of demographic and environmental factors, local-born Whites had a significantly lower proportion of extrapulmonary disease compared to local-born Non-Whites; both groups had a significantly lower proportion of extrapulmonary disease as compared to foreign-born Non-Whites. In foreign-born Non-Whites, the proportion of cases that were extrapulmonary significantly increased as time elapsed between migration and the development of active TB before stabilising. In the US dataset, states with higher levels of sunshine had significantly lower levels of extrapulmonary TB. In the London cohort, individuals with purely extrapulmonary tuberculosis (14.1 nmol/L) had significantly lower mean vitamin D levels compared to individuals with pulmonary tuberculosis only (25.8 nmol/L)($p=0.0003$). Severe vitamin D deficiency (<20 nmol/L) was significantly more common amongst individuals with purely extrapulmonary tuberculosis than subjects with purely pulmonary tuberculosis ($p=0.002$). For the first time, it was found that Vitamin D deficiency (<20 nmol/L) was independently associated with extrapulmonary disease (OR 4.70; 95% CI 1.22-18.09 for purely extrapulmonary TB, OR 4.32;95% CI 1.26-14.76 for any extrapulmonary TB).

The work contained in this thesis highlights LTBI screening for immigrants is currently very limited but that with empirical data objective cost-effective policy recommendations can be, and have

been, made about which groups to screen and with which diagnostic modalities. The distinct clinical phenotypic presentation of TB disease in immigrants appears to relate primarily to the interaction of demographic (ethnicity) and environmental (vitamin D) factors with mycobacterial lineage playing a role, albeit lesser, in comparison to other factors.

Acknowledgements

I wish to thank my supervisors Professor Ajit Lalvani, Professor Geoff Garnett and Dr. Peter White for providing me with help, encouragement and support during the three years of my PhD.

I wish to acknowledge the helpful discussions with members of the Lalvani lab particularly Saranya Sridhar, David Connell and Katrina Pollock. Similarly I wish to thank Iacopo Baussano for teaching me about TB modelling.

A number of individuals must be thanked for providing me with assistance and data over the last three years including Dr. Ibrahim Abubakar, Dr. John P. Watson, Professor Peter Ormerod, Dr. Onn Min Kon, Marion Bond, Dr. John Innes, Dr. Grace Smith and Dr. Jason Evans.

Specific help in answering the survey questions was gratefully received from TB nurses/professionals in the UK (too many to list!) and TB programme directors from high-income countries.

I wish to thank the Medical Research Council for funding my work.

Finally, I wish to my family – my wife Anubha, my lovely daughter Ishika (who was born during my PhD – and has only known me as a student!), my parents and brother Nilesh for their unflinching love, support, encouragement and belief throughout the period of my PhD. I dedicate this work to you – you made me what I am today and without you I would never have completed this thesis.

Table of Contents

Chapter 1 Background, aims and objectives 22

History of tuberculosis 23

Microbiology and transmission of *Mycobacterium tuberculosis* 23

The natural history of tuberculosis 24

Latent TB infection 24

Active TB disease 26

Methods of diagnosing active and latent tuberculosis 27

Diagnosis of latent TB infection 27

Diagnosis of active tuberculosis 32

Treatment of latent and active TB 35

Treatment of latent tuberculosis infection 35

Treatment of active TB 36

Epidemiology of tuberculosis 37

The global burden of tuberculosis 37

The impact of HIV on TB epidemiology 38

Drug-resistant tuberculosis 40

Epidemiology of tuberculosis in high-income OECD countries 41

Epidemiology of tuberculosis in the United Kingdom 51

Tuberculosis in developed countries: synergy of migration and latent TB infection 58

Concepts of immigration 58

Immigration: patterns and quantification 59

Immigration to the United Kingdom 59

Importance of reactivation of latent TB infection in immigrants 62

Public health aspects of TB control 68

Immigrant screening for TB as a tool to control TB in high-income settings 70

Immigrant screening practices in high-income countries 71

Current methods of immigrant screening for TB in the UK 73

Outcomes of immigrant screening 80

Cost-effectiveness of immigrant screening 87

Patterns of tuberculosis in immigrants in the United Kingdom 93

Influence of demographic factors on clinical phenotype 96

Influence of mycobacterial factors on clinical phenotype 97

Influence of environmental factors on clinical phenotype 100

Aims and objectives 101

Chapter 2 An international evaluation of immigrant screening practices for tuberculosis in high-income countries 103

Introduction 104

Methods 104

Sampling frame 104

Areas of interest in questionnaire 105

Country-specific data 107

Statistical analysis 107

Results 107

Response rate and profile of responding countries 107

Coverage and extent of immigrant screening for active tuberculosis 108

Coverage and extent of immigrant screening for latent tuberculosis 119

Discussion 123

Chapter 3 TB screening of migrants to low TB burden nations: lessons from evaluation of UK practice 129

Introduction 130

Methods 130

Areas of interest in questionnaire 130

Sampling frame 136

Statistical analysis 136

Results 137

Response rate and TB burden of responding PCOs 137

Selection of new-entrants for further screening action 137

Numbers of new-entrants screened and estimated yield for active TB 138

Coverage of screening for latent TB infection and the estimated yield for LTBI 140

Selection of new-entrants to screen for LTBI and adherence to NICE guidance 141

Methods of screening new-entrants for LTBI and adherence to NICE guidance 143

Discussion 145

Chapter 4 Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis 149

Introduction 150

Methods 151

Study design and study centres 151
Study participants 151
Methods of screening 151
Management of symptomatic individuals and positive IGRAs 152
Data analysis 152
Health economic evaluation 153
Results 168
Description of the cohort 168
IGRA results and prevalence of latent TB infection 171
Factors associated with positive IGRA results 171
Relationship between screening thresholds and burden of LTBI detected 172
Health-economic analyses 174
Discussion 181
Chapter 5 Community-based evaluation of immigrant tuberculosis screening using interferon gamma release assays and tuberculin skin testing: observational study and economic analysis 186
Introduction 187
Methods 188
Study design and study centre 188
Study population and participants 188
Methods of screening 188
Management of symptomatic individuals and positive IGRAs 189
Data analysis 190

Health economic evaluation 191

Results 235

Description of the cohort 235

Uptake and results of screening tests 238

Factors associated with positive screening test results 242

Concordance between screening tests and impact of prior BCG vaccination 245

Relationship between screening thresholds and screening test positivity 247

Health-economic analyses 249

Discussion 259

Chapter 6 The influence of ethnicity and mycobacterial lineage on clinical disease phenotypes in tuberculosis 265

Introduction 266

Methods 268

Study design and data source 268

MIRU-VNTR typing 268

Study population, variables and assignment to lineage 268

Definitions of tuberculosis phenotypes 269

Data analysis 270

Results 272

Description of cohort 272

Distribution, and temporal trends, of lineages in cohort 275

Distribution of lineages by geographic origin and ethnic group 276

Association of time since arrival and development of active TB for different lineages 283

Factors associated with main mycobacterial lineages 283

Patterns of disease: the impact of ethnicity and mycobacterial lineage 287

Factors associated with clinical patterns of disease: multivariate impact of mycobacterial lineage 291

Discussion 296

Chapter 7 Vitamin D deficiency plays a role in determining the clinical phenotypic presentation of tuberculosis 302

Introduction 303

Methods 305

Study design and description of data sources 305

Study populations and data variable collection 305

Vitamin D study population, measurement of vitamin D and definition of vitamin D deficiency ... 306

Definitions of patterns of tuberculous disease 307

Data analysis 307

Results 311

Description of cohorts 311

Temporal trends in tuberculous disease 317

Patterns of disease amongst different demographic groups 323

Patterns of disease amongst foreign-born individuals 326

Factors associated with extrapulmonary tuberculosis 329

Sunlight and patterns of disease in the US CDC dataset 334

Association of vitamin D levels and patterns of tuberculosis 338

Discussion 345

Chapter 8 Discussion 354

Main findings of research 355

Chapter 2: An international evaluation of immigrant screening practices for tuberculosis in high-income countries 355

Chapter 3: TB screening of migrants to low TB burden nations: lessons from evaluation of UK practice 356

Chapter 4 Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis 357

Chapter 5 Community-based evaluation of immigrant tuberculosis screening using interferon gamma release assays and tuberculin skin testing: observational study and economic analysis 358

Chapter 6: The influence of ethnicity and mycobacterial lineage on clinical disease phenotype in tuberculosis 358

Chapter 7 Vitamin D deficiency plays a role in determining the clinical phenotypic presentation of tuberculosis 360

Implications of research 360

Policy implications of immigrant screening data 360

Factors determining clinical phenotype of active tuberculosis 362

Limitations of research 363

Future work 365

Chapter 9 Publications and presentations 369

Chapter 10 References 371

Table of tables

Table 1.1 Risk factors for acquiring latent TB infection 25

Table 1.2 Incidence of active tuberculosis (TB) in persons with a positive tuberculin test, by selected risk factors..... 25

Table 1.3 Relative risk for developing active tuberculosis by selected clinical conditions 26

Table 1.4 Organ-specific clinical features of tuberculosis 27

Table 1.5 High income countries in the Organisation for Economic Cooperation and Development (OECD) with country-specific data on TB incidence and changes in TB incidence in two time periods (1995-2002 and 2003-2009) 42

Table 1.6 High income countries in the Organisation for Economic Cooperation and Development (OECD) with country-specific data on TB case notification (absolute numbers) stratified by location of birth for 2000 and 2009..... 47

Table 1.7 Studies which have used restriction fragment length polymorphisms in low/moderate TB burden countries to assess the degree of clustering by location of birth 65

Table 1.8 Studies which have assessed the yields for active tuberculosis through immigrant screening in the United Kingdom..... 82

Table 1.9 Studies which have assessed the yields for latent tuberculosis infection through immigrant screening in the United Kingdom 85

Table 1.10 Studies which have assessed the cost-effectiveness of immigrant screening 89

Table 2.1 Member states categorised as high-income OECD countries 105

Table 2.2 Questionnaire used in the study 106

Table 2.3 Current screening practices for active and latent tuberculosis in OECD high-income countries 109

Table 2.4 Immigrant screening practices for active tuberculosis in high-income OECD countries 112

Table 2.5 Location of, and selection criteria for, screening immigrants for active tuberculosis in selected OECD countries 114
Table 2.6 Initial mandatory screening methods for active tuberculosis in children in selected high-income OECD countries 117
Table 2.7 Initial mandatory screening methods for active tuberculosis in adults in selected high-income OECD countries 118
Table 2.8 Immigrant screening practices for latent tuberculosis infection in high-income OECD countries 120
Table 2.9 Location of, and selection criteria for, screening immigrants for latent tuberculosis in selected OECD countries 121
Table 3.1 Proportion of high and low TB burden Primary Care Organisations that undertake further screening action in new-entrants issued with different port notifications or referred from primary care. 138
Table 3.2 Estimated numbers of cases of active and latent TB identified amongst those primary care organisations that reported both the numbers of immigrants being screened and the yield for active or latent TB 139
Table 3.3 New-entrant sub-groups stratified by age and country of origin that are screened for latent TB infection 142
Table 3.4 Heterogeneity in the protocols and tools (including the uptake of Interferon-gamma-release assays (IGRAs)) amongst those Primary Care Organisations (PCOs) that actually undertake screening for latent TB infection 143
Table 4.1 Screening thresholds considered in the cost-effectiveness analysis 158
Table 4.2 Model assumptions of the health-economic model 161
Table 4.3 Parameters used as input values in the decision model 162
Table 4.4 Costs associated with diagnosis and treatment of active TB 166
Table 4.5 Costs associated with diagnosis and treatment of latent TB infection 167

Table 4.6 Demographics of cohort and risk factors associated with a positive IGRA test among immigrants 170

Table 4.7 Yields for latent TB infection (defined as positive QuantiFERON assay) for different age-groups and at different screening thresholds 173

Table 4.8 Projected cases of active TB and associated costs arising from undertaking immigrant screening at different TB incidence thresholds 176

Table 4.9 Univariate sensitivity analysis of probabilities/proportions used as input variables in the decision model 178

Table 4.10 Univariate sensitivity analysis of costs used as input variables in the decision model 180

Table 5.1 Model assumptions of the health-economic model 201

Table 5.2 Screening tools and thresholds considered in the health economic analysis 202

Table 5.3 Description of immigrant groups in the model who have LTBI and are at risk of progressing to active TB disease 210

Table 5.4 Parameters used as input values in the decision models 213

Table 5.5 Median HIV prevalence amongst immigrants eligible and not eligible for screening at each TB incidence threshold 214

Table 5.6 Test results for immigrants aged ≤35 years who were tested with either all three or two out of three screening tools 218

Table 5.7 Costs (2010 pounds sterling) associated with diagnosis and treatment of active TB 232

Table 5.8 Costs (2010 pounds sterling) associated with diagnosis and treatment of latent TB infection 233

Table 5.9 Demographic characteristics of immigrants screened in the study 237

Table 5.10 Size of tuberculin skin test response stratified by BCG 240

Table 5.11 Univariate and multivariate analysis of factors associated with tuberculin skin test, QuantiFERON Gold in-tube and T-SPOT.TB positivity 243

Table 5.12 Yields for test positivity by different screening tests at different screening thresholds 248

Table 5.13 Projected cases of active TB and associated costs arising from undertaking immigrant screening using different screening tools at different screening thresholds for a hypothetical cohort of 10,000 immigrants over a 20-year time horizon 250
Table 5.14 Univariate sensitivity analysis of probabilities/proportions used as input variables in the decision model 254
Table 5.15 Univariate sensitivity analysis of costs used as input variables in the decision model 257
Table 6.1 Demographic characteristics of individuals with active tuberculosis as compared to those individuals with no MIRU-VNTR value available and where no lineage could be assigned 274
Table 6.2 Distribution of *Mycobacterium tuberculosis* lineages by different world regions of birth 277
Table 6.3 Distribution of Mycobacterium tuberculosis lineages by different demographic groups (stratified by ethnicity and location of birth) 281
Table 6.4 Univariate and multivariate association of demographic, clinical and temporal factors with different *Mycobacterium tuberculosis* lineages 284
Table 6.5 Different clinical phenotypes of active tuberculosis stratified by lineage and demographic group 289
Table 6.6 Univariate and multivariate association of demographic, clinical, temporal and mycobacterial factors with extrapulmonary and extrathoracic patterns of tuberculosis 292
Table 6.7 Univariate and multivariate association of demographic, clinical and temporal factors with lymph node tuberculosis 294
Table 7.1 Demographic characteristics of individuals with active tuberculosis in the Birmingham dataset 314
Table 7.2 Demographic characteristics of individuals with active tuberculosis in the US CDC dataset .. 316
Table 7.3 Patterns of active tuberculosis in different demographic groups between 1980 and 2009 in the Birmingham dataset 318
Table 7.4 Patterns of active tuberculosis in US CDC dataset stratified by time, country of birth and ethnicity 321

Table 7.5 Demographic, clinical and temporal variables associated with different patterns of tuberculosis for Birmingham dataset 330

Table 7.6 Demographic, clinical and temporal variables associated with different patterns of tuberculosis for the whole US cohort and the Non-White ethnic groups 332

Table 7.7 Demographic characteristics of the individuals from the London cohort with active TB included in the analysis as compared against those excluded 339

Table 7.8 Demographic, clinical and temporal variables associated with different patterns of tuberculosis for the London cohort 343

Table of figures

Figure 1.1 Estimated tuberculosis incidence (per 100000) by country for 2009 38

Figure 1.2 Estimated prevalence of HIV in new TB cases by country for 2009 39

Figure 1.3 Tuberculosis incidence in OECD high-income countries between 1995 and 2009..... 44

Figure 1.4 Proportion of cases of active tuberculosis that occur amongst the foreign-born in OECD high-income countries in 2009 50

Figure 1.5 Tuberculosis incidence in selected high-income countries stratified by location of birth..... 51

Figure 1.6 TB incidence and mortality rates in England and Wales between 1913 and 2007 52

Figure 1.7 Map illustrating TB incidence rates in different geographical regions of the UK..... 53

Figure 1.8 Tuberculosis notifications (absolute numbers and incidence) in the United Kingdom stratified by location of birth..... 55

Figure 1.9 Tuberculosis incidence in foreign-born immigrants by time since arrival in the United Kingdom 57

Figure 1.10 Map showing the countries that constituted colonies of the British Empire 60

Figure 1.11 Relationship between the numbers of immigrants (in thousands) entering the UK from the New Commonwealth, Old Commonwealth, Other and Non-European Union countries and the number of UK TB notifications for the period 1985-2009..... 61

Figure 1.12 Flow chart of pathway for TB screening of new-entrants following arrival in the United Kingdom 76

Figure 1.13 Proportion of cases that are extrapulmonary in UK-, and foreign-, born individuals in the UK during the period 2005-2009..... 94

Figure 1.14 Schematic representation of potential factors determining clinical phenotype 95

Figure 1.15 The global population structure and geographical distribution of *M. tuberculosis* from the Gagneux study 99

Figure 3.1 Questionnaire (page one) used in the nationwide evaluation of immigrant screening for TB in the United Kingdom 132
Figure 3.2 Questionnaire (page two) used in the nationwide evaluation of immigrant screening for TB in the United Kingdom 133
Figure 3.3 Questionnaire (page three) used in the nationwide evaluation of immigrant screening for TB in the United Kingdom 134
Figure 3.4 Questionnaire (page four) used in the nationwide evaluation of immigrant screening for TB in the United Kingdom 135
Figure 3.5 Box plot illustrating the median proportion of immigrant new-entrants diagnosed with active TB by low and high TB burden Primary Care Organisations 140
Figure 3.6 Box plot illustrating the median proportion of new-entrants diagnosed with latent TB by low and high TB burden Primary Care Organisations 141
Figure 4.1 Decision tree used for the health economic analysis 155
Figure 4.2 Decision subtree used to describe the events that occur if an individual reactivates to active TB 157
Figure 4.3 Study flow chart 169
Figure 4.4 Line graph illustrating the proportion of immigrants aged 35 and under who test IGRA positive according to TB incidence in their country of origin 172
Figure 5.1 Decision tree outlining the potential screening outcomes (particularly with respect to chest radiography) at port-of-entry for immigrants arriving in the United Kingdom from overseas 192
Figure 5.2 Decision tree used for the health economic analysis of immigrant screening with tuberculin skin test for latent tuberculosis infection (LTBI) after port-of-entry screening 193
Figure 5.3 Decision tree used for the health economic analysis of immigrant screening with interferon gamma release assay (IGRA - either QuantiFERON Gold in-tube or T-SPOT.TB) for latent tuberculosis infection (LTBI) after port-of-entry screening 195

Figure 5.4 Decision tree used for the health economic analysis of immigrant screening with a dual tuberculin skin test plus confirmatory interferon gamma release assay (IGRA - either QuantiFERON Gold in-tube or T-SPOT.TB) approach for latent tuberculosis infection (LTBI) after port-of-entry screening 197
Figure 5.5 Decision subtree used to describe the events that occur if an individual is diagnosed with prevalent active TB at port-of-entry screening or reactivates to active TB from LTBI 199
Figure 5.6 Study flow chart 235
Figure 5.7 Study flow chart outlining uptake of screening tests 239
Figure 5.8 Histogram showing TST induration stratified by BCG vaccination status 240
Figure 5.9 Bar chart showing the proportion of immigrants were IGRA positive stratified by BCG vaccinations status 241
Figure 5.10 Venn diagram showing test results where all three screening tests were undertaken 246
Figure 5.11 Concordance between TST and both IGRAs 246
Figure 5.12 Concordance between QuantiFERON Gold in-tube and T-SPOT.TB 247
Figure 6.1 Flow chart of cases included in data analysis 273
Figure 6.2 Temporal trends in lineages causing active tuberculosis between 2004 and 2009 276
Figure 6.3 Distribution of *Mycobacterium tuberculosis* lineages by country of origin amongst individuals in the cohort 278
Figure 6.4 Distribution of dominant *Mycobacterium tuberculosis* lineages by country of origin amongst individuals in the cohort 279
Figure 6.5 Numbers of cases of active tuberculosis occurring in different demographic groups stratified by *Mycobacterium tuberculosis* lineage 282
Figure 6.6 Distribution of lineage by time since arrival for cases amongst the foreign-born 283
Figure 6.7 Patterns of tuberculosis stratified by demographic group and mycobacterial lineage 290
Figure 7.1 Flow chart of cases included from Birmingham dataset for data analysis 311
Figure 7.2 Flow chart of cases included from US Centres for Disease Control dataset for data analysis 312

Figure 7.3 Temporal trends in disease patterns amongst different ethno-demographic groups in Birmingham dataset 319
Figure 7.4 Temporal trends in patterns of disease amongst different ethno-demographic groups in the US CDC dataset 322
Figure 7.5 Patterns of tuberculosis stratified by location of birth (local or foreign) and ethnic group (White versus Non-White) for the Birmingham and US CDC datasets 325
Figure 7.6 Patterns of tuberculosis stratified by ethnic group, country of birth and time since arrival in the UK for Birmingham cohort 327
Figure 7.7 Patterns of tuberculosis stratified by ethnic group, location of birth and time since arrival in the US for the US CDC cohort 328
Figure 7.8 Scatter plots of annual hours of sunshine against percentage of cases that are extrapulmonary for US mainland states 334
Figure 7.9 Patterns of active tuberculosis amongst different demographic groups and stratified by high and low levels of sunlight exposure 336
Figure 7.10 Patterns of active tuberculosis stratified by time elapsed between arrival in the US and the development of active disease and high and low levels of sunlight exposure 337
Figure 7.11 Flow chart of cases included from the London cohort for data analysis 338
Figure 7.12 Proportion of individuals with pulmonary and extrapulmonary tuberculosis with different vitamin D concentrations at diagnosis in the London cohort 342
Figure 8.1 Algorithm for immigrant screening for TB based on results of thesis 362

Chapter 1 Background, aims and objectives

History of tuberculosis

Tuberculosis (TB) has been a cause of morbidity and mortality in humans for many centuries. Early evidence from the spines of Egyptian mummies, who appeared to have spinal TB, revealed the presence of tubercle bacilli.[1] Even in ancient times, Hippocrates had recognised the clinical features which led to him naming the disease Phitis – meaning consumption in Greek. However, it was in the late 17th century, as the TB epidemic was spreading through Europe that more significant advances started to be made in understanding the bacteria and the clinical spectrum of disease. In the late 19th century, Koch discovered that *Mycobacterium tuberculosis* was the causative organism of TB – a discovery which resulted in him winning the Nobel Prize.[2] In the time since Koch made his ground-breaking breakthrough, our understanding of TB has increased significantly but globally TB remains one of the greatest infectious public health problems more recently exacerbated by the HIV epidemic and the emergence of multi-drug resistance.

Microbiology and transmission of *Mycobacterium tuberculosis*

TB is a chronic granulomatous disease caused by bacteria from the *Mycobacterium tuberculosis* complex which includes *Mycobacterium tuberculosis*, *Mycobacterium bovis*, *Mycobacterium africanum* and *Mycobacterium microtii*.[3] Of these, *M. tuberculosis* is the main cause of TB in humans.

M. tuberculosis is a weakly gram-positive, acid fast, obligate aerobic bacillus 2-4 μm in length and 0.2-0.5 μm in width with a slow generation time of approximately 20 hours.[4] It has a characteristic cell wall which is composed of peptidoglycans and a mixture of complex lipids which consist of mycolic acids, cord factor and wax-D.[5] These facets are thought to contribute to the organism's ability to resist phagocytosis and the action of anti-tuberculous chemotherapy.[6]

Transmission of the bacterium primarily occurs when individuals with active, cavitating, smear-positive, culture-positive pulmonary tuberculosis, cough and produce droplet nuclei ranging in size from 1-5 μm containing up to 400 bacilli each.[7-9] Inhaling these droplets can set up a secondary infection, with

World Health Organisation (WHO) estimates suggesting that a person with active, smear-positive, TB can infect 10-15 other people per year[10] though this is modulated by the effectiveness of ventilation and the duration of exposure.[11-13] It should, however, also be pointed out that individuals with pulmonary smear-negative TB can still be infectious although they are estimated to account for 10-20% of transmission.[14,15]

The natural history of tuberculosis

Latent TB infection

The natural history of tuberculosis is complex and remains incompletely understood. TB infection is initially established when droplet containing bacilli are inhaled and reach the pulmonary alveoli where they are taken up by macrophages.[16] These unprimed macrophages are ineffective at phagocytosing the bacilli which are thus protected within the mycobacterial phagosome.[17,18] The bacilli are then transported via lymphatics to regional lymph nodes but can penetrate the pulmonary vasculature, from where they spread haematogenously to distant sites, including the liver, where the arriving bacilli are phagocytosed by macrophages.[17,18] Several weeks after this initial infection, CD4 T-lymphocytes infiltrate and specific cell-mediated immunity develops as cytokines, including interferon-γ, are released which activate bacilli-containing macrophages and the TB infection is contained in granulomas.[19-21]

Individuals with effective cell-mediated immunity will control the initial infection but live bacilli remain in parts of the body seeded by the early dissemination of the organism – so-called latent TB infection (LTBI).[22,23] This reservoir of latently infected individuals (see Table 1.1 for risk factors for LTBI), approximately a third of the world's population,[24] is much larger than the annual number of active TB cases that arise. These latently infected individuals are at risk of developing active TB disease in the future if immune control fails.[24,25] Evidence suggests approximately 10% of infected immunocompetent people go on to develop active disease over their lifetime – 5% in the first two years after exposure and a further 5% during the remain period of their lifetime.[26-28] Any situation which results in immunosuppression, such as age and the presence of Human Immunodeficiency Virus (HIV), will

increase the proportion of, and rates at which, those individuals who are latently infected will go on to develop active TB disease (Table 1.2 and Table 1.3)[26,27]

Table 1.1 Risk factors for acquiring latent TB infection

Risk factor[28,29]
Close contact with smear-positive TB case
Immunosuppression
HIV infection
Diabetes mellitus
End-stage renal disease
Long-term steroid use
Immunosuppressive drugs
Silicosis
Malnutrition
Old age
Birth in high TB burden region
Healthcare workers
Homeless
Prisoners
Travel to high burden region

Table 1.2 Incidence of active tuberculosis (TB) in persons with a positive tuberculin test, by selected risk factors

Risk factor[28]	Incidence (per 1000 person-years)
Immunosuppressive states	
HIV	35.0-162
Intravenous drug use and HIV positive	76.0
Intravenous drug use and HIV negative	10.0
Weight deviation	
Underweight by 15%	2.6
Underweight by 10–14%	2.0
Underweight by 5–9%	2.2
Weight within 5% of standard	1.1
Silicosis	68.0
Recent infection with TB	
<1 year ago	12.9
1-7 years ago	1.6

Table 1.3 Relative risk for developing active tuberculosis by selected clinical conditions

Risk factor[28]	Relative risk
Diabetes mellitus	2.0-4.1
Silicosis	30.0
Smoking	2.3
End-stage renal disease	10.0-25.3
Gastrectomy	2-5
Jejunoileal bypass	27-63
Solid organ transplant	
Renal	37
Cardiac	20-74
Carcinoma of head or neck	16

Active TB disease

Active TB disease can develop at different points in relation to primary infection with *Mycobacterium tuberculosis*. Following the initial infection, a minority of individuals, particularly those who are immunocompromised, develop progressive primary disease. In this situation, alveolar macrophages are unable to contain the original infection and dissemination of bacilli results in pulmonary or disseminated, miliary, tuberculosis which has a high mortality.[4,10] Alternatively, post-primary (reactivation) active disease can occur.[4] This occurs when the previously effective cell-mediated immune response which contained the latent, dormant bacilli is compromised thereby allowing the bacilli to reactivate to active TB disease.[4,10,29]

TB disease can present in virtually any organ system in the body and therefore the clinical picture can be highly variable. Nonetheless the majority of TB cases, over 75%, are pulmonary with the remainder occurring in extra-pulmonary sites such as lymph node, bone and central nervous system.[29] In HIV-positive individuals, and immigrants arriving in low TB burden countries from high burden regions, the distribution of disease is markedly different and the proportion of extra-pulmonary cases is significantly higher.[30-35]

The clinical features of active TB can be systemic or local. Systemic features, which are usually non-specific, affect most patients with TB irrespective of the site of disease and include malaise, anorexia, weight loss, fevers and night sweats.[36] Local, site-specific, features vary according to the location of disease (see Table 1.4).

Table 1.4 Organ-specific clinical features of tuberculosis

	Organ-specific clinical features[31]	
Site of tuberculosis	**Symptoms**	**Signs (physical findings)**
Pulmonary	Cough >3 weeks (dry or productive), Haemoptysis, Breathlessness, Chest pain	Often nil; occasionally crackles, wheeze over affected areas of lung
Lymph node	Painless swelling of lymph node (usually unilateral)	Firm swelling which becomes fluctuant, No erythema (cold abscess)
Skeletal TB	Bone pain, If spinal TB – symptoms of cord compression (weakness of limbs, impaired sensation)	Bony tenderness on examination
Gastrointestinal TB	Acute right iliac fossa pain, Chronic abdominal pain, Swelling of abdomen (ascites)	Right iliac fossa tenderness or mass, Abdominal distension (ascites), Generalised abdominal swelling
Pericardial TB	Oedema, Breathlessness, Pericardial rub	Raised JVP, Hypotension
CNS TB	Insidious onset, Headache, vomiting, photophobia, altered behaviour/conscious level	Mono/hemi-paresis, cranial nerve palsies, Altered conscious level
Miliary TB	Malaise, fever, anorexia, headache	Variable – may be none
Genitourinary TB	Dysuria, haematuria, nocturia, loin pain	Perinephric mass

Methods of diagnosing active and latent tuberculosis

Diagnosis of latent TB infection

Diagnosing LTBI is of particular importance in those individuals at highest risk of progressing to active TB (Table 1.2 and Table 1.3). However, accurately identifying LTBI is difficult. A low bacterial load and

weak humoral response mean that diagnosis relies on cellular immunological markers of infection.[37] This has meant that for the last 100 years, LTBI has been defined as a positive tuberculin skin test (TST) in an asymptomatic person exposed to tuberculosis with no other evidence of active disease.[38]

TST is undertaken by intradermally injecting purified protein derivative (PPD), a crude mixture of *M. tuberculosis* proteins, and measuring the resulting induration 48-72 hours later.[39] TST therefore measures a cutaneous delayed-type hypersensitivity response; the size of the response determines whether an individual is infected with TB and quantifies their risk of progressing to active TB.[28] Different countries have set various cut-off values to define a positive TST. In general ≥10mm is considered a positive response but in the UK, where bacille Calmette-Guerin (BCG) vaccination is still used in select high-risk populations,[40] positivity is ≥6mm and ≥15mm in BCG unvaccinated and vaccinated individuals respectively.[29]

Although TST is cheap and widely utilised, it is neither specific, as the antigens present in PPD cross react with BCG and environmental mycobacteria, nor sensitive, due to anergy in those individuals with a compromised immune system (such as HIV, iatrogenic immunosuppression and children).[37] A number of recent systematic reviews and meta-analyses have estimated TST specificity and sensitivity to be in the range of 59-78% and 65-77% respectively.[41-43]

Over the last decade, advances in mycobacterial genomics, which have identified a genomic segment (Region of Difference 1) which is deleted from all strains of BCG[44] and the majority of environmental mycobacteria (except *M. Kansasi*, *M. szulgai*, *M. marinum*, *M. flavescens* and *M. gastrii*),[45] have resulted in the development of new blood tests, called Interferon gamma release assays (IGRAs) - an alternative immunodiagnostic approach to the TST for detecting *M. tuberculosis* infection.[46] Currently, two ex-vivo assays are available: the ELISpot which directly counts the number of IFN-γ secreting T cells and the whole blood ELISA which measures the concentration of IFN-γ secretion.[39] Commercially, the ELISpot assay is available as the T-SPOT™.TB (Oxford Immunotec, Abingdon, UK) and the ELISA as the QuantiFERON™-TB Gold In-Tube (Cellestis, Carnegie, Australia). Both IGRAs incorporate two antigens - early secretory antigen target-6 (ESAT-6) and culture filtrate protein-10 (CFP-

10) - which are strong targets of Th1 T-cells in *M. tuberculosis* infection but also deleted from all strains of BCG and the majority of environmental mycobacteria (except *M. Kansasi*, *M. szulgai*, *M. marinum*, *M. flavescens* and *M. gastrii*). [44,45] Therefore, in comparison to the TST, T-cell responses to these antigens are not confounded by prior BCG vaccination and hence a more specific marker of TB infection.[38]

Objectively comparing the diagnostic performance of the IGRAs and the TST is hindered by the lack of a gold standard reference test for LTBI which makes it impossible to directly measure sensitivity and specificity. As a result, investigators have had to utilise proxy markers of LTBI including the degree of exposure to infectious cases,[47-53] and active TB as a surrogate for LTBI. To estimate diagnostic specificity quantitatively, BCG-vaccinated individuals at an ultra-low risk of LTBI due to the absence of epidemiologic risk factors for tuberculosis exposure have been studied. The ELISA has been assessed in larger numbers of individuals in such studies than the ELISpot. In recent systematic reviews and meta-analyses the specificity of the ELISA ranged from 96-99% for the latest generation, in-tube ELISA[41,43] and 86-93% for the ELISpot.[41,43] On the whole, both IGRAs have consistently been shown to have a higher specificity than the TST in the immunodiagnosis of LTBI - particularly in BCG vaccinated populations.

As the evidence base for the performance of IGRAs expands, there is increasing evidence that both the ELISA and ELISpot are more sensitive than the TST. Various research groups (often using different study inclusion criteria) undertaking systematic reviews and meta-analyses have computed that, in immunocompetent individuals (mainly adults), the sensitivity of the ELISA (QuantiFERON Gold in-tube) is in the range of 61-84% whilst ELISpot sensitivity is 72-89%.[41-43,54] Fewer studies have been conducted in immunocompromised populations – particularly HIV positive individuals. Cattamanichi recently summarised the literature and found that the sensitivity of the ELISA and ELISpot were 61% and 72% respectively.[54] Whilst both tests are relatively robust in HIV infection (more so than TST) the ELISpot seems to perform better than the ELISA with a higher sensitivity although a lower proportion of indeterminate results – particularly when CD4 counts are low.[55-58] Independent work by Clark *et al* and

Dheda *et al* has found that CD4 cell counts do not affect ELISpot performance in HIV-positive individuals – both in terms of positivity and the frequency of indeterminate results.[55,59]

However, the experience gained from using the ELISA in HIV-positive individuals seems to be more inconsistent. Raby and colleagues recently evaluated the ELISA in a cross-sectional study of Zambian adults with smear-positive TB, and found that the sensitivity of the ELISA in HIV-positive individuals was 63% which was significantly lower than the 84% sensitivity seen in HIV-negative individuals.[60] In a South African study of HIV-positive individuals comparing the IGRAs and TST in the diagnosis of TB infection, the sensitivity of the ELISA (28%) was lower than that for the ELISpot (61%) and the TST (41%).[61] On the other hand, Balcells *et al* found that in HIV-positive adults the ELISA had a higher positivity rate than the TST and correlated with TB exposure whilst the TST did not.[62] In addition, CD4 cell count did not have an adverse effect on ELISA results. However, other authors have found that in advanced HIV where there are low CD4 cell counts, the performance of the ELISA is compromised. Brock and colleagues conducted a large cross-sectional study of HIV-positive individuals in Denmark and found a significant association between low CD4 cell count and indeterminate ELISA results.[63] Subsequent studies have also confirmed that with declining CD4 count, false negative and indeterminate results become increasingly common which may affect the diagnostic utility of the ELISA in HIV-positive individuals.[60,61,63,64]

One of the historic benefits of TST was the knowledge that a positive result was predictive of progression from LTBI to active TB disease.[27,65-67] As experience with IGRAs has accumulated, it has become apparent that basing the decision to offer chemoprophylaxis (and expect clinical benefits) can only occur if IGRA-positive contacts are truly at increased risk of subsequently progressing to active TB compared with IGRA-negative contacts. Longitudinal data which can answer this important question have recently begun to appear from studies which aim to assess the predictive value of IGRAs.[68-72] Overall most studies suggest that IGRA are predictive of future development of active TB. [68-73] Diel and colleagues computed that over 18-24 months follow-up 8-15% of IGRA positive, as compared to 2-3% of TST positive, individuals progressed to active TB.[73] Haldar and colleagues screened contacts with single-

step QuantiFERON Gold in-tube and found that, over a two-year period of follow-up, 17% of untreated IGRA-positive contacts progressed to active disease as compared to 0% in the IGRA-negative group.[74] By contrast Rangaka et al recently undertook a meta-analysis of the predictive value of IGRAs and concluded that although the incidence rate ratio for IGRA was greater than for TST, neither test had a sufficiently high predictive value for active TB – although the IGRAs could, by virtue of resulting in a smaller number of positive results, reduce the number of individuals considered for chemoprophylaxis.[75] One of the drawbacks of this review, however, was that it primarily included studies from low and medium-income countries making it difficult to generalise the findings to a high-income setting – although, interestingly, in these high-income countries the IGRAs appeared to have a high predictive power for active TB.[75]

In addition to their improved diagnostic performance, IGRAs only require one visit and are a blood test as compared to the often painful intradermal injection. However, one of the main limitations is that indeterminate results do occur most commonly due to a failed positive control which usually reflects underlying cellular immune suppression. Recent work from Diel concluded that, overall, QFN-GIT resulted in a slightly lower proportion of indeterminate results than T-SPOT.TB (2.1% vs 3.8% respectively).[41]

Accumulating evidence has resulted in IGRAs being incorporated into national guidelines as diagnostic tools for LTBI although this is mainly in high-income, low incidence countries[76,77] with WHO recently stating an intention to develop "negative" policy recommendations to discourage the use of commercial IGRAs in low-income and middle-income countries.[78] Even those low burden countries which do use IGRAs, their exact place in diagnostic algorithms is still under debate.[29,77,79] Some countries, such as Canada, advocate IGRAs to be used in confirming positive TST results, others, such as the US, recommend that IGRAs completely replace the TST whilst others (such as the UK) state that either method can be used.[29,79] These differing positions stem from economic analyses[80,81] which have evolved over time yet reflect the dynamic, evolutionary nature of the evidence-base for IGRAs.

Diagnosis of active tuberculosis

Making the diagnosis of active tuberculosis relies on using a combination of modalities including radiology and site-specific specimens for microbiological and histological analysis. It is beyond the scope of this thesis to review in detail all aspects of TB diagnosis and therefore the section below merely summarises the tests available.

Radiology

Appropriate radiological investigations, depending on the site of disease, are usually undertaken soon after an individual presents with clinical features suggestive of TB. In active pulmonary TB, chest-radiography plays an important role in the work-up of patients even though the sensitivity and specificity of the chest radiograph (CXR) alone may not be high enough to allow it to be diagnostic.[36,82-84] A range of CXR abnormalities are seen in pulmonary TB, particularly as the disease progresses, including: infiltrates with or without cavitation (usually in the upper lobes), loss of lung volume, and associated mediastinal or hilar lymphadenopathy.[85] An important caveat is HIV infection where atypical CXR findings may be seen such as normal CXR, infiltrates without cavities in any lung zone and mediastinal or hilar lymphadenopathy with or without accompanying infiltrates.[85]

In extra-pulmonary TB, the CXR is often less useful (unless there is coexisting pulmonary or pleural disease) and more detailed imaging may be required. Computed tomography or magnetic resonance imaging allow the clinician to identify the site of disease, whether it is localised or has spread, the severity of the disease and also any incidental distant sites of disease.[31]

Site-specific samples

Site-specific clinical sampling (primarily microbiological but also histological) allows the identification of *M. tuberculosis* which is key to making a definitive diagnosis of active TB.

In pulmonary TB, sputum samples are required for analysis. Most patients, if expectorating, will be able to provide the necessary three samples of sputum required for lab analysis. If not expectorating sputum, then alternative methods to obtain specimens include induced sputum by administering nebulised hypertonic saline, gastric washings (for children) or bronchoscopy with lavage. In extra-pulmonary TB, site of disease samples (usually tissue or fluid) can also be obtained though this often requires more invasive methods.

Site of disease samples should undergo Ziehl-Nielsen staining to establish whether acid-fast bacilli are present.[29] Approximately 10000 bacilli per ml are required for an individual to be classified smear-positive, so negative sputum smears do not by any means rule out a diagnosis of pulmonary TB.[86] The importance of smear-positivity is that it provides the initial evidence that mycobacteria are present. In addition if an individual is sputum smear-positive, then they are infectious; the higher the bacilli count, the more infectious they are. In extra-pulmonary disease bacillary load is usually very low and patients are generally smear-negative. Overall estimates suggest that smear for acid-fast bacilli has a sensitivity of 34-96% for diagnosing TB with multiple specimens and cavitatory disease increasing sensitivity.[36,85,87]

Irrespective of the results of the smear for acid-fast bacilli, all clinical samples from patients suspected to have active TB should be cultured on solid (Lowenstein-Jensen) or liquid media.[29,85] Culture remains the gold standard diagnostic modality with a sensitivity of 80-85% and specificity of 98%.[29,85,87] Advantages of culture over smear microscopy are that it can detect as few as 10 bacilli per ml, it allows speciation of the bacteria as well as drug-susceptibility testing which ensures optimal therapy is given to the patient.[85] However, owing to the slow growth rate of *M. tuberculosis*, it can take six-eight weeks for detectable growth on solid media (approximately 2-3 weeks on liquid media). However, negative culture results do not rule out a diagnosis of active TB and 20-40% of patients treated for TB are microbiologically negative despite intensive investigations.

As a consequence of this, as well as the time it can take for culture to become positive, samples (especially extra-pulmonary) are also sent for histological and cytological analysis. Histological findings highly suggestive of TB include acid fast bacilli, caseating granulomata with epithelioid macrophages and

multinucleate (Langhan's) giants cells.[88] Cytological and biochemical analysis of pleural, peritoneal, pericardial or cerebrospinal fluid, will usually show a predominant lymphocytosis, a raised protein and low glucose.[85] On their own, these results cannot be diagnostic but in combination with clinical findings and other test results they may provide enough evidence to commence treatment for active TB, particularly when granulomatous histology and cytology are associated with necrosis or caseation.

Other diagnostic tests

In addition to the tests outlined above, additional tests which may be useful in making the diagnosis of TB include nucleic acid amplification tests (NAAT) which measure genetic material unique to *M. tuberculosis* (DNA or RNA target sequences) in smear-positive and smear-negative clinical samples. NAAT provide more rapid detection of the organism and are highly specific but their sub-optimal sensitivity mean that they cannot be used as a rule out test – especially in smear-negative patients.[89] Advantages of NAAT, particularly new line probe assays, over microscopy are that it can provide evidence of *M. tuberculosis* and information about first-line drug resistance, from the sputum of patients, within 24 hrs.[90]

Whilst clinicians may continue to use immunological tests such as TST and IGRA to diagnose TB disease, these tests are unlikely to be particularly helpful as they cannot differentiate active and latent TB.[39] Moreover, evidence suggests that the current IGRAs have false-negative rates in routine practice of 15-25%[39,91,92] and, until tests with higher sensitivity are available,[39,91,93] relying on IGRAs to diagnose active TB would seem misplaced.

Treatment of latent and active TB

Treatment of latent tuberculosis infection

Accurate identification of LTBI enables targeted chemoprophylaxis of infected individuals (close contacts, HIV-positive, immigrants) thereby preventing progression to active disease.[39] Although various chemoprophylactic regimens can be used (six-nine months of isoniazid monotherapy, three months of rifampicin and isoniazid and four months of rifampicin only)[28] most chemoprophylactic experience is with isoniazid monotherapy.

A Cochrane review in HIV-negative individuals found that isoniazid prevented the development of active TB (RR 0.40, 95% CI 0.31-0.52) with no significant difference in efficacy between six and twelve month courses.[94,95] The studies included in the review used the TST to diagnose LTBI and the number needed to treat (NNT) to prevent one case of active TB was 92; comorbidities associated with higher risks of progression, such as HIV co-infection, reduced the NNT.[94] In the UK, however, an alternative regimen of three months of rifampicin and isoniazid is also widely used. The evidence underpinning this regimen is more limited, although a meta-analysis comparing it with six months of isoniazid suggests equal effectiveness.[96] Therefore either regimen is acceptable in treating LTBI.[29,81] In practice, however, shorter treatment durations may be preferable as they are likely to promote adherence and result in fewer adverse events.[29,81]

A decision to test for LTBI implies that chemoprophylaxis will be commenced. Chemoprophylaxis is generally safe, but adverse events, particularly hepatotoxicity, are recognised. Transient elevation of transaminases occur in up to a fifth of patients but do not increase the risk of hepatitis.[28] Estimates suggest that clinical hepatitis occurs in 0.1%-2.3% of patients[28,97] undergoing chemoprophylaxis with isoniazid and the frequency increases with age of the recipient.[97] Similar levels have been described with rifampicin alone and combined rifampicin and isoniazid chemoprophylaxis regimens.[98] Appreciably higher levels of hepatotoxicity have been described with combined pyrazinamide and rifampicin chemoprophylaxis and this regimen is no longer recommended.[99] The resulting risk-

benefit ratio mandates caution in older individuals and therefore in the UK latently infected persons over 35 are not routinely offered chemoprophylaxis although other countries, such as the US, do treat older individuals.[29,81,100]

Treatment of active TB

Treatment of TB disease depends on using a combination of antibiotics for varying durations of time which are determined by the sensitivity of the organism and the site of disease.

In cases where the organism is fully-sensitive, four main antibiotics are used: rifampicin, isoniazid, pyrazinamide and ethambutol. Combination therapy is used as it prevents the emergence of resistance and because the drugs have different modes of action. Different durations of therapy have been reviewed and the general consensus is that therapy for less than six months results in higher relapse rates than treatment of >6 months.[101] Therefore, standard therapy for most pulmonary and extra-pulmonary disease (except TB of the central nervous system) is 6 months in duration and consists of a two month initiation phase with daily rifampicin, isoniazid, pyrazinamide and ethambutol followed by a four month continuation phase of daily rifampicin and isoniazid.[29,102] Meningeal TB is more difficult to treat as the anti-tuberculous therapy must penetrate the cerebrospinal fluid. UK and US guidelines recommend a twelve month course of therapy (two months of daily rifampicin, isoniazid, pyrazinamide and ethambutol followed by a ten month continuation phase of daily rifampicin and isoniazid).[29,102] By contrast, treatment of drug-resistant TB is challenging, expensive and highly individualised depending on the specific pattern of drug-resistance.[29,81]

.

Epidemiology of tuberculosis

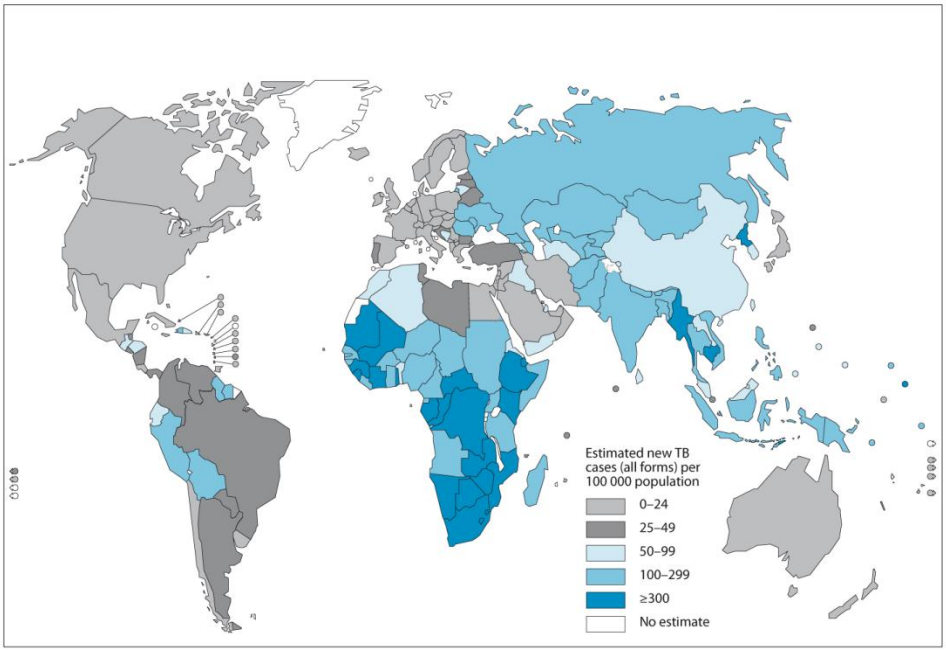
The global burden of tuberculosis

The WHO estimates that one-third of the world's population is latently infected with tubercle bacilli (but do not have overt clinical disease) and, in 2009, this reservoir of LTBI partly gave rise to an estimated 9.4 million (range 8.9-9.9 million) cases of active TB amongst which there were 1.7 million deaths.[103]

Asia and Africa accounted for 55% and 30% of cases respectively with other world regions making up much smaller proportions (Eastern Mediterranean 7%, Europe 4% and Americas 3%).[103] Over 80% of the world's incident TB cases are concentrated in 22 high-burden Asia and Sub-Saharan African countries;[103] in absolute numbers India and China, the two most populous countries, had most TB notifications reporting a total of 3.3 million cases.[103]

Overall global TB incidence (Figure 1.1), in 2009, was 137 cases per 100000 population which has been declining by a relatively modest 1% per annum since peaking at 140/100000 in 2004.[103] At present, incidence rates are falling in all regions of the world except Southeast Asia where incidence remains stable.

Figure 1.1 Estimated tuberculosis incidence (per 100000) by country for 2009



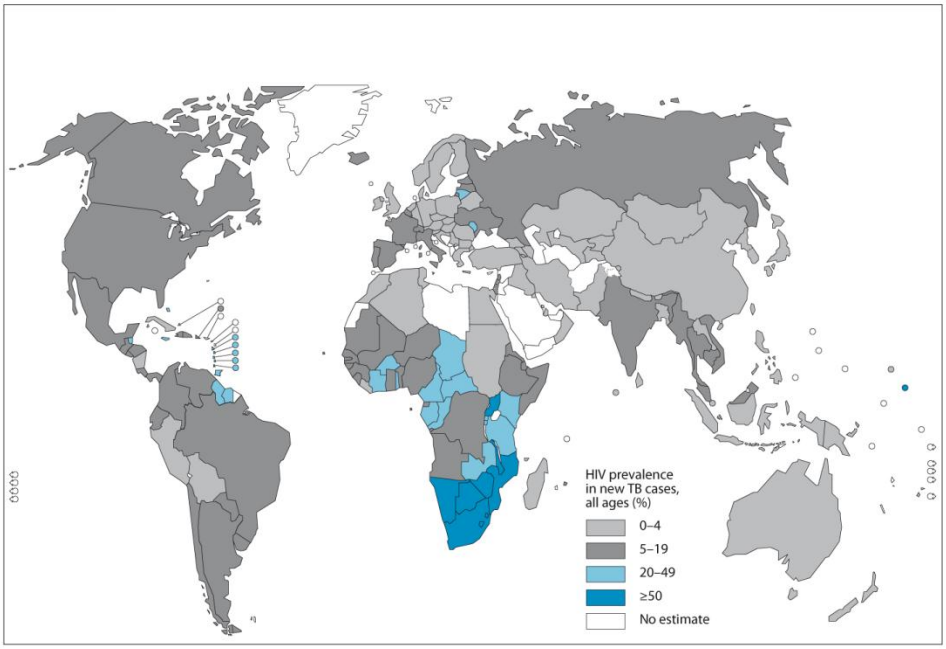
Footnote

[1]Data obtained from WHO global report[103]

The impact of HIV on TB epidemiology

Although most TB cases occur in Asia, the highest per-capita incidence rates are actually seen in Sub-Saharan Africa – as a result of TB-HIV coinfection.[103] On a global level approximately 12% of TB cases are co-infected with HIV although this ranges from as low as 1.6% in the Eastern Mediterranean region to 37% in Sub-Saharan Africa[104] (Figure 1.2) - a region which alone makes up 80% of all TB-HIV cases.[104]

Figure 1.2 Estimated prevalence of HIV in new TB cases by country for 2009



Footnote

[1]Data obtained from WHO global report[103]

Whilst the association between HIV infection and TB is well-recognised, the mechanism underlying this observation remains unclear. Earlier work suggested that this close relationship was primarily because HIV, which adversely affects cell-mediated immunity, increased the rate of reactivation from LTBI to active TB from 10% (over a person's lifetime) to 10% per annum.[27,105-107] However emerging data, using molecular genotyping, has suggested that HIV has a larger effect on re-infection (recurrent disease caused by a new infection) rather than relapse (recurrent disease caused by same strain).[108,109] In a recent systematic review and meta-analysis of six studies, Houben and colleagues[110] found that TB cases in HIV-positive individuals were significantly more likely to be clustered (indicating recent transmission), particularly with increasing age, as compared to HIV-negative individuals. Although this finding emphasises the importance of timely diagnosis and treatment of active TB cases (as compared to chemoprophylaxis for LTBI) it should be borne in mind that the overall numbers of patients in this

review were relatively small, the findings particularly dependent on the results of one study,[111] and, finally, the conclusions appeared to be particularly relevant to individuals aged over 50 years making it unclear what is the primary driving factor in younger HIV-positive individuals.[110]

Drug-resistant tuberculosis

Drug susceptibility testing has become increasingly important as drug-resistant TB has become more widespread. Factors leading to the emergence of resistance include non-completion of therapy through non-compliance, incorrect therapy being commenced by healthcare workers or because the drugs are not of the requisite quality.[112]

Different patterns of drug resistance are recognised including monoresistance which is resistance to one agent, multi-drug resistance (MDR-TB) which is in-vitro resistance to rifampicin and isoniazid[113] and, most recently, extensive drug resistance (XDR-TB) which is defined as resistance to a second-line injectable agent, a fluoroquinolone and rifampicin and isoniazid.[113] Estimates from the WHO suggest that, in 2008, 3.6% of incident TB cases are MDR-TB with over 50% of cases occurring in India and China.[114,115] However, the highest proportions of cases are seen in Eastern Europe (especially parts of the Russian Federation) and Central Asia with figures ranging from 3.8% (Turkmenistan) to 22.3% (Azerbaijan) and 18.4% (Turkmenistan) to 61.6% (Tajikistan) for new, and previously treated, cases respectively. In terms of XDR-TB, 58 countries have now reported cases although the exact prevalence is unknown.[114,115]

Epidemiology of tuberculosis in high-income OECD countries

The preceding section has focused on the global epidemiology of TB and, rightly, the significant burden of disease in low-income, high-burden, countries. However, TB also continues to be an important public health issue in high-income countries. Amongst the 31 high-income countries in the Organisation for Economic Cooperation and Development (OECD)[116] (see table 1.5 - defined by the World Bank as those countries with a gross national income of >12,276 dollars[116]) TB incidence, in 2009, ranged from 2.4 (Iceland) to 90 (South Korea) cases per 100000 population (2.4-30.7 per 100000 if countries in Asia excluded).[103,117-122] Although improvements in public health have clearly reduced TB incidence to historic low levels, if one focuses on the rates of change in these high-income countries there is evidence that TB control may be under threat.

Table 1.5 High income countries in the Organisation for Economic Cooperation and Development (OECD) with country-specific data on TB incidence and changes in TB incidence in two time periods (1995-2002 and 2003-2009)

Country	TB incidence in 2009 (per 100000 population)	Annual percentage change in TB incidence (between 1995-2002)	Annual percentage change in TB incidence (between 2003-2009)
Australia	6.4	-0.7	4.4
Austria	8.5	-2.9	-4.2
Belgium	9.6	-1	-1.2
Canada	4.7	-2.6	-1.4
Czech Republic	6.7	-4.3	-5.9
Denmark	6.0	-1.2	-2.5
Estonia	30.7	3.6	-4.9
Finland	7.9	-3.8	0
France	8.2	-3.7	-2.5
Germany	5.4	-4.7	-5.4
Greece	5.2	-5.1	-1
Hungary	14.4	-4.3	-6.2
Iceland	2.8	-4.7	9.2
Ireland	10.6	-2.3	0.6
Israel	4.8	1.2	-5.9
Italy	6.5	-2.5	-2.4
Japan	21	-2.9	-3.9
South Korea	90	-2.5	1.2
Luxembourg	5.5	-1	-7.7
Netherlands	7.0	-2.1	-2.1
New Zealand	7.0	-2.5	-5.2
Norway	7.6	0.2	0.4
Poland	21.6	-4.3	-2.5

Portugal	27.0	-2.8	-4.6
Slovak Republic	9.3	-4	-7
Slovenia	9.3	-4.1	-5.4
Spain	16.6	-2.1	-0.9
Sweden	6.8	-3.5	7.3
Switzerland	7.3	-2.8	-2.2
United Kingdom	14.6	1.6	3
United States	3.8	-4.9	-3.6

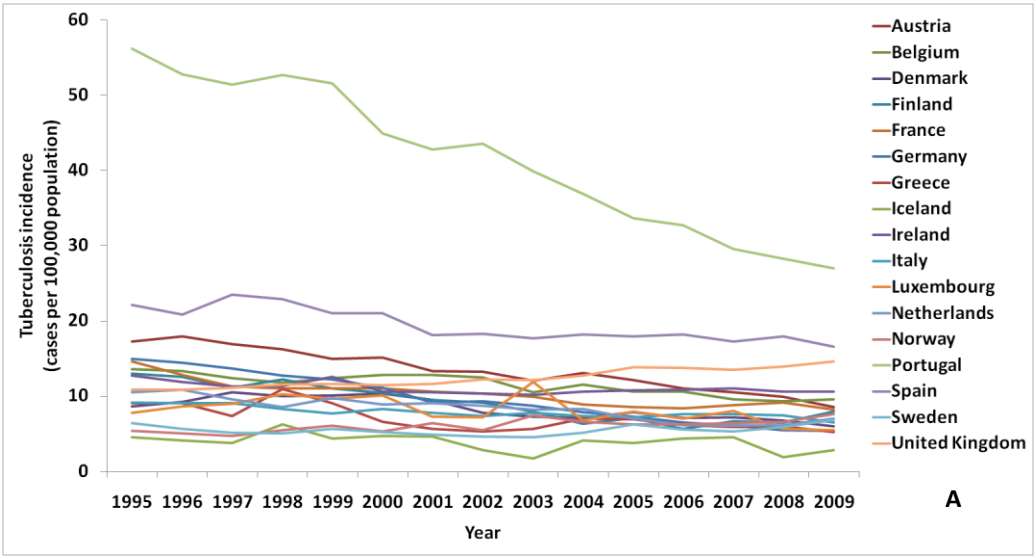
Footnote

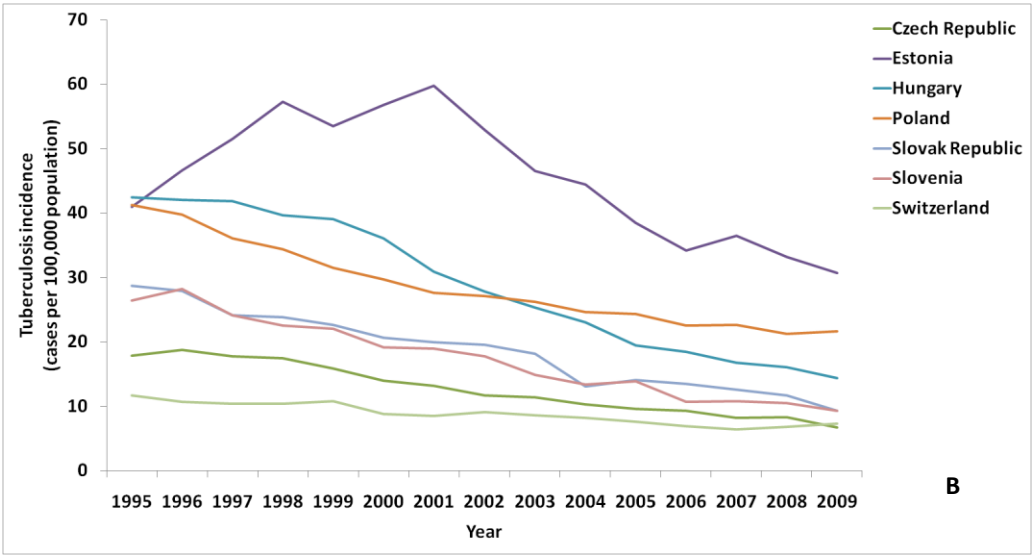
[1]Data obtained from national and international TB reports[117,120-136]

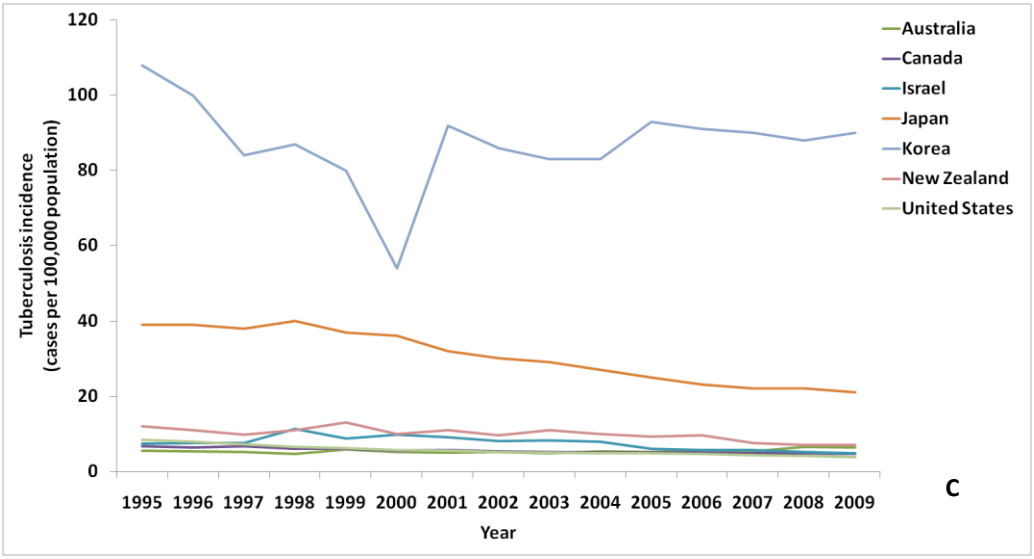
Surveillance data suggests that between 1995-2002 TB incidence in the OECD high-income countries fell annually by a median of 2.8% (interquartile range -4.1 - -1.2%, range -5.1-+3.6%) but the rate of decline had slowed to 2.5% (interquartile range -4.9 - 0%, range -7.7-+9.2%) between 2003-2009.[117,120-136] This slowing in the rate of decline has been highlighted by previous surveillance reports focusing on European countries[130,137] and by the WHO in its 2009 report on the state of the TB epidemic. This is particularly significant as it makes elimination (defined as an incidence of <1 case per 1,000,000) an even more distant prospect.[138]

One of the difficulties of extrapolating from overall trends to a diverse group of countries (Table 1.5 and figure 1.3) is that it masks the heterogeneous state of the TB epidemic in individual nations. Indeed it is evident from closer examination of surveillance data (especially from those high-income nations outside Asia) from the last decade that unique quantitative changes in TB notifications have resulted in the previous downward trends in overall TB notifications slowing, stabilising or, in some cases, reversing (see Figure 1.3 and table 1.6).

Figure 1.3 Tuberculosis incidence in OECD high-income countries between 1995 and 2009







Footnote
Data obtained from national and international TB reports[117,120-136]

(A) European Union countries in the West

(B) Countries in the European Union (East) and Non-European Union European countries

(C) Non-European high-income countries

However, even within individual countries overall trends mask a crucially important dichotomy. As socio-economic conditions, medical care and public health have improved, notifications (and

incidence rates) in the indigenous local-born population have fallen relatively sharply, while those from the overseas-born migrant population have either fallen at a much slower rate (compared to local-born individuals) or, in some countries, actually risen (such as in the United Kingdom and Australia) (Table 1.6).

Table 1.6 High income countries in the Organisation for Economic Cooperation and Development (OECD) with country-specific data on TB case notification (absolute numbers) stratified by location of birth for 2000 and 2009

Country	2000		2009		Percentage change in cases of tuberculosis in local born population (2000-2009)	Percentage change in cases of tuberculosis in foreign born population (2000-2009)
	Local born population	Foreign born population	Local born population	Foreign born population		
Australia	236	814	151[1]	960[1]	-36	17.9
Austria	884	334	392	234	-55.7	-29.9
Belgium	758	508	524	496	-30.9	-2.4
Canada	568	1102	570	1003	0.4	-9
Czech Republic	1299	143	566	136	-56.4	-4.9
Denmark	198	350	114	214	-42.4	-38.9
Estonia	608	183	333	78	-45.2	-57.4
Finland	490	47	287	126	-41.4	168.1
France	3198	2193	2393	2488	-25.2	13.5
Germany	6017	3047	2347	1877	-61	-38.4
Greece	635	68	319	254	-49.8	273.5
Hungary	3521	56	1396	33	-60.4	-41.1
Iceland	8	5	4	5	-50	0
Ireland	354	49	267	191	-24.6	289.8
Israel	91	500	48	294	-47.3	-41.2
Italy	3511	1201	1793	1838	-48.9	53
Japan	33,720	837	22,808	938	-32.4	12.1
South Korea[2]	-	-	-	-	-	-
Luxembourg	17	21	11	16	-35.3	-23.8
Netherlands	516	879	308	842	-40.3	-4.2
New Zealand	105[3]	230[3]	78	220	-25.7	-4.3
Norway	70	168	40	323	-42.9	92.3
Poland	9477[4]	16[4]	8183	53	-13.7	231.3

Portugal	4047	434	2434	437	-39.9	0.7
Slovak Republic	1103	8	499	7	-54.8	-12.5
Slovenia	286	94	133	55	-53.5	-41.5
Spain	3734	451	4895	2330	31.1	416.6
Sweden	151	305	114	513	-24.5	68.2
Switzerland	228	341	75	258	-67.1	-24.3
United Kingdom	2172	3451	2299	6010	5.8	74.2
United States	8648	7619	4571	6854	-47.1	-10

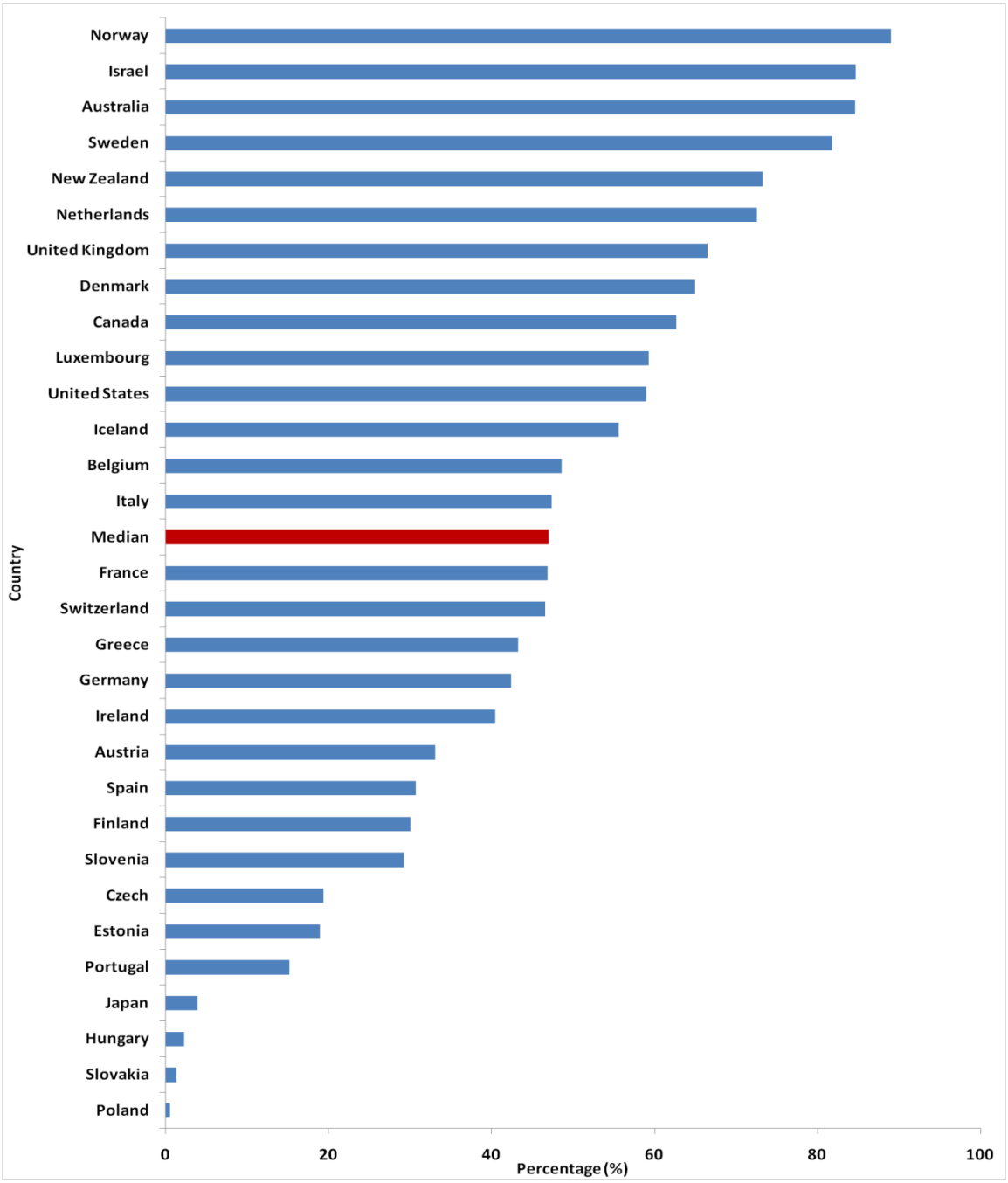
Footnote

[1]Most recent data available was for 2007
[2]Data stratified by location of birth not available
[3]Most historic data available was for 2001
[4]Most historic data available was for 2004
[5]Data obtained from references[105,108-124,127]

This is borne out by surveillance data. Amongst high-income countries, between 2000 and 2009, TB notifications (in absolute numbers) in the local born population decreased by a median 41.9% (IQR -50.0 – 25.7%, range -67.1% - 31.1%) as compared to 3.3% (IQR -24.3– 68.2%, range -57.4% - 416.6%) in the foreign-born population.[117,121-136,139] Indeed of the 30 countries that provided country of birth specific data, 13 actually reported increases in TB notifications in the foreign-born population. As a consequence of these temporal changes, foreign-born individuals, in 2009, despite making up a minority of the overall population in high-income countries, accounted for a median of 47.0% of cases (IQR 29–65%, range 1%-89%) (Figure 1.4) and, amongst those countries which provided data, had TB incidence rates which were 5.5-29.3 times higher than the local-born population (see Figure 1.5).[117,121-136,139] Similar findings were highlighted by a 2000 EURO-TB report which found that in 11 European countries providing accurate population denominator data, foreign-born individuals had a TB incidence which was seven times greater than in local-born individuals; rate ratios ranged from 2.8 (Slovenia) to 37 in the Netherlands and in Norway.[130] At this juncture it should be emphasised, however, that surveillance reports in most high-income countries do not distinguish those individuals who are local-born individuals but from different ethnic groups – even though incidence may differ significantly as compared to the local born White indigenous population.[140]

Nonetheless the inference that can be drawn from TB data in high-income countries (especially those outside Asia) is that a high, and increasing, proportion of cases now occur amongst those individuals who were born in, and have then migrated from high TB burden regions of the world.[117,120-136,139,141-146]

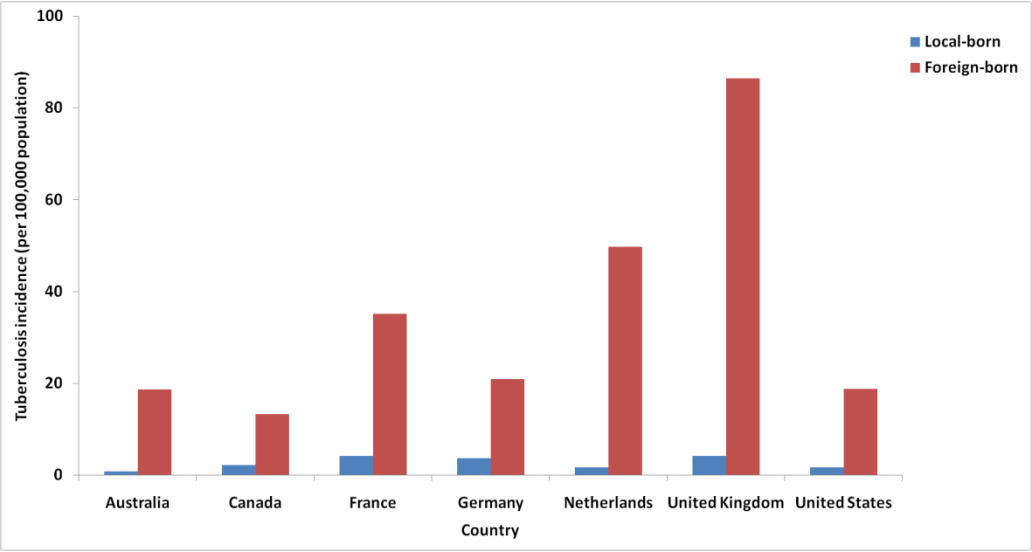
Figure 1.4 Proportion of cases of active tuberculosis that occur amongst the foreign-born in OECD high-income countries in 2009



Footnote

[1]Data obtained from national and international TB reports[105,109-124,127]
[2]Data not available for South Korea

Figure 1.5 Tuberculosis incidence in selected high-income countries stratified by location of birth



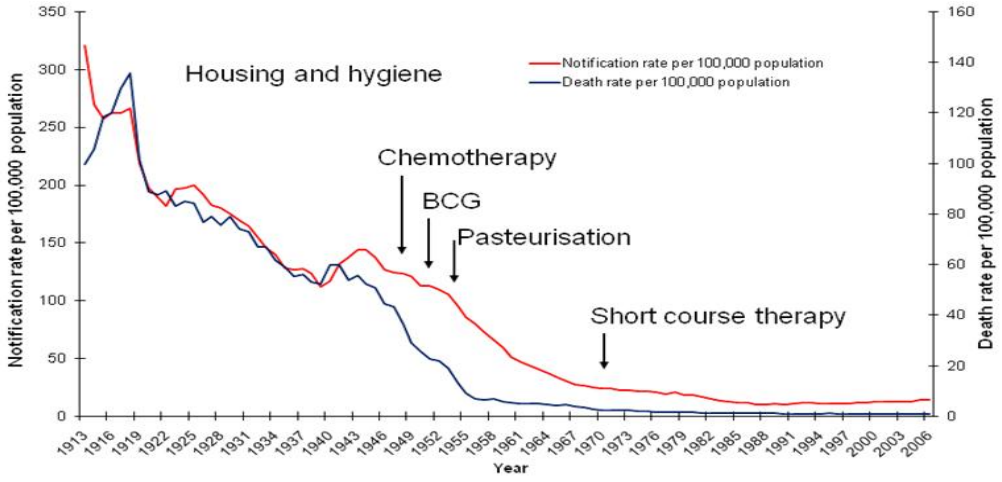
Footnote

[1]Data obtained from national and international TB reports[119,121,122,147-150]

Epidemiology of tuberculosis in the United Kingdom

At the start of the 20th century tuberculosis was a cause of significant morbidity and mortality in the United Kingdom. In 1913 (when surveillance data collection and reporting began) UK TB incidence was 320 cases per 100000 with over 117,000 cases notified.[151] Thereafter, for much of the 20th century, TB incidence fell sharply (by 97%) due to improvements in public health and the initiation of anti-tuberculous therapy reaching a nadir of 10.1 cases per 100000 (5184 cases in England, Wales and Northern Ireland – data not available for Scotland) in 1987 (see Figure 1.6). However since then TB incidence, and absolute notifications, in the UK have been rising year-on-year. Between 1987 and 2009, absolute TB notifications in the UK increased by 74% from 5184 to 9040 cases whilst incidence increased by 45% from 10.1 to 14.6 per 100000[140,152] representing one of the largest increases in notifications and incidence seen in all high-income countries.[142,153]

Figure 1.6 TB incidence and mortality rates in England and Wales between 1913 and 2007

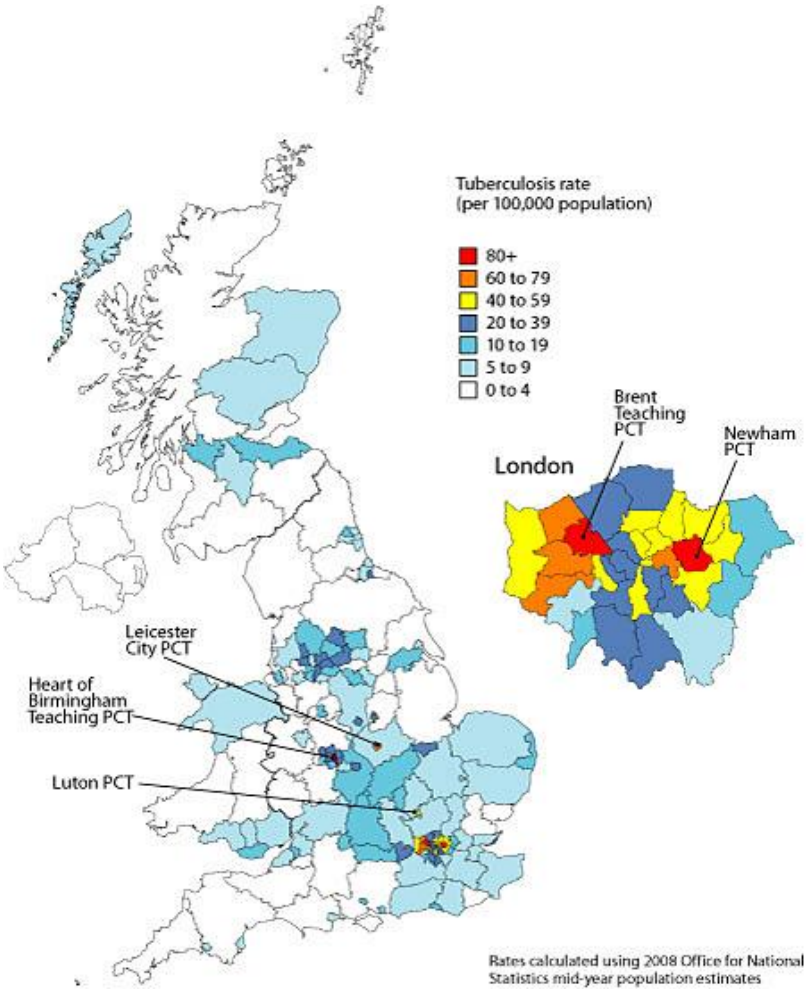


Footnote

[1]Data obtained from national historic TB reports[138,142119,121,122,147-150]

Although TB has become increasingly common in the UK it remains, in the main, a geographically restricted disease (Figure 1.7). Most cases (92%) occur in England and, within England, it is primarily the urban centres which have the highest burden of TB.[140,154] Of the urban centres, TB is particularly concentrated in London which alone accounts for 38% of all cases and, as a whole, has a TB incidence of 44.4 per 100000;[140] certain areas within London such as Newham, Brent and Ealing have extremely high TB incidence rates of 117, 109 and 70 per 100000 respectively.[154]

Figure 1.7 Map illustrating TB incidence rates in different geographical regions of the UK



Footnote

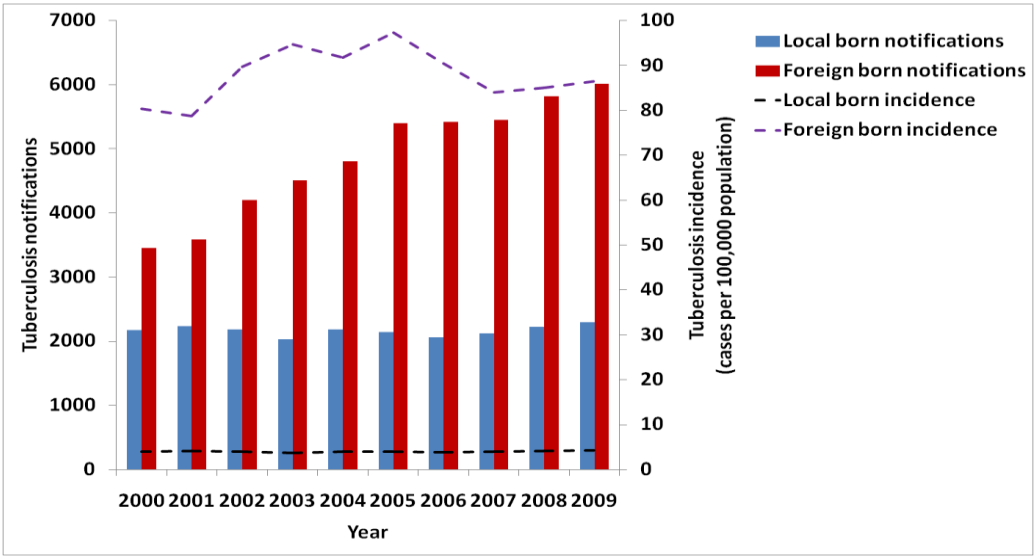
[1]Data obtained from national TB report[140,143]

If we return to consider the increasing notification rate in the UK, it is clear, as with other high-income countries, that the overall figures mask an important disparity. Between 2000 and 2009, TB notifications in the local born population were relatively static (5.8% increase) whilst those amongst overseas-born individuals increased more sharply by 74.2%.[130,140] As a result, in 2009, overseas-born individuals bore the major burden of TB in the UK accounting for 66% of all cases

with a TB incidence which is over 20 times that of UK-born individuals (86.4 cases per 100000 p.a. vs. 4.2 cases per 100000 p.a. respectively (Figure 1.8);[130,140] the TB incidence in the non-UK born Indian, Pakistani, Bangladeshi (collectively known as the Indian Subcontinent) and Black-African subgroups is even higher: 235, 234, 133 and 273 cases per 100000 p.a. respectively.[140] In 2009 these four groups alone accounted for over three-quarters, and half, of foreign-born and all cases respectively.[140] Therefore, whilst domestic TB incidence may be at stable, low, levels especially in the indigenous, UK born, White population the disproportionately large, and increasing, number of TB cases primarily occurring in foreign-born individuals has the potential to jeopardise the success of national TB control programmes.[155,156]

However, the individuals that are often neglected are the UK born non-White group. As with the heterogeneity seen in incidence rates amongst the foreign-born of different ethnicities, UK-born individuals from different ethnic groups also display high variability. In 2009, UK-born individuals of non-White ethnicity had a TB incidence which ranged from 9-55 per 100000 as compared to 3 per 100000 for the UK born White population.[140]

Figure 1.8 Tuberculosis notifications (absolute numbers and incidence) in the United Kingdom stratified by location of birth



Footnote

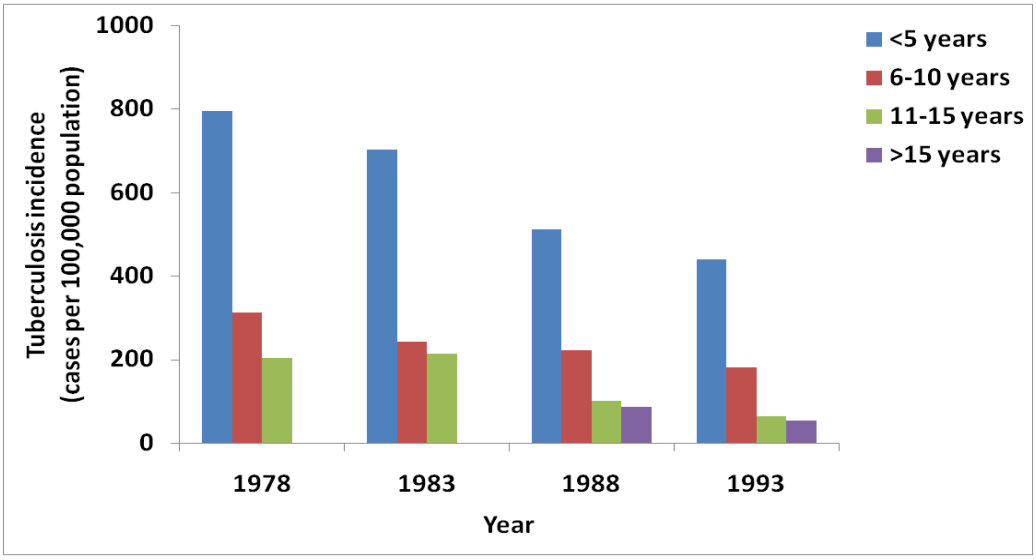
[1]Data obtained from national TB report[119,121,122,147-150,157]

Surveillance data on TB notifications amongst the foreign-born population in the UK is notable for two other observations - firstly the time elapsed between entry to the UK and diagnosis with TB and secondly the distinct clinical phenotypic presentations of TB disease.

UK data suggests that approximately a fifth of cases in the foreign-born are diagnosed in the first two years after arrival with a further quarter between two and five years (in other words an estimated 50% within 5 years of entry to the UK).[140] Of course this data merely describes when foreign-born individuals present with TB in relation to time since migration although it would be more informative to be able to assess how incidence rates change over time since arrival. In the UK, however, this is complicated by the lack of reliable population estimates (in other words a denominator) for foreign-born immigrants stratified by duration of residence in the

UK. Nonetheless, an indication of incidence by time since entry can be obtained from previous national surveys covering 1971, 1978, 1983, 1988, 1993 and 1998.[158-165] In the first of these studies, undertaken in 1971, the British Thoracic and Tuberculosis Association found that the *monthly* incidence rates for immigrants resident for less than five years ranged from 3 to 100 per 100000 population which reflected rate ratios of 2-77 as compared to the UK born population.[158,159] Although these incidence rates decreased with increasing duration of residence in the UK, the foreign-born continued to have an elevated incidence rate for up to 20 years after entry.[158,159] Subsequent national surveys conducted by the Medical Research Council (in 1978, 1983 and 1988) and British Thoracic Society/Public Health Laboratory Service (in 1993 and 1998) focused on incidence rates by time since arrival mainly in the foreign-born Indian Subcontinent population.[160,164,165] These studies clearly demonstrated that immigrants who had been resident in the UK for less than 5 years (so-called new-entrants) had higher TB incidence rates (extremely high in some cases) as compared to immigrants who had been resident for longer; in general, incidence fell as duration of residence in the UK increased although it was noteworthy that migrants who had been resident for over 15 years still had an elevated rate as compared to the UK born population (Figure 1.9).[160-165] Although these studies were undoubtedly authorative, they mainly (apart from the 1998 survey[165]) focused on immigrants from the Indian Subcontinent thereby failing to calculate incidence rates for other ethnic groups (most notably the Black African population). In addition, the population denominator data for immigrants (by time since arrival) is, in general, very poorly recorded and so the results should be viewed with this major caveat in mind.

Figure 1.9 Tuberculosis incidence in foreign-born immigrants by time since arrival in the United Kingdom



Footnote

[1]Data obtained from references [119,121,122,147-150,158-165]

The second issue of note is the distinct TB phenotype associated with foreign-born individuals who present with a predominantly extrapulmonary pattern of disease[140] which will be discussed later in this introduction (see **Patterns of tuberculosis in immigrants in the United Kingdom**).

In summary, evaluation of TB epidemiology in UK, particularly amongst the foreign-born, highlights three key issues which require further discussion:

1. The high incidence of TB in the foreign-born as compared to the UK-born population.
2. The high incidence of TB in the foreign-born in the initial years after arrival in the UK.
3. The predominantly extrapulmonary pattern of disease in the foreign-born.

Having set the scene in terms of TB epidemiology in the UK, in the next section I will first consider the reasons for points one and two above – namely the factors underlying the high incidence of TB in the foreign-born population – especially in the initial years after migration.

Tuberculosis in developed countries: synergy of migration and latent TB infection

Concepts of immigration

In order for TB to occur at all amongst the foreign-born populations living in high-income countries, such as the UK, foreign-born individuals must be resident in the migrant-receiving country and therefore an absolute prerequisite is that migration occurs. Migration is defined by the International Organisation for Migration (IOM) as:[166]

"A process of moving, either across an international border, or within a State. It is a population movement, encompassing any kind of movement of people, whatever its length, composition and causes; it includes migration of refugees, displaced persons, uprooted people, and economic migrants."

Most individuals are documented (meaning that they enter a country legally and remain in the country in accordance with their admission criteria) long-term migrants which is defined as:[166]

"A person who moves to a country other than that of his or her usual residence for a period of at least a year, so that the country of destination effectively becomes his or her new country of usual residence. From the perspective of the country of departure, the person will be a long-term emigrant and from that of the country of arrival, the person will be a long-term immigrant."

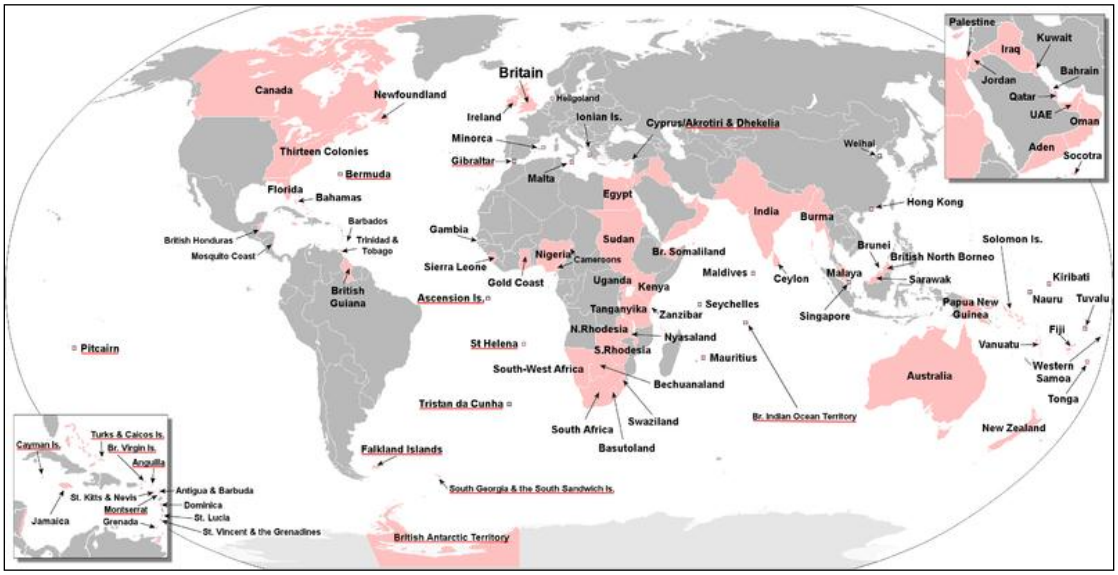
Immigration: patterns and quantification

Data from the IOM suggests that between 1960-2008, migrant numbers increased from 75 million to 214 million; 3.1% of the world's population are classed as migrants which would make them the fifth most populous country in the world.[167,168] Accompanying this increase in the number of migrants there has been a definite shift in the source regions and countries supplying migrants. In the early 20th century, migration mainly consisted of European populations moving between European home nations, colonies or former colonies.[141] However, as the 20th century progressed the European colonial structure disintegrated and globalisation, economics and internal conflict assumed increasing importance for the evolution and increase seen in global migration patterns.[169] As a consequence, an increasing proportion of permanent migrants moved from less developed regions and countries (also the areas with highest burdens of TB) to developed destination countries with a lower TB incidence.[141,170] Examples of this are seen in current migrant flows to North America,[146,171,172] Western Europe,[153] and Australia.[173]

Immigration to the United Kingdom

The situation is replicated in the UK which, in many respects, exemplifies the increases in migrant numbers and changing temporal pattern of migration. Over the last 40 years (1971-2010), data from the Office for National Statistics suggests that net annual migration has increased, fairly sharply, from 14900 to 226000 individuals.[174,175] Moreover migration patterns to the UK differ from other high-income countries[176] and are, in many respects, particularly unique due to the size and scale of the previous British Empire and attendant colonies (Figure 1.10)

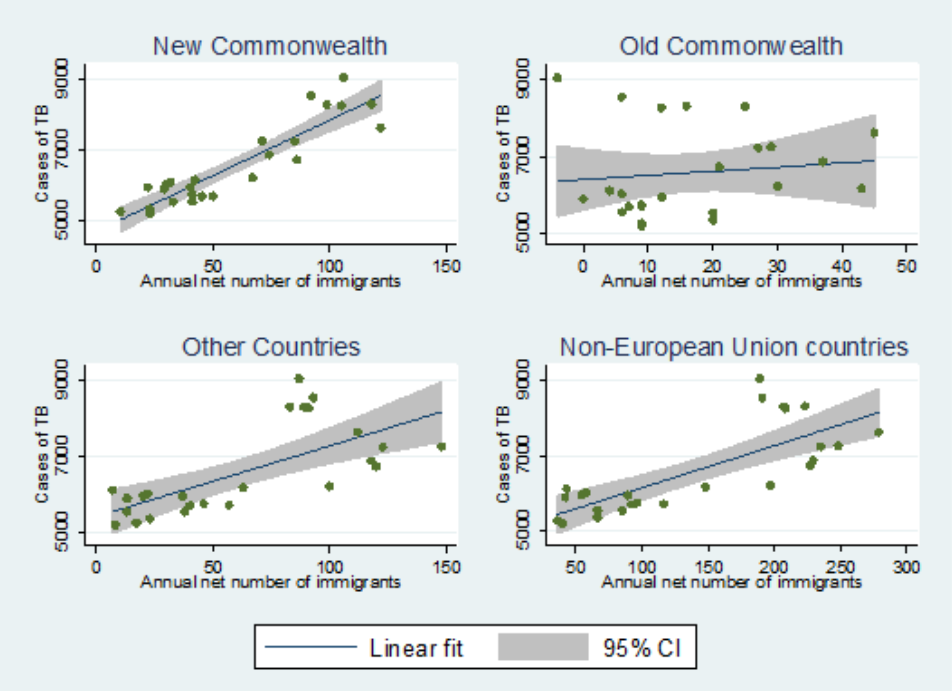
Figure 1.10 Map showing the countries that constituted colonies of the British Empire



When the colonial structure unravelled, migration into the UK (especially during the 1960s and 1970s) was primarily from previous colonies in the new Commonwealth – initially from the Caribbean followed by high levels of migration from the Indian Subcontinent and Sub-Saharan Africa.[174,175,177-179] Although legal migration from these regions has continued to the present day, in the last two decades this has been supplemented by refugees and asylum seekers from Sub-Saharan African countries (such as Zimbabwe) and, more recently, legal migrants arriving from Eastern European nations such as Poland.[174,175,177,179] However it is the high levels of migration from previous Commonwealth colonies in the Indian Subcontinent and Sub-Saharan Africa, where the TB burden is high, which appear to have been most critical in determining TB epidemiology in the UK.[170,176,180,181] Gilbert and colleagues compared all European nations with respect to TB epidemiology and migration patterns and concluded that whilst certain countries such as Spain and Germany also had high levels of migration (as seen in the UK) this was mainly from lower incidence regions such as North Africa and Turkey respectively.[176] By contrast they found that the UK, which had the third highest foreign-born population, was unique in having the highest level of migrants from countries with TB incidence rates of $\geq$500 per 100000.[176]

Figure 1.11 illustrates the relationship between the number of migrants arriving in the UK between 1985 and 2009 from different world regions and UK TB notifications. Whilst there is no clear relationship for Old Commonwealth countries (Australia, New Zealand, Canada and South Africa; ρ=0.12, p=0.57, r^2=0.01), stronger correlations are seen for New Commonwealth countries (Sub-Saharan Africa (excluding South Africa) and Indian Subcontinent; ρ=0.91, p<0.0001, r^2=0.83), Other countries (countries such as the Middle East; ρ=0.69, p<0.0001, r^2=0.48) and Non-European Union countries (includes any non-European Union country; ρ=0.77, p<0.0001, r^2=0.59).

Figure 1.11 Relationship between the numbers of immigrants (in thousands) entering the UK from the New Commonwealth, Old Commonwealth, Other and Non-European Union countries and the number of UK TB notifications for the period 1985-2009



Footnote

[1]Data obtained from sources[151,174,177]

Importance of reactivation of latent TB infection in immigrants

Migration (particularly in the UK), which merely is the means by which individuals from high TB burden regions arrive in low TB burden regions, can only partially explain the disproportionately increased TB incidence amongst immigrants both generally but especially in the initial years after migration. For disease to occur, migrants from overseas must either arrive with prevalent active TB disease, imported LTBI which reactivates post-migration and/or develop TB through transmission in immigrant communities.

Low prevalence of active TB disease in immigrants

TB epidemiology in the UK, but also from other high-income countries, indicates that only a relatively small proportion of TB disease occurs in the first year after arrival with most cases instead developing up to 5-10 years post migration.[140,143,182] This makes prevalent disease at the time of migration less likely. Confirmation of this comes from two recently published large meta-analyses which specifically addressed this issue and came to the congruent conclusion that a very small proportion of documented migrants are diagnosed with active TB at the time of migration.[183,184] In these studies Arshad et al and Klinkenberg et al both independently computed that 0.35% of migrants were diagnosed with active TB disease at the time of migration.[183,184] Their findings were based on analysing immigrant screening programme and as such primarily dealt with documented migrants and pulmonary tuberculosis. By contrast, data from the US which focused on the post-arrival follow-up of individuals with abnormal CXRs but who were smear-negative (those with abnormal CXRs and smear-positive active disease are prevented from travelling) suggests that 0.96% of migrants are eventually diagnosed with active TB although follow-up in this study was sub-optimal and up to 30% of immigrants had not been assessed thus potentially biasing the results.[185] Evaluation of retrospective studies in the UK similarly indicates

a relatively low prevalence of active TB in different immigrant groups (0-1%) at the time of arrival.[186-197]

Prevalence of latent TB infection in immigrants and progression to active TB

In contrast to the relatively low proportion of active TB disease at the time of migration, a number of studies have found that significant proportions (up to 75% depending on the population tested and the diagnostic tool used) of recently arrived individuals from high burden regions have LTBI – which will have been acquired in their country of origin prior to migration;[187,198-218] through migration these latently infected people are introduced into lower incidence, immigrant-receiving nations and, for unknown reasons, in the initial years following arrival in the destination country, the LTBI reactivates and progresses to active TB disease.[141,145,219] This results in an elevated incidence of TB post migration, particularly in the first 5 years after arrival (although it remains high for at least up to 10 years). Unfortunately very few studies have accurately quantified the rate of progression from LTBI to active TB in recent immigrants. A study from Australia in over 15,000 arriving refugees (predominantly from Southeast Asia) with no evidence of active TB found that, over a mean follow-up of 10.3 years, approximately 0.12% of individuals with a TST ≥15mm progressed to active TB disease per year although the risk was significantly higher in the first three years after arrival.[220] By contrast, in a UK study, Choudhury and Ormerod followed a cohort of predominantly Indian Subcontinent migrants and found that 15% of those with positive TST progressed to active disease over a 10 year period following arrival in the UK.[221] Other migrant receiving countries including the US,[9,222,223] Canada[224] and Western Europe[145,182] have also reported the elevated risk for active TB in the initial years after migration but this remains a poorly studied area.

Molecular epidemiology: evidence for reactivation of latent TB amongst immigrants rather than recent transmission in immigrant communities

Further evidence supporting the view that TB in the foreign born arises primarily through LTBI reactivation rather than recent transmission in communities comes from studies which have used genotyping methods (primarily restriction fragment length polymorphism - RFLP) to examine the DNA patterns of *M. tuberculosis* isolated within immigrant communities. The basic premise behind these studies is that individuals with tuberculosis caused by an isolate with a RFLP pattern that matches at least one other case in the cohort is due to recent transmission (known as a clustered case) whereas cases with unique RFLP patterns (non-clustered cases) are thought to arise due to the reactivation of LTBI.[225,226] In a comprehensive and contemporary systematic review and meta-analysis, Fok and colleagues found that in low-, intermediate- and high-incidence settings, foreign-born individuals were significantly less likely to have a clustered, non-unique, isolate as compared to those individuals who had been born locally.[226] Table 1.7 summarises the findings of studies in high-income, low-incidence settings which have used genotyping to evaluate the proportion of clustered, and non-clustered, isolates stratified by location of birth. Overall, in individuals who were local-born a median of 45.8% (range 17.7-76.5%) of cases were clustered as compared to a median of 25.0% (range 12.6-73.7%) in those individuals who were born overseas. In a large multi-centre study conducted in the US of over 10,752 cases, 34% of isolates in foreign-born immigrants were clustered as compared to 62% of US-born individuals.[227] Similarly, a study conducted in New York by Geng et al found that 36% of cases in foreign-born individuals were clustered as compared to 55% in the US-born population.[228]

Table 1.7 Studies which have used restriction fragment length polymorphisms in low/moderate TB burden countries to assess the degree of clustering by location of birth

Author	Year	Country	Genotyping	Number	Clustering (%)		
					Overall	Local born	Foreign born
Yang[229]	1995	Denamrk	IS6110-RFLP	257	31.1	36.6	12.6
Burman[230]	1997	USA	IS6110-RFLP	189	27.0	40.2	13.2
Samper[231]	1998	Spain	IS6110-RFLP	226	39.4	39.8	30.0
Gutierrez[232]	1998	France	IS6110-RFLP	272	34.9	36.3	35.4
Van Soolingen[233]	1999	The Netherlands	IS6110-RFLP	4266	46.2	49.1	44.1
Rhee[234]	2000	USA	IS6110-RFLP	1307	37.2	61.6	20.1
Solsona[235]	2001	Spain	IS6110-RFLP	165	46.1	53.0	23.0
De Bruyn[236]	2001	USA	IS6110-RFLP	1139	60.5	72.0	34.2
Ellis[227]	2002	USA	IS6110-RFLP	10752	48.1	62.0	34.0
Hayward[237]	2002	UK	IS6110-RFLP	552	27.0	41.9	19.0
Maguire[225]	2002	UK	IS6110-RFLP	2042	22.7	40.3	24.1
Weis[238]	2002	USA	IS6110-RFLP	159	47.8	62.6	23.3
Geng[228]	2002	USA	IS6110-RFLP	546	47.8	55.0	36.0
Moro[239]	2002	Italy	IS6110-RFLP	581	41.4	44.0	34.7
Kulaga[240]	2002	Canada	IS6110-RFLP	243	29.6	30.6	29.9
Heldal[241]	2003	Norway	IS6110-RFLP	765	17.5	17.7	17.4
Inigo[242]	2003	Spain	IS6110-RFLP	212	44.8	45.6	20.0
Pena[243]	2003	Spain	IS6110-RFLP	566	72.3	72.2	73.7
Blackwood[244]	2003	Canada	IS6110-RFLP	629	32.3	61.8	39.3
Diel[245]	2005	Germany	IS6110-RFLP	848	33.7	39.4	25.9
Inigo[246]	2007	Spain	IS6110-RFLP	621	36.7	29.5	21.3
Dahle[247]	2007	Norway	IS6110-RFLP	1865	20.6	19.2	21.3
Lopez-Calleja[248]	2007	Spain	IS6110-RFLP	454	52.6	33.7	56.7
Ohkado[249]	2008	Japan	IS6110-RFLP	235	65.1	71.2	18.5
Borrell[250]	2009	Spain	IS6110-RFLP	463	39.5	76.5	23.5
Franzetti[251]	2009	Italy	IS6110-RFLP	2218	41.2	46.0	46.0
Love[252]	2009	UK	IS6110-RFLP	1808	20.6	25.0	20.6
Ojo[253]	2010	Ireland	IS6110-RFLP	139	30.9	36.1	12.9
Vanhomwegen[254]	2011	USA	IS6110-RFLP	298	37.8	47.2	31.3
Borgdorff[255]	2011	The Netherlands	IS6110-RFLP	12222	47.1	56.6	50.9

In the UK, four studies have been conducted to assess the rate of clustering in different populations with three of these studies reporting the results by location of birth. Hayward et al[237] and Maguire et al[225] assessed the rate of clustering, using RFLP, in London during two separate periods (1993 and 1995-1997 respectively) whilst Love et al undertook a national (UK) based study in 1998;[252] the proportion of clustered cases in the foreign- and local-born populations in the three studies was 19%, 41.9%, 24.1%, 40.3%, 20.5% and 25.0% respectively. All three studies found, on multivariate analysis, that foreign-birth was significantly associated with unique, non-clustered, isolates indicating that disease in this group mainly was the result of LTBI reactivation rather than recent transmission.[225,237,252] Although these studies are important as they provide an indication of the relative importance of recent transmission versus the reactivation of LTBI in different demographic groups, their results must be set against the limitation that there was incomplete ascertainment of all cases in the population (approximately 50-60% of cases were included) which could bias the results.[225,237,252] In a separate, more recent, UK based study with higher levels of ascertainment, Sails et al used an alternative method of genotyping (MIRU-VNTR) and found that 61% of isolates in the White population were clustered as compared to 19% in the Asian population.[256] Although it is likely that most of the White population were born in the UK whilst those of Asian ethnicity born overseas, thereby confirming the earlier studies,[225,237,252] this assumption is not absolute as some of the individuals of Asian ethnicity may have been born in the UK-born (in other words second generation immigrants). This study is however, additionally important as it highlighted a critically important, and often politically sensitive, point that very little transmission occurred from foreign- to local-born individuals – or indeed vice-versa.

Taken together, the observed epidemiology of TB in high-income settings, published data from the UK and other high-income countries strongly supports the view that, in migrants, most TB cases occur due to reactivation of LTBI originally acquired in their country of origin rather than as a result of recent transmission in the destination country.[145,228,257-260] Reactivating LTBI in

migrants therefore plays a significant role in determining the epidemiology of TB in developed countries such as the UK. There is however an important caveat to these studies. The lack of clustering in the foreign-born migrants does not absolutely rule out recent transmission. It merely means that an identical case cannot be found in the population tested. This may be because foreign-born migrants develop TB through recent transmission following travel overseas to visit friends and relatives or through family from overseas visiting, transmitting and returning to their country of origin. In both of these scenarios, the index case would not be identified therefore leading one to incorrectly conclude that the case of TB has occurred through reactivation rather than recent transmission. However the relative importance of this remains unknown and unclear.

With an understanding of the pivotal, synergistic, role migration and reactivation of LTBI play in determining TB epidemiology in non-endemic countries, the need for coherent policies to screen immigrants is increasingly well recognised.[141,261]

Public health aspects of TB control

In order to contextualise immigrant screening as a means of TB control it is first necessary to understand the current global TB control policies in place.

Following the WHO's declaration of the TB epidemic as a global health emergency in 1993,[262] the DOTS (Directly Observed Therapy Short Course) strategy was introduced in 1995 with five key elements:[263]

1. Political commitment with increased and sustained financing
2. Case detection through quality-assured bacteriology
3. Standardised treatment, with supervision and patient support
4. An effective drug supply and management system
5. Monitoring and evaluation system, and impact measurement

Operationally the focus was on two targets: case detection of 70% of new smear-positive TB cases and 85% cure of these cases.[264] In 2006, in order to respond to TB/HIV and MDR-TB, the WHO launched the new Stop TB strategy – with DOTS, which was highly cost-effective, remaining at the heart of the new policy.[265] Six components of the new strategy were:[265]

1. Pursuing high-quality DOTS expansion and enhancement.
2. Addressing TB/HIV, MDR-TB and other challenges.
3. Contributing to health system strengthening.
4. Engaging all care providers.
5. Empowering people with TB, and communities.
6. Enabling and promoting research.

The overall aim of the 2006 Stop TB strategy was to achieve the following control targets:

- Millennium Development Goal (MDG) 6, Target 8: Halt and begin to reverse the incidence of TB by 2015
- Targets linked to the MDGs and endorsed by the Stop TB Partnership:
    - By 2015: reduce TB prevalence and death rates by 50% relative to 1990
    - By 2050: eliminate TB as a public health problem (1 case per million population[138])

The above discussion on TB control policies clearly highlights that the rapid identification, diagnosis, and treatment, of active TB cases (especially infectious) is the mainstay of TB control on a global level although, in low-burden settings, this extends to individuals actively diagnosed through screening such as household contacts of smear positive cases and immigrants.

Although the emphasis on active TB is entirely appropriate as it breaks the chain of transmission it must be borne in mind that it has little impact on disease occurring through reactivation of LTBI. Previous dynamic mathematical models have explored the impact of mass preventive therapy for LTBI on the incidence of active TB disease.[266-270] These studies have, largely, come to similar conclusions: targeting therapy against both latent and active TB in HIV negative and positive populations will significantly reduce TB incidence and mortality.[266-270] In a complicated model which was fit to global TB incidence rates, Murray et al explored the impact of adding mass chemoprophylaxis to treatment of active disease and found that at even relatively low coverage levels (33%), TB incidence would be reduced by 19% and mortality by 21% over 20 years.[270] However, they did not explicitly consider different screening frequencies or the characteristics of the screening tests which are known to be critical in the diagnosis of LTBI.[43] Cohen et al modelled the impact of chemoprophylaxis in an exclusively HIV-positive population

and also found TB incidence was reduced by 20% but with the perverse effect of increasing drug resistance[266] – though this is an issue that remains under debate with recent evidence stating the risk of acquiring drug resistance is low.[271]

Nevertheless, the general message from these models is clear: tackling both the large pool of LTBI, and active disease, can result in more rapid and efficient global TB control. This is reflected in a recent paper by Dye and Williams who used a complex dynamic mathematical model to show that combining conventional TB control measures (case detection and cure) with novel approaches such as treating LTBI were required if TB incidence is to be reduced to less than 1 per million by 2050.[268] The importance of LTBI, and its potential place in TB control programmes, is therefore becoming increasingly clear.[268,272] However, the conclusions from the Dye paper were made on the basis of providing mass community-wide chemoprophylaxis to individuals with LTBI in the developing world.[268] Currently the mechanisms to diagnose and treat such vast numbers are not available making this an impractical solution. In contrast, targeted diagnosis and therapy of LTBI in specific populations such as HIV-positive individuals, or, in low incidence settings, recent contacts of smear-positive index cases, individuals commencing anti-TNF therapy or recent immigrants arriving from high TB burden settings (a group that is receiving increasing attention)[273] may be more practicable.[9,274]

Immigrant screening for TB as a tool to control TB in high-income settings

Although it would be advantageous, at the outset, to define immigrant screening for TB, at present there is no widely accepted definition which reflects the fact that different groups of immigrants (documented/legal, refugees or asylum seekers) and different forms of TB (LTBI, active TB disease or both) can be targeted. For the purpose of this thesis I will focus on legal/documented immigrants and screening for both LTBI and active TB disease. Conceptually, however, immigrant screening is more complex than this and also comprises a number of separate

but related issues which must be considered if one is to fully understand the screening policies in place in different high-income countries. Issues of particular importance include:

1. Location of screening – pre-entry, at-entry or post-entry.
2. Which immigrants are screened – selection criteria based on one/some of: duration of stay, age, country of origin and/or incidence threshold in country of origin.
3. Screening undertaken to identify active or latent TB.
4. Diagnostic methods/tools for active and latent TB.

Immigrant screening practices in high-income countries

Despite a tacit understanding of the importance of TB in the foreign-born population resident in high-income/developed countries, as well as the increasing topicality of immigrant screening,[273] relatively little is still known about if, and how, individual countries screen immigrants for TB.

From the studies which have described screening policies, it is clear that high-income countries vary considerably in the policies they have put in place to screen immigrants for TB.[275-278] Heterogeneity particularly exists in the timing of screening in relation to the immigration process (pre-entry, at-entry and post-entry or any combination of these), which groups of immigrants are screened (documented immigrants vs refugees and asylum seekers), which stage in the natural history of TB the screening process is primarily attempting to identify (active TB disease, LTBI or both) and the specific screening tools used (CXR, TST, IGRA or a combination of these).[275,277-279]

Rieder et al, as part of a working group on migration and TB, summarised screening policies in selected European nations but their survey was limited by its focus on European countries only, not differentiating between screening for active and latent TB, not considering the criteria by which countries and TB incidence threshold were selected for screening and by the

failure to consider newer methods of screening for LTBI (IGRAs).[276] More recent work from Coker et al focused on evaluating screening methods in seven different units in four European countries.[275] Although their work was fairly in-depth in describing screening processes for the countries that were included, by specifically selecting only a small number of units in a few countries the authors may have introduced selection bias as the included centres may not have been representative of other centres in the countries; similarly by only including four countries the results could not provide a complete, more generalisable, overview of immigrant screening.[275] Alvarez and colleagues undertook a survey of screening methods in 16, European and Non-European, high-income countries which they published in two papers – separately describing the processes for children and adults.[277,278] Although this work was very detailed and it provided useful information there were a number of limitations in the work. Criteria for including countries were based on TB incidence (<15 cases per 100000), the number of migrants arriving in the country and if the country had previously published data on immigrant screening. These criteria may be pragmatic but they may have resulted in certain countries being excluded (such as Spain, Portugal and many countries that have recently joined the European Union) – thereby preventing a complete analysis of screening methods.[277,278] In terms of the content of the survey, the authors appeared to primarily focus on active TB screening with less information provided on LTBI screening (despite its importance in determining TB burden – see earlier section). In addition, important areas missing in the paper included which countries or screening threshold were selected for screening and the exact methods by which LTBI screening was undertaken (both in terms location of screening and tools used). Most recently, as part of an analysis of national guidelines on the use of IGRAs, Denkinger et al assessed how countries screen immigrants for LTBI and found significant heterogeneity in the tools used although they did not focus on any other aspects of immigrant screening and so the generalisability of this study is limited.[77]

Current methods of immigrant screening for TB in the UK

In the UK, the issue of TB in foreign-born immigrants, and how best to implement immigrant screening, has been exercising clinicians, public health physicians, policy-makers, the public and media for over 60 years.[179,273] In order to understand why, and how, current UK immigrant screening policies have come to be in place it is first necessary to understand the history of immigrant screening in the UK.

History of immigrant screening in the UK: evolution of policy

In the late 1950s and early 1960s, as epidemiological data started to emerge highlighting the high, and increasing, incidence of TB in Irish, Indian Subcontinent and Caribbean immigrants[280] the UK government came under pressure from the British Medical Association (BMA) to implement a system of medical examination for TB for immigrants.[280] Underlying this pressure was a feeling that entry to the UK should be conditional on being free of TB (in other words medical examination and CXR normal).[178]

The Ministry of Health, which Welshman points out was a relatively weak department at the time,[179] had three options available in terms of where chest radiographic screening should be undertaken: pre-entry (in country of origin), at-entry (at port-of-arrival in the UK) and post-arrival. Pre-arrival screening (in countries of origin), which would be similar to the Australian system,[178] was not popular as it was felt it would restrict immigration and harm the economy and thus, following discussions with the High Commissions in India and Pakistan who confirmed that they could not force individuals to undergo CXR pre-departure,[179] it was quickly discarded as a practicable option. Instead, as data from Springett indicated that the incidence of TB was high in the initial years after arrival,[280] the focus shifted to at- or post-entry screening. This could be mandated through the 1962 Commonwealth Immigrants' Act.[281] Although at-entry screening was the preferred option of the British Medical Association, it was not preferred by the Ministry of

Health who raised several objections including the need for trained staff, radiographic health units, the need for the system to be comprehensive (and be in place in all ports and airports), delays to immigration processes through mandating chest x-rays as individuals arrived in the UK and, finally, the potential for discrimination on the basis of colour.[179] By contrast, post-arrival screening was more popular but it was unclear what control the Government had over an immigrant after they left the port-of-arrival.[179] Therefore an amalgamated compromise appears to have been drawn up and in 1965 the Minister for Health stated that immigrants would be screened with chest radiographs on an experimental basis at Heathrow and their details would be passed on to Medical Officers of Health in areas of settlement to undergo further tests and examinations as required.[179] This was further confirmed by the 1968 Commonwealth Immigrants Act[282] and 1971 Immigration Act;[283] the latter is still in place today and forms the basis of current UK screening policy.[283]

Current immigrant screening policy in the UK

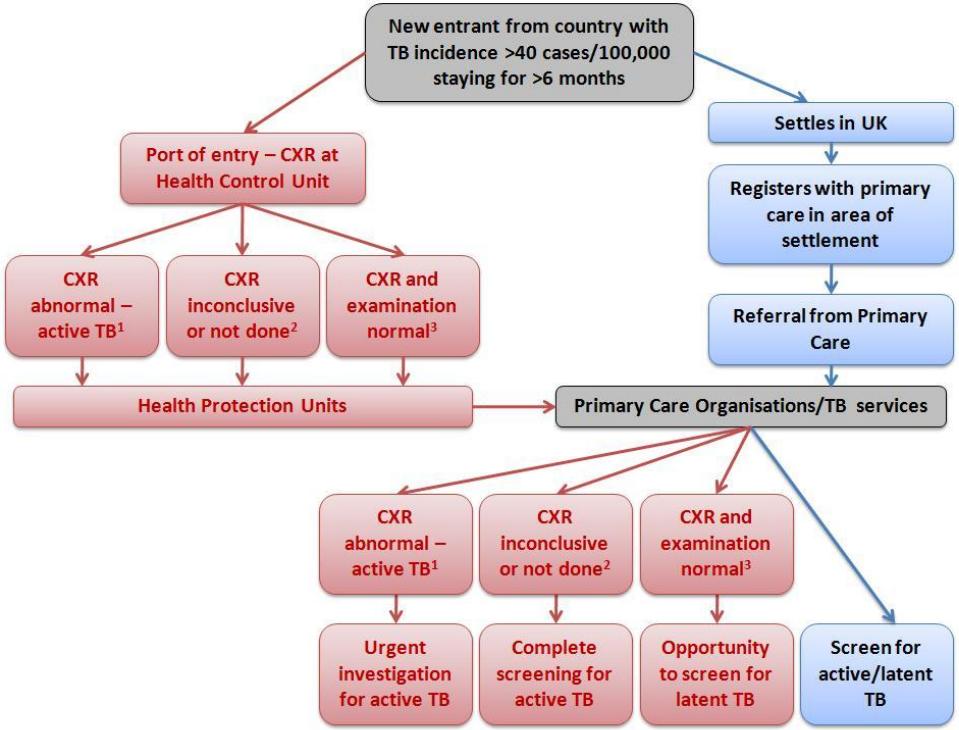
Although the port-of-entry CXR screening system was designed to be an experimental, short-term, solution,[179] in reality the methods by which new immigrants arriving in the UK are screened for TB have remained essentially unchanged for over 40 years. Notable exceptions are the recent initiation, in certain UK regions, of an alternative primary-care based system of screening and, in a select few countries overseas, pre-departure chest radiographic screening as part of visa application systems (see Figure 1.12 and section below *Adjuncts to the port-of-entry system* for further details).[178,179]

In the port-of-arrival system, which remains the main method of immigrant screening, UK policy advocates a two-step approach whereby new-entrants arriving from countries with a TB incidence greater than 40 cases per 100000 p.a. who intend to stay in the UK for more than six months are supposed to be initially identified by Immigration officers at port-of-entry and

referred to Health Control Units for further assessment.[283] Health Control Units arrange for these new-entrants to undergo chest x-rays (CXR) and a medical examination and the outcome of these will result in standard port forms being issued (port 103, port 102 and port 101). These forms have different meanings which require action at different levels of urgency:

1. Port 103 – Significant risk to health
2. Port 102 – Chest radiograph inconclusive/Not undertaken
3. Port 101 – Chest radiograph and medical examination normal

Figure 1.12 Flow chart of pathway for TB screening of new-entrants following arrival in the United Kingdom



Footnotes

[1]CXR abnormal – port 103 form
[2]CXR inconclusive/has not been undertaken – port 102 form;
[3]CXR normal – port 101 form
[4]Port referral flows in red, primary care flow in blue. The blue primary care flows are only activated when a new-entrant registers with primary care services after settling in a specific area; new-entrants are not directly referred to primary care services for TB screening on arrival in the UK

Port forms are forwarded, via local Health Protection Units, to local NHS TB services covering the Primary Care Organisation (PCO) area where the new-entrant eventually intends to settle.[283] On receiving the referrals from their local Health Protection Units, local TB services are supposed to complete the second step of the screening process which will be determined by the port form, legislation and national guidance.[29] The actions to be taken in relation to the port forms are stated in the 1971 Immigrants Act (port form 103 – screen for active TB, port form 102 – complete screening for active TB and screen for LTBI, port 101 – screen for LTBI)[283] and have been formalised by successive publications of national guidance from 1983 onwards – initially by the British Thoracic Society (BTS)[284-287] and, since 2006, by the National Institute for Health and Clinical Excellence (NICE).[29,81]

Between 1983 and 2000 the guidelines published by the British Thoracic Society remained unchanged stressing that local TB services, in addition to screening immigrants for active TB, should screen all individuals arriving from countries with a TB incidence greater than 40 cases per 100000 p.a. for LTBI using the tuberculin skin test.[284-287] In 2006, NICE issued new national guidelines for TB control and prevention with specifically new recommendations on immigrant screening by local TB services which superseded previous BTS guidance.[29] In addition to commencing screening for active TB, NICE still recommended screening for LTBI although, on the basis of a health-economic model, it drastically revised the screening threshold upwards stating that LTBI should only be diagnosed in a very select subset of new-entrants (all individuals <16 years old from countries with TB incidence >40 cases/100000 p.a. and 16-35 year olds from countries with TB incidence >500 cases/100000 p.a. or Sub-Saharan Africa).[29] NICE recommended step-wise diagnosis of LTBI beginning with a CXR which, if normal, is followed by a tuberculin skin test (TST) which, if positive, requires a confirmatory test with interferon-gamma release assays (IGRAs) prior to chemoprophylaxis.[29] These guidelines remained in place until recently, in 2011, when revised NICE guidance for the diagnosis of LTBI was published which recommended that children (<16) and adults (16-35 years) from all countries with TB

incidence >40/100000 should be screened with dual TST plus IGRA or, in adults, alternatively by single-step IGRA alone.[81]

Immigrant screening practice in the UK: disconnect between national guidelines and actual practice

In the UK, however, it is clear that there is a disconnect between what national guidelines recommend in terms of screening and actual practice. Previous work has established a number of systemic failures with the current system. At the port-of-arrival, there appears to be inconsistency in identifying new-entrants for further screening by the Health Control Units.[189,191,195] Hardie and Watson estimated that of the 140,000 immigrants entering the UK in 1990, only 36,000 (25.7%) were referred to health control units; of these only 20,000 (14.3% of total) were screened with a chest radiograph.[189] A more recent analysis of the Heathrow and Gatwick at-arrival screening mechanism by the Health Protection Agency found a higher proportion of immigrants (40%) who were referred to the Health Control Units underwent chest radiography – although this did mean that approximately 60% (approximately 111,000) of immigrants were being missed;[191] amongst those who were screened there was a low yield for active TB disease (see next section on *Outcomes of screening* for further details).[191]

Problems have also been identified at local TB services who are responsible for completing the second stage of the immigrant screening process.[186,187,189,191,194,196,288,289] Bothamley and colleagues found an extremely low proportion (17%) of immigrants referred by the port system attended for screening as compared to those referred and identified through primary care systems (54%).[187] In 2005, Hogan et al undertook a postal survey of Public Health consultants who dealt with the port forms forwarded from Heathrow.[289] They found significant heterogeneity in the actions taken in response to port 102/101 forms; overall less than half of the responders would act on these port forms with those areas receiving most notifications actually going on to

screen the fewest new-entrants.[289] Limited capacity and questionable benefits from following up these forms were cited as reasons.[289] Although this study was undoubtedly important, it was relatively small-scale, the authors did not make it clear how many regions in the UK were covered, overall response rate was suboptimal and the authors evaluated practice in different areas by the number of port notifications they received.[289] In addition the study, which was carried out prior to the 2006 NICE guidelines, was set up to focus on the system per se without obtaining data on which specific groups are screened (in term of age, countries of origin and TB incidence) and the screening tools used.[289]

Adjuncts to the port-of-entry system: pre-departure chest radiography and primary-care based screening

In 2005 the UK government, in association with the International Organisation for Migration, introduced a pilot of pre-departure chest radiographic screening in 15 high TB burden countries (Bangladesh, Cambodia, Ghana (which also takes applications from Burkina Faso, Cote d'Ivoire, Togo and Niger), Kenya (which also takes applications from residents of Eritrea and Somalia), Pakistan, Sudan, Tanzania and Thailand (which also takes applications from residents of Laos). Testing started in Sudan, Tanzania and Thailand in 2005, in Cambodia in 2006 and in the remaining countries in 2007. Immigrants seeking visas to stay in the UK for longer than 6 months are obligated to be screened for active TB (through CXR and, if appropriate, sputum examination). Although the system initially cost the UK government an estimated £1.1 million to set up, the actual cost of TB screening is now self-financing as visa applicants pay a fixed fee.

The various problems (with the port-of-entry system) highlighted earlier are likely to be partially responsible for certain regions (East London, Leeds and Blackburn) moving away from a reliance on port-of-entry notifications and instead employing an alternative, although still not widespread, primary-care based system.[217,290] At the time of registration with a primary-care

provider immigrants who have recently arrived in the UK are identified and offered screening for active and/or latent TB. Previous work from East London and Leeds has shown that this is an effective alternative to the current system although clear guidelines and education, coupled with timely registration of new immigrants with local primary care, are required.[187,290]

Outcomes of immigrant screening

Summarising the outcomes of screening is most easily done by separately considering the yields (calculated as a proportion) for active and latent TB.

Yields for active TB

Most data on the yields for active TB are drawn from national evaluations and cross-sectional studies of immigrant screening processes – usually pre-, and at-, arrival chest radiography to identify pulmonary TB. Two recently published systematic reviews have specifically assessed the outcomes and yields for active TB in high-income countries.[183,184] Klinkenberg and colleagues assessed 40 studies covering 16 different countries (11 EU, 4 Non-EU and Switzerland) and found that the overall yield for active TB was 0.35% and 0.51% in Europe and Non-European nations respectively.[184] The authors found that the yields were similar whether screening was undertaken at the port-of-arrival, in the reception holding centre or in the community after arrival (median 0.20–0.36%). However yields did appear to be higher in asylum seekers than documented immigrants.[184] Arshad and colleagues undertook, and published, a similar systematic review and computed that the overall yield for active TB was 0.35%.[183] In contrast to the Klinkenberg review, however, they found yields were not different between documented immigrants and asylum seekers though refugees had a higher yield. They did find that the yields for immigrants varied by region of origin being higher in individuals from Africa (0.66%) and Asia (1.1%) as compared to immigrants from Europe.[183]

In the UK, most studies assessing the yields for active TB have been retrospective analyses of the port-of-arrival system – predominantly in documented immigrants (Table 1.8).[186-188,190-197] Overall, yields for active TB in these studies have ranged from 0.0-1.0%; in general larger studies (with more statistical power) have found lower yields for active disease. Markey and colleagues, working in a secondary care unit which dealt with 70% of suspected cases of TB referred from Heathrow, identified 51 cases of disease – reflecting approximately 0.05% of all those screened at the port-of-arrival.[193] Smaller retrospective analyses from Newcastle, Essex and Birmingham found yields of between 0-1% although the number of individuals in two of these studies was small (99 and 226) making generalisation from these extreme values difficult.[186,192,194] Evaluations from the HPA, where larger numbers were analysed, have found yields of 0.13% and 0.10% respectively.[189,191] In contrast to these studies which have focused on post-arrival screening, there is little data available on the yields for active TB disease from the UK government's pilot pre-departure screening system. However, using a Freedom of Information request, it emerges that of 442,510 chest x-rays undertaken only 294 cases (0.06%) of active TB have been diagnosed.[291]

Table 1.8 Studies which have assessed the yields for active tuberculosis through immigrant screening in the United Kingdom

Author	Year	Location	Population	Number in study	Yield for active TB (%)
Markey[193]	1986	London	Adult legal immigrants	96638	0.05
Ormerod[195]	1990	Blackburn	Adult legal immigrants	2033	0.54
Hardie[189]	1993	London	Adult legal immigrants	20000	0.10
Bakhshi[186]	1994	Birmingham	Adult legal immigrants	226	0.0
Lavender[192]	1997	Newcastle	Adult legal immigrants	99	1.0
Ormerod[196]	1998	Blackburn	Adult legal immigrants	2242	0.45
Calllister[188]	2002	London	Adult asylum seekers	41470	0.24
Bothamley[187]	2002	London	Adult legal immigrants	416	0.72
Whitfield[197]	2003	London	Adult legal immigrants	2855	0.10
Millership[194]	2005	Essex	Adult legal immigrants	2389	0.04
HPA[191]	2006	London	Adult legal immigrants	72817	0.13
Harling[190]	2007	Dover	Asylum seekers	8258	0.13
UK Border Agency[291]	2011	Various	Adult legal immigrants	442,510	0.06

Footnote

[1]HPA – Health Protection Agency

Yields for latent tuberculosis infection

Data on the prevalence of LTBI in immigrants arriving in high-income countries is, in general, variable. Studies have, in the main, been cross-sectional, single-centre analyses using TST,[187,203-215,292-295] or more recently IGRA, in different immigrant subgroups (adults vs children, documented immigrants, refugees and asylum seekers, international adopted children, contacts of infectious index cases and immigrants identified with inactive TB on chest radiography);[203,209,211,213,215-218,292] a small number of studies have compared TST with IGRA in the immigrant population.[203,209,211,213,215,218,292,295]

Most previous authors have assessed LTBI prevalence in immigrants with TST and found that positivity varies from 12-72% depending on the setting, age (children lower prevalence than adults), type of migrants studied (legal or undocumented immigrants), TST cut-off used and history of BCG vaccination.[187,203-215,292-295] Wells et al[214] and Richards et al[212] assessed TST results in immigrants identified as having inactive TB on pre-arrival chest radiographs and found 72%

and 68% respectively were positive. Although this figure appears high it must be remembered that these immigrants were selected for screening on the *a priori* basis that their chest radiographs were abnormal – therefore making generalisation difficult. In two large retrospective studies from New York and Montreal, comprising just under 45,000 immigrants, Li and colleagues and Hernandez-Garduno estimated that TST positivity in immigrants was 40%[210] and 61%[208] respectively although these investigators included immigrants tested with TST for a variety of reasons (rather than simply as screening following arrival in the high-income country).

In contrast to these data from adults, data suggests that the prevalence of LTBI is lower in children. Minodier et al conducted a school-based paediatric immigrant screening study in Canada and found that the prevalence of LTBI was 23%[293] although they selected certain high-risk classes rather than undertaking testing in all immigrant children. Méndez-Echevarría and colleagues undertook a multi-centre study in 9 hospitals in Madrid, Spain and included immunocompetent children who were immigrants, TB contacts or had clinical suspicion of tuberculosis disease (TBD).[295] In the subset of immigrants who were asymptomatic (non-contacts) the prevalence of infection was relatively low at 12%. Lucas et al arrived at a quantitatively similar prevalence figure (18%) in a different population of children (refugees arriving in Australia).[292]

In the UK, there is very little published data on the yields for, and prevalence of, latent TB in immigrants with tuberculin testing as the diagnostic tool (Table 1.9).[187,190,195,196] Studies, which have been undertaken in documented immigrants, asylum seekers and refugees, have found the prevalence of LTBI to be between 8-58%, depending on the type and age of immigrant.[187,190,195,196] Ormerod analysed the results of screening legal immigrants through the port-of-arrival system and found that 20-25% of Pakistani and 35% of Indian immigrants had a positive Heaf (defined in the study as grade 2 and above in BCG unvaccinated subjects).[196] Later work from East London, by Bothamley and colleagues, compared different methods of identifying new immigrants and found a higher prevalence of LTBI overall – 58% of new

immigrants had a Heaf grade 3 or 4.[187] Whilst these studies were in documented immigrants, Harling et al analysed the outcomes of screening asylum seekers arriving at the port of Dover and estimated that 8% were Heaf positive although one of the major limitations of this study was that immigrants with a BCG scar were not tuberculin tested – which is likely to have led to a underestimation of LTBI prevalence in the cohort.[190]

Whereas several studies have used TST to assess LTBI prevalence, the use of IGRAs in diagnosing LTBI specifically in immigrants has only recently been increasingly evaluated. Authors have, to date, primarily focused on high-risk immigrant groups including undocumented migrants[203,211,213,215,216,292,296] or immigrant contacts of smear-positive index cases[209,218,297] with very few studies actually focusing on legal, documented migrants (adult or child) per se.[217,293,295] Nonetheless, in all populations, IGRA positivity (5-60%) has generally been lower than that seen with TST.[203,209,211,213,215-218,293,295-297] A large Italian study which prospectively assessed the performance of the ELISA (QuantiFERON Gold in-tube) in illegal immigrants accessing secondary care found that the overall prevalence of infection was 30% although they did not specifically evaluate the prevalence of infection at different incidence thresholds.[211] Kik and colleagues recruited a large cohort of immigrants who were contacts of index active TB cases and found high positivity rates for the ELISA and ELISpot of 54% and 60% respectively although their findings were severely limited by the fact that IGRA testing was only undertaken in TST positive individuals.[218]

Data on IGRA positivity in immigrant children is, however, still fairly limited although published studies suggest that the prevalence of infection is lower than in adults.[295] Mendez-Echevarria tested children attending hospitals in Spain and found that ELISA positivity was low at only 5%.[295] However the authors did not describe in any particular detail which regions and countries of the world the immigrant children had arrived from, how they were selected and how they differed from those who refused to participate in the study/the general immigrant population in the area.[295] In an Australian study of refugee children, a slightly higher prevalence of infection

(10% and 8% for the ELISA and ELISpot respectively) was computed although the population studied was high-risk and predominantly made up of African, and to a lesser extent Thai, refugees.[292]

The majority of the studies using IGRA set out above have been conducted outside the UK. There is only one published study that has assessed the prevalence of LTBI in immigrants in the UK with IGRA as the diagnostic tool.[217] Hardy and colleagues, working in Leeds, used primary-care registration systems to identify immigrants for LTBI screening. Although they had a relatively low attendance rate (32%), they found that 37% of those tested with the ELISA were positive (Table 1.9).[217] However, this single-centre study was relatively small-scale and as the investigators only invited immigrants arriving from certain high burden countries they were not able to assess the overall prevalence of LTBI in the immigrant cohort – thus limiting the study's generalisability.

Table 1.9 Studies which have assessed the yields for latent tuberculosis infection through immigrant screening in the United Kingdom

Author	Year	Location	Population	Diagnostic test	Number in study	Yield for latent TB (%)
Ormerod[195]	1990	Blackburn	Adult legal immigrants	TST	2033	30-40
Bothamley[187]	2002	London	Adult legal immigrants	TST	416	58
Harling[190]	2007	Dover	Asylum seekers	TST	8258	8
Ormerod[196]	1998	Blackburn	Adult legal immigrants	TST	2242	20-35
Hardy[217]	2010	Leeds	Adult legal immigrants	IGRA (QFN-GIT)	280	37

Amongst the studies discussed above, a minority of investigators have concurrently tested immigrants for LTBI with TST and one or both IGRAs to assess the comparative performance and concordance of the diagnostic tools (more so for TST vs ELISA than TST vs ELISpot).[203,209,211,213,215,218,292,295] In these studies, the proportion of immigrants identified as positive is higher when using TST as compared to either IGRA.[203,209,211,213,215,218,292,295]

Concordance, as measured by Cohen's kappa, has been found to range from 0.19-0.51 which equates to poor/moderate agreement.[203,209,211,213,215,218,292,295] Much of the discordance in these studies took the form of TST positive/IGRA negative results in BCG-vaccinated individuals.

For example, Winje and colleagues concurrently tested 912 asylum seekers arriving in Norway and found that whilst overall concordance was 0.51, it fell to 0.46 in those individuals who were BCG-vaccinated.[215] Some authors, using multivariate regression, have confirmed that discordancy is independently associated with prior BCG vaccination.[203] Conceptually, discordant pairs could either reflect a higher sensitivity, or a lower specificity, for TST as compared to IGRA though it is most likely that they arise as the result of false-positive TST results which has practical implications when screening a predominantly BCG-vaccinated population – such as recent immigrants from overseas.[39] An important caveat is that prospective long-term studies are still required to clarify the outcomes for these individuals with discordant results.

Although, as highlighted above, authors have undertaken two-way assessments of the performance of TST compared to IGRA (QFN-GIT or T-SPOT.TB), there is no data from three-way concurrent assessments of TST, ELISA (QFN-GIT) and the ELISpot (T-SPOT.TB) in adult immigrants (non-contacts) which would allow comparisons to be made of the performance of, and concordance between, TST and the two IGRAs as well as the two IGRAs themselves. This type of data is crucial in informing the models behind cost-effectiveness analyses (see section below). To date, two studies have concurrently examined the three diagnostic tests available in immigrants - albeit in very selected populations.[218,292] Kik et al assessed adult immigrant contacts of smear-positive index cases with TST, QFN-GIT and T-SPOT.TB and found that the TST resulted in a higher proportion of positive results than both IGRAs where the proportion positive was broadly the same (53.9% for QFN-GIT vs 59.6% for T-SPOT.TB).[218] Consequently, concordance between the two IGRAs was higher (kappa 0.68) than between TST and either of the IGRA platforms (0.20 for QFN-GIT, 0.19 for T-SPOT.TB).[218] However the conclusions and generalisability of this study are limited, and must be viewed with caution, as the study

population of recent contacts is unlikely to be representative of the general immigrant population and, more importantly, IGRA testing was only limited to TST positive individuals meaning that a priori the results are likely to have been biased.[218] Lucas and colleagues compared the three diagnostic modalities in child refugees from Africa and Southeast Asia.[292] TST (using a cut-off of 10mm) resulted in a higher proportion of positive results than either IGRA.[292] Whilst concordance between TST and both IGRAs was moderate, there was substantial concordance between the two IGRAs (kappa 0.78).[292] As with the Kik study, however, the selected study population (child refugees) is relatively niche making its generalisability rather limited.

Overall, published studies on immigrant screening with TST and IGRA have provided useful estimates for the prevalence of LTBI in different immigrant populations. However, the literature is still limited for multiple reasons: it is based on single-centre data with small sample sizes, the populations studied have predominantly been undocumented immigrants (refugees and asylum seekers) or high-risk individuals (contacts of index cases) rather than legal immigrants (non-contacts with normal chest radiography) recently arriving from high-burden countries, only immigrants from a narrow range of countries (and by inference TB incidence levels) have undergone testing and there is no data on the prevalence of, and yields for, LTBI at different TB incidence thresholds (rather than an crude overall figure) which would inform economic modelling.

Cost-effectiveness of immigrant screening

Aside from the outcomes of screening immigrants, an additional issue of import is the cost-effectiveness of screening. To date there have been eight published studies exploring the cost-effectiveness of immigrant screening (Table 1.10) which have used a variety of approaches to evaluate cost-effectiveness but most commonly decision-based, and Markov, models.[29,81,217,298-302]

In general the output from these studies has been to conclude which, if any, immigrant screening methodology (CXR, TST, IGRA or combination thereof) is most cost-effective. A notable exception, however, is the work by Dasgupta and Menzies who used empirical data from a local screening service to inform a Markov model with the aim of concluding whether screening immigrants with chest radiography pre-arrival followed by TST (if the CXR showed any abnormalities) was more, or less, cost-effective than screening close contacts of index sputum smear-positive cases (with TST followed by CXR).[298] Amongst 12,998 immigrants screened, 722 had abnormal CXRs, 658 were seen by Chest specialists with 17 cases of active TB (0.13% of all screened) and 353 cases of LTBI (TST >4mm - 53.6% of those screened with TST) diagnosed. Treating those immigrants who were tuberculin positive (but had no active disease) prevented 7.9 cases of TB at an incremental cost of 39,049 dollars per case averted as compared to contact tracing which averted 3.2 cases of TB and was cost-saving.[298] The authors therefore concluded that immigrant screening was not cost-effective. This conclusion must, however, be viewed with some caution for the following reasons: (1) all, rather than targeted high-risk, immigrants (irrespective of their country of origin) were screened with CXR first-off thereby resulting in this protocol entailing large upfront costs through radiography and evaluation of radiographs and patients (whereas contacts were initially screened with TST (which is cheaper) followed by CXR if TST positive), (2) TST was not targeted at high-risk immigrants and the cut-off used would include many immigrants with a false-positive result due to prior BCG vaccination, (3) the authors did not consider IGRA as an alternative to TST and, in terms of the model, (4) the breakdown rate from LTBI to TB disease was very low.[298]

Table 1.10 Studies which have assessed the cost-effectiveness of immigrant screening

Author	Year	Location	Tools assessed	Incidence threshold assessed	Empirical data	Model	Assessment of cost-effectiveness	Conclusion on which tool is most cost-effective
Dasgupta[298]	2000	Canada	CXR and TST	No	Yes	Decision-analysis and Markov	$/ active TB case averted	CXR
Schwartzman[302]	2000	Canada	CXR and TST	No	No	Decision-analysis and Markov	$/ active TB case averted	CXR
Khan[299]	2002	USA	TST vs No screening	No	No	Decision-analysis	$/ active TB case averted	TST
NICE[29]	2006	UK	TST, IGRA, TST+IGRA	Yes	No	Decision-analysis	£/QALY loss averted	TST+IGRA
Oxlade[301]	2007	Canada	CXR, TST, IGRA	No	No	Decision-analysis	$/ active TB case averted	CXR
Hardy[217]	2010	UK	TST+IGRA vs IGRA	No	Yes	Nil	Nil	IGRA
NICE[81]	2011	UK	TST, IGRA, TST+IGRA	No	No	Decision-analysis	£/QALY loss averted	IGRA
Linas[300]	2011	USA	TST vs IGRA	No	No	Markov	$/Life year gained	IGRA

Further, similar, work from this group has been published by Schwartzman[302] and Oxlade.[301] Schwartzman and Menzies constructed a Markov model to compare CXR versus TST for the diagnosis of TB in a hypothetical cohort of immigrants arriving in Canada.[302] Depending on the prevalence of LTBI and HIV in the population, screening with CXR prevented, per 1,000 screened, between 0.2 and 1.6 cases of active disease at an ICER of 3,943-236,496 Canadian dollars per case averted; TST screening averted more cases (0.3-4.6) but at a higher ICER of 32,601-68,799 per case averted.[302] Screening with TST was concluded to be less cost-effective than CXR screening due to the low completion rates of chemoprophylaxis in immigrants identified with LTBI.[302] However, it is likely that alternative reasons can also explain why chest radiography was the most cost-effective tool. The authors assumed a much higher prevalence of active TB in immigrants (2% in HIV negative, 9% in advanced HIV)[302] than that computed in recent meta-analyses,[183,184] a high sensitivity of CXR for diagnosing active disease, a 100% uptake for CXR screening which has been shown in other settings to be unlikely, not using IGRA (which has a superior specificity) as an alternative to TST and no consideration of targeted screening at different incidence levels based on LTBI prevalence from empirical data.

More recently Oxlade et al used a decision-based modelling approach to assess different screening methodologies (CXR, TST, QFN-GIT and TST followed by confirmatory QFN-GIT) for a hypothetical cohort of immigrants from low, intermediate and high incidence settings.[301] They found that CXR screening alone, despite having the least impact on the number of future TB cases, was the most cost-effective protocol, followed by TST, TST plus confirmatory QFN-GIT and, finally, QFN-GIT alone. TST- and IGRA-based protocols, although more expensive, did reduce TB incidence more significantly. Although an advantage of this study was that it considered IGRAs as a potential screening tool, the model assumed a very low prevalence of LTBI in the recent immigrant cohort (as it did not have any empirical data),[301] a low reactivation rate,[301] and the authors did not compare the different commercial IGRAs available.

The preceding studies, incidentally from the same research group, appear to therefore suggest that immigrant screening, if to be undertaken at all, will most cost-effectively be performed using chest radiography to identify active disease. However, these studies were undertaken with a Canadian focus

and, as outlined above, have drawbacks and limitations. There is thus a need for a contemporary health economic analysis of the UK port-of-arrival chest radiography system.

Amongst the remaining cost-effectiveness studies published to date, the focus has been on the diagnosis of LTBI in immigrants. Khan *et al* used a decision-based model to conclude that TST-based screening for LTBI in a hypothetical cohort of immigrants arriving in the US from various regions in the world reduced the number of TB cases by almost 70%, reduced overall costs and was, therefore, highly cost-effective (and cost-saving in certain scenarios).[299] Limitations of the analysis were that the authors did not make it explicitly clear what the true prevalence of LTBI (or active disease) was in the cohort, they used outdated estimates for TST performance and they failed to make it clear what proportion of individuals completed chemoprophylaxis.

Three studies have been conducted in the UK to assess how to most cost-effectively screen immigrants for LTBI.[29,81,217] In 2006, as part of the revision of UK national guidance, NICE commissioned a health-economic analysis of immigrant screening focusing on which groups should be screened for LTBI and how they should be screened.[29] Using a decision analysis model, the authors concluded that all children under 16 years of age from countries with TB incidence >40 cases/100000 per annum and 16-35 year-olds either from Sub-Saharan countries or countries with TB incidence >500 cases/100000 per annum should be screened for LTBI using TST or dual TST plus confirmatory IGRA approach;[29] screening of over 35s was not considered as the risks of chemoprophylaxis outweighed the potential benefits.[29] The detailed nature of this work allowed the framing of screening recommendations based on age, TB incidence and optimal diagnostic modality. However, it is unclear how some of these recommendations were made as the model had several limitations. One of the major drawbacks of this work was that there was an absence of empirical data in several key areas including: the prevalence of LTBI in immigrants stratified by TB incidence threshold (and so an overall prevalence figure for the whole cohort was used), the proportion of immigrants that would fall into each incidence threshold (thereby allowing computation of how many would be eligible and not eligible for screening) and the proportion of immigrants testing positive with, and the comparative performance in this population of, different screening modalities such as TST and IGRA (and at different levels of incidence). [29] Furthermore, the model did not include HIV infection and only

explored using IGRAs as a generic diagnostic tool without considering the different platforms available (ELISA – QuantiFERON Gold in-tube versus ELISpot – T-SPOT.TB) despite evidence suggesting their diagnostic performance differs.[41]

In a separate study, Hardy and colleagues drew on outcome data from a local immigrant screening programme which used single-step IGRA (QuantiFERON Gold in-tube) to calculate the relative costs of screening immigrants with different diagnostic modalities and concluded that the single-step IGRA had lower total screening costs, and was therefore more cost-effective, than the dual TST plus IGRA approach.[217] However this analysis was based on a relatively modest number of immigrants screened almost exclusively with IGRA alone with the authors making simplifying assumptions about the TST results.[217] More importantly this analysis was essentially a simple assessment of the raw costs of screening and cannot be considered a formal economic analysis as the authors did not employ a decision-analysis model with its attendant complexities.[217] For example they did not factor in the diagnostic performance of the different screening tools, they did not consider costs other than those incurred through screening (such as the costs of LTBI treatment and hepatotoxicity), the authors did not employ a time-horizon to calculate the number of cases of active TB that would occur with the different screening scenarios thereby preventing them from calculating effectiveness, cost-effectiveness and the costs associated with the diagnosis, treatment and contact-tracing of active TB cases.[217]

Most recently, in 2011, as part of the revision of the NICE guidance on immigrant screening a new health-economic analysis was undertaken[81] using the same basic model as that in the 2006 NICE guidance although the conclusions from the analysis had radically shifted. NICE recommended that all individuals (children and adults aged ≤35) from countries with TB incidence >40/100000 should be screened with dual TST plus IGRA or single-step IGRA.[81] The different conclusions, from essentially the same models, may seem incongruous but are likely to stem from the use of different model parameters in the 2011 iteration including a higher prevalence of LTBI, higher progression rate from LTBI to active TB disease and very different parameters for the diagnostic performance of TST and IGRA.[81] However, these new guidelines continue to have similar limitations to the previous 2006 guidance by being based on scenarios rather than empirical screening data and therefore have been

unable to definitively address key issues, such as which screening strategy should be preferred (dual TST plus IGRA or IGRA alone), which of the two commercially available IGRAs (QuantiFERON-Gold in-tube and T-SPOT.TB) is more cost-effective, and which, if any, intermediate incidence threshold may be most cost-effective in diagnosing LTBI in recent immigrants.[81]

Patterns of tuberculosis in immigrants in the United Kingdom

In the previous sections I have primarily concentrated on the epidemiology of tuberculosis in high-income countries (with a specific focus on the UK), the reasons underlying this pattern and the current control measures in place. In this next section, I will now shift focus and discuss the other main issue of note in immigrant TB in the UK (and in other high-income countries) which is the observed clinical phenotypes of active disease as a means of exploring what, if any, factor(s) play an important role in determining disease patterns.

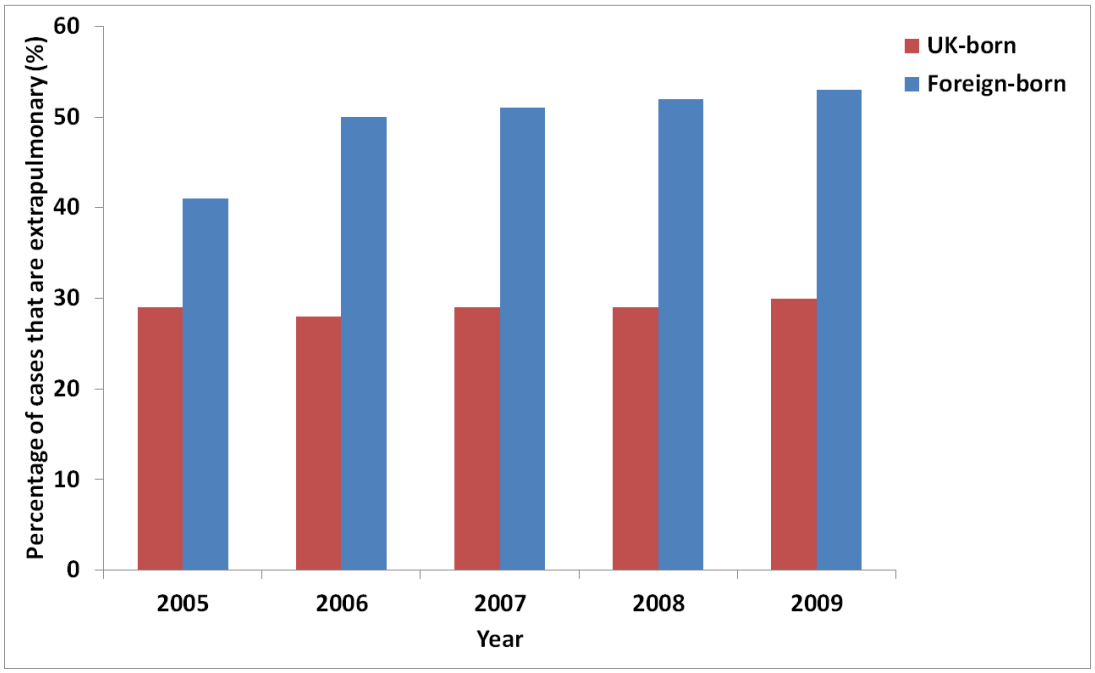
Although TB presents as a broad spectrum of clinical phenotypes, clinically categorised as pulmonary and extrapulmonary (where only one or more extrapulmonary site(s) is affected without concurrent pulmonary involvement) disease, globally, pulmonary TB makes up the vast majority of disease[103] though extrapulmonary TB, which is more difficult and expensive to diagnose and treat, whilst still less common than pulmonary disease is becoming increasingly common.

In the UK in 2009, 70% and 30% of clinical cases in the local born population were pulmonary and extrapulmonary respectively.[140] By contrast, in the foreign born population, disease was predominantly extrapulmonary (53%) rather than pulmonary (47%).[140] Previous national TB surveys did not specifically subdivide the population into UK-born vs. foreign born instead stratifying by ethnic group (White and Indian Subcontinent mainly).[158-165] In these studies, from 1978 onwards, it was clear that individuals of Indian Subcontinent ethnicity were significantly more likely than their White counterparts to present with non-respiratory disease (defined at the time as disease other than pulmonary, pleural and intrathoracic lymph nodes).[160-165] As an example, in 1978, purely non-respiratory disease (without concurrent respiratory disease) occurred in 16% of White and 33% of

Indian Subcontinent patients with a quantitatively similar figure of 19% for the White population but a higher figure of 38% for individuals from the Indian Subcontinent in 1988.[161,163] In fact extracting ethnic-specific data over the period 1978-1993 it is clear that the proportion of disease that is purely extrapulmonary within the Non-White, and to a lesser degree the White, population has increased over time.[160-163,165]

More recently, Kruijshaar and Abubakar, using national surveillance data, analysed trends in extrapulmonary disease in the UK over the period 1999-2006.[33] They found, as others have shown in high-income countries such the US, Canada, Netherlands and Germany, a significantly increasing trend, over time, for extrapulmonary TB which, on multivariate analysis, was independently associated with foreign birth and non-White ethnicity.[33,34,118,303,304] Although the authors did not specifically document the temporal changes in the local- and foreign-born populations in this study, it is possible by extracting data from the HPA's national TB reports to obtain an overview of the temporal changes between 2005 and 2009 (figure 1.13).

Figure 1.13 Proportion of cases that are extrapulmonary in UK-, and foreign-, born individuals in the UK during the period 2005-2009

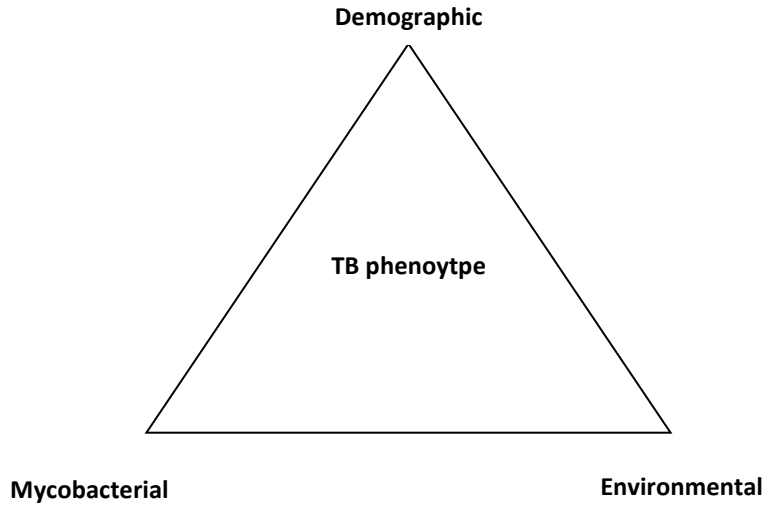


Footnote
[1]Source[304]

Although these surveys and studies from the UK are useful as they provide important descriptive information about the changing pattern of disease, one major limitation is that they fail to consider the possibility of misclassification bias. Earlier and more recent studies, by classifying on the basis of ethnic group, or indeed on the basis of country of birth, fail to pick up the non-White "second generation immigrants" – in other words individuals of non-White ethnicity but actually born in the UK. Therefore classifying by ethnic group alone (or indeed by location of birth alone) does not describe the pattern of disease in the UK born non-White ethnic groups thereby failing to capture the full heterogeneity in clinical phenotypes in the UK. Secondly, and potentially more importantly, despite the striking differences observed in disease patterns these studies do not attempt to elucidate on the factors underlying these observations.

Whilst advances have been made in understanding the biology of tuberculosis, relatively little is still know about the factors influencing clinical presentation in immigrants specifically and in the general population more broadly. Nonetheless it is possible to categorise the causative factors into demographic, mycobacterial and environmental (Figure 1.14). Below I discuss each of these factors in turn.

Figure 1.14 Schematic representation of potential factors determining clinical phenotype



Influence of demographic factors on clinical phenotype

Although extrapulmonary disease is generally less common than pulmonary disease, this rule does not, however, hold true for all population subgroups with certain factors associated with specific clinical phenotypes.

Epidemiological evidence from the pre-highly active antiretroviral therapy (HAART) era, as well as more recently, has suggested that HIV infection is one of the most important determinants of clinical phenotype resulting in a significantly increased risk for extrapulmonary disease.[35,305-308] Given that extrapulmonary TB is increasingly common as HIV-induced immunosuppression advances,[32,309] it may be inferred that extrapulmonary disease in a non-HIV setting may, in some cases, reflect impairment of host responses that mediate bacterial containment in-vivo. Other demographic factors implicated in increasing the risk of extrapulmonary disease include age, diabetes, malnutrition, gender, ethnicity (non-White) and foreign-birth[32-35,118,303-305,310-314] although the direction of effect has not always been clear. For example, whilst Spanish,[310] Dutch[34] and UK[33] studies found that increasing age was associated with extrapulmonary disease, a US-based analysis concluded the opposite.[35] However, closer examination of the results from these studies does suggest that the risk of extrapulmonary TB increases until the fourth or fifth decade of life before decreasing again which may reflect a relative decrease in host immunity with increasing age. A number of studies have also found that females are more likely to develop extrapulmonary disease as compared to males.[32-35,305,310-312] The reason(s) underlying this disparity remain unclear and may be biological or social.[315 316] As alluded to earlier, epidemiological data from high-income countries (including the UK, US, Canada, the Netherlands and Germany) shows that there has been a shift from a pulmonary to extrapulmonary pattern of disease[34,118,303,304] which has primarily been attributed to the high, and increasing, proportion of extrapulmonary cases amongst the foreign-born ethnic minority population (particularly immigrants from Africa and Asia).[33,34,118,303,304,313,314] Multivariate regression analyses have highlighted the fact that foreign-birth and non-White ethnicity are independent risk factors for developing extrapulmonary disease.[33,34,310,313,314] However, it is unclear whether these factors alone increase the risk of extrapulmonary disease or if they simply act as proxy variables for a third, unmeasured, variable.

Host factors found to be associated with extrapulmonary TB suggest a potential role for innate immunity in the prevention of extrapulmonary dissemination. Host (genetic) factors implicated in determining the clinical spectrum of disease include, amongst others, polymorphisms in vitamin D receptor,[317,318] IL-1β,[318,319] Toll-like receptor 2,[318] Lymphotoxin alpha[320] and the P2X7 gene.[321] In a study undertaken in Northwest London, Wilkinson and colleagues studied a group of Gujarati patients to assess the impact of polymorphisms in the vitamin D receptor on the risk for, and clinical pattern of, active TB and found that the f allele was associated with localised, extrapulmonary disease although the phenotypic classification used by the authors was not clear.[317] In a separate US population Motsinger-Reif and colleagues found a statistically significant association between the Fok1 polymorphism in the vitamin D receptor and extrapulmonary, as compared to pulmonary, tuberculosis.[318] However, the sample size was very small and the population was predominantly Afro-Caribbean which makes it difficult to generalise the findings to different populations and settings.

Influence of mycobacterial factors on clinical phenotype

Strain diversity has been shown, in other bacterial pathogens (such as *Staphylococcus aureus*[322]), to play a role in determining disease phenotype. Up until relatively recently, however, it was thought that this did not apply to *M .tuberculosis* which, in the absence of genotyping tools, was thought to exhibit little or no genetic variation.[323,324] However, over the last two decades, advances in genotyping methods have resulted in a rethinking of this concept.

Evolution of genotyping methods in Mycobacterium tuberculosis

In the early 1990s, independent groups[325,326] described the insertion sequence IS*6110* which was shortly followed by IS*6110*-RFLP typing which became, at the time, the routine, gold-standard method of typing *M. tuberculosis*.[327] Although RFLP was a useful tool in molecular epidemiology which allowed researchers, and public health physicians, to explore transmission dynamics in different populations (including understanding the relative importance of clustering, recent infection, reinfection and relapse) it was time-consuming, technically demanding, required a large amount of DNA and

results were difficult to compare across laboratories.[323] As a consequence, PCR-based methods such as spoligotyping and MIRU-VNTR (Mycobacterial Interspersed Repetitive Unit-Variable Number Tandem Repeats) which require smaller amounts of DNA have become increasingly popular.

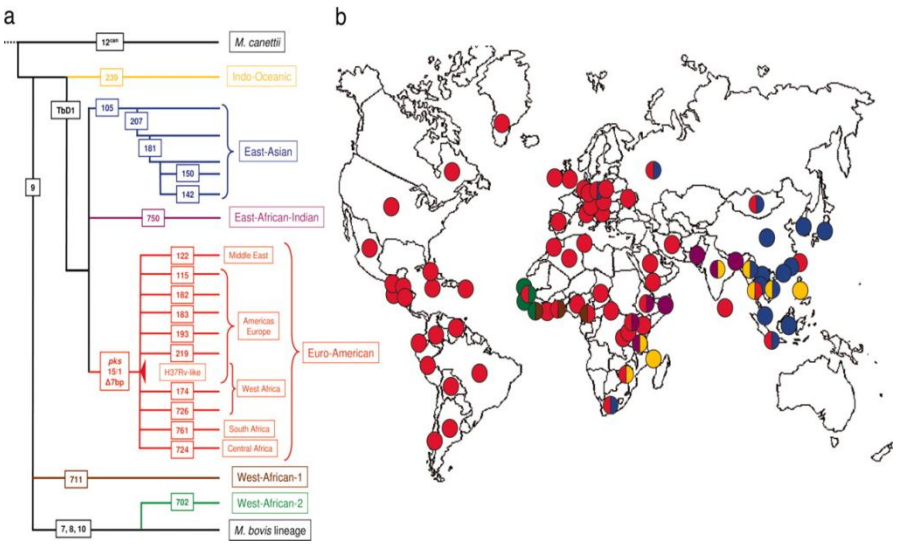
Spoligotyping is a useful, inexpensive, tool which allows both detection and strain identification simultaneously but may be less discriminatory than RFLP.[328] In 1997, Supply and colleagues discovered MIRU-VNTR typing which relied on repetitive DNA elements throughout the *M. tuberculosis* genome.[329] Initially MIRU-VNTR was based on 12 loci which were subsequently refined to a highly discriminatory set of 15 different loci and, most recently, 24 loci.[330]

Further alternative, PCR-based, methods have also been developed including single nucleotide polymorphisms (SNP) and large sequence polymorphisms (LSP).[331] LSPs are based on the theory that on-going horizontal gene transfer occurs very infrequently in *M. tuberculosis* and deleted regions cannot be reacquired.[332] This, therefore, allows robust phylogenies to be constructed.

Phylogeography of Mycobacterium tuberculosis

With the aid of LSP-based analysis, authors have analysed large datasets from multiple countries and been able to identify six main lineages of *M. tuberculosis*: Indo-Oceanic, East Asian, East African Indian, Euro-American, West African 1 and West African 2.[331,333] In addition, previous work from Gagneux[331] and others[333-336] has shown, epidemiologically, that these lineages co-associate with distinct geographic regions – such as the East-Asian lineage with East and Southeast Asia or the Euro-American lineage with Europe and the Americas (see Figure 1.15 for results of Gagneux study). However, these studies have the limitation that they presented their results by the geographic origin of individuals rather than ethnic group even though a proportion of the individuals included in the study would be second generation immigrants who may be born in the local country (such as the UK) but of non-White ethnicity.

Figure 1.15 The global population structure and geographical distribution of *M. tuberculosis* from the Gagneux study



Footnote

[1]Source[331]

Association of mycobacterial genotype and clinical phenotype

As genotyping methods have developed, experimental data from clinical strains indicates that individual lineages differ in the immune response that they induce;[323] prior work has shown that the Beijing (East Asian) lineage induces lower levels of inflammatory cytokines[337,338] such as tumour necrosis factor (TNF) whilst also exhibiting enhanced growth in macrophages.[339] Moreover, there is evidence that the Beijing (East Asian) lineage is more virulent as it causes more necrosis, and less apoptosis, in infected macrophages.[340] Whilst these *in vitro* differences in host response might be expected to result in the well-recognised different clinical phenotypes observed in distinct demographic (ethnic) groups,[34,314] in reality the impact and influence of different lineages on clinical patterns of active tuberculosis (TB) still remains unclear.

Limited data from a few settings suggest that mycobacterial lineage determines both progression from LTBI to active disease[341] and, in certain cases, particular patterns of active

disease.[342-345] Caws and colleagues found, in a Vietnamese population, that the Euro-American lineage was significantly more associated with pulmonary than meningeal TB although the number of Euro-American strains in the study was relatively small.[342] Recent studies from Italy[346] and Sweden[347] have suggested that the Central Asian lineage (also known as the East African Indian lineage) is associated with extrapulmonary disease whilst two Pakistani[348,349] studies found the opposite. More authors have studied the Beijing (East Asian) lineage which, in certain ethnic groups, has been associated with a more aggressive clinical course[350] and extrapulmonary forms of TB[343-345] although other studies have failed to document these associations.[346,351,352] One of the main drawbacks of the studies conducted to date is that they have, in the main, examined homogeneous populations where the relative impact of demographic factors (particularly ethnicity and location of birth), as compared to lineage, on disease phenotype cannot be, or have not hitherto been, independently controlled for which may explain the differing conclusions.

Influence of environmental factors on clinical phenotype

Whilst there is some evidence, albeit limited, for the association of demographic and mycobacterial factors with clinical phenotype, there has, to date, been relatively little published on the impact that environmental factors have on clinical phenotype. Previous small-scale work has indicated that cigarette smoking and alcohol are preferentially associated with pulmonary, rather than extrapulmonary, disease.[310,316,353,354] However, the magnitude of effect in these studies was variable and it is unclear whether smoking and alcohol were causal or merely markers of a third, unmeasured, factor.

Aims and objectives

The main aim of the current work was to explore in detail tuberculosis in the United Kingdom, especially in the immigrant population, with reference to investigating two separate, but related, issues.

First, in view of the high incidence of TB in the UK, the disparity in incidence rates amongst UK- and non-UK born individuals as well as the importance of migration and reactivating LTBI in determining TB incidence, I examined the issue of TB control in the UK with a specific focus on control of TB in the immigrant population.

Although the majority of TB in high-income countries, including the UK, occurs through the reactivation of LTBI in immigrants, I hypothesised, based on the failure to reduce UK TB incidence, that most high-income countries and primary care organisations in the UK would preferentially screen immigrants for active TB rather than LTBI. In order to test these hypotheses my first objective was to undertake an international assessment of immigrant screening practices for TB in high-income Organisation for Economic Cooperation and Development (OECD) countries (including the UK) (the first of its kind) to obtain contemporary, objective, data on the groups of immigrants screened, whether they are screened for active and/or latent TB and how screening is undertaken (location of screening and tools used). Second, cognisant of the fact that there may be a disconnect between national UK guidance and actual practice, I undertook the first, and most comprehensive, national evaluation of immigrant TB screening practices (by primary care organisations and local TB services) with specific areas of interest including which immigrants are being screened, which incidence thresholds are used to determine eligibility for LTBI screening, and what screening modalities are used – with responses being referenced against national guidance and TB incidence in the respondent's area to ascertain if this had any impact on screening practice.

Having understood how immigrant screening (particularly for LTBI) is undertaken in the UK, I hypothesised that it would be possible to use empirical screening data to establish how immigrant screening should be most cost-effectively undertaken – particularly with respect to optimal screening thresholds and diagnostic modalities. If this hypothesis was proven, the evidence could provide a

blueprint for immigrant screening policy in the UK. Therefore, the third objective of the thesis was to undertake a multi-centre study to collate prospective empirical immigrant screening data with single-step IGRA to calculate LTBI prevalence, yields at different incidence thresholds and, using the gathered empirical data, construct and parameterise a complex health-economic model to specifically address the question of which incidence threshold is the most cost-effective to screen for LTBI. The fourth objective aimed to build on the health-economic modelling in objective three by answering those questions that NICE guidance (which was revised in 2011) had hitherto failed to address. This was accomplished by undertaking the first community-based study of immigrant screening where different screening modalities were compared and the results then informed a different health-economic model to assess whether chest radiography on arrival should be continued and how best to screen for LTBI (which tools and which incidence thresholds).

The second issue explored in this thesis was based on the disproportionately increased risk for extrapulmonary TB in the immigrant population resident in the UK and whether it was possible to gain insights, from this selected group, into which factors were important in determining the clinical pattern and phenotype of active disease. This broad aim was subdivided into two main objectives which, leading on from objective four above, will be called objectives five and six.

Objective five was to use a well-characterised prospectively collected dataset of active TB cases with genotyping data from Birmingham to assess the relative importance of demographic factors (such as ethnicity) and mycobacterial genotype in determining clinical phenotype. The sixth, and final, objective of the thesis was to use the same Birmingham database, but expanded to incorporate 30 years' worth of data, in conjunction with the publically available US CDC database to assess which, if any, demographic and environmental factors determined phenotype with the stated aim of confirming any positive findings in a third, independent, cohort.

Chapter 2 An international evaluation of immigrant screening practices for tuberculosis in high-income countries

Introduction

As highlighted in the introduction and literature review, in high-income countries tuberculosis (TB) has increasingly become a disease of foreign-born individuals.[118,124] The high level of foreign-born TB in high-income countries is a particular cause for concern as it has the potential to jeopardise established national TB control programmes and this has reopened the debate about how best high-income, migrant-receiving, countries should screen immigrants for TB.[137,273] Although individual high-income countries have their own national guidance on immigrant screening there has been little contemporary comparison of the critical elements of these national guidelines – in particular the immigrant groups targeted for LTBI screening, the incidence threshold at which screening is initiated and the specific methodologies used.

In this chapter, I address this gap in the evidence-base by undertaking an international evaluation of immigrant screening practices in high-income countries with a specific focus on comparing and contrasting critical elements of national guidance including whether screening aims to identify active or latent TB, which groups are targeted for screening, when screening is undertaken in relation to migration and which screening tools are utilised.

Methods

Sampling frame

All 31 high-income member states, as of 2010, of the Organisation for Economic Cooperation and Development (OECD) (see table 2.1) were included in the study.[116] Together these countries have an estimated population of 1.0 billion of whom 109.5 million (10.95% - 95% CI 10.94-10.95%) are immigrants.[355] Six out of the top 10 migrant-receiving countries in the world are OECD high-income countries.[355] Overall, in 2009, median TB incidence in these countries was 7.4/100000 (IQR 6.0-10.6/100000) and a median of 46.9% (interquartile range (IQR): 30.1-65.0%) of cases occurred in foreign-born individuals.[124,356]

Table 2.1 Member states categorised as high-income OECD countries

Country	Responded	Data source
Australia	Yes	Published guidelines
Austria	Yes	Tuberculosis expert from country
Belgium	Yes	Tuberculosis expert from country
Canada	Yes	Published guidelines
Czech Republic	Yes	Tuberculosis expert from country
Denmark	No	
Estonia	Yes	Tuberculosis expert from country
Finland	Yes	Tuberculosis expert from country
France	Yes	Published guidelines
Germany	Yes	Tuberculosis expert from country
Greece	Yes	Tuberculosis expert from country
Hungary	No	
Iceland	Yes	Tuberculosis expert from country
Ireland	Yes	Tuberculosis expert from country
Israel	Yes	Tuberculosis expert from country
Italy	Yes	Tuberculosis expert from country
Japan	Yes	Tuberculosis expert from country
Korea	Yes	Tuberculosis expert from country
Luxembourg	Yes	Tuberculosis expert from country
Netherlands	Yes	Tuberculosis expert from country
New Zealand	Yes	Published guidelines
Norway	Yes	Tuberculosis expert from country
Poland	Yes	Tuberculosis expert from country
Portugal	Yes	Tuberculosis expert from country
Slovak Republic	Yes	Tuberculosis expert from country
Slovenia	Yes	Tuberculosis expert from country
Spain	Yes	Tuberculosis expert from country
Sweden	Yes	Tuberculosis expert from country
Switzerland	Yes	Tuberculosis expert from country
United Kingdom	Yes	Tuberculosis expert from country
United States	Yes	Published guidelines , Tuberculosis expert from country

Areas of interest in questionnaire

An 18-point questionnaire (see table 2.2), based on a previously published questionnaire used for an evaluation of UK screening practices,[357] was formulated to obtain information on immigrant screening practices in each high-income country. If immigrant TB screening was undertaken in the country, further points in the questionnaire included whether screening aimed to identify active or latent TB (or both), which subgroups of new-entrants were screened for LTBI (with a focus on age, country of origin and TB incidence screening threshold), when screening was undertaken in relation to arrival in the host receiving country (pre-, at- or post-arrival) and the screening tools employed.

Table 2.2 Questionnaire used in the study

1. Does [insert name of country here] screen immigrants for TB?
2. If so - do you screen immigrants for active TB, latent TB or both?
3. In terms of screening for active TB - is this compulsory or voluntary?
4. Where is screening for active TB done - pre arrival (in other words in the country of origin), at arrival or post arrival?
5. Which countries are targeted for active TB screening?
6. Is there a specific TB incidence threshold which you consider to be high-risk that requires screening? (eg. if migrant is from a country with a TB incidence >20/100000)
7. Who is targeted for active TB screening - all immigrants, refugees, asylum seekers etc?
8. Which age groups are screened for active TB?
9. How is screening for active TB undertaken - Chest x-ray alone or some other method?
10. Do you screen immigrants for latent tuberculosis?
11. In terms of screening for latent TB - is this compulsory or voluntary?
12. Where is screening for latent TB done - pre arrival (in other words in the country of origin), at arrival or post arrival?
13. Which countries are targeted for latent TB screening?
14. Is there a specific TB incidence threshold which you consider to be high-risk that requires screening for latent tb? (eg. if migrant is from a country with a TB incidence >20/100000)
15. Who is targeted for latent TB screening - all immigrants, refugees, asylum seekers etc?
16. Which age groups are screened for latent TB?
17. How is screening for latent TB undertaken - eg tuberculin skin test or IGRA?
18. Is treatment for latent TB infection compulsory or voluntary?
If you have a copy of your official guidance please could you send this to me.

Data was collected between May and December 2010. This was either through abstracting published, publicly available, national immigrant TB screening guidelines or, more frequently, by contacting named TB control professionals in each country who were intimately involved in local TB control programmes and immigrant screening for TB. In most cases this was the TB control programme director of the country. The initial email asked them to confirm that they were the correct individual to contact with regards to the study. Thereafter, the questionnaire was emailed to them and replies

obtained electronically. Non-responders were sent two further reminder e-mails. At no point were any individual, person-specific data collected on the questionnaire.

Country-specific data

Information for 2009 on country-specific TB incidence, proportion of cases occurring amongst foreign-born immigrants and net migration were obtained from national TB reports,[117,119,121,122,139,147] the WHO global database[120] and OECD migration database.[358] If data for 2009 was not available, I used the most recent, publically available data. Using country-specific TB incidence data, I also subdivided countries into low and high TB incidence countries (low TB incidence <15/100000, high TB incidence ≥15/100000) for certain analyses.

Statistical analysis

Data analysis was primarily quantitative although the open-question nature of the questionnaire and the heterogeneity that existed in each screening programme meant that certain answers had to be further categorised by the investigator. Quantitative analysis was primarily descriptive with categorical responses summarised using proportions and 95% confidence intervals(95% CI). Categorical responses were compared using Fishers exact test. Continuous data were found to be non-normally distributed and therefore summarized with median and interquartile range (IQR), and compared using non-parametric Mann-Whitney U test. Missing data were excluded on a question-by-question basis. Analyses used STATA 12.0 (StataCorp,College Station,TX). A p-value <0.05 was considered significant.

Results

Response rate and profile of responding countries

Data were obtained from 29/31 (93.5%) of high-income OECD countries (table 2.1) but were not available for Denmark and Hungary. For the 29 responding countries the median TB incidence in 2009 was 7.6/100000 (IQR 6.4-10.6/100000), 46.8% (IQR 29.7-64.6%) of TB cases occurred in the foreign-

born and the median net annual number of migrants was 30,623 (IQR 12,322-77,206). There was no significant difference between responder and non-responder countries in terms of median TB incidence (p=1.00), the median proportion of TB cases occurring in the foreign-born population (p=0.68) or median net number of immigrants (p=0.36).

Coverage and extent of immigrant screening for active tuberculosis

Overall 25/29 (86.2%, 95% CI 67.3-96.0%) high-income OECD countries had a system in place for screening immigrants for active TB (see Table 2.3 and Table 2.4). 16/25 (64.0%) screened all legal immigrants and 4/25 (16.0%) screened selected legal immigrants whilst a significantly higher number (24/25 (96.0%)) screened refugees and asylum seekers (p=0.02 as compared to all legal immigrants). 5/25 (20.0%) countries restricted screening for active TB only to refugees and asylum seekers. Screening for active TB was compulsory in 19/25 (76.0%) of the countries that responded.

Countries which screened immigrants for active TB (either refugees and asylum seekers or any legal immigrants) were significantly less likely to be high TB incidence (≥15/100000) (50% vs 95.7%, OR 0.05, 95% CI 0.003-0.59, p=0.018), had a lower median TB incidence (median 7.3/100000, IQR 5.5-9.3/100000 vs median 18.8/100000, IQR 11.6-25.9/100000; p=0.10), lower net annual number of migrants (median 27,056 (IQR 12,322-68,938 vs 77,440 (IQR 17,068-150,406); p=0.59), and higher proportion of TB cases occurring amongst foreign-born individuals (median 47.8%, IQR 31.6-70% vs 24.9%, IQR 11.5-39.1%; p=0.11).

Table 2.3 Current screening practices for active and latent tuberculosis in OECD high-income countries

Country	Screening for active tuberculosis					Screening for latent tuberculosis infection				
	Undertaken?	Compulsory?	Groups screened			Undertaken?	Compulsory?	Groups screened		
			Legal immigrants		Refugees/ asylum seekers			Legal immigrants		Refugees/ asylum seekers
			All	Selected groups				All	Selected	
Australia	Yes	Yes	Yes		Yes	No[1]				
Austria	Yes	Yes[2]	Yes		Yes	No				
Belgium	Yes	No[3]	No	Yes[4]	Yes	Yes	No	No	Yes[4]	Yes
Canada	Yes	Yes[5]	Yes		Yes	No[6]				
Czech Republic	Yes	Yes	Yes[7]		Yes	Yes	Yes	No		Yes
Estonia	No					No				
Finland	Yes	No	No	Yes[8]	Yes	No				
France	Yes	Yes	Yes		Yes	Yes	Yes	Yes		Yes
Germany	Yes	Yes	No	Yes[9]	Yes	No				
Greece	Yes	Yes	Yes		Yes	Yes	Yes	Yes		Yes
Iceland	Yes	Yes	Yes		Yes	Yes	Yes	Yes		Yes
Ireland	Yes	No	Yes		Yes	Yes	No	Yes		Yes
Israel	Yes	Yes	Yes		No	Yes	No	Yes		No
Italy	No					No				
Japan	No					No				
Korea	Yes	Yes	No	No	Yes	No				
Luxembourg	Yes	Yes	Yes		Yes	Yes	Yes	Yes		Yes
Netherlands	Yes	Yes	Yes		Yes	Yes	Yes	Yes		Yes
New Zealand	Yes	Yes	Yes		Yes	No				
Norway	Yes	Yes	Yes		Yes	Yes	Yes	Yes		Yes
Poland	Yes	Yes	No	No	Yes	No				
Portugal	Yes	No	No	No	Yes	Yes	No	No	No	Yes
Slovak Republic	Yes	Yes	Yes		Yes	Yes	Yes	Yes		Yes
Slovenia	Yes	No	No	Yes[10]	Yes	Yes	No	No	Yes[10]	Yes
Spain	No					No				
Sweden	Yes	No	No	No	Yes	Yes	No	No	No	Yes
Switzerland	Yes	Yes	No	No	Yes	No				
UK	Yes	Yes	Yes		Yes	Yes	No	Yes		Yes
US	Yes	Yes	Yes		Yes	Yes	No[11]	Yes		Yes

Footnotes

[1]No formal screening for latent TB but immigrants may have to accept post arrival health undertakings (if initial chest xray suggests inactive TB) where further investigations (including repeat chest xray, sputum examination and tuberculin skin test) are carried out although this may differ from state to state.
[2]For work permit and refugees/asylum seekers, otherwise screening is voluntary
[3]For students a normal CXR may be needed for admission to exams
[4]Selected screening of immigrants through school/university but this is not systematic or formal
[5]Although compulsory, post arrival screening cannot be enforced – although it may affect citizenship application
repeat chest xray, sputum examination and tuberculin skin test) are carried out although this may differ from state to state.
[6]No formal screening for latent TB but post arrival medical surveillance for individuals where initial chest xray suggests inactive TB
[7]Immigrants from certain countries applying for a visa of greater than 90 days or long term residence permission have to provide documentary proof that they do not have TB
[8] Screening is comprehensive for adopted children but informal for all other immigrants
[9]Run at state level not national; selected screening undertaken for Aussiedler (ethnic Germans mainly from the former USSR resettling to Germany)
[10]Selected screening undertaken for work permit (as part of pre-employment screening)
[11]Not compulsory for recent migrants but compulsory for status adjusters

Location of screening for active TB

Countries differed in where they screened for active TB (Table 2.4 and Table 2.5) with several countries tailoring the location according to the type of migrant (for example refugee and asylum seeker vs. legal immigrant). 8/25 (32.0%) countries screened pre-arrival, 5/25 (20.0%) screened at-arrival and, most commonly, 23/25 (92.0%) screened post-arrival – of whom 7/23 (30.4%) screened both pre- and post-arrival but reserved the latter mainly for asylum seekers and refugees only. The United Kingdom (UK) employs a complex system where migrants are screened pre-arrival if they are residents of certain target countries, at-arrival for most migrants and post-arrival if at-arrival screening has failed or needs to be repeated.

Demographic characteristics of immigrants selected for active TB screening

Table 2.4 and Table 2.5 describe the specific groups of immigrants, in terms of age and countries of origin, that are targeted for active TB screening. In the 25 countries that screened for active TB, 23/25 (92.0%) countries screened all age-groups for active TB. The exceptions were Israel and New Zealand which only screened immigrants aged older than 6 months and 11 years respectively.

Countries displayed more variability in the countries of origin that were targeted for screening. 6/25 (24.0%) countries determined which migrants should be screened based on TB incidence in their country of origin; incidence thresholds at which screening was instigated ranged from >15/100000 to >100/100000 although >40/100000 (2/6-33.3%) and >50/100000 (2/6-33.3%) were the commonest thresholds at which to screen for active TB.

19/25 (76.0%) nations selected migrants for screening on the basis of which country they originated from. In general, immigrants arriving from high TB burden countries were most commonly screened; 11/19 (57.9%) countries screened immigrants arriving from any country excluding the EU, North America, Australia and New Zealand. Although certain EU states, such as Romania and Bulgaria, have a high TB incidence, EU laws on the freedom of movement across borders prevent lower TB incidence European countries screening individuals originating from these nations.

Table 2.4 Immigrant screening practices for active tuberculosis in high-income OECD countries

Screen for active tuberculosis (n=29)	
Yes	25 (86.2%)
Compulsory	19 (76.0%)
Location of screening[1]	
Pre-arrival	8/25 (32.0%)
At-arrival	5/25 (20.0%)
Post-arrival	23/25 (92.0%)
Types of immigrants screened for active TB	
All legal immigrants	16/25 (64.0%)
Selected legal immigrants	4/25 (16.0%)
Refugees/asylum seekers	24/25 (96.0%)
Selection criteria for immigrants screened	
Based on age	2/25 (8.0%)
Ages screened	
All	23/25 (92.0%)
Based on TB incidence in country of origin	6/25 (24.0%)
TB incidence screened	
>15	1/6 (16.7%)
>40	2/6 (33.3%)
>50	2/6 (33.3%)
>100	1/6 (16.7%)
Based on specific countries of origin[2]	19/25 (76.0%)
Countries screened	
All	5/19 (26.3%)
All except EU, North America, Australia and New Zealand	11/19 (57.9%)
Other[3]	4/19 (21.1%)
Screening tools utilised in children	
Clinical examination	6/25 (24.0%)
Clinical examination + TST	8/25 (32.0%)
Clinical examination + CXR	0/25 (0.0%)
Clinical examination + TST+CXR	2/25 (8.0%)
TST	3/25 (12.0%)
TST+CXR	3/25 (12.0%)
CXR	3/25 (12.0%)
Screening tools utilised in adults	
Clinical examination	1/25 (4.0%)
Clinical examination + TST[4]	1/25 (4.0%)
Clinical examination + CXR[5]	9/25 (36.0%)

Clinical examination + TST+CXR	2/25 (8.0%)
TST	1/25 (4.0%)
TST+CXR	2/25 (8.0%)
CXR	9/25 (36.0%)

Footnotes

[1]Numbers do not sum to the total as some countries screened at more than one location
[2]Numbers do not sum to the total as Czech Republic screened refugees/asylum seekers from all countries but legal immigrants only from selected countries
[3]Other countries selected for screening included: Kenya, Congo, Moldova, Mongolia, Nigeria, Pakistan, Turkmenistan, Tajikistan, Uzbekistan, and Vietnam (Czech Republic), Sub-Saharan Africa Horn of Africa and South-East Asia (Israel), North Korea (South Korea), Asia, Africa and East Europe (Slovenia)
[4]TST - Tuberculin skin test
[5]CXR – Chest x-ray (chest radiograph)

Table 2.5 Location of, and selection criteria for, screening immigrants for active tuberculosis in selected OECD countries

Country	Timing of screening in relation to arrival in host country			Active tuberculosis – target groups			
	Pre	At	Post	Migrants selected for screening			
				Age	TB incidence (per 100000) threshold	Target countries/regions	Intended duration of residence that triggers screening
Australia	Yes		Yes[2]	All		All countries except Iceland, Monaco, Norway, San Marino, Sweden	>3-12 months[1]
Austria	Yes		Yes[2]	All		All countries except US, Canada and EU	
Belgium		Yes[3]	Yes[2]	All	>50		
Canada	Yes		Yes[2]	All	>15[4]		
Czech Rep	Yes			All		All (if refugee/asylum seekers) Otherwise: Kenya, Congo, Moldova, Mongolia, Nigeria, Pakistan, Turkmenistan, Tajikistan, Uzbekistan, and Vietnam	>3 months/applying for long term stay
Finland			Yes	All	>50		
France	Yes[5]		Yes	All		All countries except EU, USA, Canada, Australia, Japan New Zealand	>2 months
Germany			Yes	All		All high burden countries	
Greece			Yes	All		All countries except EU	
Iceland			Yes	All		All countries except EU (except Bulgaria and Romania), Australia, New Zealand, Switzerland, USA and Canada	
Ireland			Yes	All	>40		>3 months
Israel	Yes			>6 months		Sub-Saharan Africa, Horn of Africa and South-East Asia	
Korea			Yes	All		North Korea	
Luxembourg			Yes	All		All countries except EU	>3 months
Netherlands			Yes[6]	All		All countries except EU, Australia, Canada, Iceland, Israel, Japan, Monaco, New Zealand, Norway, Surinam, Switzerland and the USA	>3 months
New Zealand	Yes		Yes[2]	≥11 years		All countries except North America and EU All countries	>6 months >12 months
Norway		Yes	Yes[2]	All		All countries except EU, USA, Canada, Australia, Japan New Zealand	>3 months
Poland			Yes	All		All countries except EU	
Portugal			Yes	All		All	
Slovak Republic		Yes	Yes[2]	All		All countries except EU	
Slovenia			Yes	All		Asia, Africa and East Europe	
Sweden			Yes	All	>100		
Switzerland		Yes		All		All countries	
UK	Yes[7]	Yes	Yes	All	>40		>6 months
US	Yes[8]		Yes[2,9]	All[8,9]		All[8,9]	Varies[10]

Footnotes

[1]Immigrants from **low risk countries** (American Samoa, Andorra, Antigua and Barbuda, Australia, Austria, Barbados, Belgium, Bermuda, Canada, Chile, Costa Rica, Cuba, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Grenada, Iceland, Ireland, Israel, Italy, Jamaica, Jordan, Libyan Arab Jamahiriya, Liechtenstein, Luxembourg, Malta, Monaco, Netherlands, Netherlands Antilles, New Zealand, Norway, Oman, Puerto Rico, Saint Kitts and Nevis, Saint Lucia, San Marino, Slovakia, Slovenia, Sweden, Switzerland, Trinidad and Tobago, United Kingdom and Northern Ireland, United States of America, United States Virgin Islands, Vatican City) require chest radiographs with applying for permanent stay; immigrant from **medium risk countries** (Albania, Algeria, Anguilla, Argentina, Bahamas, Belize, Bosnia and Herzegovina, Brazil, Colombia, Cook Islands, Egypt, Fiji, French Polynesia, Guam, Hungary, Iran, Japan, Kuwait, Lebanon, Macedonia (the former Yugoslav Republic of), Maldives, Mauritius, Mexico, Montenegro, New Caledonia, Panama, Poland, Portugal, Saint Vincent and the Grenadines, Samoa, Serbia, Seychelles, Singapore, Spain, Syria, Tahiti, Tonga, Tunisia, Turkey, United Arab Emirates, Uruguay, Venezuela, West Bank and Gaza Strip.) are required to be screened for active TB if staying in Australia for >12 months or applying for permanent stay; those from **high risk countries** (all countries not listed above including: China, India, Indonesia, Malaysia, Pakistan, Philippines, Russia, South Africa, South Korea, Thailand and Viet Nam) need to be screened for active TB if staying for >3 months or applying for permanent stay

[2]Post arrival screening for asylum seekers/refugees

[3]Asylum seekers screened at arrival and then twice during the years after arrival (1 year in Flanders, 2 years in Brussels and in Wallonia)

[4]Countries with a 3-year average incidence of smear-positive tuberculosis of >15/100000

[5]Pre-arrival screening for Morocco, Tunisia, Turkey and Poland; otherwise post in France

[6]Immigrants/asylum seekers/refugees aged >12 (>25 in some regions) in the Netherlands from countries with TB incidence >200/100000 are screened after the initial entry CXR with half-yearly chest radiographs for two years (post entry)

[7]Pre-arrival screening for selected countries: Ghana, Burkina Faso, Cote d'Ivoire, Togo and Niger, Kenya, Eritrea, Somalia, Democratic Republic of the Congo, Rwanda, Uganda (visitor applications), Tanzania, Pakistan, Bangladesh, Sudan, Thailand, Cambodia and Laos

[8]Pre-arrival screening undertaken by panel physicians outside the US; in countries with a TB incidence ≥20/100000, immigrants >15 years old are screened with medical examination and CXR, migrants 2-14 years old undergo medical examination and TST/IGRA (and CXR if TST/IGRA positive) and those aged under 2 have a medical examination which, if suggestive of active TB, is followed by TST/IGRA +/- CXR. In countries with a TB incidence <20/100000, migrants aged >15 years undergo CXR whilst those <15 years undergo medical examination which, if suggestive of active TB, is followed by TST/IGRA +/- CXR.

[9]Post arrival screening can either be a repeat CXR of the radiograph for the immigrant (who was previously screened overseas) or screening for active TB (using medical examination, TST/IGRA +/- CXR (if TST/IGRA positive)) in migrants (aged >2 years – originating from all countries) who are already resident in the US and are applying for adjustment of their visa status (undertaken by civil surgeons).

[10]Any duration of stay or individuals applying for ling-term visa status

Methods of screening new-entrants for active TB

Amongst the countries that screened for active TB, the specific screening methods and tools used are summarised in tables 2.4, 2.6 and 2.7

In children, and certain groups of adults such as pregnant women, where chest radiography (CXR) is generally avoided, the commonest methods of initially screening for active TB were clinical examination plus TST (8/25-32.0%) and clinical examination alone (6/25-24.0%).

Adults, and older children, were screened using similar screening methods although responding countries markedly differed in the minimum age at which they used CXRs to screen for active TB – ranging from birth to over 18 years. Overall, screening using clinical examination plus CXR (9/25-36.0%) and CXR alone (9/25-36.0%) were the most frequently used methods of screening adults for active TB.

Table 2.6 Initial mandatory screening methods for active tuberculosis in children in selected high-income OECD countries

Country	Children[1]							
	Clinical examination	Clinical examination and TST	Clinical examination and CXR	Clinical examination and TST and CXR	TST	TST and CXR	CXR	Age applies to (years)
Australia	Yes	No	No	No	No	No	No	<16
Austria	No	No	No	No	No	Yes	No	All
Belgium	No	No	No	No	Yes	No	No	<5
Canada	Yes	No	No	No	No	No	No	<11
Czech Republic	No	No	No	No	No	Yes	No	<15
Finland	No	No	No	No	No	Yes[2]	No	<7
France	No	Yes	No	No	No	No	No	<15[3]
Germany	No	Yes[2]	No	No	No	No	No	<15
Greece	No	No	No	Yes	No	No	No	All
Iceland	No	Yes	No	No	No	No	No	<18[4]
Ireland	No	Yes	No	No	No	No	No	<16
Israel	Yes	No	No	No	No	No	No	<0.5
Korea	No	No	No	No	No	No	Yes	All
Luxembourg	No	No	No	No	Yes	No	No	All
Netherlands	No	Yes[5]	No	No	No	No	No	<12[6]
New Zealand	No	No	No	No	No	No	No	<11
Norway	No	No	No	No	Yes	No	No	<15
Poland	Yes	No	No	No	No	No	No	<18
Portugal	No	No	No	No	No	No	Yes	All
Slovak Republic	No	No	No	Yes	No	No	No	All
Slovenia	No	No	No	No	No	No	Yes	All
Sweden	No	Yes	No	No	No	No	No	All
Switzerland	Yes[7]	No	No	No	No	No	No	All
UK	No	Yes[8]	No	No	No	No	No	<11
US	Yes[9]	Yes[10]	No	No	No	No	No	<15

Footnotes

[1]Although chest radiography may not be the initial screening tool (especially for children) if other screening tools (such as the clinical examination or TST/IGRA) suggest active TB then chest radiography is undertaken regardless of age

[2]IGRA can be used instead of TST

[3]Children aged <10 years only have clinical examination; children aged 10-15 years have clinical examination and TST

[4]Individuals aged between 18 and 35 are screened as per the methods used for children under 18 – ie. clinical examination and TST

[5]In the Netherlands screening with TST only undertaken if the subject has not previously been BCG-vaccinated

[6]In some centres in the Netherlands, legal immigrants not vaccinated with BCG and aged <25 yrs are screened with TST

[7]Questionnaire used to risk stratify

[8]IGRA may be used to confirm positive TST

[9]In the US system, migrants aged <2 years from countries with a TB incidence ≥20/100000 and those aged <15 years from countries with a TB incidence <20/100000 are screened with a clinical examination only. If this is positive/suggestive of active TB, TST/IGRA +/- CXR are undertaken

[10]In the US system, migrants aged 2-14 from countries with a TB incidence ≥20/100000 are screened with clinical examination and TST (or IGRA). If any of these screening tests are positive/suggestive of active TB a CXR is undertaken

Table 2.7 Initial mandatory screening methods for active tuberculosis in adults in selected high-income OECD countries

Country	Adults[1]							
	Clinical examination	Clinical examination and TST	Clinical examination and CXR	Clinical examination and TST and CXR	TST	TST and CXR	CXR	Age applies to (years)
Australia	No	No	Yes	No	No	No	No	>16
Austria	No	No	No	No	No	Yes	No	All
Belgium	No	No	No	No	No	No	Yes	>5
Canada	No	No	No	No	No	No	Yes	>11
Czech Republic	No	No	No	No	No	No	Yes	>15
Finland	No	No	No	No	No	No	Yes	>7
France	No	No	Yes	No	No	No	No	>15
Germany	No	No	No	No	No	No	Yes	>15
Greece	No	No	No	Yes	No	No	No	All
Iceland	No	No	Yes	No	No	No	No	>35[2]
Ireland	No	No	Yes	No	No	No	No	>16
Israel	No	No	Yes	No	No	No	No	>0.5
Korea	No	No	No	No	No	No	Yes	All
Luxembourg	No	No	No	No	Yes	No	No	All
Netherlands	No	No	No	No	No	No	Yes	>12[3,4]
New Zealand	No	No	Yes	No	No	No	No	>11
Norway	No	No	No	No	No	Yes	No	>15
Poland	No	No	Yes	No	No	No	No	>18
Portugal	No	No	No	No	No	No	Yes	All
Slovak Republic	No	No	No	Yes	No	No	No	All
Slovenia	No	No	No	No	No	No	Yes	All
Sweden	No	Yes	No	No	No	No	No	All
Switzerland	Yes[5]	No	No	No	No	No	No	All
UK	No	No	Yes	No	No	No	No	>11
US	No	No	Yes[6]	No	No	No	No	>15

Footnotes

[1]Although chest radiography may not be the initial screening tool (especially for children) if other screening tools (such as the clinical examination or TST/IGRA) suggest active TB then chest radiography is undertaken regardless of age

[2]Individuals aged between 18 and 35 years are screened as per the methods used for children under 18 years – ie. clinical examination and TST

[3]In some centres in the Netherlands, legal immigrants not vaccinated with BCG and aged <25 yrs are screened with TST

[4]Immigrants/asylum seekers/refugees aged >12 (>25 in some regions) in the Netherlands from countries with TB incidence >200/100000 are screened after the initial entry CXR with half-yearly chest radiographs for two years (post entry)

[5]Questionnaire used to risk stratify

[6]In the US system, migrants aged >15 from any country are screened with clinical examination and CXR

Coverage and extent of immigrant screening for latent tuberculosis

Tables 2.3 and 2.8 outline the proportion of high-income OECD countries that screen immigrants for latent TB infection. 16/29 (55.1%) of responding countries screened immigrants for LTBI although it was only compulsory in 8/16 (50.0%). Of these 16 countries – 11 (73.3%), 2 (13.3%) and 15 (93.8%) screened for LTBI in all legal migrants, selected legal migrants and asylum seekers/refugees respectively.

Countries which screened for LTBI had a slightly lower TB incidence (7.3/100000 (IQR 5.4-9.5/100000) vs 7.9/100000 (IQR 6.5-21.0/100000; p=0.30); when categorised as low and high TB incidence (< or ≥15/100000) there was a suggestion that high TB incidence countries were less likely to screen all legal immigrants (as compared to selected legal immigrants and refugees) for LTBI (0.0% vs 47.8%, p=0.058). Countries which screened for LTBI had a higher proportion of TB cases occurring amongst the foreign-born population (52.1% (IQR 34.9-69.6%) vs 37.8% (IQR 24.6-55.1); p=0.25) and a higher number of net migrants (32,123 (IQR 11,720-66,507) vs 27,506 (IQR 14,050-119,740); p=0.93) than those countries that did not screen for LTBI.

Location of screening for latent TB

In contrast to the variety of locations where active TB screening was undertaken, countries were more consistent in where they screened immigrants for LTBI (see tables 2.8 and 2.9). However, as when screening for active TB, more than one location was often utilised depending on the status of the migrant.

2/16 (12.5%) countries screened pre-arrival; this was undertaken by the US in certain children (see section below) and Israel which undertakes the first step of the TST for Jewish immigrants migrating from Ethiopia and the second step post-arrival in Israel. 2/16 (12.5%) countries screened at-arrival although this was primarily reserved for asylum seekers and refugees. LTBI screening was most frequently undertaken post-arrival in the host country (16/16-100%).

Table 2.8 Immigrant screening practices for latent tuberculosis infection in high-income OECD countries

Screen for latent tuberculosis infection (n=16)	
Yes	16 (55.7%)
Location of screening	
Pre-arrival	2/16 (12.5%)
At-arrival	2/16 (12.5%)
Post-arrival	16/16 (100.0%)
Selection criteria for immigrants screened	
Based on age	
Ages screened	
No age cut off (ie. all ages screened)	6/16 (37.5%)
Age cut-offs for screening	10/16 (62.5%)
<5	1/10 (10.0%)
<15	2/10 (10.0%)
<35	3/10 (30.0%)
<40	1/10 (10.0%)
Other	3/10 (30.0%)
Based on TB incidence in country of origin	5/16 (31.3%)
TB incidence at which screened[1,2]	
>20	1/5 (20.0%)
>40	2/5 (40.0%)
>50	1/5 (20.0%)
>100	1/5 (20.0%)
>500	1/5 (20.0%)
Based on specific countries of origin[2]	13/16 (81.3%)
Countries screened	
All	5/13 (38.5%)
All except EU, North America, Australia and New Zealand	5/13 (38.5%)
Other[3]	3/13 (23.1%)
Screening tools utilised for LTBI[3]	
TST[4] only	11/16 (68.8%)
TST and confirmatory IGRA[5]	4/16 (25.0%)
IGRA only	3/16 (18.8%)

Footnotes

[1]Numbers do not sum to the total because certain countries (such as Ireland) screened at different incidence thresholds for children and adults.

[2]Certain countries base screening criteria on both incidence threshold and country of origin which is why it does not sum to 15.

[3]Other countries screened: Ethiopia (Israel), Sub-Saharan Africa (Ireland), Asia, Africa and Eastern Europe (Slovenia)

[4]Numbers do not sum to the total because in some countries (such as the UK and US) more than one screening method is allowed/recommended.

[4]TST – tuberculin skin test

[5]IGRA – Interferon gamma release assay

Table 2.9 Location of, and selection criteria for, screening immigrants for latent tuberculosis in selected OECD countries

Country	Location of screening			Criteria by which migrants are selected for latent tuberculosis screening						Screening tools used
	Pre	At	Post	Type of migrants		Age (years)	TB incidence (cases per 100000)	Target countries	Intended duration of residence that triggers screening	
				Legal Immigrants	Refugees/Asylum seekers					
Belgium		Yes	Yes	Yes (selected)	Yes	<5[1]	>50			TST
Czech Republic			Yes	No	Yes	<15		All		TST
France			Yes	Yes	Yes	<15		All countries except EU, North America, Japan, New Zealand and Australia	>2 months	TST
Greece			Yes	Yes	Yes	All		All		TST[2]
Iceland			Yes	Yes	Yes	<35		All countries except EU (except Bulgaria and Romania), Australia, New Zealand, Switzerland, USA and Canada	>1 year	TST
Ireland			Yes	Yes	Yes	<35	>40[3] >500/Sub-Saharan Africa[3]	>500/Sub-Saharan Africa[3]	>3 months	TST
Israel	Yes[5]		Yes[5]	Yes	No	>6 months		Ethiopia		TST
Luxembourg			Yes	Yes	Yes	All		All	>3 months	TST
Netherlands			Yes	Yes	Yes	<12[6]		All countries except EU, Australia, Canada, Iceland, Israel, Japan, Monaco, New Zealand, Norway, Surinam, Switzerland and the USA	>3 months	TST[2]
Norway		Yes	Yes	Yes	Yes	<40		All countries except EU, USA, Canada, Australia, Japan and New Zealand	>3 months	TST plus confirmatory IGRA
Portugal			Yes	No	Yes	All		All		TST plus confirmatory IGRA
Slovak Republic			Yes	Yes	Yes	All		All countries except EU		TST plus confirmatory IGRA
Slovenia			Yes	Yes (selected)	Yes	All		Asia, Africa and Eastern Europe		IGRA

Sweden			Yes	No	Yes	All	>100			TST
UK			Yes	Yes	Yes	<35	>40[4]		>6 months	TST plus confirmatory IGRA or IGRA alone
US	Yes[7]		Yes	Yes[8]	Yes	2-14[7] or >2[9]	≥20[7]	All[9]		TST or IGRA

Footnotes

[1]In general children aged <5 are screened for latent TB although pregnant women of any age can also be screened

[2]TST used mainly although IGRA can be used optionally if diagnosis is unclear/ to confirm the TST result

[3]If aged <16; screening adults (aged 16-35 years) from >500/100000 or from Sub-Saharan Africa

[4]Previous threshold for UK was >40/100000 if aged <16 years and 500/100000 or Sub-Saharan Africa if aged 16-35 years

[5]Frst step for TST for Jewish immigrants from Ethiopia is performed in Addis Ababa (ie. pre-arrival) and the second step post arrival in Israel

[6]Applies to individuals who are not bacilli-Calmette Guerin vaccinated; in some centres in the Netherlands immigrants <25 years are screened for LTBI

[7]In the US system, migrants aged 2-14 years from countries with TB incidence ≥20/100000 are screened with TST or IGRA pre arrival in their country of origin. Some individuals are therefore identified as having latent TB and are advised to seek medical attention on arrival in the US.

[8]In the US system, migrants can be screened post-arrival if their initial screening tests suggest they have inactive TB.

[9]All migrants aged >2 years who apply to have their visa status adjusted (status adjusters) are screened with TST or IGRA.

Demographic characteristics of immigrants selected for latent TB screening

Tables 2.8 and 2.9 detail which immigrant subgroups are targeted for LTBI screening. In the 16 countries that screened for LTBI (and imposed age cut-offs) there was a wide range of ages which were selected for screening (from birth to any migrant aged under 40 years). In general children and young adults (9/16-56.3%) were most commonly targeted for screening although 8 countries (50.0%) imposed no upper age-boundary for LTBI screening.

Selection of migrants to screen for LTBI as determined by TB incidence in the country of origin or by specific countries of origin was undertaken in 5/16 (31.3%) and 13/16 (81.3%) countries respectively; the US and Ireland's selection criteria used both TB incidence and country of origin (see table 2.9). The incidence threshold at which immigrants were screened for LTBI ranged from >20/100000 to >500/100000. Amongst the 13 countries which screened for LTBI based on specific countries of origin, 5/13 (38.5%) screened immigrants arriving from high TB burden regions outside the EU, North America, Australia and New Zealand whilst 5/13 (38.5%) screened immigrants from all countries.

Methods of screening new-entrants for latent TB

Table 2.9 summarises the specific screening methods and tools utilised by the 16 high-income countries that screened immigrants for LTBI.

The most common screening protocol was to use the TST alone (11/16-68.8%). Overall six (37.5%) countries used IGRAs in some form when diagnosing LTBI; three countries used a step-wise TST plus confirmatory IGRA approach, two countries advocated single-step IGRA testing and one country (the UK) recommended both the TST plus confirmatory IGRA approach (for children <16 years and adults aged 16-35 years) and single-step IGRA testing (for adults aged 16-35 years only).

Discussion

Increasing importance is being accorded to immigrant TB as a public health issue in high-income countries[137] which underscores the significance of my data in informing debate about how best to

augment current TB control programmes. This international evaluation of the provision of immigrant screening by high-income OECD countries has revealed that while screening for active TB is frequently undertaken and prioritised, LTBI screening is much less commonly practised. Moreover, the screening that is undertaken, for both active and latent TB, varies greatly between countries with my work indicating that heterogeneity particularly exists in screening location, selection criteria of which immigrant subgroups to screen as well as the specific methods used.

The primary objective of immigrant screening in high-income countries appears to be to diagnose active TB – either prior to migration or soon after arrival in the host country. Whilst it is important to diagnose infectious TB to reduce onward transmission, data from a number of settings suggests that the yields for active TB diagnosed at, or around, the time of migration are low;[186-189,191-197,359,360] this was recently confirmed in two European meta-analyses which found the yields for active TB to be an estimated 0.35% whilst recent data from the UK suggests yields of 0.06-0.1%.[183,184,291,357]

Although most countries did screen for active TB, this was not universal and countries differed in which migrants they elected to screen. Amongst those countries which did screen for active TB, asylum seekers and refugees were most commonly targeted. Whilst these groups are high-risk for having both TB infection and disease, and thus the yields from, and impact of, screening are likely to be higher,[183] they only constitute 2.1% of all immigrants to high-income OECD countries.[355]

There was also evidence of significant heterogeneity in the specific countries of origin and TB incidence in country of origin that were selected for active TB screening. In general, migrants from high TB burden countries were targeted although those high-income countries which used TB incidence as the selection criteria instigated screening at a range of incidence thresholds from as low as >15/100000 to >100/100000. It is unclear why countries had such different recommendations although by setting the threshold at a higher level, it may be that fewer immigrants would be eligible to be screened and thus the yield, in theory at least, would be higher. Moreover, it may reflect the product of each country's unique migration pattern, financial resources and infrastructure to deal with immigrants.

Similar variation was observed in the initial screening tools countries utilised to diagnose active TB. Younger children were often screened with clinical examination+/-TST even though

making the diagnosis of active TB in children is often extremely difficult when based on such limited evidence.[361] Therefore it is preferable to gather as much data as possible in children who are at particular risk of acquiring infection and going on to develop disseminated disease.[361] Adults, and older children, were usually screened with a CXR although the lower age limit at which chest radiographs were permissible varied from birth to 18 years. The wide range likely reflects reluctance to unnecessarily expose children to radiation and the different, more adult-like, patterns of pulmonary disease seen in older children.[362] Nonetheless it should be emphasised that the prevalence of active TB at entry is extremely small and imported active disease which is detectable at the point of arrival amongst immigrants is not driving the increasing disease burden that is seen in the foreign-born in high-income OECD countries.[184] Moreover with epidemiological data suggesting that there is a high, and increasing, proportion of extra-pulmonary TB in the foreign-born population, CXR would play a limited role in diagnosis.[34,314] This would therefore undermine the screening systems (by compromising the yield for TB) that many high-income countries have in place for adults. Indeed, in the United Kingdom a Health Protection Agency review of port health recommended urgent review of the benefits of continuing with chest-radiography as the initial diagnostic test for new-entrants (which is currently underway).[191]

By contrast the epidemiology of TB in OECD nations, combined with data from molecular typing studies, indicates that it is reactivation of imported LTBI in the first few years after migration that is driving the increase in foreign-born TB cases.[225,226,234,236,237,245,247,252,255] Therefore, whilst screening for active TB is clearly important, without commensurate targeting of LTBI it is unlikely to contain TB at a population level.[29,37,363] However, I found that only half of high-income countries screened immigrants for LTBI – with refugees and asylum seekers most commonly targeted for screening. This indicates that screening legal immigrants for LTBI remains a relatively low priority in terms of TB control in high-income countries.

Amongst those countries which do screen for LTBI, there was significant heterogeneity in which immigrant subgroups were screened. In terms of age, children and young adults were most commonly targeted for screening as these are the groups at the highest risk of progression to active TB and hence the most likely to benefit from chemoprophylaxis. However, 47% screened all age-

groups for LTBI suggesting that, in certain countries, older aged immigrants are given chemoprophylaxis – despite the oft-cited concerns about hepatotoxicity.[364]

Similar variability was seen in which immigrant countries of origin were targeted for screening. Amongst those high-income nations which selected on the basis of TB incidence in the country of origin, we found that the TB incidence screening threshold ranged from as low as >20/100000 to >500/100000. This wide variation likely reflects ongoing uncertainty about the optimal threshold at which to screen. A TB incidence threshold which is set too low would result in large numbers of migrants needing to be screened. This would increase costs and likely overwhelm TB services despite many of the migrants from lower incidence countries, who often do not contribute significantly to the TB burden in high-income countries, having a very low prevalence of LTBI.[365] By contrast, if the incidence threshold at which screening is instigated is set too high, very few immigrants would be screened meaning that a large proportion of the immigrant population that has LTBI, and subsequently converts to active TB, would actually be missed.[365] In reality, the most cost-effective policy option is likely to be to screen at an intermediate incidence which balances, most cost-effectively, the numbers being screened (and therefore the associated costs) against the prevalence of, and yield for, LTBI in the immigrant population.[366] However, in many OECD countries, making cost-effective coherent policy decisions about which immigrant groups to screen for LTBI is hampered by the lack of a sound evidence base which results in uncertainty, variability and a lack of consensus in the screening models adopted by individuals countries. This could be appropriately addressed by obtaining prospective data on the prevalence of LTBI in immigrants and calculating the yields, and relative cost-effectiveness of screening at different incidence thresholds as was recently done in the UK.[366] This model could be adopted more widely so that individual countries could formulate country-specific, evidence-based immigrant screening policies.

The methods used for LTBI screening also varied widely. The most commonly used screening method was TST alone. Although TST is widely used, and cheap, it is acknowledged to have shortcomings including poor specificity in BCG-vaccinated populations, such as those migrants arriving in high-income countries, due to antigenic cross-reactivity, poor sensitivity in immunocompromised individuals and several logistic drawbacks including the need for a return visit

and trained staff.[367] Although data suggests that IGRAs have a higher specificity and sensitivity than TST,[367] their use was limited to 40% of high-income countries - both as a confirmatory test for a positive TST but increasingly as a single-step test to replace TST. This may reflect recent, emergent evidence which suggests that IGRAs are cost-effective and, if positive, can predict progression to active TB.[69,217] However, the predictive power of IGRA for progression to active TB does not appear to be significantly higher than TST.[75] Nonetheless there remains a need to obtain empirical data on the relative performance of these tests in immigrant populations, so that contemporary health economic analyses can conclude which screening modality is most cost-effective. Given the pivotal importance of predictive power in improving the cost-effectiveness of testing for LTBI,[366] a more powerfully prognostic test would transform the cost-benefit equation for LTBI screening.

However, an important factor when considering the potential impact of screening for, and treating, LTBI is that sub-optimal completion rates for chemoprophylactic regimens adversely impact on the efficacy of screening programmes thereby underscoring the importance of adopting a patient-centred approach and the need for new, faster-acting, drugs for LTBI.[368,369] Indeed, given these potential drawbacks, an alternative approach, depending on patient preference and risk-perception, could be to register persons testing positive for LTBI, counsel and follow them up for clinical signs for a defined period of time with the aim of rapidly identifying, and treating, infections when they become active. This approach is commonly used in parts of the UK and the Netherlands.[370]

The current study builds on previous research which focused on fewer high-income countries,[275] was undertaken some years ago thereby failing to capture recent changes in guidance,[275] did not specifically focus on LTBI and failed to draw out the critical elements of immigrant screening programmes – such as which immigrants are selected for screening. [275,277]

This study has several limitations. The information was gathered through a questionnaire (either by contacting TB specialists or abstraction of guidelines) with the potential for recall and responder bias although this was minimised, as far as possible, by clarifying any ambiguous responses with the responder and cross-referencing against national guidelines. In addition, this study only captures what screening is currently recommended and thus presents an idealised situation of how screening should be undertaken which may be very different to actual practice at the local level.[357]

Only a detailed assessment of national practice can determine the extent to which national guidance is actually followed.

TB in high-income countries primarily occurs in foreign-born individuals. Current immigrant screening policies in these high-income countries primarily focus on identifying active TB but the prevalence of active disease in immigrants arriving from high TB burden countries is negligible[183,184] making the value of the current strategy doubtful. By contrast, epidemiological data clearly shows that the reactivation of LTBI in immigrants plays a central role in determining national TB burdens, yet LTBI screening, paradoxically, is very limited with no consensus on which immigrants to screen and how to screen. Addressing these areas is critical to effective TB control in high-income countries as it is the identification and treatment of LTBI, where control measures should be targeted whilst remaining vigilant about timely diagnosis and treatment of active disease. In order to address this problem effectively there is an urgent need to generate a large, robust evidence-base to develop affordable, effective and cost-effective policies on which immigrant subgroups to screen, as was recently done in the UK.[366]

Chapter 3 TB screening of migrants to low TB burden nations: lessons from evaluation of UK practice

Introduction

In the previous chapter (chapter two), I presented the results of an international evaluation of immigrant screening practices for TB in high-income OECD countries. This contemporary, comprehensive analysis adds to the evidence-base by highlighting several issues of import to policy-makers including the prioritisation of screening for active TB as compared to LTBI, the wide inter-country heterogeneity in screening practices, particularly in terms of which groups of immigrants are eligible for testing, target countries, TB incidence screening thresholds and methodology. However, the work outlined in the previous chapter represents an idealised situation of what national guidelines advocate should happen in terms of immigrant screening. Actual screening practice, on the ground amongst health care professionals, may differ significantly.

With this in mind, in this chapter, I move on to focus on the UK situation with respect to immigrant screening for TB. Given that the UK exemplifies the enormous impact that migration from high TB burden nations has on the rapidly-growing burden of TB among the foreign-born in low TB burden European nations,[140] and has had revised national guidelines for screening legal, documented, new-entrants in place since 2006[29] (the NICE 2006[29] guidelines were in place at the time that I undertook this section of the thesis), it is an ideal setting in which to evaluate actual (rather than idealised) screening provision for legal, documented, new-entrants by local TB services, the level of adherence to national guidance (NICE 2006) and whether screening provision differs according to regional TB burden. In this chapter, therefore, I address these hitherto unexplored issues by undertaking, for the first time, a nationwide evaluation of immigrant screening for TB in the UK.

Methods

Areas of interest in questionnaire

A 20-point anonymous questionnaire was developed (figures 3.1-3.4) to ask which groups of new-entrants are routinely screened further (which port forms are acted on and whether new-entrants identified through primary-care registrations are screened), the numbers of new-entrants screened and

identified to have active TB or LTBI, which subgroups of new-entrants are screened for LTBI and the methods employed. The questionnaire was pre-piloted amongst TB nurses and Public Health specialists involved in new-entrant screening.

Figure 3.1 Questionnaire (page one) used in the nationwide evaluation of immigrant screening for TB in the United Kingdom

National Survey of TB nurses exploring current methods of screening new entrants

Thank you for filling in the questionnaire. Please tick the boxes which reflect your practice in screening new entrants. Some questions need a typed answer.

Which hospital and PCT do you work in? (please type): ☐

1. Does this PCT have a policy for screening new entrants for tuberculosis? Yes ☐ No ☐ Don't know ☐

2. Which new entrants do YOU screen/investigate further? TICK ANY THAT APPLY:

- New entrants issued with a Port 103 form (abnormal CXR suggests TB) from port of entry ☐
- New entrants issued with a Port 102 form (the CXR cannot exclude TB) from port of entry ☐
- New entrants issued with a Port 101 form (normal CXR) from port of entry ☐
- New entrants identified through GP registrations ☐

3. If you do screen new entrants with a Port 103 form which specific individuals (age groups and countries of origin) do you screen further? TICK ALL THAT APPLY.

	<16 years			16-35 years			>35 years		
	Yes	No	Don't know	Yes	No	Don't know	Yes	No	Don't know
From all countries	☐	☐	☐	☐	☐	☐	☐	☐	☐
From countries with TB incidence >500/100000	☐	☐	☐	☐	☐	☐	☐	☐	☐
From Sub-Saharan Africa	☐	☐	☐	☐	☐	☐	☐	☐	☐
From countries with TB incidence >40/100000	☐	☐	☐	☐	☐	☐	☐	☐	☐

Other: Please specify (type in the box) ☐

4. If you do screen new entrants with a Port 102 form which specific individuals (age groups and countries of origin) do you screen further? TICK ALL THAT APPLY.

	<16 years			16-35 years			>35 years		
	Yes	No	Don't know	Yes	No	Don't know	Yes	No	Don't know
From all countries	☐	☐	☐	☐	☐	☐	☐	☐	☐
From countries with TB incidence >500/100000	☐	☐	☐	☐	☐	☐	☐	☐	☐
From Sub-Saharan Africa	☐	☐	☐	☐	☐	☐	☐	☐	☐
From countries with TB incidence >40/100000	☐	☐	☐	☐	☐	☐	☐	☐	☐

Other: Please specify (type in the box) ☐

Page 1

Figure 3.2 Questionnaire (page two) used in the nationwide evaluation of immigrant screening for TB in the United Kingdom

National Survey of TB nurses exploring current methods of screening new entrants

5. If you do screen new entrants with a Port 101 form which specific individuals (age groups and countries of origin) do you screen further? TICK ALL THAT APPLY.

	<16 years			16-35 years			>35 years		
	Yes	No	Don't know	Yes	No	Don't know	Yes	No	Don't know
From all countries	☐	☐	☐	☐	☐	☐	☐	☐	☐
From countries with TB incidence >500/100000	☐	☐	☐	☐	☐	☐	☐	☐	☐
From Sub-Saharan Africa	☐	☐	☐	☐	☐	☐	☐	☐	☐
From countries with TB incidence >40/100000	☐	☐	☐	☐	☐	☐	☐	☐	☐

Other: Please specify (type in the box) ☐

6. If you screen new entrants identified through GP registrations which specific individuals (age groups and countries of origin) do you screen further? TICK ALL THAT APPLY.

	<16 years			16-35 years			>35 years		
	Yes	No	Don't know	Yes	No	Don't know	Yes	No	Don't know
From all countries	☐	☐	☐	☐	☐	☐	☐	☐	☐
From countries with TB incidence >500/100000	☐	☐	☐	☐	☐	☐	☐	☐	☐
From Sub-Saharan Africa	☐	☐	☐	☐	☐	☐	☐	☐	☐
From countries with TB incidence >40/100000	☐	☐	☐	☐	☐	☐	☐	☐	☐

Other: Please specify (type in the box) ☐

7. Approximately how many new entrants were screened by in this area in these years: 2006 ☐ 2007 ☐ 2008 ☐

8. Approximately how many new entrants (as a percentage) were screened positive for active TB in: 2006 ☐ 2007 ☐ 2008 ☐

9. Approximately how many new entrants (as a percentage) were screened positive for latent TB in: 2006 ☐ 2007 ☐ 2008 ☐

10. Which tools do you use in screening for active TB? PLEASE TICK ALL THAT APPLY

a. Symptom questionnaire	Yes ☐	No ☐	Don't know ☐
b. Sputum if chronic cough (>3 weeks)	Yes ☐	No ☐	Don't know ☐
c. Chest X-ray (CXR)	Yes ☐	No ☐	Don't know ☐

Page 2

Figure 3.3 Questionnaire (page three) used in the nationwide evaluation of immigrant screening for TB in the United Kingdom

National Survey of TB nurses exploring current methods of screening new entrants

11. Do you perform a Mantoux/tuberculin skin test (TST)? Yes ☐ No ☐ Don't know ☐

12a. IF YES TO QUESTION 11. When do you perform the Mantoux/TST in ADULTS? Before CXR ☐ After abnormal CXR ☐ After normal CXR ☐

12b. IF YES TO QUESTION 11. When do you perform the Mantoux/TST in CHILDREN (<11 Before CXR ☐ After abnormal CXR ☐ After normal CXR ☐

13. If you do perform a Mantoux/TST - which specific groups of individuals (ages and countries of origin) do you perform the Mantoux/TST in? TICK ALL BOXES THAT APPLY

	<16 years			16-35 years			>35 years		
	Yes	No	Don't know	Yes	No	Don't know	Yes	No	Don't know
From all countries	☐	☐	☐	☐	☐	☐	☐	☐	☐
From countries with TB incidence >500/100000	☐	☐	☐	☐	☐	☐	☐	☐	☐
From Sub-Saharan Africa	☐	☐	☐	☐	☐	☐	☐	☐	☐
From countries with TB incidence >40/100000	☐	☐	☐	☐	☐	☐	☐	☐	☐

Other: Please specify (type in the box) ☐

14. If you use the Mantoux/TST - What are your criteria for a positive Mantoux in new entrants?

a. If BCG vaccinated?	≥6 mm ☐	≥10 mm ☐	≥15 mm ☐
b. If not BCG vaccinated?	≥6 mm ☐	≥10 mm ☐	≥15 mm ☐

15. Do you use Interferon-gamma release assays (IGRAs)? Yes ☐ No ☐ Don't know ☐

15a. If YES to 15: How are IGRAs used?

a. Standalone	Yes ☐	No ☐	Don't know ☐
b. To confirm a positive Mantoux/TST	Yes ☐	No ☐	Don't know ☐

15b. Which IGRA do you use? QuantiFERON ☐ T-SPOT ☐ Don't know ☐

Page 3

Figure 3.4 Questionnaire (page four) used in the nationwide evaluation of immigrant screening for TB in the United Kingdom

National Survey of TB nurses exploring current methods of screening new entrants

The next few questions deal with preventive therapy/chemoprophylaxis for Latent TB infection (LTBI).

16. Which groups of new entrants do you select for preventive therapy/chemoprophylaxis for LTBI if they have a normal CXR? PLEASE TICK ALL BOXES THAT APPLY

	<16 years			16-35 years			>35 years		
	Yes	No	Don't know	Yes	No	Don't know	Yes	No	Don't know
a.If Mantoux positive and IGRA negative/not don	☐	☐	☐	☐	☐	☐	☐	☐	☐
b.If IGRA positive and Mantoux negative/not don	☐	☐	☐	☐	☐	☐	☐	☐	☐
c.If Mantoux positive AND IGRA positive	☐	☐	☐	☐	☐	☐	☐	☐	☐

17. Do you know which drug regimens are used for chemoprophylaxis? Yes ☐ No ☐

18. IF YES to question 17: Which drug regimes are used? PLEASE TICK ALL THAT APPLY.

a. 6 months of isoniazid ☐
b. 9 months of isoniazid ☐
c.12 months of isoniazid ☐
d. 3 months of rifampicin and isoniazid ☐

19. Approximately how many new entrants did you treat between January 1st 2007-December 31st 2008? (please type) ☐ Don't know ☐

20. What percentage of these completed therapy? (please type in box) ☐ % Don't know ☐

Thank you for filling out this questionnaire. I appreciate it very much.

Page 4

Sampling frame

All 192 UK primary care organisations (PCOs) (152 Primary Care Trusts in England, 22 Local Health Boards in Wales, 14 NHS Health Boards in Scotland and 4 Health and Social Care Trusts in Northern Ireland) were contacted by telephone to identify who had responsibility for screening new-entrants. If there was uncertainty, local Health Protection/Public Health Units in each PCO were also contacted to confirm to whom they forwarded the port forms. In most cases, local respiratory clinics and TB services undertook new-entrant screening (usually TB Clinical Nurse Specialists or Respiratory Physicians) although some areas delegated the task to specialist migrant nurses, health protection nurses, or health visitors.

Anonymous questionnaires were then emailed to those individuals who were most intimately involved in immigrant screening (usually in the local TB service), with a reminder email and telephone call four weeks after the initial mailing. To take account of the fact that immigrant screening is complex and often undertaken in multiple locations, I ensured that the most knowledgeable individual completed the questionnaire to encompass all possible avenues of screening immigrants. If the completed questionnaire was returned electronically it was coded and the accompanying email destroyed. In some cases, the questionnaires were completed over the phone. At no point were any individual, person-specific data collected on the questionnaire.

Statistical analysis

PCOs were categorised as low- or high-TB-burden (incidence less than or greater than 20 TB cases/100000 p.a. respectively) according to their reported incidence in 2007.[371-376] Classification of port forms was in line with national guidance: port 103 - CXR abnormal, port 102 – CXR inconclusive/has not been undertaken, port 101 – CXR normal. PCOs which screened port 102 forms and/or port 101 forms/new-entrants identified through primary-care registrations and offered chemoprophylaxis if appropriate were defined as actively screening for LTBI. Adherence to NICE guidance was defined as following national guidelines without deviation on: which new-entrants should be screened for LTBI (all individuals <16 years old from countries with TB incidence >40

cases/100000 p.a. and 16-35 year olds from countries with TB incidence >500 cases/100000 p.a. or Sub-Saharan Africa)[29] and the methods by which LTBI should be identified (step-wise diagnosis of LTBI beginning with a CXR which, if normal, is followed by a tuberculin skin test (TST) which, if positive, requires a confirmatory test with interferon-gamma release assays (IGRAs) prior to chemoprophylaxis.[29])

Categorical responses from low- and high-burden regions were compared using Pearson's chi-square test (or Fishers exact test if appropriate) and unadjusted univariate odds ratios (with 95% confidence intervals). Continuous data were found to be non-normally distributed and therefore summarized with median and interquartile (IQR), and compared using non-parametric Mann-Whitney U test. Missing data were excluded on a question-by-question basis. Analyses used STATA 9.2 (StataCorp,College Station,TX). A p-value <0.05 was considered significant.

Results

Response rate and TB burden of responding PCOs

Responses were received from 177/192 (92.2%) of PCOs; 76.3% (135/177) were categorised as low-TB-burden areas. There was no significant difference between responders and non-responders in terms of TB incidence (χ^2 =0.06, p=0.79).

Selection of new-entrants for further screening action

Table 3.1 outlines which new-entrants are selected for further screening action. All responding PCOs (177/177) reported that they screened new-entrants issued with an abnormal CXR form. Fewer PCOs screened new-entrants issued with inconclusive CXRs/CXRs not undertaken (134/177-75.7%), normal CXRs (96/177–54.2%) and those identified through new-patient registrations in primary-care (62/177–35.0%).

High-burden PCOs were significantly less likely to screen new-entrants where the CXR was inconclusive/not undertaken (61.9% vs. 80.0%; OR 0.41, 95% CI 0.19-0.86, p=0.019) and where the CXR was normal (28.6% vs. 62.2%; OR 0.24, 95% CI 0.11-0.52, p<0.0001). In addition there was a trend towards high-burden PCOs being less likely to undertake further screening of new-entrants identified through primary care (23.8% vs. 38.5%; OR 0.50, 95% CI 0.23-1.1,p=0.08).

Table 3.1 Proportion of high and low TB burden Primary Care Organisations that undertake further screening action in new-entrants issued with different port notifications or referred from primary care

Method of Referral	Low TB burden PCO n=135(%)	High TB burden PCO n=42 (%)	OR (95% CI)	p value
CXR abnormal[1]	135 (100)	42 (100)	-	-
CXR inconclusive/has not been undertaken[2]	108 (80.0)	26 (61.9)	0.41 (0.19-0.86)	0.019
CXR normal[3]	84 (62.2)	12 (28.6)	0.24 (0.11-0.52)	<0.0001
Primary Care	52 (38.5)	10 (23.8)	0.50 (0.23-1.1)	0.08

Footnotes
[1]CXR abnormal – port 103 form
[2]CXR inconclusive/has not been undertaken – port 102 form
[3]CXR normal – port 101 form

Numbers of new-entrants screened and estimated yield for active TB

78/177 (44.1%) PCOs provided estimates for the numbers of new-entrants screened annually. A median of 70.5 new-entrants (IQR 20-200) were screened annually with no significant difference between low-TB-burden areas (median 60.0, IQR 20-278) and high-TB-burden areas (median 100.0, IQR 25-200)(p=0.91).

Of the 65/177 (36.7%) PCOs that provided details on the proportion of new-entrants identified with active TB (there was no significant difference in those providing versus not providing yield data for active TB in terms of TB incidence (p=1.0); see table 3.2 for numbers of active TB cases identified), the reported yield was very low with a median of 0.0% new-entrants (IQR 0.0-0.5%) eventually diagnosed with active disease. There was no significant difference between low (median

0.0%, IQR 0.0-0.9%) and high-TB-burden PCOs (median 0.0%, IQR 0.0-0.5%) in the yield for active TB (p=0.45) (figure 3.5).

Table 3.2 Estimated numbers of cases of active and latent TB identified amongst those primary care organisations that reported both the numbers of immigrants being screened and the yield for active or latent TB

Active tuberculosis	**Overall (n=64)** [1]
Numbers screened (median, interquartile range)[2]	60.0 (22.5-195.0)
Numbers of active TB cases identified (median, interquartile range)	0.0 (0.0-0.78)
Latent Tuberculosis infection	**Overall (n=38)** [1]
Numbers screened (median, interquartile range)[3]	104.5 (30.0-300.0)
Numbers of latent TB cases identified (median, interquartile range)	7.8 (3.0-30.0)

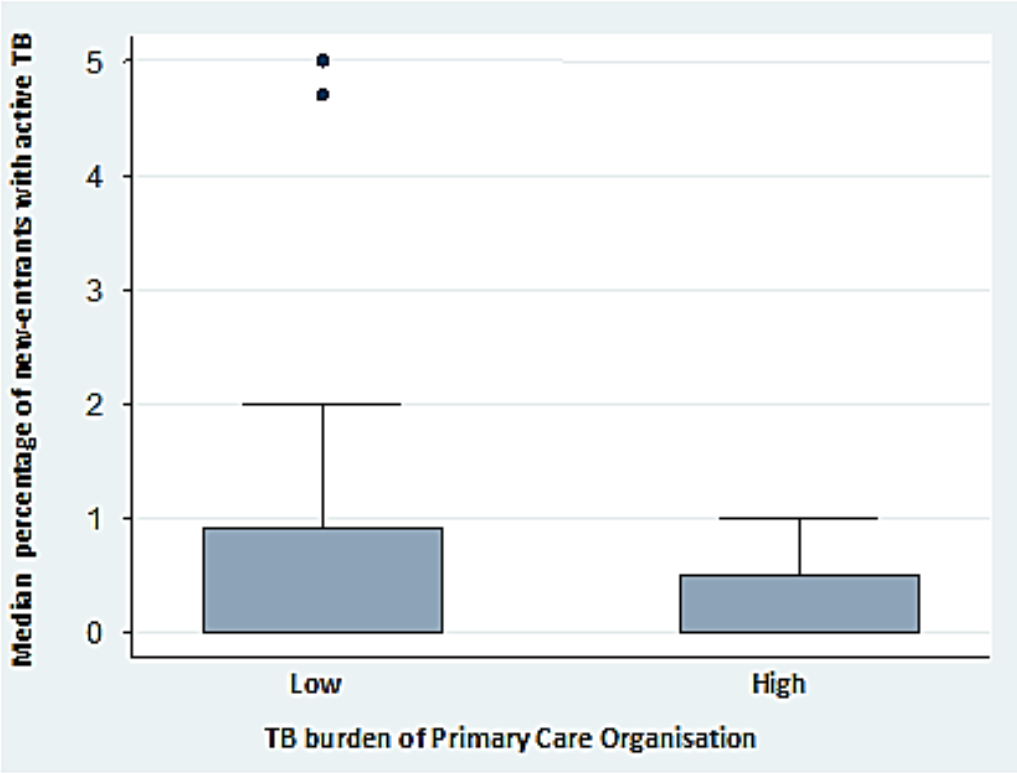
Footnotes

[1]This data will be slightly different to that reported in the text because it only includes those organisation that provided data on both the numbers screened annually and the percentage yield for active (n=64 instead of 65 as in the text because one primary care organisation only provided information on the percentage yield for active TB and not the numbers screened) and latent TB (n=38 instead of 40 as in the text because two primary care organisations only provided information on the percentage yield for latent TB and not the numbers screened.

[2]This refers to the median total number of new-entrants screened by those primary care organisations that screen for active TB (ie. screen individuals with abnormal chest radiographs) and are also able to provide data on both the numbers screened and yield for active TB (n=64).

[3]This refers to the median total number of new-entrants screened by those primary care organisations that screen for latent TB (ie. screen port 102 forms (CXR inconclusive/has not been undertaken) and/or port 101 forms (CXR normal) and/or new-entrants identified through primary care registrations) and are also able to provide data on both the numbers screened and yield for active TB (n=38).

Figure 3.5 Box plot illustrating the median proportion of immigrant new-entrants diagnosed with active TB by low and high TB burden Primary Care Organisations

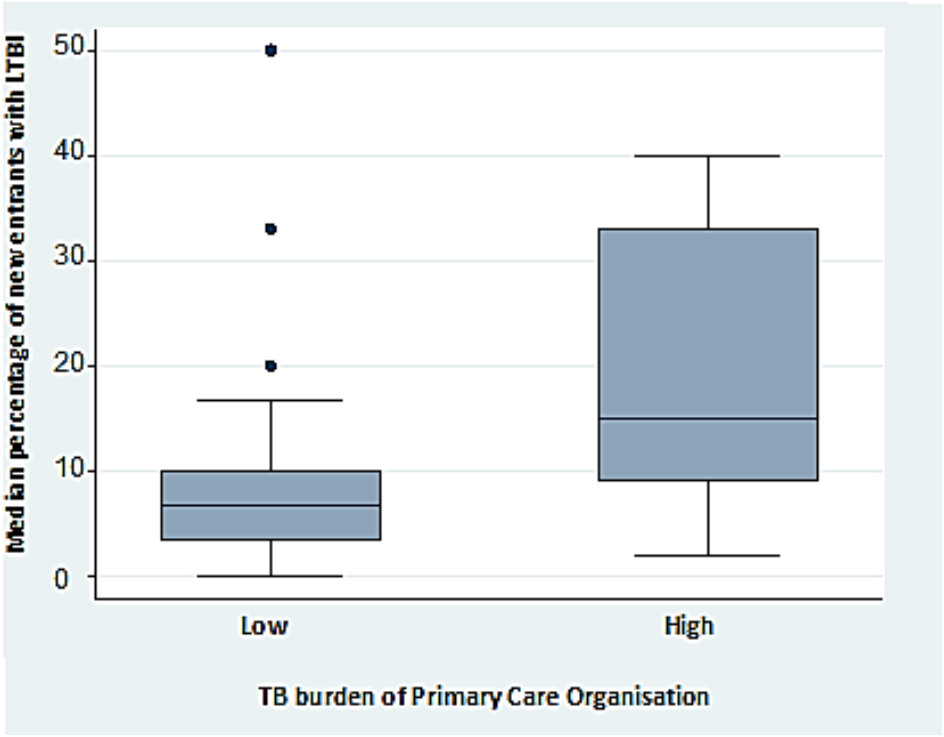


Coverage of screening for latent TB infection and the estimated yield for LTBI

Only 107/177 (60.4%) PCOs screened new-entrants for LTBI; high-burden PCOs were significantly less likely to screen new-entrants for LTBI (35.7% vs. 68.1%; OR 0.26, 95% CI 0.12-0.54,p<0.0001). 105/177 (59.3%) PCOs screened those under 16 years of age, 104/177 (58.8%) screened those aged 16-35 years and 6/177 (3.4%) screened those over 35 years of age.

In the 40/107 PCOs (37.4%) that could provide details for the proportion of new-entrants identified with LTBI (there was no significant difference in those providing versus not providing yield data for latent TB in terms of TB incidence (p=1.0)), 7.85% (IQR 4.30-13.50%) of new-entrants were diagnosed with LTBI. Amongst the PCOs that screened for LTBI, low-burden PCOs identified a lower proportion of new-entrants with LTBI (median 6.70%,IQR 4.30-10.00%) than high-burden PCOs (median 15.00%, IQR 9.00-33.00%)(table 3.2 for numbers of cases of LTBI identified and figure 3.6 for percentage yield for latent TB).

Figure 3.6 Box plot illustrating the median proportion of new-entrants diagnosed with latent TB by low and high TB burden Primary Care Organisations



Selection of new-entrants to screen for LTBI and adherence to NICE guidance

Table 3.3 documents which sub-groups of new-entrants, as defined by incidence in their country of origin, PCOs selected to screen for LTBI. In the 107 PCOs which screened for LTBI overall, 98/107 (91.6%), 105/107 (98.1%), 105/107 (98.1%) and 4/107 (3.7%) reported that they screened under 16 year-olds for LTBI arriving from: countries with TB incidence >40 cases/100000 p.a., countries with TB incidence >500 cases/100000 p.a., Sub-Saharan Africa and other countries respectively. Low TB burden and high TB burden PCOs did not significantly differ in which new-entrants under 16 years of age they selected to screen for LTBI.

PCOs displayed more variability in which new-entrants aged 16-35 years they screened. Whilst 47/105 (data missing for 2 PCOs-44.8%) PCOs screened those from countries with a TB incidence >40/100000 p.a., higher proportions (104/107–97.2%) screened those from countries with a TB incidence >500 cases/100000 p.a. and those from Sub-Saharan Africa.

Fewer PCOs screened individuals over 35 years of age. 2/105(1.9%)(data missing for 2 PCOs) screened new-entrants from countries with TB incidence >40/100000 p.a., 6/105(5.7%) screened individuals from countries with a TB incidence >500/100000 p.a. or Sub-Saharan Africa.

Table 3.3 New-entrant sub-groups stratified by age and country of origin that are screened for latent TB infection

New-entrants aged under 16 years	Low TB burden PCO n=92 (%)	High TB burden PCO n=15 (%)	OR (95% CI)	p
>40 cases/100000 p.a.	84 (91.3)	14 (93.3)	1.3 (0.16-11.5)	0.79
>500 cases/100000 p.a.	91 (98.9)	14 (93.3)	0.15 (0.01-2.6)	0.20
Sub-Saharan Africa	91 (98.9)	14 (93.3)	0.15 (0.01-2.6)	0.20
Other countries	4 (4.3)	0 (0.0)	-	1.00

New-entrants aged 16-35 years	Low TB burden PCO n=92 (%)	High TB burden PCO n=15 (%)	OR (95% CI)	p
>40 cases/100000 p.a.	37 (41.1)[1]	10 (66.7)	2.9 (0.91-9.1)	0.07
>500 cases/100000 p.a.	90 (97.8)	14 (93.3)	0.31 (0.03-3.7)	0.35
Sub-Saharan Africa	90 (97.8)	14 (93.3)	0.31 (0.03-3.7)	0.35
Other countries	4 (4.3)	0 (0.0)	-	1.00

New-entrants aged over 35 years	Low TB burden PCO n=90 (%)[2]	High TB burden PCO n=15 (%)	OR (95% CI)	p
>40 cases/100000 p.a.	1 (1.1)	1 (6.7)	6.4 (0.37-107.5)	0.20
>500 cases/100000 p.a.	5 (5.6)	1 (6.7)	1.2 (0.13-11.2)	0.86
Sub-Saharan Africa	5 (5.6)	1 (6.7)	1.2 (0.13-11.2)	0.86
Other countries	0 (0.0)	0 (0.0)	-	-

Footnotes

Note: Data in table are restricted to the subset of high and low TB burden Primary Care Organisations in the United Kingdom that actually undertake screening for latent TB in new-entrants

[1]For the 16-35 age-group there were missing data for 2 PCOs for the >40/100000 p.a. category and so the denominator was 90 not 92

[2]For the over 35 age-group there were missing data for 2 PCOs and so the denominator was 90 not 92 for all categories

As a consequence, whilst a high proportion of PCOs adhered to 2006 NICE guidance on which under 16 and over 35 year-olds to screen for LTBI (91.6% and 94.3% respectively) far fewer (49.5%) followed NICE guidance on which 16-35 year-olds (who comprise the largest proportion of new-

entrants) to screen. There was no significant difference found between high-burden and low-burden PCOs with respect to adherence to this aspect of NICE guidance.

Methods of screening new-entrants for LTBI and adherence to NICE guidance

Amongst the PCOs which screened for LTBI, the specific screening methods used are summarised in table 3.4.

Table 3.4 Heterogeneity in the protocols and tools (including the uptake of Interferon-gamma-release assays (IGRAs)) amongst those Primary Care Organisations (PCOs) that actually undertake screening for latent TB infection

Sequence of tests used	Low TB burden PCO n=91 (%)[1]	High TB burden PCO n=14 (%)[1]	OR (95% CI)	p-value
New-entrant children				
TST+CXR	23 (25.3)	5 (35.7)	1.6 (0.50-5.4)	0.41
TST+IGRA+CXR	66 (72.5)	9 (64.3)	0.68 (0.21-2.2)	0.52
IGRA+CXR	5 (5.5)	1 (7.1)	1.3 (0.14-12.2)	0.81
Other	2 (2.2)	0 (0.0)	NA	1.0
IGRA used	66 (72.5)	9 (64.3)	0.68 (0.21-2.2)	0.52
New-entrant adults	**Low TB burden PCO n=90 (%)[2]**	**High TB burden PCO n=14 (%)**	**OR (95% CI)**	**p-value**
CXR+TST	5 (5.6)	0 (0.0)	NA	1.0
CXR+TST+IGRA	27 (30.0)	1 (7.1)	0.18 (0.02-1.4)	0.11
CXR+IGRA	3 (3.3)	0 (0.0)	NA	1.0
TST+CXR	18 (20.0)	6 (42.9)	3.0 (0.92-9.7)	0.07
TST+ IGRA+CXR	39 (43.3)	6 (42.9)	0.98 (0.3-3.1)	0.97
IGRA+CXR	2 (2.2)	1 (7.1)	3.4 (0.29-40.0)	0.33
IGRA used	67 (74.4)	8 (57.1)	0.45 (0.14-1.5)	0.19

Footnotes

Note: <16 age-group – n=105 PCOs screened for LTBI, 16-35 age-group n=104 PCOs screened for LTBI; overall n=107 screened for LTBI).

[1]Numbers do not add up to total as 5 low burden PCOs and 1 high burden PCO use more than 1 method of screening

[2]Numbers do not add up to total as 4 PCOs in low burden areas use more than one method of screening

In children (under 16 years-old) 75/105 (71.4%) PCOs use the dual TST and confirmatory IGRA approach, 28/105 (26.6%) still use TST alone, with 6/105 (5.7%) using IGRA as a stand-alone test.

There is considerable variability in the current screening processes for adult new-entrants (table 3.4), which extends to the screening tools used (TST alone, dual TST + confirmatory IGRA or IGRA alone) and the sequence in which they are used. The most common screening protocol for adults is the step-wise TST and IGRA approach (73/104 PCOs–70.2%), although 29/104(27.9%) still use the TST alone. It was interesting to note that high-burden PCOs were more likely than low-burden PCOs to use the TST alone (42.9% vs 25.6%, p=0.18) but less likely to use the TST plus IGRA (50.0% vs 73.3%, p=0.08) with little difference in the proportions using the IGRA alone (5.0% vs 5.6%, p=0.60.)

77/107 (72.0%) PCOs use IGRAs in screening new-entrants (children and adults) for LTBI with fewer high TB burden PCOs (60.0%) than low TB burden areas (73.9%)(OR 0.53, 95% CI 0.17-1.6, p=0.27) routinely using IGRA in new-entrant screening. The use of IGRAs is relatively similar in the under 16(75/105 – 71.4%), 16-35(75/104 – 72.1%) and over 35 age-groups (5/6 – 83.3%). Almost all PCOs which used the IGRA used it as a confirmatory test (76/77 – 98.7%) although a number of PCOs also appear to be using it as a stand-alone diagnostic tool (8/77 – 10.4%). Of the 2 commercially available IGRAs, 59/76 (77.6% - one PCO did not know the name) use the QuantiFERON-Gold (Cellestis, Australia) and 20/76 (26.3%) use T.SPOT.TB (Oxford Immunotec, UK).

Adherence to NICE guidance on the methods by which to screen adult (16-35 years old) and child (<16 years old) new-entrants occurred in 69/104 PCOs (66.3% - 68.9% in low-burden vs 50.0% in high-burden areas (p=0.22)) and 69/105 PCOs (65.7% - 67.0% in low-burden areas vs. 57.1% in high-burden areas (p=0.46)) respectively.

Discussion

This nationwide evaluation of the provision of new-entrant immigrant screening by local primary-care organisations in the UK has revealed that whilst screening for active TB is consistently undertaken, screening for LTBI is highly variable, deviates from national guidance and is inversely related to regional TB burden. This work suggests that heterogeneity particularly exists in the selection of new-entrant subgroups to screen for LTBI and the specific methods used.

Migration and infectious diseases, particularly immigrant TB, are gaining increasing importance as a health policy issue in high-income countries[137] suggesting that these findings have wider implications for most high-income nations. Indeed the study methodology provides a basic template from which high-income nations can evaluate their own new-entrant screening programmes to gain objective insights into how screening is undertaken at the front-line, whether national guidance is being adhered to and whether screening relates to regional heterogeneity of TB burden within and across OECD high-income countries.

I found that all PCOs screened new-entrants issued with an abnormal CXR form presumably as they are suspected to have active TB and thus perceived as the greatest threat to public health.[283] However, abnormal CXR forms comprise only a fraction of all port forms issued. More often port forms indicate that the CXR is either inconclusive/has not been undertaken or normal, but our findings show that fewer PCOs, 75.7% and 54.2% respectively, attempt to undertake further screening action for these port notifications. Only 35% of PCOs reported routinely screening new-entrants identified through primary-care registrations. Therefore, the port-of-entry system remains the main method by which new-entrants are identified and referred for further assessment by local TB services.

Few cases of active TB were diagnosed through new-entrant screening (median 0.0%). Although only 65/177 PCOs provided these data, the yields are similar to previous UK Health Protection Agency (HPA) estimates (0.12%) and local experience from port screening.[183,187,191] This reinforces the view that there is little pulmonary TB to identify amongst new-entrants arriving in the UK, suggesting that the current emphasis on CXR for initial screening may be misplaced.[377] Indeed, a

recent HPA review recommended urgently reassessing the benefits of continuing with the CXR as the initial diagnostic test for new-entrants.[191]

Low yields of active TB and the fact that TB in the foreign-born results largely from reactivation of LTBI[225,252] reinforce the potential of tackling LTBI in new-entrants.[29,37,363] However, we found only 60.4% of PCOs screen new-entrants for LTBI, despite the yield being higher than for active TB. Thus, a substantial proportion of UK PCOs are not implementing NICE guidance on LTBI screening.[29]

In addition, our study has revealed, for the first time, that high-burden PCOs are significantly less likely to attempt to screen new-entrants with normal CXRs for LTBI. This important finding suggests that high TB burden areas in the UK, which account for most foreign-born TB, are the most ethnically-diverse (with individuals who have migrated from TB endemic regions such as the Indian Subcontinent and Sub-Saharan Africa)[378,379] and also have the highest prevalence of LTBI, are actually following-up and screening the lowest proportion of new-entrants. This potentially undermines national policy. Remedying this disparity between current practice and actual need requires a regionally-targeted increase in resources.

Although it was beyond the scope of this study to identify reasons for the disparity in screening for LTBI, it is likely that PCOs determine which new-entrants to screen based on pragmatic considerations such as limited service capacity, a lack of dedicated funds for undertaking organised screening and a feeling that screening asymptomatic persons with normal CXRs provides little benefit in preventing TB.[191,380] It is possible that systematically auditing immigrant screening practices may reduce the heterogeneity that this study has uncovered.

Amongst PCOs which do screen for LTBI, most were relatively consistent, and in line with NICE guidance, in which individuals aged <16 (from countries with TB incidence >40/100000 p.a.) and >35 (screening not recommended) new-entrant subgroups they screened. However, most immigrants are 16-35 years-old and in this group PCOs vary considerably in whom they screen for LTBI.[174] Whilst almost all PCOs screen individuals from countries with a TB incidence >500/100000 p.a. and Sub-Saharan Africa, in accordance with NICE, nearly half of PCOs still screened individuals from countries with a TB incidence >40/100000 p.a.[29] This heterogeneity likely reflects uncertainty

about current NICE guidance which has resulted in targeting only immigrants from Sub-Saharan African countries even though over 60% of foreign-born cases occur in immigrants from non-Sub-Saharan African regions including the Indian Subcontinent, South-East Asia and Latin America where TB incidence ranges from 40-500 cases/100000.[29,284,381]

In addition, PCOs used variable screening methods for adult new-entrants. Although 72.2% of PCOs use IGRAs to identify LTBI, over a quarter still use TST alone. Amongst PCOs that do employ IGRAs, most still use them to confirm a positive TST as per NICE guidance, though a few areas have now moved to single-step IGRA testing. This shift may have been driven by recent evidence suggesting IGRAs are cost-effective and, if positive, can predict progression to active TB.[69,217]

Previous work in this area has been small-scale, hampered by poor response-rates, not focused on comparing screening practices by TB burden and, often, conducted prior to NICE guidance. Nonetheless, a prior smaller-scale survey undertaken by the British Thoracic Society found that a low proportion of TB clinicians undertook new-entrant screening.[382] A previous survey also found that less than half of Public Health Consultants would act on port forms which indicate the CXR is either inconclusive/has not been undertaken or normal-with areas receiving most notifications actually screening the fewest new-entrants.[289]

This study has several limitations. The information was gathered through a questionnaire with the potential for recall and responder bias especially for the small proportions that provided estimates of the yield for active and latent TB. In addition, this cross-sectional survey only provides a snap-shot at one time-point. Although we focused on legal migrants, undocumented migrants are also a high-risk population who are likely to benefit from TB screening although they are often difficult to identify.

Future work should consider emergent data highlighting the high prevalence of LTBI in new-entrants and their elevated rate of progression to active TB[187,212,217,221] to inform revised health-economic models. The resultant cost-effective analyses should, in turn, clarify the optimal threshold of TB incidence threshold in immigrants' countries of origin at which to initiate screening for LTBI and whether screening programmes should move from port-of-entry screening to a primary-care based model which may facilitate wider migrant health programmes such as blood-borne virus

screening.[187,290,363] An urgent reappraisal of screening policy has recently been called for in the UK,[383] where the recently-initiated review of 2006 NICE guidance provides a timely opportunity to prioritise screening for LTBI in a wider spectrum of new-entrants to include those from the Indian Subcontinent, especially in high-burden regions.

Chapter 4 Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis

Introduction

In chapter three, I presented the results of a nationwide evaluation of immigrant TB screening practices in the UK which highlighted the relative prioritisation of screening for active TB as compared to LTBI, the inverse relationship between TB burden (as measured by TB incidence) in primary care organisations and actual screening for LTBI and, despite national guidance being in place since 2006, the highly variable methods of screening for LTBI – both in terms of which immigrants are screened (according to TB incidence) and the methods by which they are screened.

Heterogeneity in selection of which immigrants to screen (as determined by TB incidence in their countries of origin)[357] likely stems from a lack of clarity on the evidence-based rationale underpinning the specific recommendations of the 2006 iteration of the NICE guidelines to target adults (aged 16-35 years) from countries with TB incidence of >500/100000 or Sub-Saharan Africa, particularly in the absence of contemporary empirical data on the prevalence of LTBI, as measured by interferon gamma release assays (IGRAs), and the yields when screening at different incidence thresholds. Furthermore, whilst NICE's recommendation for the 2-step method of screening (tuberculin skin test - TST plus confirmatory IGRA) has been officially adopted by guidelines in most European countries,[77] the US,[384] and many centres in the UK, increasingly use single-step IGRA testing to screen for LTBI.[217,357] This may, in part, be due to their higher specificity[38,47,48] - an important attribute for a screening tool. Additional reasons include emerging evidence suggesting that IGRAs may have the ability to prognosticate future development of active TB in contacts[69,71,72,74,385-390] and residual uncertainty about the optimal cut-off for positive TST in the context of prior bacille Calmette Guerin (BCG) vaccination.[391]

In this chapter, therefore, I present, for the first time, the results of a multi-centre evaluation of single-step IGRA-based new-entrant screening to determine the prevalence of LTBI in immigrants to the UK, how this varies by region of origin and TB incidence in country of origin and the factors associated with LTBI. Using this data I go on to compute the yields from, and cost-effectiveness of,

LTBI screening at different incidence thresholds depending on TB incidence in immigrants' countries of origin.

Methods

Study design and study centres

This project was a multi-centre service evaluation of immigrant screening prospectively undertaken in three UK centres: Westminster (London), Leeds, and Blackburn. Together these three centres serve a combined population of 1.6 million people,[392] of whom 6.5% (IQR 4.3%-9.9%) are foreign-born.[378] Between 2007 and 2009, in these three centres, the 3-year average TB notifications ranged from 54-126 whilst TB incidence varied from 16-33 per 100000 population per year.[393]

Study participants

Study participants comprised foreign-born new-entrants (arrival within preceding 5 years) aged ≤35 years, who were referred for, and underwent, tuberculosis screening during the period 2008-2010.

Referrals to these centres were made either through port-of-entry screening systems and health protection units or following registration with primary care services. Ethical approval was not required because the study utilised fully-anonymised observational data collected as part of the routine delivery of clinical services.

Methods of screening

All immigrants who attended were screened with an initial symptom questionnaire followed by single-step IGRA - QuantiFERON Gold in-tube (Cellestis, Australia), a whole blood ELISA containing ESAT-6, CFP-10 and TB7.7 (Rv2654), which was carried out in accordance with the manufacturer's instructions; results were defined as positive, negative or indeterminate depending on the manufacturer's criteria. A recent meta-analysis of the test performance of the QuantiFERON Gold in-tube suggests that sensitivity is 84% whilst specificity is estimated to be 99%.[41]

Management of symptomatic individuals and positive IGRAs

Immigrants who were symptomatic and/or had a positive IGRA result were referred for chest radiography and further clinical assessment to rule out active TB disease.[29]

LTBI was defined as immigrants with positive IGRA (as defined by the manufacturer) and normal chest radiography in the absence of any clinical features suggestive of active TB.[39] Immigrants diagnosed with LTBI were offered chemoprophylaxis with either 3 months of rifampicin and isoniazid or 6 months of isoniazid, in accordance with UK guidelines[29] - depending on clinician and patient preference.

Data analysis

Data was collected on demographics (age - categorised as <16, 16-25, 26-35 years respectively; gender – male and female), BCG vaccination status (ascertained through documentary evidence, reliable history of vaccination or a characteristic scar[394]) and country of origin. From reported country of origin further classification into region of origin (categorised as Europe/Americas, Middle East/North Africa, Other Asia, Indian Subcontinent, Sub-Saharan Africa) and reported TB incidence in the country (categorised as 0-50/100000, 51-150/100000, 151-250/100000, 251-350/100000 and ≥350/100000) was extracted from the 2009 WHO Global Report on TB.[104]

Continuous data were summarised with median and interquartile range (IQR), and compared using the non-parametric Mann-Whitney U-test. Categorical responses were expressed as simple descriptive percentage (with 95% confidence intervals (95% CI)) and comparisons made using Pearson's chi-square test (or Fishers exact test if appropriate). Yield for LTBI was calculated as the proportion of IGRA positives; indeterminate results were included in the denominator when calculating IGRA-positivity.

Univariate associations of the presence of LTBI (defined as a positive IGRA) with age, gender, region of origin, TB incidence in country of origin and BCG status were assessed using logistic regression and reported as crude odds ratios (OR) and 95% confidence intervals. I subsequently calculated adjusted odds ratios by mutually adjusting, in a multivariate logistic regression, for age, gender and TB incidence in country of origin (to take into account potential

confounders) - using the same categories outlined above. I did not include BCG status in the multivariate model due to the high proportion of missing values. Variables were examined for confounding and for effect modification, and the significance of interaction terms was tested.

Assessment of the different incidence screening thresholds was undertaken by calculating, at each incidence level cut-off, the absolute number of immigrants who would need to be screened, the yield for LTBI and the proportion of individuals with LTBI who would not be detected if screening was undertaken at a particular threshold. As screening of children is a priority in TB control, and because the numbers of child immigrants (<16 years) is small, the only threshold other than the NICE-recommended >40/100000 that I considered was to screen all children irrespective of TB incidence in their country of origin.

Analyses used STATA 9.2 (StataCorp, College Station, TX). All tests were two tailed; p-value of <0.05 was considered significant.

Health economic evaluation

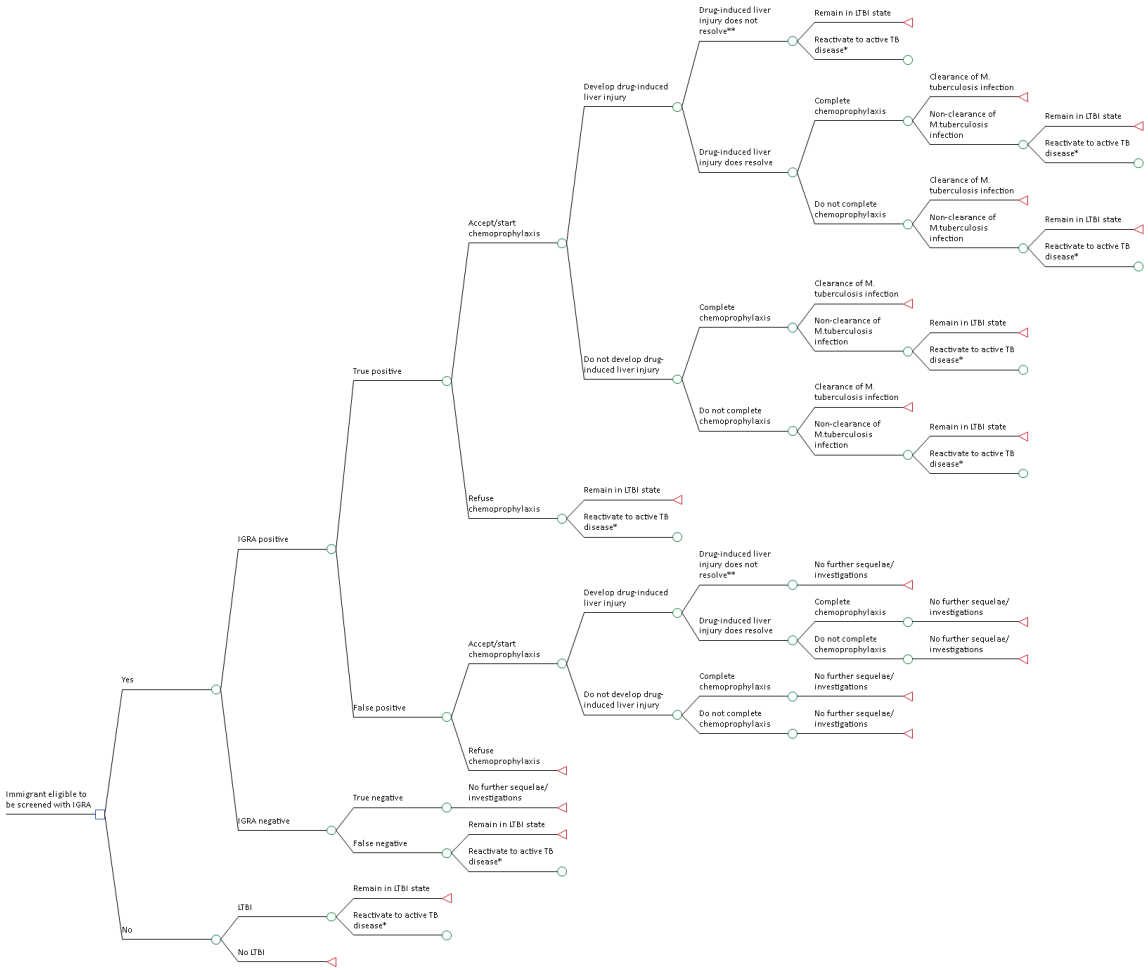
An economic evaluation was conducted from a National Health Service perspective to consider two main questions related to using a single-step IGRA (QuantiFERON-Gold In-tube) LTBI screening strategy over a 20-year time horizon: (a) What are the relative costs of screening at different incidence thresholds? (b) Is it cost-effective to screen at certain thresholds and, if so, which threshold, if any, is the most cost-effective?

Description of decision-analysis model

A decision-tree (figures 4.1 and 4.2) was developed to simulate the clinical (specifically the number of cases of active TB) and economic outcomes of screening a hypothetical cohort of 10,000 recent immigrants to the UK (aged ≤35 years) for LTBI over a 20-year time horizon. Eligibility for LTBI screening is predicated on the migrant's age (whether <16 or 16-35 years) and tuberculosis (TB) incidence in their country of origin (using increments of 50/100000) as shown in table 4.1. I considered screening using QuantiFERON Gold-In-Tube (QFT-GIT) alone and varying the incidence

threshold (in the country of origin) at which individuals became eligible for screening. At each threshold cut-off, I evaluated the number of immigrants who would be eligible for screening, the number who would be IGRA-positive and the number of IGRA-positives that would be missed relative to screening the whole cohort. One of the thresholds considered was the NICE guideline of screening <16 year olds from countries with a TB incidence >40/100000 and 16-35 year olds from countries with a TB incidence of >500/100000 or Sub-Saharan Africa.

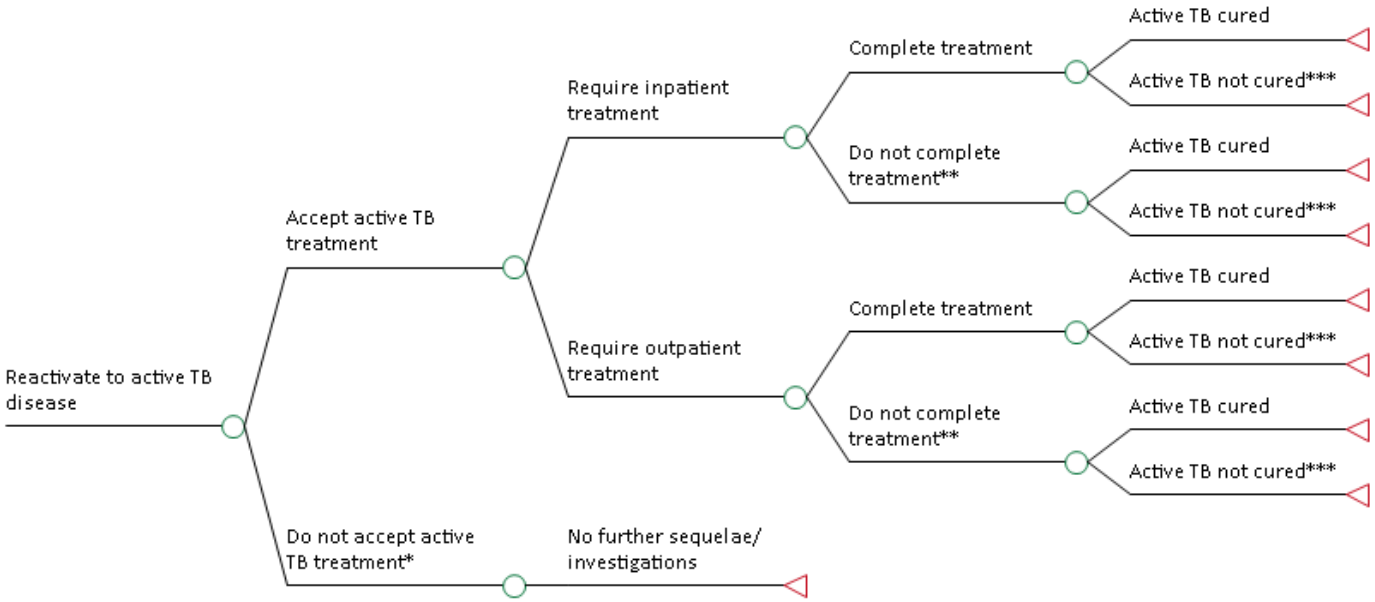
Figure 4.1 Decision tree used for the health economic analysis



Footnotes

1. Individuals fully cured of LTBI are assumed to remain free of further infection for the 20-year time horizon of the model
2.For clarity all "reactivate to active TB subtrees" (denoted by *) are shown in figure 4.2 below. Please note that as data is available on all migrants we are able to compute, at each incidence threshold, the number of migrants screened/not screened and subsequently the proportions that are IGRA positive and IGRA negative
3. Individuals are only eligible for screening if they originate from a country which has a TB incidence equal or greater to the screening threshold selected
4. In the model all individuals who are fully cured of LTBI are assumed to have cleared infection with *Mycobacterium tuberculosis* (a terminal node)
5. Not cured LTBI individuals remain at risk of progressing to active TB in the future
6. Individuals who develop hepatotoxicity after starting chemoprophylaxis but which subsequently does not resolve are assumed to stop the drug. In the model it is assumed that they complete only 4 weeks of treatment and this has negligible efficacy thereby leaving them latently infected and thus at future risk of reactivating to active TB
7. Individuals who develop hepatotoxicity after starting chemoprophylaxis but which subsequently resolves are assumed to continue the drug. In the model it is assumed that they can either complete or not complete treatment with their attendant outcomes

Figure 4.2 Decision subtree used to describe the events that occur if an individual reactivates to active TB



Footnotes

1. For completeness we have shown a branch/node for not accepting treatment for active TB, in the model we assume that all individuals do accept treatment for active TB
2. Individuals who do not accept treatment(*) are represented in the model for completeness but, in reality, it is assumed that no individuals refuse treatment for active TB (ie. this is a terminal node)
3. Individuals who do not complete treatment(**) are represented in the model for completeness but, in reality, it is assumed that all patients complete treatment
4. Individuals who are active TB not cured(***) are represented in the model for completeness but, in reality, it is assumed that as they have all completed treatment none of them move into the active TB not cured group

Table 4.1 Screening thresholds considered in the cost-effectiveness analysis

Screening threshold for immigrants (number of cases of TB/100000)[1]	
Under 16	**16-35 years**
None	None
40	500
40	450
40	400
40	350
40	300
40	250
40	500+Sub-Saharan Africa
40	200
40	150
40	100
40	40
All	All

Footnote

[1]Refers to TB incidence in the country of origin

In the model, depending on the incidence threshold at which screening is instigated, a proportion of these migrants are eligible to be screened and undergo interferon gamma release assay (IGRA) testing which will yield either a positive or negative result. In the multi-centre cohort, which I used to parameterise the model, the proportion of indeterminate results was low (0.16%). Therefore, I assumed that the indeterminate rate was negligible in this hypothetical model cohort. A proportion of the immigrants who are not eligible to be tested at a specific threshold will also have LTBI and remain at risk of progressing to active TB; those immigrants who are ineligible, and uninfected, have no further sequelae in the model.

Individuals who are IGRA positive (which can be either true or false positive) will go on to be assessed for active TB with chest radiography. As a simplification it is assumed that there are no prevalent cases of active TB identified in the immigrant cohort at the time of screening. In reality, however, a very small proportion of migrants will have active TB (0.3% in our cohort). Nonetheless, this is extremely rare and, in most cases, the chest radiographic assessment for active TB will be normal and the immigrant will be offered chemoprophylaxis with three months of rifampicin and isoniazid.

A proportion of true and false positive individuals will commence therapy. Amongst those individuals who do commence therapy, a proportion will develop drug-induced liver injury (DILI) even though this is rare (0.2%[364]) in the age-group I considered (immigrants ≤35 years). In those who develop DILI, extra costs in the form of additional clinic visits, inpatient admission and blood tests are required. Eventually, chemoprophylaxis will need to be stopped in a small proportion as the DILI will not improve. It is assumed that these individuals will have only completed four weeks of therapy and so the efficacy of the chemoprophylaxis is negligible. Therefore these individuals remain latently infected and thus at future risk of progressing to active TB disease. However, in the vast majority, the DILI will usually improve. In those individuals where the liver function tests return to normal, treatment will be (re)continued and defined proportions will complete and not complete therapy.

In those individuals who do not develop DILI, uncomplicated treatment will ensue with fixed proportions completing and not completing therapy.

Complete chemoprophylactic treatment will have a 65% efficacy in preventing progression from LTBI to active TB.[395] This means that there will be some patients who complete therapy but in whom the drug regimen has been ineffectual. As an added layer of complexity it is assumed that the proportion of immigrants in whom hepatotoxic effects have improved but do not complete therapy will have completed 50% of the drug regimen (ie. six weeks) and, based on data suggesting equivalence of three months of rifampicin and isoniazid and six months isoniazid, I assume, in keeping with previous authors,[396,397] that this reduces the risk of reactivation by 21%.[395] It is important to note that therapy is only efficacious in truly infected individuals and is of no benefit (in terms of preventing reactivation to active TB) for those immigrants who test false-positive with the IGRA.

In those individuals, who are true positive, who have completed chemoprophylactic therapy (either fully or partially) which has been successful I assume that infection with *Mycobacterium tuberculosis* is cleared ("Clearance of *M. tuberculosis* infection") with no further sequelae for these individuals. However, if therapy has not been successful ("Non-clearance of *M. tuberculosis* infection") it is assumed that the individuals have not cleared *M. tuberculosis* infection and so remain latently infected. Over the time horizon of the model, these individuals can either "remain in LTBI

state" or "reactivate to active TB disease". False-positive individuals, irrespective of whether or not they completed the therapeutic course, are not actually infected and so there are no further sequelae.

Immigrants with negative IGRA results are assumed to be uninfected and will be discharged from the screening clinic. For those individuals who are truly uninfected no further costs or effects are incurred following screening. In contrast, individuals who are false-negative actually have LTBI and are at risk of progressing to active TB disease (with its attendant costs) over the 20-year horizon of the model. In fact, it is important to note that a number of different groups within the immigrant cohort will have LTBI and remain at risk of progressing to active TB disease over the time horizon of the model including:

1. Immigrants with LTBI who are not eligible to be screened as they originate from a country with a TB incidence which does not meet the screening criteria (eg. an individual arriving from India (TB incidence 170/100000) but screening is limited to individuals arriving from countries with a TB incidence ≥200/100000.)
2. Immigrants with LTBI who screen positive but decline to commence chemoprophylaxis.
3. Immigrants with LTBI who screen positive, accept chemoprophylaxis, do not develop hepatotoxicity, complete therapy but it is not effective.
4. Immigrants with LTBI who screen positive, accept chemoprophylaxis, do not develop hepatotoxicity but do not complete therapy which is therefore not effective.
5. Immigrants with LTBI who screen positive, accept chemoprophylaxis, develop hepatotoxicity which resolves, complete therapy but it is not effective.
6. Immigrants with LTBI who screen positive, accept chemoprophylaxis, develop hepatotoxicity which resolves, do not complete therapy but it is not effective.
7. Individuals with LTBI who screen positive, accept chemoprophylaxis, develop hepatotoxicity which does not resolve resulting in them stopping therapy early. This renders them still latently infected.
8. Immigrants with LTBI but who test false-negative with the IGRA.

These individuals remain at risk of progressing from the latent state to active TB disease at a fixed rate. In the absence of reliable data about the proportion of migrants with HIV infection it is assumed, as a simplification, that none of the immigrants have HIV.

If an individual with LTBI breaks down to active TB disease all strains are assumed to be fully drug-sensitive. Individuals with active TB are modelled to have a fixed number of contacts which will result in a fixed number of secondary active TB cases and latent infections. Depending on the severity of disease, a proportion of individuals will need to be hospitalised whilst the remainder

will be managed as outpatients. It is assumed that all subjects accept treatment and that treatment for all cases of active TB follows national guidelines with compliance, and cure, fixed at 100%. Once an individual has been treated for active TB they cannot be re-infected during the course of the 20 year model. In view of the low mortality rate from TB in the UK it is assumed that there is no TB or background mortality during the 20-year horizon of the model.

Implementation of decision analysis model

The decision tree was constructed, and analysed, using Microsoft Excel 2007 (Microsoft, USA) and TreeAge Pro 2011 (Tree Age Software, Inc., Williamstown, MA).

Model assumptions

Model assumptions are detailed in table 4.2.

Table 4.2 Model assumptions of the health-economic model

Assumption
Immigrants are screened for LTBI once at the start of the time horizon.
All IGRA results are determinate and no repeat testing is required.
At the time of screening the immigrants there are no prevalent cases of active TB disease in the cohort.
There are no HIV coinfected individuals in the cohort.
All active TB cases are caused by a fully drug-sensitive strain.
Amongst those individuals identified with LTBI and treated with chemoprophylaxis, a three month course of rifampicin and isoniazid is considered to have equivalent efficacy to six months of isoniazid.[96]
Individuals who commence chemoprophylaxis and subsequently develop drug-induced liver injury which does not resolve are assumed to only complete 4 weeks of therapy which affords no reduction in the risk of progressing to active TB.
An individual with LTBI who has completed successful chemoprophylaxis is assumed to have cleared the infection with Mycobacterium tuberculosis and will not experience any further outcomes during the time course of the model (such as reinfection).
An individual who does not have LTBI on arrival in the UK does not become infected during the time-period considered by the model.
Data on the test performance of the IGRA was based on the most recent meta-analysis obtained from meta-analyses where sensitivity was calculated using culture-confirmed active TB as the reference standard whilst specificity was calculated from BCG-vaccinated individuals at low risk of infection.[41]
All individuals diagnosed with active tuberculosis are assumed to accept treatment for active TB and to complete the six month course of drugs.

Model input parameters and probabilities

Input data were obtained from the present multi-centre study whilst probabilities for transitioning between states were obtained from previous literature (table 4.3).

Table 4.3 Parameters used as input values in the decision model

Probabilities	Base case (range)[1]	References
IGRA positivity/prevalence of LTBI in under 35 year old cohort	Varies (table 2 in main text)	Current study
Proportion undergoing screening	Varies (table 3 in main text)	
Specificity of QuantiFERON	0.99 (0.9-1.0)	41,398
Sensitivity of QuantiFERON	0.84 (0.78-0.90)	41
Proportion of new entrants with pre-existing active TB (ie. prevalent cases)	0.0	Assumed
Proportion of IGRA positive new entrants accepting chemoprophylaxis	0.95 (0.3-1.0)	80
Proportion of IGRA positive new entrants completing chemoprophylaxis	0.85 (0.3-1.0)	80
Duration of chemoprophylaxis with rifampicin and isoniazid (course completed)	3 months	29
Duration of chemoprophylaxis with rifampicin and isoniazid (course partially completed)	1.5 months	Assumed
Efficacy of 3 months of Rifampicin and Isoniazid	0.65 (0.5-0.8)	94,395
Efficacy of 1.5 months of Rifampicin and isoniazid (partial chemoprophylaxis)	0.21[2] (0.1-0.3)	395
Proportion of IGRA positive individuals progressing to active TB (post-exposure TB) over 20 years	0.05[3] (0.025-0.10)	27
Proportion of those who are cured of LTBI who can be reinfected	0	Assumed
Proportion of those who are cured of LTBI who can reactivate to active TB	0	Assumed
Proportion of those who are not cured of LTBI who can reactivate to active TB (over 20 years)	0.05	27
Proportion of individuals on chemoprophylaxis who develop hepatotoxicity	0.002	364
Proportion of individuals on chemoprophylaxis who develop hepatotoxicity which resolves	0.9	Assumed
Proportion of individuals on chemoprophylaxis requiring inpatient hospital stay	0.2	302,397
Proportion of individuals with active TB accepting treatment	1.0	Assumed
Proportion of individuals with active TB completing therapy	1.0	Assumed
Proportion of individuals with active TB cured	1.0	Assumed
Discount rate	0.035	399

Footnotes

[1]Refers to the range explored in the univariate sensitivity analysis
[2]Data from IUAT study was the basis of an assumed estimate[395]
[3]Estimates for the proportion of IGRA positive individuals progressing to active TB drawn from Horsburgh et al which is based on TST data[27]

Key to the cost-effectiveness analysis were the parameters used to describe the performance of the IGRA (QuantiFERON-Gold In-tube) in diagnosing LTBI. These were obtained from the most recent meta-analysis on IGRA performance which concluded the QuantiFERON Gold In-tube has a specificity of 99% and sensitivity, in developed countries, of 84%.[41] The high specificity means that the proportion of false-positive results is relatively small, given the relatively high prevalence of LTBI in the cohort.[397,398] In contrast, the sensitivity of the IGRA impacts on the proportion of false-negative results.

When calculating the true prevalence of LTBI in the tested cohort, it is important to take into account test performance. If, for example, 20% of individuals are IGRA positive it would be incorrect and inaccurate to simply assume that these 20% represent all truly infected individuals. The reason for this is that, depending on test sensitivity and specificity, a proportion of positives will be falsely-positive whilst some negatives will be falsely-negative. I therefore calculated the true prevalence of LTBI in the cohort by using the following formula:

Probability of a positive result = (Test sensitivity*Prevalence of LTBI) + ((1-Test specificity)*(1-Prevalence))

(Equation 1)

Rearranging for Prevalence of LTBI, the formula becomes:

Prevalence of LTBI = Probability of a positive result – (1-Test specificity)/((Test sensitivity)-(1-Test specificity))

(Equation 2)

This is important because, returning to our example of 20% of individuals being IGRA positive when test performance suggests a sensitivity of 84% and specificity of 99%, the true prevalence is actually 22.9%.

From the prevalence of LTBI it is possible to calculate the probability of a true positive and true negative result.

$$\text{Probability of true positive result} = \frac{\text{Sens} \times \text{Prevalence of LTBI}}{\text{Probability of positive result}} \quad \text{(Equation 3)}$$

$$\text{Probability of true negative result} = \frac{\text{Spec} \times (1-\text{Prevalence of LTBI})}{\text{Probability of negative result}} \quad \text{(Equation 4)}$$

Another important, but poorly understood, parameter was the rate at which immigrants with LTBI reactivated and progressed to active TB disease. Although immigrants should, in theory, have a lower rate of progression than recent contacts of smear-positive tuberculosis, it could be argued that those individuals arriving from high TB burden countries are, in fact, akin to recent contacts as they will have been recently and repeatedly exposed to individuals with infectious tuberculosis. This makes it difficult to parameterise the progression rate with full certainty. For example whilst Marks et al calculated 6.7% progression over a 40 year period in TST positive (>15mm) Southeast Asian refugees,[220] data from the UK, in a predominantly Southeast Asian population suggests that over a 10 year period approximately 13% of TST positive, untreated, immigrants (primarily from the Indian Subcontinent) will go on to develop active TB.[221] Horsburgh estimated that in 16-35 year olds with a >15mm TST (not recently converted) the annual risk of reactivation was 0.19%.[27] If the skin test was >15mm and there was recent conversion then the annual risk of reactivation would rise to 0.56%.[27] In view of the large difference in published data I assumed that 5% of the cohort with LTBI, in the absence of chemoprophylaxis, would progress to active TB over the 20 year time horizon; a suitably wide range was explored in the sensitivity analysis.

Costs

Component costs considered were primarily direct costs obtained from economic evaluations conducted for the UK NICE TB guidelines, and its forthcoming update, uplifted to 2010 prices (see

tables 4.4 and 4.5) using the Consumer Prices Index. In the present analysis, indirect costs such as transportation and loss of earnings by patients were not considered. Both costs and non-monetary health effects were discounted at an annual rate of 3.5%, which reflects UK Treasury and NICE recommendations.[29,399]

Table 4.4 Costs associated with diagnosis and treatment of active TB

Active TB cases (all costs in 2010 GB pounds sterling)	Base case (range)[1]	Reference(s)
Contact tracing		
Contact tracing per contact (£)	482 (241-723)	[80]
Mean number of contacts examined per primary case	6.5 (3.25-10)	[80]
Mean number of secondary active TB cases per index case	0.2 (0.1-0.3)	[80]
Mean number of latent infections per primary case of active TB disease	0.18 (0.09-0.27)	[400]
Inpatient care		
Cost of inpatient episode for acute TB (£ per spell)	4012.97 (2006.5-6019.46)	[80,401,402]
Proportion of patients with acute TB who are admitted	0.53 (0.265-0.795)	[80]
Cost of inpatient care (£ per active case)	2126.87	Calculated
Cost of tests		
Costs of culture test (£ per test)	10	[80]
Costs of chest X-ray (£ per X-ray)	28	[80]
Costs of liver functions tests	1	[80]
Culture tests per case treated	4	[80]
Chest X-ray per case treated	2	[80]
Liver functions tests per case treated	4	[80]
Total cost of tests (£ per TB case treated)	100[3]	Calculated
Cost of chemotherapy		
Rifampicin (£ per month)	10.76	[80]
Isoniazid (£ per month)	17.87	[80]
Pyrazinamide (£ per month)	6.88	[80]
Ethambutol (£ per month))	18.48	[80]
Duration of rifampicin (months)	6	[80]
Duration of isoniazid (months)	6	[80]
Outpatient care		
Cost of outpatient consultation (first visit)	257	[80]
Cost of outpatient consultation (follow-up visit)	130	[80]
Cost of TB Nurse home visit	22	[80]
Number of outpatient clinic visits per case treated	4	[80]
Visits from TB Nurse per case treated	6	[80]
Total costs of non-drug outpatient care (£ per case treated)	779[3]	Calculated

Footnotes

[1]Refers to the range explored in the univariate sensitivity analysis

[2]In the sensitivity analysis the costs of outpatient care for an active TB case and the tests required were considered together (total = 879, range explored 439.5-1318.5)

Table 4.5 Costs associated with diagnosis and treatment of latent TB infection

Latent TB cases (all costs in 2010 GB pounds sterling)	Base case (range)[1]	Reference(s)
Cost of screening		
QuantiFERON (test kit, consumables and phlebotomy)	45 (22.5-90)	[80]
Cost of evaluating positive QuantiFERON		
Cost of outpatient consultation: first visit (£ per visit)	257	[80]
CXR	28	
LFT	1	
Number of outpatient consultation	1	
Number of CXR	1	
Number of LFT	1	
Total cost of evaluating positive QuantiFERON	286 (143-429)	Calculated
Cost of follow-up and chemoprophylactic therapy for positives undergoing treatment		
Follow up via TB nurses	22	[80]
Rifampicin (£ per month)	10.76	[80]
Isoniazid (£ per month)	17.87	[80]
Number of TB Nurses appointments	2	[80]
Duration of rifampicin (months)	3	[80]
Duration of isoniazid (months)	3	[80]
Total cost of chemoprophylaxis (£ per course) plus TB nurse follow-up	130 (65-195)	Calculated
Cost of managing a case of chemoprophylaxis induced liver injury		
Cost of additional clinic visits and blood tests	362	[403]
Cost of inpatient stay	1000	[403]

Footnote

[1]Refers to the range explored in the univariate sensitivity analysis

Effects

The main effects considered in the model were the number of cases of active tuberculosis that would be predicted to occur over the 20-year time horizon.

Cost-effectiveness

As recommended by the Panel of Cost-effectiveness in Health and Medicine, the comparative performance of the different screening protocols was measured using the Incremental Cost-effectiveness ratio (ICER – see equation 1) which quantifies the trade-offs between switching from one competing, mutually-exclusive, intervention to another.[404] The higher the ICER, the less cost-effective the intervention is.

$$ICER = \frac{Cost_{screening protocol A} - Cost_{screening protocol B}}{Effectiveness_{screening protocol A} - Effectiveness_{screening protocol B}} \quad \text{(Equation 5)}$$

Sensitivity analysis

Parameter uncertainty can potentially affect the results of the cost-effectiveness analysis. A simple one-way sensitivity analysis was therefore undertaken to explore the impact that changes in all key parameters and costs had on the number of cases of active TB occurring over 20 years, the costs and the associated ICERs.

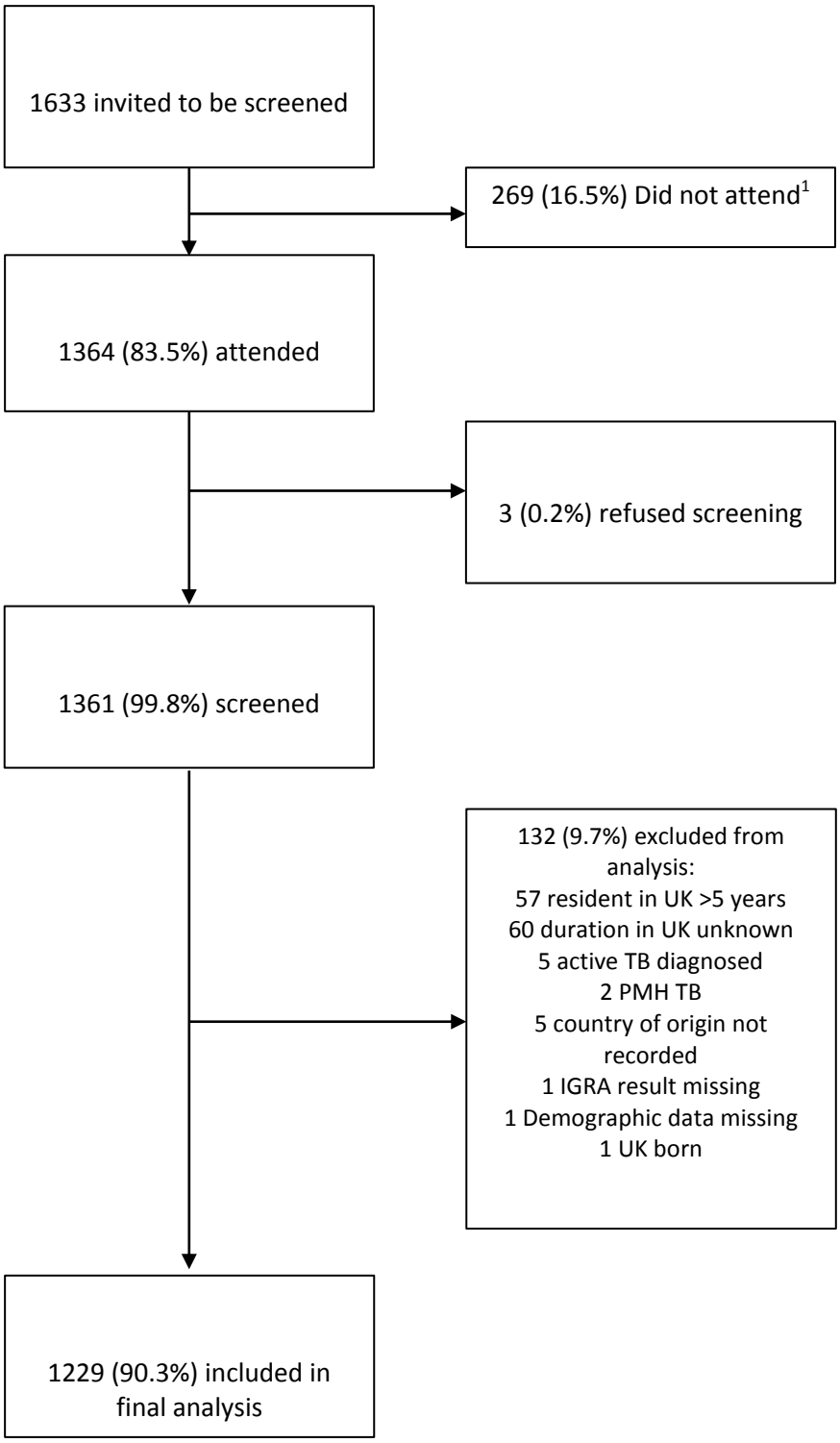
Results

Description of the cohort

Recruitment into the study is outlined in figure 1. Amongst the 1361 individuals that were screened, 132 (9.2%) individuals were excluded from the final analysis for the following reasons: 117 subjects had been resident in the UK >5 years or their exact date of entry was unknown, 5 subjects were diagnosed with active TB, 2 had a past history of active TB, 1 was UK-born and 7 subjects had

demographic information and/or IGRA results missing. This left 1229 subjects for the final analysis who were screened by virtue of being recent arrivals to the UK. Characteristics of all 1229 subjects are shown in table 4.6.

Figure 4.3 Study flow chart



Footnote

[1] Data on non-attenders only available for two out of three centres included in the study.

Table 4.6 Demographics of cohort and risk factors associated with a positive IGRA test among immigrants

Variable	Number (%) in total cohort (n=11229)	No. IGRA Positive/ Total No.Tested (%)	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age						
Under 16[2]	36 (2.9%)	7/36 (19.4%)	1	0.0051[4]	1[6]	<0.0001[9]
16-25	589 (47.9%)	86/589 (14.6%)	0.7 (0.3-1.7)		0.9 (0.4-2.1)	
26-35	604 (49.2%)	152/604 (25.2%)	1.4 (0.6-3.2)		1.7 (0.7-4.1)	
Gender						
Female	629 (51.2%)	109/629(17.3%)	1	0.02	1[7]	0.046
Male	600 (48.8%)	136/600 (22.7%)	1.4 (1.1-1.9)		1.3 (1.0-1.8)	
World region of origin[3]						
Europe, Americas	50 (4.1%)	2/50 (4.0%)	1	0.0011		
Middle East, North Africa	26 (2.1%)	1/26 (3.9%)	1.0 (0.1-11.1)			
Other Asia	162 (13.2%)	29/162 (17.9%)	5.2 (1.2-22.8)			
Indian Subcontinent	740 (60.2%)	144/741 (19.5%)	5.8 (1.4-24.1)			
Sub-Saharan Africa	251 (20.4%)	69/251 (27.5%)	9.1 (2.2-38.5)			
TB incidence in country of origin[3]						
0-50	32 (2.6%)	1/32 (3.1%)	1	<0.0001[4]	1[8]	0.0006
51-150	150 (12.2%)	19/150 (12.7%)	4.5 (0.60-34.9)		4.5 (0.60-35.3)	
151-250	835 (67.9%)	164/835 (19.6%)	7.6 (1.0-55.9)		7.9 (1.1-58.3)	
251-350	139 (11.3%)	41/139 (29.5%)	13.0 (1.7-98.2)		13.3 (1.8-101.5)	
>350	73 (5.9%)	20/73 (27.4%)	11.7 (1.5-91.5)		13.1 (1.7-102.7)	
BCG vaccinated[5]						
No	113 (17.2%)	16/113 (14.2%)	1	0.17		
Yes	544 (82.8%)	107/544 (19.7%)	1.5 (0.8-2.6)			

Footnotes

[1]Attenders were less likely to be male (OR: 0.6 95% CI 0.5-0.9), to have originated from the Indian Subcontinent (OR:2.2, 95% CI 1.6-2.9) but less likely to have been born in Europe/the Americas(OR:0.20, 95% CI 0.1-0.3).

[2]Age distributions of the 36 under 16 year-olds was as follows: 1(2.8%) ≤4 years old, 1(2.8%) 5-9 years old and 34(94.4%) 10-15 years old.

[3]World region of origin and TB incidence in country of origin were strongly correlated, so, in the multivariate analysis, world region of origin was dropped

[4]χ^2 p for trend

[5]Data available for 657 subjects

[6]Mutually adjusted for gender and TB incidence in country of origin

[7]Mutually adjusted for age and TB incidence in country of origin

[8]Mutually adjusted for age and gender

[9]p value denotes overall effect of age in the model (ie. analogous to considering it as a continuous variable)

Immigrants who underwent screening were primarily young adults (1193/1229–97.0% were aged 16-35); 51.2% were female and 82.8% had previously been BCG vaccinated. Screened immigrants most commonly originated from the Indian Subcontinent (60.2%) and Sub-Saharan Africa (20.4%); Pakistan and India (32.9% and 22.5% respectively) were the commonest countries of origin. The overall composition of immigrants screened in the study was broadly representative of the foreign-born population resident in the UK, with our study population containing slightly more immigrants from the Indian Subcontinent and slightly fewer from sub-Saharan Africa than the national average.[378]

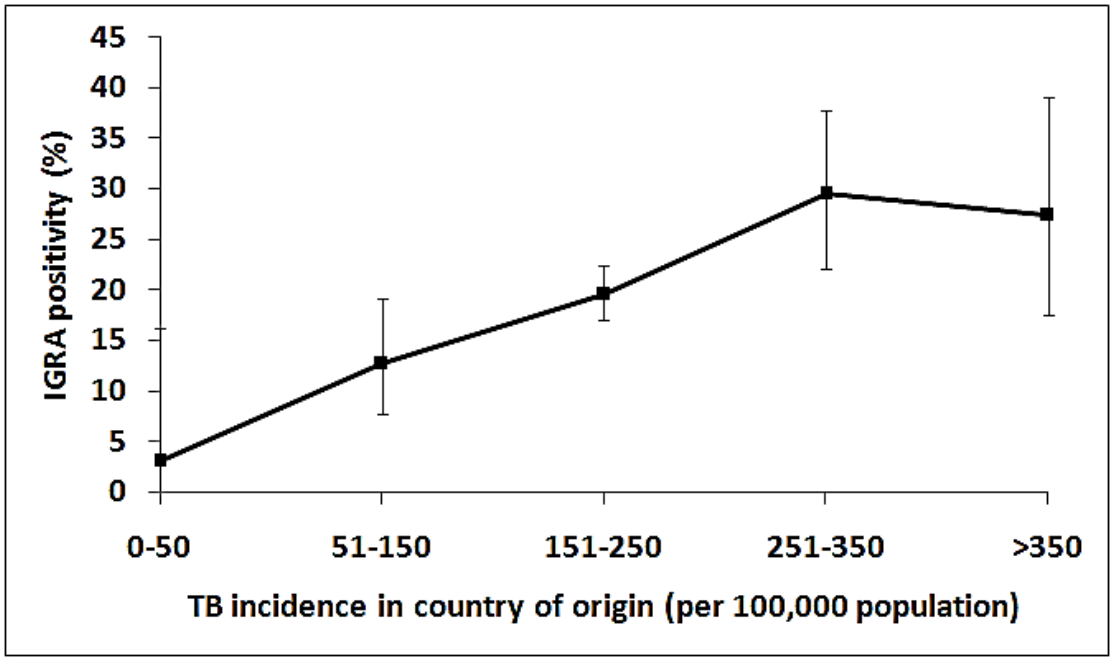
IGRA results and prevalence of latent TB infection

IGRA results were available for all 1229 subjects. Overall, 245 subjects (19.9% - 95% CI 17.7-22.3%) tested positive and 982 (79.9% - 95% CI 77.6-82.1%) were negative; 2 subjects (0.2% - 95% CI 0.02-0.6%) had indeterminate results. Westminster had a significantly lower proportion of IGRA-positive individuals than the two other centres (p=0.02). The proportion of immigrants positive in the under 16, 16-25 and 26-35 age-groups was 19.4%, 14.6% and 25.2% respectively.

Factors associated with positive IGRA results

Univariate and multivariate analyses of factors associated with IGRA positivity in the immigrant cohort are shown in table 4.6. On multivariate analysis, increasing age, male gender and increasing TB incidence in country of origin were associated with a positive IGRA result (table 4.6 and figure 4.4).

Figure 4.4 Line graph illustrating the proportion of immigrants aged 35 and under who test IGRA positive according to TB incidence in their country of origin



Footnote

[1]Error bars represent 95% confidence intervals

Relationship between screening thresholds and burden of LTBI detected

Table 4.7 sets out the outcomes of LTBI immigrant screening stratified by age and TB incidence in the immigrants' countries of origin. In all age-groups as the incidence threshold at which screening is instigated increases, fewer immigrants within the cohort are eligible to be screened and consequently the number of LTBI cases identified also decreases.

Table 4.7 Yields for latent TB infection (defined as positive QuantiFERON assay) for different age-groups and at different screening thresholds

Age group and TB incidence screening threshold (per 100000)	Number tested	Number positive	Yield at incidence level, ie. proportion of those tested giving a positive result (%)	% of all LTBI identified if threshold set at this level
<16 years				
Screen ≥500 and SSA[1]	16	4	25.0	57.1
Screen ≥500	6	2	33.3	28.6
Screen ≥450	6	2	33.3	28.6
Screen ≥400	6	2	33.3	28.6
Screen ≥350	7	2	28.6	28.6
Screen ≥300	12	2	16.7	28.6
Screen ≥250	15	3	20.0	42.9
Screen ≥200	23	4	17.4	57.1
Screen ≥150	34	6	17.7	85.7
Screen ≥100	34	6	17.7	85.7
Screen ≥40	**36**	**7**	**19.4**	**100**
Screen all	36	7	19.4	100
16-35 years				
Screen ≥500 and SSA[1]	**235**	**65**	**27.7**	**27.3**
Screen ≥500	46	12	26.1	5.0
Screen ≥450	54	13	24.1	5.5
Screen ≥400	55	13	23.6	5.5
Screen ≥350	66	18	27.3	7.6
Screen ≥300	135	38	28.2	15.9
Screen ≥250	197	58	29.4	24.4
Screen ≥200	668	127	19.0	53.4
Screen ≥150	1013	219	21.6	92.0
Screen ≥100	1068	222	20.8	93.3
Screen ≥40	1180	238	20.2	100
Screen all	1193	238	20.0	100

Footnotes

[1]SSA – Sub-Saharan Africa
[2]Pink shaded rows in bold are 2006 NICE guidance

Applying current NICE guidance to our cohort (screen under 16s from countries with TB incidence ≥40/100000 and 16-35 year-olds from countries with TB incidence ≥500/100000 and Sub-Saharan Africa) would result in 271/1229 (22.1%) being eligible for screening, of whom 72/271 (26.6%) were IGRA positive, representing 29.4% of all LTBI cases. Lowering the screening threshold for adults to

150/100000 (with the threshold for <16s unchanged) increases the number of immigrants eligible to be screened to 1049/1229 (85.4%) ($p<0.0001$), with a similar proportionate yield of 226/1049 (21.5%) and a significantly higher proportion of all LTBI cases (92.2%) identified ($p<0.0001$).

Health-economic analyses

Table 4.8 presents the results of the health-economic analysis including the predicted number of TB cases and associated costs that will occur with each protocol for a cohort of 10,000 immigrants over a 20-year time horizon.

Whilst strategies which employed screening with IGRA were more expensive than the no screening approach, they also resulted in fewer cases of active TB over the 20-year time horizon; costs increased as the threshold at which immigrants were eligible to be screened shifted downwards (table 4.8). Screening all immigrants aged ≤35 from any countries, irrespective of TB incidence, would cost £1,532,256.6 and avert 44.5 cases of TB whereas applying current NICE guidance would cost £850,103.1 and prevent, as compared to no screening, 13.2 cases of active TB. The strategy of undertaking no immigrant screening for LTBI was the least expensive option (£608,370.0) but resulted in the most cases of active TB (95.4) over the time-horizon explored.

Following exclusion of dominated strategies (table 4.8) four cost-effective strategies remained. In decreasing order of cost-effectiveness these strategies (in addition to screening <16 year-olds from countries ≥40/100000) were to screen 16-35s from countries with TB incidence ≥250/100000, ≥150/100000 and >40/100000, respectively; the fourth strategy was to screen all ≤35 year-olds from all countries irrespective of TB incidence. The associated ICERs were £17,956.0, £20,818.8, £29,403.1 and £101,938.3 respectively per active TB case averted. Therefore, in terms of the ICERs, the most cost-effective strategies would be to instigate screening at 40/100000 for under 16s and 250/100000 for 16-35 year olds although the ICER for the next most cost-effective strategy (screen under 16s at 40/100000 and 16-35 year-olds at 150/100000) was only just under three thousand pounds higher. Moving the threshold even lower to screen all under 35s from countries ≥40/100000, or indeed all immigrants, were both non-dominated options although the associated ICERs were much higher.

Numbers needed to screen (NNS) and numbers needed to treat (NNT) ranged from 165.5-231.9 and 42.0-42.7 respectively; screening 16-35 year-olds at 250/100000 had the lowest NNT (42.0) whilst screening at a threshold higher than this generally resulted in a higher NNT.

Table 4.8 Projected cases of active TB and associated costs arising from undertaking immigrant screening at different TB incidence thresholds

Screening threshold for immigrants (annual incidence per 100000) stratified by age		Cases of active TB (over 20 years)[1]	Costs over 20 years (2010 GB pounds)	Incremental cases of active TB averted[2] (over 20 years)	Incremental costs[3] (GB pounds over 20 years)	ICER[4] (GB pounds per TB case averted)
Under 16	**16-35 years**					
Screen none	Screen none	95.4	608,370.0	Baseline	Baseline	Baseline
40/100000	500/100000	91.9	678,586.5	Extended dominance	Extended dominance	Extended dominance
40/100000	400/100000	91.8	683,710.0	Strict dominance[5]	Strict dominance	Strict dominance
40/100000	450/100000	91.7	683,267.9	Extended dominance[6]	Extended dominance	Extended dominance
40/100000	350/100000	90.8	697,208.7	Extended dominance	Extended dominance	Extended dominance
40/100000	300/100000	87.1	761,431.6	Extended dominance	Extended dominance	Extended dominance
40/100000	250/100000	83.4	823,312.8	12.0	214,942.8	**17,956.0**
40/100000[7]	500/100000+sub-Saharan Africa	82.2	850,103.1	Extended dominance	Extended dominance	Extended dominance
40/100000	200/100000	71.1	1,121,093.2	Extended dominance	Extended dominance	Extended dominance
40/100000[8]	150/100000	54.2	1,431,928.5	29.2	608,615.7	**20,818.8**
40/100000	100/100000	53.7	1,456,820.1	Extended dominance	Extended dominance	Extended dominance
40/100000	40/100000	50.9	1,527,478.5	3.2	95,550.1	**29,403.1**
Screen all	Screen all	50.9	1,532,256.6	0.0	4,778.0	**101,938.3**

Footnotes

[1]Arranged in order increasing effectiveness – ie. fewer cases of active TB for a hypothetical cohort of 10,000 immigrants over a 20-year time horizon

[2]Incremental number of cases are calculated as the difference (ie. number of cases averted) from the previous non-dominated option

[3]Incremental costs are calculated as the difference (ie. extra GB pounds) from the previous non-dominated option

[4]Ranking different strategies from least effective to most effective(ie. number of cases of active TB predicted to occur) results in the incremental cost-effectiveness ratios (ICERs) of most screening options, including current NICE guidance, being excluded through extended dominance, which is where the ICER for a particular screening threshold is higher than for the next most effective strategy (screening threshold) and so the higher ICER is removed from the cost-effectiveness analysis

[5]Strict dominance: This is the situation where a particular screening threshold is both less effective and more expensive than the next most effective screening threshold.

[6]Extended dominance: This is the situation where the incremental cost-effectiveness ratio (ICER) for a particular screening threshold is higher than for the next most effective strategy (screening threshold) and so the higher ICER is removed from the cost-effectiveness analysis.

[7]Pink shaded row: This represents the situation if screening is undertaken as per 2006 UK national (NICE) guidance.

[8]Blue shaded row: This represents the situation if screening included immigrants from the Indian Subcontinent.

Results of the univariate sensitivity analysis are presented in tables 4.9 and 4.10. In general, varying several of the parameters affected estimates for the ICERs of each of the strategies but did not significantly impact on the rank-order of the most cost-effective strategies. The most important parameters were the rate at which new-entrants progress to active TB and the prevalence of LTBI in the screened cohort. Higher values for both parameters increased cost-effectiveness (i.e. resulted in lower ICERs).

Cost-effectiveness was more significantly affected by diagnostic specificity rather than sensitivity. Reducing specificity increased ICER estimates (ie. reduced cost-effectiveness) as more false-positive, uninfected, individuals would be treated unnecessarily. In terms of costs, reductions in the costs of screening for LTBI or evaluating those who screened positive significantly reduced ICER values (ie. increased cost-effectiveness).

Table 4.9 Univariate sensitivity analysis of probabilities/proportions used as input variables in the decision model

Model parameter	Point Estimate	Range explored	Screening thresholds for <16 and 16-35 (UK pound sterling per case averted)			
			<16 from >40/100000 16-35 from >250/100000	<16 from >40/100000 16-35 from >150/100000	<16 from >40/100000 16-35 from >40/100000	<16 All 16-35 All
Prevalence of LTBI	0.22	0.1	28,853.7	36,319.9	61,481.5	136,739.3
		0.4	14,527.9	16,081.0	20,650.3	73,864.9
Sensitivity of IGRA	0.84	0.78	17,932.7	20,788.3	29,442.5	86,066.0
		0.90	17,973.1	20,841.2	29,374.3	117,507.2
Specificity of IGRA	0.99	0.88	29,372.8	50,789.5	SD	SD
		1.00	17,365.2	19,751.4	26,108.0	272,290.5
Proportion progressing to active TB (over 20 years)	0.05	0.025	41,823.6	47,494.4	64,498.4	208,178.6
		0.15	2,049.3	3,040.8	6,013.6	31,133.8
Number of contacts	6.5	3.25	19,522.5	22,385.3	30,969.6	103,504.8
		10	16,269.0	19,131.8	27,716.1	100,251.3
Efficacy of complete chemoprophylaxis (risk reduction)	0.65	0.5	24,772.0	28,418.9	39,717.1	161,114.4
		0.8	13,587.3	15,943.5	22,860.8	85,522.9
Efficacy of partial chemoprophylaxis (risk reduction)	0.21	0.1	18,654.1	21,597.6	30,453.4	99,352.9
		0.3	17,413.2	20,213.3	28,587.3	104,149.4
Proportion starting chemoprophylaxis	0.95	0.3	60,149.2	68,786.9	SD	98,102.9
		1.0	16,985.3	19,710.9	27,841.5	107,085.1
Proportion completing chemoprophylaxis	0.85	0.3	32,756.6	37,561.9	53,089.1	554,774.1
		1.0	15,836.0	18,417.1	26,072.5	91,930.3
Number of secondary active TB cases per index case	0.2	0.1	20,162.9	23,285.6	32,648.9	111,673.0
		0.3	16,088.1	18,731.1	26,655.9	93,539.9
Number of secondary latent TB cases per index case	0.18	0.09	17,983.4	20,848.5	29,439.3	102,030.7
		0.27	17,928.6	20,789.3	29,366.9	101,846.0

Proportion of active TB cases admitted as inpatient	0.53	0.265	19,019.4	21,882.3	30,466.5	103,001.7
		0.795	16,892.6	19,755.4	28,339.6	100,874.9
Proportion receiving chemoprophylaxis developing drug induced liver injury	0.002	0.001	17,944.4	20,808.4	29,396.1	101,895.2
		0.003	17,967.6	20,829.2	29,410.0	101,981.5

Footnote

[1]The figures presented are the incremental cost-effectiveness ratios (ICERs); moving from lowest to highest ICER indicates decreasing cost-effectiveness. Please note that only non-dominated options are presented.

Table 4.10 Univariate sensitivity analysis of costs used as input variables in the decision model

Parameter	Screening thresholds for <16 and 16-35 (2010 UK pound sterling per case averted)											
	<16 All 16-35 All	<16 40 16-35 40	<16 40 16-35 100	<16 40 16-35 150	<16 40 16-35 200	<16 40 16-35 250	<16 40 16-35 300	<16 40 16-35 350	<16 40 16-35 400	<16 40 16-35 450	<16 40 16-35 500	<16 40 16-35 500+SSA
Cost of initial screening												
22.50	44,942.7	20,771.3	ED	15,907.0	ED	14,357.4	ED	ED	SD	ED	ED	ED
90	215,929.6	46,666.7	ED	30,642.5	ED	25,153.2	ED	ED	SD	ED	ED	ED
Cost of evaluating of IGRA positive												
143	103,960.2	22,806.1	ED	14,629.5	ED	11,850.9	ED	ED	SD	ED	ED	ED
429	99,916.4	36,000.0	ED	27,008.2	ED	24,061.1	ED	ED	SD	ED	ED	ED
Cost of LTBI treatment												
65	102,754.9	26,774.5	ED	18,353.2	ED	15,524.0	ED	ED	SD	ED	ED	ED
195	101,121.7	32,031.7	ED	23,284.5	ED	20,387.9	ED	ED	SD	ED	ED	ED
Cost of active TB follow-up												
439.5	102,377.8	29,842.6	ED	21,258.3	ED	18,395.5	ED	ED	SD	ED	ED	ED
1318.5	101,498.8	28,963.6	ED	20,379.3	ED	17,516.5	ED	ED	SD	ED	ED	ED
Cost of active TB drugs												
111	102,049.3	29,514.1	ED	20,929.8	ED	18,067.0	ED	ED	SD	ED	ED	ED
333	101,827.3	29,292.1	ED	20,707.8	ED	17,845.0	ED	ED	SD	ED	ED	ED
Cost of active TB inpatient treatment												
2006.5	103,001.7	30,466.5	ED	21,882.3	ED	19,019.4	ED	ED	SD	ED	ED	ED
6019.46	100,874.9	28,339.6	ED	19,755.4	ED	16,892.5	ED	ED	SD	ED	ED	ED
Cost of contact tracing												
241	103,504.8	30,969.6	ED	22,385.3	ED	19,522.5	ED	ED	SD	ED	ED	ED
723	100,371.8	27,836.6	ED	19,252.3	ED	16,389.5	ED	ED	SD	ED	ED	ED
Cost of Hepatotoxicity with chemoprophylaxis												
181	101,948.5	29,369.7	ED	20,787.5	ED	17,925.1	ED	ED	SD	ED	ED	ED
1862	101,903.4	29,517.0	ED	20,925.8	ED	18,061.4	ED	ED	SD	ED	ED	ED

Footnote

[2]Costs are in pounds sterling

[2]The figures presented are the incremental cost-effectiveness ratios (ICERs); moving from lowest to highest ICER indicates decreasing cost-effectiveness. ED = Extended dominance - this the situation where the incremental cost-effectiveness ratio (ICER) for a particular screening threshold is higher than for the next most effective strategy (screening threshold) and so the higher ICER is removed from the cost-effectiveness analysis

Discussion

This multi-centre study is the largest of LTBI prevalence in new-entrants, and the first to provide estimates stratified by age, TB incidence in the countries of origin and risk factors for LTBI. This enabled me to perform the first health-economic analysis of immigrant screening at different incidence thresholds using real-life IGRA data collected in routine clinical practice. This evaluation of the outcomes, and cost-effectiveness, of immigrant screening with IGRA at different incidence thresholds found that new-entrants to the UK have a high prevalence of LTBI which varies by age, gender and TB incidence in their country of origin. Current national guidance on which groups to screen excludes the majority of immigrants with LTBI and my analysis suggests that current policy could be modified, in centres undertaking, or considering the implementation of, single-step IGRA testing, to substantially reduce TB incidence while remaining cost-effective.

In this cohort, the prevalence of LTBI was moderately high at 19.9%. Previous studies, from a variety of settings, which used TST to diagnose LTBI, found 34-55.1% of immigrants to be TST-positive.[203,206,207,211] These high proportions are likely to reflect cross-reactivity of prior vaccination with Bacille Calmette-Guérin (BCG), resulting in many false-positive TST results.[39] The main implication of screening with TST, therefore, is that a higher number of uninfected individuals will be unnecessarily treated with chemoprophylaxis. However IGRAs, which have a higher specificity in BCG-vaccinated subjects, result in fewer false-positive results and so may provide a lower, but more accurate, estimated prevalence of LTBI in immigrants.[39] Data on the burden of LTBI diagnosed by IGRA in immigrants are scarce and generally relate to immigrant TB contacts or undocumented immigrants;[203,211,216-218] these studies from various parts of Europe, including the UK, have suggested that 15-38% of new-entrants have positive IGRA results. However, this is the first study to provide estimates of LTBI prevalence by age[211,217] and by TB incidence in the immigrants' countries of origin[203,216,217] key factors for determining policy on which immigrant groups should be screened.

Immigrants to the UK (other than from within the European Union) largely arrive from regions which have amongst the highest burdens of TB in the world.[176] In this cohort, immigrants from the Indian Subcontinent and Sub-Saharan Africa accounted for approximately 80.6% of all

screened immigrants and just under 87% of all LTBI cases. However, by including several UK centres, with different patterns of migration, the current study is able to provide reliable estimates for the prevalence of LTBI in immigrants arriving from countries with a wide range of TB burden.

I found that LTBI prevalence was independently correlated with TB incidence in the immigrants' country of origin. No immigrants from countries below 50/100000 had a positive IGRA, consistent with recent smaller-scale European studies which however used only a binary classification of incidence less than or greater than 50/100000.[211,216,218]

Increasing age was also independently associated with an increasing likelihood of a positive IGRA result. Older immigrants (aged 26-35 years) had a relatively higher IGRA positivity rate. Previous work from both developed and developing country settings has shown that IGRA positivity correlates with increasing age.[50,215,405,406] However, in the absence of prospective data it is difficult to know whether this represents a truly higher prevalence of LTBI (due to more cumulative exposure in a high-TB burden setting) or sub-optimal IGRA-sensitivity in the comparator younger age-groups.[407]

Despite national guidance (NICE 2006) in the UK recommending screening for LTBI in only a very select subset of immigrants[29] there is increasing evidence that many areas of the UK do not follow these guidelines and have set their own criteria for screening – perhaps reflecting uncertainty in the very high and restrictive incidence threshold from the 2006 NICE guidance.[217,357] Indeed the data suggest that the NICE 2006 cut-off in 16-35 year-olds may be too restrictive. If I applied 2006 national guidance to the ≤35 year olds in our cohort, only 29.4% of LTBI cases would be identified, leaving nearly three-quarters (mostly those from the Indian Subcontinent) undiagnosed and at risk of developing active TB disease and possibly infecting others. Indeed it is these immigrants from the Indian Subcontinent that constitute the largest proportion of foreign-born cases in the UK.[381] If the threshold incidence in the country of origin for screening 16-35-year-olds were reduced to 150/100000 then 92.2% of those with LTBI would be identified, leaving only a relatively small fraction undiagnosed and at risk of developing active disease.

The health-economic analysis indicated that if single-step IGRA screening of 16-35 year-olds was implemented, four incidence thresholds were cost-effective, and all were more cost-effective than the current threshold recommended by national guidance. The two most cost-effective strategies were

to screen at ≥250/100000 (with an ICER of £17,956.0 per TB case averted) and to screen at 150/100000 which would avert an additional 29.2 cases of active TB per 10,000 immigrants (compared to screening at ≥250/100000) at a marginally higher ICER of £20,818.8 per each additional case averted. This latter strategy would encompass individuals from many Asian countries who are currently excluded - including those from the Indian Subcontinent who comprise a large proportion of those migrating to the UK.[174] Reducing the threshold further to 40/100000 or even lower (ie. screen all immigrants) would avert more cases of active TB but implementing screening at these lower thresholds would of course incur substantially increased total costs, requiring consideration of resource availability and the funds policy-makers are willing to spend to control the incidence of active TB.

Earlier health-economic analyses primarily compared TST versus chest radiography in screening new-entrants from high TB burden countries (especially for active TB).[298,302] Schwartzman et al found screening with chest radiographs was more cost-effective than TST, although this conclusion may not be universally relevant as the authors assumed that most unscreened immigrants developing active TB would require prolonged in-patient management.[302] By contrast, Dasgupta et al found that screening and treating immigrants for LTBI amongst a subset who had undergone chest radiography and TST had significant public health impacts but would be expensive due to limited programme efficiency (such as the proportion of immigrants completing chemoprophylaxis).[298] More recently, Oxlade et al compared a range of immigrant-screening scenarios, including chest radiography, TST and IGRAs and found all had a modest impact on TB notifications although chest radiography alone was the most cost-effective option.[301] However, the model was based on putative scenarios rather than on actual data and assumed both a very low prevalence of LTBI in recent immigrants (0.08-2.1%) and a low reactivation rate. This study advances the evidence-base by using unique, accurate, empirical IGRA screening data from multiple centres to objectively parameterise a decision-model to evaluate, for the first time, the key question of yields, and cost-effectiveness, of immigrant screening at different incidence thresholds.

I chose a conservative progression rate from LTBI to active TB, of 5% over 20 years but this rate remains poorly understood. Whilst Marks et al calculated a progression rate of 6.7% over a 40

year period in TST-positive (>15mm) Southeast Asian refugees[220], data from the UK, in a population similar to ours, suggests that over a 10 year period approximately 13% of TST-positive, untreated, immigrants (primarily from the Indian Subcontinent) progress to active TB making our results a likely underestimate of the true cost-effectiveness.[221] However, further work is needed to investigate the actual rates of progression of IGRA-positive immigrants following arrival and, more specifically, whether this progression rate differs according to age and country of origin.

However, the success of screening will depend on robust systems being in place which allow immigrants to be identified in a timely fashion although the overall impact of screening will largely be determined by patient, and physician, adherence – both to having the test and completing the chemoprophylactic drug regimen; it is plausible that a single, more specific, blood test (ie. IGRA) may increase compliance in immigrants compared to two visits for TST which is frequently false positive in this predominantly BCG vaccinated population.[39,41]

This work had several limitations. Routine surveillance data is likely to under report the prevalence of infection whereas any selection bias in which immigrants attended for screening could inflate the prevalence of LTBI in our study. Moreover, I did not have concurrent TST results as a comparator for IGRA results because the participating centres no longer routinely undertake TST in new-entrants. In terms of test performance one of the most significant obstacles is the lack of a gold-standard test for LTBI making it difficult to formally calculate the sensitivity of diagnostic tests for LTBI. I therefore used figures from the most up-to-date meta-analysis of IGRA performance where culture-confirmed active TB was the surrogate reference standard.[41] As IGRA sensitivity is likely to be lower in patients with active TB compared to healthy individuals undergoing screening for LTBI, this assumption may underestimate the sensitivity of the test and therefore the cost effectiveness estimates. By contrast, basing specificity estimates on pre-selected subjects with a very low probability of TB disease may result in overestimating the specificity of the test. Higher specificity estimates would give fewer false-positive results thereby overestimating the cost-effectiveness of screening.

In my health-economic analysis I made certain simplifying assumptions about TB natural history (such as onward transmission to contacts and complete clearance of infection, with no risk of

reinfection following chemoprophylaxis) as this was not a formal dynamic model which would allow me to capture the intrinsic transmission dynamics of TB. Whilst I included secondary cases of active and latent TB, it is likely that incorporating tertiary and quaternary cases would further increase cost-effectiveness. Moreover, I did not incorporate drug-resistant strains or HIV infection. Although data from the multi-centre study parameterised the model, uncertainty surrounds several parameters and I made assumptions about these. For example it was assumed that there were no prevalent cases of active TB in the screened cohort although in reality a small proportion of individuals were found to have active TB as a result of screening. By not incorporating these factors into the decision-analysis it is likely that my analysis, if anything, underestimates the cost-effectiveness of screening. In contrast I assumed that all subjects with active TB would be diagnosed, accept, and complete, treatment and this assumption is likely to result in an over-estimate cost-effectiveness.

In comparison to the cost-utility analysis undertaken by NICE where assessments of different strategies are made using cost per quality adjusted life year (QALY), I assessed cost-effectiveness as cost per TB case averted, in line with previous authors,[301,302,397,398] as there is still very limited objective data on QALYS for patients with active TB or those on chemoprophylaxis.

As national guidelines for LTBI screening with new tools (such as IGRA) evolve, they will need to quantitatively integrate the prevalence of LTBI in immigrant populations from different world regions in order to formulate policy that improves TB control and prevention most cost-effectively.[81] Moreover, whilst the current work focused on assessing the cost-effectiveness of screening at different thresholds with single-step IGRA, further work should compare different screening protocols (such as TST+IGRA vs TST only) and different IGRA platforms (QuantiFERON Gold in-tube vs T-SPOT.TB vs next generation tests).[39,91,408]

In conclusion, immigrants arriving in the UK have a high prevalence of LTBI which is strongly associated with TB incidence in their country of origin. Single-step IGRA screening for LTBI in immigrants can be most cost-effectively implemented at selected incidence thresholds (≥250/100000 or ≥150/100000) which identify the majority of those with LTBI, thereby preventing substantial numbers of future active TB cases

Chapter 5 Community-based evaluation of immigrant tuberculosis screening using interferon gamma release assays and tuberculin skin testing: observational study and economic analysis

Introduction

In the preceding chapter (chapter four), I presented the results of a multi-centre evaluation of immigrant screening which, for the first time, provided robust estimates of LTBI prevalence in immigrants to the UK (as determined by single-step IGRA) stratified both by country of origin and TB incidence in country of origin. The analysis suggests that screening adults (aged 16-35 years) at the levels suggested by the 2006 NICE guidance (Sub-Saharan Africa and other countries with TB incidence >500/100000) would miss the vast majority of latently infected individuals and that it would be more cost-effective to revise the screening threshold down to 150-250/100000. However, these results were based on the 2006 national guidelines and guidance in the UK for immigrant screening is in a state of flux. Revised 2011 NICE guidance, which has recently been published, has radically shifted and currently recommends that adults from all countries with TB incidence >40/100000 should be screened with dual TST plus IGRA or single-step IGRA.[81] However, these new guidelines continue to be based on putative scenarios rather than empirical screening data and therefore have been unable to definitively address key issues such as which screening strategy should be preferred (dual TST plus IGRA or IGRA alone), which of the two commercially available IGRAs (QuantiFERON-Gold in-tube, Cellestis, Carnegie, Australia and T-SPOT.TB, Oxford Immunotec, Oxford, UK) is more cost-effective, and which, if any, intermediate incidence threshold may be most cost-effective in diagnosing LTBI in recent immigrants. An additional area where national guidance provides little direction is the current requirement for compulsory port-of-entry chest radiographs for immigrants. Although this system has been in place for over 40 years with the aim of diagnosing active TB,[178] its high costs and low yields for active disease[183,191,370] underscore the need for a comprehensive contemporary assessment of its cost-effectiveness.

In this chapter I therefore present results from the first prospective comparative assessment, in routine primary care, of TST and both commercially available IGRAs as diagnostic tools for LTBI in new-entrants with a specific focus on LTBI prevalence, how this varies by region of origin and the factors associated with LTBI. In addition I go on to compute the relative cost-effectiveness of LTBI

screening using different screening modalities at different incidence thresholds in a primary care based setting, with and without chest radiographic screening on arrival at port-of-entry.

Methods

Study design and study centre

This prospective assessment of immigrant screening was undertaken in the City of Westminster (London, UK) which has an estimated population of 247,000 people, of whom 53.0% (95% confidence interval 52.8%-53.2%) are foreign-born.[409] Between 2007 and 2009, the 3-year average annual number of TB notifications in this area was 78 whilst TB incidence averaged 33 cases (95% CI 26-41 cases) per 100000 population per year.[393]

Study population and participants

Between October 2008 and June 2010, all foreign-born immigrants registered with one of four participating primary care practices in Westminster were identified and referred to the new-entrant screening service and, if eligible, were invited to participate in TB screening. Eligibility criteria for participation in the study included foreign-born new-entrants (arrival within the preceding 5 years) aged ≥16 years from all countries (if displaying symptoms of active TB) or from a country with a TB incidence of ≥40/100000 (if asymptomatic). Country-specific TB incidence figures were based on 2007 World Health Organisation (WHO) figures - the most current at the time that the study commenced. Ethical approval was not required because the study utilised fully-anonymised observational data collected as part of the routine delivery of a clinical service.

Methods of screening

Eligible immigrants who agreed to participate in the study were prospectively enrolled and initially screened with a questionnaire which obtained information on demographics, country of origin, past history of TB, history of TB contact, bacille Calmette Guerin (BCG) vaccination status (ascertained using scar, reliable history or documentary evidence)[394] and clinical symptoms of active TB.

Following completion of the questionnaire, screening for LTBI was undertaken. Peripheral venous blood samples were collected for the two commercially available IGRAs, QuantiFERON Gold in-tube (QFN-GIT; Cellestis, Australia), a whole blood ELISA containing ESAT-6, CFP-10 and TB7.7 (Rv2654), and T-SPOT.TB (Oxford Immunotec, Oxford, UK), an ELISPOT platform. Due to funding and logistic issues, IGRA screening was only available with QFN-GIT for the first 6 weeks of the study although for the remainder of the study period all individuals were concurrently tested using both IGRA platforms. IGRAs were carried out in accordance with the manufacturer's instructions; results were defined as positive, negative or indeterminate depending on the manufacturer's criteria.

Tuberculin skin testing was undertaken at the first visit after blood samples had been collected to avoid the possible boosting effect of TST on the IGRAs.[410] A trained TB nurse performed TST using 2 tuberculin units of purified protein derivative RT23 (Statens Serum Institut, Copenhagen, Denmark) injected into the forearm following the Mantoux method. Transverse induration (in mm) was measured 48-72 hours later; observers were blind to IGRA results. In general, cut-off for a positive TST was stratified by BCG status ("stratified cut-off") as per national guidelines - ≥6mm and ≥15mm in BCG unvaccinated and vaccinated individuals respectively.[29] In addition, a cut-off of ≥10mm ("non-stratified cut-off") was used to evaluate which factors (including BCG vaccination status) were associated with a positive TST, as this was not predefined by BCG status.

In strict accordance with UK national guidelines,[81] and routine clinical practice, HIV testing was not undertaken in immigrants at the time of LTBI screening. Instead participants were asked to self-report previous HIV testing and if they knew if they were HIV seropositive.

Management of symptomatic individuals and positive IGRAs

Immigrants who were symptomatic at the initial screening visit and/or had a positive IGRA/TST result were referred for CXR and further clinical assessment to rule out active TB disease.[29]

For clinical decision-making purposes, immigrants with a positive IGRA (QFN-GIT and/or T.SPOT.TB, as defined by the manufacturers) and/or positive TST and normal chest radiography in the absence of any clinical features suggestive of active TB were defined as having LTBI.[39] Immigrants diagnosed with LTBI who were aged ≤35 years were offered chemoprophylaxis in

accordance with UK guidelines[29] - either 3 months of rifampicin plus isoniazid or 6 months of isoniazid, depending on clinician and patient preference.

Data analysis

Continuous data were summarised with median and interquartile range (IQR), and compared using the non-parametric Mann-Whitney U-test. Categorical responses were expressed as a simple descriptive percentage (with 95% confidence intervals (95% CI)) and comparisons made using Pearson's chi-square test (or Fishers exact test if appropriate). When calculating the proportion of individuals that were IGRA positive, indeterminate results were included in the denominator.

Univariate association of risk factors individually associated with a positive TST (using the "non-stratified cut-off" of ≥10mm), ELISA (QFN-GIT) and ELISpot (T-SPOT.TB) was assessed using logistic regression and reported as crude odds ratios (OR) and 95% confidence intervals. To calculate adjusted odds ratios (and 95% CI), three separate multivariate logistic regression models were constructed for each of the screening tools where I mutually adjusted for the following factors: age, gender, TB incidence in country of origin, time since arrival in the UK, BCG vaccination status, history of TB contact, employment status, smoking status, alcohol use and history of imprisonment. Variables were examined for confounding and for effect modification, and the significance of interaction terms was tested.

Concordance between each of the three screening tools (TST with ELISA, TST with ELISpot, and ELISA with ELISpot) was assessed using percentage agreement and Cohen's κ coefficients; strength of agreement was considered 'poor' for $\kappa \leq 0.20$, 'fair' for $0.20 < \kappa \leq 0.40$, 'moderate' for $0.40 < \kappa \leq 0.60$, 'substantial' for $0.60 < \kappa \leq 0.80$ and 'optimal' for $0.80 < \kappa \leq 1.00$.[411] Pairwise comparisons of the proportion of positive results with each screening test were undertaken using McNemar's test.

Assessment of the different incidence screening thresholds was undertaken by calculating individually for TST, the ELISA and ELISpot, at each incidence threshold (increasing from 0/100000 (ie. screen all) to 350/100000 in increments of 50/100000) the absolute number of immigrants who would need to be screened, the proportion positive with each screening test and the proportion of

individuals with a positive test who would not be detected if screening was undertaken at a particular threshold.

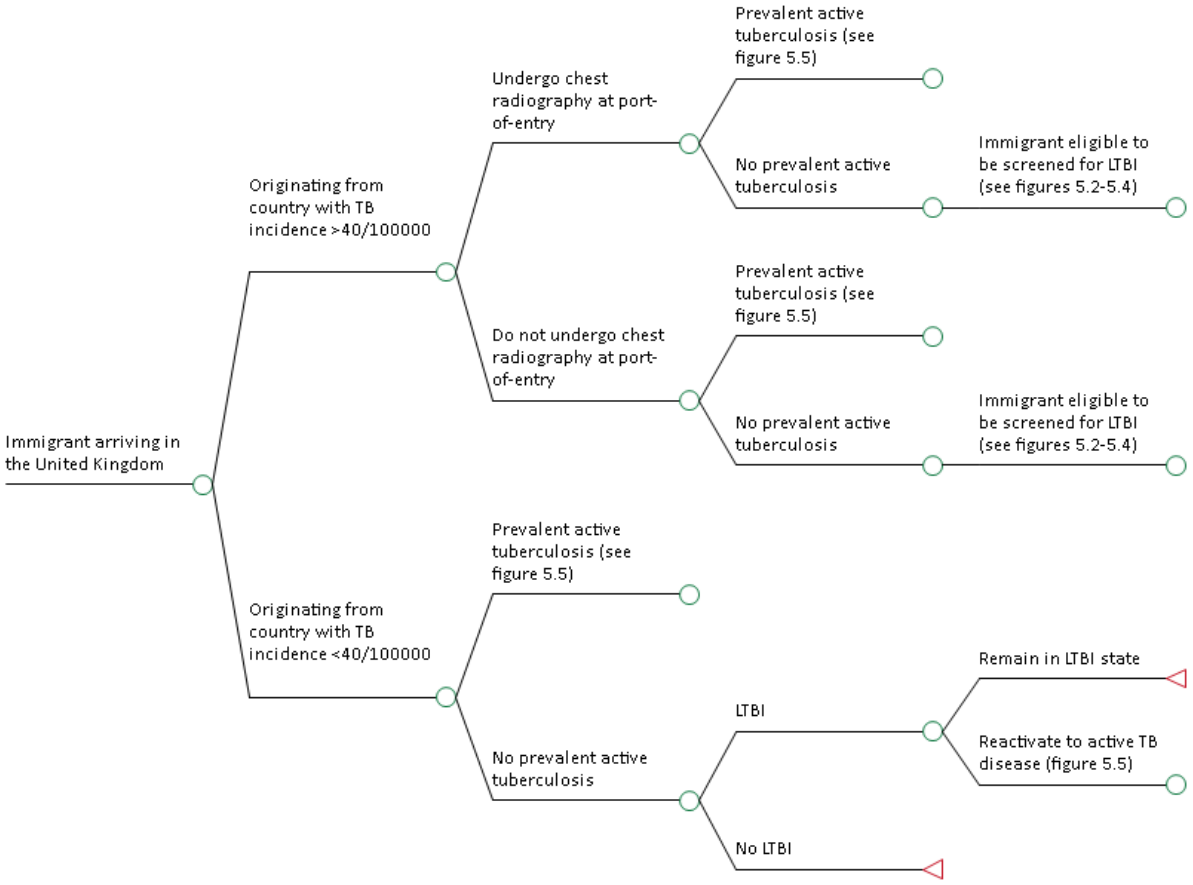
Analyses used STATA 9.2 (StataCorp, College Station, TX). All tests were two tailed; p-value of ≤0.05 was considered significant.

Health economic evaluation

A health-economic analysis was conducted from a National Health Service (NHS) perspective to consider the cost-effectiveness of supplementing chest radiography at port-of-entry with immigrant screening for LTBI with different strategies and tools at different incidence thresholds.

I developed a decision-tree model (figures 5.1-5.5), incorporating HIV infection and drug resistance, based on empiric data from the prospective three-way comparison of tuberculin skin test (TST), QuantiFERON Gold in-tube (QFN-GIT) and T-SPOT.TB described above to simulate the clinical (numbers of active TB cases) and economic outcomes of screening a hypothetical cohort of 10,000 recently arrived immigrants (aged ≤35 years) for active TB (at port-of-entry) and LTBI over a 20-year time horizon. One important exception to this was HIV status. Given the lack of data on HIV infection in our cohort (and immigrants in general) I used country, and incidence, specific HIV prevalence figures from the World Health Organisation to estimate HIV prevalence at each screening threshold (table 5.5) which were used to parameterise the economic analysis.

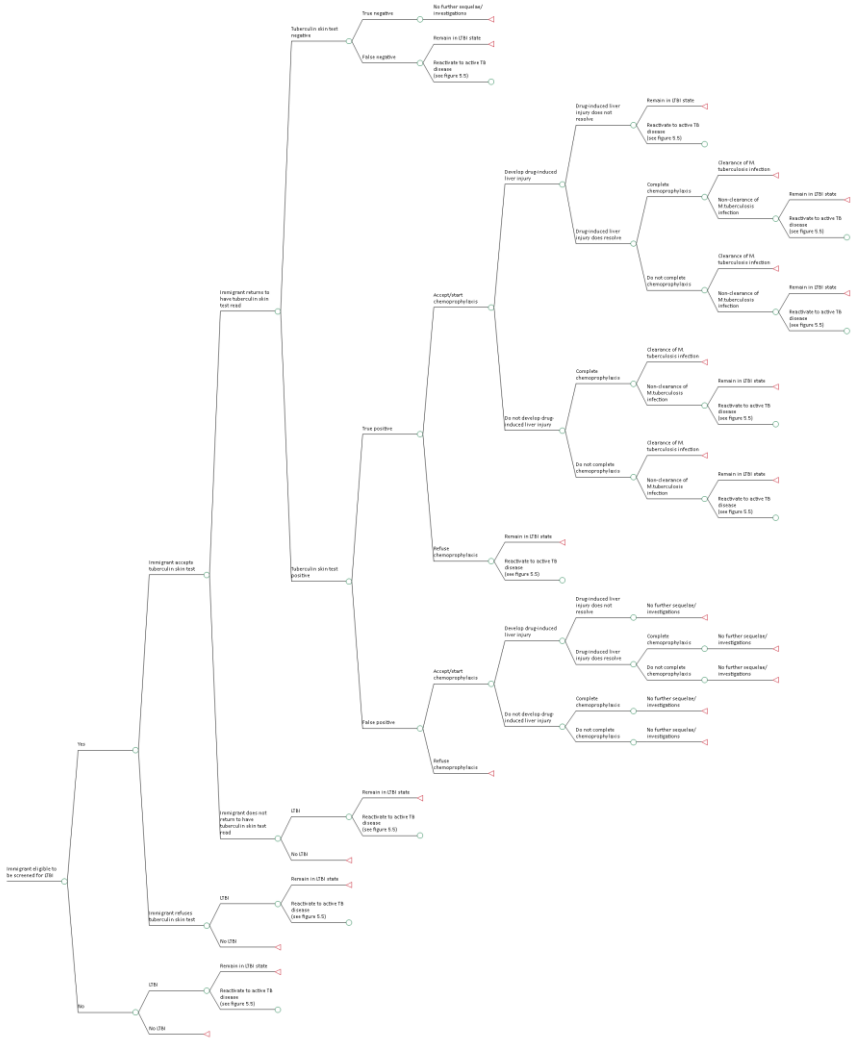
Figure 5.1 Decision tree outlining the potential screening outcomes (particularly with respect to chest radiography) at port-of-entry for immigrants arriving in the United Kingdom from overseas



Footnote

1. For clarity all “prevalent active tuberculosis” and “reactivate to active TB subtrees” are shown in figure 5.5 below.

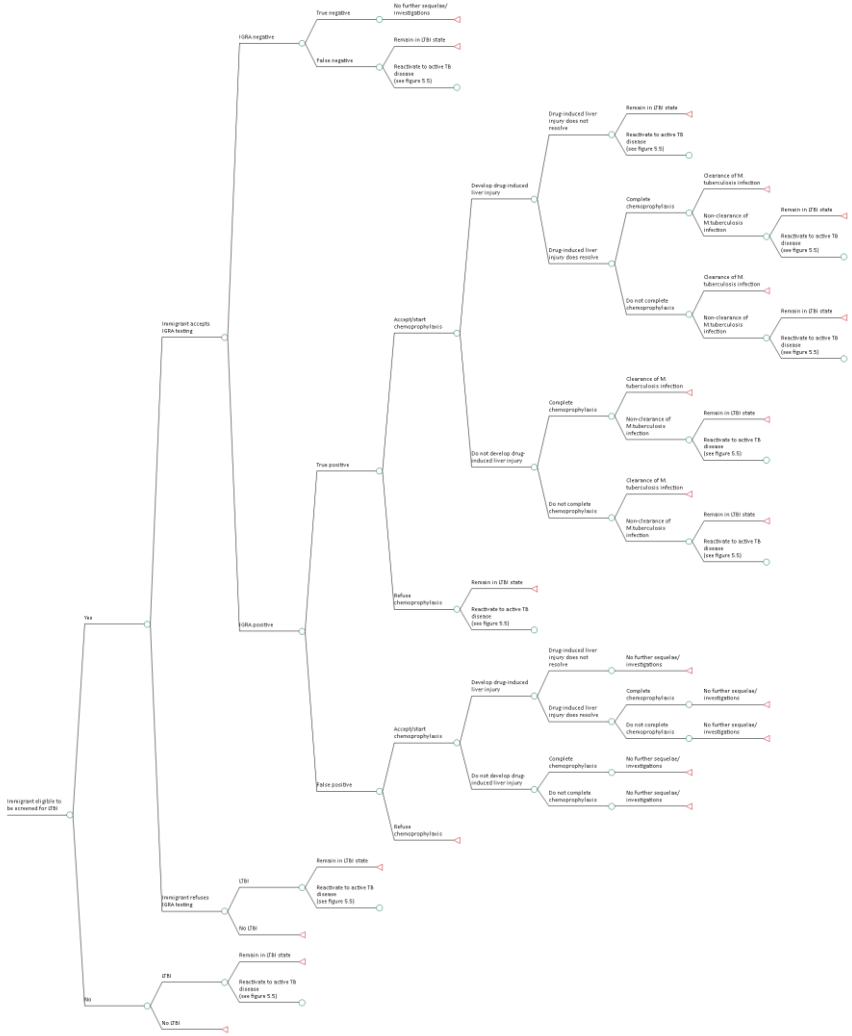
Figure 5.2 Decision tree used for the health economic analysis of immigrant screening with tuberculin skin test for latent tuberculosis infection (LTBI) after port-of-entry screening



Footnotes

1. For clarity/space restrictions HIV infection and drug-resistance (which were included in the analysis) are not represented in the diagram
2. Individuals are only eligible for screening for LTBI if they originate from a country which has a TB incidence equal or greater to the screening threshold selected.
3. In the model all individuals who are fully cured of LTBI are assumed to have cleared infection with *Mycobacterium tuberculosis* (a terminal node)
4. Individuals who do not clear LTBI remain at risk of progressing to active TB in the future
5. Individuals who develop hepatotoxicity after starting chemoprophylaxis but which subsequently does not resolve are assumed to stop the drug. In the model it is assumed that they complete only 4 weeks of treatment and this has negligible efficacy thereby leaving them latently infected and thus at future risk of reactivating to active TB
6. Individuals who develop hepatotoxicity after starting chemoprophylaxis but which subsequently resolves are assumed to continue the drug. In the model it is assumed that they can either complete or not complete treatment with their attendant outcomes
7. For clarity all “reactivate to active TB subtrees” are shown in figure 5.5

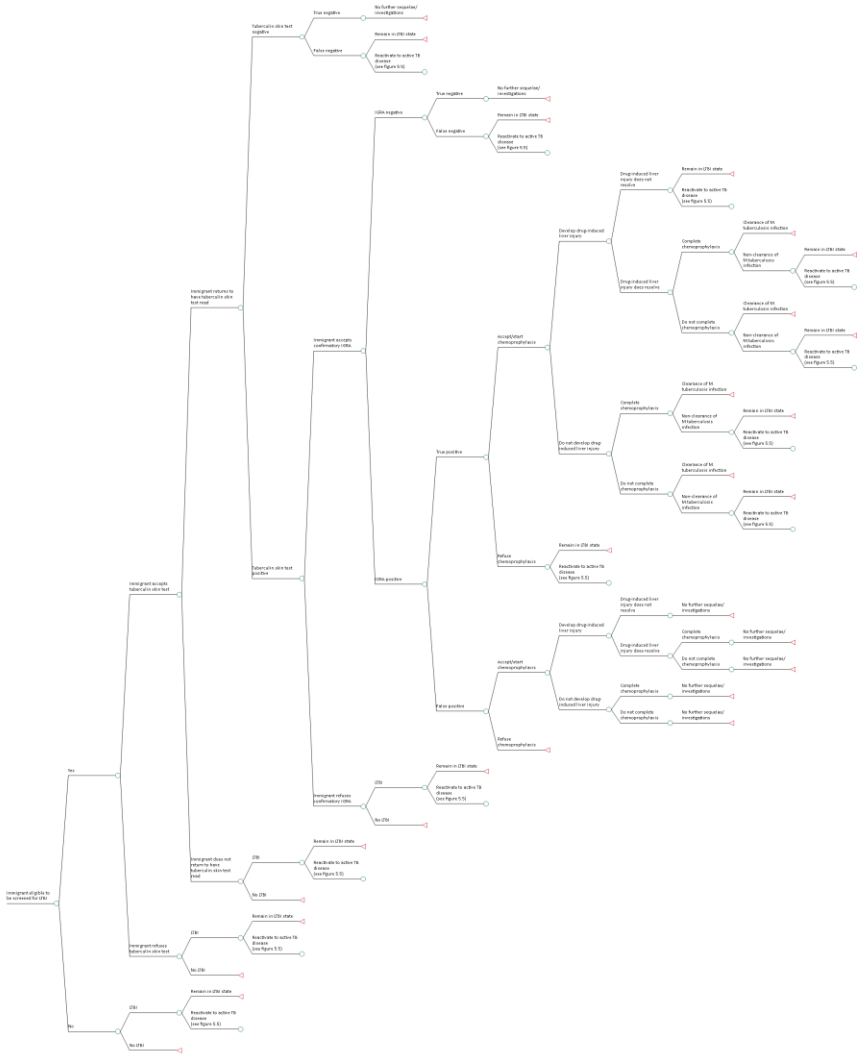
Figure 5.3 Decision tree used for the health economic analysis of immigrant screening with interferon gamma release assay (IGRA - either QuantiFERON Gold in-tube or T-SPOT.TB) for latent tuberculosis infection (LTBI) after port-of-entry screening



Footnotes

1. For clarity HIV infection and drug-resistance (which were included in the analysis) are not represented in the diagram.
2. Individuals are only eligible for screening for LTBI if they originate from a country which has a TB incidence equal or greater to the screening threshold selected.
3. In the model all individuals who are fully cured of LTBI are assumed to have cleared infection with *Mycobacterium tuberculosis* (a terminal node).
4. Individuals who do not clear LTBI remain at risk of progressing to active TB in the future.
5. Individuals who develop hepatotoxicity after starting chemoprophylaxis but which subsequently does not resolve are assumed to stop the drug. In the model it is assumed that they complete only 4 weeks of treatment and this has negligible efficacy thereby leaving them latently infected and thus at future risk of reactivating to active TB.
6. Individuals who develop hepatotoxicity after starting chemoprophylaxis but which subsequently resolves are assumed to continue the drug. In the model it is assumed that they can either complete or not complete treatment with their attendant outcomes.
7. For clarity all “reactivate to active TB subtrees” are shown in figure 5.5

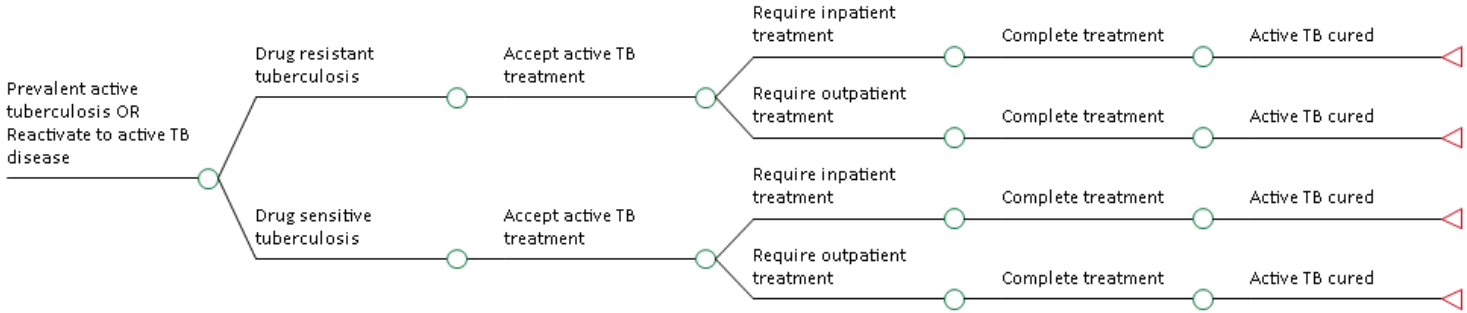
Figure 5.4 Decision tree used for the health economic analysis of immigrant screening with a dual tuberculin skin test plus confirmatory interferon gamma release assay (IGRA - either QuantiFERON Gold in-tube or T-SPOT.TB) approach for latent tuberculosis infection (LTBI) after port-of-entry screening



Footnotes

1. For clarity HIV infection and drug-resistance (which were included in the analysis) are not represented in the diagram.
2. Individuals are only eligible for screening for LTBI if they originate from a country which has a TB incidence equal or greater to the screening threshold selected.
3. In the model all individuals who are fully cured of LTBI are assumed to have cleared infection with *Mycobacterium tuberculosis* (a terminal node).
4. Individuals who do not clear LTBI remain at risk of progressing to active TB in the future.
5. Individuals who develop hepatotoxicity after starting chemoprophylaxis but which subsequently does not resolve are assumed to stop the drug. In the model it is assumed that they complete only 4 weeks of treatment and this has negligible efficacy thereby leaving them latently infected and thus at future risk of reactivating to active TB.
6. Individuals who develop hepatotoxicity after starting chemoprophylaxis but which subsequently resolves are assumed to continue the drug. In the model it is assumed that they can either complete or not complete treatment with their attendant outcomes.
7. For clarity all “reactivate to active TB subtrees” are shown in figure 5.5

Figure 5.5 Decision subtree used to describe the events that occur if an individual is diagnosed with prevalent active TB at port-of-entry screening or reactivates to active TB from LTBI



Footnotes

1. Individuals who are diagnosed with active tuberculosis through active screening with chest radiography (at port-of-entry) or passively after reactivating from latent tuberculosis infection to active tuberculosis are managed in the same way
2. Onward transmission to contacts, the subsequent secondary cases of active tuberculosis and latent infections and the contact tracing procedures are not represented due to clarity

Screening strategies and incidence thresholds considered in health-economic analysis

In this cost-effectiveness analysis, I first considered that immigrants arriving in the UK could either be screened with chest radiography (CXR) at port-of-entry or, in an alternative scenario, that this initial CXR would not be undertaken. Subsequently immigrants could be screened for LTBI with one of five strategies (TST alone, T-SPOT.TB alone, QFN-GIT alone, TST followed by confirmatory T-SPOT.TB if TST positive and TST followed by confirmatory QFN-GIT if TST positive) at seven different incidence thresholds (screening at ≥40/100000, ≥100/100000, ≥150/100000, ≥200/100000, ≥250/100000, ≥300/100000, ≥350/100000). At each threshold cut-off, I evaluated the number of immigrants who would be eligible for screening, the number of true positive individuals with LTBI and the number of individuals with LTBI that would be missed relative to screening the whole cohort. Model assumptions are outlined in table 5.1. In total, this resulted in 70 potential active TB and LTBI screening policies (table 5.2) which were included in the current analysis with the primary aim being to understand which screening policy (or policies) would be most cost-effective for the United Kingdom (UK). The decision tree was constructed, and analysed, using Microsoft Excel 2007 (Microsoft, USA) and TreeAge Pro 2011 (Tree Age Software, Inc., Williamstown, MA).

Table 5.1 Model assumptions of the health-economic model

Assumption
Immigrants are screened for LTBI once at the start of the time horizon
Tuberculin skin test positivity is classified as per UK guidelines (≥6mm in BCG unvaccinated and ≥15mm in BCG vaccinated
All IGRA results are determinate and no repeat testing is required
The proportion of immigrants with HIV is reflective of the HIV prevalence in their country of origin
A proportion of immigrants with latent tuberculosis infection are infected by a resistant strain of *Mycobacterium tuberculosis*
A proportion of active tuberculosis cases are drug-resistant
Amongst those individuals identified with LTBI and treated with chemoprophylaxis, a three month course of rifampicin and isoniazid is considered to have equivalent efficacy to six months of isoniazid[96]
Individuals who commence chemoprophylaxis and subsequently develop drug-induced liver injury which does not resolve are assumed to only complete 4 weeks of therapy which affords no reduction in the risk of progressing from LTBI to active TB
No individuals who develop drug induced liver injury die due to this adverse effect
Equal proportions of HIV negative and positive immigrants develop drug-induced liver injury from chemoprophylaxis
Chemoprophylaxis will have no efficacy in those immigrants who have a resistant strain causing their LTBI
An individual with LTBI who has completed successful chemoprophylaxis is assumed to have cleared the infection with *Mycobacterium tuberculosis* and will not experience any further outcomes during the time course of the model (such as reinfection)
An individual who does not have LTBI on arrival in the UK does not become infected during the time-period considered by the model.
Drug sensitive and drug resistant strains are assumed to be equally transmissible (in other words drug resistance does not result in any fitness cost)
There is no HIV acquisition within the cohort during the time horizon of the model
Data on the test performance of the IGRA was based on the most recent meta-analysis obtained from meta-analyses where sensitivity was calculated using culture-confirmed active TB as the reference standard whilst specificity was calculated from BCG-vaccinated individuals at low risk of infection.[41]
Point estimates for test sensitivity were assumed to be different for HIV positive individuals
All individuals diagnosed with drug-sensitive active tuberculosis are assumed to accept treatment for active TB and to complete the 6 month course of drugs
All individuals diagnosed with drug-resistant active tuberculosis are assumed to accept treatment for active TB and to complete the course of drugs

Table 5.2 Screening tools and thresholds considered in the health economic analysis

Chest radiography undertaken at port of entry	Screening for latent tuberculosis infection	
	Screening tool[1]	Screening threshold for immigrants (number of cases of TB/100000)
Yes	Tuberculin skin test	40
Yes	Tuberculin skin test	100
Yes	Tuberculin skin test	150
Yes	Tuberculin skin test	200
Yes	Tuberculin skin test	250
Yes	Tuberculin skin test	300
Yes	Tuberculin skin test	350
No	Tuberculin skin test	40
No	Tuberculin skin test	100
No	Tuberculin skin test	150
No	Tuberculin skin test	200
No	Tuberculin skin test	250
No	Tuberculin skin test	300
No	Tuberculin skin test	350
Yes	T-SPOT.TB	40
Yes	T-SPOT.TB	100
Yes	T-SPOT.TB	150
Yes	T-SPOT.TB	200
Yes	T-SPOT.TB	250
Yes	T-SPOT.TB	300
Yes	T-SPOT.TB	350
No	T-SPOT.TB	40
No	T-SPOT.TB	100
No	T-SPOT.TB	150
No	T-SPOT.TB	200
No	T-SPOT.TB	250
No	T-SPOT.TB	300
No	T-SPOT.TB	350
Yes	QuantiFERON Gold in-tube	40
Yes	QuantiFERON Gold in-tube	100
Yes	QuantiFERON Gold in-tube	150
Yes	QuantiFERON Gold in-tube	200
Yes	QuantiFERON Gold in-tube	250
Yes	QuantiFERON Gold in-tube	300
Yes	QuantiFERON Gold in-tube	350
No	QuantiFERON Gold in-tube	40
No	QuantiFERON Gold in-tube	100
No	QuantiFERON Gold in-tube	150
No	QuantiFERON Gold in-tube	200
No	QuantiFERON Gold in-tube	250
No	QuantiFERON Gold in-tube	300
No	QuantiFERON Gold in-tube	350
Yes	Tuberculin skin test + T-SPOT.TB	40
Yes	Tuberculin skin test + T-SPOT.TB	100
Yes	Tuberculin skin test + T-SPOT.TB	150
Yes	Tuberculin skin test + T-SPOT.TB	200
Yes	Tuberculin skin test + T-SPOT.TB	250
Yes	Tuberculin skin test + T-SPOT.TB	300
Yes	Tuberculin skin test + T-SPOT.TB	350
No	Tuberculin skin test + T-SPOT.TB	40
No	Tuberculin skin test + T-SPOT.TB	100
No	Tuberculin skin test + T-SPOT.TB	150
No	Tuberculin skin test + T-SPOT.TB	200
No	Tuberculin skin test + T-SPOT.TB	250
No	Tuberculin skin test + T-SPOT.TB	300
No	Tuberculin skin test + T-SPOT.TB	350
Yes	Tuberculin skin test + QuantiFERON Gold in-tube	40
Yes	Tuberculin skin test + QuantiFERON Gold in-tube	100
Yes	Tuberculin skin test + QuantiFERON Gold in-tube	150
Yes	Tuberculin skin test + QuantiFERON Gold in-tube	200
Yes	Tuberculin skin test + QuantiFERON Gold in-tube	250
Yes	Tuberculin skin test + QuantiFERON Gold in-tube	300
Yes	Tuberculin skin test + QuantiFERON Gold in-tube	350
No	Tuberculin skin test + QuantiFERON Gold in-tube	40
No	Tuberculin skin test + QuantiFERON Gold in-tube	100
No	Tuberculin skin test + QuantiFERON Gold in-tube	150
No	Tuberculin skin test + QuantiFERON Gold in-tube	200

No	Tuberculin skin test + QuantiFERON Gold in-tube	250
No	Tuberculin skin test + QuantiFERON Gold in-tube	300
No	Tuberculin skin test + QuantiFERON Gold in-tube	350

Footnote

[1]Where the tuberculin skin test and IGRA are shown, the IGRA is used to confirm a positive result

Description of the decision models

All decision models (figures 5.1-5.5) considered a hypothetical cohort of 10,000 immigrants, aged ≤35 years, who had recently arrived in the UK.

Chest radiography at port-of-entry

Amongst those immigrants arriving in the UK, a proportion will have originated from countries with a TB incidence of ≥40/100000. As per UK national policy, these individuals are subject to immigration control measures which require that if they are intending to stay in the UK for >6 months they should undergo CXR on arrival.[283] In the model port-of-entry screening is explored through two scenarios. In scenario one, I assume a proportion of those immigrants (from countries with TB incidence ≥40/100000) are screened with CXR on arrival in the UK; the remainder either refuse or are not appropriately identified for, and thus miss, CXR screening. In contrast those who come from countries with a TB incidence <40/100000 do not undergo CXR screening. In scenario two I assume that there is no port-of-entry screening system in place and therefore immigrants do not undergo CXR screening on arrival in the UK.

Amongst those immigrants who do, and do not, undergo chest radiography a fixed proportion (in keeping with meta-analytical and national data) will be diagnosed with active TB – with a fixed proportion of these cases being caused by drug sensitive and drug-resistant strains of *Mycobacterium tuberculosis*. However the model makes an important distinction between those immigrants actively diagnosed with active TB (through port-of-entry CXR screening) and those individuals who are passively diagnosed after presenting with symptoms (in other words those individuals who have not been screened at port-of-entry with CXR). Actively diagnosed individuals are assumed to be

infectious for a shorter duration than passively diagnosed individuals with the model assuming a 50% reduction in the number of their close contacts becoming latently infected or developing active TB.

All individuals diagnosed with active TB are assumed to accept and complete treatment; as a simplifying assumption I assume that there is a 100% cure rate. Immigrants who have been cured of active TB cannot be re-infected during the course of the 20-year model – in other words they have no further sequelae in the model.

Immigrants who have not been diagnosed with active TB at this initial stage, but have arrived from countries with a TB incidence of ≥40/100000, represent the cohort that will be targeted, depending on the specific incidence threshold at which screening is to be instigated (see ***Screening strategies and incidence thresholds considered in health-economic analysis*** above), for LTBI screening an identification. On the other hand, in keeping with national guidelines, immigrants who have arrived from countries with a TB incidence of <40/100000 are not eligible to be screened for LTBI. However, it is important to note that this does not mean they have no further sequelae in the model. In fact a proportion of this subgroup will actually have LTBI and therefore remain at risk of progressing to active TB over the time course of the model and this eventuality is included in the model.

Screening strategies for latent tuberculosis infection

The five screening strategies (TST alone, T-SPOT.TB alone, QFN-GIT alone, TST followed by confirmatory T-SPOT.TB if TST positive and TST followed by confirmatory QFN-GIT if TST positive) were encapsulated in three related, but distinct, decision models.

Model 1 considers the TST only screening approach (figure 5.2), model 2 the IGRA only approach (either single-step testing with QuantiFERON Gold in-tube (QFN-GIT) or T-SPOT.TB – figure 5.3) and model 3 considers a scenario where TST is followed by a confirmatory IGRA – if the TST is positive (figure 5.4). For models 2 and 3, although the actual model flows are identical, both IGRAs (QFN-GIT and T-SPOT.TB) were considered independently, with unique input parameter values (such as test sensitivity and specificity).

In many respects the three models overlap although the initial flows which deal with acceptance of the screening tests do differ as set out below.

Eligibility for testing and acceptance of screening test

Depending on the specific incidence threshold at which immigrant screening is to be instigated, a proportion of migrants will either be eligible or ineligible to be screened for LTBI. Of these individuals, fixed proportions are assumed to be HIV positive and negative respectively (*see section* ***Input parameters and probabilities – HIV prevalence*** for details***)***. Immigrants who are eligible will be offered initial testing with either TST (which applies to model 1 the TST only approach and model 3 the TST plus confirmatory IGRA approach) or IGRA (which applies to model 2 the IGRA only approach). Immigrants who are ineligible for screening are not offered appointments and if they have LTBI (which can be caused by either a drug-sensitive or drug-resistant strain of *M. tuberculosis*) they remain at risk of progressing to active TB over the twenty-year time horizon of the model at a rate which is determined by their HIV status – with HIV-positive individuals experiencing a higher annual progression rate than HIV-negative individuals. As highly active anti-retroviral therapy (HAART) coverage is high in the UK, and would render HIV positive individuals immunocompetent, I assumed that their pattern of disease would be similar to the rest of the HIV-negative cohort.

Amongst those eligible immigrants who are offered testing with TST, a proportion will accept and have the Mantoux test administered at this first visit. If TST testing is not accepted, the immigrant will be discharged from clinical care. Forty-eight to seventy-two hours following administration of TST, a proportion of immigrants will return to have the size of induration read and measured. If the immigrant does not return to have the TST reaction read, they are also discharged from clinical care.

In the IGRA only approach, a proportion of those individuals offered testing with the IGRA will accept and have blood drawn at this first visit. Those who decline the screening test are discharged from clinical care. In contrast to TST testing, no further visits are required (we assume that all results are determinate and no repeat IGRA testing is required).

Confirmation of positive TST in dual TST plus confirmatory IGRA testing model

In contrast to models 1 (TST only approach) and 2 (IGRA only approach) where clinical decisions are made solely on the basis of one test result, model 3, the TST plus confirmatory IGRA approach, has an additional step. Immigrants who have had the initial TST will return to have the reaction read. If it is negative, they will be discharged. However if the immigrant is found to have a positive TST, then further, confirmatory, testing is offered with an IGRA (we separately consider both QFN-GIT and T-SPOT.TB). If IGRA testing is accepted by the immigrant, blood is drawn for the IGRA whilst those who refuse are discharged from clinical care.

Assessment and confirmation of positive screening tests

As a result of reading the TST (in the TST only model), or obtaining the IGRA result from the laboratory (in the IGRA only and TST plus confirmatory IGRA models), immigrants will be classified positive or negative. Depending on the HIV status of the individual, and the performance of the screening tests (which can be adversely affected by HIV infection[39]) subjects with a positive test result can either be classified true positive (determined by the positive predictive value of the test) or false positive (1-positive predictive value of the test); conversely if the test is negative subjects can be true negative (which is determined by the negative predictive value of the test) or false negative (1-negative predictive value of the test). Amongst those individuals with LTBI (in other words those who test true positive or false negative) it is assumed that fixed proportions are latently infected with drug-resistant and drug-sensitive strains of *Mycobacterium tuberculosis* respectively. However, it should be noted in routine clinical practice there is no way of being able to differentiate these individuals and therefore their subsequent management (including drug therapy) will be identical.

Individuals who are TST or IGRA positive (both true and false) will go on to be assessed for active TB with chest radiography. As a simplification, in the current model it is assumed that there are no prevalent cases of active TB in the immigrant cohort at the time of screening. In reality, however, a very small proportion of migrants will have active TB although this is extremely rare and in most cases, the chest radiographic assessment for active TB will be normal.

Uptake of chemoprophylaxis by individuals who test positive

All TST and IGRA positive (both true and false) individuals, where active TB has been excluded, are assumed to have LTBI and so will be offered chemoprophylaxis with three months of rifampicin and isoniazid. Identical proportions of these true positive and false positive individuals will accept therapy with the remainder, who refuse treatment, being discharged. However, the potential outcomes are different. If an immigrant with a true positive LTBI screening test refuses therapy, they can either remain in the LTBI state or progress to active TB disease over the 20 year time horizon of the model; the actual drug sensitivity of the active TB case will depend on the whether the reactivating strain is drug-sensitive or drug-resistant. On the other hand if a false positive individual refuses therapy, as they are actually uninfected with TB, there are no further sequelae.

Drug-induced liver injury amongst individuals who commence chemoprophylaxis

Amongst those individuals who commence chemoprophylaxis, a fixed proportion develop drug-induced liver injury (DILI) even though this is relatively rare (approximately 0.2%[364]) in the age-group considered (immigrants ≤35 years). In those immigrants who develop DILI, extra costs in the form of additional clinic visits, blood tests and, in a proportion, inpatient admission are required. In a small proportion of those with DILI, there is no resolution of symptoms and the chemoprophylaxis will be discontinued. It is assumed that these individuals will have only completed four weeks of therapy and so chemoprophylaxis is assumed to have no efficacy. Therefore these individuals remain latently infected and thus at future risk of progressing to active TB disease. In most cases, however, the DILI will usually improve and liver function tests will return to normal.

Completion of chemoprophylaxis and efficacy in preventing progression from LTBI to active TB disease

In those individuals where drug-induced liver injury has resolved, or does not occur at all, fixed proportions will complete and not complete the chemoprophylactic regimen.

Complete treatment is 65% efficacious in preventing progression from LTBI to active TB - in those individuals who are truly infected with drug-sensitive LTBI.[395] This means that there will be some patients (with drug-sensitive LTBI) who complete therapy but in whom the drug regimen has been ineffectual. As an added layer of complexity it is assumed that the proportion of true-positive immigrants (with drug-sensitive LTBI) in whom DILI has resolved but do not complete therapy will have completed 50% of the drug regimen (ie. 6 weeks) and, based on data suggesting equivalence of 3 months of rifampicin and isoniazid and 6 months isoniazid, I assume, in keeping with previous authors,[396,397] that this reduces the risk of reactivation by 21%.[395] Therefore ineffective therapy, either if treatment has been fully or partially completed, in true positive individuals with drug sensitive LTBI, means that they will remain as true positive, uncured, drug-sensitive LTBI and therefore at risk of progressing, over the 20-year time horizon of the model, to active TB disease.

It should be noted that the preceding discussion focuses on the situation where the immigrant is latently infected with a drug-sensitive strain of *Mycobacterium tuberculosis*. However in the model a proportion of those individuals with a true-positive screening test will actually have drug-resistant LTBI. In these individuals although identical proportions either fully or partially complete chemoprophylaxis, it is assumed that the drug regimen has no efficacy in reducing the risk of progression from LTBI to active TB.

Outcomes for negative screening tests

Immigrants who test negative with TST or IGRA are considered to be uninfected in the model and will be discharged from clinical care. For true negative individuals no further costs or health effects are incurred. Individuals who are false negative actually have LTBI, either drug-sensitive or drug-

resistant, and are at risk of progressing to drug-sensitive or drug-resistant active TB disease (with its attendant costs) respectively over the 20-year time horizon of the model.

Groups at risk of progressing from latent TB to active TB

In the three decision models there are a number of different immigrant groups with LTBI who remain at risk of progressing to active TB disease over the time horizon of the model (see table 5.3). It is important to note that the outcomes of these groups are incorporated into the cost-effectiveness models.

Table 5.3 Description of immigrant groups in the model who have LTBI and are at risk of progressing to active TB disease

Groups with latent TB infection who remain at risk of progressing to active TB disease	Applies to which models
Immigrants with LTBI who are not eligible to be screened as they originate from a country with a TB incidence which does not meet the screening criteria	1,2,3
Immigrants with LTBI who are eligible to be screened but refuse the TST screening test	1,3
Immigrants with LTBI who are eligible to be screened but refuse the IGRA screening test (where it is used as the only screening tool)	2
Immigrants with LTBI who are eligible to be screened, have had the initial TST administered and read but refuse the confirmatory IGRA	3
Immigrants with LTBI who are screened by TST but do not return to have the size of induration read	1,3
Immigrants with LTBI who screen true positive with TST or IGRA but decline to commence chemoprophylaxis	1,2
Immigrants with LTBI who screen true positive with TST or IGRA, accept chemoprophylaxis, fully complete therapy but it is not effective	1,2
Immigrants with LTBI who screen true positive with TST or IGRA, accept chemoprophylaxis, partially complete therapy but it is not effective	1,2
Immigrants with LTBI who screen true positive with TST or IGRA, accept chemoprophylaxis, start chemoprophylaxis but develop drug-induced liver injury which does not resolve and so they must stop the therapy (which is assumed to have no efficacy in this short period of time)	1,2
Immigrants with LTBI but who actually test false-negative with TST	1,3
Immigrants with LTBI but who actually test false-negative with IGRA (where it is used as the only screening tool)	2
Immigrants with LTBI who screen true positive with TST and the confirmatory IGRA but decline to commence chemoprophylaxis	3
Immigrants with LTBI who screen true positive with TST and the confirmatory IGRA, accept chemoprophylaxis, fully complete therapy but it is not effective	3
Immigrants with LTBI who screen true positive with TST and the confirmatory IGRA, accept chemoprophylaxis, partially complete therapy but it is not effective	3
Immigrants with LTBI who screen true positive with TST and the confirmatory IGRA, accept chemoprophylaxis, start chemoprophylaxis but develop drug-induced liver injury which does not resolve and so they must stop the therapy (which is assumed to have no efficacy in this short period of time)	3
Immigrants with LTBI but who actually test false-negative with the confirmatory IGRA after the initial TST is positive	3

Modelling progression of latently infected individuals to active TB

Certain individuals, in the model, with LTBI (table 5.3) remain at risk of progressing to active TB disease. I assume that as many of the immigrants will have been remotely infected that the rate of progression from LTBI to active TB disease occurs at a constant hazard (in other words risk per unit time). In the subset of immigrants who are HIV positive a higher annual rate of progression is applied as compared to those immigrants with LTBI who are HIV negative.[27]

In those immigrants with LTBI a proportion will be caused by a drug-sensitive strain whilst the remainder will be due to a drug-resistant strain. The relevance of this is that if, and when, an individual progresses from LTBI to active TB disease, the resulting active TB disease will either be drug-sensitive or drug-resistant (depending on the original LTBI strain). The development and diagnosis of active TB will result in TB services initiating contact tracing procedures as per national guidance.[29] As a consequence, a fixed number of contacts will be identified amongst whom a fixed number of secondary active TB cases and latent infections will be diagnosed. One area of ongoing controversy is whether drug-resistant TB strains are as transmissible as drug-sensitive strains or whether drug-resistance imparts a fitness cost which reduces their onward transmissibility to close contacts. As there is no consensus on this, in the base case model I adopt the approach taken by Dye[412] and others[413,414] in assuming that drug-resistance imparts little or no fitness cost (in other words the same number of secondary active TB cases and latent infections will be diagnosed in contacts of drug-resistant cases as drug sensitive cases) although in the sensitivity analysis I consider a fitness cost of up to 50%. Secondary cases of LTBI, identified through contact tracing, are managed according to whether the index case was drug-sensitive or drug-resistant. If the index case was drug-sensitive, then latently infected contacts are managed and treated in an identical manner (with identical input parameters) to latently infected immigrants identified through screening. However, as per UK guidelines, latently infected contacts of drug-resistant index cases are not offered chemoprophylaxis as the choice of drugs is limited.[81] Instead these individuals are closely monitored for clinical features of active TB – at which point appropriate treatment for drug-resistant tuberculosis will be initiated.[81]

A proportion of those individuals who develop active TB disease, either as a result of reactivation from LTBI or as a consequence of being a contact of an index case, will require inpatient management with the remainder treated as outpatients. It is assumed that all subjects with active TB (both drug-sensitive and drug-resistant) accept treatment and that treatment will be undertaken as per national guidelines.[29] An important consideration is that drug-resistant cases of active TB require a significantly longer duration of treatment and much higher treatment costs.[29,415] As a simplification, compliance with, and cure from, anti-tuberculous therapy were fixed at 100% for both drug-sensitive and drug-resistant cases of active TB. Once an individual has been treated for active TB they cannot be re-infected during the course of the 20-year model. In view of the low mortality rate from TB in the UK it is assumed that there is no TB or background mortality during the 20-year horizon of the model.

Input parameters and probabilities

Parameters for the health economic model were drawn from the published literature and the current three-way assessment of LTBI screening methods (see tables 5.4 and 5.5). However, as UK guidelines only recommend treatment for latently infected immigrants aged ≤35 years,[29] specific input parameters (such as the prevalence of LTBI) were only obtained from the subset of tested immigrants who were aged ≤35 years.

Table 5.4 Parameters used as input values in the decision models

Parameter	Base case	Range explored	References
Proportion of immigrants ≤35 with latent tuberculosis	0.13	0.1-0.4	Current study
Prevalence of HIV infection	Varies (table 5.5)	Varies (table 5.5)	416
Proportion undergoing screening	Varies (table 5.6)	Varies (table 5.6)	Current study
Prevalence of multi-drug resistant tuberculosis	0.01	0.005-0.02	140
Specificity of tuberculin skin test in HIV negative individuals	0.78	0.70-0.90	42
Sensitivity of tuberculin skin test in HIV negative individuals	0.77	0.65-0.82	42,43
Specificity of QuantiFERON Gold in –tube in HIV negative individuals	0.99	0.75-1.0	41
Sensitivity of QuantiFERON Gold in –tube in HIV negative individuals	0.84	0.75-0.87	41,42
Specificity of T-SPOT.TB in HIV negative individuals	0.86	0.72-0.95	41
Sensitivity of T-SPOT.TB in HIV negative individuals	0.89	0.78-0.91	41,42
Specificity of tuberculin skin test in HIV positive individuals	0.78	0.70-0.90	42
Sensitivity of tuberculin skin test in HIV positive individuals	0.71	0.61-0.75	42,43
Specificity of QuantiFERON Gold in –tube in HIV positive individuals	0.99	0.75-1.0	41
Sensitivity of QuantiFERON Gold in –tube in HIV positive individuals	0.75	0.61-0.78	41,54
Specificity of T-SPOT.TB in HIV positive individuals	0.86	0.72-0.95	41-43
Sensitivity of T-SPOT.TB in HIV positive individuals	0.81	0.62-0.83	41,54
Proportion of new-entrants from countries with TB incidence >40/100000 undergoing chest-radiography at port-of entry	0.4	0.3-0.6	183,191,370
Proportion of new-entrants from countries with TB incidence <40/100000 undergoing chest-radiography at port-of entry	0.0	Fixed	191
Proportion of new-entrants from countries with TB incidence >40/100000 with pre-existing active TB (ie. prevalent cases)	0.0035	0.001-0.005	183,191,370
Proportion of new-entrants from countries with TB incidence <40/100000 with pre-existing active TB (ie. prevalent cases)	0.0010	0.0005-0.005	183,370
Proportion of new-entrants accepting tuberculin skin test administration	0.81	0.6-1.0	Current study
Proportion of new-entrants returning to have tuberculin skin test read	0.94	0.6-1.0	Current study
Proportion of new-entrants accepting QuantiFERON Gold in-tube	0.99	0.6-1.0	Current study
Proportion of new-entrants accepting QuantiFERON Gold in-tube	0.99	0.6-1.0	Current study
Proportion of IGRA positive new entrants accepting chemoprophylaxis	0.95	0.3-1.0	81
Proportion of IGRA positive new entrants completing chemoprophylaxis	0.85	0.3-1.0	81
Duration of chemoprophylaxis with rifampicin and isoniazid (course completed)	3 months	3 months	29
Duration of chemoprophylaxis with rifampicin and isoniazid (course partially completed)	1.5 months	1.5 months	Assumed
Efficacy of 3 months of Rifampicin and Isoniazid	0.65	0.5-0.8	94,395
Efficacy of 1.5 months of Rifampicin and isoniazid (partial chemoprophylaxis)	0.21	0.1-0.3	395
Efficacy of chemoprophylaxis in immigrants with drug-resistant latent tb infections	0.0	Fixed	Assumed
Proportion of immigrants receiving chemoprophylaxis who develop drug-induced liver injury	0.002	0.001-0.003	364
Proportion of TST or IGRA positive, untreated, HIV negative individuals progressing to active TB (post-exposure TB) in 20 years	0.05	0.025-0.15	27
Proportion of TST or IGRA positive, untreated, HIV positive individuals progressing to active TB (post-exposure TB) over 20 years	0.40	0.20-0.80	27
Proportion of individuals with active TB accepting treatment	1.0	Fixed	Assumed
Proportion of individuals with active TB completing therapy	1.0	Fixed	Assumed
Proportion of individuals with active TB cured	1.0	Fixed	Assumed
Discount rate	0.035	0.035	399

Table 5.5 Median HIV prevalence amongst immigrants eligible and not eligible for screening at each TB incidence threshold

Screening threshold for immigrants (number of cases of TB/100000)[1]	HIV prevalence[2] amongst immigrants eligible to be screened at this TB incidence threshold	HIV prevalenc[2]e amongst immigrants not eligible to be screened at this TB incidence threshold
All[3]	0.004	0
40	0.008	0.002
100	0.013	0.002
150	0.018	0.002
200	0.021	0.002
250	0.031	0.002
300	0.041	0.002
350	0.041	0.003

Footnotes

[1]Refers to TB incidence in the country of origin
[2]Prevalence figures are proportions
[3]Data shown for illustrative/comparative purposes as this threshold was not included in the economic analysis

HIV prevalence

The model builds on previous work[366] by incorporating the fact that a proportion of the immigrant cohort is assumed to be HIV infected. HIV prevalence data were based on country-specific 2007 UNAIDS/WHO figures (in adults aged 15-49 years).[416] However I did not simply assume that there was an average proportion across the whole cohort. Instead, I first stratified countries, and their HIV prevalence, by the TB incidence thresholds considered in the health-economic model. This allowed us to calculate, at each TB incidence threshold, the median HIV prevalence for those eligible, and not eligible, for LTBI screening (see table 5.5). This does, of course, in the absence of empiric data, depend on the assumption that migrants have the same prevalence of HIV as the general population in their countries of origin.

The importance of including HIV infection is that it allows one to model:

1. The differential performance of screening tests (TST and both commercial IGRAs) in HIV infected individuals.
2. The differential progression rate from LTBI to active TB in HIV infected individuals

Drug-resistant tuberculosis

The multiple forms of drug-resistance, including mono-, multi- and extensive-, make it difficult to include all aspects of these subtypes. Therefore I made a simplifying assumption that all drug-resistance is in the form of multi-drug resistance, as this has the most important implications for health outcomes, treatment, and costs. This means that a proportion of the active TB cases identified through port-of-entry screening will be MDR-TB and that a fixed proportion of immigrants with LTBI are infected with a multi-drug resistant strain of *Mycobacterium tuberculosis* where chemoprophylaxis has no effect. If these latently infected individuals progress to active TB, multi-drug resistant active tuberculosis will result – with significantly greater management costs than drug-sensitive TB.

Performance of screening tests

Estimates for the performance (in other words sensitivity and specificity) of the screening tools for LTBI, stratified by HIV seropositivity, were obtained from contemporary meta-analyses. Importantly, many of these studies based their pooled estimates on culture-confirmed active TB as the reference standard (particularly with respect to sensitivity).

In HIV-negative individuals, three recent analyses have concluded that tuberculin skin test sensitivity is 70%, 77% and 65%;[41-43] in the base-case model I used the highest of these estimates (77%) to be conservative with respect to the relative benefits of IGRA vs TST, although I explored a suitably wide range in the sensitivity analyses. In HIV-positive individuals TST has reduced sensitivity.[39] However, in the absence of reliable meta-analytical estimates for TST sensitivity in HIV positive individuals, I used the lower bound of the 95% confidence interval for TST sensitivity in HIV negative subjects (71%) from Pai et al[43] as our estimate.

TST specificity, in both HIV negative and positive individuals, is reduced by bacilli Calmette Guerin (BCG) vaccination and cross-reactivity with environmental mycobacteria.[39] A meta-analysis estimated TST specificity is 59% (range 46%-73%) in BCG vaccinated individuals, but significantly higher (97%) in BCG unvaccinated individuals.[43] More recently, Sester and colleagues calculated a

lower TST specificity of 75% (95% CI 72-78%).[42] In the current immigrant cohort, most individuals had been BCG vaccinated and therefore TST specificity is likely to have been adversely affected. However I felt that the estimate for BCG vaccinated subjects (59%) from Pai and colleagues was too low whereas the estimate in unvaccinated individuals was too high (97%).[43] In addition, there is the possibility that the effect of BCG vaccination may have waned with increasing age in the immigrants and I therefore elected to use a "middle-ground" estimate of 78% from Sester and colleagues[42] in our base-case model – although, again, a wide range was explored in the sensitivity analyses.

Test performance of the IGRAs was obtained from recent meta-analyses although many of these studies have come to widely differing conclusions about IGRA performance. In HIV-negative individuals, meta-analyses have calculated that the sensitivity of QuantiFERON Gold in-tube and T-SPOT.TB is in the range of 67-84% and 81-89% respectively.[41-43] In the base-case model I used sensitivity estimates from Diel and colleagues who calculated QFN-GIT and T-SPOT.TB sensitivity to be 84% and 89% respectively.[41] In HIV-positive individuals, fewer studies have been conducted. However, a recent systematic review and meta-analysis from Cattamanchi et al estimated that in HIV positive individuals, QFN-GIT sensitivity was 61% (95% CI 47-75%) whilst T-SPOT.TB sensitivity was 72% (95% CI 62-81);[54] in view of the prevailing opinion that IGRAs have a superior sensitivity to TST in HIV positive individuals I elected to use the upper bound of the 95% confidence intervals in the base-case model although I explored a wide range in the sensitivity analysis.

IGRAs have been found in most meta-analyses to have greater specificity than TST[41,43] and seem to be less adversely affected by prior BCG vaccination.[39] In the base-case model I used specificity values of 99% and 86% for QFN-GIT and T-SPOT.TB respectively.[41] However, in view of ongoing debate about the specificity of IGRAs I examined a suitably wide range in the sensitivity analysis.

Prevalence of LTBI

One of the key, but also most poorly understood, model parameters is the prevalence of LTBI in immigrants. Whilst previous authors have estimated an overall prevalence of infection when

undertaking economic modelling, this does not take account of differences by TB burden in the countries of origin. In the current analysis I base the estimates for LTBI prevalence (stratified by the threshold at which screening is instigated) on empiric data from the immigrant cohort that I have studied.

In order to avoid bias or overestimate LTBI prevalence, I based all LTBI prevalence estimates only on those immigrants who were aged ≤35 years of age (excluding immigrants aged >35 years) and had been tested in parallel with either all three screening tools (in other words TST, QFN-GIT and T-SPOT.TB) or two screening tools (in other words TST/QFN-GIT or QFN-GIT/T-SPOT.TB – no subjects were actually tested with TST/T-SPOT.TB). I defined "actual positives" as the following:

1. Individuals who tested positive with all three screening tools where all three had been undertaken.
2. Individuals who tested positive with two out of three screening tools where all three had been undertaken.
3. Individuals who tested positive with both screening tools where two had been undertaken.

The results for these 148 individuals, stratified by TB incidence screening thresholds, are set out in table 5.6.

Table 5.6 Test results for immigrants aged ≤35 years who were tested with either all three or two out of three screening tools

Screening threshold	Individuals who were triple tested					Individuals who were dual tested only					
	TST plus QFN plus TSPOT.TB undertaken					TST plus QFN		TST plus TSPOT[1]		QFN plus TSPOT	
	Number tested	Number triple positive	Number dual positive: TST plus QFN	Number dual positive: TST plus TSPOT.TB	Number dual positive: QFN plus T.SPOT.TB	Number tested	Number dual positive: TST plus QFN	Number tested	Number dual positive: TST plus TSPOT	Number tested	Number dual positive: QFN plus TSPOT
Screen all	86	7	1	2	3	37	3	0	0	25	3
40	84	7	1	2	3	35	3	0	0	25	3
100	61	6	1	1	2	18	1	0	0	21	3
150	44	6	1	0	2	9	1	0	0	17	3
200	29	4	0	0	1	6	1	0	0	12	3
250	10	3	0	0	1	3	1	0	0	5	2
300	2	0	0	0	0	2	0	0	0	3	2
350	2	0	0	0	0	2	0	0	0	2	1

Footnotes

[1]There were no immigrants aged ≤35 years who were dual-tested with TST and TSPOT.

Using estimates on HIV prevalence I estimated the proportion of the tested cohort (at each incidence threshold) that was HIV positive/negative. I could therefore calculate (at each incidence threshold) the proportion of individuals that screened positive (as defined in points 1-3 above) stratified by whether they were HIV negative and positive. However it is incorrect to simply conclude that the proportion positive at each incidence threshold is the actual prevalence of LTBI as this assumes that the screening tools used are 100% sensitive and 100% specific. As the proportion positive is the result of an algorithm using two or three screening tools the sensitivity and specificity of the algorithm using multiple tests in parallel will be different than if a single test was used (and will also differ according to HIV status as the screening tools are acknowledged to perform differently in HIV positive and HIV negative individuals).

At each incidence threshold it is easiest to consider that there are three separate groups (those triple tested with TST/QFN-GIT/T-SPOT.TB, those dual tested with TST/QFN-GIT and those dual tested with QFN-GIT/T-SPOT.TB – all stratified by HIV status) in whom LTBI prevalence needs to be calculated separately.

To calculate LTBI prevalence one must first define the sensitivity and specificity of the diagnostic algorithm using screening tools in parallel. Amongst those individuals who were tested with all three screening tools (TST/QFN-GIT/T-SPOT.TB), I defined actual positives to be those individuals who were triple or dual positive – separately for HIV negative and positive individuals. The sensitivity of this algorithm, that requires two or three of three test results to be positive to regard the overall result as positive, is defined in equation 1.

$$Sensitivity_{triple\_tested} = (Sens_{TST} \times Sens_{QFN\text{-}GIT}) + (Sens_{TST} \times Sens_{TSPOT.TB}) + (Sens_{QFN\text{-}GIT} \times Sens_{TSPOT.TB}) - 2(Sens_{TST} \times Sens_{QFN\text{-}GIT} \times Sens_{TSPOT.TB}) \quad \text{(Equation 1)}$$

The specificity of an algorithm that requires two or three of three test results to be positive to regard the overall result as positive is defined in equation 2.

$$Specificity_{triple\ tested} = (Spec_{TST} \times Spec_{QFN\text{-}GIT} \times Spec_{T\text{-}SPOT.TB}) + (Spec_{TST} \times Spec_{QFN\text{-}GIT}) + (Spec_{TST} \times Spec_{T\text{-}SPOT.TB}) + (Spec_{QFN\text{-}GIT} \times Spec_{T\text{-}SPOT.TB}) - 3(Spec_{TST} \times Spec_{QFN\text{-}GIT} \times Spec_{T\text{-}SPOT.TB})$$

(Equation 2)

In those individuals who were tested with two screening tools (TST/QFN-GIT or QFN-GIT/T-SPOT.TB), where actual positives were defined as those individuals who were dual positive, the combined sensitivity of an algorithm that requires both test results to be positive to regard the overall result as positive can be represented by equations 3 (for those individuals tested by both TST and QFN-GIT) and 4 (for those individuals tested by both QFN-GIT and T-SPOT.TB).[417]

$$Sensitivity_{dualtestedTSTandQFN\text{-}GIT} = (Sens_{TST} \times Sens_{QFN\text{-}GIT}) \quad \text{(Equation 3)}$$

$$Sensitivity_{QFN\text{-}GITandT\text{-}SPOT.TB} = (Sens_{QFN\text{-}GIT} \times Sens_{T\text{-}SPOT.TB}) \quad \text{(Equation 4)}$$

The specificity of this algorithm (which requires both test results to be positive to regard the overall result as positive) regards individuals who test negative by one/both tools to be classified negative (see equations 5 and 6). [417]

$$Specificity_{dualtestedTSTandQFN\text{-}GIT} = Spec_{TST} + Spec_{QFN\text{-}GIT} - (Spec_{TST} \times Spec_{QFN\text{-}GIT}) \quad \text{(Equation 5)}$$

$$Specificity_{dualtestedQFN\text{-}GITandT\text{-}SPOT.TB} = Spec_{QFN\text{-}GIT} + Spec_{T\text{-}SPOT.TB} - (Spec_{QFN\text{-}GIT} \times Spec_{T\text{-}SPOT.TB})$$

(Equation 6)

Now the sensitivities and specificities of the algorithms have been defined, the next step is to separately calculate the prevalence of LTBI for each of the three groups (those triple tested with TST/QFN-GIT/T-SPOT.TB, those dual tested with TST/QFN-GIT and those dual tested with QFN-

GIT/T-SPOT.TB) at each incidence screening threshold. For those individuals who were triple, and dual, tested the prevalence of LTBI (at each incidence threshold) was calculated using equations 7, 8 and 9 respectively.

$$\text{Prevalence of LTBI}_{\text{tripletested}} = \frac{\text{Prop positive result}_{\text{dual or triple positive in tripletested}} - (1\text{-Specificity}_{\text{tripletested}})}{\text{Sensitivity}_{\text{tripletested}} - (1\text{-Specificity}_{\text{tripletested}})} \quad \text{(Equation 7)}$$

$$\text{Prevalence of LTBI}_{\text{dualtested QFN-GIT and T-SPOT.TB}} = \frac{\text{Prop positive result}_{\text{dual positive in dualtested QFN-GIT and T-SPOT.TB}} - (1\text{-Specificity}_{\text{dualtested QFN-GIT and T-SPOT.TB}})}{\text{Sensitivity}_{\text{dualtested QFN-GIT and T-SPOT.TB}} - (1\text{-Specificity}_{\text{dualtested QFN-GIT and T-SPOT.TB}})} \quad \text{(Equation 8)}$$

$$\text{Prevalence of LTBI}_{\text{dualtested TST and QFN-GIT}} = \frac{\text{Prop positive result}_{\text{dual positive in dualtested TST and QFN-GIT}} - (1\text{-Specificity}_{\text{dualtested TST and QFN-GIT}})}{\text{Sensitivity}_{\text{dualtested TST and QFN-GIT}} - (1\text{-Specificity}_{\text{dualtested TST and QFN-GIT}})} \quad \text{(Equation 9)}$$

Following calculation of LTBI prevalence for each of the three groups separately as outlined above, I then calculated, at each incidence threshold, a combined weighted prevalence. The weighted LTBI prevalence, at each incidence threshold, was the prevalence that I used for the remainder of the analysis when exploring the impact of screening with different diagnostic tests.

In the single screening approaches (in other words TST alone, QFN-GIT alone and T-SPOT.TB alone) I used the weighted prevalence of LTBI (at each incidence threshold) to calculate the probability of a positive result (at each incidence threshold) for each screening test using equations 10a, 10b and 10c.

$$\text{Probability of positive result}_{\text{QFN-GIT}} = \text{Sens}_{\text{QFN-GIT}} \times \text{PrevalenceofLTBI}_{\text{weighted}} + (1\text{-Spec}_{\text{QFN-GIT}}) \times (1\text{-Prevalence of LTBI}_{\text{weighted}}) \quad \text{(Equation 10a)}$$

$$\text{Probability of positive result}_{\text{T-SPOT.TB}} = \text{Sens}_{\text{T-SPOT.TB}} \times \text{PrevalenceofLTBI}_{\text{weighted}} + (1\text{-Spec}_{\text{T-SPOT.TB}}) \times (1\text{-Prevalence of LTBI}_{\text{weighted}}) \quad \text{(Equation 10b)}$$

$$\text{Probability of positive result}_{\text{TST}} = \text{Sens}_{\text{TST}} \times \text{PrevalenceofLTBI}_{\text{weighted}} + (1\text{-Spec}_{\text{TST}}) \times (1\text{-Prevalence of LTBI}_{\text{weighted}}) \quad \text{(Equation 10c)}$$

The proportion of those who test positive by these screening tests who are actually truly infected (the positive predictive value) is given by equations 11a, 11b and 11c:

$$\text{Probability of true positive result}_{TST} = \frac{\text{Sens}_{TST} \times \text{Prevalence of LTBI}_{weighted}}{\text{Probability of positive result}_{TST}} \quad \text{(Equation 11a)}$$

$$\text{Probability of true positive result}_{QFN\text{-}GIT} = \frac{\text{Sens}_{QFN\text{-}GIT} \times \text{Prevalence of LTBI}_{weighted}}{\text{Probability of positive result}_{QFN\text{-}GIT}} \quad \text{(Equation 11b)}$$

$$\text{Probability of true positive result}_{T\text{-}SPOT.TB} = \frac{\text{Sens}_{T\text{-}SPOT.TB} \times \text{Prevalence of LTBI}_{weighted}}{\text{Probability of positive result}_{T\text{-}SPOT.TB}} \quad \text{(Equation 11c)}$$

The probability of a negative result for each of the screening tests is given by equations 12a, 12b and 12c:

$$\text{Probability of negative result}_{TST} = \text{Spec}_{TST} \times (1\text{-Prevalence of LTBI}_{weighted}) + (1\text{-Sens}_{TST}) \times \text{Prevalence of LTBI}_{weighted} \quad \text{(Equation 12a)}$$

$$\text{Probability of negative result}_{QFN\text{-}GIT} = \text{Spec}_{QFN\text{-}GIT} \times (1\text{-Prevalence of LTBI}_{weighted}) + (1\text{-Sens}_{QFN\text{-}GIT}) \times \text{Prevalence of LTBI}_{weighted} \quad \text{(Equation 12b)}$$

$$\text{Probability of negative result}_{T\text{-}SPOT.TB} = \text{Spec}_{T\text{-}SPOT.TB} \times (1\text{-Prevalence of LTBI}_{weighted}) + (1\text{-Sens}_{T\text{-}SPOT.TB}) \times \text{Prevalence of LTBI}_{weighted} \quad \text{(Equation 12c)}$$

Of those individuals who test negative, the proportion who are truly uninfected – the negative predictive value – is given by equations 13a, 13b and 13c:

$$\text{Probability of true negative result}_{TST} = \frac{\text{Spec}_{TST} \times (1\text{-Prevalence of LTBI}_{weighted})}{\text{Probability of negative result}_{TST}} \quad \text{(Equation 13a)}$$

$$\text{Probability of true negative result}_{QFN\text{-}GIT} = \frac{\text{Spec}_{QFN\text{-}GIT} \times (1\text{-Prevalence of LTBI}_{weighted})}{\text{Probability of negative result}_{QFN\text{-}GIT}} \quad \text{(Equation 13b)}$$

$$\text{Probability of true negative result}_{T\text{-}SPOT.TB} = \frac{\text{Spec}_{T\text{-}SPOT.TB} \times (1\text{-Prevalence of LTBI}_{weighted})}{\text{Probability of negative result}_{T\text{-}SPOT.TB}} \quad \text{(Equation 13c)}$$

Testing all patients with more than one test is not the same as testing patients with one test and then confirming positive results with a second, different, test. In the two-step strategies (TST followed by confirmatory QFN-GIT or T-SPOT.TB if TST positive) it is important to note that the prevalence of infection is not the weighted prevalence but the proportion who test true positive by TST (positive predictive value) amongst all TST positives. The probability of positive IGRA results (in the two-step strategy where TST is positive) is given by equations 14a and 14b (for QFN-GIT and T-SPOT.TB respectively) and the probability of negative IGRA results by equations 15a and 15b (for QFN-GIT and T-SPOT.TB respectively).

$$\text{Probability of positive result}_{\text{confirmatoryQFN-GITifTSTpositive}} = \text{Sens}_{\text{QFN-GIT}} \times \text{Prevalence of LTBI}_{\text{TSTpositive}} + (1\text{-Spec}_{\text{QFN-GIT}}) \times (1\text{- Prevalence of LTBI}_{\text{TSTpositive}})$$

(Equation 14a)

$$\text{Probability of positive result}_{\text{confirmatoryT-SPOT.TBifTSTpositive}} = \text{Sens}_{\text{T-SPOT.TB}} \times \text{Prevalence of LTBI}_{\text{TSTpositive}} + (1\text{-Spec}_{\text{T-SPOT.TB}}) \times (1\text{-Prevalence of LTBI}_{\text{TSTpositive}})$$

(Equation 14b)

$$\text{Probability of negative result}_{\text{confirmatoryQFN-GITifTSTpositive}} = \text{Spec}_{\text{QFN-GIT}} \times (1\text{-Prevalence of LTBI}_{\text{TSTpositive}}) + (1\text{-Sens}_{\text{QFN-GIT}}) \times (\text{Prevalence of LTBI}_{\text{TSTpositive}})$$

(Equation 15a)

$$\text{Probability of negative result}_{\text{confirmatoryT-SPOT.TBifTSTpositive}} = \text{Spec}_{\text{T-SPOT.TB}} \times (1\text{-Prevalence of LTBI}_{\text{TSTpositive}}) + (1\text{-Sens}_{\text{T-SPOT.TB}}) \times (\text{Prevalence of LTBI}_{\text{TSTpositive}})$$

(Equation 15b)

From the probability of positive and negative results, I can then calculate the positive and negative predictive values for QFN-GIT and T-SPOT.TB (for the dual step screening approach) (equations 16a, 16b, 17a and 17b):

$$\text{Probability of true positive result}_{\text{confirmatoryQFN-GITifTSTpositive}} = \frac{\text{Sens}_{\text{QFN-GIT}} \times \text{Prevalence of LTBI}_{\text{TSTpositive}}}{\text{Probability of positive result}_{\text{confirmatoryQFN-GITifTSTpositive}}} \quad \text{(Equation 16a)}$$

$$\text{Probability of true positive result}_{\text{confirmatoryT-SPOT.TBifTSTpositive}} = \frac{\text{Sens}_{\text{T-SPOT.TB}} \times \text{Prevalence of LTBI}_{\text{TSTpositive}}}{\text{Probability of positive result}_{\text{confirmatoryT-SPOT.TBifTSTpositive}}} \quad \text{(Equation 16b)}$$

$$\text{Probability of true negative result}_{\text{confirmatoryQFN-GITifTSTpositive}} = \frac{\text{Spec}_{\text{QFN-GIT}} \times (1\text{-Prevalence of LTBI}_{\text{TSTpositive}})}{\text{Probability of negative result}_{\text{confirmatoryQFN-GITifTSTpositive}}} \quad \text{(Equation 17a)}$$

$$\text{Probability of true negative result}_{\text{confirmatoryT-SPOT.TBifTSTpositive}} = \frac{\text{Spec}_{\text{T-SPOT.TB}} \times (1\text{-Prevalence of LTBI}_{\text{TSTpositive}})}{\text{Probability of negative result}_{\text{confirmatoryT-SPOT.TBifTSTpositive}}} \quad \text{(Equation17b)}$$

Progression rate from latent tuberculosis infection to active tuberculosis disease

One of the most poorly understood parameters is the rate at which latently infected immigrants progress to active TB disease. Immigrants from high-TB-burden countries with LTBI may be similar to recently infected contacts of smear-positive tuberculosis index cases in terms of having a high rate of progression, as they are likely to have been repeatedly exposed, and potentially infected, by infectious individuals. Literature reports are conflicting: a study of a cohort of Southeast Asian refugees arriving in Australia found a relatively low progression rate of 6.7% over 40 years[220] whereas a more recent UK study, predominantly of immigrants from the Indian Subcontinent, calculated that over 13% of TST positive, untreated, immigrants developed active TB over a 10-year period.[221]

A detailed review of progression rates (albeit based on TST data) has been conducted by Horsburgh.[27] In this seminal paper he estimated that in 16-35 year-olds with a non-recently converted TST of >15mm that the annual risk of reactivation was 0.19%.[27] If the skin test was >15mm and there was recent conversion then the annual risk of reactivation would increase to 0.56%.[27] I therefore, conservatively, assumed that 5% of the HIV negative cohort with LTBI, in the absence of chemoprophylaxis, would progress to active TB over the 20 year time horizon of the model, i.e. the progression rate is approximately 0.0025 per year (using the formula $-ln\ (1-p)/t$ where p is the proportion that progress over time t (in years). By contrast, HIV-positive individuals have impaired cell-mediated immunity and therefore experience a much higher rate of progression to active TB disease. In the Horsburgh review, the lifetime risk for an individual aged 16-35 with HIV infection is 73-83% (equating to an annual rate of 0.024 – assuming a further 55 years of life) and the relative risk of HIV infected (versus HIV uninfected) individuals progressing to active TB was approximately 10 (per year). Therefore in the base case analysis I assumed that the annual rate of progression for immigrants with HIV infection was approximately 0.025 per year which equates to an estimated 40% of HIV positive immigrants progressing from LTBI to active TB over a 20 year time horizon. This figure takes account, to some degree, of HAART mitigating progression in the HIV-positive

cohort. However, I fully acknowledge that there is a lack of consensus on progression rates (in both HIV negative and positive individuals) and thus assessed a suitably wide range of progression rates in the sensitivity analysis.

Costs

Component costs considered were primarily direct costs obtained from economic evaluations conducted for the UK NICE TB guidelines,[1] and its forthcoming 2011 update, uplifted to 2010 prices (see tables 5.7 and 5.8 for costs) using the Consumer Prices Index. In the present analysis, indirect costs such as transportation and loss of earnings by patients were not considered. Both costs and non-monetary health effects were discounted at an annual rate of 3.5%, which reflects UK Treasury and NICE recommendations.[29,399]

Table 5.7 Costs (2010 pounds sterling) associated with diagnosis and treatment of active TB

Active TB cases	Base case	Range[1]	Reference(s)
Contact tracing			
Contact tracing per contact (£)	482	241-723	81
Mean number of contacts examined per primary case	6.5	3.25-10	81
Mean number of secondary active TB cases per index case (drug sensitive and drug resistant)	0.24	0.1-0.3	400,418
Mean number of latent infections per primary case of active TB disease (drug sensitive and drug resistant)	0.18	0.09-0.27	400
Proportion reduction in mean number of secondary active TB cases per index case (if identified through chest x-ray screening)	0.5	0.25-0.75	302
Proportion reduction in mean number of latent infections per primary case of active TB disease (if identified through chest x-ray screening)	0.5	0.25-0.75	302
Inpatient care (drug sensitive tuberculosis)			
Cost of inpatient episode for acute TB (£ per episode)	4012.97 (2006.5-6019.46)	2006.5-6019.5	401,402
Proportion of patients with acute TB who are admitted	0.53 (0.265-0.795)	0.25-0.75	81
Cost of inpatient care (£ per active case)	2126.87		Calculated
Cost of tests (drug sensitive tuberculosis)			
Costs of culture test (£ per test)	10		81,401
Costs of chest X-ray (£ per X-ray)	28		81,401
Costs of liver functions tests (£ per test)	1		81,401
Culture tests per case treated (number)	4		81,401
Chest X-ray per case treated (number)	2		81,401
Liver functions tests per case treated (number)	4		81,401
Total cost of tests (£ per TB case treated)	100[2]		Calculated
Cost of chemotherapy (drug sensitive tuberculosis)			
Rifampicin (£ per month)	10.76		81,401
Isoniazid (£ per month)	17.87		81,401
Pyrazinamide (£ per month)	6.88		81,401
Ethambutol (£ per month))	18.48		81,401
Duration of rifampicin (months)	6		81
Duration of isoniazid (months)	6		81
Duration of pyrazinamide (months)	2		81
Duration of ethambutol (months)	2		81
Total cost of drugs (drug sensitive TB)	222	111-333	Calculated
Outpatient care (drug sensitive tuberculosis)			
Cost of outpatient consultation (first visit)	230		Local tariff
Cost of outpatient consultation (follow-up visit)	104		81,401
Cost of TB Nurse home visit	22		81,401,419
Number of outpatient clinic visits per case treated	4		81,401
Visits from TB Nurse per case treated	6		81,401
Total costs of non-drug outpatient care (£ per case treated)	674[2]		Calculated
Total cost of diagnosis, management and follow-up of drug resistant tuberculosis case	32299	16,150.0-48,450.0	81,401

Footnotes

[1]Refers to the range explored in the univariate sensitivity analysis

[2]In the sensitivity analysis the costs of outpatient care for an active TB case and the tests required were considered together (total = 774, range explored 387-1161).

Table 5.8 Costs (2010 pounds sterling) associated with diagnosis and treatment of latent TB infection

	Base case (range)	Range[1]	Reference(s)
Cost of screening for single-step strategies			
Tuberculin skin test	34.22	17.11-51.33	[81,401]
QuantiFERON (test kit, consumables and phlebotomy)	52	26-78	Local laboratory cost
T-SPOT.TB	82	41-123	Local laboratory cost
Cost of confirmatory IGRA testing in dual-step strategies			
QuantiFERON (test kit, consumables and phlebotomy)	41	20.5-61.5	Local laboratory cost
T-SPOT.TB	71	35.5-106.5	Local laboratory cost
Cost of evaluating positive LTBI screening tests (or tests if dual step strategy used)			
Cost of outpatient consultation: first visit (£ per visit)	230		Local tariff
CXR	28		[81,401]
LFT	1		[81,401]
Number of outpatient consultation	1		[81,401]
Number of CXR	1		[81,401]
Number of LFT	1		[81,401]
Total cost of evaluating positive QuantiFERON	259	130-389	Calculated
Cost of follow-up and chemoprophylactic therapy for positives undergoing treatment			
Follow up via TB nurses	22		[419]
Rifampicin (£ per month)	10.76		[81,401]
Isoniazid (£ per month)	17.87		[81,401]
Number of TB Nurses appointments	2		[81,401]
Duration of rifampicin (months)	3		[81,401]
Duration of isoniazid (months)	3		[81,401]
Total cost of chemoprophylaxis (£ per course) plus TB nurse follow-up	130	65-195	Calculated
Cost of managing a case of chemoprophylaxis induced liver injury			
Cost of additional clinic visits and blood tests	362	181-1362	[403]
Cost of inpatient stay	1000		[403]

Footnote

[1]Refers to the range explored in the univariate sensitivity analysis

Effects

The main effects considered in the model were the number of cases of active tuberculosis that would be predicted to occur over the 20-year time horizon to prevent one case of active TB.

Cost-effectiveness

As recommended by the Panel of Cost-effectiveness in Health and Medicine, the comparative performance of the different screening protocols was measured using the Incremental Cost-effectiveness ratio (ICER – see equation 18) which quantifies the trade-offs between switching from one competing, mutually-exclusive, intervention to another.[404] The higher the ICER, the less cost-effective the intervention is.

$$ICER = \frac{Cost_{screening protocol A} - Cost_{screening protocol B}}{Effectiveness_{screening protocol A} - Effectiveness_{screening protocol B}} \quad \text{(Equation 18)}$$

Sensitivity analysis

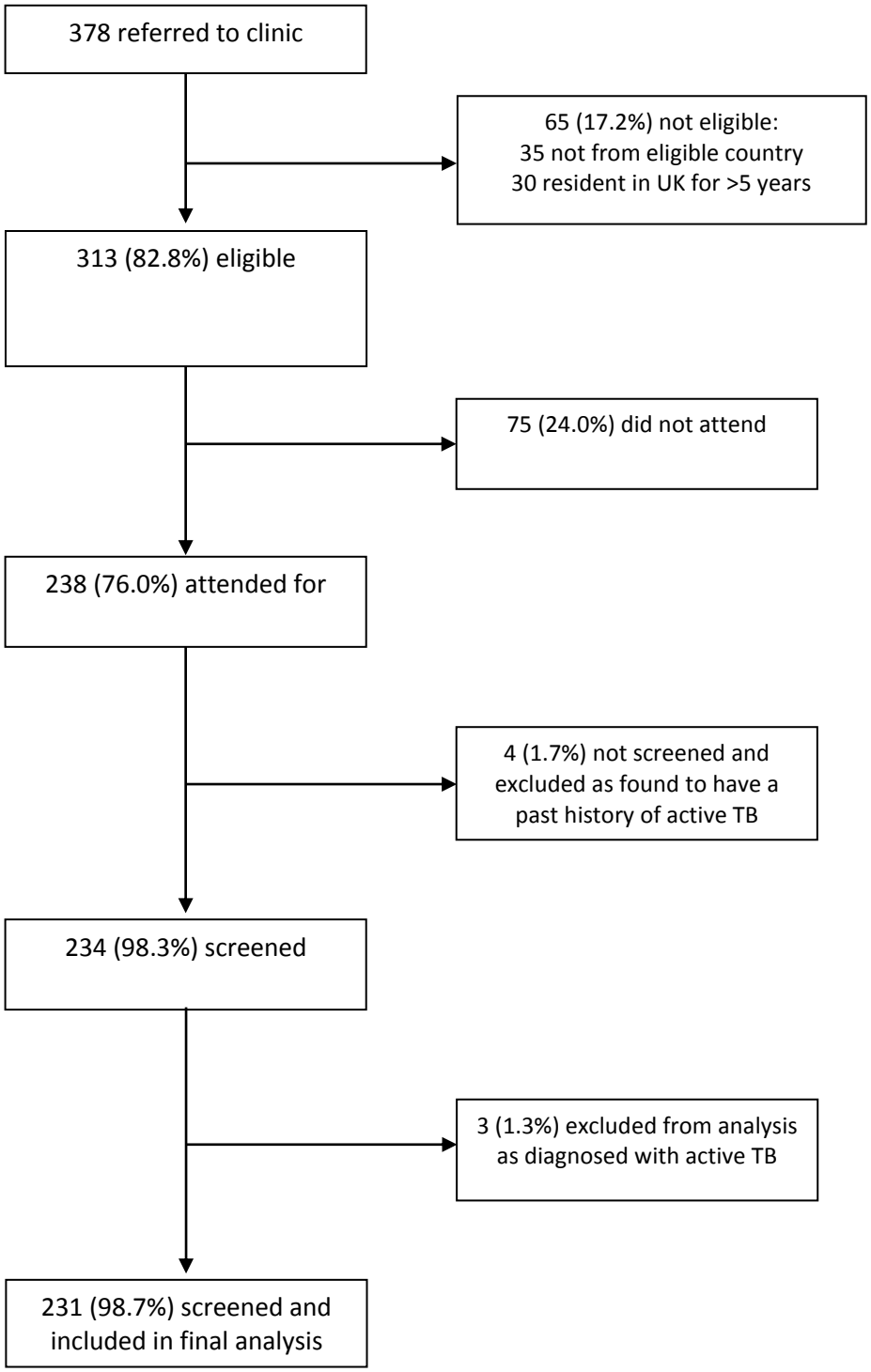
Parameter uncertainty can potentially affect the results of the cost-effectiveness analysis. A one-way sensitivity analysis was therefore undertaken to explore the impact that changes in all key parameters and costs had on the number of cases of active TB occurring over 20 years, the costs and the associated ICERs.

Results

Description of the cohort

Recruitment into the study is outlined in Figure 5.6.

Figure 5.6 Study flow chart



Of the 378 individuals who were referred to the immigrant screening service, 65 (17.2%) did not meet the eligibility criteria to be included in the study. Amongst the 313 immigrants who were eligible to be screened, 75 (24.0%) did not attend for screening leaving 238 individuals who did attend for screening. Of these 238 individuals, 4 (1.7%) were found to have a past history of active TB and therefore not screened which left 234 individuals who underwent screening as per the protocol. As part of the screening process 3 of these 234 individuals were diagnosed with active tuberculosis therefore excluded from the final analysis. This left 231 subjects for the final analysis whose characteristics are shown in table 5.9.

Screened immigrants were mainly young adults (74.1% were aged 16-35 years); 64.5% were female and 83.7% had previously been BCG vaccinated. Immigrants in this cohort most commonly originated from Other Asian countries (excluding Indian Subcontinent) (42.2%) and the Indian Subcontinent (21.2%); 61.9% of the cohort had been resident in the UK for ≤2 years.

There were no significant demographic differences between immigrants who were eligible, and screened, versus those who did not attend (table 5.9).

Table 5.9 Demographic characteristics of immigrants screened in the study

Variable	Immigrants who were screened (n=231)	Immigrants who did not attend (n=75)[1]	p-value
Age categories			
16-25	87 (37.7%)	23 (30.7%)	0.33
26-35	84 (36.4%)	33 (44.0%)	0.27
36-45	35 (15.2%)	14 (18.7%)	0.47
Over 45	25 (10.8%)	5 (6.7%)	0.38
Gender			
Female	149 (64.5%)	43 (57.3%)	0.27
Male	82 (35.5%)	32 (42.7%)	
World region of origin[2]			
Europe, North America	16 (6.9%)	5 (8.9%)	0.57
South America	14 (6.1%)	6 (10.7%)	0.24
Middle East	19 (8.2%)	3(5.4%)	0.59
Other Africa	5 (2.2%)	3 (5.3%)	0.20
Other Asia	98 (42.4%)	17 (30.4%)	0.13
Indian Subcontinent	49 (21.2%)	16 (28.6%)	0.29
Sub-Saharan Africa	30 (12.9%)	6 (10.7%)	0.82
TB incidence in country of origin[2]			
0-65	39 (16.9%)	11 (19.6%)	0.70
66-170	105 (45.5%)	33 (58.9%)	0.08
171-300	74 (32.0%)	11 (19.6%)	0.08
>300	13 (5.6%)	1 (1.8%)	0.32
Time since entry to the UK (years)			
<1	38 (15.6%)		
1 - 2	107 (46.3%)		
3 - 5	88 (38.1%)		
BCG vaccinated[3]			
No	37 (16.3%)		
Yes	190 (83.7%)		
History of TB contact[4]			
No	216 (94.3%)		
Yes	13 (5.7%)		
Travel to TB endemic country			
No	161 (69.7%)		
Yes	70 (30.3%)		
Employed			
Student	66 (28.6%)		
No/Housewife	66 (28.6%)		
Yes	99 (28.6%)		
History of imprisonment			
No	228 (98.7%)		
Yes	3 (1.3%)		
Previous HIV test[5]			
No	139 (60.2%)		
Yes	85 (36.8%)		
HIV positive	0 (0.0%)		
Unsure	7 (3.0%)		
Current smoker			
No	195 (84.4%)		
Yes	36 (15.6%)		
Consumes alcohol			
No	169 (73.2%)		
Yes	62 (26.8%)		

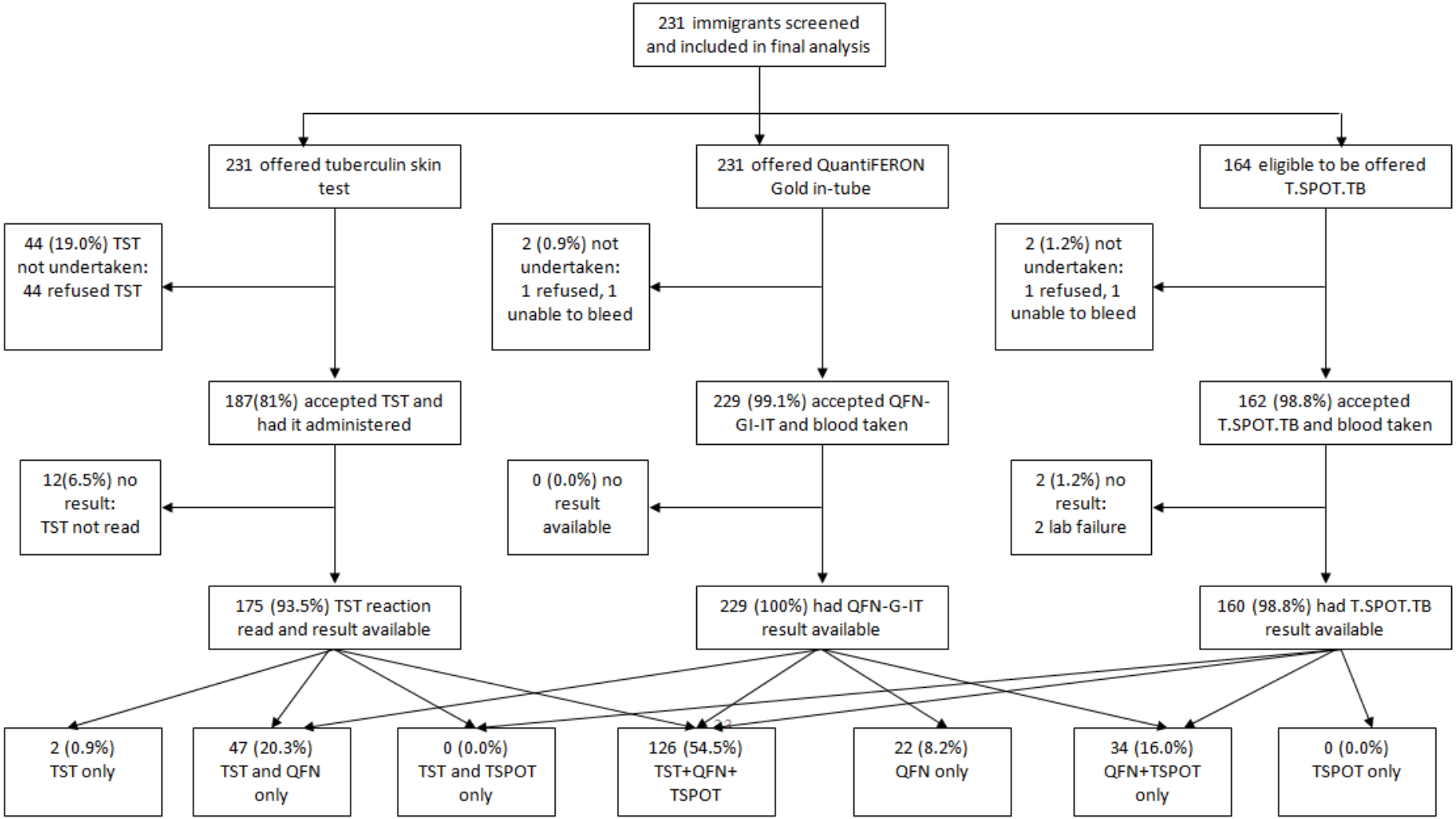
Footnotes

[1]Selected characteristics (where data was available) are compared against those of immigrants who were screened
[2]For those immigrants who were not screened, data on world region of origin and TB incidence in country of origin were available for 56 individuals.
[3]Data available for 227 individuals
[4]Data available for 229 individuals
[5]HIV testing was not undertaken in this study but no subjects self-reported themselves as being HIV positive

Uptake and results of screening tests

Figure 5.7 outlines the uptake of the three screening tools – TST, QFN-GIT and T-SPOT.TB. Of the 231 individuals who were offered TST, 44 (19%) refused the test; in the remaining 187 immigrants who had TST administered, 12 (6.4%) individuals did not return to have the size of induration read resulting in valid TST results being available in 175 (93.6%) immigrants.

Figure 5.7 Study flow chart outlining uptake of screening tests



Footnote

[1]As testing with T-SPOT.TB started later than with TST and QuantiFERON Gold in-tube the numbers offered T-SPOT.TB were smaller

Figure 5.8 and table 5.10 outline the TST results stratified by BCG vaccination status. Overall, if the stratified cut-off for TST positivity was used 53/175 immigrants (30.3%, 95% CI 23.6-37.7%) had a positive TST, whereas if the non-stratified cut-off (in other words ≥10mm) was used 66/175 (37.7%, 95% CI 30.5-45.3%) were deemed TST positive. There was no significant difference in size of induration between BCG vaccinated (median 7mm (IQR 0-15)) and unvaccinated (median 6mm (IQR 0-10)) individuals (p=0.51).

Figure 5.8 Histogram showing TST induration stratified by BCG vaccination status

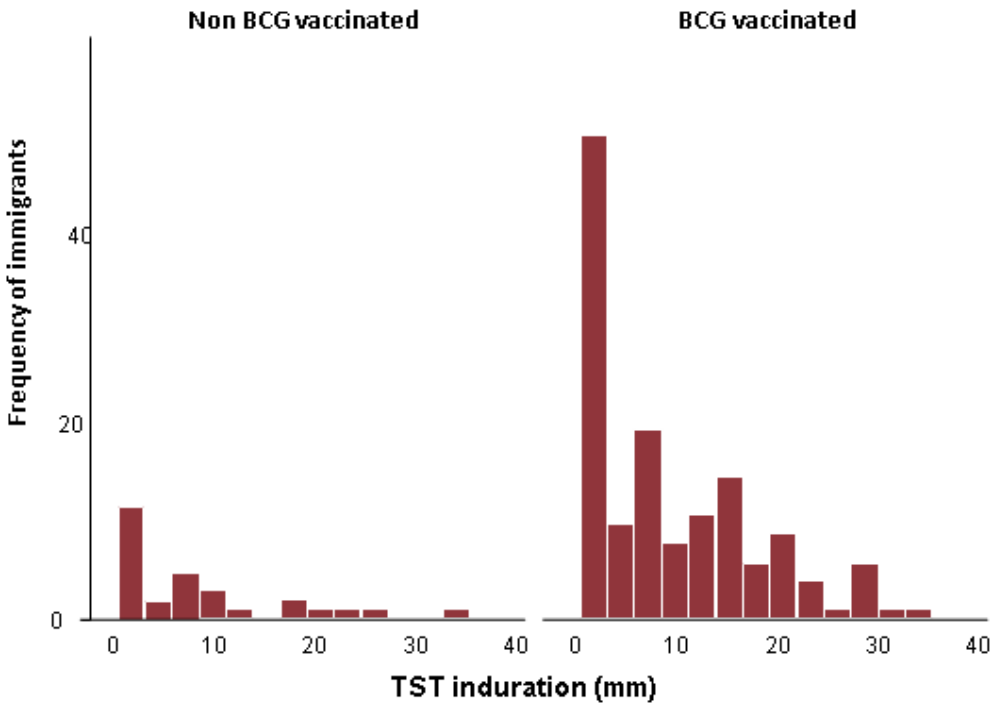


Table 5.10 Size of tuberculin skin test response stratified by BCG

TST (mm)	Non BCG vaccinated (n=29)	BCG vaccinated (n=143)	BCG status unsure (n=3)
<6	14 (48.3%)	61 (42.7%)	2 (66.7%)
6-9	7 (24.1%)	25 (17.5%)	0 (0.0%)
10-14	2 (6.9%)	20 (14.0%)	0 (0.0%)
≥15	6 (20.7%)	37 (25.9%)	1 (33.3%)

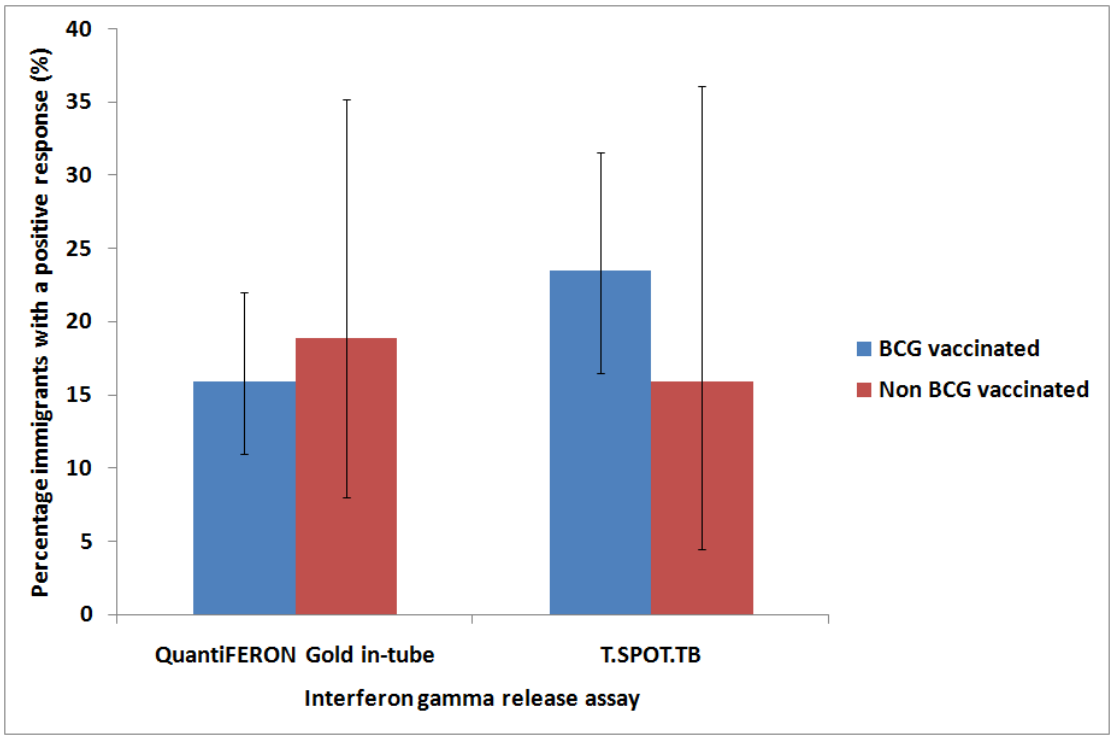
Footnote

[1]Pink shaded area is classed negative and blue shaded area is positive – as per the stratified threshold recommended by UK guidelines

QuantiFERON Gold in-tube was also offered to 231 immigrants but blood was not drawn from two individuals (one refused venepuncture and one individual could not be bled). In the

remaining 229 individuals who had blood collected, there were no lab failures and therefore results were available for 229 individuals. Overall, 38 individuals (16.6%, 95% CI 12.0-22.1%) tested positive and 189 (82.5%, 95% CI 77.0-87.2%) were negative; 2 subjects (0.87%, 95% CI 0.1-3.1%) had indeterminate results (see figure 5.9).

Figure 5.9 Bar chart showing the proportion of immigrants were IGRA positive stratified by BCG vaccinations status



Footnote

[1]Error bars denote 95% confidence intervals

Testing with T-SPOT.TB, which commenced a few weeks later than TST and QGN-GIT, was offered to 164 individuals and undertaken in 162 (98.7%); one subject refused venepuncture and one individual could not be bled. In the 162 who had blood drawn, there were two laboratory failures which meant T-SPOT.TB results were available in 160 (97.6%) immigrants. 36 individuals (22.5%, 95% CI 16.3-29.8%) were positive, 117 (73.1%, 95% CI 65.6-79.8%) were negative and 7 (4.4%, 95% CI 1.8-8.8%) individuals had an indeterminate result (see figure 5.9).

Pairwise comparisons, using McNemar's test, were undertaken to compare the proportion positive by TST or IGRA and the proportion of indeterminate results by either of the IGRAs. The proportion of immigrants positive by TST was significantly higher than QFN-GIT ($p=0.0025$ for stratified TST cut-off, $p<0.0001$ for unstratified 10mm TST cut-off) and T-SPOT.TB ($p=0.02$ for stratified TST cut-off, $p<0.0001$ for unstratified 10mm TST cut-off). In contrast there was no significant difference in the proportion of immigrants positive by QFN-GIT and T-SPOT.TB ($p=0.49$). However, there was a significantly lower proportion of indeterminate results with QFN-GIT as compared to T-SPOT.TB ($p=0.02$).

Factors associated with positive screening test results

Univariate and multivariate analyses of factors associated with TST and IGRA positivity in the immigrant cohort are shown in table 5.11. On multivariate analysis, for TST, QFN-GIT and T-SPOT.TB, increasing TB incidence in country of origin and increasing age were independently associated with positive screening test results (table 5.11).

Table 5.11 Univariate and multivariate analysis of factors associated with tuberculin skin test, QuantiFERON Gold in-tube and T-SPOT.TB positivity

Variable	NumberTST Positive/ Total No.Tested n=175 (%)	Unadjusted OR (95% CI)	Adjusted OR[2] (95% CI)	p	Number QFN-G-IT Positive/ Total No.Tested n=229(%)	Unadjusted OR (95% CI)	Adjusted OR[2] (95% CI)	p	Number T.SPOT.TB Positive/ Total No.Tested n=160 (%)	Unadjusted OR (95% CI)	Adjusted OR[2] (95% CI)	p
Age												
16-25	16/63 (25.4%)	1	1	0.008	12/86 (14.0%)	1	1	0.003	11/63 (17.5%)	1	1	0.03
26-35	23/61 (37.7%)	1.78 (0.82-3.83)	2.82 (1.06-7.46)		10/84 (11.9%)	0.83 (0.34-2.05)	1.49 (0.51-4.41)		8/49 (16.3%)	0.92 (0.34-2.50)	1.40 (0.42-4.69)	
36-45	18/28 (64.3%)	5.29 (2.03-13.79)	7.49 (2.31-24.31)		8/34 (23.5%)	1.90 (0.70-5.16)	2.49 (0.68-9.06)		11/30 (36.7%)	2.74 (1.02-7.34)	5.76 (1.55-21.39)	
>45	9/23 (39.1%)	1.89 (0.69-5.19)	4.51 (1.22-16.69)		8/25 (32.0%)	2.90 (1.03-8.20)	6.23 (1.47-26.33)		6/18 (33.3%)	2.36 (0.73-7.66)	3.54 (0.72-17.33)	
Gender												
Female	33/106 (31.1%)	1	1	0.19	23/147 (15.7%)	1	1	0.72	22/105 (21.0%)	1	1	0.33
Male	33/69 (22.4%)	2.03 (1.08-3.79)	1.71 (0.77-3.79)		15/82 (18.3%)	1.21 (0.59-2.47)	1.19 (0.46-3.06)		14/55 (25.5%)	1.29 (0.60-2.78)	0.59 (0.20-1.72)	
World region of origin[1]												
Europe, Americas	3/56 (11.5%)	1			0/30 (0.0%)	-			1/16 (6.3%)	1		
Middle East, North Africa	7/19 (36.8%)	4.47 (0.98-20.49)			2/24 (8.3%)	1			2/12 (16.7%)	3 (0.24-37.67)		
Other Asia	36/78 (46.2%)	6.57 (1.82-23.70)			20/96 (20.8%)	2.89 (0.63-13.36)			20/71 (28.2%)	5.88 (0.73-47.52)		
Indian Subcontinent	11/32 (34.4%)	4.02 (0.98-16.40)			7/49 (14.3%)	1.83 (0.35-9.58)			5/42 (11.9%)	2.03 (0.22-18.84)		
Sub-Saharan Africa	9/20 (45.0%)	6.27 (1.41-27.86)			9/30 (30.0%)	4.71 (0.91-24.42)			8/19 (42.1%)	10.91 (1.19-100.41)		
TB incidence in country of origin[1]												
≤65	6/30 (20.0%)	1	1	0.007	2/39 (5.1%)	1	1	0.007	2/18 (11.1%)	1	1	0.037
66-170	31/84(36.9%)	2.34 (0.86-6.35)	4.50 (1.44-14.07)		12/103 (11.7%)	2.44 (0.52-11.44)	3.58 (0.69-18.62)		12/73 (16.4%)	1.57 (0.32-7.76)	1.75 (0.31-9.84)	
171-300	27/56 (48.2%)	3.72 (1.32-10.5)	10.29 (2.79-37.97)		22/74 (29.7%)	7.83 (1.73-35.35)	13.92 (2.48-78.07)		19/63 (30.2%)	3.45 (0.72-16.53)	6.28 (1.07-36.92)	
>300	2/5 (40.0%)	2.67 (0.36-19.71)	5.95 (0.61-58.18)		2/13 (15.4%)	3.36 (0.42-26.72)	8.07 (0.82-79.49)		3/6 (50.0%)	8.00 (0.91-70.27)	9.64 (0.77-121.31)	
Time since arrival in the UK												
<1 year	10/25 (40.0%)	1	1	0.11	5/36 (13.9%)	1	1	0.88	5/13 (38.5%)	1	1	0.09
1-2years	35/89 (39.3%)	0.97 (0.39-2.41)	0.89 (0.31-2.56)		15/105 (14.3%)	1.03 (0.35-3.08)	0.8 (0.23-2.84)		16/81 (19.8%)	0.39 (0.11-1.37)	0.22 (0.05-1.00)	
3-5years	21/61 (34.4%)	0.79 (0.30-2.05)	0.37 (0.12-1.20)		18/88 (20.5%)	1.59 (0.54-4.68)	0.98 (0.27-3.59)		15/66 (22.7%)	0.47 (0.13-1.65)	0.17 (0.03-0.85)	
BCG vaccinated[4]												
No	8/29 (27.6%)	1	1	0.40	7/37 (18.9%)	1	1	0.75	4/25 (16.0%)	1	1	0.57
Yes	57/143 (39.9%)	1.74 (0.72-4.20)	1.56 (0.56-4.33)		30/188 (16.0%)	0.81 (0.33-2.02)	0.84 (0.30-2.40)		31/132 (23.5%)	1.61 (0.51-5.05)	1.46 (0.40-5.28)	
Travel to TB endemic country												
No	41/121 (33.9%)	1	1	0.18	21/159 (13.2%)	1	1	0.06	21/111 (18.9%)	1	1	0.08
Yes	25/54 (46.3%)	1.68 (0.87-3.24)	1.77 (0.77-4.06)		17/70 (24.3%)	2.11 (1.03-4.30)	2.25 (0.96-5.26)		15/49 (30.6%)	1.89 (0.87-4.09)	2.37 (0.90-6.28)	
TB contact												
No	60/164 (36.6%)	1	1	0.23	33/215 (15.4%)	1	1	0.14	31/148 (21.0%)	1	1	0.07
Yes	6/9 (66.7%)	3.47 (0.84-14.36)	2.71 (0.53-13.82)		5/13 (38.5%)	3.44 (1.06-11.19)	2.93 (0.72-12.01)		5/11 (45.5%)	3.15 (0.9-10.99)	4.01 (0.92-17.48)	
Employment status												
Unemployed	18/51 (35.3%)	1	1	0.55	15/65 (23.1%)	1	1	0.25	11/53 (20.8%)	1	1	0.10
Employed	27/70 (38.6%)	1.15 (0.54-2.44)	0.92 (0.36-2.37)		13/99 (13.1%)	0.50 (0.22-1.14)	0.46 (0.16-1.3)		14/63 (22.2%)	1.09 (0.45-2.66)	0.96 (0.31-2.98)	
Student	21/54 (38.9%)	1.20 (0.50-2.60)	1.49 (0.58-3.83)		10/65 (15.4%)	0.61 (0.25-1.47)	1.06 (0.36-3.1)		11/44 (25.0%)	1.27 (0.49-3.30)	3.13 (0.94-10.4)	
Alcohol												
No	48/131 (36.6%)	1	1	0.79	30/167 (18.0%)	1	1	0.97	27/126 (21.4%)	1	1	0.10
Yes	18/44 (40.9%)	1.20 (0.60-2.41)	1.13 (0.46-2.78)		8/62 (12.9%)	0.68 (0.29-1.57)	1.02 (0.35-3.02)		9/34 (26.5%)	1.32 (0.55-3.16)	2.78 (0.83-9.23)	

Smoker												
No	56/146 (38.4%)	1	1	0.73	34/193 (17.6%)	1	1	0.75	33/136 (24.3%)	1	1	0.75
Yes	10/29 (34.5%)	0.85 (0.37-1.95)	1.21 (0.41-3.58)		4/36 (11.1%)	0.58 (0.19-1.76)	1.25 (0.32-4.80)		3/24 (12.5%)	0.45 (0.13-1.59)	0.77 (0.15-3.88)	
History of imprisonment												
No	65/172 (37.8%)	1	1	0.83	38/226 (16.8%)	-	-		35/157 (22.3%)	1	1	0.16
Yes	1/3 (33.3%)	0.82 (0.07-9.26)	1.34 (0.09-19.49)		0/3 (0.0%)	-	-		1/3 (33.3%)	1.74 (0.15-19.79)	7.79 (0.46-132.76)	

Footnotes

[1]World region of origin and TB incidence in country of origin were strongly correlated, so, in the multivariate analysis, world region of origin was dropped

[2]Models mutually adjusted for the following factors: age, gender, TB incidence in country of origin, time since arrival in the UK, BCG vaccination status, travel to TB endemic country, history of TB contact, employment status, alcohol use, smoking status and history of imprisonment (except for QuantiFERON Gold in-tube)

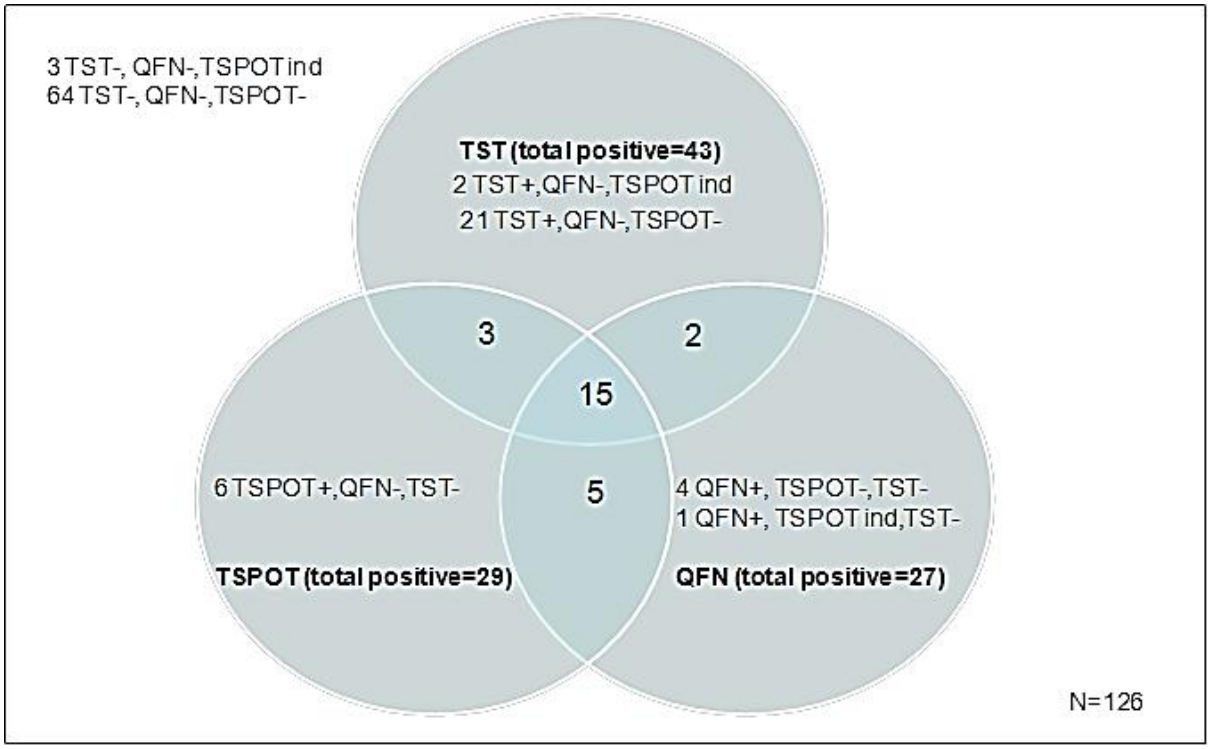
Concordance between screening tests and impact of prior BCG vaccination

Figure 5.10 outlines the results amongst those subjects who were tested with all three screening tools whilst figures 5.11-5.12 illustrate the pair-wise analysis of test results. In general, test agreement between TST and both IGRAs was fair to moderate. Using the stratified (κ 0.30, 95% CI 0.15-0.46, p<0.0001) and unstratified (κ 0.29, 95% CI 0.15-0.42, p<0.0001) TST cut-offs, levels of concordance between TST and QFN-GIT were fair. Likewise, agreement between TST and T-SPOT.TB was fair at the stratified TST cut-off (κ 0.29, 95% CI 0.11-0.47, p=0.0002) but improved using the unstratified cut-off (κ 0.38, 95% CI 0.23-0.54, p<0.0001).

When subdivided by BCG vaccination status, agreement at the unstratified 10mm TST cut-off with both IGRAs was higher for BCG unvaccinated (κ 0.55, 95% CI 0.17-0.74, p=0.0014 for QFN-GIT and κ 0.41, 95% CI 0.11-0.65, p=0.02 for T-SPOT.TB) than BCG vaccinated individuals (κ 0.26, 95% CI 0.17-0.35, p=0.0001 for QFN-GIT and κ 0.39, 95% CI 0.28-0.50, p<0.0001 for T-SPOT.TB). Discordancy, in the BCG vaccinated cohort, most commonly took the form of TST positive/IGRA negative results (TST positive/QFN-GIT negative in 39 of 45 discordant pairs; TST positive/T-SPOT.TB negative in 26 of 29 discordant pairs).

In contrast, overall agreement between QFN-GIT and T-SPOT.TB was higher (κ 0.58, 95% CI 0.51-0.67, p<0.0001) although it was interesting to note that concordance appeared to be lower for BCG unvaccinated (κ 0.43, 95% CI 0.16-0.68, p=0.008) than BCG vaccinated (κ 0.60, 95% CI 0.47-0.70, p<0.0001) individuals.

Figure 5.10 Venn diagram showing test results where all three screening tests were undertaken



Footnote
[1]Ind=Indeterminate

Figure 5.11 Concordance between TST and both IGRAs

IGRA	Result/agreement	Tuberculin skin test (using stratified cut-off[1])		Tuberculin skin test (using non-stratified cut-off[2])	
		Negative	Positive	Negative	Positive
QuantiFERON Gold in-tube	Negative	107	33	97	43
	Positive	12	20	9	23
	Indeterminate	1	0	1	0
	Agreement (%)	73.4		69.4	
	Kappa (95% CI)	0.30 (0.15-0.46)		0.29 (0.15-0.42)	
T.SPOT.TB	Negative	68	23	64	27
	Positive	11	18	5	24
	Indeterminate	4	2	3	3
	Agreement (%)	68.3		69.8	
	Kappa (95% CI)	0.29 (0.11-0.47)		0.38 (0.23-0.54)	

Footnotes
[1]TST positive if induration ≥6mm (in BCG unvaccinated) and ≥15mm (in BCG unvaccinated)
[2]TST positive if induration ≥10mm (irrespective of BCG status)

Figure 5.12 Concordance between QuantiFERON Gold in-tube and T-SPOT.TB

	Result/agreement	QuantiFERON Gold in-tube		
		Negative	Positive	Indeterminate
T.SPOT.TB	Negative	110	7	0
	Positive	11	25	0
	Indeterminate	6	1	0
	Agreement (%)	84.4		
	Kappa (95% CI)	0.58 (0.51-0.67)		

Relationship between screening thresholds and screening test positivity

Table 5.12 sets out the outcomes of LTBI immigrant screening stratified by screening test and TB incidence in the migrants' countries of origin. For all three tests (TST, QFN-GIT and T-SPOT.TB) as the incidence threshold at which screening is instigated increases, fewer immigrants within the cohort are eligible to be screened, the number of individuals identified with a positive test result also decreases although the proportion testing positive remains relatively constant.

Nonetheless, at most incidence thresholds, the proportion of TST results that were positive was greater than the proportion of IGRA results that were positive. As an example, if screening was instigated for immigrants from a country with a TB incidence ≥150/100000, then 36.6%, 25.7% and 29.8% would be positive by TST, QFN-GIT and T-SPOT.TB respectively.

For all three screening tests, as the screening incidence threshold increased, the proportion of all positives in the cohort identified decreased. For example if screening was instigated at 40/100000 TST, QFN-GIT and T-SPOT.TB would have identified 98.1%, 100% and 100% of all positives respectively whereas if the threshold was increased to ≥150/100000, then a significantly lower proportion (49.1%, 71.1% and 69.4% respectively) of all positives in the cohort would be diagnosed ($p<0.0001$ for all three tests). At each incidence threshold TST, in comparison to both IGRAs, identified a lower proportion of the total positives as compared to both IGRAs; if screening was instigated at 150/100000, TST would only identify 49% of positives and require 41% of the cohort to be tested whereas QFN-GIT and T-SPOT.TB would identify 71% and 69% of positives respectively but only require around half of all immigrants to be screened.

Table 5.12 Yields for test positivity by different screening tests at different screening thresholds

TB incidence screening threshold (per 100000)	Number tested			Number positive			Yield at incidence level, ie. proportion of those tested giving a positive result (%)			% of all positives identified if threshold set at this level		
	TST	QFN	TSPOT	TST	QFN	TSPOT	TST	QFN	TSPOT	TST	QFN	TSPOT
Screen ≥350	4	11	4	1	1	1	25.0	9.1	25.0	1.9	2.6	2.8
Screen ≥300	5	13	6	1	2	3	20.0	15.4	50.0	1.9	5.3	8.3
Screen ≥250	23	37	28	10	13	12	43.5	35.1	42.9	18.9	34.2	33.3
Screen ≥200	50	75	59	20	19	17	40.0	25.3	28.8	37.7	50.0	47.2
Screen ≥150	71	105	84	26	27	25	36.6	25.7	29.8	49.1	71.1	69.4
Screen ≥100	104	143	110	30	29	28	28.9	20.3	25.5	56.6	76.3	77.8
Screen ≥40[1]	**170**	**222**	**158**	**52**	**38**	**36**	**30.6**	**17.1**	**22.8**	**98.1**	**100**	**100**
Screen all	175	229	160	53	38	36	30.3	16.6	22.5	100	100	100

Footnotes

[1]Current threshold recommended by NICE guidance (2011)

[2]TST positivity defined according to stratified cut-off

Health-economic analyses

Numbers of cases of active TB, and the associated costs, predicted to arise with each screening strategy for a hypothetical cohort of 10,000 immigrants over the 20-year time horizon of the health economic model are presented in table 5.13.

Strategies which supplemented screening for LTBI with port-of-entry chest radiography for immigrants arriving from countries with TB incidence >40 cases per 100000 prevented a modest number of additional cases of active TB but also incurred substantial extra costs as compared to those strategies which only employed screening for LTBI (in other words no chest radiography undertaken at port-of-entry).

Although having no LTBI screening in place was less expensive than any screening strategy for LTBI, it also resulted in more cases of active TB over the time course of the model. With reference to the specific LTBI screening tools used, at any screening threshold, single-step T-SPOT.TB was consistently the most expensive screening protocol followed by TST only and single-step QFN-GIT – both of which had relatively similar overall costs. However, single-step T-SPOT.TB was also the most effective strategy, resulting in the fewest cases of active TB, followed by QFN-GIT and then TST, which was the least effective of the single testing protocols due to T-SPOT.TB having the highest sensitivity. By contrast the dual TST plus confirmatory IGRA (QFN-GIT or T-SPOT.TB) approaches were the least expensive protocols (TST plus QFN-GIT less expensive than TST plus T-SPOT.TB) but resulted in the most cases of active TB (TST plus T-SPOT.TB prevented more cases than TST plus QFN-GIT), due to the low sensitivity of TST.

For all screening tools, irrespective of whether port-of-entry CXR was undertaken or not, costs increased as the threshold at which immigrants were eligible to be screened shifted downwards (Table 5.13) although, in general, there was also a concomitant increase in the number of cases prevented (as compared to no screening).

Table 5.13 Projected cases of active TB and associated costs arising from undertaking immigrant screening using different screening tools at different screening thresholds for a hypothetical cohort of 10,000 immigrants over a 20-year time horizon

Chest radiography at port of entry	Screening for latent tuberculosis infection		Number of cases of active TB (over 20 years)	Costs in UK pounds sterling (2010)	Incremental cases	Incremental costs	Incremental cost-effectiveness ratio
	Screening tool(s)	Screening threshold for immigrants (number of cases of TB/100000)					
No	None	None	100.5	659,609.4	Baseline	Baseline	Baseline
No	Tuberculin skin test plus QuantiFERON Gold in-tube	350	100.4	690,521.6	Extended dominance	Extended dominance	Extended dominance
No	Tuberculin skin test plus T-SPOT.TB	350	100.3	696,433.4	Extended dominance	Extended dominance	Extended dominance
No	Tuberculin skin test	350	100.1	706,478.7	Strict dominance	Strict dominance	Strict dominance
No	Tuberculin skin test plus QuantiFERON Gold in-tube	300	100.0	707,756.2	Strict dominance	Strict dominance	Strict dominance
No	Tuberculin skin test plus T-SPOT.TB	300	99.8	715,317.0	Strict dominance	Strict dominance	Strict dominance
No	QuantiFERON Gold in-tube	350	99.4	701,675.9	Extended dominance	Extended dominance	Extended dominance
No	Tuberculin skin test	300	99.4	721,759.0	Extended dominance	Extended dominance	Extended dominance
No	T-SPOT.TB	350	99.3	728,560.7	Strict dominance	Strict dominance	Strict dominance
Yes	None	None	98.9	754,339.9	Strict dominance	Strict dominance	Strict dominance
Yes	Tuberculin skin test plus QuantiFERON Gold in-tube	350	98.8	785,252.0	Strict dominance	Strict dominance	Strict dominance
Yes	Tuberculin skin test plus T-SPOT.TB	350	98.7	791,163.9	Strict dominance	Strict dominance	Strict dominance
Yes	Tuberculin skin test	350	98.5	801,209.1	Strict dominance	Strict dominance	Strict dominance
Yes	Tuberculin skin test plus QuantiFERON Gold in-tube	300	98.4	802,486.6	Strict dominance	Strict dominance	Strict dominance
Yes	Tuberculin skin test plus T-SPOT.TB	300	98.2	810,047.5	Strict dominance	Strict dominance	Strict dominance
No	QuantiFERON Gold in-tube	300	98.0	723,513.2	Extended dominance	Extended dominance	Extended dominance
Yes	QuantiFERON Gold in-tube	350	97.8	796,406.3	Strict dominance	Strict dominance	Strict dominance
Yes	Tuberculin skin test	300	97.8	816,489.4	Strict dominance	Strict dominance	Strict dominance
No	Tuberculin skin test plus QuantiFERON Gold in-tube	250	97.8	793,192.7	Strict dominance	Strict dominance	Strict dominance
No	T-SPOT.TB	300	97.7	751,926.8	Extended dominance	Extended dominance	Extended dominance
Yes	T-SPOT.TB	350	97.7	823,291.1	Strict dominance	Strict dominance	Strict dominance
No	Tuberculin skin test plus T-SPOT.TB	250	97.3	813,690.1	Extended dominance	Extended dominance	Extended dominance
Yes	QuantiFERON Gold in-tube	300	96.4	818,243.7	Extended dominance	Extended dominance	Extended dominance
Yes	Tuberculin skin test plus QuantiFERON Gold in-tube	250	96.2	887,923.2	Strict dominance	Strict dominance	Strict dominance
No	Tuberculin skin test	250	96.2	823,749.7	Extended dominance	Extended dominance	Extended dominance
Yes	T-SPOT.TB	300	96.1	846,657.3	Strict dominance	Strict dominance	Strict dominance
Yes	Tuberculin skin test plus T-SPOT.TB	250	95.7	908,420.5	Strict dominance	Strict dominance	Strict dominance
No	Tuberculin skin test plus QuantiFERON Gold in-tube	200	95.6	867,394.4	Strict dominance	Strict dominance	Strict dominance
No	Tuberculin skin test plus T-SPOT.TB	200	95.0	913,943.4	Strict dominance	Strict dominance	Strict dominance
Yes	Tuberculin skin test	250	94.6	918,480.1	Strict dominance	Strict dominance	Strict dominance
Yes	Tuberculin skin test plus QuantiFERON Gold in-tube	200	94.0	962,124.9	Strict dominance	Strict dominance	Strict dominance
No	Tuberculin skin test	200	93.8	995,462.9	Strict dominance	Strict dominance	Strict dominance
Yes	Tuberculin skin test plus T-SPOT.TB	200	93.4	1,008,673.9	Strict dominance	Strict dominance	Strict dominance
No	Tuberculin skin test plus QuantiFERON Gold in-tube	150	93.0	954,636.7	Strict dominance	Strict dominance	Strict dominance
No	Tuberculin skin test plus T-SPOT.TB	150	92.3	1,023,409.3	Strict dominance	Strict dominance	Strict dominance
Yes	Tuberculin skin test	200	92.2	1,090,193.4	Strict dominance	Strict dominance	Strict dominance
No	QuantiFERON Gold in-tube	250	92.1	839,713.7	8.4	180,104.3	21,565.3
No	Tuberculin skin test plus QuantiFERON Gold in-tube	100	91.5	1,018,843.7	Strict dominance	Strict dominance	Strict dominance

Yes	Tuberculin skin test plus QuantiFERON Gold in-tube	150	91.4	1,049,367.2	Strict dominance	Strict dominance	Strict dominance
No	T-SPOT.TB	250	91.3	909,426.7	Extended dominance	Extended dominance	Extended dominance
No	Tuberculin skin test plus T-SPOT.TB	100	90.7	1,113,644.2	Strict dominance	Strict dominance	Strict dominance
Yes	Tuberculin skin test plus T-SPOT.TB	150	90.7	1,118,139.7	Strict dominance	Strict dominance	Strict dominance
No	Tuberculin skin test	150	90.6	1,149,671.8	Strict dominance	Strict dominance	Strict dominance
Yes	QuantiFERON Gold in-tube	250	90.6	934,444.2	Extended dominance	Extended dominance	Extended dominance
Yes	Tuberculin skin test plus QuantiFERON Gold in-tube	100	89.9	1,113,574.1	Strict dominance	Strict dominance	Strict dominance
Yes	T-SPOT.TB	250	89.7	1,004,157.2	Strict dominance	Strict dominance	Strict dominance
No	QuantiFERON Gold in-tube	200	89.1	959,014.5	Extended dominance	Extended dominance	Extended dominance
Yes	Tuberculin skin test plus T-SPOT.TB	100	89.1	1,208,374.6	Strict dominance	Strict dominance	Strict dominance
No	Tuberculin skin test	100	89.0	1,319,841.4	Strict dominance	Strict dominance	Strict dominance
Yes	Tuberculin skin test	150	89.0	1,244,402.3	Strict dominance	Strict dominance	Strict dominance
No	T-SPOT.TB	200	88.2	1,171,831.5	Strict dominance	Strict dominance	Strict dominance
Yes	QuantiFERON Gold in-tube	200	87.6	1,053,744.9	Extended dominance	Extended dominance	Extended dominance
Yes	Tuberculin skin test	100	87.4	1,414,571.9	Strict dominance	Strict dominance	Strict dominance
Yes	T-SPOT.TB	200	86.6	1,266,562.0	Strict dominance	Strict dominance	Strict dominance
No	Tuberculin skin test plus QuantiFERON Gold in-tube	40	86.5	1,159,835.9	Strict dominance	Strict dominance	Strict dominance
No	Tuberculin skin test plus T-SPOT.TB	40	85.5	1,296,089.2	Strict dominance	Strict dominance	Strict dominance
Yes	Tuberculin skin test plus QuantiFERON Gold in-tube	40	84.9	1,254,566.3	Strict dominance	Strict dominance	Strict dominance
No	QuantiFERON Gold in-tube	150	84.3	1,089,176.5	7.8	249,462.8	31,867.1
Yes	Tuberculin skin test plus T-SPOT.TB	40	83.9	1,390,819.6	Strict dominance	Strict dominance	Strict dominance
No	Tuberculin skin test	40	83.3	1,597,273.1	Strict dominance	Strict dominance	Strict dominance
No	T-SPOT.TB	150	83.0	1,408,873.0	Strict dominance	Strict dominance	Strict dominance
No	QuantiFERON Gold in-tube	100	82.8	1,195,634.0	Strict dominance	Strict dominance	Strict dominance
Yes	QuantiFERON Gold in-tube	150	82.7	1,183,906.9	Extended dominance	Extended dominance	Extended dominance
Yes	Tuberculin skin test	40	81.7	1,692,003.5	Strict dominance	Strict dominance	Strict dominance
No	T-SPOT.TB	100	81.5	1,666,546.8	Strict dominance	Strict dominance	Strict dominance
Yes	T-SPOT.TB	150	81.4	1,503,603.4	Strict dominance	Strict dominance	Strict dominance
Yes	QuantiFERON Gold in-tube	100	81.2	1,290,364.5	Extended dominance	Extended dominance	Extended dominance
Yes	T-SPOT.TB	100	79.9	1,761,277.3	Strict dominance	Strict dominance	Strict dominance
No	QuantiFERON Gold in-tube	40	74.9	1,414,623.3	9.4	325,446.8	34,753.5
Yes	QuantiFERON Gold in-tube	40	73.4	1,509,353.7	1.6	94,730.4	59,489.1
No	T-SPOT.TB	40	73.3	2,095,182.0	Extended dominance	Extended dominance	Extended dominance
Yes	T-SPOT.TB	40	71.7	2,189,912.4	1.7	680,558.7	402,421.8

Footnotes

[1]Ranking different strategies from least effective to most effective (ie. number of cases of active TB predicted to occur) results in the incremental cost-effectiveness ratios (ICERs) of most screening options being excluded through extended dominance, which is where the ICER for a particular screening threshold is higher than for the next most effective strategy (screening threshold) and so the higher ICER is removed from the cost-effectiveness analysis.

[2]Current NICE guidance recommends screening with chest radiography at entry, using single step IGRA or dual TST plus confirmatory IGRA at an incidence threshold of 40/100000 (pink shaded rows)

Applying current UK national guidance (port-of-entry chest radiography, screening with single-step IGRA or dual TST plus confirmatory IGRA at an incidence of 40/100000) would avert (as compared to no screening) between 15.6 and 28.8 cases of active TB and incur additional costs of £578,569.3 to £1,473,6454.9 over 20 years depending on whether the dual TST plus IGRA approach or single-step IGRA approach was employed and which specific IGRA was utilised (QFN-GIT less expensive and less effective than T-SPOT.TB). If port-of-entry screening was removed from national policy then savings of almost £100000 would be made with little impact on the number of TB cases averted. Increasing the threshold at which screening was instigated (for example to 150/100000 – which includes the Indian Subcontinent) but keeping port-of-entry chest radiography and using the identical screening tools would avert 58-66% of cases and incur 55-65% of costs as compared to screening at 40/100000.

With dominated options excluded (table 5.13) five cost-effective strategies remained which, in decreasing order of cost-effectiveness, were: no CXR at port-of-entry and screen with single-step QFN-GIT at 250/100000; no CXR at port-of-entry and screen with single-step QFN-GIT at 150/100000; no CXR at port-of-entry and screen with single-step QFN-GIT at 40/100000; CXR at port-of-entry and screen with single-step QFN-GIT at 40/100000; and, finally, CXR at port-of-entry and screen with single-step T-SPOT.TB at 40/100000. The associated ICERs (incremental cost-effectiveness ratios) for these strategies were £21,565.3, £31,867.1, £34,7543.5, £59,489.1 and £402,421.8 respectively per active TB case averted. Whilst the three most cost-effective strategies (no port-of-entry CXR and screening with single-step QFN-GIT at incidence thresholds of 250, 150 and 40/100000) had broadly similar ICERs, the next two most cost-effective strategies, port-of-entry CXR and screening with single-step QFN-GIT and T-SPOT.TB at an incidence threshold of 40/100000 (which is the strategy currently recommended by UK national guidance) had much higher ICERs.

Results of the univariate sensitivity analysis are presented in tables 5.14 and 5.15. Varying several parameters affected the ICER estimates for each of the strategies although, in general, the order of most cost-effective strategies remained relatively unaffected. Natural history parameters which particularly impacted on ICER values and the rank order of the most cost-effective strategies were the cohort prevalence of LTBI and HIV as well as the progression rate of latently infected

individuals to active TB. Higher values for all of these parameters reduced ICER values (in other words increased cost-effectiveness) and made it more cost-effective to screen at lower TB incidences (40/100000) with single-step QFN-GIT remaining the most cost-effective tool.

The test characteristic which particularly affected the outputs of the cost-effectiveness model was the diagnostic specificity of the different screening tests. Reductions in specificity resulted in higher ICER estimates and, for QFN-GIT, actually resulted in the test becoming a dominated strategy and replaced by single-step T-SPOT.TB at an incidence of 250/100000 as the most cost-effective screening option. Programmatic factors, such as the proportion of immigrants commencing, and completing, chemoprophylaxis also affected cost-effectiveness – with reductions in both parameters increasing ICER estimates (in other words making screening less cost-effective). In terms of cost parameters, ICER estimates were most sensitive to changes in the costs of screening for LTBI or evaluating those who screened positive with reductions significantly reducing ICER values (ie. increased cost-effectiveness).

Table 5.14 Univariate sensitivity analysis of probabilities/proportions used as input variables in the decision model

Model parameter			Screening protocols for latent tuberculosis infection (stratified by chest radiography at port of entry, screening tools and screening incidence)							
			No CXR QFN-GIT only	No CXR T-SPOT.TB only	CXR T-SPOT.TB only	No CXR QFN-GIT only	CXR T-SPOT.TB only	No CXR QFN-GIT only	CXR QFN-GIT only	CXR T-SPOT.TB only
	Point Estimate	Range	>250	>250	>250	>150	>150	>40	>40	>40
Prevalence of latent tuberculosis infection	0.13	0.1	22,871.7	ED	SD	40,812.9	SD	45,585.8	59,489.1	533,781.1
		0.4	SD[2]	ED[3]	SD	ED	SD	16,520.5	59,489.1	115,523.1
Prevalence of HIV	0.004	0.002	17,620.0	ED	SD	32,950.4	SD	38,732.2	59,489.1	417,409.7
		0.01	SD	ED	SD	ED	SD	26,122.6	59,489.1	363,151.4
Prevalence of multi-drug resistant tuberculosis	0.01	0.005	21,248.5	ED	SD	31,695.1	SD	34,634.9	59,631.5	400,332.2
		0.02	22,214.7	ED	SD	32,216.1	SD	34,993.4	59,204.3	406,666.1
Proportion accepting TST	0.81	0.6	21,565.3	ED	SD	31,867.1	SD	34,753.5	59,489.1	402,421.8
		1	21,565.3	ED	SD	31,867.1	SD	34,753.5	59,489.1	402,421.8
Proportion TST read	0.94	0.6	21,565.3	ED	ED	31,867.1	SD	34,753.5	59,489.1	402,421.8
		1	21,565.3	ED	ED	31,867.1	SD	34,753.5	59,489.1	402,421.8
Proportion accepting QFN-GIT testing	0.99	0.6	ED	ED	31,863.8	ED	SD	32,113.8	ED	74,578.3
		1	21,390.6	ED	SD	31,889.7	SD	34,857.1	59,489.1	477,815.5
Proportion accepting T-SPOT.TB	0.99	0.6	21,565.3	SD	SD	31,867.1	SD	34,753.5	59,489.1	ED
		1	21,565.3	ED	SD	31,867.1	SD	34,753.5	59,489.1	349,020.9
Sensitivity of QFN-GIT in HIV neg	0.84	0.75	21,432.8	ED	ED	33,214.2	SD	35,936.2	59,489.1	149,541.2
		0.87	21,589.2	ED	SD	31,472.1	SD	34,396.3	59,489.1	875,064.3
Sensitivity of TST in HIV neg	0.77	0.65	20,611.4	ED	SD	31,433.0	SD	32,531.7	59,489.1	372,124.3
		0.82	21,934.4	ED	SD	32,048.1	SD	35,607.3	59,489.1	414,163.7
Sensitivity of T-SPOT.TB in HIV neg	0.89	0.78	20,431.4	SD	SD	30,714.6	SD	34,187.8	59,489.1	SD
		0.91	21,768.2	ED	SD	32,069.2	SD	34,851.8	59,489.1	301,351.4
Sensitivity of QFN-GIT in HIV positive	0.75	0.61	27,182.4	ED	SD	31,382.7	SD	32,641.1	59,489.1	301,251.5
		0.78	20,716.3	ED	SD	31,971.5	SD	35,177.2	59,489.1	428,998.4

Sensitivity of TST in HIV positive	0.71	0.61	22,241.0	ED	SD	31,494.6	SD	34,622.0	59,489.1	408,700.2
		0.75	21,347.2	ED	SD	31,981.4	SD	34,803.3	59,489.1	400,159.5
Sensitivity of T-SPOT.TB in HIV positive	0.81	0.62	23,648.3	SD	SD	30,988.5	SD	33,800.6	59,489.1	686,342.1
		0.83	21,418.1	ED	SD	31,922.0	SD	34,832.8	59,489.1	386,673.4
Specificity of QFN-GIT	0.99	0.75	ED	30,595.7	59,489.1	ED	175,719.7	SD	SD	392,557.9
		1	21,201.6	ED	SD	29,844.3	SD	32,271.1	59,489.1	412,426.3
Specificity of TST	0.78	0.7	21,764.5	ED	SD	33,182.7	SD	37,459.5	59,489.1	425,885.4
		0.9	21,285.0	ED	SD	30,212.7	SD	31,567.6	59,489.1	372,344.9
Specificity of T-SPOT.TB	0.86	0.72	22,118.2	SD	SD	36,206.2	SD	42,842.0	59,489.1	772,301.4
		0.95	21,248.5	SD	SD	29,874.0	SD	31,407.8	59,489.1	221,514.0
Proportion HIV negative progressing to active TB (over 20 years)	0.05	0.025	ED	ED	SD	ED	SD	ED	65,734.0	745,855.7
		0.10	5,315.9	ED	SD	13,070.0	SD	16,110.2	59,487.2	202,851.6
Proportion HIV positive progressing to active TB (over 20 years)	0.40	0.20	17,229.9	ED	SD	33,078.3	SD	39,287.3	59,489.1	419,095.8
		0.80	ED	ED	SD	ED	SD	27,097.2	59,489.1	368,659.4
Number of contacts	6.5	3.25	23,131.8	ED	SD	33,433.6	SD	36,320.0	61,055.6	403,988.3
		10	19,878.3	ED	SD	30,180.1	SD	33,066.5	57,802.1	400,734.8
Efficacy of complete chemoprophylaxis (risk reduction proportion)	0.65	0.5	36,853.3	ED	SD	41,713.0	SD	42,764.8	59,342.8	518,747.6
		0.8	14,284.3	ED	SD	25,378.6	SD	28,996.6	59,636.0	328,347.2
Efficacy of partial chemoprophylaxis (risk reduction proportion)	0.21	0.1	22,903.3	ED	SD	32,907.1	SD	35,639.3	59,470.1	414,481.5
		0.3	20,558.7	ED	SD	31,056.6	SD	34,056.2	59,504.6	393,058.2
Proportion starting chemoprophylaxis	0.95	0.3	SD	SD	SD	SD	SD	ED	109,522.6	1,165,096.7
		1	19,679.1	ED	SD	30,315.4	SD	33,427.2	59,520.0	385,466.6
Proportion completing chemoprophylaxis	0.85	0.3	ED	ED	SD	ED	SD	56,449.5	59,236.9	660,994.7
		1	17,677.4	ED	SD	28,561.9	SD	31,889.0	59,558.3	365,814.8
Number of secondary active TB cases per index case (drug sensitive)	0.24	0.12	25,056.5	ED	SD	36,370.8	SD	39,285.2	148,336.7	448,254.4
		0.36	19,100.2	ED	SD	28,510.1	SD	31,148.6	37,840.6	366,409.7
Number of secondary active TB cases per index case (drug resistant)	0.24	0.12	21,530.9	ED	SD	31,871.0	SD	34,770.5	59,962.2	402,414.9
		0.36	21,599.7	ED	SD	31,863.3	SD	34,736.6	59,020.7	402,428.8
Number of secondary latent TB cases per	0.18	0.09	21,596.2	ED	SD	31,906.2	SD	34,794.8	59,801.9	402,760.1

index case (drug sensitive)		0.27	21,534.4	ED	SD	31,828.2	SD	34,712.3	59,178.9	402,084.2
Number of secondary latent TB cases per index case (drug resistant)	0.18	0.09	21,565.2	ED	SD	31,867.2	SD	34,753.5	59,490.0	402,421.8
		0.27	21,565.4	ED	SD	31,867.1	SD	34,753.5	59,488.2	402,421.9
Proportion of active TB cases admitted as inpatient	0.53	0.25	22,695.9	ED	SD	32,990.1	SD	35,874.3	60,601.6	403,545.7
		0.75	20,676.9	ED	SD	30,984.8	SD	33,872.9	58,615.0	401,538.8
Proportion of immigrants having CXR on arrival	0.4	0.3	21,565.3	ED	SD	31,867.1	SD	34,753.5	59,489.1	402,421.8
		0.6	21,565.3	ED	SD	31,867.1	SD	34,753.5	59,489.1	402,421.8
Prevalence of active TB in immigrants from countries with TB incidence >40/100000	0.0035	0.001	21,570.0	ED	SD	31,869.0	SD	34,763.4	224,786.7	402,421.8
		0.005	21,562.5	ED	SD	31,866.0	SD	34,747.5	39,653.4	402,421.8
Prevalence of active TB in immigrants from countries with TB incidence <40/100000	0.001	0.0005	21,564.4	ED	SD	31,866.8	SD	34,751.5	59,489.1	402,421.8
		0.005	21,572.8	ED	SD	31,870.1	SD	34,769.4	59,489.1	402,421.8
Proportion reduction in number of secondary active cases for actively diagnosed active TB	0.5	0.25	21,565.3	ED	SD	ED	SD	33,439.3	124,449.8	402,421.8
		0.75	21,565.3	ED	ED	31,867.1	SD	34,753.5	37,597.7	402,421.8
Proportion reduction in number of secondary latent infection for actively diagnosed active TB	0.5	0.25	21,565.3	ED	SD	31,867.1	SD	34,753.5	59,802.8	402,421.8
		0.75	21,565.3	ED	SD	31,867.1	SD	34,753.5	59,178.0	402,421.8
Proportion receiving chemoprophylaxis developing hepatotoxicity	0.002	0.001	21,532.3	ED	SD	31,841.3	SD	34,730.0	59,489.1	402,039.5
		0.003	21,598.4	ED	SD	31,893.0	SD	34,777.0	59,489.1	402,804.3

Footnotes

[1]Only non-dominated **options** are presented - the figures presented are the incremental cost-effectiveness ratios (ICERs); moving from lowest to highest ICER indicates decreasing cost-effectiveness

[2]Strict dominance (SD): This is the situation where a particular screening threshold is both less effective and more expensive than the next most effective screening threshold

[3]Extended dominance (ED): This is the situation where the incremental cost-effectiveness ratio (ICER) for a particular screening threshold is higher than for the next most effective strategy (screening threshold) and so the higher ICER is removed from the cost-effectiveness analysis

Table 5.15 Univariate sensitivity analysis of costs used as input variables in the decision model

Parameter	Point estimate	Range	Screening protocols for latent tuberculosis infection (stratified by chest radiography at port of entry, screening tools and screening incidence)								
			No CXR QFN-GIT only >250	No CXR T-SPOT.TB only >250	CXR T-SPOT.TB only >250	No CXR QFN-GIT only >200	No CXR QFN-GIT only >150	CXR T-SPOT.TB only >150	No CXR QFN-GIT only >40	CXR QFN-GIT only >40	CXR T-SPOT.TB only >40
Cost of initial screening (using single-step TST)	34.22	17.11	21,565.3	ED	SD	ED	31,867.1	SD	34,753.5	59,489.1	402,421.8
		51.33	21,565.3	ED	SD	ED	31,867.1	SD	34,753.5	59,489.1	402,421.8
Cost of in2itial screening (using single-step QuantiFERON-Gold in-tube)	52	26	17,956.3	ED	SD	ED	20,744.1	SD	21,521.2	59,489.1	545,003.0
		78	ED	ED	SD	SD	33,794.1	SD	47,985.8	59,489.1	259,840.7
Cost of initial screening (using single-step T-SPOT.TB)	82	41	ED	ED	ED	ED	26,549.6	SD	34,753.5	59,489.1	177,582.3
		123	21,565.3	SD	SD	ED	31,867.1	SD	34,753.5	59,489.1	627,261.4
Cost of confirmatory IGRA screening in dual-step strategy (using QuantiFERON-Gold in-tube)	41	20.5	21,565.3	ED	SD	ED	31,867.1	SD	34,753.5	59,489.1	402,421.8
		61.5	21,565.3	ED	SD	ED	31,867.1	SD	34,753.5	59,489.1	402,421.8
Cost of confirmatory IGRA screening in dual-step strategy (using T-SPOT.TB)	71	35.5	21,565.3	ED	SD	ED	31,867.1	SD	34,753.5	59,489.1	402,421.8
		106.5	21,565.3	ED	SD	ED	31,867.1	SD	34,753.5	59,489.1	402,421.8
Cost of evaluating of new-entrants who test positive for TST/IGRA	259.0	130.0	14,521.3	ED	SD	ED	26,383.4	SD	29,709.7	59,489.1	318,265.4
		389.0	28,663.9	ED	SD	ED	37,393.4	SD	39,836.4	59,489.1	487,230.7
Cost of treating new-entrants	130.0	65.0	18,707.5	ED	SD	ED	29,644.0	SD	32,709.3	59,527.8	368,194.7
		195.0	24,423.2	ED	SD	ED	34,090.3	SD	36,797.7	59,450.5	436,649.0
Cost of active drug sensitive TB OP follow-up	774.0	387.0	21,954.7	ED	SD	ED	32,253.9	SD	35,139.5	59,872.3	402,808.9
		1,161.0	21,175.9	ED	SD	ED	31,480.4	SD	34,367.5	59,106.0	402,034.8
Cost of active drug sensitive TB OP drugs	222.0	111.0	21,677.0	ED	SD	ED	31,978.1	SD	34,864.2	59,599.0	402,532.9
		333.0	21,453.6	ED	SD	ED	31,756.2	SD	34,642.8	59,379.2	402,310.8
Cost of active TB inpatient treatment	4,013.0	2,006.5	22,635.4	ED	SD	ED	32,930.0	SD	35,814.3	60,542.0	403,485.5
		6,019.5	20,495.2	ED	SD	ED	30,804.3	SD	33,692.7	58,436.2	401,358.2
Cost of contact tracing	482.0	241.0	23,131.8	ED	SD	ED	33,433.6	SD	36,320.0	61,055.6	403,988.3
		723.0	19,998.8	ED	SD	ED	30,300.6	SD	33,187.0	57,922.6	400,855.3

Cost of treatment for drug resistant active TB	32,299.0	16,150.0	21,464.5	ED	SD	ED	31,876.6	SD	34,793.8	59,649.6	402,419.2
		48,450.0	21,666.1	ED	SD	ED	31,857.7	SD	34,713.2	59,328.6	402,424.5
Cost of Hepatotoxicity with chemoprophylaxis	362.0	181.0	21,525.8	ED	SD	ED	31,836.4	SD	34,725.2	59,489.1	401,949.6
		1,862.0	21,575.7	ED	SD	ED	31,875.2	SD	34,760.9	59,489.1	402,545.8

Footnotes

[1]Only non-dominated options are presented - the figures presented are the incremental cost-effectiveness ratios (ICERs); moving from lowest to highest ICER indicates decreasing cost-effectiveness

[2]Strict dominance (SD): This is the situation where a particular screening threshold is both less effective and more expensive than the next most effective screening threshold

[3]Extended dominance (ED): This is the situation where the incremental cost-effectiveness ratio (ICER) for a particular screening threshold is higher than for the next most effective strategy (screening threshold) and so the higher ICER is removed from the cost-effectiveness analysis

Discussion

This analysis, which has immediate health-policy implications, reveals that UK policy could be modified by removing the current requirement for CXR on arrival and concentrating on LTBI testing using single-step IGRA testing targeted at adult immigrants arriving from countries with moderate TB incidence (rather than from countries with TB incidence >40/100000 as recommended currently).[81]

I have been able to do this by undertaking the first three-way assessment of different screening methods for LTBI, which provides comparative estimates of test performance and positivity stratified by demographic factors and risk factors for LTBI in recent immigrants. Consequently I have been able to evaluate, using a decision-analysis model, the cost-effectiveness of screening immigrants with port-of-entry chest radiographs and for LTBI.

In this cohort of adult immigrants the proportion positive by TST (30.3%; 36.7% if using the 10mm cut-off) was significantly higher than with QFN-GIT and T-SPOT.TB (16.6% and 22.5% respectively). Most previous studies have assessed LTBI prevalence in immigrants with TST and found that positivity varies from 26-72% depending on the setting, type of migrants studied (legal or undocumented immigrants), TST cut-off and history of BCG vaccination.[187,203-208,210-215] IGRA performance in diagnosing LTBI in legal (adult) immigrants is poorly studied. Instead authors have primarily focused on undocumented migrants[203,211,213,215,216] or immigrant contacts of smear-positive index cases[209,218] with very few studies, to date, actually focusing on legal, documented migrants per se.[217,366] Nonetheless, in all populations, IGRA positivity (15-60%) has generally been lower than that seen with TST.[203,209,211,213,215-218] However, many of these studies have been additionally hampered by the fact that they have utilised single-step IGRA only[216,217] (without a TST comparator – although suboptimal uptake of the skin test could adversely impact on screening programmes) or only undertaken IGRA in those individuals who have had a positive TST – thereby potentially introducing bias in patient selection.[218]

The higher proportion of immigrants who were TST, rather than IGRA, positive in this study affected the levels of concordance between the screening modalities. Overall concordance between TST and either QFN-GIT, or T–SPOT.TB, using the stratified TST cut-off was generally only fair in

this cohort with κ values of 0.30 and 0.29 respectively (0.29 and 0.38 for QFN-GIT and T-SPOT.TB using the unstratified cut-off). Concordance (with the unstratified 10mm cut-off) improved when subdivided by BCG vaccination status. Previous authors assessing concordance of TST and IGRAs in immigrants, and indeed other risk groups, have also computed κ values in the same range with higher levels of concordance in BCG unvaccinated individuals.[203,209,211,213,215,420] Much of the discordance in this study took the form of TST positive/IGRA negative results in BCG vaccinated individuals. Although these discordant pairs could either reflect a higher sensitivity, or a lower specificity, for TST as compared to IGRA it is most likely that they arise as the result of false-positive TST results which has implications when screening a predominantly BCG vaccinated population.[39] An important caveat is that prospective long-term studies are still required to clarify the outcomes for these individuals with discordant results.

Agreement between the two IGRAs, QFN-GIT and T-SPOT.TB, was moderate and not negatively impacted by prior BCG vaccination. Although there is no data on concordance between the two IGRAs in adult immigrants (non-contacts), Kik et al found a higher level of agreement (0.68) in immigrant contacts although IGRA testing in their study was limited to TST positive individuals[218] whereas Lucas and colleagues calculated concordance to be 0.78 in child refugees from Africa and Southeast Asia.[292] In other settings and risk groups concordance between the two commercially available IGRAs has also found to be moderate to good with BCG vaccination having little impact on degree of agreement.[421]

Although there was no significant difference in the proportion of results that were positive by both IGRAs, QFN-GIT had significantly fewer indeterminate results than T-SPOT.TB. Whilst current evidence is conflicting about whether QFN-GIT or T-SPOT.TB gives more indeterminate results,[56,420,421] a recent meta-analysis by Diel and colleagues concluded that, overall, QFN-GIT resulted in a slightly lower proportion of indeterminate results than T-SPOT.TB (2.1% vs 3.8% respectively).[41]

I found that positive TST, QFN-GIT and T-SPOT.TB were all independently associated with increasing TB incidence in the immigrants' countries of origin. It is likely that this reflects higher degrees of exposure to *Mycobacterium tuberculosis* in high TB incidence settings. These findings are

in keeping with previous analyses for TST[209,210] and IGRA,[209,211] although there are few data on test positivity in immigrants subcategorised into multiple strata of TB incidence.

An additional risk factor which was associated with test positivity (for all three tests) was increasing age. Previous studies from a variety of settings in different patient groups (including immigrants) have shown that TST[207,210,215,422] and IGRA[215,405,406,422] positivity correlates with increasing age. Although this is likely to be due to older immigrants having a higher cumulative probability of TB exposure in their countries of origin prior to migration, other possible reasons include higher cumulative exposure to environmental *Mycobacteria* resulting in false positive results (for TST) and sub-optimal sensitivity in younger age groups resulting in false negative results (for TST and IGRA).[407]

UK national guidance for immigrant TB screening is currently in flux. The previously restrictive, and poorly adhered to,[357] LTBI screening threshold (adults from Sub-Saharan Africa or countries with TB incidence >500/100000[29]) which would miss the vast majority of imported latent infections[366] has been revised downwards to an incidence threshold of 40/100000.[81] Whilst almost all positives would be identified if this threshold was applied to our cohort, it would also entail screening most of the immigrant cohort. This would put significant cost and practical stresses on TB services already stretched by the need to undertake immigrant screening.[357] In contrast, with an intermediate threshold (such as 150/100000), just under three-quarters of all positives (with single-step IGRA) would be identified but only half the immigrant cohort would need to be tested thereby offering a balance between diagnostic need and practical service capacity.[357]

The health economic analysis provides important insights, with potential policy implications, about immigrant screening which are likely to have wider relevance to countries other than the UK. Although five immigrant screening strategies were cost-effective, three strategies were more cost-effective than current national guidance. These strategies were: no CXR at port-of-entry and screen with single-step QFN-GIT at incidence thresholds of 250/100000, 150/100000 or 40/100000. Introducing CXR at port-of-entry and screening with single-step QFN-GIT or T-SPOT.TB at 40/100000 (in other words currently recommended NICE guidance) was cost-effective but at much higher ICERs.

The results indicate that, whilst undertaking CXR at port-of-arrival averts a few additional cases of active TB, it is not highly cost-effective (with the findings robust to changes in the prevalence of active TB in immigrants). This is the first demonstration of this in the UK and is consistent with the biology and epidemiology of TB in the UK where there is little active TB at the time of immigration[186,191,194] with most cases instead occurring through reactivation in latently infected foreign-born immigrants after arrival.[140] Therefore the need for mandatory CXR on arrival for active TB should be reassessed.[191] Other cost-effectiveness analyses, based on scenarios rather than real-life data, have suggested that CXR screening can be a cost-effective intervention. However these studies assumed very high proportions of the immigrant cohort having prevalent active TB,[302] a very low prevalence of LTBI[301] and a low reactivation rate from LTBI to active TB.[301,302]

I also found that single-step IGRA was the most cost-effective screening tool. Although previous health economic analyses of immigrant screening, which predated the widespread availability of IGRAs, were only able to consider TST as a diagnostic modality,[298,302] more recent studies have compared TST and IGRA.[217,301] Hardy et al concluded that single-step IGRA was more cost-effective than dual TST plus IGRA, although they did not undertake formal economic modelling, parameterisation or costing.[217] In contrast, Oxlade and colleagues found that the most cost-effective strategy for LTBI screening would be TST followed by QFN-GIT, although their estimates of test performance predated most meta-analyses on TST and IGRA performance and they did not consider the ELISpot (T-SPOT.TB) platform.[301] In non-immigrant risk groups, the data are conflicting with some authors concluding that TST plus confirmatory IGRA is superior,[301,397,423,424] whilst others found that IGRA alone is most cost-effective.[398,425,426] UK guidance, which previously recommended dual TST plus IGRA testing, has recently been revised so that either dual TST plus IGRA or single-step IGRA can be used in adults.[81] Although all three individuals with active TB in this dataset were IGRA positive, an important caveat to moving wholly to single-step IGRA, as per the current work and national guidance, would be a requirement to supplement testing with a symptom questionnaire to avoid missing those immigrants with false-negative IGRAs in the setting of active TB - especially if port-of-entry chest radiography was also withdrawn.

This work goes further than current national guidance as I illustrate that, of the two commercially available IGRAs, QFN-GIT is the most cost-effective, primarily due to the higher unit costs for T-SPOT.TB. Previous economic analyses of IGRAs (including amongst immigrants) have, in general, only focused on one or other IGRA. Only Pooran et al assessed the relative cost-effectiveness of QFN-GIT and T-SPOT.TB, but their analysis focused on contacts, only considered a 2-year time horizon, did not include discounting and, most importantly, used outdated estimates of test performance.[397]

Central to our analysis is the specific threshold at which screening should be instigated. 250/100000, 150/100000 and 40/100000 were all cost-effective thresholds, confirming previous work,[366] and the latter two strategies would incorporate many Asian countries - including immigrants from the Indian Subcontinent who contribute both a large proportion of the individuals migrating to, and a high proportion of the foreign-born active TB cases occurring in, the UK.[140,174] Implementing screening at these thresholds would of course incur increased total costs, requiring consideration of resource availability and the funds policy-makers are willing to spend to control the incidence of active TB.

This work had several limitations. The number of participants was relatively small (particularly in terms of the numbers arriving from very high incidence countries) and not all immigrants were concurrently screened with all three tests. As per UK guidelines and routine practice, HIV testing was not undertaken and thus data on immigrants' HIV status was not available. Consequently I used estimates for this parameter but this work highlights the wider implications and potential of incorporating testing for blood-borne viruses into community-based screening for TB.

In the absence of a gold-standard for LTBI diagnosis I used data from recent meta-analyses which based their point estimates for sensitivity on active TB and specificity on results from individuals at a low risk of infection – although even these studies varied in their point estimates.[41-43] Basing IGRA specificity estimates on individuals at low risk of infection may have resulted in overestimates which would reduce the false-positive rate and thereby increase cost-effectiveness. As IGRA sensitivity is likely to be lower in patients with active TB compared to healthy individuals

undergoing screening for LTBI, this assumption may underestimate the sensitivity of the test and therefore underestimate the cost effectiveness.

The health-economic model was non-dynamic and I therefore only considered transmission to contacts resulting in secondary cases of active TB and LTBI. Incorporating further generations of transmission would increase the cost-effectiveness of LTBI screening. In contrast I assumed relatively high rates of acceptance, and completion, of chemoprophylaxis which, whilst broadly in line with the estimates used by NICE,[81] may have over-estimated the cost-effectiveness of screening (although the results remained broadly unchanged with reductions in completion rates).

In line with previous published work[301,302,397,398] I elected to assess cost-effectiveness by presenting the cost per active TB case averted rather than the cost per quality adjusted life year (QALY) as this is more intuitive and, importantly, there are still unfortunately limited objective data on utility states for individuals with active and latent tuberculosis.

In conclusion, immigrant screening in the UK could cost-effectively remove the requirement for mandatory CXR on arrival and concentrate on screening for LTBI with single step IGRA at an incidence threshold which balances the need to identify those with LTBI against limited service capacity whilst still reducing UK TB notifications in the future.

Chapter 6 The influence of ethnicity and mycobacterial lineage on clinical disease phenotypes in tuberculosis

Introduction

The preceding chapters (chapters two to five) have dealt with the issue of immigrant screening for TB with a specific focus on ascertaining national guidelines in place in high-income countries, how actual practice differs from guidance in the UK and the yields, as well as cost-effectiveness, of screening immigrants at different incidence thresholds with different diagnostic modalities.

In the next two chapters I concentrate on the important, but understudied, issue of clinical patterns of TB in the immigrant population in the UK. Although epidemiological data, from the UK and other high-income countries, clearly highlights that foreign-born, as compared to local-born, individuals clinically present with a predominantly extrapulmonary pattern of disease, relatively little is known about the factors driving these phenotypic differences and the relative importance of demographic, mycobacterial and, to a lesser extent, environmental factors.

The impact of mycobacterial linage on clinical phenotype is of particular interest. Recent advances in molecular techniques have identified different lineages of *M. tuberculosis*. Previous work from Gagneux[331] and others[333-336] has clearly shown, epidemiologically, that these lineages co-associate with distinct geographic regions – such as the East-Asian lineage with East/Southeast Asia or the Euro-American lineage with Europe and the Americas. Moreover, individual lineages differ in the immune response that they induce;[323] prior work has shown that the Beijing (East Asian) lineage induces lower levels of inflammatory cytokines[337,338] such as tumour necrosis factor (TNF) whilst also exhibiting enhanced growth in macrophages.[339]

Although these *in vitro* differences in host response might be expected to result in the well-recognised different clinical phenotypes observed in distinct demographic groups[33,34,314] the impact and influence of different lineages on clinical patterns of active tuberculosis (TB) still remains unclear. A notable exception is the Beijing (East Asian) lineage which, in certain ethnic groups, has been associated with a more aggressive clinical course[350] and extrapulmonary forms of TB[343-345] although other studies have failed to document these associations.[346,351,352] More recently, studies from Italy[346] and Sweden[347] have suggested that the Central Asian lineage (akin to the East African Indian

strain) is associated with extrapulmonary disease whilst two Pakistani[348,349] studies found the opposite. One of the main drawbacks of the studies conducted to date is that they have, in the main, examined homogeneous populations where the relative impact of demographic factors (such as ethnicity), as compared to lineage, on disease phenotype cannot be, or have not hitherto been, independently examined.

Given the recognised association of different lineages and ethnic groups,[331,333,335,336] and the known link between extrapulmonary disease and non-White ethnic groups,[33,34,314] it can be reasoned that in order to determine whether lineages influence clinical patterns of disease it would be necessary to dissect out the relative influence of the lineage itself from the different ethnic groups. In this chapter, therefore, I present the results of a project where I prospectively collated data on host factors, clinical patterns of disease and mycobacterial genotype for confirmed cases of TB in an ethnically diverse single-centre UK setting to assess the global phylogeography of the strains, assess the demographic factors associated with different lineages and to establish which, if any, factors (including lineage) were associated with distinct clinical patterns of disease.

Methods

Study design and data source

I analysed data from a routine, anonymised, centralised clinical surveillance database maintained as part of usual care (by Dr. John Innes) for all patients diagnosed with active TB in two closely related metropolitan areas in the UK (Birmingham and Solihull – combined population approximately 1.2 million;[409] TB incidence varies from 9-88 per 100000 population per year[393]).

MIRU-VNTR typing

Since mid-2003 all culture-positive *Mycobacterium tuberculosis* isolates received, and identified, as *M. tuberculosis* complex by the HPA Midlands Regional Centre for Mycobacteriology (strains banked by Dr. E. Grace Smith) have been routinely analysed by 15 loci mycobacterial interspersed repetitive units containing variable numbers of tandem repeats (MIRU-VNTR) typing (ETR-A, -B, -C, -D, -E and MIRU-02, -10, -16, -20, -23, -24, -26, -27, -39, -40) (strain typing undertaken by Dr. Jason Evans). MIRU-VNTR typing analyses the number of repetitive DNA sequences at multiple independent genetic loci.[330] The values generated are automatically recorded on the clinical surveillance database to facilitate epidemiological investigations, if necessary.

Study population, variables and assignment to lineage

I included all cases of active TB diagnosed between July 1st 2003 and February 28th 2010 with complete information in the dataset on age, sex, country of birth (specifically whether local- or foreign-born), ethnicity, site of disease and MIRU-VNTR value; patients with missing information for one or more of these variables or culture-negative disease were excluded from analysis.

Information on year of notification, age, sex, local/foreign-born, country of birth if foreign-born, ethnicity, time since entry (only applies to foreign-born immigrants and calculated as time between arrival in the UK and diagnosis of active TB), employment status, HIV status, previous

history of TB, site of disease, specific organs involved, duration of symptoms before treatment commencement, drug sensitivity and MIRU-VNTR value were retrieved from the datasets.

I used the MIRU-VNTR*plus* database[427] (available at: http://www.miru-vntrplus.org/) to assign strains with MIRU-VNTR values to one of six global lineages as defined by Gagneux:[331] East Asian, Euro-America, East African Indian, Indo-Oceanic, West African-1 and West African-2. Strains which could not be assigned to any lineage and those which were identified as being non *Mycobacterium tuberculosis* (such as *Mycobacterium bovis*) were excluded from analysis.

Ethnicity was broadly defined in line with the Office for National Statistics classification[428] (five ethnic groups: White, Indian Subcontinent, Afro-Caribbean, Oriental/Other Asia, Other). I further explored the patterns of disease in local-born ethnic groups versus foreign-born ethnic groups by creating a composite variable "location of birth/ethnicity" where individuals were categorised as being of local, or foreign, born Non-White ethnicity.

HIV testing of patients diagnosed with active TB is highly inconsistent in the UK and this was reflected by this variable being inconsistently recorded. Therefore, I considered patients either as HIV positive (if this was recorded) or as negative/unknown (for all other individuals).

Definitions of tuberculosis phenotypes

I initially defined all cases of active TB into three clinical phenotypes: pulmonary only (only lung parenchyma involved), extrapulmonary only (only one or more extrapulmonary site(s) involved) and both pulmonary and extrapulmonary (pulmonary disease and one or more extrapulmonary sites involved concurrently). This classification was used to describe the overall patterns of disease in the cohort. For comparative analyses I excluded all patients with concurrent pulmonary-extrapulmonary disease as Peto[314] and others[34,310] have done as it is impossible to be sure which disease site is dominant thereby risking misclassification bias.

To examine patterns of disease in more detail I also further sub-classified disease affecting extrapulmonary sites only into extrathoracic disease only (only extrapulmonary site(s) outside the

thoracic cavity involved) and lymph node disease only (only lymph nodes – either intrathoracic or extrathoracic involved).

Data analysis

Demographic characteristics of the cohort were described using median and interquartile range (IQR) (for continuous variables) and proportions (categorical variables); comparisons were made using the non-parametric Mann-Whitney U-test and Pearson's chi-square test (or Fishers exact test if appropriate) respectively.

I initially described the temporal dynamics and distribution of the global lineages in our cohort separately by the individuals' country of origin, region of origin and ethnic group. Comparisons of which lineages caused disease in UK- and foreign-born individuals were made using Fisher's exact test.

Assessment of factors associated with *Mycobacterium tuberculosis* lineage was undertaken by constructing separate regression models for each of the four main lineages in our study - East Asian, Euro-America, East African Indian and Indo-Oceanic. I did not undertake regression analyses for two lineages (West African-1 and West African-2) due to the very small number of cases caused by these lineages in our dataset. Univariate association of clinical and demographic factors individually associated with each lineage was assessed using logistic regression and reported as crude odds ratios (OR) and 95% confidence intervals (CI). To calculate adjusted odds ratios (and 95% CI) I mutually adjusted for the following factors: year of notification, age, gender, ethnicity, country of birth, HIV status, previous history of TB, drug sensitivity and smear positivity.

For the next stage of the analysis I described the broad clinical phenotypes (pulmonary only, extrapulmonary only and concurrent pulmonary-extrapulmonary) associated with each of the lineages. I then compared, for each lineage, the proportion of cases that were pulmonary only as compared to extrapulmonary only, extrathoracic only and lymph node only respectively; comparisons were made using univariate logistic regression.

I then assessed the factors (especially *Mycobacterium tuberculosis* lineage) associated with extrapulmonary only, extrathoracic only and lymph node only disease respectively versus exclusively pulmonary disease with three separate logistic regression models (for each clinical phenotype). Univariate, and multivariate, associations of factors individually associated with each of the three clinical phenotypes detailed above (compared against pulmonary cases only) was reported as crude, and adjusted, odds ratios (OR) respectively (and 95% confidence intervals). Adjusted odds ratios (and 95% CI) were obtained by mutually adjusting for the following factors in all three models: year of notification, season of notification, age, gender, ethnicity, country of birth, time since arrival, HIV status, previous history of TB, drug sensitivity and mycobacterial lineage. In the regression models, I specifically concentrated on the four main lineages present in our cohort (East Asian, Euro-America, East African Indian and Indo-Oceanic) and excluded the West African-1 and -2 strains as the number of cases caused by these lineages was very small thereby making accurate analysis with these two groups difficult – particularly with respect to calculating odds ratios and 95% confidence intervals. I used the East Asian lineage as the reference category as this strain has been previously shown to be associated with extrapulmonary disease although,[343-345] as a sensitivity analysis, I reran the multivariate model using the Euro-American lineage (which was the commonest) as the reference lineage against which the other lineages were compared.

Analyses used STATA 9.2 and 12.0 (StataCorp, College Station, TX). All tests were two tailed; p-value of ≤ 0.05 was considered significant.

Results

Description of cohort

Study recruitment is outlined in figure 6.1. Between July 1st 2003 and February 28th 2010, there were 2882 suspected cases of active TB of which 67 were eventually denotified resulting in 2815 notified cases of TB in the database. 1187 of these notified cases were culture negative and excluded from our analysis. Of the remaining 1628 culture positive case, 242 did not have a MIRU-VNTR value available and were excluded. Amongst the 1386 individuals with culture positive disease and a valid MIRU-VNTR value, lineages could be not be assigned to 312 – and these were also excluded. This left 1074 individuals with a lineage assigned; four cases identified as *Mycobacterium bovis* were excluded and so 1070 individuals were available for the final analysis.

Demographic and clinical details of the cohort are set out in table 6.1. Individuals in the cohort were generally young adults (median age 34.8 years, IQR: 25.0-49.7), male (54.1%) and foreign-born (70.3%); median time between arrival in the UK and development of active TB was 5 years (IQR 2-21). The commonest ethnic groups were Indian Subcontinent (53.9%) and Afro-Caribbean (26.0%).

Overall, disease was pulmonary only, extrapulmonary only and concurrent pulmonary-extrapulmonary in 52.1%, 36.9% and 11.0% of the cohort respectively. Sub-classification of the extrapulmonary only category revealed that 29.7% was extrathoracic only and 19.1% lymph node only (both intra-and extrathoracic). Extrapulmonary disease (either alone or with pulmonary disease) most commonly affected extrathoracic lymph nodes (41.8%), pleura (11.7%) and intrathoracic lymph nodes (11.5%). Broadly, individuals in the final analysed cohort (n=1070) were similar, in terms of demographic and clinical features, to individuals who did not have a MIRU-VNTR value and individuals who had a MIRU-VNTR value that could not be assigned to a lineage (see table 1). However this latter group did have a higher proportion of foreign-born individuals (p=0.001) and, therefore, a lower proportion of individuals of White ethnicity (p=0.003).

Figure 6.1 Flow chart of cases included in data analysis

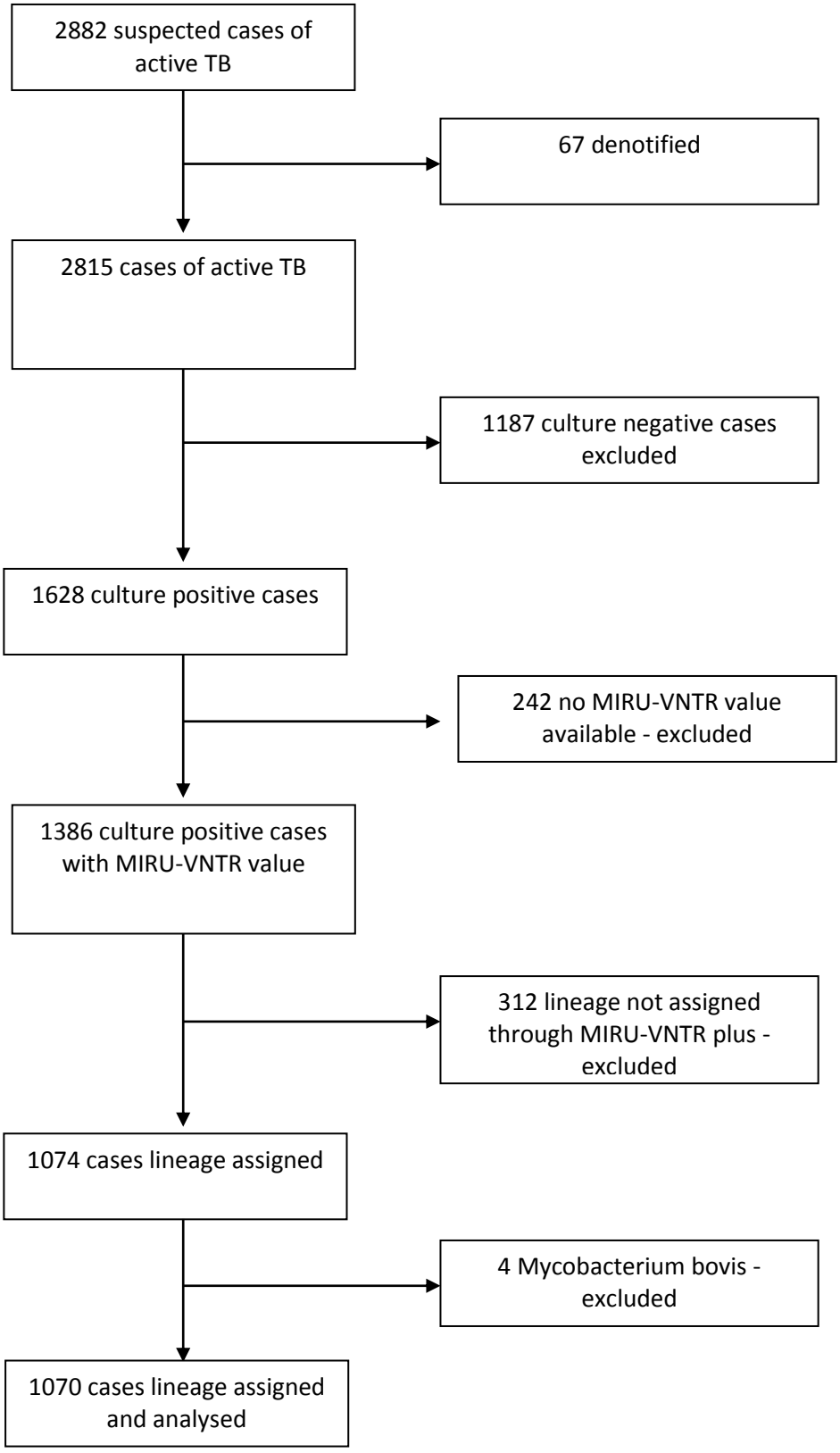


Table 6.1 Demographic characteristics of individuals with active tuberculosis as compared to those individuals with no MIRU-VNTR value available and where no lineage could be assigned

Variable	Subjects included in study (n=1070)	Subjects with no MIRU available (n=242)	p[1]	Subjects with no lineage assigned (n=312)	p[2]
Age					
Median (interquartile range)	34.8 (25.0-49.7)	36.2 (24.0-49.6)	0.11	32 (25.3-52.2)	0.42
Age categories					
Under 16	36 (3.4%)	12 (5.0%)		18 (5.8%)	
16-25	273 (25.5%)	54 (22.3%)		66 (21.2%)	
26-35	261 (24.4%)	53 (21.9%)		98 (31.4%)	
36-45	194 (18.1%)	36 (14.9%)		34 (10.9%)	
46-55	96 (9.0%)	21 (8.7%)		32 (10.3%)	
over 55	210 (19.6%)	66 (27.3%)		64 (20.5%)	
Gender					
Male	579 (54.1%)	145 (59.9%)	0.12	159 (51.0%)	0.33
Female	491 (45.9%)	492 (40.1%)		153(49.0%)	
Ethnicity					
White	148 (13.8%)	30 (12.4%)	0.50	24 (7.7%)	0.024
Indian Subcontinent	577 (53.9%)	125 (51.7%)		185 (59.3%)	
Afro-Caribbean	278 (26.0%)	72 (29.8%)		89 (28.5%)	
Oriental/Other Asia	23 (2.2%)	8 (3.3%)		3 (1.0%)	
Other	44 (4.1%)	7 (2.9%)		11 (3.5%)	
Place of birth					
United Kingdom	318 (29.7%)	61 (25.2%)	0.16	64 (20.5%)	0.001
Foreign-born	752 (70.3%)	181 (74.8%)		248 (79.5%)	
Time since entry to the UK (years)					
Median (interquartile range)	5 (2-21)[3]	6 (3-20)	0.54	6 (3-18)	0.76
<1	24 (3.4%)	8 (4.9%)		11 (4.8%)	
1 - 5	338 (48.0%)	72 (44.2%)		95 (41.1%)	
6-10	95 (13.5%)	24 (14.7%)		47 (20.4%)	
>10	247 (35.1%)	59 (36.2%)		78 (33.8%)	
Employment status					
Unemployed	118 (17.0%)[4]	36 (21.7%)	0.17	37 (18.9%)	0.63
Retired	71 (10.2%)	19 (11.5%)		16 (8.2%)	
Employed/housewife	395 (56.9%)	79 (47.6%)		107 (54.6%)	
Student/child	110 (15.9%)	32 (19.3%)		36 (18.4%)	
HIV status					
Negative	70 (84.3%)[5]	13 (85.7%)	0.82	23 (95.8%)	0.14
Positive	13 (15.7%)	2 (13.3%)		1 (4.2%)	
Previous TB					
No	1030 (96.3%)	228 (94.2%)	0.14	299 (95.8%)	0.72
Yes	40 (3.7%)	14 (5.8%)		13 (4.2%)	
Duration of symptoms (days)	63 (31-114)[6]	68 (27-123)	0.89	65 (30-115)	0.95
Type of disease					
Pulmonary only	557 (52.1%)	115 (47.5%)	0.23	155 (49.7%)	0.48
Pulmonary and extrapulmonary	118 (11.0%)	37 (15.3%)	0.08	40 (12.8%)	0.42
Extrapulmonary only	395 (36.9%)	90 (37.2%)	0.94	117 (37.5%)	0.89
Extrathoracic only	318 (29.7%)	73 (30.2)	0.88	96 (30.8)	0.73
Lymph node only	204 (19.1%)	44 (18.2)	0.79	63 (20.2)	0.68
Site of extrapulmonary disease					
Intrathoracic lymph node	52 (10.1%)	11 (8.7%)	0.74	21 (13.4%)	0.24
Extrathoracic lymph node	218 (42.5%)	52 (40.9%)	0.84	75 (47.8%)	0.27
Bone and joint	85 (16.6%)	14 (11.0%)	0.13	22 (14.0%)	0.53
Central nervous system	25 (4.9%)	8 (6.3%)	0.50	7 (4.5%)	1.00
Pleura	78 (15.2%)	19 (15.0%)	1.00	20 (12.7%)	0.52
Peritoneum	12 (2.3%)	1 (0.8%)	0.48	4 (2.6%)	0.77

Genitourinary	21 (4.1%)	6 (4.7%)	0.81	4 (2.6%)	0.48
Intestinal	30 (5.9%)	10 (7.9%)	0.41	10 (6.4%)	0.85
Miliary	24 (4.7%)	9 (7.1%)	0.37	7 (4.5%)	1.00
Pericardial	3 (0.6%)	1 (0.8%)	0.59	0 (0.0%)	1.00
Soft tissue	3 (0.6%)	0 (0.0%)	1.00	1 (0.6%)	1.00
Other	40 (7.8%)	24 (18.9%)	<0.0001	17 (29.8%)	0.25
Smear result					
Negative	525 (49.1%)	134 (55.4%)	0.09	162 (51.9%)	0.40
Positive	545 (50.9%)	108 (44.6%)		150 (48.1%)	
Drug sensitivity[5]					
Fully sensitive	976 (95.2%)	117 (88.0%)	0.007	288 (96.6%)	0.43
Mono-drug resistant	37 (3.6%)	12 (9.0%)		9 (3.0%)	
Multi-drug resistant	12 (1.2%)	4 (3.0%)		1 (0.3%)	
Lineages					
East Asian	130 (12.2)				
Euro-American	468 (43.7)				
East African Indian	323 (30.2)				
Indo-Oceanic	145 (13.6)				
West African 1	0 (0.0)				
West African 2	4 (0.7)				

Footnotes

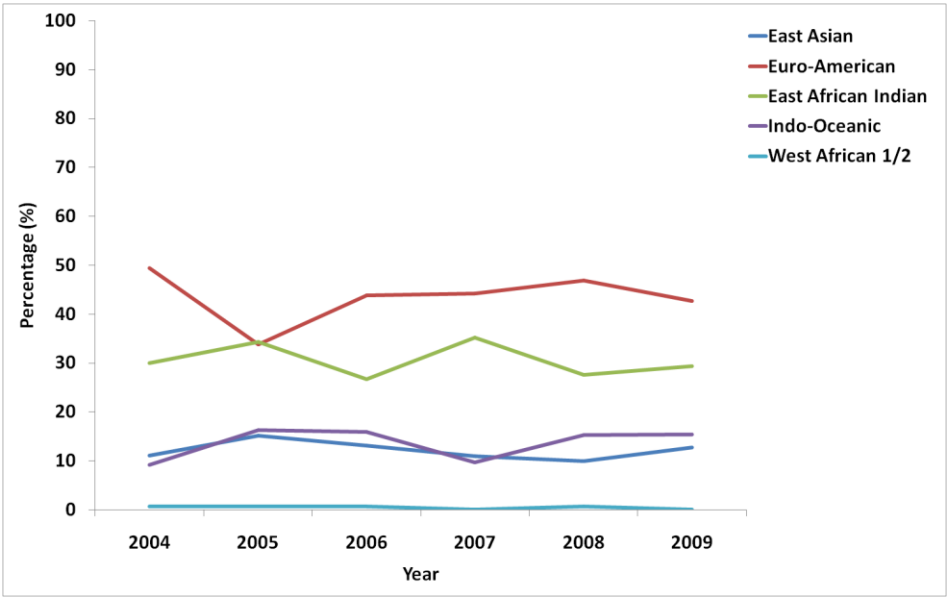
[1]p-value for subjects with no MIRU-VNTR available vs subjected included in study
[2]p-value for subjects with no lineage assigned vs subjected included in study
[3]Data available for 704 individuals
[4]Data available for 694 individuals
[5]Data available for 83 individuals
[6]Data available for 462 individuals
[7]Data available for 1025 individuals

Distribution, and temporal trends, of lineages in cohort

Table 6.1 outlines the frequency of the different lineages in our cohort. Euro-American was the commonest lineage (43.7%), followed by East African Indian (30.2%), Indo-Oceanic (13.6%) and Beijing (12.2%). West African-1 (0.0%) and West African-2 lineages (0.7%) were both rarely found in this cohort.

Figure 6.2 describes the temporal trends in lineages between 2004 and 2009. Overall there was no evidence that the proportion of cases caused by any specific lineage in any given year changed significantly over the course of the study period.

Figure 6.2 Temporal trends in lineages causing active tuberculosis between 2004 and 2009



Footnotes

[1]Last complete year was 2009

Distribution of lineages by geographic origin and ethnic group

Table 6.2 and figures 6.3 and 6.4 present the global distribution of lineages in our cohort stratified by region, and country, of origin respectively. In general, lineages were geographically restricted and associated with specific regions. For example, whilst the Euro-American lineage was present in almost all regions, it was predominantly found in Europe, the Americas and Africa which together accounted for 74.7% of all cases caused by this lineage. East African Indian and Indo-Oceanic lineages were largely found in the Indian Subcontinent/East Africa (75.7%) and Indian Subcontinent/East Africa/Asia (83.3%). By contrast, the East Asian strain appeared to be more geographically widespread being found in the Indian Subcontinent and East Africa – although it did account for 55.6% of cases in the small number of individuals (9) from East Asia in our cohort.

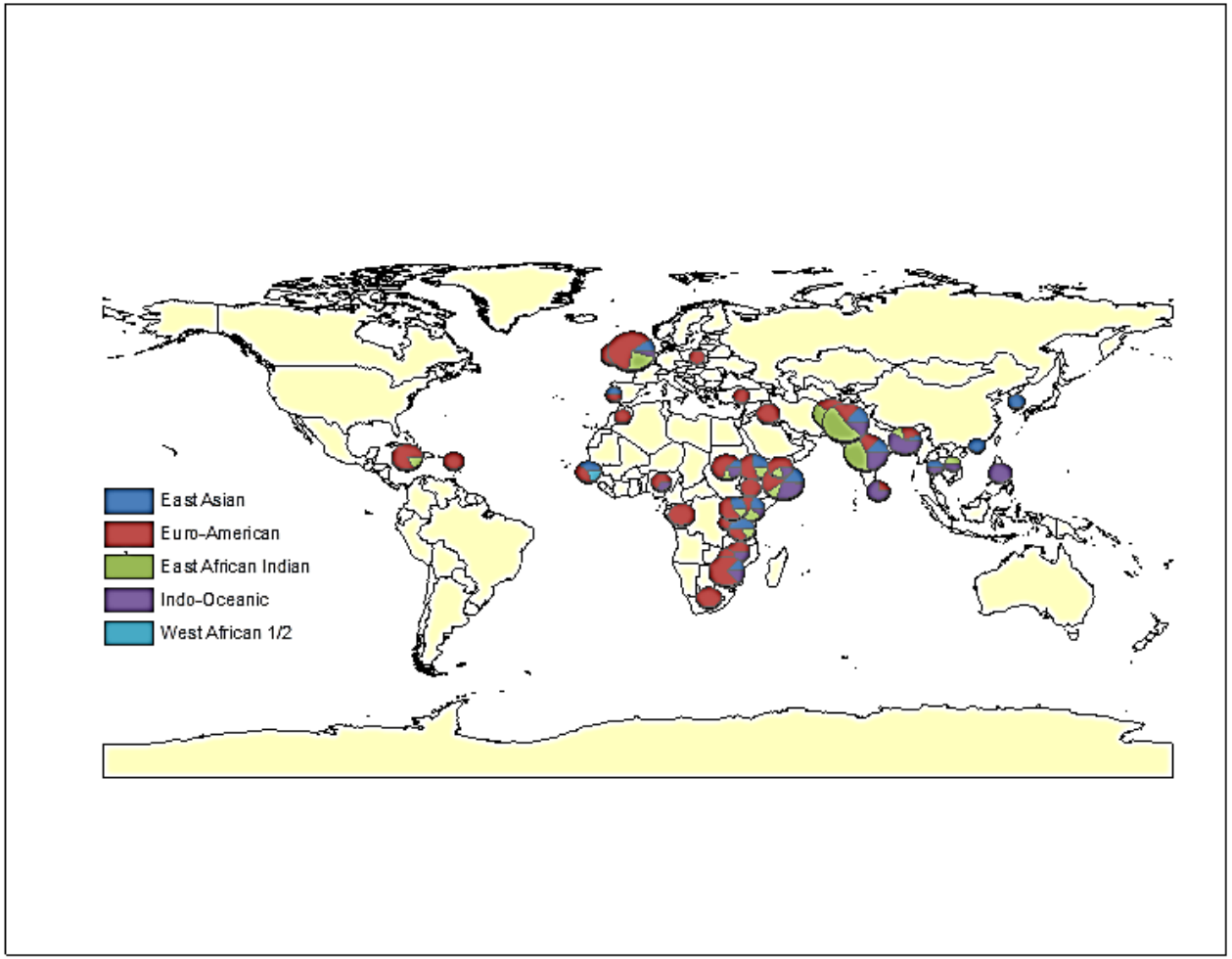
Table 6.2 Distribution of *Mycobacterium tuberculosis* lineages by different world regions of birth

World Region of birth	Lineage				
	East Asian (n=130)	Euro-American[2] (n=459)	East African Indian[3] (n=321)	Indo-Oceanic[4] (n=144)	West African 1/2 (n=4)
Americas	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Caribbean	0 (0.0)	13 (86.7)	2 (13.3)	0 (0.0)	0 (0.0)
Western Europe	34 (10.4)	205 (62.5)	73 (22.3)	15 (4.6)	1 (0.3)
Eastern Europe	0 (0.0)	4 (80.0)	1 (20.0)	0 (0.0)	0 (0.0)
Middle East/North Africa	0 (0.0)	11 (84.6)	1 (7.69)	1 (7.7)	0 (0.0)
South Africa	4 (8.7)	36 (78.3)	0 (0.0)	6 (13.0)	0 (0.0)
West Africa	2 (20.0)	6 (60.0)	0 (0.0)	1 (10.0)	1 (10.0)
East Africa	25 (16.8)	74 (49.7)	16 (10.7)	32 (21.5)	2 (1.3)
Central Africa	0 (0.0)	6 (85.7)	0 (0.0)	1 (14.3)	0 (0.0)
Indian Subcontinent	59 (12.6)	101 (21.5)	227 (48.4)	82 (17.5)	0 (0.0)
Southeast Asia	1 (20.0)	1 (20.0)	1 (20.0)	2 (40.0)	0 (0.0)
East Asia	5 (55.6)	0 (0.0)	0 (0.0)	4 (44.4)	0 (0.0)
Central Asia	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)

Footnotes

[1]Data shown are number (%); please note that percentages refer to rows (in other words the numbers/percentages should be read across and not down)
[2]Data missing for 9
[3]Data missing for 2
[4]Data missing for 1

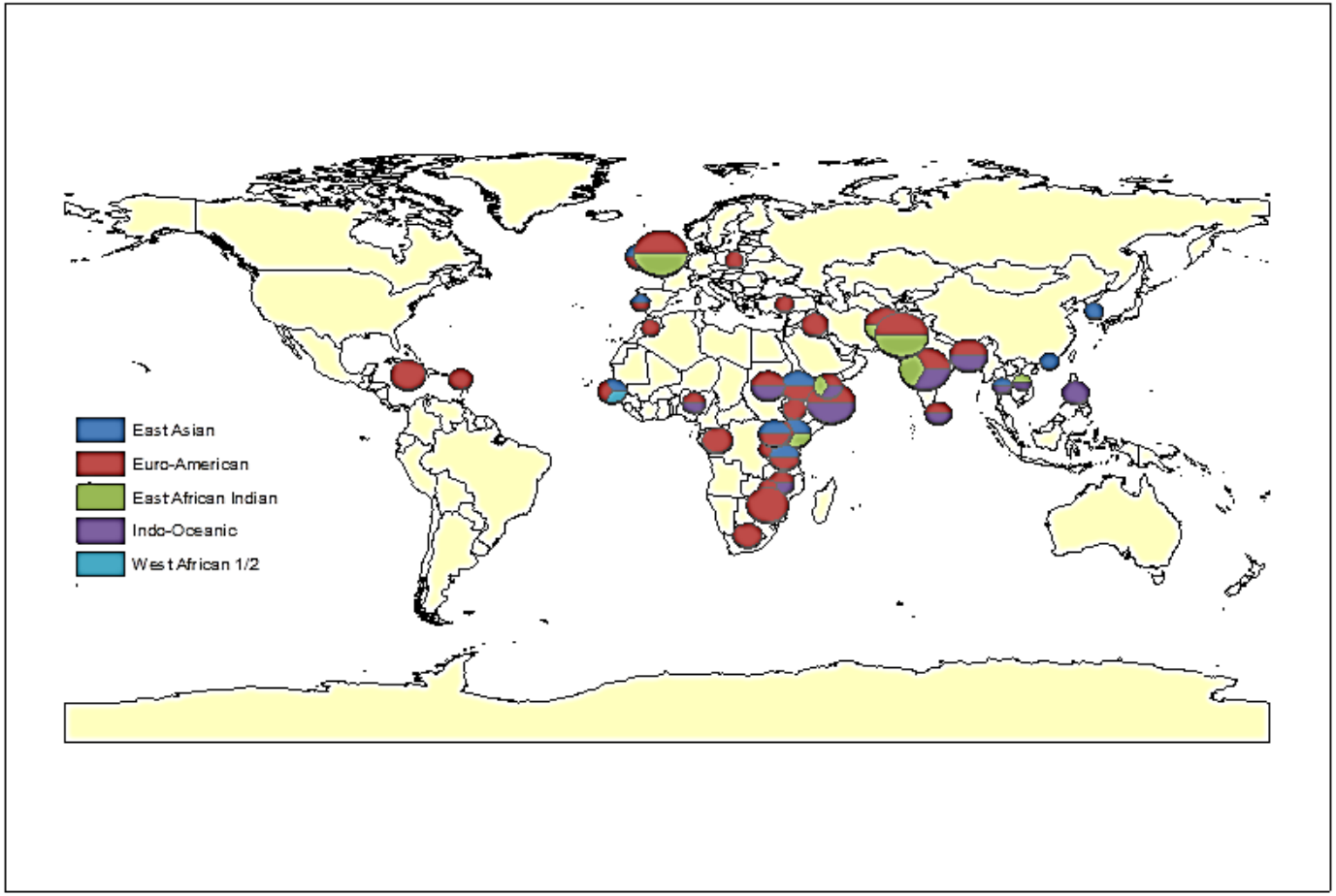
Figure 6.3 Distribution of *Mycobacterium tuberculosis* lineages by country of origin amongst individuals in the cohort



Footnote

[1]The size of pie charts is scaled relative to the number of cases from that country and the proportion of cases from each lineage

Figure 6.4 Distribution of dominant *Mycobacterium tuberculosis* lineages by country of origin amongst individuals in the cohort



Footnote

[1]The size of pie charts is scaled relative to the number of cases from that country and only the dominant lineages in each country (which make up >25% of cases) are presented

Stratification of lineages by ethnic group (table 6.3 and figure 6.5) illustrated that, within specific regions and countries, individuals of certain ethnicity were preferentially associated with particular lineages. Individuals of White (OR 4.56, 95% CI 3.08-6.75) and Afro-Caribbean (OR 3.21, 95% CI 2.42-4.28) ethnicity were significantly more likely to present with disease caused by the Euro-American lineage. By contrast, individuals in the Indian Subcontinent group were significantly associated with the East African Indian (OR 5.89, 95% CI 4.30-8.06) and Indo-Oceanic lineages (OR 1.69, 95% CI 1.17-2.43) whereas the Oriental/Other Asia group was associated with the East Asian lineage (OR 3.29, 95% CI 1.33-8.15).

Differences in lineage were also evident when comparing UK, and foreign, born individuals of Non-White ethnicity (table 6.3 and figure 6.5). The Euro-American lineage was significantly less common amongst foreign-born (as compared to the UK-born) individuals of Indian Subcontinent (OR 0.38, 95% CI 0.25-0.58) and Afro-Caribbean (OR 0.40, 95% CI 0.20-0.82) ethnicity.

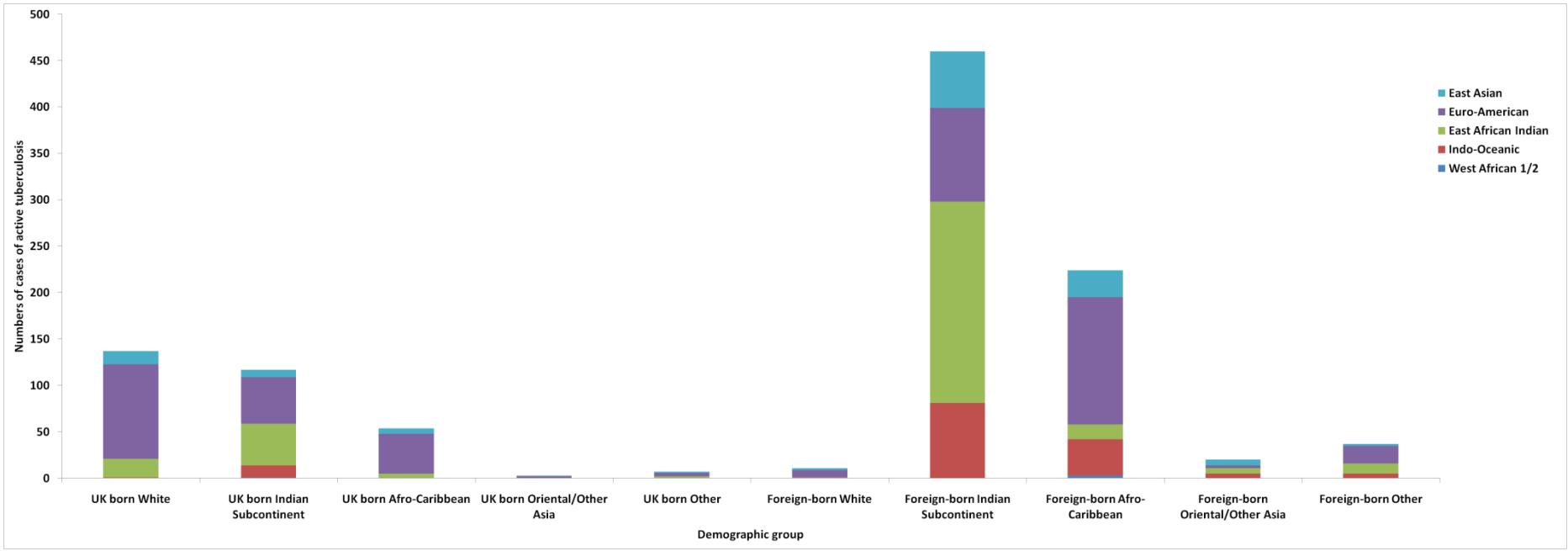
Table 6.3 Distribution of Mycobacterium tuberculosis lineages by different demographic groups (stratified by ethnicity and location of birth)

Location of birth/ethnicity	Lineage				
	East Asian (n=130)	Euro-American (n=468)	East African Indian (n=323)	Indo-Oceanic (n=145)	West African 1/2 (n=4)
Total White	**16 (10.8)**	**110 (74.3)**	**21 (14.2)**	**1 (0.7)**	**0 (0.0)**
UK born White	14 (10.2)	102 (74.5)	20 (14.6)	1 (0.7)	0 (0.0)
Foreign-born White	2 (18.2)	8 (72.7)	1 (9.1)	0 (0)	0 (0.0)
Total Indian Subcontinent	**69 (12.0)**	**151 (26.2)**	**262 (45.4)**	**94 (16.3)**	**1 (0.2)**
UK born Indian Subcontinent	8 (6.8)	50 (42.7)	45 (38.5)	13 (11.1)	1 (0.9)
Foreign-born Indian Subcontinent	61 (13.3)	101 (22.0)	217 (47.2)	81 (17.6)	0 (0.0)
Total Afro-Caribbean	**35 (12.6)**	**180 (64.8)**	**21 (7.6)**	**39 (14.0)**	**3 (1.1)**
UK born Afro-Caribbean	6 (11.1)	43 (79.6)	5 (9.3)	0 (0.0)	0 (0.0)
Foreign-born Afro-Caribbean	29 (13.0)	137 (61.2)	16 (7.1)	39 (17.4)	3 (1.4)
Total Oriental/Other Asia	**7 (30.4)**	**4 (17.4)**	**6 (26.1)**	**6 (26.1)**	**0 (0.0)**
UK born Oriental/Other Asia	1 (33.3)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)
Foreign-born Oriental/Other Asia	6 (30.0)	3 (15.0)	6 (30.0)	5 (25.0)	0 (0.0)
Total Other	**3 (6.8)**	**23 (52.3)**	**13 (29.6)**	**5 (11.4)**	**0 (0.0)**
UK born Other	1 (14.3)	4 (57.1)	2 (28.6)	0 (0.0)	0 (0.0)
Foreign-born Other	2 (5.4)	19 (51.4)	11 (29.7)	5 (13.5)	0 (0.0)

Footnotes

[1]Data shown are number (%); please note that percentages reflect the percentage of each lineage in each demographic group – ie. should be read across for each row)

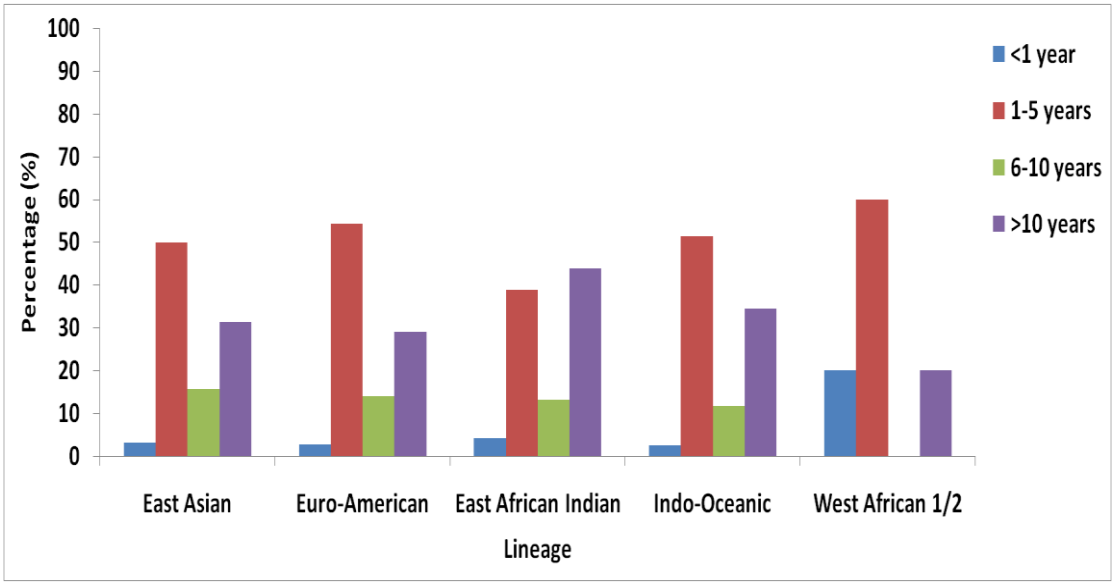
Figure 6.5 Numbers of cases of active tuberculosis occurring in different demographic groups stratified by *Mycobacterium tuberculosis* lineage



Association of time since arrival and development of active TB for different lineages

Figure 6.6 illustrates, for the foreign-born cohorts, the time between arrival in the UK and the development of active TB for the lineages in our cohort. Overall, the East African Indian lineage presented later (median 7 years, IQR 3-29) than the Euro-American lineage (median 5 years, IQR 2-18) (p=0.001).

Figure 6.6 Distribution of lineage by time since arrival for cases amongst the foreign-born



Factors associated with main mycobacterial lineages

Results of the univariate and multivariate analysis of the demographic and clinical factors associated with the four main lineages in the cohort (East Asian, Euro-American, East African Indian and Indo-Oceanic) are set out in table 6.4.

Table 6.4 Univariate and multivariate association of demographic, clinical and temporal factors with different *Mycobacterium tuberculosis* lineages

Variable	East Asian (n=130)	Unadjusted OR (95% CI)	Adjusted OR[1] (95% CI)	p	Euro-American (n=468)	Unadjusted OR (95% CI)	Adjusted OR[2] (95% CI)	p
Period								
2003-2004	25/227 (11)	1	1[2]	0.43	113/227 (49.8)	1	1	0.15
2005-2006	48/342 (14)	1.32 (0.79-2.21)	1.27 (0.75-2.14)		133/342 (38.9)	0.64 (0.46-0.90)	0.65 (0.44-0.96)	
2007-2008	35/336 (10.4)	0.94 (0.55-1.62)	0.89 (0.51-1.57)		153/336 (45.5)	0.84 (0.60-1.18)	0.86 (0.58-1.26)	
2009-2010	22/165 (13.3)	1.24 (0.67-2.29)	1.32 (0.69-2.50)		69/165 (41.8)	0.73 (0.48-1.09)	0.71 (0.44-1.15)	
Age categories n (%)								
Under 16	4/36 (11.1)	1	1	0.55	19/36 (52.8)	1	1	0.40
16-25	32/273 (11.7)	1.06 (0.35-3.2)	0.88 (0.28-2.74)		128/273 (46.9)	0.79 (0.39-1.58)	1.10 (0.50-2.44)	
26-35	31/261 (11.9)	1.08 (0.36-3.26)	0.86 (0.27-2.75)		104/261 (39.8)	0.59 (0.29-1.19)	1.01 (0.45-2.29)	
36-45	31/194 (16)	1.52 (0.5-4.61)	1.25 (0.39-4.03)		87/194 (44.8)	0.73 (0.36-1.48)	0.88 (0.38-2.04)	
46-55	11/96 (11.5)	1.04 (0.31-3.49)	0.73 (0.20-2.69)		40/96 (41.7)	0.64 (0.3-1.38)	1.19 (0.47-3.01)	
Over 55	21/210 (10)	0.89 (0.29-2.76)	0.71 (0.21-2.42)		90/210 (42.9)	0.67 (0.33-1.36)	1.50 (0.63-3.56)	
Gender								
Male	71/579 (12.3)	1	1	0.77	263/579 (45.4)	1	1	0.37
Female	59/491 (12.0)	0.98 (0.68-1.41)	0.94 (0.64-1.4)		205/491 (41.8)	0.86 (0.68-1.10)	1.14 (0.85-1.52)	
Place of birth								
UK	30/318 (9.4)	1	1	0.16	200/318 (62.9)	1	1	<0.0001
Foreign-born	100/752 (13.3)	1.47 (0.96-2.27)	1.52 (0.84-2.75)		268/752 (35.6)	0.33 (0.25-0.43)	0.40 (0.27-0.60)	
Ethnicity								
White	16/148 (10.8)	1	1	0.09	110/148 (74.3)	1	1	<0.0001
Indian Subcontinent	69/577 (12)	1.12 (0.63-1.99)	0.79 (0.36-1.71)		151/577 (26.2)	0.12 (0.08-0.19)	0.23 (0.14-0.39)	
Afro-Caribbean	35/278 (12.6)	1.19 (0.63-2.23)	0.77 (0.33-1.81)		180/278 (64.7)	0.63 (0.41-0.99)	1.54 (0.85-2.82)	
Oriental/Other Asia	7/23 (30.4)	3.61 (1.29-10.1)	2.63 (0.78-8.84)		4/23 (17.4)	0.07 (0.02-0.23)	0.12 (0.03-0.47)	
Other	3/44 (6.8)	0.60 (0.17-2.18)	0.43 (0.10-1.75)		23/44 (52.3)	0.38 (0.19-0.76)	0.98 (0.43-2.23)	
HIV status								
Negative/Unknown	128/1057 (12.1)	1	1	0.81	460/1057 (43.5)	1	1	0.93
Positive	2/13 (15.4)	1.32 (0.29-6.02)	1.21 (0.25-5.91)		8/13 (61.5)	2.08 (0.67-6.39)	1.06 (0.31-3.61)	
Previous TB								
No	130/1030 (12.6)	-		-	447/1030 (43.4)	1	1	0.41
Yes	0/40 (0.0)				21/40 (52.5)	1.44 (0.77-2.71)	1.35 (0.66-2.76)	
Drug sensitivity								
Fully sensitive	119/976 (12.2)	1	1	0.65	431/976 (44.2)	1	1	0.22
Drug-resistant	7/49 (14.3)	1.20 (0.53-2.73)	1.21 (0.52-2.83)		15/49 (30.6)	0.56 (0.30-1.04)	0.65 (0.33-1.29)	
Duration of symptoms before treatment								
0-15 days	5/59 (8.5)	1			29/59 (49.2)	1		
16-30 days	6/56 (10.7)	1.30(0.37-4.51)			25/56 (44.6)	0.83 (0.40-1.74)		
31-45 days	7/61 (11.5)	1.40 (0.42-4.69)			25/61 (41)	0.72 (0.35-1.48)		
46-60 days	5/43 (11.6)	1.42 (0.38-5.25)			20/43 (46.5)	0.90 (0.41-1.98)		
61 days and over	31/243 (12.8)	1.58 (0.59-4.25)			99/243 (40.7)	0.71 (0.40-1.26)		
Smear positive								
No	74/525 (14.1)	1	1	0.11	211/525 (40.2)	1	1	0.90
Yes	56/545 (10.3)	0.70 (0.48-1.01)	0.73 (0.49-1.08)		257/545 (47.2)	1.33 (1.04-1.69)	0.98 (0.74-1.31)	

Variable	East African Indian	Unadjusted OR (95% CI)	Adjusted OR[2] (95% CI)	p	Indo-Oceanic (n=145)	Unadjusted OR (95% CI)	Adjusted OR[2] (95% CI)	p
Period								
2003-2004	64/227 (28.2)	1	1[2]	0.86	24/227 (10.6)	1	1	0.43
2005-2006	104/342 (30.4)	1.11 (0.77-1.61)	1.08 (0.72-1.63)		55/342 (16.1)	1.62 (0.97-2.70)	1.47 (0.87-2.50)	
2007-2008	105/336 (31.3)	1.16 (0.80-1.68)	1.18 (0.79-1.78)		42/336 (12.5)	1.21 (0.71-2.06)	1.14 (0.65-2.00)	
2009-2010	50/165 (30.3)	1.11 (0.71-1.72)	1.03 (0.63-1.70)		24/165 (14.5)	1.44 (0.79-2.64)	1.46 (0.76-2.78)	
Age categories n (%)								
Under 16	9/36 (25)	1	1	0.92	4/36 (11.1)	1	1	0.19
16-25	75/273 (27.5)	1.14 (0.51-2.53)	0.90 (0.37-2.20)		35/273 (12.8)	1.18 (0.39-3.53)	0.95 (0.30-2.96)	
26-35	82/261 (31.4)	1.37 (0.62-3.05)	0.90 (0.36-2.24)		43/261 (16.5)	1.58 (0.53-4.69)	1.09 (0.35-3.46)	
36-45	46/194 (23.7)	0.93 (0.41-2.13)	0.75 (0.29-1.93)		30/194 (15.5)	1.46 (0.48-4.44)	1.28 (0.39-4.13)	
46-55	29/96 (30.2)	1.3 (0.54-3.1)	0.83 (0.30-2.28)		16/96 (16.7)	1.6 (0.5-5.15)	1.11 (0.32-3.87)	
Over 55	82/210 (39)	1.92 (0.86-4.29)	0.99 (0.38-2.54)		17/210 (8.1)	0.7 (0.22-2.23)	0.53 (0.15-1.82)	
Gender								
Male	162/579 (28.0)	1	1	0.94	81/579 (14.0)	1	1	0.39
Female	161/491 (32.8)	1.26 (0.97-1.63)	0.99 (0.73-1.33)		64/491 (13.0)	0.92 (0.65-1.31)	0.85 (0.58-1.24)	
Place of birth								
UK	72/318 (22.6)	1	1	0.19	15/318 (4.7)	1	1	0.005
Foreign-born	251/752 (33.4)	1.71 (1.26-2.32)	1.34 (0.87-2.08)		130/752 (17.3)	4.22 (2.43-7.33)	2.44 (1.31-4.53)	
Ethnicity								
White	21/148 (14.2)	1	1	<0.0001	1/148 (0.7)	1	1	0.015
Indian Subcontinent	262/577 (45.4)	5.03 (3.08-8.21)	4.04 (2.19-7.45)		94/577 (16.3)	28.61 (3.95-207.00)	14.02 (1.81-108.52)	
Afro-Caribbean	21/278 (7.6)	0.49 (0.26-0.94)	0.38 (0.18-0.84)		39/278 (14)	23.99 (3.26-176.45)	9.21 (1.15-73.58)	
Oriental/Other Asia	6/23 (26.1)	2.13 (0.76-6.03)	1.78 (0.56-5.62)		6/23 (26.1)	51.88 (5.89-457.01)	21.99 (2.28-212.42)	
Other	13/44 (29.5)	2.54 (1.14-5.62)	1.84 (0.73-4.66)		5/44 (11.4)	18.85 (2.14-166.03)	6.38 (0.64-63.52)	
HIV status								
Negative/Unknown	322/1057 (30.5)	1	1	0.82	143/1057 (13.5)	1	1	0.97
Positive	1/13 (7.7)	0.19 (0.02-1.47)	0.78 (0.09-6.90)		2/13 (15.4)	1.16 (0.25-5.29)	0.97 (0.20-4.69)	
Previous TB								
No	306/1030 (29.7)	1	1	0.05	143/1030 (13.9)	1	1	0.18
Yes	17/40 (42.5)	1.75 (0.92-3.32)	2.07 (1.00-4.31)		2/40 (5.0)	0.33 (0.08-1.37)	0.37 (0.09-1.58)	
Drug sensitivity								
Fully sensitive	293/976 (30.0)	1	1	0.85	130/976 (13.3)	1	1	0.55
Drug-resistant	17/49 (34.7)	1.24 (0.68-2.27)	1.07 (0.55-2.07)		9/49 (18.4)	1.46 (0.69-3.09)	1.27 (0.58-2.78)	
Duration of symptoms before treatment								
0-15 days	18/59 (30.5)	1			7/59 (11.9)	1		
16-30 days	17/56 (30.4)	0.99 (0.45-2.2)			8/56 (14.3)	1.24 (0.42-3.67)		
31-45 days	21/61 (34.4)	1.2 (0.56-2.57)			8/61 (13.1)	1.12 (0.38-3.32)		
46-60 days	10/43 (23.3)	0.69 (0.28-1.7)			8/43 (18.6)	1.70 (0.56-5.11)		
61 days and over	83/243 (34.2)	1.18 (0.64-2.18)			30/243 (12.3)	1.05 (0.44-2.51)		
Smear positive								
No	162/525 (30.9)	1	1	0.27	76/525 (14.5)	1	1	0.82
Yes	161/545 (29.5)	0.94 (0.72-1.22)	1.18 (0.88-1.59)		69/545 (12.7)	0.86 (0.60-1.22)	1.04 (0.71-1.53)	

Footnote

[1]Model mutually adjusted for year of notification, age, gender, ethnicity, country of birth, HIV status, drug sensitivity and smear positivity

[2]Model mutually adjusted for year of notification, age, gender, ethnicity, country of birth, HIV status, previous TB, drug sensitivity and smear positivity

On multivariate analysis, foreign location of birth (OR 0.40, 95% CI 0.27-0.60; p<0.0001) and, in comparison to White ethnicity, certain non-White ethnic groups (Indian Subcontinent OR 0.23, 95% CI 0.14-0.39; Oriental/Other Asia OR 0.12, 95% CI 0.03-0.47; p<0.0001) were negatively associated with Euro-American lineage. By contrast, Afro-Caribbean individuals were equally likely, as White individuals, to harbour the Euro-American lineage (OR 1.54 95% CI 0.85-2.82). Certain ethnic groups were either associated (Indian Subcontinent OR 4.04, 95% CI 2.19-7.45 p<0.0001) or negatively associated (Afro-Caribbean OR 0.38, 95% CI 0.18-0.86) with the East African Indian lineage. Foreign-birth (OR 2.44, 95% CI 1.31-4.53; p=0.005) and ethnicity (Indian Subcontinent OR 14.02, 95% CI 1.81-108.52; Afro-Caribbean OR 9.21, 95% CI 1.15-73.58; Oriental/Other Asia OR 21.99, 95% CI 2.28-212.42; p=0.015) were significantly associated with the Indo-Oceanic lineage.

Patterns of disease: the impact of ethnicity and mycobacterial lineage

Table 6.5 and figure 6.7 illustrate the clinical phenotypes of active tuberculosis stratified by lineage and ethnic group. In general, extrapulmonary only, extrathoracic only and lymph node only disease were more common in individuals who were foreign-born (p<0.0001 for all three) and of Non-White ethnicity (p<0.0001 for all three). More specifically, individuals of UK born White ethnicity had a significantly lower proportion of extrapulmonary only (7.7%), extrathoracic only (2.4%) and lymph node only (0.8%) disease as compared to individuals of UK born Non-White ethnicity (31.9%, 25.9% and 20.4% respectively) (p<0.0001 for all three) and both these groups had significantly lower proportions of all three extrapulmonary phenotypes as compared to individuals of foreign-born Non-White ethnicity (51.2%, 46.5% and 35.4%; p<0.0001 for UK born White and UK born Non-White except lymph node - p=0.0001).

In the cohort as a whole, on simple univariate comparisons, East Asian and Indo-Oceanic lineages were significantly more likely to cause extrapulmonary only (East Asian OR 1.64, 95% CI 1.10-2.44, Indo-Oceanic OR 2.10, 95% CI 1.44-3.05), extrathoracic only (East Asian OR 1.73, 95% CI 1.14-2.63, Indo-Oceanic OR 2.43, 95% CI 1.66-3.58) and lymph node only (East Asian OR 2.15, 95% CI 1.36-3.40, Indo-Oceanic OR 1.79, 95% CI 1.13-2.84) disease as compared to pulmonary only

disease (table 6.5). By contrast, the Euro-American lineage was significantly more likely to cause pulmonary disease and hence negatively associated with than extrapulmonary only (OR 0.57, 95% CI 0.44-0.74), extrathoracic only (OR 0.49, 95% CI 0.37-0.66) and lymph node only disease (OR 0.49, 95% CI 0.35-0.69) (see table 6.5).

Table 6.5 Different clinical phenotypes of active tuberculosis stratified by lineage and demographic group

		Pulmonary only (557)	Extrapulmonary only (395)	p-value[1]	Extrathoracic only (318)	p-value[2]	Lymph node only (204)	p-value[3]
Total cohort	**East Asian**	52 (9.3)	57 (14.4)	0.02	48 (15.1)	0.01	37 (18.1)	0.001
	Euro-American	275 (49.4)	141 (35.7)	<0.0001	103 (32.4)	<0.0001	66 (32.4)	<0.0001
	East African Indian	171 (30.7)	121 (30.6)	1.00	98 (30.8)	1.00	66 (32.4)	0.66
	Indo-Oceanic	56 (10.1)	75 (19.0)	<0.0001	68 (21.4)	<0.0001	34 (16.7)	0.016
	West African 1/2	3 (0.5)	1 (0.3)	0.65	1 (0.3)	1.00	1 (0.5)	1.00
		Pulmonary only (120)	**Extrapulmonary only (10)**	**p-value[1]**	**Extrathoracic only (3)**	**p-value[2]**	**Lymph node only (1)**	**p-value[3]**
UK born White	**East Asian**	12 (10.0)	0 (0.0)	0.60	0 (0.0)	1.00	0 (0.0)	1.00
	Euro-American	88 (73.3)	9 (90.0)	0.45	2 (66.7)	1.00	1 (100.0)	1.00
	East African Indian	19 (15.8)	1 (10.0)	1.00	1 (33.3)	0.42	0 (0.0)	1.00
	Indo-Oceanic	1 (0.8)	0 (0.0)	1.00	0 (0.0)	1.00	0 (0.0)	1.00
	West African 1/2	0 (0.0)	0 (0.0)	-	0 (0.0)	-	0 (0.0)	-
		Pulmonary only (9)	**Extrapulmonary only (0)**	**p-value[1]**	**Extrathoracic only (0)**	**p-value[2]**	**Lymph node only (0)**	**p-value[3]**
Foreign born White	**East Asian**	1 (11.1)	0 (0.0)	1.00	0 (0.0)	1.00	0 (0.0)	1.00
	Euro-American	7 (77.8)	0 (0.0)	1.00	0 (0.0)	1.00	0 (0.0)	1.00
	East African Indian	1 (11.1)	0 (0.0)	1.00	0 (0.0)	1.00	0 (0.0)	1.00
	Indo-Oceanic	0 (0.0)	0 (0.0)	-	0 (0.0)	-	0 (0.0)	-
	West African 1/2	0 (0.0)	0 (0.0)	-	0 (0.0)	-	0 (0.0)	-
		Pulmonary only (109)	**Extrapulmonary only (51)**	**p-value[1]**	**Extrathoracic only (38)**	**p-value[2]**	**Lymph node only (28)**	**p-value[3]**
UK born Non-White	**East Asian**	5 (4.6)	6 (11.8)	0.11	3 (7.9)	0.43	5 (17.9)	0.03
	Euro-American	62 (56.9)	24 (47.1)	0.31	18 (47.4)	0.35	13 (46.4)	0.40
	East African Indian	33 (30.8)	15 (29.4)	1.00	12 (31.6)	1.00	6 (21.4)	0.48
	Indo-Oceanic	8 (7.3)	6 (11.8)	0.37	5 (13.2)	0.32	4 (14.3)	0.27
	West African 1/2	1 (0.9)	0 (0.0)	1.00	0 (0.0)	1.00	0 (0.0)	1.00
		Pulmonary only (319)	**Extrapulmonary only (334)**	**p-value[1]**	**Extrathoracic only (277)**	**p-value[2]**	**Lymph node only (175)**	**p-value[3]**
Foreign born Non-White	**East Asian**	34 (10.7)	51 (15.3)	0.08	45 (16.3)	0.052	32 (18.3)	0.02
	Euro-American	118 (37.0)	108 (32.3)	0.22	83 (30.0)	0.08	52 (29.7)	0.11
	East African Indian	118 (37.0)	105 (31.4)	0.14	85 (30.7)	0.12	60 (34.3)	0.56
	Indo-Oceanic	47 (14.7)	69 (20.7)	0.05	63 (22.7)	0.015	30 (17.1)	0.52
	West African 1/2	2 (0.6)	1 (0.3)	0.62	1 (0.4)	1.00	1 (0.6)	1.00

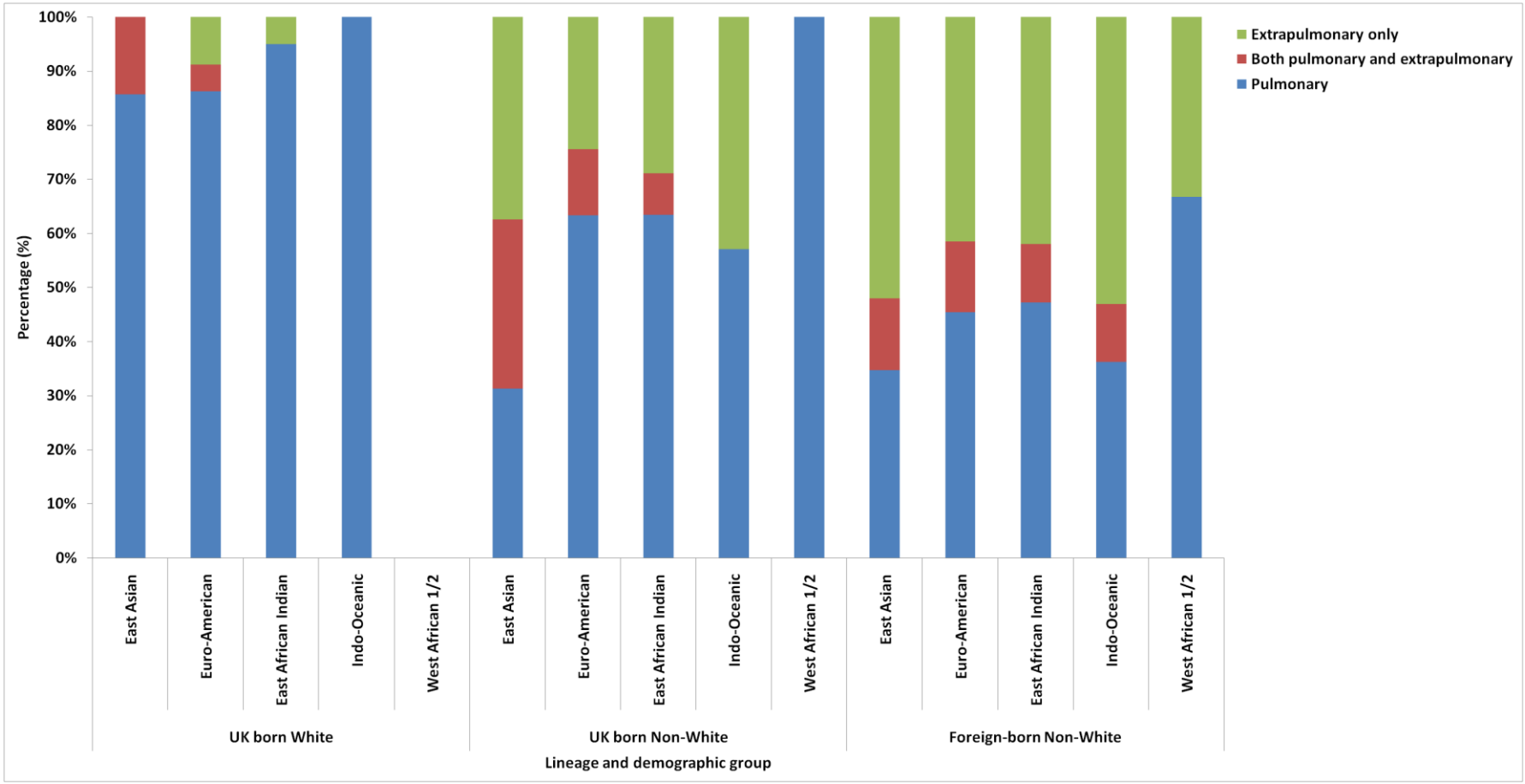
Footnotes

[1]p-value for pulmonary only disease vs extrapulmonary only disease

[2]p-value for pulmonary only disease vs extrathoracic only disease

[3]p-value for pulmonary only disease vs lymph node only disease

Figure 6.7 Patterns of tuberculosis stratified by demographic group and mycobacterial lineage



Factors associated with clinical patterns of disease: multivariate impact of mycobacterial lineage

Multivariate associations of factors associated with different clinical phenotypes are set out in tables 6.6 and 6.7. Certain mycobacterial lineages (with East Asian as the referent category) were negatively associated with extrapulmonary only (East African Indian OR 0.53, 95% CI 0.32-0.88; Euro-American OR 0.64, 95% CI 0.39-1.04), extrathoracic only (East African Indian OR 0.49, 95% CI 0.29-0.85; Euro-American OR 0.54, 95% CI 0.32-0.92) and lymph node only (East African Indian OR 0.37, 95% CI 0.20-0.60; Euro-American OR 0.48, 95% CI 0.27-0.86) disease. If Euro-American lineage (the most frequent lineage in this cohort) was used as the reference category, on multivariate analysis, the East Asian lineage (OR 1.86, 95% CI 1.10-3.15) was positively associated with extrathoracic disease but the East African Indian lineage was not (OR 0.92, 95% CI 0.60-1.40) (data not shown).

However, ethnicity was most strongly associated with clinical phenotype (and more strongly than lineage) with Afro-Caribbean and Indian Subcontinent ethnicities conferring adjusted odds ratios of 15 to 24 for extrathoracic disease and 33 to 74 for lymph node disease respectively (tables 6.6 and 6.7).

Additional factors found to be independently associated with the different extrapulmonary phenotypes were increasing age, female gender, summer season of notification, location of birth overseas and duration of residence (see tables 6.6 and 6.7).

Table 6.6 Univariate and multivariate association of demographic, clinical, temporal and mycobacterial factors with extrapulmonary and extrathoracic patterns of tuberculosis

Variable	Extrapulmonary TB only[2] (n=395)	Unadjusted OR (95% CI)	Adjusted OR[4] (95% CI)	p	Extrathoracic TB only[3] (n=318)	Unadjusted OR (95% CI)	Adjusted OR[4] (95% CI)	p
Period								
2003-2004	71/209 (34.0)	1	1	0.42	54/192 (28.1)	1	1	0.45
2005-2006	137/303 (45.2)	1.60 (1.11-2.31)	1.38 (0.92-2.09)		114/280 (40.7)	1.76 (1.18-2.60)	1.44 (0.92-2.27)	
2007-2008	127/296 (42.9)	1.46 (1.01-2.11)	1.31 (0.86-2.00)		100/269 (37.2)	1.51 (1.01-2.26)	1.28 (0.80-2.04)	
2009-2010	60/144 (41.7)	1.39 (0.90-2.15)	1.13 (0.67-1.88)		50/134 (37.3)	1.52 (0.95-2.44)	1.19 (0.68-2.07)	
Season								
Winter	69/187 (36.9)	1	1	0.005	55/173 (31.8)	1	1	0.03
Spring	101/259 (39.0)	1.09 (0.74-1.61)	0.85 (0.55-1.31)		84/242 (34.7)	1.14 (0.75-1.73)	0.82 (0.51-1.32)	
Summer	120/242 (49.6)	1.68 (1.14-2.48)	1.71 (1.09-2.68)		94/216 (43.5)	1.65 (1.09-2.51)	1.55 (0.95-2.53)	
Autumn	105/264 (39.8)	1.13 (0.77-1.66)	0.99 (0.64-1.54)		85/244 (34.8)	1.15 (0.76-1.74)	0.96 (0.60-1.56)	
Age categories n (%)								
Under 16	11/29 (37.9)	1	1	0.008	9/27 (33.3)	1	1	0.005
16-25	86/251 (34.3)	0.85 (0.39-1.89)	0.76 (0.31-1.85)		69/234 (29.5)	0.84 (0.36-1.95)	0.71 (0.28-1.80)	
26-35	109/229 (47.6)	1.49 (0.67-3.29)	1.20 (0.49-2.97)		88/208 (42.3)	1.47 (0.63-3.42)	1.09 (0.42-2.82)	
36-45	83/175 (47.4)	1.48 (0.66-3.31)	1.67 (0.66-4.23)		71/163 (43.6)	1.54 (0.65-3.64)	1.73 (0.65-4.58)	
46-55	44/86 (51.2)	1.71 (0.72-4.06)	1.99 (0.71-5.60)		33/75 (44)	1.57 (0.63-3.95)	1.96 (0.65-5.91)	
Over 55	62/182 (34.1)	0.85 (0.38-1.90)	1.04 (0.39-2.76)		48/168 (28.6)	0.80 (0.34-1.90)	0.89 (0.32-2.49)	
Gender								
Male	196/510 (38.4)	1	1	0.28	147/461 (31.9)	1	1	0.024
Female	199/442 (45.0)	1.31 (1.01-1.70)	1.18 (0.87-1.59)		171/414 (41.3)	1.590 (1.14-1.98)	1.45 (1.05-2.02)	
Country of birth/time since entry								
UK born	61/290 (21)	1	1	0.005	41/270 (15.2)	1	1	0.0016
Foreign born/<1 year	7/22 (31.8)	1.75 (0.68-4.49)	0.86 (0.29-2.51)		5/20 (25)	1.86 (0.64-5.40)	0.72 (0.21-2.50)	
Foreign born/1-5 years	153/301 (50.8)	3.88 (2.70-5.57)	2.01 (1.28-3.15)		130/278 (46.8)	4.91 (3.26-7.37)	2.27 (1.38-3.73)	
Foreign born/6-10 years	50/83 (60.2)	5.69 (3.37-9.59)	2.81 (1.53-5.18)		42/75 (56)	7.11 (4.04-12.5)	3.11 (1.61-6.00)	
Foreign born/>10 years	104/217 (47.9)	3.46 (2.34-5.09)	1.33 (0.76-2.32)		82/195 (42.1)	4.05 (2.62-6.28)	1.35 (0.73-2.48)	
Foreign born/time not known	20/39 (51.3)	3.95 (1.99-7.87)	1.91 (0.87-4.20)		18/37 (48.6)	5.29 (2.56-10.93)	2.27 (0.99-5.23)	
Ethnicity								
White	10/139 (7.2)	1	1	<0.0001	3/132 (2.3)	1	1	<0.0001
Indian Subcontinent	254/514 (49.4)	12.60 (6.47-24.53)	10.91 (4.82-24.67)		206/466 (44.2)	34.07 (10.69-108.59)	23.80 (6.80-83.29)	
Afro-Caribbean	103/237 (43.5)	9.92 (4.96-19.82)	6.73 (2.90-15.59)		88/222 (39.6)	28.24 (8.71-91.52)	15.34 (4.31-54.59)	
Oriental/Other Asia	5/21 (23.8)	4.03 (1.22-13.29)	2.95 (0.75-11.52)		4/20 (20)	10.75 (2.2-52.43)	5.29 (0.94-29.76)	
Other	23/41 (56.1)	16.48 (6.76-40.19)	12.75 (4.53-35.88)		17/35 (48.6)	40.61 (10.82-152.44)	24.17 (5.81-100.44)	
Lineage[1]								
East Asian	57/109 (52.3)	1	1	0.056	48/100 (48)	1	1	0.018
Euro-American	141/416 (33.9)	0.47 (0.31-0.72)	0.64 (0.39-1.04)		103/378 (27.2)	0.41 (0.26-0.64)	0.54 (0.32-0.92)	
East African Indian	121/292 (41.4)	0.65 (0.41-1.00)	0.53 (0.32-0.88)		98/269 (36.4)	0.62 (0.39-0.99)	0.49 (0.29-0.85)	
Indo-Oceanic	75/131 (57.3)	1.22 (0.73-2.04)	0.82 (0.47-1.44)		68/124 (54.8)	1.32 (0.78-2.23)	0.84 (0.47-1.52)	

Employment status								
Unemployed	42/106 (39.6)	1			34/98 (34.7)	1		
Retired	18/60 (30.0)	0.65 (0.33-1.28)			12/54 (22.2)	0.54 (0.25-1.16)		
Employed/housewife	170/354 (48.0)	1.41 (0.91-2.19)			140/324 (43.2)	1.43 (0.89-2.29)		
Student/child	30/91 (33.0)	0.75 (0.42-1.35)			24/85 (28.2)	0.74 (0.39-1.39)		
HIV status								
Negative/Unknown	391/944 (41.4)	1	1	0.94	314/867 (36.2)	1	1	0.97
Positive	4/8 (50.0)	1.41 (0.35-5.69)	0.95 (0.22-4.02)		4/8 (50.0)	1.76 (0.44-7.09)	0.97 (0.23-4.14)	
Previous TB								
No	385/918 (41.9)	1	1	0.24	308/841 (36.6)	1	1	0.71
Yes	10/34 (29.4)	0.58 (0.27-1.22)	0.61 (0.27-1.39)		10/34 (29.4)	0.72 (0.34-1.53)	0.85 (0.37-1.97)	
Drug sensitivity								
Fully sensitive	356/868 (41.0)	1	1	0.64	288/800 (36.0)	1	1	0.74
Drug-resistant	21/46 (45.7)	1.21 (0.67-2.19)	1.17 (0.61-2.25)		16/41 (39.0)	1.14 (0.60-2.17)	1.13 (0.55-2.32)	

Footnotes

[1]Data shown for four main lineages (excludes West Africa 1 and 2)

[2]Comparison of extrapulmonary TB cases only versus pulmonary TB only (concurrent pulmonary-extrapulmonary cases excluded)

[3]Comparison of extrathoracic TB cases only versus pulmonary TB only (concurrent pulmonary-extrapulmonary cases excluded)

[4]Models mutually adjusted for year of notification, season of notification, age, gender, location of birth, time since arrival in the UK, ethnicity, TB lineage, HIV status, past history of TB and drug sensitivity

Table 6.7 Univariate and multivariate association of demographic, clinical and temporal factors with lymph node tuberculosis

Variable	Lymph node TB Only[2] (n=204)	Unadjusted OR (95% CI)	Adjusted OR[3] (95% CI)	p
Period				
2003-2004	42/180 (23.3)	1	1	0.54
2005-2006	61/227 (26.9)	1.21 (0.77-1.90)	1.03 (0.62-1.72)	
2007-2008	70/239 (29.3)	1.36 (0.87-2.12)	1.39 (0.83-2.32)	
2009-2010	31/115 (27.0)	1.21 (0.71-2.08)	1.07 (0.57-2.00)	
Season				
Winter	34/152 (22.4)	1	1	0.003
Spring	46/204 (22.6)	1.01 (0.61-1.67)	0.79 (0.45-1.40)	
Summer	66/188 (35.1)	1.88 (1.16-3.05)	2.03 (1.15-3.57)	
Autumn	58/217 (26.7)	1.27 (0.78-2.06)	1.12 (0.64-1.96)	
Age categories n (%)				
Under 16	4/22 (18.2)	1[2]	1	0.008
16-25	47/212 (22.2)	1.28 (0.41-3.97)	1.22 (0.36-4.11)	
26-35	55/175 (31.4)	2.06 (0.67-6.38)	1.83 (0.53-6.35)	
36-45	40/132 (30.3)	1.96 (0.62-6.15)	3.10 (0.87-11.08)	
46-55	24/66 (36.4)	2.57 (0.78-8.49)	4.66 (1.15-18.77)	
Over 55	34/154 (22.1)	1.28 (0.40-4.02)	1.90 (0.50-7.17)	
Gender				
Male	78/392 (19.9)	1	1	0.01
Female	126/369 (34.2)	2.09 (1.50-2.90)	1.92 (1.31-2.81)	
Country of birth/time since entry				
UK born	29/258 (11.2)	1	1	0.04
Foreign born/<1 year	6/21 (28.6)	3.16 (1.14-8.78)	1.36 (0.41-4.59)	
Foreign born/1-5 years	80/228 (35.1)	4.27 (2.66-6.85)	2.14 (1.21-3.77)	
Foreign born/6-10 years	22/55 (40)	5.26 (2.71-10.22)	2.01 (0.93-4.36)	
Foreign born/>10 years	57/170 (33.5)	3.98 (2.41-6.57)	1.01 (0.50-2.04)	
Foreign born/time not known	10/29 (34.5)	4.16 (1.76-9.8)	1.72 (0.64-4.59)	
Ethnicity				
White	1/130 (0.8)	1	1	<0.0001
Indian Subcontinent	147/407 (36.1)	72.93 (10.09-527.06)	74.26 (9.5-580.18)	
Afro-Caribbean	44/178 (24.7)	42.36 (5.75-311.93)	33.26 (4.16-265.66)	
Oriental/Other Asia	2/18 (11.1)	16.13 (1.38-187.97)	10.97 (0.82-147.5)	
Other	10/28 (35.7)	71.67 (8.66-593.37)	54.47 (5.97-496.69)	
Lineage[1]				
East Asian	37/89 (41.6)	1	1	0.01
Euro-American	66/341 (19.4)	0.34 (0.20-0.56)	0.48 (0.27-0.86)	
East African Indian	66/237 (27.8)	0.54 (0.33-0.90)	0.37 (0.20-0.66)	
Indo-Oceanic	34/90 (37.8)	0.85 (0.47-1.55)	0.55 (0.28-1.09)	

Employment status				
Unemployed	22/86 (25.6)	1		
Retired	9/51 (17.6)	0.62 (0.26-1.48)		
Employed/housewife	94/278 (33.8)	1.49 (0.86-2.56)		
Student/child	16/77 (20.8)	0.76 (0.37-1.59)		
HIV status				
Negative/Unknown	204/757 (27.0)	-		
Positive	0/4 (0.0)			
Previous TB				
No	197/730 (27.0)	1	1	0.99
Yes	7/31 (22.6)	0.79 (0.33-1.86)	1.00 (0.39-2.61)	
Drug sensitivity				
Fully sensitive	189/701 (27.0)	1	1	0.71
Drug-resistant	10/35 (28.6)	1.08 (0.51-2.30)	0.85 (0.37-1.98)	

Footnotes

[1]Data shown for four main lineages (excludes West Africa 1 and 2)

[2]Comparison of lymph node TB cases only (intra- and extrathoracic) versus pulmonary TB only (concurrent pulmonary-extrapulmonary cases excluded)

[3]Models mutually adjusted for year of notification, season of notification, age, gender, location of birth, time since arrival in the UK, ethnicity, TB lineage, past history of TB and drug sensitivity

Discussion

In this analysis of a large, prospectively collated, dataset from an ethnically-diverse high-income setting I analysed the geographic associations of the lineages causing active TB and the association of lineages with different clinical phenotype. I found that the distribution of *Mycobacterium tuberculosis* lineages was geographically, and ethnically, restricted though differences in lineages were also evident between UK-born and foreign-born Non-White individuals. Even after adjustment for demographic factors such as ethnicity and HIV, the Euro-American and East African Indian lineages were significantly less likely to cause extrapulmonary TB whereas the East Asian lineage was associated with extrapulmonary disease.

Overall, the relative occurrence of the individual lineages - Euro-American, East African Indian, Indo-Oceanic, East Asian and West African1/2 (in decreasing order of frequency) in this cohort was similar to that seen in other UK centres[335,336] but different from other settings.[331,333,346] This likely reflects the different pattern of migration to the UK, through colonial links with the Indian Subcontinent and Sub-Saharan Africa, as compared to other high-income settings.[180]

I found that the main lineages in the current study were geographically associated: Euro-American with Europe/Americas/Africa, East African Indian with the Indian Subcontinent/East Africa, Indo-Oceanic with the Indian Subcontinent/East Africa/Asia and East Asian with the Indian Subcontinent/East Africa/Asia. Our findings are broadly in line with previous studies[331,333,335] although the relatively high proportion of individuals in our cohort from the Indian Subcontinent, as compared to the very small proportion from East, and Southeast, Asia may have masked the association of these latter regions with the Indo-Oceanic and East Asian lineages – as documented by other UK based studies.[335,336] Conversely, it is possible that North American studies which had a relatively small proportion of isolates from individuals born in the Indian Subcontinent may have underestimated the association of this region with the Indo-Oceanic and East Asian strains.[331,333]

This analysis highlighted an important shortcoming of merely restricting analysis of lineage association to regions and countries of origin (or birth). Whilst this may be suitable for ethnically homogeneous settings, I found that this did not capture the heterogeneity seen in settings such as the

UK where a subsection of the population will be UK born but from a minority ethnic group. When I examined associations between lineage and ethnic group, I found that the Euro-American lineage was strongly associated with White and Afro-Caribbean individuals, East African Indian and Indo-Oceanic with Indian Subcontinent ethnicity and East Asian with Oriental/Other Asia ethnicity. Similar results were found by Evans et al, in a UK study, who used a software algorithm to classify individuals by name into distinct cultural ethnic groups.[336] In a North American study, Gagneux et al found that US-born individuals of Non-White ethnicity (mainly Chinese and Filipino) generally had the same lineages as those individuals born in China and the Philippines.[331] This close association of lineages with self-reported ethnicity, which is an accurate marker of ancestry,[429] adds weight to the argument of host-bacteria co-evolution. Conversely, it could possibly reflect infection with similar lineages following transmission within ethnic communities in the UK, after travel to countries of origin to visit friends and relatives or visits from family based overseas to the UK.[430] However, stratification by country of birth and ethnicity revealed that foreign-born individuals of Indian and Afro-Caribbean ethnicity were significantly less likely to be infected with the Euro-American strain as compared to their UK born compatriots. This may reflect ongoing transmission from the White ethnic group who are predominantly associated the Euro-American lineage but is a poorly studied area which requires further attention.

In this study I found that certain lineages, even after multivariate adjustment, were more associated with specific clinical phenotypes. With East Asian strain as a reference, the Euro-American and East African Indian lineages were both negatively associated with extrapulmonary tuberculosis and, therefore, more associated with pulmonary tuberculosis. This was particularly marked when comparing extrapulmonary, extrathoracic and pulmonary only disease. Previous work on delineating the phenotypic association of these two lineages has been relatively limited and small-scale. Caws and colleagues showed in a Vietnamese population that the Euro-American lineage was more likely to cause pulmonary tuberculosis as compared to TB meningitis.[342] However, the number of Euro-American isolates in their study was small and the population ethnically homogeneous thereby preventing an analysis of the relative impact of host. More recently, Lari and colleagues found that the Haarlem strain (which falls within the Euro-American lineage) was significantly associated with

pulmonary disease although they did not adjust for demographic variables in their multivariate analysis and this lineage was not predominant.[346] The current work confirms in a large dataset that the Euro-American lineage is predominantly associated with pulmonary disease and, taken together with previously published work, suggests that this lineage is less likely to disseminate and cause disease in extrapulmonary sites. Reasons for this remain unclear although previous authors have suggested that this occurs due to an inability to produce phenolic glycolipid – a highly bioactive lipid which has been implicated in inhibiting the innate immune system and thus facilitating extrapulmonary dissemination.[342,431,432]

Less clear is the phenotypic association of the East African Indian lineage. Although I found it was negatively associated with extrapulmonary tuberculosis, the literature is conflicting. In an Italian study, the Central Asian lineage (akin to the East African Indian lineage) was associated with extrapulmonary tuberculosis although the absolute numbers with this lineage was very small (2.6% of the cohort) and the authors did not adjust for ethnicity or other demographic variables.[346] In a recent small study from Sweden, Svensson and colleagues also found that the Central Asian lineage was associated with extrapulmonary disease although the association was only borderline significant, the number of Central Asian isolates was small, individuals were categorised by geographic origin rather than ethnic group (which may have masked heterogeneity in disease patterns) and they failed to adjust for demographic variables which are known to influence disease type – such as sex.[34,305,313,347] In addition, the authors considered any extrapulmonary involvement as extrapulmonary disease (in other words those with concurrent pulmonary/extrapulmonary involvement) making direct comparisons with our study, where I only considered exclusively pulmonary and extrapulmonary cases, limited. By contrast, two studies from Pakistan, where the Central Asian strain was the predominant lineage, found that the lineage more commonly caused pulmonary disease although the difference was not statistically significant.[348,349]

With the Euro-American lineage as the reference, I found that the East Asian lineage was significantly associated, on multivariate analysis, with extrapulmonary disease. The East Asian lineage has been extensively studied and there is some consensus, albeit limited and from small studies,[323] that it is preferentially associated with extrapulmonary disease.[343-345] Kong et al in two studies found that

the Beijing lineage (akin to the East Asian lineage) was significantly associated with extrathoracic disease although the absolute numbers of individuals with the lineage were very small making it difficult to draw strong conclusions.[343,344] In a South African study of children only, Hesseling and colleagues found that the Beijing lineage, as compared to the Latin-American lineage, was associated with extrathoracic disease although their classification of extrathoracic disease differed from the current study.[345] By contrast other studies from South Africa,[351] Sweden,[347] Italy[346] and Holland[352] have found no association between the East Asian lineage and clinical phenotype. In addition, in contrast to previous studies, I found no association between East Asian lineage and drug resistance,[433-435] HIV infection[435] or more aggressive disease.[350]

I found no association between the Indo-Oceanic lineage and extrapulmonary disease. Previous work has been conflicting; a small study from the US found no link between this lineage and pattern of disease[343] whilst a slightly larger study found that it was associated with extrapulmonary disease although the authors did not correct for potential confounders and some of the other genotype-phenotype associations in that study (Beijing lineage associated with pulmonary tuberculosis) appeared to contradict the published literature.[347]

Although this study found lineages associate with clinical phenotype, it is over-simplistic to assume that TB lineage has the only impact on disease patterns. In reality, the clinical spectrum of disease will be the end result of an "interaction trinity" between host, environment and mycobacterial lineage. However, the relative importance of these factors can only be reliably explored in ethnically heterogeneous populations.[436] This is partly highlighted in the current analysis by the strong association between non-White ethnicity (especially Indian Subcontinent and Afro-Caribbean groups) and extrapulmonary disease. Indeed, I found that with mutual adjustment in a multivariate model ethnicity was more strongly associated with phenotype than lineage. My finding corroborates previous observations from the US,[314] UK,[33] Netherlands,[34] Germany[313] and Canada – although these previous reports did not take *M. tuberculosis* lineage differences into account.[303] This suggests that the host (and/or host-environment interaction) plays a more important role in determining clinical phenotype than mycobacterial lineage. The difficulty remains in disentangling whether it is the host per se (in other words genotype) or whether the host is merely a proxy for another factor - possibly

environmental (such as vitamin D).[317] This is exemplified by the situation in individuals of Indian Subcontinent ethnicity. It is known that this group of individuals are predominantly associated with the East African Indian lineage[331,333] which, in turn, I have shown is predominantly associated with pulmonary disease. This is confirmed in their countries of origin, where with this host-strain interaction, the predominant clinical phenotype is, indeed, pulmonary.[103] However, following migration to high-income countries, where the host (and strain) should remain unchanged, the clinical phenotype changes and these individuals are now very strongly associated with extrapulmonary disease. In effect the host and strain have remained the same but some factor, possibly environmental (such as vitamin D through reduced sunlight exposure), is now playing a role and perhaps allowing a pulmonary associated strain to disseminate and clinically present as extrapulmonary disease. This hypothesis is speculative but further epidemiological and laboratory work should focus on this area.

This study had several limitations. One of the main limitations was lineage assignment. Although I used 15 loci MIRU-VNTR (this was the standard method at the time) via an online database (MIRU-VNTRplus), and previously published literature, to assign lineages to isolates, a proportion could still not be definitively classified into any of the major lineages. The demographic and clinical profile of these individuals did not differ from the cohort that was analysed but I cannot rule out the potential of bias being introduced. In addition, our method of lineage assignment may have resulted in bias through misclassification of strain types. However, the strength and direction of the associations, even after multivariate analyses, make this less likely. Nonetheless it would be advantageous to use the newer 24 loci MIRU-VNTR in future.

In the final analysis I restricted the regression analyses to the four major lineages in our cohort (East Asian, Euro-American, East African Indian and Indo-Oceanic) as the numbers of isolates from the West African 1 and 2 lineages was extremely small. Therefore I could make no definitive conclusions about these lineages and their phenotypic associations should be a focus for future work.

Similarly, I classified, for the purposes of the detailed regression analyses, cases as exclusively pulmonary or extrapulmonary – thereby excluding those individuals with concurrent disease possibly resulting in some associations being missed.

As an observational study, albeit with large numbers, the analyses and conclusions were dependent on the variables that were collected. I cannot rule out that information on potential confounding variables was not recorded. One such variable is HIV status. This was inconsistently recorded in the dataset as it has been in many national surveillance systems[34,314,347,437] although its relative importance in determining clinical phenotype in this predominantly Indian Subcontinent study population is uncertain as previous UK-based work has found TB-HIV coinfection is low[438] and that that there is no association between HIV and pattern of disease (albeit in the post anti-retroviral therapy era).[33] In addition it would have been helpful to supplement host demographic data with information on host genotype (for example vitamin D receptor polymorphisms) and specific environmental factors (for example vitamin D levels) which have previously been shown to be associated with tuberculosis.[317]

In conclusion, although *Mtb* lineages, which are geo-ethnically restricted, can be associated with specific clinical phenotypes, host ethnicity appears to be more important in determining the clinical pattern of tuberculous disease, at least in the case of Indian subcontinent ethnicity and extrathoracic and extrapulmonary disease. Future work should integrate detailed host demographic data with host genotypic data, such as known TB susceptibility loci, and environmental data for factors associated with tuberculosis, such as smoking and vitamin D levels.

Chapter 7 Vitamin D deficiency plays a role in determining the clinical phenotypic presentation of tuberculosis

Introduction

In the previous chapter, where the focus was on demographic and mycobacterial factors, I found that *Mycobacterium tuberculosis* lineages, which are geo-ethnically restricted, are associated with specific clinical phenotypes but host factors (especially ethnicity) appear to be more, and indeed most, strongly associated with observed patterns of tuberculous disease. Globally, the most important demographic risk factor for extrapulmonary TB is HIV infection.[35,305] Given that extrapulmonary TB is increasingly common as HIV-induced immunosuppression advances,[309] it may be inferred that extrapulmonary disease in a non-HIV setting may reflect impairment of host responses that mediate bacterial containment in-vivo. Other host and environmental factors (which thus far have been very poorly studied) found to be associated with extrapulmonary TB suggest a potential role for innate immunity in the prevention of extrapulmonary dissemination. Host (genetic) factors implicated in determining the clinical spectrum of disease include, amongst others, polymorphisms in the vitamin D receptor,[317,318] IL-1β,[318,319] Toll-like receptor 2[318] and the P2X7 gene.[321] Environmental factors, such as vitamin D (25-hydroxycholecalciferol), have been shown to modulate macrophage function[439] and deficiency has been associated with an increased susceptibility to TB in individuals with a particular vitamin D receptor genotype[317,440] but it is unknown whether this independently relates to disease phenotype by increasing the risk for extrapulmonary TB.

Epidemiological data from high-income countries (including the UK, US, Canada and the Netherlands) shows that there has been a shift from a pulmonary to extrapulmonary pattern of disease[34,118,303,304] which has primarily been attributed to the high, and increasing, proportion of extrapulmonary cases amongst the foreign-born ethnic minority population.[34,118,303,304] Therefore, understanding the factors underlying this disproportionate clinical pattern of disease in the foreign-born immigrant population may provide additional insights into the relatively understudied environmental and demographic contributions to immune containment and clinical disease phenotype.

In this chapter, building on the work of the previous chapter (chapter six) where the relative association of demographic and mycobacterial factors with clinical phenotype was explored, I present

the results of a detailed analysis of the epidemiology of active TB, in two independent Northern hemisphere high-income countries, in different ethnic groups to determine what, if any, demographic and environmental factors including levels of sunlight (a proxy for vitamin D) and actual vitamin D levels in TB patients are important in determining the patterns of TB disease that are seen in immigrant, and non-immigrant, populations.

Methods

Study design and description of data sources

This study utilised routine anonymous active TB surveillance data prospectively notified in two independent high-income settings – Birmingham/Solihull, UK and US CDC.

Birmingham/Solihull are situated in the West Midlands, have a population of 1.2 million[409] and are made up of four distinct primary care organisations. Between 2007 and 2009, the 3-year average TB notifications and incidence ranged from 18-241 and 9-88 (per 100000 population per year) respectively.[393] All TB cases are managed and recorded by a centralised Chest clinic database (set up and maintained by Dr. John Innes) which allows ascertainment of notified cases between 1980 and the present.

To confirm that any patterns found during the study were not only UK-specific, I further analysed data from an independent US dataset - the publicly available US TB surveillance dataset (Online Tuberculosis Information System - OTIS http://wonder.cdc.gov/tb.html) which holds aggregate data (individual level information is not publicly available) for all verified cases of active TB in the US between 1993 and 2008.[441]

Study populations and data variable collection

I included all cases of active TB diagnosed between January 1st 1980 and December 31st 2009 (Birmingham and Solihull) and January 1st 1993 and December 31st 2008 (US CDC) with complete data on age, sex, country of birth (whether local- or foreign-born), ethnicity and site of disease; patients with missing information for one or more of these variables were excluded from analysis.

For both datasets information was retrieved on date of notification, age, sex, local/foreign-born, ethnicity, time since entry (only applies to foreign-born immigrants and calculated as time between arrival in the UK/US and diagnosis of active TB), site of disease, HIV status, culture result and drug sensitivity. Certain information was only available from one dataset: specific organs involved (Birmingham only) and state of notification (US only).

Routine HIV testing of patients diagnosed with active TB is highly inconsistent in the UK and this was reflected by this variable being inconsistently recorded in the Birmingham dataset. Therefore, I considered patients either as HIV positive (if this was recorded) or as negative/unknown (for all other individuals).

In the UK datasets, ethnicity was broadly defined in line with the Office for National Statistics classification[428] (five ethnic groups: White, Indian Subcontinent, Afro-Caribbean, Oriental/Other Asia, Other). Ethnicity in the US dataset was predefined into five categories (Hispanic or Latino, White, American Indian or Alaska Native, Asian/Pacific Islander and Black/African American).

To further compare and explore disease patterns in local-born (either UK or US) ethnic groups versus foreign-born ethnic groups I created a composite variable "country of birth/ethnicity" where I subcategorised individuals as being local/foreign-born and from different ethnic groups.

To investigate the effect of time since immigration on patterns of disease I also created a composite variable "country of birth/time since entry" as per previous authors[33] which subdivided individuals into local and foreign-born, with the foreign-born further subdivided by time since entry.

The potential effect of sunlight (a proxy for vitamin D exposure) on state-wide patterns of TB was investigated by linking state specific notifications in the US TB dataset with climatic data from the US National Climatic Data Centre/NASA on the annual average hours of sunshine in all 48 continental states (data available for 1871-1990).[442,443]

Vitamin D study population, measurement of vitamin D and definition of vitamin D deficiency

Assessment of the impact of vitamin D on disease patterns was undertaken through an independent population of active TB patients at St. Mary's hospital (London, UK) who have serum 25-hydroxycholecalciferol concentrations measured either before, or soon after, commencement of anti-tuberculous therapy using an immunoassay (Diasorin Liaison, Diosorin Ltd, Stillwater, Minnesota, USA).

I included, and obtained data on, all cases of active TB recruited between November 1st 2007 and 30th June 2011 (with complete demographic and clinical data) where the serum 25-hydroxycholecalciferol sample had been drawn before, or within 30 days, of commencing anti-tuberculous therapy. Information was retrieved as from the Birmingham and CDC datasets (see earlier) although additional data was obtained on the season (Winter – December-February; Spring – March-May; Summer – June-August; Autumn – September-November) of notification as well as concentration (nmol/L), of serum 25-hydroxycholecalciferol. For the current analysis I defined profound 25-hydroxycholecalciferol deficiency as a serum concentration of <20 nmol/l in keeping with previous literature.[444-446]

Definitions of patterns of tuberculous disease

Active TB cases were initially defined by the major sites of disease into three distinct clinical patterns: pulmonary only (only lung parenchyma involved), extrapulmonary only (only one or more extrapulmonary site(s) involved) and both pulmonary and extrapulmonary (pulmonary disease and one or more extrapulmonary sites involved concurrently). This broad classification was only used to describe overall disease distribution for the cohort. However, for the more detailed comparative analyses (such as temporal trends, patterns between different demographic groups and regression modelling) I adopted the approach taken by Peto[314] and others[34,310] in excluding the concurrent pulmonary and extrapulmonary TB category which cannot be definitively assigned to a specific category (and therefore are likely to result in misclassification bias).

Extrapulmonary sites of disease (either with or without pulmonary TB) included: intrathoracic lymph nodes, extrathoracic lymph nodes, bone and/or joint, central nervous system, pleural, peritoneal, genitourinary, intestinal, miliary, pericardial, soft tissue and other. If an individual had more than one extrapulmonary site involved all sites were included and therefore numbers would sum to greater than the total.

Data analysis

For both datasets (Birmingham and US CDC) data analysis was undertaken in similar steps.

I first analysed the demographic characteristics of the cohort. Continuous data were summarised with median and interquartile range (IQR), and compared using the non-parametric Mann-Whitney U-test. Categorical responses were expressed as a simple descriptive percentage and comparisons made using Pearson's chi-square test (or Fishers exact test if appropriate).

Temporal trends for the main sites of disease (pulmonary only and extrapulmonary only) were summarised by calculating the numbers and relative proportions of each disease type for distinct time periods for the Birmingham (six five-yearly time intervals - 1980-1984, 1985-1989, 1990-1994, 1995-1999, 2000-2004 and 2005-2009) and US CDC (four time intervals - 1993-1996, 1997-2000, 2001-2004 and 2005-2008) datasets; changes in proportions over time were calculated using the χ^2 test for trend.

Thereafter I calculated, and compared, the numbers (and proportion) of cases of each disease type stratified by local/foreign-birth and White/Non-White ethnicity to create three main groups of interest: local-born White ethnicity, local-born Non-White ethnicity and foreign-born Non-White ethnicity. Two way comparisons were undertaken using Fisher's exact test. In addition for the foreign-born (non-White) population I also examined differences in the proportion of cases that were pulmonary and extrapulmonary stratified by time since entry to the receiving country using the χ^2 test for trend. Individuals who were foreign-born of White ethnicity were not specifically examined as they accounted for a relatively small proportion of cases in all the datasets

To explore factors associated with extrapulmonary involvement I compared individuals with exclusively extrapulmonary versus pulmonary patterns of disease. For the Birmingham dataset (but not US CDC), where individual level data was available, I undertook separate regression modelling for the whole cohort and for the non-White ethnic groups. Univariate association of factors individually associated with extrapulmonary tuberculosis only (compared against pulmonary cases only) was assessed using logistic regression and reported as crude odds ratios (OR) and 95% confidence intervals. To calculate adjusted odds ratios (and 95% CI) I mutually adjusted for the following factors: year, and season, of notification, age, gender, ethnicity, country of birth, time since arrival and HIV status. Interaction terms (age and time since entry) were assessed and found to be non-significant and

not included in the final multivariate models. For the US dataset, only aggregate data was available and therefore only univariate comparisons using logistic regression could be performed.

In the US dataset only I explored the potential impact of sunshine (a proxy for vitamin D levels) on patterns of TB disease. I first extracted mainland US state-specific data from the National Climatic Data Centre on annual hours of sunshine.[442] Although publicly available data was only available until 1987 I also cross-referenced this data against a more contemporary (1961-1990) sunshine climatic map[443] to ensure there were no significant discrepancies in sunshine hours. Where there was missing data or the data were very outdated I used the sunshine map. For each state I then calculated the median annual number of hours of sunshine. From the US CDC TB dataset I obtained state-specific data (overall and stratified into US-born White, US-born Non-White and Foreign-born Non-White demographic groups) on the numbers, and proportions, of cases that were exclusively pulmonary or extrapulmonary. Those states which reported no cases in any category (Maine, Montana, New Hampshire, Vermont and Wyoming) were excluded from this part of the analysis.

Using Spearman's rank, the correlation between sunshine hours and the proportion of cases that were extrapulmonary only was calculated for the whole cohort, US-born White, US-born non-White and foreign-born non-White individuals respectively. In addition, I calculated the median annual number of sunshine hours for the US as whole and categorised those states whose hours of sunshine were above the median (>2700 hours) as "sun high" and those equal or below as "sun low". Differences in the proportion of cases that were extrapulmonary only between "sun high" and "sun low" states were calculated using Fisher's exact test.

For the London vitamin D dataset, I used absolute serum 25-hydroxycholecalciferol concentrations except in individuals whose vitamin D measurement was below the lower limit of detection (15 nmol/L) where a value half of the lower limit (7.5 nmol/L) was used.[447] As vitamin D concentrations were found to be non-normally distributed, they were $\log_{10}$-transformed with geometric mean titres (and 95% confidence intervals) calculated by exponentiating the mean and the lower and upper limits of the 95% confidence intervals of the $\log_{10}$-transformed titres. Comparisons between groups were made using a one-way analysis of variance (on the log transformed concentrations) with Bonferroni correction, if appropriate. The proportions of subjects who were vitamin D deficient

(<20nmol/L) were compared between groups using Fisher's exact test. I further assessed the factors associated with extrapulmonary TB in this dataset using logistic regression and reported results as odds ratios (with 95% confidence intervals); in the multivariate model I adjusted for year, and season, of notification, age, gender, ethnic group, location of birth, time since arrival, HIV status and vitamin D status.

Analyses used STATA 9.2 and 12.0 (StataCorp, College Station, TX). All tests were two tailed; p-value of ≤ 0.05 was considered significant.

Results

Description of cohorts

Recruitment into the study for the Birmingham and US CDC cohorts is outlined in figures 7.1 and 7.2 respectively.

Figure 7.1 Flow chart of cases included from Birmingham dataset for data analysis

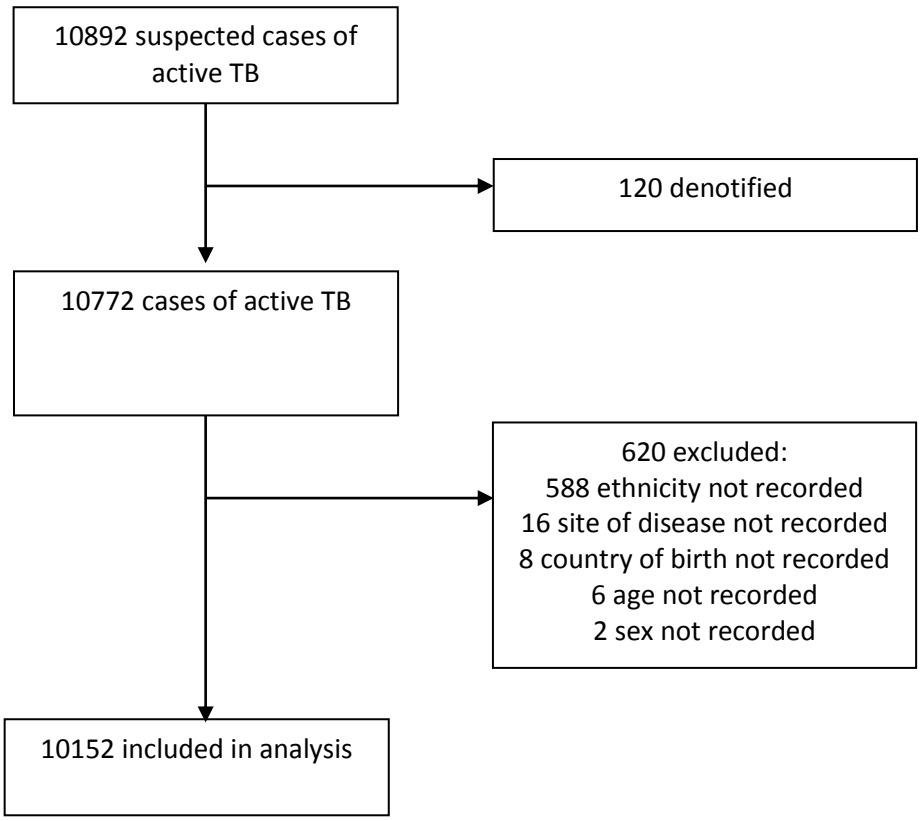
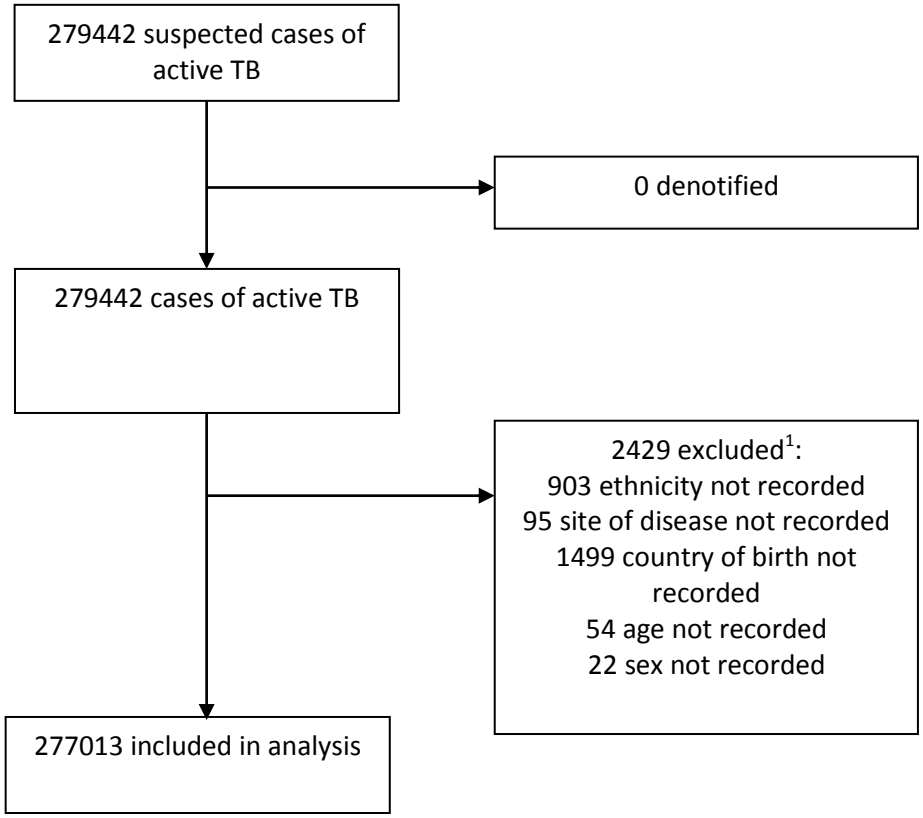


Figure 7.2 Flow chart of cases included from US Centres for Disease Control dataset for data analysis



Footnote

[1]Numbers sum to greater than 2429 (2573) as some individuals were excluded for more than one reason

The Birmingham cohort (table 7.1) primarily comprised young adults (median age 35.0 years (IQR 23.0-55.0 years), 38.9% were aged 16-35 years) and 51.7% were male. Overall 35.6% were UK-born – of whom 48.0% and 52.0% were of White and Non-White ethnicity respectively. Amongst the 64.4% who were foreign-born, where the commonest ethnic groups were Indian Subcontinent (75.9%) and Afro-Caribbean (14.3%), median time from arrival in the UK and clinical presentation with active disease was 9 years (IQR 3-22 years).

Individuals in the UK-born White ethnic group were significantly older than their UK-born Non-White (51 (IQR 30-68) years vs 18 (IQR 10-25) years) p=0.0001) and foreign-born Non-White

counterparts (38 (IQR 27-56) years, p=0.0001) who, in turn, were significantly older than the UK-born Non-White ethnic group (p=0.0001).

In total, there were 5590 (55.1%) cases of pulmonary TB only, 3799 (37.4%) extrapulmonary TB only and 763 (7.5%) concurrent pulmonary and extrapulmonary disease. Commonest sites of extrapulmonary disease (either alone or in conjunction with pulmonary disease) were extrathoracic lymph nodes (41.8%), pleura (11.7%) and intrathoracic lymph nodes (11.5%). Culture positivity was 46.8% overall but significantly higher in pulmonary cases only than extrapulmonary cases only (56.1% vs 32.8%, p<0.0001).

Demographic characteristics of the US CDC dataset (n=277013) are set out in table 7.2.

Table 7.1 Demographic characteristics of individuals with active tuberculosis in the Birmingham dataset

Variable	Birmingham (n=10,152)
Age (median, interquartile range)	35.0 (23.0-55.0)
Age categories	
Under 16	1264 (12.5%)
16-25	1960 (19.3%)
26-35	1990 (19.6%)
36-45	1358 (13.4%)
46-55	1101 (10.6%)
over 55	2479 (24.4%)
Gender	
Female	4902 (48.3%)
Male	5250 (51.7%)
Ethnicity	
White	1991 (19.6%)
Indian Subcontinent	6233 (61.4%)
Afro-Caribbean	1484 (14.6%)
Oriental/Other Asia	220 (2.2%)
Other	224 (2.2%)
Place of birth	
United Kingdom	3612 (35.6%)
Foreign-born	6540 (64.4%)
Time since entry to the UK (years)[1]	
<1	331 (5.7%)
1 - 5	1943 (33.3%)
6-10	818 (14.0%)
>10	2740 (47.0%)
Employment status[2]	
Unemployed	447 (11.4%)
Retired	334 (8.5%)
Employed/housewife	1670 (42.4%)
Student/child	1486 (37.7%)
HIV status[3]	
Negative	171 (88.6%)
Positive	22 (11.4%)
Previous TB[4]	
No	4777 (95.3%)
Yes	236 (4.7%)
Type of disease	
Pulmonary only	5590 (55.1%)
Pulmonary and extrapulmonary	763 (7.5%)
Extrapulmonary only	3799 (37.4%)
Site of extrapulmonary disease	
Intrathoracic lymph node	525 (11.5%)
Extrathoracic lymph node	1907 (41.8%)
Bone and joint	461 (10.1%)
Central nervous system	169 (3.7%)
Pleura	505 (11.7%)
Peritoneum	108 (2.4%)
Genitourinary	180 (4.0%)
Intestinal	212 (4.7%)
Miliary	198 (4.3%)
Pericardial	51 (1.1%)
Soft tissue	101 (2.2%)
Other	538 (11.8%)
Culture positive	
Culture negative	5398 (53.2%)
Culture positive	4754 (46.8%)

Drug sensitivity[5]	
Fully sensitive	1634 (91.8%)
Mono-drug resistant	116 (6.5%)
Multi-drug resistant	30 (1.7%)

Footnotes

[1]Only applies to foreign-born individuals; data available for 5832 individuals

[2]Data available for 3937 individuals

[3]Data available for 193 individuals

[4]Data available for 5013 individuals

[5]Data available for 1780 individuals

Table 7.2 Demographic characteristics of individuals with active tuberculosis in the US CDC dataset

Variable	CDC USA (n=277013)
Age categories	
Under 5	10217 (3.7%)
5-14	7123 (2.6%)
15-24	25534 (9.2%)
25-44	97349 (35.1%)
45-64	76262 (27.5%)
>64	60528 (21.9%)
Gender	
Male	173621 (62.7%)
Female	103392 (37.3%)
Ethnicity	
American Indian or Alaska Native	3532 (1.3%)
Asian or Pacific Islander	56962 (20.6%)
Black or African American	86697 (31.3%)
Hispanic or Latino	66934 (24.2%)
White, Non-Hispanic	62888 (22.7%)
Place of birth	
United States of America	153598 (55.4%)
Foreign-born	123415 (44.6%)
Time since entry to the US (years) [1]	
< 1 year	23897 (23.7%)
1-4 years	24990 (24.8%)
5-14 years	27467 (27.3%)
15+ years	24280 (24.1%)
Employment status[2]	
Unemployed	144308 (59.0%)
Employed	100345 (41.0%)
HIV status[3]	
Negative	101606 (77.9%)
Positive	28836 (22.1%)
Previous TB[4]	
No	260527 (94.8%)
Yes	14350 (5.2%)
Type of disease	
Pulmonary only	203449 (73.4%)
Extrapulmonary only	52040 (18.8%)
Pulmonary and extrapulmonary	21524 (7.8%)
Culture positive	
Yes	220941 (80.4%)
No	56072 (20.4%)
Drug sensitivity[5]	
Not multi-drug resistant	206274 (98.5%)
Multi-drug resistant	3154 (1.5%)
Resident in correctional facility[6]	
No	264422 (96.3%)
Yes	10237 (3.7%)

Footnotes

[1]Only applies to foreign-born individuals; unknown for 22781
[2]Unknown for 32360
[3]Unknown for 146571
[4]Unknown for 2136
[5]Only relevant to culture positive cases; unknown for 11513
[6]Unknown for 2354

Temporal trends in tuberculous disease

Trends in patterns of disease in the Birmingham cohort for selected ethno-demographic groups are outlined in table 7.3 and figure 7.3. Overall, for the cohort as a whole, during the study period (1980-2009) the combined number of pulmonary and extrapulmonary only cases (in other words with the concurrent pulmonary-extrapulmonary category excluded) increased by 7.3% from 1798 (1980-1984) to 1929 (2005-2009). However, during this same time period, cases of pulmonary only disease decreased by 26.1% whilst extrapulmonary only disease increased by 96.6% ($p<0.0001$). As a result, the proportion of cases that were exclusively extrapulmonary (as compared to pulmonary only) increased from 31.6% to 52.9% (χ^2 for trend <0.0001).

Temporal trends were, however, heterogeneous between different demographic groups. In the UK-born White group, overall case notifications decreased by 47.5% with relatively similar decreases amongst the pulmonary only (52.2%) and extrapulmonary only (45.1%) cases ($p=0.24$). By contrast, the number of cases amongst the UK-born and foreign-born Non-White ethnic groups increased by 49.6% and 28.7% respectively; pulmonary only cases decreased in both of these groups (by 0.97% and 10.9% respectively) whilst extrapulmonary only cases increased by 273.9% and 82.3% ($p<0.0001$) in the UK-born and Non UK-born Non-White ethnic groups respectively.

As a result of the changing pattern of TB notifications the proportion of cases that were classified as exclusively extrapulmonary (as compared to pulmonary only) for the UK-born White, UK-born Non-White and foreign-born Non-White ethnic groups increased from 17.2% to 19.3% (χ^2 for trend $p=0.34$), 18.4% to 45.7% (χ^2 for trend $p<0.0001$) and 42.4% to 60.1% (χ^2 for trend $p<0.0001$) respectively.

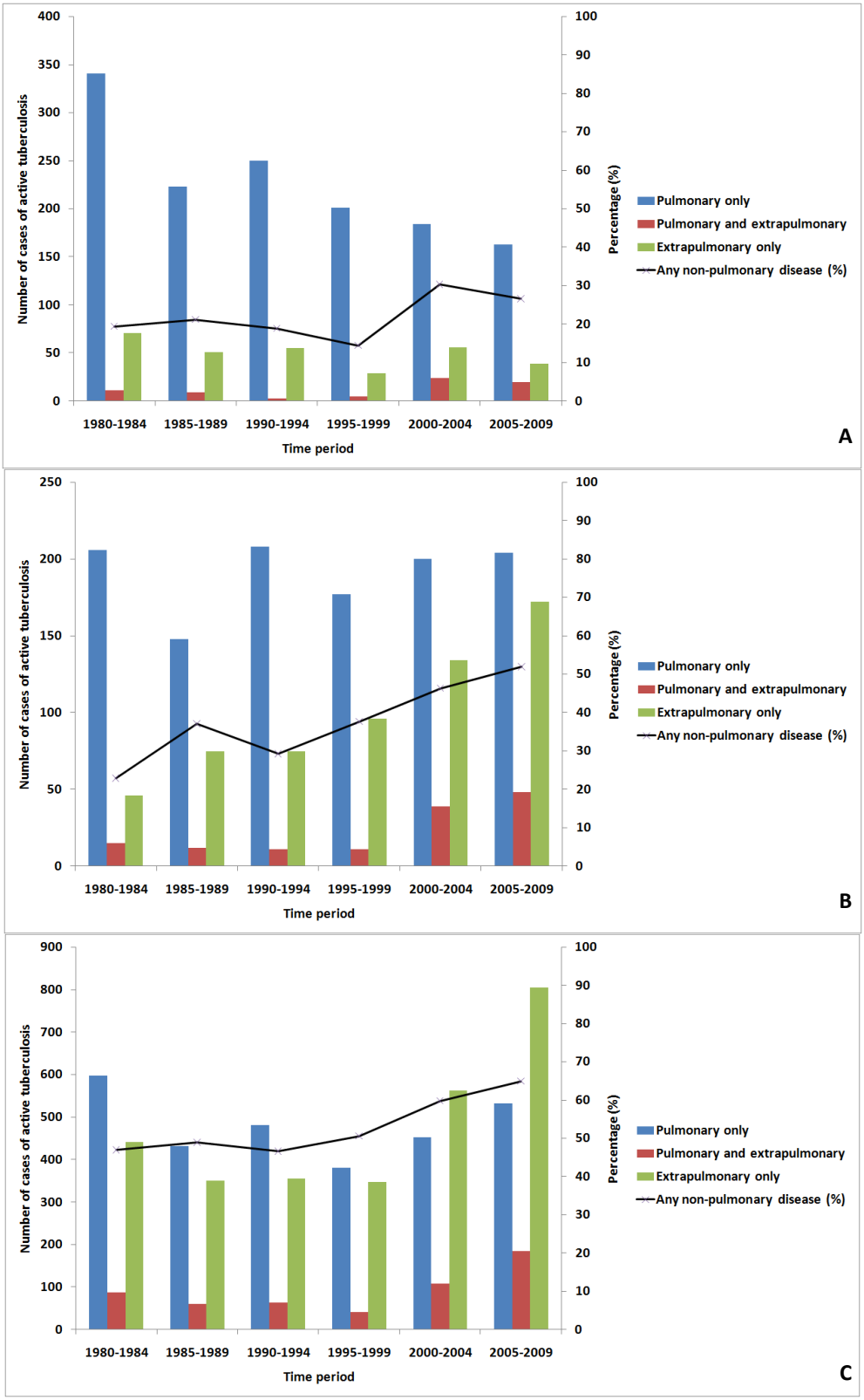
Table 7.3 Patterns of active tuberculosis in different demographic groups between 1980 and 2009 in the Birmingham dataset

Period	UK-born White (n=1735)			UK-born non-white ethnic groups (n=1877)			Foreign-born non-white ethnic groups (n=6284)		
	Pulmonary only (n=1362)	Pulmonary and extrapulmonary (n=72)	Extrapulmonary only (n=301)	Pulmonary only (n=1143)	Pulmonary and extrapulmonary (n=136)	Extrapulmonary only (n=598)	Pulmonary only (n=2875)	Pulmonary and extrapulmonary (n=547)	Extrapulmonary only (n=2862)
1980-1984	341 (80.6%)	11 (2.6%)	71 (16.8%)	206 (77.2%)	15 (5.6%)	46 (17.2%)	598 (53.1%)	88 (7.8%)	441 (39.1%)
1985-1989	223 (78.8%)	9 (3.2%)	51 (18.0%)	148 (63.0%)	12 (5.1%)	75 (31.9%)	431 (51.1%)	61 (7.2%)	351 (41.6%)
1990-1994	250 (81.2%)	3 (1.0%)	55 (17.9%)	208 (70.8%)	11 (3.7%)	75 (25.5%)	481 (53.4%)	64 (7.1%)	356 (39.5%)
1995-1999	201 (85.5%)	5 (2.1%)	29 (12.3%)	177 (62.3%)	11 (3.9%)	96 (33.8%)	380 (49.4%)	41 (5.3%)	348 (45.3%)
2000-2004	184 (69.7%)	24 (9.1%)	56 (21.2%)	200 (53.6%)	39 (10.5%)	134 (35.9%)	452 (40.3%)	109 (9.7%)	562 (50.0%)
2005-2009	163 (73.4%)	20 (9.0%)	39 (17.6%)	204 (48.1%)	48 (11.3%)	172 (40.6%)	533 (35.0%)	184 (12.1%)	804 (52.9%)

Footnotes

[1]Data not presented foreign-born White ethnic group (n=256)

Figure 7.3 Temporal trends in disease patterns amongst different ethno-demographic groups in Birmingham dataset



Footnote

[1](A) UK-born Whites (B) UK-born non-White ethnic groups and (C) Foreign-born non-White ethnic groups in the Birmingham dataset

Temporal trends for the US CDC database are outlined in table 7.4 and figure 7.4. Although overall tuberculosis notifications decreased by 43.2% during the study period (between the time periods 1993-1996 and 2005-2008), the decrease in pulmonary only cases (46.5%) was greater than for extrapulmonary only cases (27.8%). As a result of this slower reduction in the number of extrapulmonary cases, the proportion of cases that were exclusively extrapulmonary (as compared to pulmonary only) increased from 17.8% to 22.6% (χ^2 for trend $p<0.0001$). The heterogeneity seen between different demographic groups in the Birmingham dataset was also evident in the US dataset. Whilst the number of TB notifications decreased amongst all demographic groups, the reductions were greatest amongst the US-born White population (overall 66.7%, pulmonary only 66.8% and extrapulmonary only 66.2%) as compared to the US-born Non-White (overall 61.3%, pulmonary only 63.5% and extrapulmonary only 50.2%) and foreign-born Non-White group (overall 2.2%, pulmonary only 6.9% and extrapulmonary only 15.3% *increase rather than decrease*). The smaller reductions in extrapulmonary notifications (particularly amongst the Non-White ethnic groups) resulted in the proportion of exclusively extrapulmonary cases marginally increasing, for the US-born White group, from 14.7% to 14.9% (χ^2 for trend $p=0.43$) but more substantially for the US-born (16.6% to 21.4% (χ^2 for trend $p<0.0001$)) and foreign-born Non-White group (21.3% to 25.1%) (χ^2 for trend $p<0.0001$).

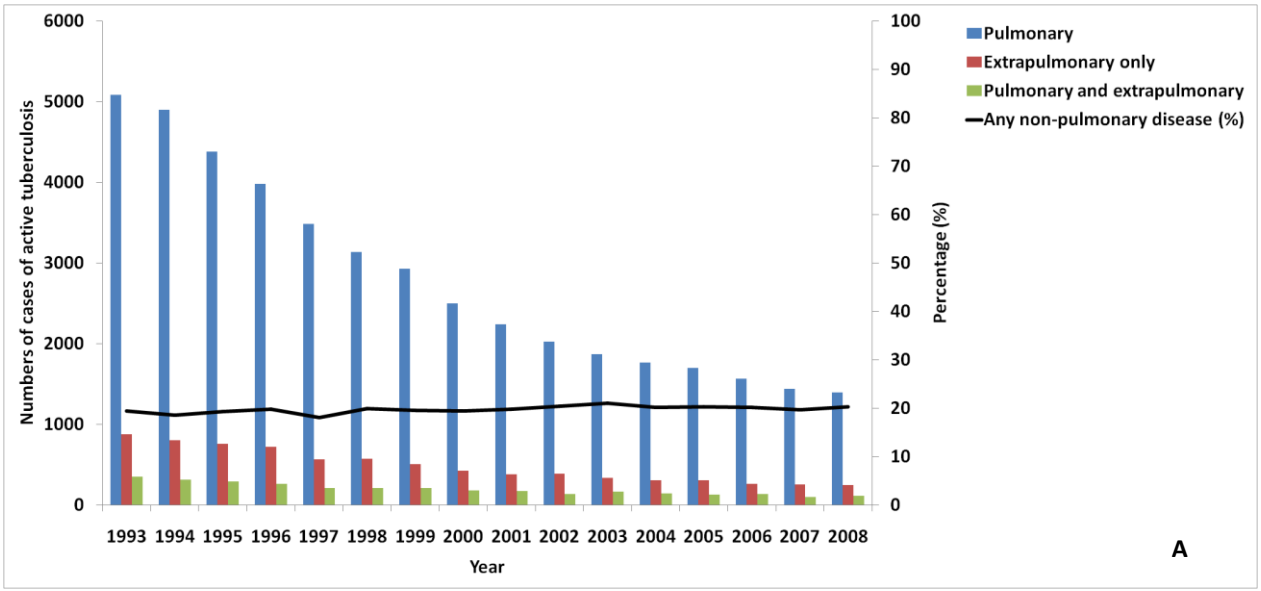
Table 7.4 Patterns of active tuberculosis in US CDC dataset stratified by time, country of birth and ethnicity

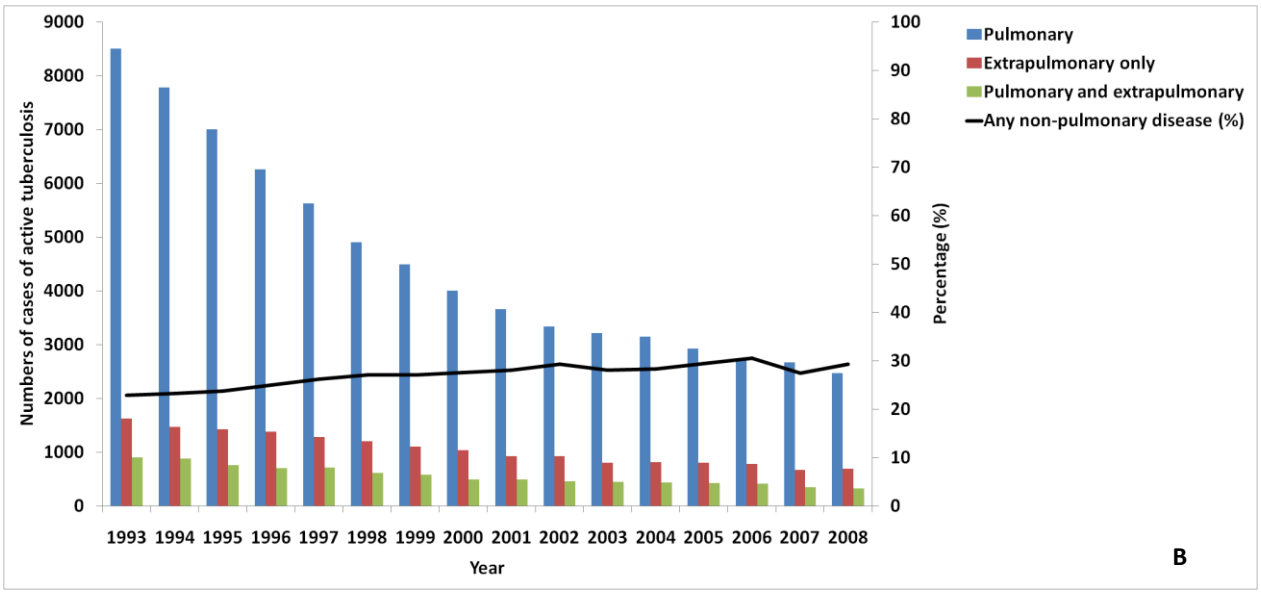
Period	US-born White, Non-Hispanic (n=55097)			US-born non-white ethnic groups (n=98501)			Non-US-born non-white ethnic groups (n=115624)		
	Pulmonary only (n=44350)	Extrapulmonary only (n=7672)	Pulmonary and extrapulmonary (n=3075)	Pulmonary only (n=72668)	Extrapulmonary only (n=16894)	Pulmonary and extrapulmonary (n=8939)	Pulmonary only (n=80921)	Extrapulmonary only (n=25694)	Pulmonary and extrapulmonary (n=9009)
1993-1996	18328 (80.8)	3149 (13.9)	1203 (5.3)	29534 (76.4)	5889 (15.2)	3233 (8.4)	21214 (73.8)	5753 (20)	1786 (6.2)
1997-2000	12039 (80.8)	2056 (13.8)	796 (5.3)	19017 (73.1)	4606 (17.7)	2386 (9.2)	19802 (69.9)	6349 (22.4)	2168 (7.7)
2001-2004	7891 (79.7)	1402 (14.2)	610 (6.2)	13346 (71.6)	3468 (18.6)	1821 (9.8)	20155 (68.3)	6957 (23.6)	2405 (8.1)
2005-2008	6092 (79.9)	1065 (14.0)	466 (6.1)	10771 (70.9)	2931 (19.3)	1499 (9.9)	19750 (68)	6635 (22.9)	2650 (9.1)

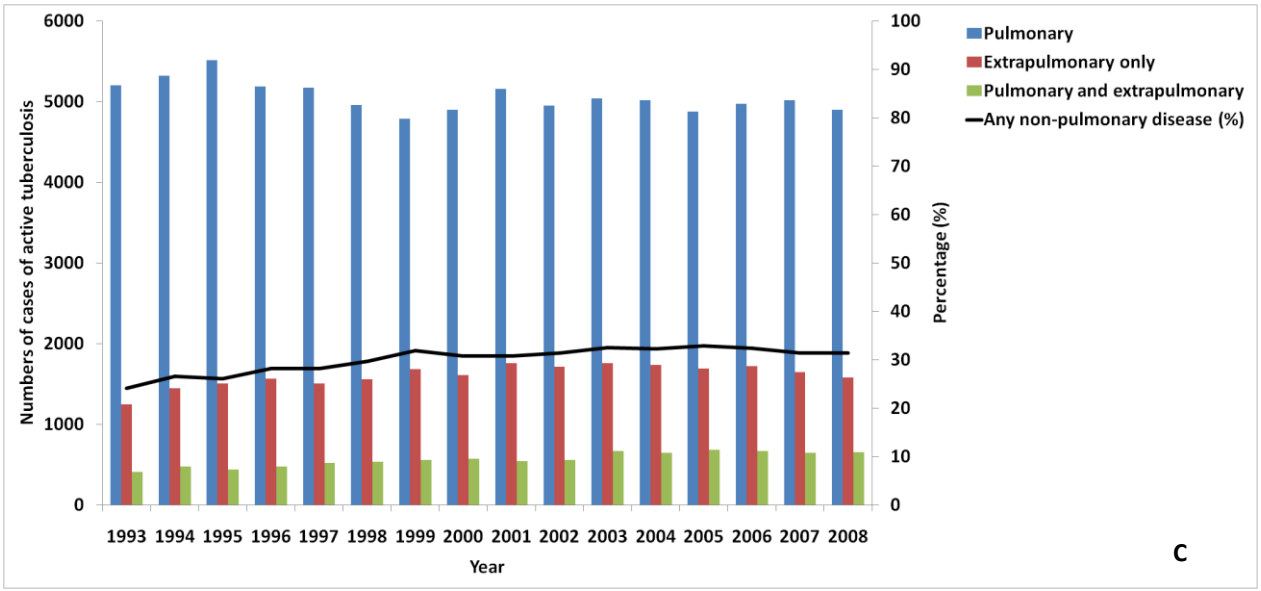
Footnotes

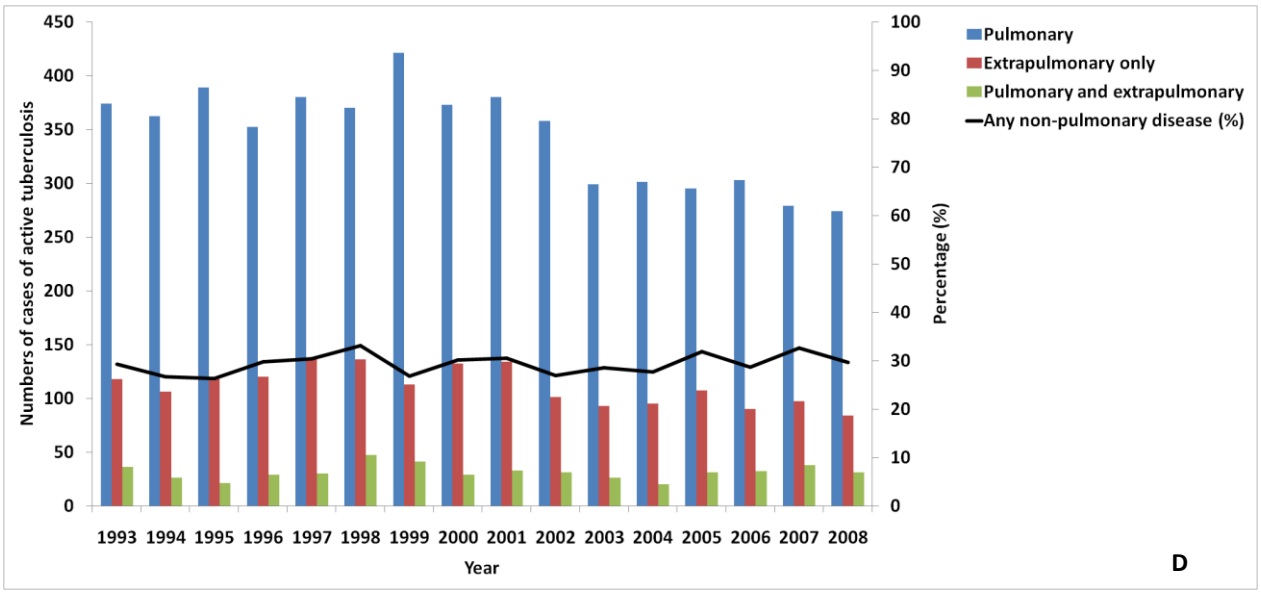
[1]Data not presented foreign-born White ethnic group (n=7791)

Figure 7.4 Temporal trends in patterns of disease amongst different ethno-demographic groups in the US CDC dataset









Footnotes

[1]US-born Whites, (B) US-born non-White ethnic groups, (C) Foreign-born non-White ethnic groups and (D) Foreign-born Whites in the US CDC dataset

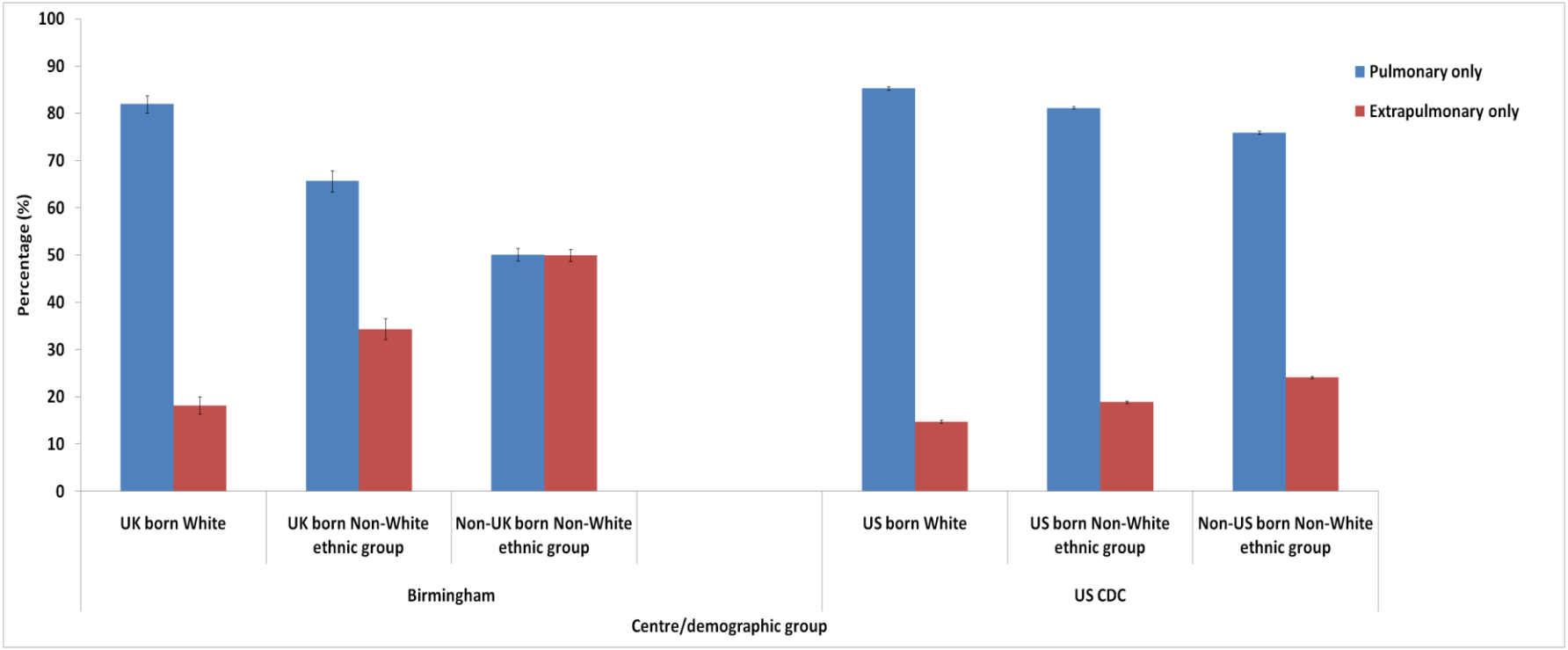
[2]Please note the differences in scales for absolute numbers of active tuberculosis cases

Patterns of disease amongst different demographic groups

Table 7.3 and figure 7.5 outline, for the Birmingham dataset, the proportion of cases that are pulmonary and extrapulmonary in different demographic groups. Individuals of UK-born White

ethnicity had a significantly lower proportion of extrapulmonary only disease (18.1%) as compared to individuals of UK-born Non-White ethnicity (34.4%) ($p<0.0001$) and both these groups had a significantly lower proportion of extrapulmonary disease as compared to individuals of foreign-born Non-White ethnicity (49.9%) ($p<0.0001$ for UK-born White and UK-born Non-White).

Figure 7.5 Patterns of tuberculosis stratified by location of birth (local or foreign) and ethnic group (White versus Non-White) for the Birmingham and US CDC datasets



Footnote

[1]The error bars represent the 95% confidence interval for each proportion

Table 7.4 and figure 7.5 describe the patterns of TB disease in the US CDC dataset. In general the US CDC dataset mirrored the pattern seen in the Birmingham dataset. US-born individuals of White ethnicity had a significantly lower proportion of extrapulmonary only disease (14.8%) compared to individuals of US-born Non-White ethnicity (18.9%) ($p<0.0001$) and both these groups had a significantly lower proportion of extrapulmonary disease as compared to individuals of foreign-born Non-White ethnicity (24.1%) ($p<0.0001$ for US-born White and US-born Non-White).

Patterns of disease amongst foreign-born individuals

Patterns of TB disease in foreign-born Non-White individuals by time since arrival in the UK/US for the Birmingham and US CDC datasets are set out in figures 7.6 and 7.7 respectively.

As the time between arrival in the receiving country (either the UK or US) and the development of active TB increased, the proportion of cases that were extrapulmonary increased and then stabilised (Birmingham - 24.9% <1year, 52.8% 1-5 years, 55.5% in 6-10 years, 50.0% >10 years after arrival; US CDC – 13.3% <1year, 27.3% 1-4 years, 27.6% in 5-14 years, 25.3% >14 years)(χ^2 for trend $p=0.004$ for UK and $p<0.0001$ for US) (see figures 7.6 and 7.7). Overall, foreign-born individuals who developed TB within the first year after arrival in the UK/US had a distinctly different pattern of disease, characterised by a significantly lower proportion of extrapulmonary disease, compared to foreign-born individuals who developed TB more than one year after arrival ($p<0.0001$ for both Birmingham and US). Foreign-born individuals, who developed TB within the first year after arrival, had a higher proportion of extrapulmonary TB than UK-born White individuals in the Birmingham cohort ($p=0.007$) but a lower proportion of extrapulmonary TB than US-born White individuals in the CDC cohort ($p<0.0001$). By contrast to the overall trends described above, foreign-born Non-White individuals had a significantly lower proportion of extrapulmonary TB than local-born Non-Whites ($p=0.001$ and $p<0.0001$ for Birmingham and US CDC respectively).

Figure 7.6 Patterns of tuberculosis stratified by ethnic group, country of birth and time since arrival in the UK for Birmingham cohort

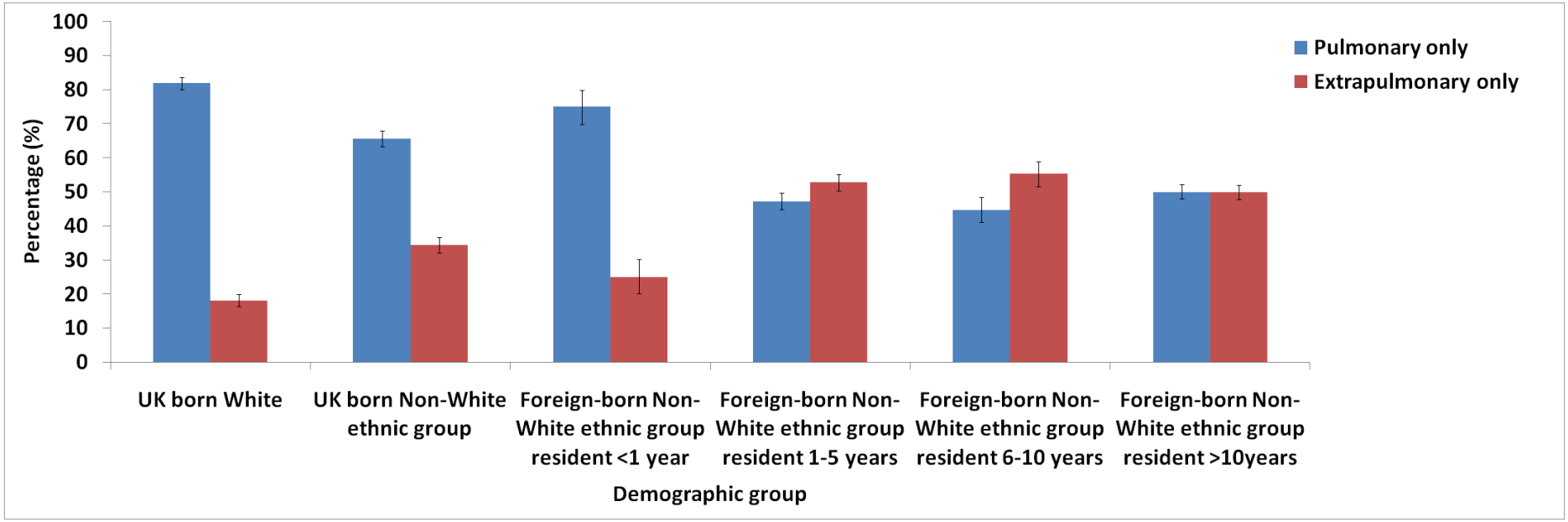
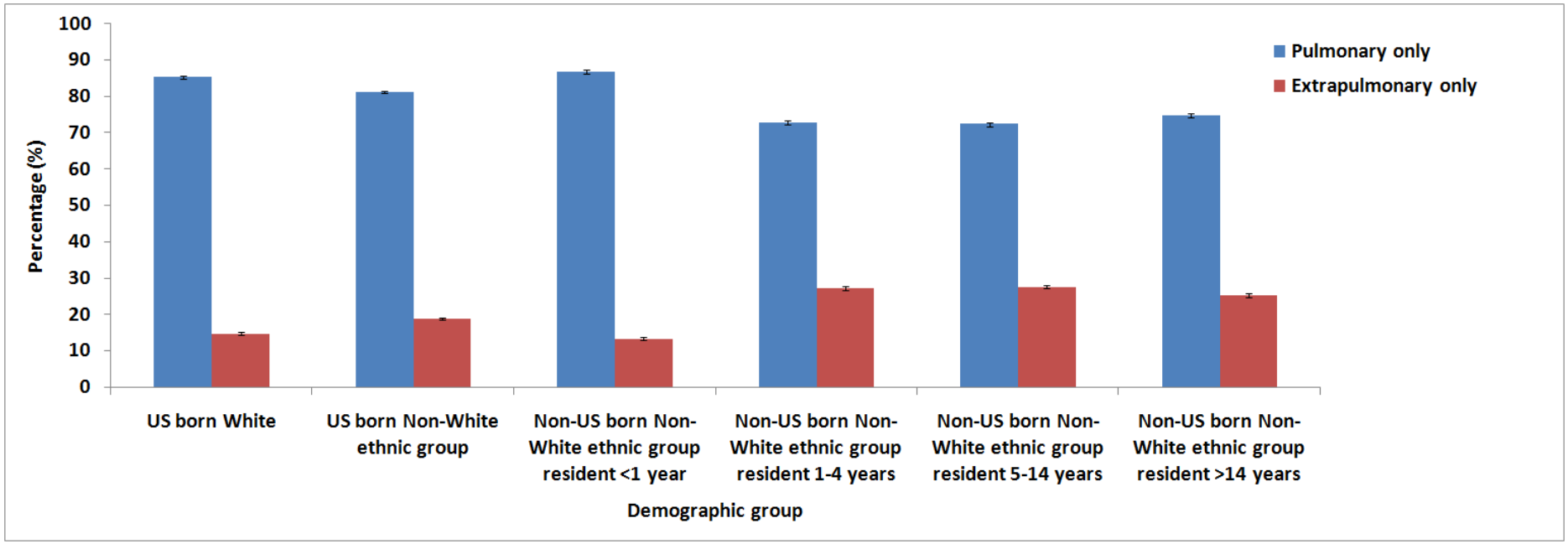


Figure 7.7 Patterns of tuberculosis stratified by ethnic group, location of birth and time since arrival in the US for the US CDC cohort



Factors associated with extrapulmonary tuberculosis

In the Birmingham dataset (table 7.5), multivariate analysis revealed that extrapulmonary tuberculosis was associated with later year of notification, increasing age, female gender, location of birth/ethnicity (UK born Non-White ethnicity and foreign-born Non-White ethnicity) and in addition, for the model restricted to the Non-White ethnic groups, location of birth/time since arrival (foreign-birth and increasing time between arrival and clinical presentation).

Univariate analysis of the US CDC dataset (table 7.6), which was only available as aggregate data and thus did not allow multivariate analysis, revealed that factors associated with extrapulmonary TB included later year of notification, increasing age, female gender, location of birth/ethnicity (UK birth Non-White ethnicity and Foreign-birth Non-White ethnicity), employment status, previous TB, HIV status (HIV-seropositivity), no past history of TB, drug sensitive disease and in addition, for the model restricted to the Non-White ethnic groups, location of birth/time since arrival (foreign-birth and increasing time between arrival and presentation of clinical TB).

Table 7.5 Demographic, clinical and temporal variables associated with different patterns of tuberculosis for Birmingham dataset

	Whole cohort (n=9389)[1]				Non-White ethnic groups (n=7478)[1]				
Variable	**Extrapulmonary TB only[1] (n=3799)**	**Unadjusted OR (95% CI)**	**Adjusted OR[2] (95% CI)**	**p-value**	**Variable**	**Extrapulmonary TB only[1] (n=3460)**	**Unadjusted OR (95% CI)**	**Adjusted OR[3] (95% CI)**	**p-value**
Period					**Period**				<0.0001
1980-1984	568/1798 (31.6)	1	1	<0.0001	1980-1984	487/1291 (37.7)	1	1	
1985-1989	487/1345 (36.2)	1.23 (1.06-1.43)	1.24 (1.06-1.46)		1985-1989	426/1005 (42.4)	1.21 (1.03-1.44)	1.28 (1.08-1.53)	
1990-1994	494/1471 (33.6)	1.09 (0.95-1.27)	1.09 (0.94-1.28)		1990-1994	431/1120 (38.5)	1.03 (0.88-1.22)	1.09 (0.92-1.3)	
1995-1999	475/1242 (38.2)	1.34 (1.15-1.56)	1.28 (1.09-1.50)		1995-1999	444/1001 (44.4)	1.32 (1.11-1.56)	1.41 (1.18-1.68)	
2000-2004	755/1604 (47.1)	1.93 (1.67-2.21)	1.85 (1.60-2.15)		2000-2004	696/1348 (51.6)	1.76 (1.51-2.06)	1.96 (1.67-2.31)	
2005-2009	1020/1929 (52.9)	2.43 (2.13-2.78)	2.24 (1.94-2.59)		2005-2009	976/1713 (57.0)	2.19 (1.89-2.53)	2.34 (2.01-2.74)	
Season					**Season**				
Winter	818/2118 (38.6)	1	1	0.37	Winter	732/1661 (44.1)	1	1	0.17
Spring	956/2404 (39.8)	1.05 (0.93-1.18)	0.99 (0.87-1.12)		Spring	876/1908 (45.9)	1.08 (0.94-1.23)	1.01 (0.88-1.16)	
Summer	1062/2581 (41.2)	1.11 (0.99-1.25)	1.04 (0.92-1.18)		Summer	979/2075 (47.2)	1.13 (1.00-1.29)	1.11 (0.97-1.27)	
Autumn	963/2286 (42.1)	1.16 (1.03-1.31)	1.09 (0.96-1.24)		Autumn	873/1834 (47.6)	1.15 (1.01-1.32)	1.14 (0.99-1.31)	
Age categories					**Age categories**				
Under 16	383/1167 (32.8)	1	1	<0.0001	Under 16	334/958 (34.9)	1	1	<0.0001
16-25	652/1828 (35.7)	1.13 (0.97-1.33)	0.80 (0.68-0.94)		16-25	634/1678 (37.8)	1.13 (0.96-1.34)	0.86 (0.72-1.03)	
26-35	923/1840 (50.2)	2.06 (1.77-2.4)	1.34 (1.13-1.60)		26-35	889/1651 (53.8)	2.18 (1.85-2.57)	1.42 (1.18-1.72)	
36-45	623/1240 (50.2)	2.07 (1.75-2.44)	1.49 (1.23-1.80)		36-45	579/999 (58.0)	2.58 (2.15-3.09)	1.70 (1.37-2.10)	
46-55	468/1022 (45.8)	1.73 (1.45-2.06)	1.31 (1.07-1.60)		46-55	419/770 (54.4)	2.23 (1.84-2.71)	1.47 (1.17-1.85)	
Over 55	750/2292 (32.7))	1.00 (0.86-1.16)	0.81 (0.68-0.98)		Over 55	605/1422 (42.5)	1.38 (1.17-1.64)	0.83 (0.67-1.03)	
Gender					**Gender**				
Male	1716/4831 (35.5)	1	1	<0.0001	Male	1541/3622 (42.6)	1	1	<0.0001
Female	2083/4558 (45.7)	1.53 (1.41-1.66)	1.43 (1.31-1.56)		Female	1919/3856 (46.0)	1.34 (1.22-1.47)	1.37 (1.24-1.50)	
Country of birth/Ethnicity									
UK-born White	301/1663 (18.1)	1	1	<0.0001					
UK-born Indian Subcontinent	421/1180 (35.7)	2.51 (2.11-2.98)	2.29 (1.89-2.78)		**Country of birth/time since entry**				
UK-born Afro-Caribbean	156/505 (30.9)	2.02 (1.61-2.54)	1.81 (1.43-2.30)		UK-born	598/1741 (34.3)	1	1	<0.0001
UK-born Oriental/Other Asia	3/13 (23.1)	1.36 (0.37-4.96)	1.10 (0.30-4.10)		Foreign-born/<1 year	77/309 (24.9)	0.63 (0.48-0.84)	0.61 (0.45-0.81)	
UK-born Other	18/43 (41.9)	3.26 (1.76-6.05)	2.91 (1.54-5.50)		Foreign-born/1-5 years	931/1763 (52.8)	2.14 (1.87-2.45)	1.87 (1.61-2.18)	
Foreign-born White	38/248 (15.3)	0.82 (0.57-1.18)	0.94 (0.65-1.36)		Foreign-born/6-10 years	405/733 (55.3)	2.36 (1.98-2.81)	1.98 (1.63-2.42)	
Foreign-born Indian Subcontinent	2308/4544 (50.8)	4.67 (4.07-5.36)	4.10 (3.56-4.73)		Foreign-born/>10 years	1169/2340 (50.0)	1.91 (1.68-2.17)	1.64 (1.39-1.94)	
Foreign-born Afro-Caribbean	390/836 (46.7)	3.96 (3.29-4.76)	2.78 (2.29-3.38)		Foreign-born/time not known	280/592 (47.3)	1.72 (1.42-2.07)	1.67 (1.34-2.07)	
Foreign-born Oriental/Other Asia	80/194 (41.2)	3.18 (2.32-4.34)	2.78 (2.01-3.83)						
Foreign-born Other	84/163 (51.5)	4.81 (3.45-6.70)	3.82 (2.72-5.37)						
Employment status					**Ethnicity[4]**	2729/5724 (47.7)	1		
Unemployed	167/401 (41.6)	1			Indian Subcontinent	546/1341 (40.7)	0.75 (0.67-0.85)	1	<0.0001

Retired	106/292 (36.3)	0.80 (0.59-1.09)			Afro-Caribbean	185/413 (44.8)	0.89 (0.73-1.09)	0.69 (0.60-0.78)	
Employed/housewife	819/1528 (53.6)	1.62 (1.30-2.02)			Oriental/Other Asia/Other			0.83 (0.67-1.02)	
Student/child	459/1365 (33.6)	0.71 (0.57-0.89)							
					Employment status				
Previous TB					Unemployed	161/325 (49.5)	1		
No	2092/4321 (48.4)	1			Retired	86/210 (41.0)	0.71 (0.50-1.00)		
Yes	81/215 (37.7)	0.64 (0.49-0.85)			Employed/housewife	795/1393 (57.1)	1.35 (1.06-1.72)		
					Student/child	410/1149 (35.7)	0.57 (0.44-0.72)		
HIV status					**Previous TB**				
Negative/Unknown	3793/9375 (40.5)	1	1	0.26	No	1971/3700 (53.3)	1		
Positive	6/14 (42.9)	1.10 (0.38-3.18)	0.54 (0.18-1.59)		Yes	76/181 (42.0)	0.63 (0.47-0.86)		
Drug sensitivity					**HIV status**				
Fully sensitive	585/1452 (40.3)	1			Negative/Unknown	3454/7464 (46.3)	1	1	0.23
Monoresistant	44/110 (40.0)	0.99 (0.67-1.47)			Positive	6/14 (42.9)	0.87 (0.30-2.51)	0.51 (0.17-1.52)	
Multi-drug resistant	7/26 (26.9)	0.55 (0.23-1.31)							
					Drug sensitivity				
					Fully sensitive	566/1244 (45.5)	1		
					Monoresistant	44/100 (44.0)	0.94 (0.62-1.42)		
					Multi-drug resistant	7/19 (36.8)	0.70 (0.27-1.79)		

Footnotes

[1]Comparison of extrapulmonary TB cases only versus pulmonary TB only (concurrent pulmonary-extrapulmonary cases excluded)

[2]Models mutually adjusted for year of notification, season of notification, age, gender, country of birth, ethnicity and HIV status

[3]Model mutually adjusted for year of notification, season of notification, age, gender, country of birth, time since arrival, ethnicity and HIV status

[4]For the model restricted to non-White individuals, due to small numbers of individuals in the Other category I collapsed together Oriental/Other Asian with the Other category

Table 7.6 Demographic, clinical and temporal variables associated with different patterns of tuberculosis for the whole US cohort and the Non-White ethnic groups

Whole cohort (n=255489) [1]				Non-White ethnic groups (n=196177) [1]			
Variable	**Extrapulmonary TB only (n=52040)**	**Unadjusted OR (95% CI)**	**p**	**Variable**	**Extrapulmonary TB only (n=42588)**	**Unadjusted OR (95% CI)**	**p**
Period				**Period**			
1993-1996	15253/85806 (17.8)	1	<0.0001	1993-1996	11642/62390 (18.7)	1	<0.0001
1997-2000	13528/65930 (20.5)	1.19 (1.16-1.23)		1997-2000	10955/49774 (22)	1.23 (1.19-1.27)	
2001-2004	12250/54980 (22.3)	1.33 (1.29-1.36)		2001-2004	10425/43926 (23.7)	1.36 (1.32-1.40)	
2005-2008	11009/48773 (22.6)	1.35 (1.31-1.39)		2005-2008	9566/40087 (23.9)	1.37 (1.33-1.41)	
Age categories n (%)				**Age categories n (%)**			
Under 5	1949/9356 (20.8)	1	<0.0001	Under 5	1680/8210 (20.5)	1	<0.0001
5-14	1875/6756 (27.8)	1.46 (1.36-1.57)		5-14	1706/6092 (28.0)	1.51 (1.40-1.63)	
15-24	5034/23705 (21.2)	1.02 (0.97-1.09)		15-24	4678/21842 (21.4)	1.06 (1.00-1.13)	
25-44	19863/88342 (22.5)	1.10 (1.05-1.16)		25-44	17793/74678 (23.8)	1.22 (1.15-1.29)	
45-64	12739/70916 (18.0)	0.83 (0.79-0.88)		45-64	10398/52672 (19.7)	0.96 (0.90-1.01)	
>64	10580/56414 (18.8)	0.88 (0.83-0.93)		>64	6333/32683 (19.4)	0.93 (0.88-0.99)	
Gender				**Gender**			
Male	26995/159371 (16.9)	1	<0.0001	Male	21607/120234 (18.0)	1	<0.0001
Female	25045/96118 (26.1)	1.73 (1.69-1.76)		Female	20981/75943 (27.6)	1.74 (1.71-1.78)	
Country of birth/Ethnicity							
US-born White	7672/52022 (14.7)	1	<0.0001				
US-born American Indian	635/3079 (20.6)	1.50 (1.37-1.64)					
US-born Asian	748/3010 (24.9)	1.91 (1.75-2.08)		**Ethnicity**			
US-born Black	11553/65093 (17.7)	1.25 (1.21-1.29)		American Indian or Alaska Native, NH	661/3156 (20.9)	1	<0.0001
US-born Hispanic	3958/18380 (21.5)	1.59 (1.52-1.66)		Asian or Pacific Islander, NH	13742/53251 (25.8)	1.31 (1.20-1.43)	
Foreign-born White	1780/7290 (24.4)	1.87 (1.76-1.98)		Black or African American, NH	15884/78773 (20.2)	0.95 (0.87-1.04)	
Foreign-born American Indian	26/77 (33.8)	2.95 (1.84-4.73)		Hispanic or Latino	12301/60997 (20.2)	0.95 (0.87-1.04)	
Foreign-born Asian	12994/50241 (25.9)	2.02 (1.95-2.08)					
Foreign-born Black	4331/13680 (31.7)	2.68 (2.56-2.80)					
Foreign-born Hispanic	8343/42617 (19.6)	1.41 (1.36-1.46)					
				Country of birth/time since arrival			
				US-born	16894/89562 (18.9)	1	<0.0001
Employment status				Foreign-born/<1 year	2817/21219 (13.3)	0.66 (0.63-0.69)	
Unemployed	25750/132732 (19.4)	1	<0.0001	Foreign-born/1-4 years	5947/21755 (27.3)	1.62 (1.56-1.67)	
Employed	20445/92635 (22.1)	1.18 (1.15-1.20)		Foreign-born/5-14 years	6590/23851 (27.6)	1.64 (1.59-1.70)	
				Foreign-born/≥15 years	5158/20390 (25.3)	1.46 (1.41-1.51)	
				Foreign-born/time not known	5182/19400 (26.7)	1.57 (1.51-1.63)	
Previous TB				**Employment status**			<0.0001
No	49779/239985 (20.7)	1	<0.0001	Unemployed	20257/98781 (20.5)	1	
Yes	1803/13538 (13.3)	0.59 (0.56-0.62)		Employed	17570/73625 (23.9)	1.21 (1.19-1.24)	
HIV status				**Previous TB**			<0.0001
Negative	18335/94526 (19.4)	1		No	40876/184563 (22.1)	1	

Positive	4848/23354 (20.8)	1.09 (1.05-1.13)	Yes	1328/10112 (13.1)	0.53 (0.50-0.56)	
Drug sensitivity			**HIV status**			
Not multi-drug resistant	34166/188723 (18.1)	1	Negative	38520/176150 (21.9)	1	0.001
Multi-drug resistant	319/2869 (11.1)	0.57 (0.50-0.64)	Positive	4068/20027 (20.3)	0.94 (0.90-0.97)	
Resident in correctional facility			**Drug sensitivity**			
No	50697/243677 (20.8)	1	Not multi-drug resistant	28112/144210 (19.5)	1	<0.0001
Yes	979/9550 (10.3)	0.43 (0.41-0.46)	Multi-drug resistant	269/2442 (11.0)	0.51 (0.45-0.58)	
			Resident in correctional facility			
			No	41451/186698 (22.2)	1	<0.0001
			Yes	863/7840 (11.0)	0.43 (0.40-0.47)	

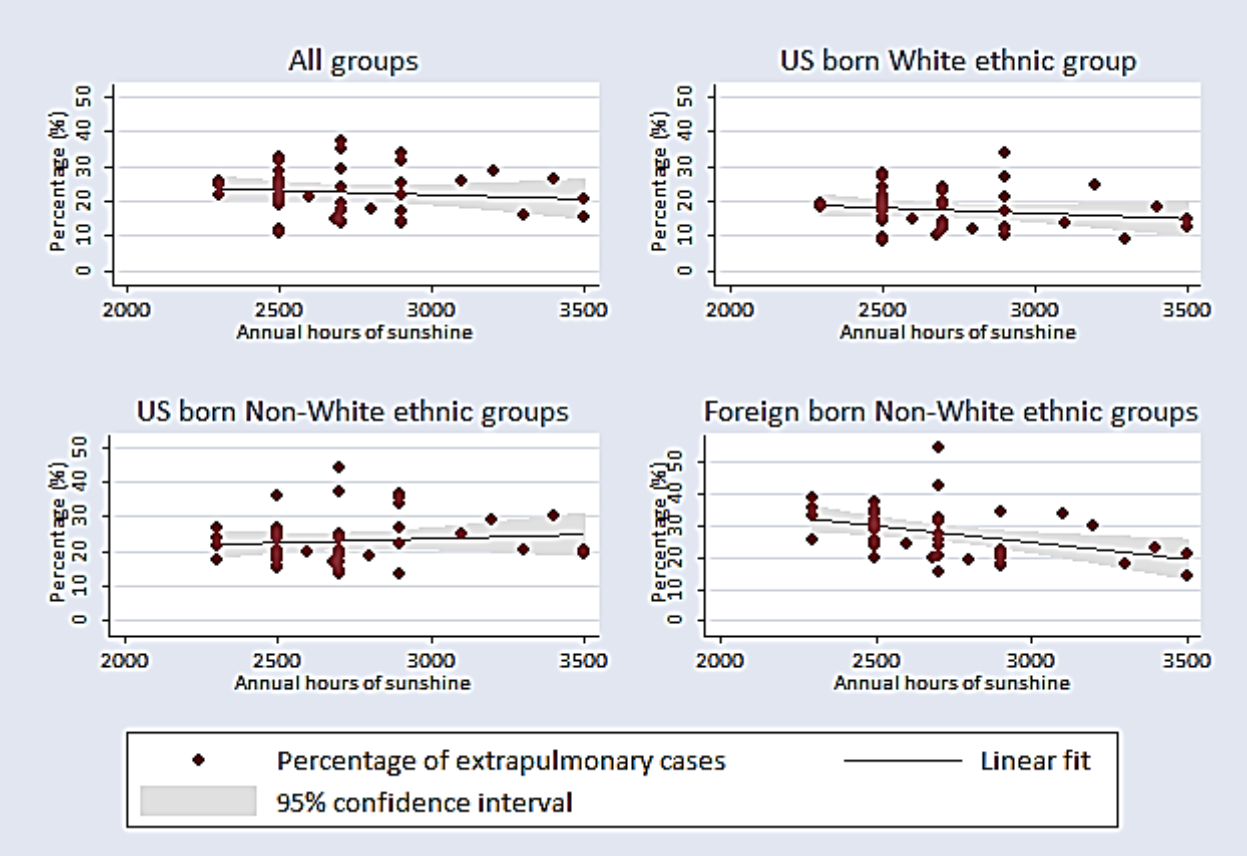
Footnote

[1]Comparison of extrapulmonary TB cases only compared to pulmonary TB only (concurrent pulmonary-extrapulmonary cases excluded

Sunlight and patterns of disease in the US CDC dataset

Figures 7.8, 7.9 and 7.10 describe the effect of sunlight on patterns of disease in the US CDC dataset. For the cohort as a whole, there was no correlation between annual hours of sunlight and the proportion of cases that were extrapulmonary (ρ=-0.11, p=0.46). When stratified by demographic group there was no correlation between hours of sunshine and the proportion of cases that were extrapulmonary for US-born Whites (ρ=-0.17, p=0.28) and US-born Non-Whites (ρ=0.10, p=0.51) but there was a moderate negative correlation for foreign-born Non-Whites (ρ=-0.44, p=0.003) (figure 7.8).

Figure 7.8 Scatter plots of annual hours of sunshine against percentage of cases that are extrapulmonary for US mainland states



Footnote

[1]Excludes Maine, Montana, New Hampshire, Vermont, Wyoming) and District of Columbia (not strictly a US state)

States which were classified as sun "high" (>2700 hours of sunshine per year) as compared to where it was "low" had a lower proportion of extrapulmonary disease for all demographic groups - US-born Whites (12.% vs 15.8%, p<0.0001), US-born Non-Whites (18.6% vs 19.1%, p=0.08) and foreign-born Non-Whites (20.4% vs 29.1%, p<0.0001) (figure 7.9). In addition, states with higher levels of sunshine were significantly less likely than states with lower levels of sunshine to exhibit the "Birmingham" pattern of TB disease (42.9% vs 76.7%, p=0.04) (in other words proportion of extrapulmonary disease lowest in local-born Whites followed by the local-born Non-Whites and finally, highest, in the foreign-born Non-Whites).

When the foreign-born Non-White population was stratified by time since arrival and levels of sunshine, states with higher levels of sunshine had, at all time points, a lower proportion of extrapulmonary disease than states with lower sunshine levels (p<0.0001 at all time points) (figure 7.10).

Figure 7.9 Patterns of active tuberculosis amongst different demographic groups and stratified by high and low levels of sunlight exposure

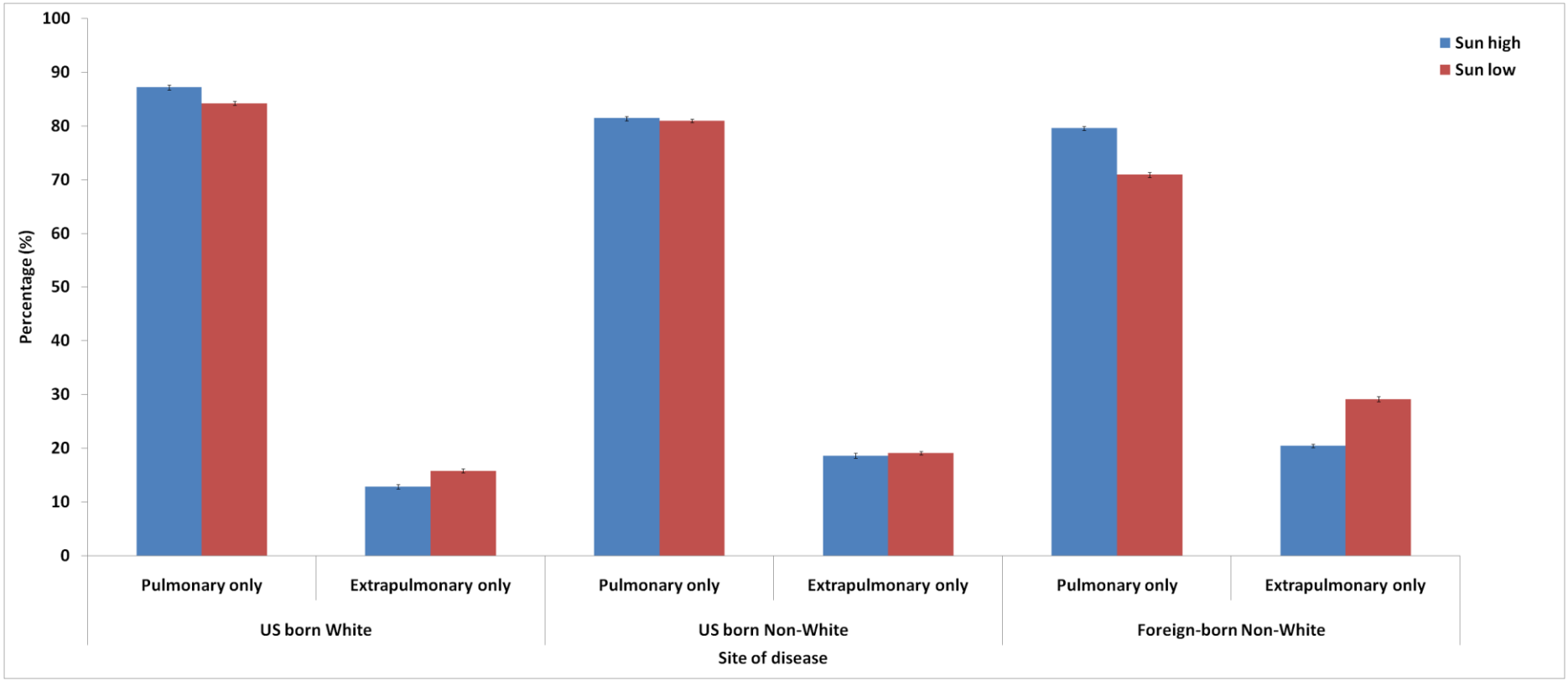
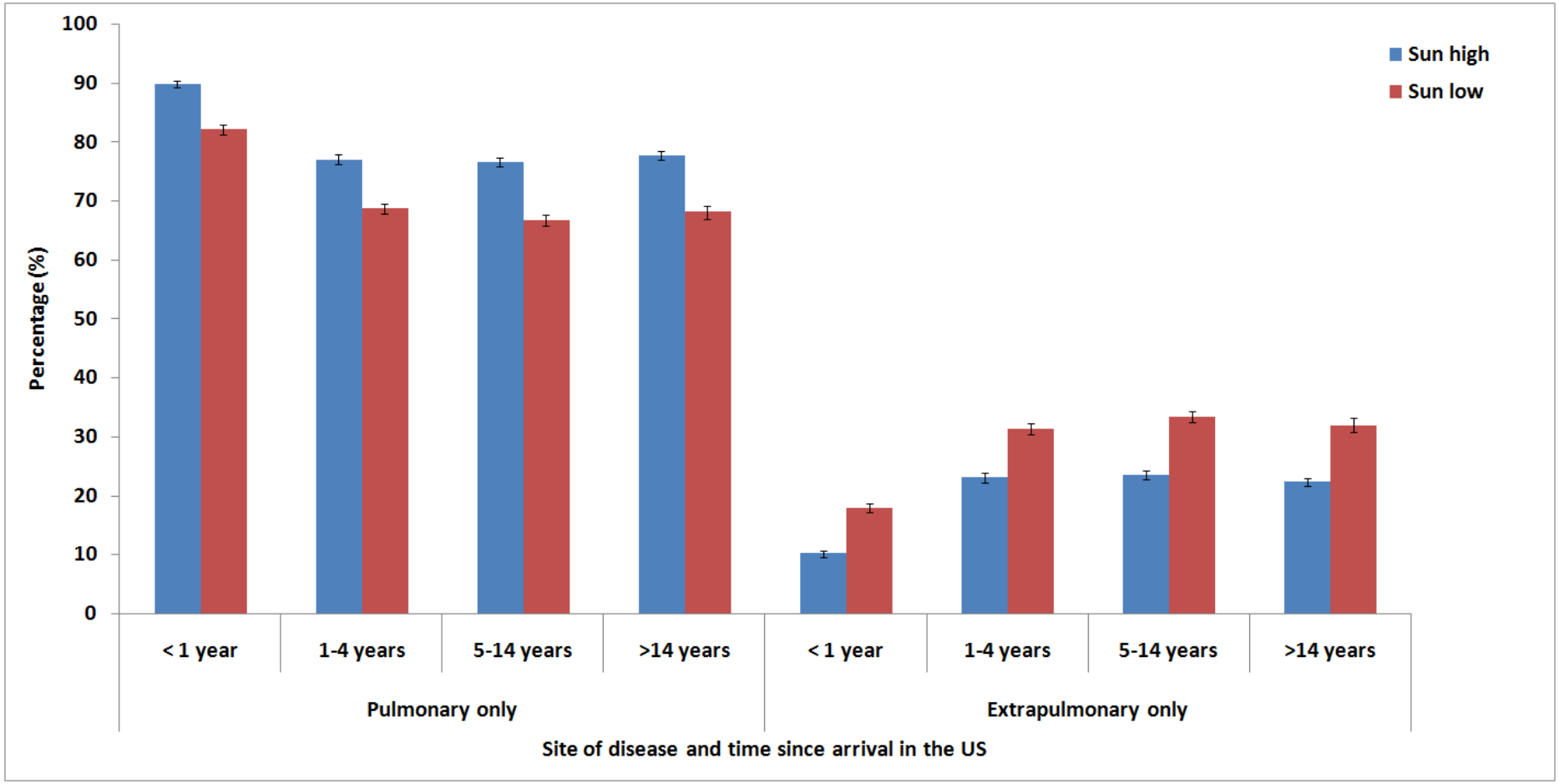


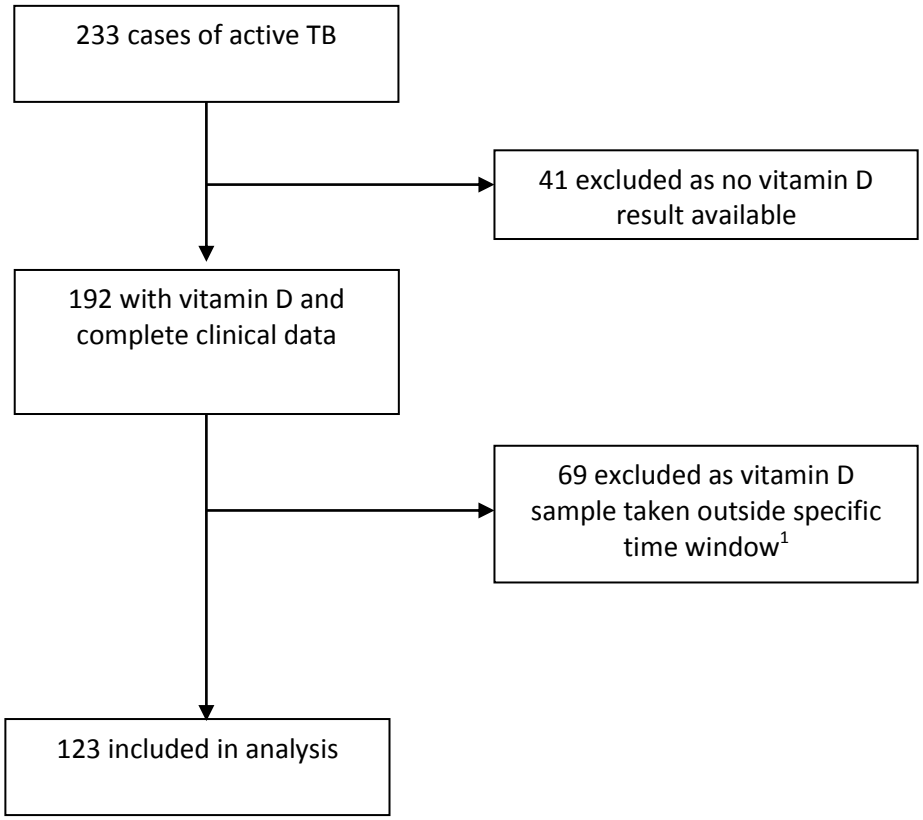
Figure 7.10 Patterns of active tuberculosis stratified by time elapsed between arrival in the US and the development of active disease and high and low levels of sunlight exposure



Association of vitamin D levels and patterns of tuberculosis

Given the strong observational associations that I found between different ethnic groups and clinical phenotype, the changing pattern of disease in the foreign-born by time since arrival and the association between sunlight and TB disease, I postulated that vitamin D deficiency may be a key factor determining clinical phenotype. I therefore directly tested the hypothesis that vitamin D deficiency affected disease patterns in a clinically precisely-defined local patient cohort in London (for flow chart see figure 7.11). Demographic details of the cohort are presented in table 7.7; in general there were no significant differences between subjects included in our analysis and either those who did not have a vitamin D level taken or those who were excluded on account of the vitamin D level being taken outside the specified time window (apart from a slightly higher proportion of men in this latter group).

Figure 7.11 Flow chart of cases included from the London cohort for data analysis



Footnote

[1]Individuals excluded if vitamin D sample taken more than 30 days after commencing anti-tuberculous therapy

Table 7.7 Demographic characteristics of the individuals from the London cohort with active TB included in the analysis as compared against those excluded

Variable	Subjects included in study (n=123)	Subjects excluded as vitamin D sample outside time window (n=69)	p[1]	Subjects excluded as no vitamin D sample taken (n=41)	p[2]
Age					
Median (interquartile range)	33.6 (27.1-46.3)	34.1 (24.5-48.7)	0.90	34.0 (24.0-44.0)	0.69
Age categories					
16-25	25 (20.3%)	20 (29.0%)		11 (26.8%)	
26-35	43 (35.0%)	18 (26.1%)		11 (26.8%)	
36-45	23 (18.7%)	11 (15.9%)		9 (22.0%)	
46-55	16 (13.0 %)	12 (17.4%)		5 (12.2%)	
over 55	16 (13.0%)	8 (11.6%)		5 (12.2%)	
Gender					
Male	61 (49.6%)	42 (60.9%)	0.17	28 (68.3%)	0.047
Female	62 (50.4%)	27 (39.1%)		13 (31.7%)	
Ethnicity					
White	23 (18.7%)	10 (14.5%)	0.27	8 (19.5%)	1.00
Indian Subcontinent	49 (39.8%)	19 (27.5%)		17 (41.5%)	
Afro-Caribbean	33 (26.8%)	27 (39.1%)		11 (26.8%)	
Oriental/Other Asia	13 (10.6%)	10 (14.5%)		4 (9.8%)	
Other	5 (4.1%)	3 (4.4%)		1 (2.4%)	
Place of birth					
United Kingdom	17 (13.8%)	9 (13.0%)	1.00	8 (19.5%)	0.45
Foreign-born	106 (86.2%)	60 (87.0%)		33 (80.5%)	
Time since entry to the UK (years)					
Median (interquartile range)	6 (2-17)[3]	6 (2-18)	0.87	10 (5-17)	0.32
<1	7 (6.7%)	3 (5.0%)		0 (0.0%)	
1 - 5	41 (39.1%)	24 (40.0%)		10 (35.7%)	
6-10	18 (17.1%)	14 (23.3%)		5 (17.9%)	
>10	39 (37.1%)	19 (31.7%)		13 (46.4%)	
HIV status					
Negative/Not known	111 (97.4%)[5]	53 (96.4%)	0.66	-	-
Positive	3 (2.6%)	2 (3.6%)			

Type of disease					
Pulmonary only	39 (31.7%)	24 (34.8%)	0.75	14 (34.1%)	0.85
Pulmonary and extrapulmonary	19 (15.4%)	10 (14.5%)	1.00	8 (19.5%)	0.63
Extrapulmonary only	65 (52.8%)	35 (50.7%)	0.88	19 (46.3%)	0.48
Serum vitamin D (nmol/L)					
Mean (95% confidence interval)	16.5 (14.2-19.1)	17.5 (14.6-21.1)	0.60		
Vitamin D category					
<20nmol/L	71 (57.7%)	35 (50.7%)			
<50nmol/L	109 (88.6%)	66 (88.4%)			
<75nmol/L	116 (94.3%)	69 (100.0%)			

Footnotes

[1]p for difference between subjects included in the study and subjects excluded as vitamin D sample was outside time window

[2]pfor difference between subjects included in the study and subjects excluded as no vitamin D sample was taken

Overall, mean vitamin D levels in the cohort were 16.5 nmol/L (95% CI 14.2-19.1 nmol/L); 57.7% and 94.3% of the cohort had vitamin D levels <20 nmol/L and <75 nmol/L respectively.

Individuals with purely extrapulmonary tuberculosis (14.1 nmol/L; 95% CI 11.7-17.0 nmol/L) and any extrapulmonary tuberculosis (13.4 nmol/L; 95% CI 11.4-15.7 nmol/L) had significantly lower vitamin D levels as compared to individuals with pulmonary tuberculosis only (25.8 nmol/L; 95% CI 19.6-33.9 nmol/L) ($p=0.0003$ and $p<0.0001$ respectively). Severe vitamin D deficiency (<20 nmol/L) was significantly more common in individuals with purely extrapulmonary tuberculosis ($p=0.002$) and individuals with any extrapulmonary involvement ($p<0.0001$) than in subjects with purely pulmonary tuberculosis (figure 7.12).

Among foreign-born non-White individuals who had been resident for over a year, those who presented with purely extrapulmonary and any extrapulmonary TB had lower mean vitamin D levels than those with purely pulmonary TB ($p=0.06$ and $p=0.03$ respectively).

On multivariate analysis (table 7.8), vitamin D deficiency (<20 nmol/L) (OR 4.70, 95% CI 1.22-18.09 for purely extrapulmonary, OR 4.32, 95% CI 1.26-14.76 for any extrapulmonary TB) and female gender (OR 3.79, 95% CI 1.31-10.94) were independently associated with extrapulmonary disease.

Figure 7.12 Proportion of individuals with pulmonary and extrapulmonary tuberculosis with different vitamin D concentrations at diagnosis in the London cohort

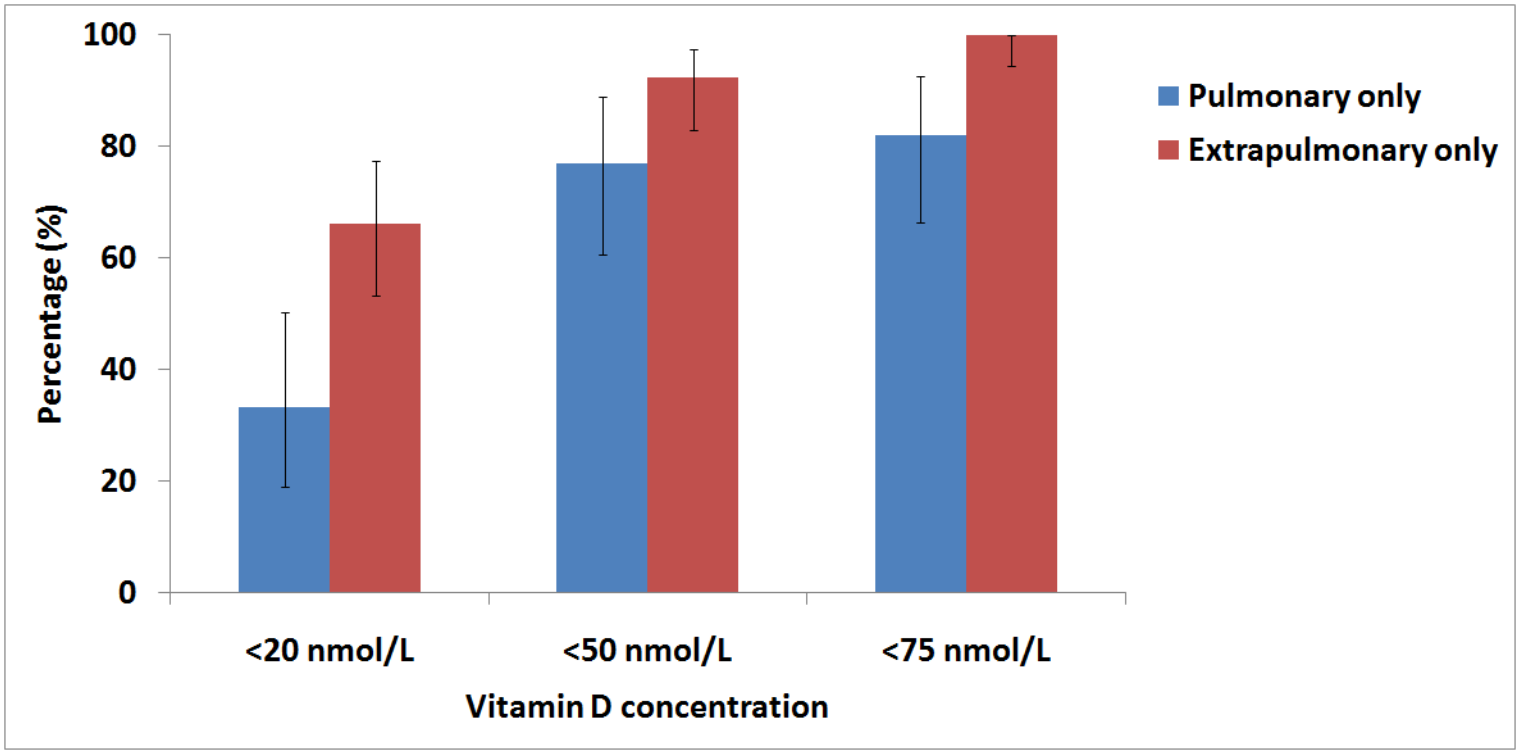


Table 7.8 Demographic, clinical and temporal variables associated with different patterns of tuberculosis for the London cohort

Variable	Extrapulmonary TB only[1] (n=65)	Unadjusted OR (95% CI)	Adjusted OR[2] (95% CI)	p-value	Variable	Any extrapulmonary involvement (n=84)	Unadjusted OR (95% CI)	Adjusted OR[3] (95% CI)	p-value
Period of notification					**Period of notification**				
2007-2009	37/63 (58.7)	1	1	0.95	2007-2009	48/74 (64.9)	1	1	0.98
2010-2011	28/41 (68.3)	1.51 (0.66-3.46)	1 (0.34-2.96)		2010-2011	36/49 (73.5)	1.50 (0.68-3.32)	1.02 (0.37-2.78)	
Season					**Season**				
Winter	14/22 (63.6)	1	1	0.13	Winter	19/27 (70.4)	1	1	0.11
Spring	22/31 (71.0)	1.40 (0.44-4.48)	2.27 (0.50-10.37)		Spring	29/38 (76.3)	1.36 (0.45-4.13)	1.98 (0.49-8.09)	
Summer	22/36 (61.1)	0.90 (0.30-2.69)	2.38 (0.53-10.62)		Summer	28/42 (66.7)	0.84 (0.30-2.40)	2.23 (0.55-9.11)	
Autumn	7/15 (46.7)	0.50 (0.13-1.90)	0.39 (0.07-2.04)		Autumn	8/16 (50.0)	0.42 (0.12-1.52)	0.37 (0.08-1.73)	
Age categories n (%)					**Age categories n (%)**				
16-25	11/21 (52.4)	1	1	0.08	16-25	15/25 (60.0)	1	1	0.12
26-35	18/35 (51.4)	0.96 (0.33-2.84)	0.88 (0.22-3.53)		26-35	26/43 (60.5)	1.02 (0.37-2.79)	1.06 (0.29-3.86)	
36-45	17/23 (73.9)	2.58 (0.73-9.12)	3.81 (0.71-20.4)		36-45	17/23 (73.9)	1.89 (0.55-6.45)	2.85 (0.57-14.28)	
46-55	7/11 (63.6)	1.59 (0.36-7.11)	2.16 (0.25-19.11)		46-55	12/16 (75.0)	2.00 (0.50-8.00)	2.44 (0.35-16.93)	
Over 55	12/14 (85.7)	5.45 (0.97-30.6)	11.8 (1.30-106.79)		Over 55	14/16 (87.5)	4.67 (0.87-25.14)	11.45 (1.41-93.03)	
Gender					**Gender**				
Male	23/49 (46.9)	1	1	0.014	Male	35/61 (57.4)	1	1	0.053
Female	42/55 (76.4)	3.65 (1.58-8.44)	3.79 (1.31-10.94)		Female	49/62 (79.0)	2.80 (1.26-6.20)	2.72 (0.99-7.48)	
Country of birth/ time since entry					**Country of birth/ time since entry**				
UK-born	6/16 (37.5)	1	1	0.20	UK-born	7/17 (41.2)	1	1	0.08
Foreign-born/<1 year	3/7 (42.9)	1.25 (0.21-7.62)	0.36 (0.02-6.73)		Foreign-born/<1 year	3/7 (42.9)	1.07 (0.18-6.36)	0.29 (0.02-4.61)	
Foreign-born/>1 year	56/81 (69.1)	3.73 (1.22-11.4)	2.32 (0.45-11.95)		Foreign-born/>1 year	73/98 (74.5)	4.17 (1.43-12.13)	2.75 (0.59-12.82)	
Ethnicity[4]					**Ethnicity**				
White	7/22 (31.8	1	1	0.42	White	8/23 (34.8)	1	1	0.29
Indian Subcontinent	32/44 (72.7)	5.71 (1.87-17.44)	3.31 (0.64-17.03)		Indian Subcontinent	37/49 (75.5)	5.78 (1.97-16.98)	3.65 (0.78-17.00)	
Afro-Caribbean	16/23 (69.6)	4.90 (1.39-17.31)	2.74 (0.49-15.34)		Afro-Caribbean	26/33 (78.8)	6.96 (2.10-23.05)	4.02 (0.82-19.64)	
Oriental/Other Asia/Other	10/15 (66.7)	4.29 (1.06-17.36)	4.28 (0.66-27.78)		Oriental/Other Asia/Other	13/18 (72.2)	4.88 (1.27-18.65)	5.06 (0.88-28.93)	
Vitamin D					**Vitamin D**				
≥20nmol/L	22/48 (45.8)	1	1	0.02	≥20nmol/L	26/52 (50.0)	1	1	0.02
<20nmol/L	43/56 (76.8)	3.90 (1.69-9.06)	4.70 (1.22-18.09)		<20nmol/L	58/71 (81.7)	4.46 (1.98-10.04)	4.32 (1.26-14.79)	

HIV status					**HIV status**				
Negative/Unknown	64/102 (62.8)	1	1	0.71	Negative/Unknown	82/120 (68.3)	1	1	0.76
Positive	1/2 (50.0)	0.59 (0.04-9.77)	1.88 (0.07-50.72)		Positive	2/3 (66.6)	0.93 (0.08-10.53)	1.66 (0.06-45.20)	

Footnotes

[1]Comparison of extrapulmonary TB cases only versus pulmonary TB only (concurrent pulmonary-extrapulmonary cases excluded)

[2]Model mutually adjusted for period of notification, season of notification, age, gender, country of birth/time since entry, ethnicity, vitamin D level and HIV status

[3]Model mutually adjusted for period of notification, season of notification, age, gender, country of birth/time since entry, ethnicity, vitamin D level and HIV status

Discussion

In this analysis of prospective TB surveillance data from two independent, high-income, Northern hemisphere settings, I found that patterns of disease significantly differed by demographic group (particularly ethnic group), time since arrival (for those born overseas) and, for the US, by the hours of sunlight a state received. Using accurate empirical data in an independent cohort I subsequently found, for the first time, that vitamin D deficiency, after multivariate adjustment, was significantly associated with extrapulmonary TB.

Local-born Whites, local-born Non-Whites and foreign-born Non-Whites differed in their pattern of disease with low, intermediate and high proportions of extrapulmonary disease respectively. Whilst this finding is novel in the field of TB, parallels can be drawn from other diseases such as ischaemic heart disease[448] and multiple sclerosis[449] where second generation immigrants (in other words local-born Non-Whites) have a pattern of disease which differs from both their first generation compatriots and the local-born White population thereby suggesting environmental factors play a role in determining clinical disease phenotype.

Extrapulmonary disease was commonest amongst the foreign-born. Previous authors have highlighted the increased risk of extrapulmonary TB amongst foreign-born immigrants to high-income settings.[33-35,313,314] Foreign-born immigrants who developed their active TB within the first year after arrival had a significantly different pattern of disease, characterised by a lower proportion of extrapulmonary TB (more akin to the local-born White population) than foreign-born immigrants who developed TB after having been resident for more than one year. This data infers that as the duration between migration and TB development increased, after adjusting for other demographic factors, the proportion of extrapulmonary disease increased then stabilised. Limited literature from the UK[33] and Minnesota[450] has also documented this changing disease pattern as time since arrival increases. A Dutch study found that pulmonary disease presented significantly sooner after migration than extrapulmonary disease although the authors did not specifically stratify disease types by time since arrival.[34] The current work confirms this observation, for the first time, nationally for the US.

The multiple settings where this observation has been made suggests that it is a real phenomenon caused by an environmental factor.

Comparison of patterns of TB disease by hours of sunshine in different US states indicated that states with the lowest levels of sunshine had the highest proportion of extrapulmonary TB and were significantly more likely to have a pattern of TB similar to the Birmingham dataset (in terms of extrapulmonary tuberculosis - local-born Whites<local-born Non-Whites<foreign-born Non-Whites). To our knowledge this data is new although there is some limited, related data from Spain which suggests that sunnier regions have a significantly lower incidence of TB – although the authors did not explore the impact of sunlight on disease phenotype.[451]

All of the above evidence points towards an environmental factor – the nature of which indirectly suggests sunlight and vitamin D is playing a role in determining tuberculosis clinical phenotype.

Vitamin D is a fat-soluble secosteroid which humans obtain from sunlight (Ultraviolet B radiation) but also from diet (food sources such as oily fish) and supplementation.[452,453] The major source of vitamin D is sunlight which penetrates the skin and converts 7-dehydrocholesterol, via previtamin-D_3, to vitamin D_3 which can circulate bound to vitamin D binding-protein.[452-454] Dietary vitamin D (vitamin D_2 or D_3) is ingested and carried in chylomicrons from the lymphatic system to the venous circulation. Circulating vitamin D is metabolised in the liver by 25-hydroxylase to the biologically inactive 25-hydroxycholecalciferol (also known as 25-hydroxy-vitamin D_3) – the form of vitamin D that is measured by serum assays. 25-hydroxycholecalciferol is transported to the proximal tubules of the kidneys where it is converted by 25-hydroxy-vitamin D-1-alpha-hydroxylase to 1,25-dihydroxycholecalciferol (also known as 1-25-dihydroxy-vitamin D_3) which is biologically active and binds to the vitamin D receptor.[455]

One of the major difficulties of computing the prevalence of vitamin D deficiency (both globally and in specific populations) is that there is no universally accepted definition of optimal serum levels. As a consequence, it is difficult to directly compare findings from studies which have been conducted in different countries and heterogeneous populations with the additional complication of using different assays and serum cut-offs. Nonetheless, two recent authorative reviews state that

vitamin D deficiency should be classified as a serum concentration of <50nmol/L[452,456] although other studies suggest levels <20nmol/L should be used to classify severe or profound deficiency.[444] Using a serum cut-off of <50nmol/L, Holick estimates that globally 1 billion individuals are vitamin D deficient.[452] Of course this is merely an aggregate figure and certain factors, alone or in combination, increase the risk and prevalence of vitamin D deficiency including geography and latitude (higher latitude regions),[457,458] pigmented skin (non-White immigrants to Western countries),[459] extremes of age,[452] gender (women),[460] season[457,458] and concomitant medical conditions.[452]

In the UK, estimates suggest that overall around 50-60% of the general population has a vitamin D level of <50nmol/L.[460] In a recent national survey of 7437 middle-aged (45 year-old) adults from the 1958 British birth cohort, Hyppönen and Power found that just under 50% of the cohort had serum concentrations <40nmol/L, men had higher concentrations, vitamin D levels varied by seasons and individuals living in Scotland were significantly more likely to be vitamin D deficient.[457] However, the study did not include any individuals from ethnic minority backgrounds (either UK or Non-UK born). Similarly, a Scottish study found 64% of adults were deficient (<40nmol/L) although, again, the population was ethnically homogeneous.[461]

General estimates for the prevalence of vitamin D deficiency in individuals of Indian Subcontinent ethnicity residing in the UK suggests an overall prevalence of 38-95%.[460] Smaller studies have also examined other ethnic minority groups and found vitamin D deficiency is more common amongst immigrants with pigmented skin. In a recent study of pregnant women attending an antenatal clinic in London vitamin D deficiency (<50nmol/L) was present in 99% and 100% of Afro-Caribbean and Asians respectively – as compared to 60% of White British individuals.[462] Older work from Leicester found that 54% of Gujarati Indians had serum levels <12.5nmol/L[463] whilst a similar study in Birmingham found 82% of Asian, 75% of Afro-Caribbeans and 47% of Whites were vitamin D deficient (<25nmol/L).[464] In the US, the NHANES III survey was used to compute an overall prevalence of vitamin D deficiency (defined by the authors as <70nmol/L) of 45.8% - with an increased risk in women and ethnic minority individuals with pigmented skin.[459]

Over the last few years increasing research interest in vitamin D has resulted in a number of studies finding associations between vitamin D deficiency and a range of medical conditions including cancer,[465] cardiovascular disease,[466] multiple sclerosis[467] and diabetes.[468]

By contrast, the association between vitamin D and tuberculosis has been recognised for over a hundred years with cod-liver oil and sanatoriums, which had abundant exposure to sunlight, being used as therapeutic modalities.[469] Indeed, in 1903, Finsen was awarded the Nobel Prize for Medicine for his discovery that ultraviolet light therapy could be useful successfully in lupus vulgaris – a form of cutaneous tuberculosis.[470]

The clinical associations of vitamin D deficiency can be considered separately for latent TB infection and active TB disease. To date, relatively few studies have examined the association of vitamin D deficiency and LTBI – most commonly using TST (and in some cases IGRA) to diagnose infection. Grange and colleagues found in an Indonesian study that controls who were vitamin D deficient were significantly more likely to be TST positive.[471] In a retrospective Australian study of exclusively Sub-Saharan African immigrants, Gibney and colleagues found that vitamin D deficiency was significantly associated, on multivariate analysis, with LTBI (defined as a positive TST or IGRA). However, the study was limited by its retrospective nature and failure to control for season and BCG status.[472] Martineau and colleagues undertook a randomised controlled trial in 192 healthy contacts and found that a single-dose of vitamin D (as compared to placebo) significantly enhanced immunity to *M. tuberculosis* at 6 weeks after administration.[445] Recently Talat and colleagues undertook a prospective study of vitamin D levels in household contacts of smear-positive TB patients in Pakistan to ascertain the impact vitamin D deficiency had on progression to active TB disease. The authors found that contacts in the lowest tertile of vitamin D were significantly more likely to progress to active disease over 2-years of follow-up than those in the intermediate or highest tertiles; overall the relative risk for progression was 5.1 per 1-log decrement in vitamin D levels.[473]

More studies have been published examining the association between vitamin D and active tuberculosis. In a recent systematic review of seven studies,[317,471,474-478] Nnoaham concluded that low serum vitamin D levels were associated with active TB –with vitamin D levels in active TB patients 0.68 standard deviations lower than controls.[479] However, the studies included in this review were

limited by small sample size (numbers of patients varied from 15-103), heterogeneous results (a significant difference was seen in 5 out of 7 studies) and the patients analysed were those with pulmonary disease; none of the authors specifically examined/explored vitamin D levels in patients with extrapulmonary TB. Further, larger, studies undertaken more recently in the UK (children[480] and adults[481]) and Australia[472] have confirmed the association between vitamin D deficiency and active pulmonary TB but these studies, as with those discussed earlier, failed to examine vitamin D levels in extrapulmonary disease and either failed to undertake multivariate analyses, or did not appropriately control for confounders (such as season or time since arrival in the UK – if foreign-born).

However, I feel that the vitamin D deficiency hypothesis could explain the changing patterns of disease seen in the foreign-born by time since arrival – as highlighted by the current study. Foreign-born non-White individuals generally arrive from sunny countries which protects against vitamin D deficiency. On arrival in the receiving country, a carry-over effect results in vitamin D levels being maintained for a period of time.[482] If an individual reactivates in this initial time period, when vitamin D levels are not deficient (as found in the country of origin), then pulmonary disease appears to be more likely to occur – as is seen in India for example.[483] However as time since arrival increases, and the effect of sunshine from the country of origin wanes, vitamin D levels will decrease before stabilising at a lower equilibrium;[482] reactivation to active TB at this point appears to be more likely to result in extrapulmonary disease. Finally the higher levels of extrapulmonary disease seen in those US states with the lowest levels of sunlight provides additional supportive evidence for the vitamin D deficiency hypothesis. Moreover, it is plausible, although untested, that vitamin D levels in local-born Non-Whites are at an intermediate level between UK-born Whites, and foreign-born Non-Whites due to different sun exposure behaviour and diet.[484] This could partly explain the different proportions of extrapulmonary TB that I observed in this population.

I therefore analysed vitamin D levels in an accurately characterised cohort of patients with active TB and found that, even after correcting for demographic and temporal factors, vitamin D deficiency was significantly, and strongly, associated with extrapulmonary tuberculosis at the time of diagnosis. The current study therefore provides the first evidence for an environmental factor determining clinical phenotype in active TB. Previous authors have found associations between

vitamin D deficiency and latent,[472] and active,[317] TB but, to date, there has been no data on vitamin D deficiency and clinical phenotype. The generalisability of my findings is reinforced by the large sample size, independent Northern hemisphere settings and multiple ethnic groups that I studied. In addition the size of effect for the association between vitamin D and extrapulmonary disease is not inconsequential. Our odds ratios were over 4 which are higher than, or in line with, the odds ratios associated with other known factors such as mycobacterial strain (Beijing)[343,345], IL1-beta[318] and P2X7.[318,321]

These findings are likely to have significant public health implications for immigrant communities in high-income countries. It is already known that individuals in high-income countries with pigmented skin have both a higher prevalence of vitamin D deficiency and higher incidence of active TB (especially extrapulmonary) than their White compatriots.[140,464,485,486] This combination of diseases, coupled with our novel data, raise the issue of vitamin D supplementation being used as an adjunct to anti-tuberculous therapy – in extrapulmonary disease. However, to date, clinical trials have failed to find any significant benefit of vitamin D therapy in patients with active disease[487,488] although this may be due to the fact that recruited patients have, almost exclusively, had pulmonary disease.[487,488]

Biologically, vitamin D deficiency affects host immunity[440,445] by adversely impacting on macrophage and T cell function. Following infection with *Mycobacterium tuberculosis*, macrophages increase and upregulate expression of the genes encoding the vitamin D receptor and 25-hydroxy-vitamin D-1-alpha-hydroxylase resulting in increased production of the active form of vitamin D (1-25-dihydroxy-vitamin D_3) and binding with the vitamin D receptor.[489] The exact mechanism by which vitamin D augments immunity against *M. tuberculosis* is unclear but may relate to 1-25-dihydroxy-vitamin D_3 increasing production of cathelicidins, which are antimicrobial peptides.[490] In addition, vitamin D appears to enhance macrophage phagocytic activity and deficient states adversely impact on macrophages with this effect significantly more pronounced in non-White individuals.[439,491] Crowle and Elkins found that in macrophages from Black, as compared to White, donors mycobacterial growth was faster and that, crucially, vitamin D gave significantly less protection

against tubercle bacilli.[439] This lower response to the protective effects of vitamin D may be genetically determined and compounded by pigmented skin preventing vitamin D synthesis.

Whilst the specific role vitamin D deficiency plays in determining phenotype remains unclear, I postulate two mechanisms. The first hypothesis is that following initial infection of alveolar macrophages with *Mycobacterium tuberculosis*, some bacteria spread haematogenously and seed to distant, extrapulmonary sites. Although the innate immune response through macrophages, and subsequently T cells, contains the bacilli at these distant sites it is possible that this containment is more vitamin D dependent in the periphery (as compared to the lung). As a consequence if, and when, vitamin D deficiency occurs it preferentially results in loss of containment in peripheral extrapulmonary sites (rather than pulmonary) and thus extrapulmonary disease occurs. The second hypothesis is that following initial infection the bacteria are held in containment at pulmonary sites but the occurrence of vitamin D deficiency and its associated general impairment in macrophage and T cell function[452] predisposes for bacilli to disseminate more widely resulting in extrapulmonary disease. On the basis of current knowledge I am unable to distinguish which of these two mechanisms is more likely and further work is needed in this area.

Irrespective of whether case counts were increasing (Birmingham) or decreasing (US CDC), the proportion of cases that were classified as exclusively extrapulmonary increased year–on-year. This finding, which is consistent with work from diverse settings, has been mainly attributed to the high number, and proportion, of extrapulmonary cases amongst the foreign-born[33,34,313,314]– which my work further confirms. However, I additionally found that, within the foreign-born cohort, the proportion of cases that were classified as extrapulmonary increased over time. It is unclear what is causing this temporal change but heightened clinical suspicion coupled with increasing use of complex radiological investigations may partly explain this observation. There was also significant heterogeneity in the prevalence of extrapulmonary disease within the local-born population: stable proportions in local-born Whites but high, and increasing, proportions amongst the local-born Non-White population.

The current work had several limitations. Data was obtained from surveillance systems and I was limited to analysing those variables that are routinely collected. HIV status, which has previously

been associated with certain forms of extrapulmonary disease,[35,305] was incompletely or poorly recorded, both in our datasets but also more widely in the UK wide setting.[33] The US CDC data was aggregate in nature and therefore I was limited in the analyses I could undertake – especially with respect to regression modelling which was entirely univariate rather than multivariate. Similarly the use of US climatic data was based on calculating average hours of sunshine for each state and then assuming that this median value applied to the whole state. In reality, however, sunshine hours do vary between different part of each state (although data at such a high resolution was not available) which may have resulted in misclassification bias. Another limitation of the aggregate nature of the US CDC dataset and the climatic data was that when I combined these two sets of data and analysed types of TB disease by hours of sunshine I made a simplifying assumption that the hours of sunshine in a state would apply to all individuals (although clearly factors such as behaviour and clothing would modulate this). Similarly when stratifying type of TB by duration of residence in the US and sunshine hours I did not know exactly how long an individual had been resident in each state and therefore could not be sure that all cases in a particular state reflected sunshine exposure in that state or from a previous state.

Sun exposure was used as a proxy for vitamin D levels although it is unclear how accurate this is,[492] and other sources, such as diet, contribute to vitamin D levels.[493] Furthermore in the St. Mary's dataset I did not have data on whether individuals where already taking vitamin D supplementation at the time of blood sampling and it is possible that serum concentrations may have been affected by anti-tuberculous treatment in those individuals who had already commenced treatment when vitamin D sampling was undertaken although levels were done within 30 days and would have affected all subtypes equally – not only patients with extrapulmonary TB.

I cannot exclude the possibility that susceptibility to extrapulmonary TB may be mediated by an interaction between vitamin D deficiency and vitamin D receptor polymorphisms that are common in pigmented populations including individuals of Indian Subcontinent ethnicity.[317,494] The classification of TB disease used in this study was based on exclusively pulmonary and extrapulmonary involvement. As extrapulmonary disease was significantly more likely to be culture negative there is a possibility that our results were biased by clinicians overdiagnosing or

misdiagnosing extrapulmonary TB in certain demographic groups – particularly Non-White ethnic groups. However, this is unlikely as the findings were based on complete surveillance datasets and were robust to both changes in the classification of extrapulmonary TB (where extrapulmonary TB was defined as pulmonary and extrapulmonary disease) and when data analysis was limited to culture positive active TB cases only.

In conclusion, in the current study, epidemiological and biochemical data collectively identify vitamin D deficiency as a major risk factor for extrapulmonary dissemination in TB. If vitamin D deficiency plays a causal role, the implication for immigrant public health as well as the biology of *Mycobacterium tuberculosis* containment in vitro could be considerable.

Chapter 8 Discussion

Main findings of research

In this thesis I have researched immigrant TB in high-income countries which, with a focus on the UK, has allowed me to analyse two specific issues: immigrant screening for TB (chapters two to five) and the clinical phenotypic presentation of TB in immigrant populations (chapters six and seven).

Chapter 2: An international evaluation of immigrant screening practices for tuberculosis in high-income countries

Immigrant screening programmes for TB in high-income countries have come into sharp focus in the recent past[137] as epidemiological data has highlighted the high incidence (and proportion) of cases occurring amongst foreign-born immigrants[33] which arises through the reactivation of LTBI following arrival in the receiving country rather than the importation of prevalent active TB disease.[191,225,226,252] Despite this, there is little contemporary data on immigrant TB screening programmes in high-income countries particularly with respect to LTBI screening and the elements that are central to LTBI screening - namely which groups of immigrants are screened and how they are screened. In chapter two of this thesis, the results of a prospective international evaluation of immigrant TB screening practices in 29 (out of 31) high-income OECD countries is presented. The analysis reveals that national TB control programmes prioritise screening immigrants for active TB whereas LTBI screening, paradoxically, is extremely limited. Moreover, amongst those countries which do screen for LTBI there is a complete lack of consensus in which immigrant groups to screen (legal migrants vs refugees vs all migrants), which countries/TB incidence thresholds to screen and which screening methodologies to use. My work therefore builds on previous work from others which also found high levels of heterogeneity in screening practices although these earlier studies focused on fewer countries and primarily examined the policies in place for identifying active TB with little examination of LTBI screening policies – particularly with respect to which groups should be screened.[276-278] The lack of consensus in screening practices identified by the work set out in this chapter highlights the absence

of objective evidence from which policy-makers in high-income countries can make evidence-based policy decisions.

Chapter 3: TB screening of migrants to low TB burden nations: lessons from evaluation of UK practice

Amongst high-income countries, the UK, in many respects, epitomises the impact that immigration and reactivating LTBI have on determining TB burden both in the immigrant population and the country as a whole. Although national guidelines on immigrant TB screening have been in place since 2006,[29] there has been no assessment of actual immigrant screening practices which is critical when formulating revised guidance. In chapter three, I present the results of a nationwide evaluation of immigrant screening practices undertaken by local primary-care organisations in the UK. This reveals that whilst screening for active TB was consistently undertaken, screening for LTBI was highly variable with respect to the incidence threshold at which immigrants were considered eligible for screening and the actual screening methodologies used, deviated from national guidance and was inversely related to regional TB burden. Although previous authors have also indicated that immigrant screening practices in the UK are heterogeneous these earlier studies have been small-scale, failed to examine screening practices in detail (especially with respect to LTBI) and have not attempted to relate practice to TB burden.[289,382] Although it is not entirely clear what underlies the stark intra-country variation in immigrant screening practices, the lack of consensus clearly underscores the need for contemporary evidence which can more robustly inform objective health-economic analyses and thereby aid policy-makers in making fully informed decisions.

Chapter 4 Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis

The 2006 iteration of UK national guidance on immigrant screening recommended that only a very select subset of immigrants should be eligible to be screened for LTBI (<16 year-olds from countries with TB incidence >40/100000 and 16-35 year-olds from countries with TB incidence >500/100000 or situated in Sub-Saharan Africa).[29] However, as highlighted in chapter three, a sizeable proportion of local TB services in the UK used different criteria by which to select immigrants for screening – reflecting a lack of consensus – despite the presence of national guidance. One of the problems with the 2006 NICE guidelines was that it was based on little or no empirical data (especially with respect to the prevalence of LTBI as measured by IGRA) which may have resulted in a lack of confidence in the recommendations that were framed. In order to address this lack of empirical data, in chapter four I presented results from the largest multi-centre study of LTBI prevalence in new-entrants, to date, and the first to provide estimates stratified by age, TB incidence in the countries of origin and risk factors for LTBI. As a result I was able to undertake the first health-economic analysis of immigrant screening at different incidence thresholds using real-life IGRA data collected in routine clinical practice. The analysis of the outcomes, and cost-effectiveness, of immigrant screening with IGRA at different incidence thresholds found that new-entrants to the UK have a high prevalence of LTBI which varies by age, gender and TB incidence in their country of origin. Moreover I found, for the first time, that the 2006 national guidance on which groups to screen excludes most latently infected immigrants and this policy could be modified, in centres undertaking or considering the implementation of single-step IGRA testing, by screening at an intermediate threshold (150-250/100000) to substantially reduce TB incidence while remaining cost-effective and practical for TB services. Although previous studies have examined the prevalence of LTBI using IGRA, these studies, in general, have been small and therefore not been able to compute the prevalence of, or the screening yields for, LTBI at different incidence thresholds.[203,209,211,213,215-218,292,295] Furthermore, authors have not used such empirical data to parameterise health-economic modelling – instead using an overall prevalence figure (often 30%) from which cost-effectiveness estimates are obtained.

Chapter 5 Community-based evaluation of immigrant tuberculosis screening using interferon gamma release assays and tuberculin skin testing: observational study and economic analysis

Immigrant screening for TB in the UK is highly topical[273] and during the course of this project, in 2011, revised national guidance on LTBI screening was published stating that all immigrants from countries with a TB incidence >40/100000 should be candidates for LTBI screening with either dual TST plus confirmatory IGRA or single-step IGRA.[81] Despite the major revision in the threshold at which to screen and the methods by which screening could be undertaken, the 2011 iteration of the national guidelines had similar limitations to its predecessor – namely a lack of empirical data informing the health economic modelling. In order to address this drawback, in chapter five I present the results of the first three-way assessment of different screening methods for LTBI, which provides comparative estimates of test performance and positivity stratified by demographic factors and risk factors for LTBI in recent immigrants. Using the data from this prospective study, I parameterised a decision-analysis model to assess the cost-effectiveness of port-of-entry chest radiographs and, with respect to LTBI, incidence thresholds and screening modality. The analysis revealed that UK policy could be modified by removing the current requirement for CXR on arrival and concentrating on LTBI testing using targeted single-step IGRA testing of adult immigrants arriving from countries with intermediate (150-250/100000) TB incidence (rather than from countries with TB incidence >40/100000 as recommended currently).[81] Although previous authors have explored the cost-effectiveness of immigrant screening their analyses have failed to examine incidence thresholds, different combinations of screening tools and have not been underpinned by empirical data.[29,81,299-302]

Chapter 6: The influence of ethnicity and mycobacterial lineage on clinical disease phenotype in tuberculosis

Chapters six and seven focused on the clinical phenotypic presentation of TB disease in immigrants in the UK.

Globally, pulmonary disease is the most common form of active TB[103] but in certain groups extrapulmonary disease is becoming increasingly well-recognised. Immigrants in high-income countries (from high TB burden regions) are one such group who present with a predominantly extrapulmonary pattern of disease yet it is unknown if this relates to demographic, mycobacterial or environmental factors.[33,34,313,314] Advances in genotyping techniques have identified six main lineages of *M. tuberculosis*[331 333] and this has led to renewed interest in the impact that mycobacterial factors have on clinical phenotype.[323] In this chapter, I analysed a large, prospectively collated, dataset from an ethnically-diverse high-income setting to elucidate the ethnic, and geographic, associations of the lineages causing active TB and the association of lineages with different clinical phenotypes. *Mycobacterium tuberculosis* lineages were found to be geographically, and ethnically, restricted. On multivariate adjustment, demographic variables (particularly ethnicity) were most strongly associated with extrapulmonary disease phenotypes (and more strongly than lineage). Certain mycobacterial lineages (Euro-American and East African Indian) were significantly less likely to cause extrapulmonary TB whilst other lineages (East Asian) were independently associated with extrapulmonary disease. The results build on conflicting evidence from previous studies which were limited by their failure to control for demographic factors, being undertaken in settings where the populations are ethnically homogeneous or in populations where distribution of TB lineages is limited.[342,346-349]

Chapter 7 Vitamin D deficiency plays a role in determining the clinical phenotypic presentation of tuberculosis

Although the determinants of clinical phenotype in immigrant populations have been poorly studied, the research that has been undertaken, to date, has primarily focused on demographic and mycobacterial factors. As a result there is very little data on the potential associations of environmental factors, such as vitamin D (through sunlight) on disease pattern, though data indicates that vitamin D plays an important role in host immunity.[439,445,489] In chapter seven, I analysed prospective TB surveillance data from two independent, high-income, Northern hemisphere settings, and found that disease phenotypes differed by demographic (ethnic) group, time since arrival (for those born overseas) and, for the US, by the hours of sunlight a state received. This indirect evidence pointed towards vitamin D (deficiency) playing a role in determining clinical phenotype. Therefore, using empirical data from an independent cohort, I found, for the first time, that vitamin D deficiency, after multivariate adjustment, was significantly associated with extrapulmonary TB. Although previous studies have found that individuals with active TB have significantly lower vitamin D levels, studies have not, to date, examined the associations of vitamin D levels with TB phenotype.[317,471,474-478]

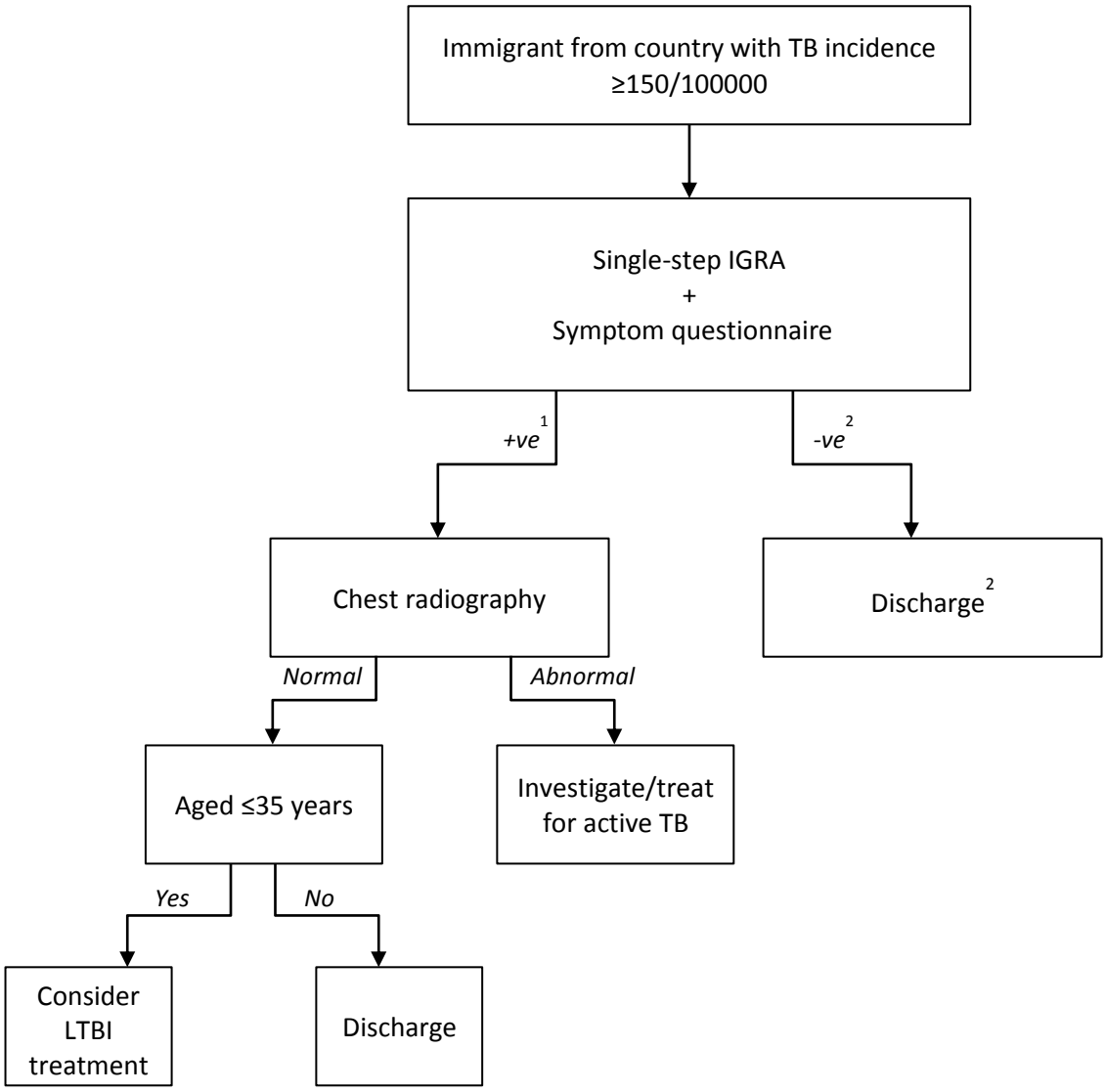
Implications of research

Policy implications of immigrant screening data

Taking together the results from chapters two to five, which focused on immigrant screening for TB, it is possible to identify key issues of import for policy-makers. Although epidemiological data indicates that immigrant TB in high-income countries arises primarily through the reactivation of LTBI, rather than through the importation of prevalent active disease,[186-189,191-197,226] the surveys of international, and UK, practice conducted here highlight that whilst screening for active TB is widely practised and prioritised, LTBI screening is limited and heterogeneous. Using clinico-epidemiological data (chapters four and five), the health-economic analyses undertaken in this thesis suggest that UK

policy on LTBI screening could be modified by removing chest radiography at port-of-entry and using targeted single-step IGRA testing, possibly via a community-based setting, in immigrants originating from intermediate TB incidence settings (threshold around 150-250/100000). This approach would have the additional benefit of balancing the need to identify immigrants with LTBI against limited service capacity whilst still reducing UK TB notifications in the future. Below I present a potential immigrant screening algorithm which could be adopted by policy-makers which incorporates the findings from the thesis.

Figure 8.1 Algorithm for immigrant screening for TB based on results of thesis



Footnotes

[1]If either IGRA or symptom questionnaire is positive then chest radiography should be undertaken
[2]If both IGRA and symptom questionnaire are negative individuals may be discharged although the decision to discharge without undertaking chest-radiography must be made with caution as false negative TST/IGRA results do occur in active TB. Chest-radiography should be undertaken if the clinical suspicion is high and some may argue that it should always be undertaken

Factors determining clinical phenotype of active tuberculosis

Putting together the results from chapters six and seven, where I have explored the factors associated with different clinical phenotypes of active TB disease, it is clear that demographic, mycobacterial

and environmental factors all play some role in determining observed patterns of disease although the relative importance of each factor is unclear. Overall, it appears that host, and environmental factors play a more dominant role than mycobacterial lineage in defining disease pattern. Of these host factors ethnicity, and most likely vitamin D levels, which are determined by pigmented skin and diet, appear to be key elements. This work advances knowledge in mycobacterial mechanisms but also suggests that vitamin D supplementation has important clinical and public health implications, for immigrant communities.

Limitations of research

In each of the individual chapters (chapters two to seven) I have discussed in detail the limitations of the research methods and results. Below I will discuss, in broader general terms, limitations of the work contained in the thesis.

In chapters two and three of the thesis I undertook international, and national, surveys of immigrant screening practices. As the data was primarily obtained by questionnaire, there was the potential for responder and recall bias although I endeavoured to minimise this by clarifying answers with respondents. Moreover, the surveys only provide a snap-shot of immigrant screening practices at one time-point although, as evidenced by the recent change in screening guidance in the UK,[81] they continue to evolve and change in response to new evidence. Finally, the data I obtained for the UK survey primarily focused on legal and documented immigrants (as opposed to refugees and asylum seekers) as this group makes up the majority of immigrants in the UK.

Chapters four and five present two clinico-epidemiological studies which ascertained LTBI prevalence, yields for LTBI and the cost-effectiveness of immigrant screening at different incidence thresholds with different screening tools. For both studies, the distribution of individuals that were tested was very similar, but not identical, to the immigrant population in the UK[409] which must be borne in mind when applying the results to different settings. In the multi-centre study (chapter four) immigrants were only tested with single-step IGRA and so concurrent TST results were not available

(as the centres no longer routinely undertook TST). Similarly, in the three-way assessment not all individuals were concurrently tested with all three screening tools.

In terms of the health economic analyses undertaken in chapters four and five, decision-based models were used. These models were non-dynamic and therefore it was not possible to fully model transmission dynamics although the models used in the current work do include secondary cases of disease and infection. With respect to the model structures, certain simplifying assumptions about TB natural history were made (such as complete clearance of infection, with no risk of reinfection following chemoprophylaxis). Model parameters were obtained, as far as possible, from the most contemporary literature although certain important parameters remain poorly understood including the progression rate from LTBI to active TB disease and the proportion of immigrants that accept and complete chemoprophylaxis. Estimates for test sensitivity and specificity were obtained from a range of meta-analyses[41,43] but it is possible that these values were over- or underestimates which would have affected the results of the cost-effectiveness analyses. In contrast to the cost-utility analysis undertaken by NICE where assessments of different strategies were made using cost per quality adjusted life year (QALY), cost-effectiveness in the current study was quantified as cost per TB case averted, in line with previous authors,[301,302,397,398] as there is still very limited objective data on QALYS for immigrant patients with active TB or those on chemoprophylaxis.

In chapters six and seven, where I explored the factors associated with clinical phenotypes, analyses were based on databases collated as part of routine care and thus limited to those variables which had been recorded (certain variables, such as HIV status, were poorly recorded). When exploring the association of mycobacterial lineage and clinical phenotype, one of the main limitations was that the assignation of MIRU-VNTRs to lineage was primarily undertaken by cross-referencing against an online database (MIRU-VNTRplus[427]), and a proportion of isolates could not be categorised into any specific lineage. In chapter seven, the US-specific analyses were limited by the aggregate nature of the CDC data which prevented multivariate modelling. Misclassification bias could have occurred as data on state-specific hours of sunshine was applied to the states as a whole although it is possible that there would be within state variations in sunshine levels (although data of

that detail was not available). Another limitation of the aggregate nature of the US CDC dataset and the climatic data was that I made a simplifying assumption that the hours of sunshine in a state would apply to all individuals (although clearly factors such as behaviour and clothing would modulate this). Similarly, stratification of TB phenotype by duration of residence in the US and sunshine hours must be viewed with the caveat that the exact duration of residence of an individual in each state was not known and therefore one could not be sure that all cases in a particular state reflected sunshine exposure in that state or from a previous state.

Sun exposure was used as a proxy for vitamin D levels in the US state analysis although it is unclear how accurate this is,[492] and other sources, such as diet, also contribute to vitamin D levels.[493] In the London (vitamin D) dataset information on vitamin D supplementation at the time of blood sampling was not available and anti-tuberculous therapy may have affected vitamin D levels – although I only included patients who had sampling done within 30 days of commencing treatment and the impact of TB therapy should therefore have affected all types of TB equally. A further limitation of the datasets in chapter seven was that data on host genetics (such as vitamin D receptor polymorphisms) was not available and thus it was not possible to control for these host genetic factors. As a consequence it was not possible to exclude the possibility that observed clinical phenotypes reflected interaction between vitamin D and vitamin D receptor polymorphisms which are common in pigmented populations including individuals of Indian Subcontinent ethnicity.[317,494]

Future work

The aim of this thesis was to explore the issue of immigrant TB in the UK with a specific focus on TB control and assess the factors determining the distinct clinical phenotypes observed in this population. Although the current work has answered the research questions posed at the outset, it has also resulted in uncovering several avenues for future research.

The international survey of immigrant screening practices only provided an idealised picture of how screening is undertaken but, as I highlighted in the UK, actual practice may deviate substantially from national guidance. The work contained in chapter three could be used as a template in other high-income countries to evaluate how immigrant screening is actually being implemented,

on the ground, by healthcare professionals. Determinants of immigrant TB screening policies internationally, and in the UK (as well as the reasons for the deviation from national guidelines), remain poorly understood and future work should focus, by way of quantitative and qualitative surveys of TB programme directors and policy-makers, on the exact reasons underpinning the different policies and practices adopted by individual countries (potential issues to explore include cost, practicalities and a lack of resources).

Although LTBI prevalence in my work was computed from moderately large sample sizes, it would be advantageous to undertake larger prospective studies of recent immigrants to the UK in diverse settings (as different areas may have different ethnic mixes) using all three screening methodologies concurrently (TST, QuantiFERON Gold in-tube and T-SPOT.TB). This type of study would provide more accurate estimates of LTBI prevalence thereby allowing more robust parameterisation of health-economic models. Moreover it would be possible to assess the acceptability of screening amongst the immigrant community which is critical if the programme is to be successful. In addition, this study could be extended by following-up immigrants to provide answers to two other understudied areas of controversy. Firstly, it would be possible to accurately ascertain the proportion of immigrants accepting, and completing, chemoprophylaxis for LTBI stratified by age, gender and incidence in country of origin. Secondly, if these immigrants (particularly those who have refused chemoprophylaxis) could be followed up prospectively it would be possible to calculate the rate of progression from LTBI to active TB by recording incident cases of TB. This is a key issue which has not been explored in any detail by researchers to date but is of crucial importance when computing the cost-effectiveness of immigrant screening. In fact, this raises the more general issue of why immigrants who have recently immigrated from high TB burden regions are thought to have an elevated rate of progression from LTBI to active TB. Although this area has been poorly studied it would be of specific importance to the public health of immigrants but also more generally would have the potential to reveal important biological mechanisms underlying the progression from LTBI to active TB disease.

Modelling of immigration and tuberculosis in future studies could, instead of the decision-based approach used here, adopt a transmission-dynamic model (using ordinary and partial

differential equations) which would more accurately take account of transmission dynamics between the local, and foreign, born populations. Outputs from this more complex model could be used to undertake further health-economic modelling although this would require studies to be undertaken which specifically calculated utility weights for immigrants in different health states in active (such as pre-treatment, during treatment and post-treatment) and latent TB (pre-screening, during screening, during chemoprophylaxis, post chemoprophylaxis and, if it occurs, during or post hepatotoxicity).

An alternative to using modelling to assess the relative effectiveness of screening methods would be to undertake a randomised clinical trial of immigrant screening. Although it would be expensive and require the cooperation of the UK government/UK Border Agency, it would likely impact on health policy. One method by which the clinical trial could be undertaken would be for immigrants who have had work/education/spouse visas to be randomised (either just before departing from country of origin or at time of arrival) to no screening, screening with TST/IGRA or routine care (ie. screening with CXR on arrival followed by the possibility of LTBI screening by local TB services) with the main outcome measures being the number of active TB cases, and costs, arising with each of the screening protocols.

Ongoing monitoring of immigrant screening practices and compliance with national immigrant screening guidelines, as undertaken in this thesis, is likely to be necessary to understand what impact screening is having on national TB burden.

Road testing of community-based screening for LTBI, as undertaken in this thesis, on a larger platform (perhaps nationally) would also offer up a conduit by which testing for other infectious diseases (including HIV, hepatitis B and hepatitis C), and ensuring a full vaccination history, could be achieved.

Future work on factors determining clinical phenotype should be undertaken in diverse settings (other than the UK) using large numbers of patients prospectively recruited with data concurrently collected on demographics, host genetics, mycobacterial lineage (using 24 loci MIRU-VNTR which is the standard genotyping method undertaken by the HPA as part of the national genotyping project), and environmental variables including accurate measurement of vitamin D status as well as sun-exposure behaviour. Exploring the impact of host genetics would be particularly

interesting to exclude the possibility that observed clinical phenotypes reflected interaction between vitamin D and vitamin D receptor polymorphisms which are common in pigmented populations including individuals of Indian Subcontinent ethnicity.[317,494]

The association of vitamin D and extrapulmonary TB needs to be confirmed in other settings but it would also be useful if simple data, which is currently unavailable, could be obtained on the temporal dynamics of vitamin D concentrations in adult immigrants following arrival in the UK and the relative concentrations of vitamin D in UK-born and foreign-born non-White immigrants.

Chapter 9 Publications and presentations

The following papers, letters and conference presentations have been completed at the time of submission of the thesis:

Chapter 1

- Lalvani A and **Pareek M**. A 100 year update on diagnosis of tuberculosis infection. British Medical Bulletin 2010; 93:69-84.
- Lalvani A and **Pareek M**. Interferon gamma release assays: principles and practice. Spanish Journal of Infectious Diseases and Clinical Microbiology 2010; 28(4):245-52.
- Lalvani A and **Pareek M**. Interferon gamma release assays in the diagnosis of latent tuberculosis infection. In Tuberculosis: progress in diagnosis & treatment Ed: McHugh T. First Edition. CABI. London (book chapter in press).

Chapter 3

- **Pareek M**, Abubakar I, White PJ, Garnett GP, Lalvani A. Tuberculosis screening of migrants to low-burden nations: insights from evaluation of UK practice. European Respiratory Journal; 37(5):1175-82.
- **Pareek M**, Abubakar I, White PJ, Garnett GP, Lalvani A. UK immigrant screening is inversely related to regional tuberculosis burden. Thorax 2011.
- **Pareek M**, Abubakar I, White PJ, Garnett GP, Lalvani A. Inconsistent and incoherent? Methods of screening new-entrants for tuberculosis in the United Kingdom. British Thoracic Society Winter Meeting London: December 2009.

Chapter 4

- **Pareek M**, Watson JP, Ormerod LP, Kon OM, Woltmann G, White PJ, Abubakar I, Lalvani A. Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis. Lancet Infectious Diseases 2011;11(6):435-44.
- **Pareek M**, Watson JP, Ormerod LP, Kon OM, Woltmann G, Lalvani A. Prevalence of latent tuberculosis infection in immigrants to the UK: findings from a multi-centre study. British Thoracic Society Winter Meeting London: December 2010.

Chapter 5

- **Pareek M,** Bond M, Shorey J, Seneviratne S, Guy M, Lalvani A, Kon O M. Community-based evaluation of immigrant TB screening using interferon gamma release assays and tuberculin skin testing: yields and cost-effectiveness. British Thoracic Society Winter Meeting London: December 2011.

Chapter 10 References

1.Zink AR, Sola C, Reischl U, et al. Characterization of Mycobacterium tuberculosis complex DNAs from Egyptian mummies by spoligotyping. J Clin Microbiol 2003;41:359-67.
2.The Nobel Prize in Physiology or Medicine 1905. (Accessed 28 December, 2009, at http://nobelprize.org/nobel_prizes/medicine/laureates/1905/.)
3.Maartens G, Wilkinson RJ. Tuberculosis. Lancet 2007;370:2030-43.
4.Palomino JC, Leao SC, Ritacco V. Textbook of Tuberculosis: from basic science to patient care. Sao Paulo: BourcillierKamps; 2007.
5.Brennan PJ. Structure, function, and biogenesis of the cell wall of Mycobacterium tuberculosis. Tuberculosis (Edinburgh, Scotland) 2003;83:91-7.
6.Takayama K, Wang C, Besra GS. Pathway to Synthesis and Processing of Mycolic Acids in Mycobacterium tuberculosis. Clin Microbiol Rev 2005;18:81-101.
7.Jensen PA, Lambert LA, Iademarco MF, Ridzon R. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. MMWR Recomm Rep 2005;54:1-141.
8.Nardell EA. Catching droplet nuclei: toward a better understanding of tuberculosis transmission. Am J Respir Crit Care Med 2004;169:553-4.
9.Institute of Medicine. Ending Neglect: The Elimination of Tuberculosis in the United States. Washington: National Academies Press; 2000.
10.World Health Organisation. Tuberculosis: fact sheet number 104. Geneva: WHO; 2007.
11.CDC. Treatment of tuberculosis. MMWR Recomm Rep 2003;52:1-77.
12.Riley RL, Mills CC, Nyka W, et al. Aerial dissemination of pulmonary tuberculosis. A two-year study of contagion in a tuberculosis ward. 1959. Am J Epidemiol 1995;142:3-14.
13.Wells WF. Airborne contagion and air hygiene. An ecological study of droplet infection. Cambridge (MA): Harvard University Press; 1955.
14.Behr MA, Warren SA, Salamon H, et al. Transmission of Mycobacterium tuberculosis from patients smear-negative for acid-fast bacilli. The Lancet 1999;353:444-9.
15.Tostmann A, Kik SV, Kalisvaart NA, et al. Tuberculosis Transmission by Patients with Smear-Negative Pulmonary Tuberculosis in a Large Cohort in The Netherlands. Clinical Infectious Diseases 2008;47:1135-42.
16.Sundaramurthy V, Pieters J. Interactions of pathogenic mycobacteria with host macrophages. Microbes and Infection 2007;9:1671-9.
17.Nguyen L, Pieters J. The Trojan horse: survival tactics of pathogenic mycobacteria in macrophages. Trends Cell Biol 2005;15:269-76.
18.Houben EN, Nguyen L, Pieters J. Interaction of pathogenic mycobacteria with the host immune system. Curr Opin Microbiol 2006;9:76-85.
19.Murray PJ. Defining the requirements for immunological control of mycobacterial infections. Trends in Microbiology 1999;7:366-72.
20.Cooper AM, Flynn JL. The protective immune response to Mycobacterium tuberculosis. Current Opinion in Immunology 1995;7:512-6.
21.Bean AG, Roach DR, Briscoe H, et al. Structural deficiencies in granuloma formation in TNF gene-targeted mice underlie the heightened susceptibility to aerosol Mycobacterium tuberculosis infection, which is not compensated for by lymphotoxin. J Immunol 1999;162:3504-11.
22.Pai M, Dheda K, Cunningham J, Scano F, O'Brien R. T-cell assays for the diagnosis of latent tuberculosis infection: moving the research agenda forward. The Lancet Infectious Diseases 2007;7:428-38.
23.Barnes PF. Diagnosing Latent Tuberculosis Infection. The 100-year Upgrade. Am J Respir Crit Care Med 2001;163:807-8.
24.Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA 1999;282:677-86.
25.Corbett EL, Watt CJ, Walker N, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med 2003;163:1009-21.
26.Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. Am J Epidemiol 1974;99:131-8.
27.Horsburgh CR, Jr. Priorities for the Treatment of Latent Tuberculosis Infection in the United States. N Engl J Med 2004;350:2060-7.
28.American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC). Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. Am J Respir Crit Care Med 2000;161:221-47.
29.National Collaborating Centre for Chronic Conditions. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. London: Royal College of Physicians; 2006.
30.Lawn SD. Tuberculosis and HIV co-infection. Medicine 2005;33:112-3.
31. Golden MP, Vikram HR. Extrapulmonary tuberculosis: an overview. Am Fam Physician 2005;72:1761-8.

32.Kingkaew N, Sangtong B, Amnuaiphon W, et al. HIV-associated extrapulmonary tuberculosis in Thailand: epidemiology and risk factors for death. International Journal of Infectious Diseases 2009;13:722-9.
33.Kruijshaar ME, Abubakar I. Increase in extrapulmonary tuberculosis in England and Wales 1999–2006. Thorax 2009;64:1090-5.
34.te Beek LA, van der Werf MJ, Richter C, Borgdorff MW. Extrapulmonary tuberculosis by nationality, The Netherlands, 1993-2001. Emerg Infect Dis 2006;12:1375-82.
35.Ong A, Creasman J, Hopewell PC, et al. A Molecular Epidemiological Assessment of Extrapulmonary Tuberculosis in San Francisco. Clinical Infectious Diseases 2004;38:25-31.
36.Escalante P. Tuberculosis. Annals of internal medicine 2009;150:ITC1-614.
37.Lalvani A. Spotting latent infection: the path to better tuberculosis control. Thorax 2003;58:916 - 8.
38.Lalvani A. Diagnosing tuberculosis infection in the 21st century: new tools to tackle an old enemy. Chest 2007;131:1898 - 906.
39.Lalvani A, Pareek M. A 100 year update on diagnosis of tuberculosis infection. British Medical Bulletin 2009;93:69-84.
40.Joint Committee on Vaccination and Immunisation. BCG Statement. London: Department of Health; 2007.
41.Diel R, Loddenkemper R, Nienhaus A. Evidence-Based Comparison of Commercial Interferon-Gamma Release Assays for Detecting Active TB. Chest 2010;137:952-68.
42.Sester M, Sotgiu G, Lange C, et al. Interferon-γ release assays for the diagnosis of active tuberculosis: a systematic review and meta-analysis. European Respiratory Journal 2011;37:100-11.
43.Pai M, Zwerling A, Menzies D. T-Cell-Based Assays for the Diagnosis of Latent Tuberculosis Infection: An Update. Ann Intern Med 2008;149:177 - 84.
44.Mahairas GG, Sabo PJ, Hickey MJ, Singh DC, Stover CK. Molecular analysis of genetic differences between Mycobacterium bovis BCG and virulent M. bovis. J Bacteriol 1996;178:1274-82.
45.Harboe M, Oettinger T, Wiker HG, Rosenkrands I, Andersen P. Evidence for occurrence of the ESAT-6 protein in Mycobacterium tuberculosis and virulent Mycobacterium bovis and for its absence in Mycobacterium bovis BCG. Infect Immun 1996;64:16-22.
46.Lalvani A, Pathan AA, McShane H, et al. Rapid detection of Mycobacterium tuberculosis infection by enumeration of antigen-specific T cells. Am J Respir Crit Care Med 2001;163:824-8.
47.Ewer K, Deeks J, Alvarez L, et al. Comparison of T-cell-based assay with tuberculin skin test for diagnosis of Mycobacterium tuberculosis infection in a school tuberculosis outbreak. Lancet 2003;361:1168-73.
48.Lalvani A, Pathan AA, Durkan H, et al. Enhanced contact tracing and spatial tracking of Mycobacterium tuberculosis infection by enumeration of antigen-specific T cells. Lancet 2001;357:2017-21.
49.Dominguez J, Ruiz-Manzano J, De Souza-Galvao M, et al. Comparison of Two Commercially Available Gamma Interferon Blood Tests for Immunodiagnosis of Tuberculosis. Clin Vaccine Immunol 2008;15:168-71.
50.Soysal A, Millington KA, Bakir M, et al. Effect of BCG vaccination on risk of Mycobacterium tuberculosis infection in children with household tuberculosis contact: a prospective community-based study. Lancet 2005;366:1443-51.
51.Connell TG, Ritz N, Paxton GA, Buttery JP, Curtis N, Ranganathan SC. A Three-Way Comparison of Tuberculin Skin Testing, QuantiFERON-TB Gold and T-SPOT.TB in Children. PLoS ONE 2008;3:e2624.
52.Diel R, Loddenkemper R, Meywald-Walter K, Gottschalk R, Nienhaus A. Comparative Performance of Tuberculin Skin Test, QuantiFERON-TB-Gold In Tube Assay, and T-Spot.TB Test in Contact Investigations for Tuberculosis. Chest 2009;135:1010-18.
53.Nicol MP, Davies M-A, Wood K, et al. Comparison of T-SPOT.TB Assay and Tuberculin Skin Test for the Evaluation of Young Children at High Risk for Tuberculosis in a Community Setting. Pediatrics 2009;123:38-43.
54.Cattamanchi A, Smith R, Steingart KR, et al. Interferon-Gamma Release Assays for the Diagnosis of Latent Tuberculosis Infection in HIV-Infected Individuals: A Systematic Review and Meta-Analysis. JAIDS Journal of Acquired Immune Deficiency Syndromes 2011;56:230-8
55.Dheda K, Lalvani A, Miller RF, et al. Performance of a T-cell-based diagnostic test for tuberculosis infection in HIV-infected individuals is independent of CD4 cell count. AIDS 2005;19:2038-41.
56.Stephan C, Wolf T, Goetsch U, et al. Comparing QuantiFERON-tuberculosis gold, T-SPOT tuberculosis and tuberculin skin test in HIV-infected individuals from a low prevalence tuberculosis country. AIDS 2008;22:2471-9.
57.Liebeschuetz S, Bamber S, Ewer K, Deeks J, Pathan AA, Lalvani A. Diagnosis of tuberculosis in South African children with a T-cell-based assay: a prospective cohort study. Lancet 2004;364:2196-203.
58.Rangaka MX, Diwakar L, Seldon R, et al. Clinical, Immunological, and Epidemiological Importance of Antituberculosis T Cell Responses in HIV-Infected Africans. Clinical Infectious Diseases 2007;44:1639-46.
59.Clark SA, Martin SL, Pozniak A, et al. Tuberculosis antigen-specific immune responses can be detected using enzyme-linked immunospot technology in human immunodeficiency virus (HIV)-1 patients with advanced disease. Clin Exp Immunol 2007;150:238-44.
60.Raby E, Moyo M, Devendra A, et al. The Effects of HIV on the Sensitivity of a Whole Blood IFN-γ Release Assay in Zambian Adults with Active Tuberculosis. PLoS ONE 2008;3:e2489.

61.Mandalakas AM, Hesseling AC, Chegou NN, et al. High level of discordant IGRA results in HIV-infected adults and children. Int J Tuberc Lung Dis 2008;12:417-23.
62.Balcells ME, Perez CM, Chanqueo L, et al. A comparative study of two different methods for the detection of latent tuberculosis in HIV-positive individuals in Chile. Int J Infect Dis 2008;12:645-52.
63.Brock I, Ruhwald M, Lundgren B, Westh H, Mathiesen LR, Ravn P. Latent tuberculosis in HIV positive, diagnosed by the M. tuberculosis specific interferon-gamma test. Respir Res 2006;7:56.
64.Luetkemeyer AF, Charlebois ED, Flores LL, et al. Comparison of an Interferon-gamma Release Assay with Tuberculin Skin Testing in HIV-infected Individuals. Am J Respir Crit Care Med 2007;175:737-42.
65.Sutherland I. The ten-year incidence of clinical tuberculosis following 'conversion' in 2,550 individuals aged 14 to 19 years. Tuberculosis Surveillance and Research Unit Progress Report 1968. The Hague: Royal Netherlands Tuberculosis Association (KNCV); 1968.
66.Sutherland I. Recent studies in the epidemiology of tuberculosis, based on the risk of being infected with tubercle bacilli. Advances in Tuberculosis Research 1976;19:1-63.
67.Sutherland I, Svandova E, Radhakrishna S. The development of clinical tuberculosis following infection with tubercle bacilli. Tubercle 1982;63:255-68.
68.Diel R, Loddenkemper R, Meywald-Walter K, Niemann S, Nienhaus A. Predictive value of a whole blood IFN-gamma assay for the development of active tuberculosis disease after recent infection with Mycobacterium tuberculosis. Am J Respir Crit Care Med 2008;177:1164-70.
69.Bakir M, Millington KA, Soysal A, et al. Prognostic Value of a T-Cell-Based, Interferon-gamma Biomarker in Children with Tuberculosis Contact. Ann Intern Med 2008;149:777-86.
70.Hill PC, Jackson-Sillah DJ, Fox A, et al. Incidence of Tuberculosis and the Predictive Value of ELISPOT and Mantoux Tests in Gambian Case Contacts. PLoS ONE 2008;3:e1379.
71.Doherty TM, Demissie A, Olobo J, et al. Immune Responses to the Mycobacterium tuberculosis-Specific Antigen ESAT-6 Signal Subclinical Infection among Contacts of Tuberculosis Patients. J Clin Microbiol 2002;40:704-6.
72.Aichelburg MC, Rieger A, Breitenecker F, et al. Detection and Prediction of Active Tuberculosis Disease by a Whole-Blood Interferon-gamma Release Assay in HIV-1-Infected Individuals. Clin Infect Dis 2009;48:954-62.
73.Diel R, Goletti D, Ferrara G, et al. Interferon-γ release assays for the diagnosis of latent Mycobacterium tuberculosis infection: a systematic review and meta-analysis. European Respiratory Journal 2011;37:88-99.
74.Haldar P, Thuraisingham H, Hoskyns W, Woltmann G. Contact screening with single-step TIGRA testing and risk of active TB infection: The Leicester Cohort Analysis. Thorax 2009;64:A13.
75.Rangaka MX, Wilkinson KA, Glynn JR, et al. Predictive value of interferon-gamma release assays for incident active tuberculosis: a systematic review and meta-analysis. The Lancet Infectious Diseases 2012;12:45-55.
76.Guidelines on IGRA: Concordant or Discordant? , 2009. (Accessed 12th August 2010, at http://www.tbevidence.org/documents/guidelines/surveyIGRAs.pdf.)
77.Denkinger CM, Dheda K, Pai M. Guidelines on interferon-γ release assays for tuberculosis infection: concordance, discordance or confusion? Clinical Microbiology and Infection 2011;17:806-14.
78.STAG-TB WHO. Strategic and Technical Advisory Group for Tuberculosis. Report of the Tenth Meeting. Geneva: World Health Organisation; 2011.
79.Mazurek GH, Jereb J, Lobue P et al. Guidelines for using the QuantiFERON-TB Gold test for detecting Mycobacterium tuberculosis infection, United States. MMWR Recomm Rep 2005;54:49-55.
80.National Collaborating Centre for Chronic Conditions. Tuberculosis: appendices. London: Royal College of Physicians; 2006.
81.National Collaborating Centre for Chronic Conditions. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. London: Royal College of Physicians; 2011.
82.Van Cleeff MR, Kivihya-Ndugga L, Githui W, Ng'ang'a LW, Odhiambo JA, Klatser PR. A comprehensive study on the efficiency of the routine pulmonary tuberculosis diagnostic process in Nairobi. Int J Tuberc Lung Dis 2003;7:186 - 90.
83.van Cleeff MRA, Kivihya-Ndugga LE, Meme H, Odhiambo JA, Klatser PR. The role and performance of chest X-ray for the diagnosis of tuberculosis: A cost-effectiveness analysis in Nairobi, Kenya. BMC Infectious Diseases 2005;5:111.
84.Toman K. Tuberculosis case-finding and chemotherapy. Questions and Answers. Geneva: WHO; 2004.
85.American Thoracic Society (ATS). Diagnostic Standards and Classification of Tuberculosis in Adults and Children. Am J Respir Crit Care Med 2000;161:1376-95.
86.Hobby GL, Holman AP, Iseman MD, Jones J. Enumeration of tubercle bacilli in sputum of patients with pulmonary tuberculosis. Antimicrob Agents Chemother 1973;4:94-104.
87.Davies PDO, Pai M. The diagnosis and misdiagnosis of tuberculosis [State of the art series. Tuberculosis. Edited by I. D. Rusen. Number 1 in the series]. The International Journal of Tuberculosis and Lung Disease 2008;12:1226-34.
88.Wilks D, Farrington M, Rubenstein D. The Infectious Diseases Manual. Oxford: Blackwell 2003.

89.Innes JD, Deeks J, Kunst H, et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 2007;11.
90.Ling DI, Zwerling AA, Pai M. GenoType MTBDR assays for the diagnosis of multidrug-resistant tuberculosis: a meta-analysis. Eur Respir J 2008;32:1165-74.
91.Dosanjh DP, Hinks TS, Innes JA, et al. Improved diagnostic evaluation of suspected tuberculosis. Ann Intern Med 2008;148:325-36.
92.Goletti D, Stefania C, Butera O, et al. Accuracy of Immunodiagnostic Tests for Active Tuberculosis Using Single and Combined Results: A Multicenter TBNET-Study. PLoS ONE 2008;3:e3417.
93.Lalvani A, Millington KA. T-cell interferon-γ release assays: can we do better? Eur Respir J 2008;32:1428-30.
94.Smieja MJ, Marchetti CA, Cook DJ, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane database of systematic reviews (Online) 2000:CD001363.
95.Woldehanna S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. The Cochrane Library 2004;1:CD0001171.
96.Ena J, Valls V. Short-Course Therapy with Rifampin plus Isoniazid, Compared with Standard Therapy with Isoniazid, for Latent Tuberculosis Infection: A Meta-analysis. Clinical Infectious Diseases 2005;40:670-6.
97.Kopanoff DE, Snider DE, Jr., Caras GJ. Isoniazid-related hepatitis: a U.S. Public Health Service cooperative surveillance study. Am Rev Respir Dis 1978;117:991-1001.
98.Saukkonen JJ, Cohn DL, Jasmer RM, et al. An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy. Am J Respir Crit Care Med 2006;174:935-52.
99.American Thoracic Society. Update: Fatal and Severe Liver Injuries Associated With Rifampin and Pyrazinamide for Latent Tuberculosis Infection, and Revisions in American Thoracic Society/ CDC Recommendations-United States, 2001. Am J Respir Crit Care Med 2001;164:1319-20.
100.American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. . MMWR Recomm Rep 2000;49:1 - 51.
101.Gelband H. Regimens of less than six months for treating tuberculosis. The Cochrane Library 1999;4:CD001362.
102.American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America. Treatment of Tuberculosis. Am J Respir Crit Care Med 2003;167:603-62.
103.World Health Organisation. Global tuberculosis control - surveillance, planning, financing. Geneva: WHO; 2010.
104.World Health Organisation. Global tuberculosis control - surveillance, planning, financing. Geneva: WHO; 2009.
105.McShane H. Co-infection with HIV and TB: double trouble. Int J STD AIDS 2005;16:95-101.
106.Horsburgh CR, Rubin EJ. Latent Tuberculosis Infection in the United States. New England Journal of Medicine 2011;364:1441-8.
107.Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med 1989;320:545 - 50.
108.Crampin AC, Mwaungulu JN, Mwaungulu FD, et al. Recurrent TB: relapse or reinfection? The effect of HIV in a general population cohort in Malawi. AIDS 2010;24:417-26.
109.Sonnenberg P, Murray J, Glynn JR, Shearer S, Kambashi B, Godfrey-Faussett P. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. The Lancet 2001;358:1687-93.
110.Houben RM, Crampin AC, Ndhlovu R, et al. Human immunodeficiency virus associated tuberculosis more often due to recent infection than reactivation of latent infection The International Journal of Tuberculosis and Lung Disease 2011;15:24-31.
111.Glynn JR, Crampin AC, Yates MD, et al. The Importance of Recent Infection with Mycobacterium tuberculosis in an Area with High HIV Prevalence: A Long-Term Molecular Epidemiological Study in Northern Malawi. Journal of Infectious Diseases 2005;192:480-7.
112.Ormerod LP. Multidrug-resistant tuberculosis (MDR-TB): epidemiology, prevention and treatment. Br Med Bull 2005;73-74:17-24.
113.Chan ED, Iseman MD. Multidrug-resistant and extensively drug-resistant tuberculosis: a review. Current Opinion in Infectious Diseases 2008;21:587-95.
114.Wright A, Zignol M, Van Deun A, et al. Epidemiology of antituberculosis drug resistance 2002-07: an updated analysis of the Global Project on Anti-Tuberculosis Drug Resistance Surveillance. The Lancet 2009;373:1861-73.
115.XDR-TB: Extensively drug-resistant tuberculosis. 2009. (Accessed 30 December, 2009, at http://www.who.int/tb/challenges/xdr/en/index.html.)
116.Country and lending groups: high income OECD countries. 2011. (Accessed 30th August, 2011, at http://data.worldbank.org/about/country-classifications/country-and-lending-groups#OECD_members.)
117.European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance in Europe 2009. Stockholm: European Centre for Disease Prevention and Control; 2011.

118.CDC. Reported Tuberculosis in the United States, 2009. Atlanta: Department of Health and Human Services, CDC; 2010.
119.Tuberculosis in Canada 1995-2009. Public Health Agency of Canada, 2011. (Accessed 30th August, 2011, at http://www.phac-aspc.gc.ca/tbpc-latb/pubs/tbcan09pre/index-eng.php.)
120.Global Health Observatory Database. World Health Organisation, 2011. (Accessed 14th February, 2011, at http://apps.who.int/ghodata/.)
121.Annual tuberculosis reports 2007-2009. 2011. (Accessed 30th August, 2011, at http://www.surv.esr.cri.nz/surveillance/AnnualTBReports.php.)
122.Tuberculosis notifications in Australia annual reports. 2011. (Accessed 30th August, 2011, at http://www.health.gov.au/internet/main/publishing.nsf/content/cda-pubs-annlrpt-tbannrep.htm.)
123.European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance in Europe 2007. Stockholm: European Centre for Disease Prevention and Control; 2009.
124.European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance in Europe 2008. Stockholm: European Centre for Disease Prevention and Control; 2010.
125.EURO-TB. EuroTB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005. Saint-Maurice: European Commission; 1995.
126.EURO-TB. EuroTB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005. Saint-Maurice: European Commission; 1996.
127.EURO-TB. EuroTB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005. Saint-Maurice: European Commission; 1997.
128.EURO-TB. EuroTB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005. Saint-Maurice: European Commission; 1998.
129.EURO-TB. EuroTB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005. Saint-Maurice: European Commission; 1999.
130.EURO-TB. EuroTB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005. Saint-Maurice: European Commission; 2000.
131.EURO-TB. EuroTB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005. Saint-Maurice: European Commission; 2001.
132.EURO-TB. EuroTB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005. Saint-Maurice: European Commission; 2002.
133.EURO-TB. EuroTB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005. Saint-Maurice: European Commission; 2003.
134.EURO-TB. EuroTB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005. Saint-Maurice: European Commission; 2004.
135.EURO-TB. EuroTB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005. Saint-Maurice: European Commission; 2005.
136.EURO-TB. EuroTB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005. Saint-Maurice: European Commission; 2006.
137.European Centre for Disease Prevention and Control. Migrant health: Background report to the ECDC Report on migration and infectious diseases in the EU. Stockholm: European Centre for Disease Prevention and Control; 2009.
138.World Health Organisation Stop TB Partnership. The Global Plan to Stop TB 2011-2015. Geneva: World Health Organisation; 2010.
139.Japan Research Institute of Tuberculosis. Tuberculosis Annual Report 2009: TB in foreigners. Tokyo: JATA; 2009.
140.Health Protection Agency. Tuberculosis in the UK: Annual report on tuberculosis surveillance and control in the UK 2010. London: Health Protection Agency Centre for Infections; 2010.

141.MacPherson DW, Gushulak BD. Balancing prevention and screening among international migrants with tuberculosis: population mobility as the major epidemiological influence in low-incidence nations. Public Health 2006;120:712-23.
142.EURO-TB. EuroTB and the national coordinators for tuberculosis surveillance in the WHO European Region. Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2005. Saint-Maurice: European Commission; 2007.
143.Cohen T, Murray M. Incident tuberculosis among recent US immigrants and exogenous reinfection. Emerg Infect Dis 2005;11:725-8.
144.Centre for Disease Control. Recommendations for Prevention and Control of Tuberculosis Among Foreign-Born Persons Report of the Working Group on Tuberculosis Among Foreign-Born Persons. MMWR 1998;47:1-26.
145.Lillebaek T, Andersen AB, Dirksen A, Smith E, Skovgaard LT, Kok-Jensen A. Persistent high incidence of tuberculosis in immigrants in a low-incidence country. Emerg Infect Dis 2002;8:679-84.
146.Public Health Agency of Canada. Tuberculosis among the foreign-born in Canada. CCDR 2003;29.
147.Tuberculosis data and statistics. 2011. (Accessed 30th August, 2011, at http://www.cdc.gov/tb/statistics/default.htm.)
148.Epidemiology of tuberculosis in France 2009. 2011. (Accessed 30th August 2011, at http://www.invs.sante.fr/surveillance/tuberculose/default.htm.)
149.KNCV. Tuberculosis in the Netherlands 2009. The Hague: KNCV; 2010.
150. Robert Koch Institute. Tuberculosis surveillance in Germany 2009. Berlin: Robert Koch Institute; 2011.
151.TB notifications since 1913 by site of disease. Health Protection Agency, 2011. (Accessed 30th August, 2011, at http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/Tuberculosis/TBUKSurveillanceData/TBUKSurveillanceViaNOIDs/TBNOIDs011913/.)
152. EURO-TB. Total TB cases and TB notification rates, 1995-2006, WHO European Region 2006.
153.Health Protection Agency. Tuberculosis in the UK: Annual report on tuberculosis surveillance and control in the UK 2007. London: Health Protection Agency Centre for Infections; 2007.
154.TB data by UK primary care organisation. Health Protection Agency, 2011. (Accessed 30th August, 2011, at http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1287147465528.)
155.Heath TC, Roberts C, Winks M, Capon AG. The epidemiology of tuberculosis in New South Wales 1975-1995: the effects of immigration in a low prevalence population. Int J Tuberc Lung Dis 1998;2:647-54.
156. Yew WW, Leung CC. Update in Tuberculosis 2007. Am J Respir Crit Care Med 2008;177:479-85.
157.Enhanced TB surveillance data by place of birth and ethnic group, showing numbers and rates for 2000-2009. Health Protection Agency, 2011. (Accessed 14th June, 2011, at http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/Tuberculosis/TBUKSurveillanceData/EnhancedTuberculosisSurveillance/TBEnhanced11site/.)
158.British Thoracic and Tuberculosis Association. A tuberculosis survey in England and Wrales 1971; the influence ofimmigration and country ofbirth upon notifications. A report from the research committee of the British Thoracic and Tuberculosis Association. Tuhercle 1973;54:249-60.
159.British Thoracic and Tuberculosis Association. Tuberculosis among immigrants related to length of residence in England and Wales. Br Med J 1975;iii:698-9.
160.Kumar D, Watson JM, Charlett A, Nicholas S, Darbyshire JH. Tuberculosis in England and Wales in 1993: results of a national survey. Public Health Laboratory Service/British Thoracic Society/Department of Health Collaborative Group. Thorax 1997;52:1060-7.
161.Medical Research Council Tuberculosis and Chest Diseases Unit. National survey of tuberculosis notifications in England and Wales 1978-9. Br Med J 1980;281:895-8.
162.Medical Research Council Tuberculosis and Chest Diseases Unit. National survey of tuberculosis notifications in England and Wales 1983. Br Med J 1985;291:658-61.
163.Medical Research Council Tuberculosis and Chest Diseases Unit. National survey of notifications of tuberculosis in England and Wales in 1988. Medical Research Council Cardiothoracic Epidemiology Group. Thorax 1992;47:770-5.
164.Ormerod LP, Charlett A, Gilham C, Darbyshire JH, Watson JM. Geographical distribution of tuberculosis notifications in national surveys of England and Wales in 1988 and 1993: report of the Public Health Laboratory Service/British Thoracic Society/Department of Health Collaborative Group. Thorax 1998;53:176-81.
165.Rose AMC, Watson JM, Graham C, et al. Tuberculosis at the end of the 20th century in England and Wales: results of a national survey in 1998. Thorax 2001;56:173-9.
166.International Organisation for Migration. Glossary on migration. Geneva: International Organisation for Migration; 2004.
167.United Nations Department of Economic and Social Affairs. Trends in total migrant stock: the 2008 revision. Geneva: UN; 2008.

168.United Kingdom Pre-Departure Tuberculosis Detection Programme. IOM, 2009. (Accessed 25th March, 2010, at http://www.iom.int/jahia/Jahia/activities/by-theme/migration-health/assessments-and-travel-assistance/uktb-detection-programme.)
169.Castles S, Davidson A. Citizenship and migration: globalization and the politics of belonging. New York: Routledge; 2000.
170.Health Protection Agency. Migrant Health. Infectious diseases in non-UK born populations in England, Wales and Northern Ireland. A baseline report - 2006. London: Health Protection Agency Centre for Infections; 2006.
171.Reported tuberculosis in the United States, 2004. US Department of Health and Human Services, CDC, 2005. (Accessed 7 July, 2008, at http://www.cdc.gov/nchstp/tb/surv/surv2004/default.htm)
172.Tuberculosis in Canada 2002. Public Health Agency of Canada, 2004. (Accessed 7 July, 2008, at http://www.phac-aspc.gc.ca/publicat/tbcan02/pdf/tbcan_2002_e.pdf)
173.Li J, Roche P, Spencer J, et al. Tuberculosis Notifications in Australia, 2003. Commun Dis Intell 2004;28:464-73.
174.Total International Migration (TIM) tables: 1991- latest. ONS, 2010. (Accessed at http://www.statistics.gov.uk/STATBASE/Product.asp?vlnk=15053&More=Y.)
175.Office for National Statistics. Total International Migration (TIM) tables: 1971-1974. London: ONS; 1974.
176.Gilbert RL, Antoine D, French CE, Abubakar I, Watson JM, Jones JA. The impact of immigration on tuberculosis rates in the United Kingdom compared with other European countries. Int J Tuberc Lung Dis 2009;13:645-51.
177.Total International Migration (TIM) tables: 1975-1990. ONS, 1990. (Accessed at http://www.statistics.gov.uk/STATBASE/Product.asp?vlnk=15053&More=Y.)
178.Convery I, Welshman J, Bashford A. Where is the border? Screening for tuberculosis in the United Kingdom and Australia, 1950-2000. In: Bashford A, ed. Medicine at the Border Disease, Globalization and Security, 1850 to the Present. New York: Palgrave MacMillan; 2006:97-115.
179.Welshman J. Compulsion, Localism, and Pragmatism: The Micro-Politics of Tuberculosis Screening in the United Kingdom, 1950–1965. Social History of Medicine 2006;19:295-312.
180.Dobson J, Koser K, McLaughlan G, Salt J. International Migration and the United Kingdom: Recent patterns and trends. London: UK Home Office Communication Development Unit; 2001.
181.Quarterly Labour Force Survey, October-December 2007 Office for National Statistics. Social and Vital Statistics Division 2007. (Accessed at http://www.esds.ac.uk/findingData/snDescription.asp?sn=5796.)
182.Farah MG, Meyer HE, Selmer R, Heldal E, Bjune G. Long-term risk of tuberculosis among immigrants in Norway. Int J Epidemiol 2005;34:1005-11.
183.Arshad S, Bavan L, Gajari K, Paget SNJ, Baussano I. Active screening at entry for tuberculosis among new immigrants: a systematic review and meta-analysis. European Respiratory Journal 2010;35:1336-45.
184.Klinkenberg E, Manissero D, Semenza JC, Verver S. Migrant tuberculosis screening in the EU/EEA: yield, coverage and limitations. Eur Respir J 2009;34:1180-9.
185.Liu Y, Weinberg MS, Ortega LS, Painter JA, Maloney SA. Overseas Screening for Tuberculosis in U.S.-Bound Immigrants and Refugees. New England Journal of Medicine 2009;360:2406-15.
186.Bakhshi S. Screening immigrants at risk of tuberculosis. BMJ 1994;308:416a.
187.Bothamley GH, Rowan JP, Griffiths CJ, et al. Screening for tuberculosis: the port of arrival scheme compared with screening in general practice and the homeless. Thorax 2002;57:45-9.
188.Callister ME, Barringer J, Thanabalasingam ST, Gair R, Davidson RN. Pulmonary tuberculosis among political asylum seekers screened at Heathrow Airport, London, 1995-9. Thorax 2002;57:152 - 6.
189.Hardie RM, Watson JM. Screening migrants at risk of tuberculosis. BMJ 1993;307:1539-40.
190.Harling R, Pearce M, Chandrakumar M, Mueller K, Hayward A. Tuberculosis screening of asylum seekers: 1 years' experience at the Dover Induction Centres. Public Health 2007;121:822-7.
191.Health Protection Agency. Port health and medical inspection review: report from the project team. London: Health Protection Agency; 2006.
192.Lavender M. Screening immigrants for tuberculosis in Newcastle upon Tyne. Journal of Public Health 1997;19:320-3.
193.Markey AC, Forster SM, Mitchell R, Larson E, Smith H, Dore CJ. Suspected cases of pulmonary tuberculosis referred from port of entry into Great Britain, 1980-3. Br Med J (Clin Res Ed) 1986;292:378.
194.Millership S, Cummins A. Identification of tuberculosis cases by port health screening in Essex 1997-2003. J Public Health (Oxf) 2005;27:196-8.
195.Ormerod LP. Tuberculosis screening and prevention in new immigrants 1983-88. Respiratory Medicine 1990;84:269-71.
196.Ormerod LP. Is new immigrant screening for tuberculosis still worthwhile? J Infect 1998;37:39-40.
197.Whitfield RJ, Khan R, Smith A, Rayner CF. Current medical treatment for tuberculosis. Resources used for screening could be spent more usefully elsewhere. BMJ 2003;326:550.

198.Chin DP, DeRiemer K, Small PM, et al. Differences in contributing factors to tuberculosis incidence in U.S. - born and foreign-born persons. Am J Respir Crit Care Med 1998;158:1797-803.
199.Jasmer RM, Hahn JA, Small PM, et al. A molecular epidemiologic analysis of tuberculosis trends in San Francisco, 1991-1997. Ann Intern Med 1999;130:971-8.
200.Tornieporth NG, Ptachewich Y, Poltoratskaia N, et al. Tuberculosis among foreign-born persons in New York City, 1992-1994: implications for tuberculosis control. Int J Tuberc Lung Dis 1997;1:528-35.
201.Brassard P, Steensma C, Cadieux L, Lands LC. Evaluation of a School-Based Tuberculosis-Screening Program and Associate Investigation Targeting Recently Immigrated Children in a Low-Burden Country. Pediatrics 2006;117:e148-56.
202.Breuss E, Helbling P, Altpeter E, JP. Z. Screening and treatment for latent tuberculosis infection among asylum seekers entering Switzerland. Swiss Med Wkly 2002 132:197-200.
203.Carvalho AC, Pezzoli MC, El-Hamad I, et al. QuantiFERON-TB Gold test in the identification of latent tuberculosis infection in immigrants. Journal of Infection 2007;55:164 - 8.
204.Carvalho AC, Saleri N, El-Hamad I, et al. Completion of screening for latent tuberculosis infection among immigrants. Epidemiol Infect 2005;133:179-85.
205.Gany FM, Trinh-Shevrin C, Changrani J. Drive-by Readings: A Creative Strategy for Tuberculosis Control Among Immigrants. Am J Public Health 2005;95:117-9.
206.Gibney KB, Mihrshahi S, Torresi J, Marshall C, Leder K, Biggs B-A. The Profile of Health Problems in African Immigrants Attending an Infectious Disease Unit in Melbourne, Australia. Am J Trop Med Hyg 2009;80:805-11.
207.Haley CA, Cain KP, Yu C, Garman KF, Wells CD, Laserson KF. Risk-Based Screening for Latent Tuberculosis Infection. Southern Medical Journal 2008;101:142-9
208.Hernandez-Garduno E, Elwood RK. The prevalence and predictors of tuberculin positivity in subjects screened for reasons other than contact investigation. Can Respir J 2008;15:181-7.
209.Janssens JP, Roux-Lombard P, Perneger T, Metzger M, Vivien R, Rochat T. Contribution of a IFN-gamma assay in contact tracing for tuberculosis in a low-incidence, high immigration area. Swiss Med Wkly 2008;138:585-93.
210.Li J, Munsiff SS, Agerton TB. Prevalence of tuberculin skin test positivity in clinical population in New York City. J Immigr Minor Health 2010;12:816-22.
211.Orlando G, Merli S, Cordier L, et al. Interferon-γ releasing assay versus tuberculin skin testing for latent tuberculosis infection in targeted screening programs for high risk immigrants. Infection 2010;38:195-204.
212.Richards B, Kozak R, Brassard P, Menzies D, Schwartzman K. Tuberculosis surveillance among new immigrants in Montreal. Int J Tuberc Lung Dis 2005;9:858-64.
213.Saracino A, Scotto G, Fornabaio C, et al. QuantiFERON-TB Gold In-Tube test (QFT-GIT) for the screening of latent tuberculosis in recent immigrants to Italy. New Microbiol 2009;32:369-76.
214.Wells Charles D, Zuber Patrick LF, Nolan Charles M, Binkin Nancy J, Goldberg Stefan V. Tuberculosis Prevention Among Foreign-born Persons in Seattle-King County, Washington. Am J Respir Crit Care Med 1997;156:573-7.
215.Winje B, Oftung F, Korsvold G, et al. Screening for tuberculosis infection among newly arrived asylum seekers: Comparison of QuantiFERON(R)TB Gold with tuberculin skin test. BMC Infectious Diseases 2008;8:65.
216.Bodenmann P, Vaucher P, Wolff H, et al. Screening for latent tuberculosis infection among undocumented immigrants in Swiss healthcare centres; a descriptive exploratory study. BMC Infectious Diseases 2009;9:34.
217.Hardy AB, Varma R, Collyns T, Moffitt SJ, Mullarkey C, Watson JP. Cost-effectiveness of the NICE guidelines for screening for latent tuberculosis infection: the QuantiFERON-TB Gold IGRA alone is more cost-effective for immigrants from high burden countries. Thorax 2010;65:178-80.
218.Kik SV, Franken WPJ, Arend SM, et al. Interferon-gamma release assays in immigrant contacts and effect of remote exposure to Mycobacterium tuberculosis. The International Journal of Tuberculosis and Lung Disease 2009;13:820-8.
219.Marks GB, Bai J, Stewart GJ, Simpson SE, Sullivan EA. Effectiveness of Postmigration Screening in Controlling Tuberculosis Among Refugees: A Historical Cohort Study, 1984-1998. Am J Public Health 2001;91:1797-9.
220.Marks GB, Bai J, Simpson SE, Sullivan EA, Stewart GJ. Incidence of tuberculosis among a cohort of tuberculin-positive refugees in Australia: reappraising the estimates of risk. Am J Respir Crit Care Med 2000;162:1851 - 4.
221.Choudry IW, Ormerod LP. The outcome of a cohort of tuberculin positive, predominantly South Asian, new entrants aged 16-34 to the UK: Blackburn 1989-2001. Thorax 2007;62:A22.
222.Jasmer RM, Nahid P, Hopewell PC. Latent Tuberculosis Infection. N Engl J Med 2002;347:1860-6.
223.Zuber PL, McKenna MT, Binkin NJ, Onorato IM, Castro KG. Long-term risk of tuberculosis among foreign-born persons in the United States. JAMA 1997;278:304-7.

224.Uppaluri A, Naus M, Heywood N, Brunton J, Kerbel D, Wobeser W. Effectiveness of the Immigration Medical Surveillance Program for tuberculosis in Ontario. Can J Public Health 2002;93:88-91.
225.Maguire H, Dale JW, McHugh TD, et al. Molecular epidemiology of tuberculosis in London 1995-7 showing low rate of active transmission. Thorax 2002;57:617-22.
226.Fok A, Numata Y, Schulzer M, FitzGerald MJ. Risk factors for clustering of tuberculosis cases: a systematic review of population-based molecular epidemiology studies [Review Article]. The International Journal of Tuberculosis and Lung Disease 2008;12:480-92.
227.Ellis B, Crawford J, Braden C, McNabb S, Moore M, Kammerer S. Molecular Epidemiology of Tuberculosis in a Sentinel Surveillance Population. Emerg Infect Dis 2002;8:1197 - 209.
228.Geng E, Kreiswirth B, Driver C, et al. Changes in the transmission of tuberculosis in New York City from 1990 to 1999. N Engl J Med 2002;346:1453-8.
229.Yang Z, de Haas P, Wachmann C, van Soolingen D, van Embden J, Andersen A. Molecular epidemiology of tuberculosis in Denmark in 1992. J Clin Microbiol 1995;33:2077-81.
230.Burman W, Reves R, Hawkes A, et al. DNA fingerprinting with two probes decreases clustering of Mycobacterium tuberculosis. Am J Respir Crit Care Med 1997;155:1140-6.
231.Samper S, Iglesias MJ, Rabanaque MJ, et al. The molecular epidemiology of tuberculosis in Zaragoza, Spain: a retrospective epidemiological study in 1993. The International Journal of Tuberculosis and Lung Disease 1998;2:281-7.
232.Gutierrez MC, Vincent V, Aubert D, et al. Molecular Fingerprinting of Mycobacterium tuberculosis and Risk Factors for Tuberculosis Transmission in Paris, France, and Surrounding Area. J Clin Microbiol 1998;36:486-92.
233.van Soolingen D, Borgdorff MW, de Haas PEW, et al. Molecular Epidemiology of Tuberculosis in the Netherlands: A Nationwide Study from 1993 through 1997. Journal of Infectious Diseases 1999;180:726-36.
234.Rhee JT, Tanaka MM, Behr MA, et al. Use of multiple markers in population-based molecular epidemiologic studies of tuberculosis. The International Journal of Tuberculosis and Lung Disease 2000;4:1111-9.
235.Solsona J, Cayl, agrave, et al. Molecular and conventional epidemiology of tuberculosis in an inner city district. The International Journal of Tuberculosis and Lung Disease 2001;5:724-31.
236.de Bruyn G, Adams GJ, Teeter LD, Soini H, Musser JM, Graviss EA. The contribution of ethnicity to Mycobacterium tuberculosis strain clustering. The International Journal of Tuberculosis and Lung Disease 2001;5:633-41.
237.Hayward AC, Goss S, Drobniewski F, et al. The molecular epidemiology of tuberculosis in inner London. Epidemiol Infect 2002;128:175-84.
238.Weis SE, Pogoda JM, Yang Z, et al. Transmission dynamics of tuberculosis in Tarrant county, Texas. Am J Respir Crit Care Med 2002;166:36-42.
239.Moro ML, Salamina G, Gori A, et al. Two-year population-based molecular epidemiological study of tuberculosis transmission in the metropolitan area of Milan, Italy. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 2002;21:114-22.
240.Kulaga S, Behr M, Musana K, et al. Molecular epidemiology of tuberculosis in Montreal. Canadian Medical Association Journal 2002;167:353-4.
241.Heldal E, Dahle UR, Sandven P, et al. Risk factors for recent transmission of Mycobacterium tuberculosis. Eur Respir J 2003;22:637-42.
242.Iñigo J, Arce A, Martín-Moreno J, Herruzo R, Palenque E, Chaves F. Recent transmission of tuberculosis in Madrid: application of capture–recapture analysis to conventional and molecular epidemiology. International Journal of Epidemiology 2003;32:763-9.
243.Pena MJ, Caminero JA, Campos-Herrero MI, et al. Epidemiology of tuberculosis on Gran Canaria: a 4 year population study using traditional and molecular approaches. Thorax 2003;58:618-22.
244.Blackwood K, Al-Azem A, Elliott L, Hershfield E, Kabani A. Conventional and molecular epidemiology of Tuberculosis in Manitoba. BMC Infectious Diseases 2003;3:18.
245.Diel R, Seidler A, Nienhaus A, Rusch-Gerdes S, Niemann S. Occupational risk of tuberculosis transmission in a low incidence area. Respiratory Research 2005;6:35.
246.Inigo J, Garcia d, Arce A, Palenque E, Alonso R, Rodriguez E. Analysis of changes in recent tuberculosis transmission patterns after a sharp increase in immigration. J Clin Microbiol 2007;45:63 - 9.
247.Dahle UR, Eldholm V, Winje BA, Mannsaker T, Heldal E. Impact of immigration on the molecular epidemiology of Mycobacterium tuberculosis in a low-incidence country. Am J Respir Crit Care Med 2007;176:930 - 5.
248.Lopez-Calleja AI, Lezcano MA, Vitoria MA, et al. Genotyping of Mycobacterium tuberculosis over two periods: a changing scenario for tuberculosis transmission. The International Journal of Tuberculosis and Lung Disease 2007;11:1080-6.
249.Ohkado A, Nagamine M, Murase Y, et al. Molecular epidemiology of Mycobacterium tuberculosis in an urban area in Japan, 20022006. The International Journal of Tuberculosis and Lung Disease 2008;12:548-54.

250.Borrell S, Español M, Orcau À, et al. Tuberculosis transmission patterns among Spanish-born and foreign-born populations in the city of Barcelona. Clinical Microbiology and Infection 2010;16:568-74.
251.Franzetti F, Codecasa L, Matteelli A, et al. Genotyping analyses of tuberculosis transmission among immigrant residents in Italy. Clinical Microbiology and Infection 2010;16:1149-54.
252.Love J, Sonnenberg P, Glynn JR, et al. Molecular epidemiology of tuberculosis in England, 1998. Int J Tuberc Lung Dis 2009;13:201-7.
253.Ojo OO, Sheehan S, Corcoran DG, et al. Molecular epidemiology of Mycobacterium tuberculosis clinical isolates in Southwest Ireland. Infection, Genetics and Evolution 2010;10:1110-6.
254.Vanhomwegen J, Kwara A, Martin M, et al. Impact of Immigration on the Molecular Epidemiology of Tuberculosis in Rhode Island. J Clin Microbiol 2011;49:834-44.
255.Borgdorff MW, van den Hof S, Kalisvaart N, Kremer K, van Soolingen D. Influence of Sampling on Clustering and Associations With Risk Factors in the Molecular Epidemiology of Tuberculosis. American Journal of Epidemiology 2011;174:243-51.
256.Sails AD, Barrett A, Sarginson S, et al. Molecular epidemiology of Mycobacterium tuberculosis in East Lancashire 2001–2009. Thorax 2011;66:709-13.
257.Cronin WA, Golub JE, Lathan MJ, et al. Molecular epidemiology of tuberculosis in a low- to moderate-incidence state: are contact investigations enough? Emerg Infect Dis 2002;8:1271-9.
258.Dahle UR, Sandven P, Heldal E, Caugant DA. Continued Low Rates of Transmission of Mycobacterium tuberculosis in Norway. J Clin Microbiol 2003;41:2968-73.
259.Hernandez-Garduno E, Kunimoto D, Wang L, et al. Predictors of clustering of tuberculosis in Greater Vancouver: a molecular epidemiologic study. CMAJ 2002;167:349-52.
260.Murray MB. Molecular epidemiology and the dynamics of tuberculosis transmission among foreign-born people. CMAJ 2002;167:355-6.
261.Cain KP, Benoit SR, Winston CA, Mac Kenzie WR. Tuberculosis Among Foreign-Born Persons in the United States. JAMA 2008;300:405-12.
262.World Health Organisation. WHO declares tuberculosis a global emergency. Soz Praventivmed 1993;38:251-2.
263.The five elements of DOTS. 2008. (Accessed 23 August, 2008, at http://www.who.int/tb/dots/whatisdots/en/index.html.)
264.Dye C, Garnett GP, Sleeman K, Williams BG. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. Lancet 1998;352:1886-91.
265.World Health Organisation: Stop TB Partnership. The STOPTB Strategy: Building on and enhancing DOTS to meet the TB-related Millenium Development Goals. Geneva: WHO; 2006.
266.Cohen T, Lipsitch M, Walensky RP, Murray M. Beneficial and perverse effects of isoniazid preventive therapy for latent tuberculosis infection in HIV-tuberculosis coinfected populations. 2006;103:7042-7.
267.Currie CS WB, Cheng RC, Dye C. Tuberculosis epidemics driven by HIV: is prevention better than cure? AIDS 2003;17:2501-8.
268.Dye C, Williams BG. Eliminating human tuberculosis in the twenty-first century. J R Soc Interface 2008;5:653-62.
269.Ziv E, Daley CL, Blower SM. Early Therapy for Latent Tuberculosis Infection. Am J Epidemiol 2001;153:381-5.
270.Murray CJL, Salomon JA. Modeling the impact of global tuberculosis control strategies. Proceedings of the National Academy of Sciences of the United States of America 1998;95:13881-6.
271.Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid preventive therapy and risk for resistant tuberculosis. Emerg Infect Dis 2006;12:744-51.
272.Brewer TF, Heymann SJ. To control and beyond: moving towards eliminating the global tuberculosis threat. J Epidemiol Community Health 2004;58:822-5.
273.Moore-Gillon J, Davies PDO, Ormerod LP. Rethinking TB screening: politics, practicalities and the press. Thorax 2010;65:663-5.
274.Sterling TR, Bethel J, Goldberg S, et al. The Scope and Impact of Treatment of Latent Tuberculosis Infection in the United States and Canada. Am J Respir Crit Care Med 2006;173:927-31.
275.Coker R, Bell A, Pitman R, et al. Tuberculosis screening in migrants in selected European countries shows wide disparities. Eur Respir J 2006;27:801-7.
276.Rieder HL, Zellweger JP, Raviglione MC, Keizer ST, Migliori GB. Tuberculosis control in Europe and international migration. Eur Respir J 1994;7:1545 - 53.
277.Alvarez G, Gushulak B, Rumman K, et al. A comparative examination of tuberculosis immigration medical screening programs from selected countries with high immigration and low tuberculosis incidence rates. BMC Infectious Diseases 2010;11:3.
278.Alvarez GG, Clark M, Altpeter E, et al. Pediatric tuberculosis immigration screening in high-immigration, low-incidence countries. The International Journal of Tuberculosis and Lung Disease 2010;14:1530-7.

279.CDC. CDC immigration requirements: Technical Instructions for Tuberculosis Screening and Treatment CDC; 2009.
280.Springett V. H., Adams J. C. S., T DC, M. HB. Tuberculosis in Immigrants in Birmingham, 1956–1957. British Journal of Preventative and Social Medicine 1958;12:135-40.
281.Public General Acts and Measures. Commonwealth Immigrants Act, 1962. London: HMSO; 1963.
282.Department of Health. Commonwealth Immigrants' Act 1968. London: Department of Health; 1968.
283.Department of Health. Medical examination under the Immigration Act 1971 - Instructions to medical inspectors. London: Department of Health; 1992.
284.Joint Tuberculosis Committee of the British Thoracic Society. Control and prevention of tuberculosis in the United Kingdom: Code of Practice 2000. Thorax 2000;55:887-901.
285.Joint Tuberculosis Committee of the British Thoracic Society. Control and prevention of tuberculosis in the United Kingdom: Code of Practice British Medical Journal 1983;287:1118-21.
286.Joint Tuberculosis Committee of the British Thoracic Society. Control and prevention of tuberculosis in the United Kingdom: Code of Practice 1994. Thorax 1994;49:1193-200.
287.Joint Tuberculosis Committee of the British Thoracic Society. Control and prevention of tuberculosis in Britain: an update code of practice. British Medical Journal 1990;300:995-9.
288.Van den Bosch CA, Roberts JA. Tuberculosis screening of new entrants; how can it be made more effective? J Public Health Med 2000;22:220-3.
289.Hogan H, Coker R, Gordon A, Meltzer M, Pickles H. Screening of new entrants for tuberculosis: responses to port notifications. J Public Health (Oxf) 2005;27:192-5.
290.Griffiths C, Sturdy P, Brewin P, et al. Educational outreach to promote screening for tuberculosis in primary care: a cluster randomised controlled trial. Lancet 2007;369:1528-34.
291.UK Border Agency. Freedom of Information request: Immigrant screening for tuberculosis - pre-departure screening. London: Home Office; 2011.
292.Lucas M, Nicol P, McKinnon E, et al. A prospective large-scale study of methods for the detection of latent Mycobacterium tuberculosis infection in refugee children. Thorax 2010;65:442-8.
293.Minodier P, Lamarre Vr, Carle M-E, Blais D, Ovetchkine P, Tapiero B. Evaluation of a school-based program for diagnosis and treatment of latent tuberculosis infection in immigrant children. Journal of Infection and Public Health 2010;3:67-75.
294.Fortin K, Carceller A, Robert M, Chevalier I, Lamarre V, Lebel MH. Prevalence of positive tuberculin skin tests in foreign-born children. Journal of Paediatrics and Child Health 2007;43:768-72.
295.Mendez-Echevarria A, Gonzalez-Munoz M, Mellado MJ, et al. Interferon-{gamma} release assay for the diagnosis of tuberculosis in children. Arch Dis Child 2011;online first.
296.Dewan PK, Grinsdale J, Liska S, Wong E, Fallstad R, Kawamura LM. Feasibility, acceptability, and cost of tuberculosis testing by whole-blood interferon-gamma assay. BMC Infect Dis 2006;6:47.
297.Mahan CS, Johnson DF, Curley C, van der Kuyp F. Concordance of a positive tuberculin skin test and an interferon gamma release assay in bacille Calmette-Guerin vaccinated persons. The International Journal of Tuberculosis and Lung Disease 2011;15:174-8.
298.Dasgupta K, Schwartzman K, Marchand R, Tennenbaum TN, Brassard P, Menzies D. Comparison of cost-effectiveness of tuberculosis screening of close contacts and foreign-born populations. Am J Respir Crit Care Med 2000;162:2079 - 86.
299.Khan K, Muennig P, Behta M, Zivin JG. Global Drug-Resistance Patterns and the Management of Latent Tuberculosis Infection in Immigrants to the United States. N Engl J Med 2002;347:1850-9.
300.Linas BP, Wong AY, Freedberg KA, Horsburgh J, C Robert. Priorities for Screening and Treatment of Latent Tuberculosis Infection in the United States. Am J Respir Crit Care Med 2011:201101-0181OC.
301.Oxlade O, Schwartzman K, Menzies D. Interferon-gamma release assays and TB screening in high-income countries: a cost-effectiveness analysis. Int J Tuberc Lung Dis 2007;11:16-26.
302.Schwartzman K, Menzies D. Tuberculosis Screening of Immigrants to Low-Prevalence Countries . A Cost-effectiveness Analysis. Am J Respir Crit Care Med 2000;161:780-9.
303.Cowie RL, Sharpe JW. Extra-pulmonary tuberculosis: a high frequency in the absence of HIV infection. The International Journal of Tuberculosis and Lung Disease 1997;1:159-62.
304.Enhanced TB surveillance data by site of disease, covering 2000 to 2009. Health Protection Agency, 2011. (Accessed 14th June, 2011, at http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/Tuberculosis/TBUKSurveillanceData/EnhancedTuberculosisSurveillance/TBEnhanced11site/.)
305.Yang Z, Kong Y, Wilson F, et al. Identification of Risk Factors for Extrapulmonary Tuberculosis. Clinical Infectious Diseases 2004;38:199-205.
306.Barnes PF, Bloch AB, Davidson PT, Snider DE. Tuberculosis in Patients with Human Immunodeficiency Virus Infection. New England Journal of Medicine 1991;324:1644-50.

307.Modilevsky T, Sattler FR, Barnes PF. Mycobacterial Disease in Patients With Human Immunodeficiency Virus Infection. Arch Intern Med 1989;149:2201-5.
308.Theuer CP, Hopewell PC, Elias D, Schecter GF, Rutherford GW, Chaisson RE. Human Immunodeficiency Virus Infection in Tuberculosis Patients. Journal of Infectious Diseases 1990;162:8-12.
309.Jones BE, Young SM, Antoniskis D, Davidson PT, Kramer F, Barnes PF. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. Am Rev Respir Dis 1993;148:1292-7.
310.García-Rodríguez JF, Álvarez-Díaz H, Lorenzo-García MV, Mariño-Callejo A, Fernández-Rial Á, Sesma-Sánchez P. Extrapulmonary tuberculosis: epidemiology and risk factors. Enfermedades Infecciosas y Microbiología Clínica 2011;In Press.
311.Noertjojo K, Tam CM, Chan SL, Chan-Yeung MMW. Extra-pulmonary and pulmonary tuberculosis in Hong Kong. The International Journal of Tuberculosis and Lung Disease 2002;6:879-86.
312.Chan-Yeung M, Noertjojo K, Chan SL, Tam CM. Sex differences in tuberculosis in Hong Kong. The International Journal of Tuberculosis and Lung Disease 2002;6:11-8.
313.Forssbohm M, Zwahlen M, Loddenkemper R, Rieder HL. Demographic characteristics of patients with extrapulmonary tuberculosis in Germany. European Respiratory Journal 2008;31:99-105.
314.Peto HM, Pratt RH, Harrington TA, LoBue PA, Armstrong LR. Epidemiology of Extrapulmonary Tuberculosis in the United States, 1993-2006. Clinical Infectious Diseases 2009;49:1350-7.
315.Martinez AN, Rhee JT, Small PM, Behr MA. Sex differences in the epidemiology of tuberculosis in San Francisco. The International Journal of Tuberculosis and Lung Disease 2000;4:26-31.
316.Sreeramareddy CT, Panduru KV, Verma SC, Joshi HS, Bates MN. Comparison of pulmonary and extrapulmonary tuberculosis in Nepal - a hospital-based retrospective study. BMC Infect Dis 2008;8:8.
317.Wilkinson RJ, Llewelyn M, Toossi Z, et al. Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: a case-control study. The Lancet 2000;355:618-21.
318.Motsinger-Reif A, Antas P, Oki N, Levy S, Holland S, Sterling T. Polymorphisms in IL-1beta, vitamin D receptor Fok1, and Toll-like receptor 2 are associated with extrapulmonary tuberculosis. BMC Medical Genetics 2010;11:37.
319.Wilkinson RJ, Patel P, Llewelyn M, et al. Influence of Polymorphism in the Genes for the Interleukin (IL)-1 Receptor Antagonist and IL-1Î² on Tuberculosis. The Journal of Experimental Medicine 1999;189:1863-74.
320.Taype CA, Shamsuzzaman S, Accinelli RA, Espinoza JR, Shaw MA. Genetic susceptibility to different clinical forms of tuberculosis in the Peruvian population. Infection, Genetics and Evolution 2010;10:495-504.
321.Fernando SL, Saunders BM, Sluyter R, et al. A Polymorphism in the P2X7 Gene Increases Susceptibility to Extrapulmonary Tuberculosis. Am J Respir Crit Care Med 2007;175:360-6.
322.Lalani T, Federspiel JJ, Boucher HW, et al. Associations between the Genotypes of Staphylococcus aureus Bloodstream Isolates and Clinical Characteristics and Outcomes of Bacteremic Patients. J Clin Microbiol 2008;46:2890-6.
323.Coscolla M, Gagneux S. Does M. tuberculosis genomic diversity explain disease diversity? Drug Discov Today Dis Mech 2010;7:e43-e59.
324.Gagneux S, Small P. Global phylogeography of Mycobacterium tuberculosis and implications for tuberculosis product development. Lancet Infect Dis 2007;7:328 - 37.
325.McAdam RA, Hermans PWM, van Soolingen D, et al. Characterization of a Mycobacterium tuberculosis insertion sequence belonging to the IS3 family. Molecular Microbiology 1990;4:1607-13.
326.Thierry D, Brisson-Noel A, Vincent-Levy-Frebault V, Nguyen S, Guesdon JL, Gicquel B. Characterization of a Mycobacterium tuberculosis insertion sequence, IS6110, and its application in diagnosis. J Clin Microbiol 1990;28:2668-73.
327.van Embden JD, Cave MD, Crawford JT, et al. Strain identification of Mycobacterium tuberculosis by DNA fingerprinting: recommendations for a standardized methodology. J Clin Microbiol 1993;31:406-9.
328.Roring S, Brittain D, Bunschoten AE, et al. Spacer oligotyping of Mycobacterium bovis isolates compared to typing by restriction fragment length polymorphism using PGRS, DR and IS6110 probes. Veterinary Microbiology 1998;61:111-20.
329.Supply P, Magdalena J, Himpens S, Locht C. Identification of novel intergenic repetitive units in a mycobacterial two-component system operon. Molecular Microbiology 1997;26:991-1003.
330.Supply P, Allix C, Lesjean S, et al. Proposal for Standardization of Optimized Mycobacterial Interspersed Repetitive Unit-Variable-Number Tandem Repeat Typing of Mycobacterium tuberculosis. J Clin Microbiol 2006;44:4498-510.
331.Gagneux S, DeRiemer K, Van T, et al. Variable host-pathogen compatibility in Mycobacterium tuberculosis. Proceedings of the National Academy of Sciences of the United States of America 2006;103:2869-73.

332.Flores L, Van T, Narayanan S, DeRiemer K, Kato-Maeda M, Gagneux S. Large sequence polymorphisms classify Mycobacterium tuberculosis strains with ancestral spoligotyping patterns. J Clin Microbiol 2007;45:3393-5.
333.Reed MB, Pichler VK, McIntosh F, et al. Major Mycobacterium tuberculosis Lineages Associate with Patient Country of Origin. J Clin Microbiol 2009;47:1119-28.
334.Filliol I, Motiwala AS, Cavatore M, et al. Global Phylogeny of Mycobacterium tuberculosis Based on Single Nucleotide Polymorphism (SNP) Analysis: Insights into Tuberculosis Evolution, Phylogenetic Accuracy of Other DNA Fingerprinting Systems, and Recommendations for a Minimal Standard SNP Set. J Bacteriol 2006;188:759-72.
335.Brown T, Nikolayevskyy V, Velji P, Drobniewski F. Associations between Mycobacterium tuberculosis strains and phenotypes. Emerg Infect Dis 2010;16:272-80.
336.Evans JT, Gardiner S, Smith EG, Webber R, Hawkey PM. Global Origin of Mycobacterium tuberculosis in the Midlands, UK. Emerg Infect Dis 2010;16:542-5.
337.Portevin D, Gagneux S, Comas I, Young D. Human Macrophage Responses to Clinical Isolates from the Mycobacterium tuberculosis Complex Discriminate between Ancient and Modern Lineages. PLoS Pathog;7:e1001307.
338.Wang C, Peyron P, Mestre O, et al. Innate Immune Response to *Mycobacterium tuberculosis* Beijing and Other Genotypes. PLoS ONE;5:e13594.
339.Li Q, Whalen CC, Albert JM, et al. Differences in Rate and Variability of Intracellular Growth of a Panel of Mycobacterium tuberculosis Clinical Isolates within a Human Monocyte Model. Infect Immun 2002;70:6489-93.
340.Sohn H, Lee KS, Kim SY, et al. Induction of Cell Death in Human Macrophages by a Highly Virulent Korean Isolate of Mycobacterium tuberculosis and the Virulent Strain H37Rv. Scand J Immunol 2009;69:43-50.
341.de Jong BC, Hill PC, Aiken A, et al. Progression to active tuberculosis, but not transmission, varies by Mycobacterium tuberculosis lineage in The Gambia. The Journal of Infectious Diseases 2008;198:1037-43.
342.Caws M, Thwaites G, Dunstan S, et al. The Influence of Host and Bacterial Genotype on the Development of Disseminated Disease with *Mycobacterium tuberculosis*. PLoS Pathog 2008;4:e1000034.
343.Kong Y, Cave MD, Zhang L, et al. Association between Mycobacterium tuberculosis Beijing/W Lineage Strain Infection and Extrathoracic Tuberculosis: Insights from Epidemiologic and Clinical Characterization of the Three Principal Genetic Groups of M. tuberculosis Clinical Isolates. J Clin Microbiol 2007;45:409-14.
344.Kong Y, Cave MD, Yang D, et al. Distribution of Insertion- and Deletion-Associated Genetic Polymorphisms among Four Mycobacterium tuberculosis Phospholipase C Genes and Associations with Extrathoracic Tuberculosis: a Population-Based Study. J Clin Microbiol 2005;43:6048-53.
345.Hesseling AC, Marais BJ, Kirchner HL, et al. Mycobacterial genotype is associated with disease phenotype in children. The International Journal of Tuberculosis and Lung Disease 2010;14:1252-8.
346.Lari N, Rindi L, Cristofani R, Rastogi N, Tortoli E, Garzelli C. Association of Mycobacterium tuberculosis complex isolates of Bovis and Central Asian (CAS) genotypic lineages with extrapulmonary disease. Clin Microbiol Infect 2009;15:538-43.
347.Svensson E, Millet J, Lindqvist A, Olsson M, Ridell M, Rastogi N. Impact of immigration on tuberculosis epidemiology in a low-incidence country. Clin Microbiol Infect 2011;17:881-7.
348.Hasan Z, Tanveer M, Kanji A, Hasan Q, Ghebremichael S, Hasan R. Spoligotyping of Mycobacterium tuberculosis Isolates from Pakistan Reveals Predominance of Central Asian Strain 1 and Beijing Isolates. J Clin Microbiol 2006;44:1763-8.
349.Tanveer M, Hasan Z, Siddiqui A, et al. Genotyping and drug resistance patterns of M. tuberculosis strains in Pakistan. BMC Infectious Diseases 2008;8:171.
350.Thwaites G, Caws M, Chau TTH, et al. The relationship between Mycobacterium tuberculosis genotype and the clinical phenotype of pulmonary and meningeal tuberculosis. J Clin Microbiol 2008:JCM.02180-07.
351.Nicol MP, Sola C, February B, Rastogi N, Steyn L, Wilkinson RJ. Distribution of Strain Families of Mycobacterium tuberculosis Causing Pulmonary and Extrapulmonary Disease in Hospitalized Children in Cape Town, South Africa. J Clin Microbiol 2005;43:5779-81.
352.Borgdorff MW, van Deutekom H, de Haas PEW, Kremer K, van Soolingen D. Mycobacterium tuberculosis, Beijing genotype strains not associated with radiological presentation of pulmonary tuberculosis. Tuberculosis (Edinburgh, Scotland) 2004;84:337-40.
353.Lin JN, Lai CH, Chen YH, et al. Risk factors for extra-pulmonary tuberculosis compared to pulmonary tuberculosis. The International Journal of Tuberculosis and Lung Disease;13:620-5.
354.Musellim B, Erturan S, Sonmez Duman E, Ongen G. Comparison of extra-pulmonary and pulmonary tuberculosis cases: factors influencing the site of reactivation. The International Journal of Tuberculosis and Lung Disease 2005;9:1220-3.
355.Ratha D, Mohapatra S, Silwal A. The Migration and Remittances Factbook: World Bank; 2011.
356.CDC. Reported Tuberculosis in the United States, 2008. Atlanta: Department of Health and Human Services, CDC; 2009.

357.Pareek M, Abubakar I, White PJ, Garnett GP, Lalvani A. TB screening of migrants to low TB burden nations: insights from evaluation of UK practice. European Respiratory Journal 2011;37:1175-82.
358.International Migration Database. 2011. (Accessed 1st September, 2011, at http://stats.oecd.org/Index.aspx?DataSetCode=MIG.)
359.Laifer G, Widmer AF, Simcock M, et al. TB in a low-incidence country: differences between new immigrants, foreign-born residents and native residents. The American journal of medicine 2007;120:350 - 6.
360.Mor Z, Lerman Y, Leventhal A. Pre-immigration screening process and pulmonary tuberculosis among Ethiopian migrants in Israel. Eur Respir J 2008;32:413-8.
361.Newton SM, Brent AJB, Anderson S, Whittaker E, Kampmann B. Paediatric tuberculosis. Lancet Infect Dis 2008;8:498-510.
362.Marais BJ, Gie RP, Hesseling AH, Beyers N. Adult-type pulmonary tuberculosis in children 10-14 years of age. Paediatr Infect Dis J 2005;24:743-4.
363.Hargreaves S, Carballo M, Friedland JS. Screening migrants for tuberculosis: where next? Lancet Infect Dis 2009;9:139-40.
364.Kunst H, Khan KS. Age-related risk of hepatotoxicity in the treatment of latent tuberculosis infection: a systematic review. Int J Tuberc Lung Dis 2010;14:1374-81.
365.Pareek M, Watson JP, Ormerod LP et al. Current UK immigrant screening misses the majority of imported latent tuberculosis: an evidence-based case for wider, cost-effective screening. In: British Thoracic Society Winter meeting. London; 2010:A5-A6.
366.Pareek M, Watson JP, Ormerod LP, et al. Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis. The Lancet Infectious Diseases 2011;11:435-44.
367.Lalvani A, Pareek M. A 100 year update on diagnosis of tuberculosis infection. Br Med Bull 2009:ldp039.
368.Zhang T, Zhang M, Rosenthal IM, Grosset JH, Nuermberger EL. Short-Course Therapy with Daily Rifapentine in a Murine Model of Latent Tuberculosis Infection. Am J Respir Crit Care Med 2009;180:1151-7.
369.Zhang T, Li S-Y, Williams KN, Andries K, Nuermberger EL. Short-Course Chemotherapy with TMC207 and Rifapentine in a Murine Model of Latent Tuberculosis Infection. Am J Respir Crit Care Med 2011;184:732-7.
370.Erkens C, Slump E, Kamphorst M, et al. Coverage and yield of entry and follow-up screening for tuberculosis among new immigrants. Eur Respir J 2008;32:153 - 61.
371.Health Protection Agency. Tuberculosis in the UK: Annual report on tuberculosis surveillance and control in the UK 2008. London: Health Protection Agency Centre for Infections; 2008.
372.Shakir E, Johnston F, Rayner A, et al. Enhanced Surveillance of Mycobacterial Infections (ESMI) in Scotland: 2007 tuberculosis annual report for Scotland HPS Weekly Report 2008;42:428-33.
373.Kearns CA. Epidemiology of tuberculosis in Northern Ireland 2007. In; 2009.
374.Final Mid-2007 Population Estimates: Quinary age groups for Primary Care Organisations in England; estimated resident population (experimental). 2007. (Accessed 24th August, 2009, at http://www.statistics.gov.uk/statbase/Product.asp?vlnk=15106.)
375.Mid-2007 Population Estimates: Selected age groups for health areas in the United Kingdom; estimated resident population., 2007. (Accessed 24th August, 2009, at http://www.statistics.gov.uk/statbase/Product.asp?vlnk=15106.)
376.National Public Health Service for Wales. Interactive Surveillance Data: Time Trend: Tuberculosis: National Public Health Service for Wales; 2009.
377.Rieder H. What is the role of case detection by periodic mass radiographic examination in tuberculosis control? In: Frieden T, ed. Toman's Tuberculosis: Case Detection, Treatment and Monitoring. Geneva: World Health Organisation; 2006.
378.Country of birth by Primary Care Organisation (table UV08). ONS, 2001. (Accessed 15th October, 2009, at http://www.statistics.gov.uk/cci/nugget.asp?id=455.)
379.Country of birth by Health and Social Services Boards (table CAS015). Northern Ireland Statistics and Research Agency, 2001. (Accessed 15th October, 2009, at http://www.statistics.gov.uk/cci/nugget.asp?id=455.)
380.Ormerod LP. Serial Surveys of Tuberculosis Nurse and Support Staff in England and Wales in 1998 and 2001. Communicable Disease and Public Health 2002;5:336-7.
381.Health Protection Agency. Tuberculosis in the UK: Annual report on tuberculosis surveillance and control in the UK 2009. London: Health Protection Agency Centre for Infections; 2009.
382. British Thoracic Society. British Thoracic Society survey of Tuberculosis Leads. London: BTS; 2007.
383.All Parliamentary Group on Global TB, British Thoracic Society, TB Alert, Royal College of Nursing. Tackling tuberculosis in England: the PCT response to the challenge. Second national TB survey of English Primary Care Trusts. London; 2009.
384.Centers for Disease Control and Prevention (CDC). Updated guidelines for using interferon gamma release assays to detect Mycobacterium tuberculosis infection. MMWR 2010;59:1-25.

385.Yoshiyama T, Harada N, Higuchi K, Sekiya Y, Uchimura K. Use of the QuantiFERON-TB Gold test for screening tuberculosis contacts and predicting active disease. The International Journal of Tuberculosis and Lung Disease 2010;14:819-27.
386.Kik SV, Franken WPJ, Mensen M, et al. Predictive value for progression to tuberculosis by IGRA and TST in immigrant contacts. Eur Respir J 2010;35:1346-53.
387.Diel R, Loddenkemper R, Niemann S, Meywald-Walter K, Nienhaus A. Negative and Positive Predictive Value of a Whole-Blood IGRA for Developing Active TB - An Update. Am J Respir Crit Care Med 2010:201006-0974OC.
388.Leung CC, Yam WC, Yew WW, et al. T-Spot.TB Outperforms Tuberculin Skin Test in Predicting Tuberculosis Disease. Am J Respir Crit Care Med 2010.
389.Lienhardt C, Fielding K, Hane AA, et al. Evaluation of the Prognostic Value of IFN-γ Release Assay and Tuberculin Skin Test in Household Contacts of Infectious Tuberculosis Cases in Senegal. PLoS ONE 2010;5:e10508.
390.Mahomed H, Hawkridge T, Verver S, et al. The Tuberculin Skin Test versus QuantiFERON TB GoldÂ® in Predicting Tuberculosis Disease in an Adolescent Cohort Study in South Africa. PLoS ONE 2011;6:e17984.
391.Bakir M, Dosanjh DPS, Deeks JJ, et al. Use of T Cell-Based Diagnosis of Tuberculosis Infection to Optimize Interpretation of Tuberculin Skin Testing for Child Tuberculosis Contacts. Clinical Infectious Diseases 2009;48:302-12.
392.Final Mid-2008 Population Estimates: Quinary age groups for Primary Care Organisations in England; estimated resident population (experimental). 2008. (Accessed 2nd November, 2010, at http://www.statistics.gov.uk/statbase/Product.asp?vlnk=15106.)
393.Three-year average tuberculosis case reports and rates by Primary Care Trust, England, 2006-2008. 2009. (Accessed 16th September, 2010, at http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1226565422987.)
394.Department of Health. Immunisation against infectious disease – "The Green Book". London: HMSO; 2006.
395.World Health Organisation. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis. Bull World Health Organ 1982;60:555-64.
396.de Perio MA, Tsevat J, Roselle GA, Kralovic SM, Eckman MH. Cost-effectiveness of interferon gamma release assays vs tuberculin skin tests in health care workers. Archives of internal medicine 2009;169:179 - 87.
397.Pooran A, Booth H, Miller R, et al. Different screening strategies (single or dual) for the diagnosis of suspected latent tuberculosis: a cost effectiveness analysis. BMC Pulmonary Medicine 2010;10:7.
398.Diel R, Nienhaus A, Loddenkemper R. Cost-effectiveness of interferon-gamma release assay screening for latent tuberculosis infection treatment in Germany. Chest 2007;131:1424-34.
399.HM Treasury. The Green Book: Appraisal and Evaluation in Central Government. London: HM Treasury; 2003.
400.Underwood BR, White VL, Baker T, Law M, Moore-Gillon JC. Contact tracing and population screening for tuberculosis--who should be assessed? J Public Health Med 2003;25:59-61.
401.Focus on Consumer Price Indices. Office for National Statistics, 2010. (Accessed 4th October, 2010, at http://www.statistics.gov.uk/StatBase/Product.asp?vlnk=867.)
402.Department of Health. NHS Reference Costs 2005-2006. London: Department of Health; 2006.
403.Department of Health. Confirmation of Payment by Results (PbR) arrangements for 2010-11. London: Crown; 2010.
404.Weinstein M, Siegel J, Gold M et al. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA 1996;276:1253-8.
405.Lien LT, Hang NTL, Kobayashi N, et al. Prevalence and Risk Factors for Tuberculosis Infection among Hospital Workers in Hanoi, Viet Nam. PLoS ONE 2009;4:e6798.
406.Mutsvangwa J, Millington KA, Chaka K, et al. Identifying recent Mycobacterium tuberculosis transmission in the setting of high HIV and TB burden. Thorax 2010;65:315-20.
407.Bamford ARJ, Crook AM, Clark JE, et al. Comparison of interferon-gamma release assays and tuberculin skin test in predicting active tuberculosis (TB) in children in the UK: a paediatric TB network study. Archives of disease in childhood;95:180-6.
408.Casey R, Blumenkrantz D, Millington K, et al. Enumeration of Functional T-Cell Subsets by Fluorescence-Immunospot Defines Signatures of Pathogen Burden in Tuberculosis. PLoS ONE 2010;5:e15619.
409.Office for National Statistics. Annual Population Survey: Population by country of birth and nationality October 2009 to September 2010 London: Office for National Statistics; 2010.
410.van Zyl-Smit RN, Zwerling A, Dheda K, Pai M. Within-Subject Variability of Interferon-g Assay Results for Tuberculosis and Boosting Effect of Tuberculin Skin Testing: A Systematic Review. PLoS ONE 2009;4:e8517.
411.Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-74.

412.Dye C, Williams BG. Criteria for the control of drug-resistant tuberculosis. Proceedings of the National Academy of Sciences of the United States of America 2000;97:8180-5.
413.Resch SC, Salomon JA, Murray M, Weinstein MC. Cost-Effectiveness of Treating Multidrug-Resistant Tuberculosis. PLoS Med 2006;3:e241.
414.Luciani F, Sisson SA, Jiang H, Francis AR, Tanaka MM. The epidemiological fitness cost of drug resistance in Mycobacterium tuberculosis. Proceedings of the National Academy of Sciences 2009;106:14711-5.
415.White VLC, Moore-Gillon J. Resource implications of patients with multidrug resistant tuberculosis. Thorax 2000;55:962-3.
416.Global Health Observatory Database - HIV prevalence. World Health Organisation, 2011. (Accessed 14th February, 2011, at http://apps.who.int/ghodata/.)
417.Weinstein S, Obuchowski NA, Lieber ML. Clinical Evaluation of Diagnostic Tests. Am J Roentgenol 2005;184:14-9.
418.Borgdorff MW, Van Den Hof S, Kremer K, et al. Progress towards tuberculosis elimination: secular trend, immigration and transmission. European Respiratory Journal 2010;36:339-47.
419.Unit Costs of Health and Social Care 2010. 2010. (Accessed at http://www.pssru.ac.uk/uc/uc2010contents.htm.)
420.Talati N, Seybold U, Humphrey B, et al. Poor concordance between interferon-gamma release assays and tuberculin skin tests in diagnosis of latent tuberculosis infection among HIV-infected individuals. BMC Infectious Diseases 2009;9:15.
421.Ferrara G, Losi M, D'Amico R, et al. Use in routine clinical practice of two commercial blood tests for diagnosis of infection with Mycobacterium tuberculosis: a prospective study. Lancet 2006;367:1328 - 34.
422.Shanaube K, Hargreaves J, Fielding K, et al. Risk Factors Associated with Positive QuantiFERON-TB Gold In-Tube and Tuberculin Skin Tests Results in Zambia and South Africa. PLoS ONE 2011;6:e18206.
423.Diel R, Wrighton-Smith P, Zellweger JP. Cost-effectiveness of interferon-gamma release assay testing for the treatment of latent tuberculosis. Eur Respir J 2007;30:321-32.
424.Marra F, Marra CA, Sadatsafavi M, et al. Cost-effectiveness of a new interferon-based blood assay, QuantiFERON-TB Gold, in screening tuberculosis contacts. Int J Tuberc Lung Dis 2008;12:1414 - 24.
425.Kowada A, Takahashi O, Shimbo T, Ohde S, Tokuda Y, Fukui T. Cost Effectiveness of Interferon-[gamma] Release Assay for Tuberculosis Contact Screening in Japan. Molecular Diagnosis & Therapy 2008;12:235-51 10.2165/1250444-200812040-00005.
426.Diel R, Schaberg T, Loddenkemper R, Welte T, Nienhaus A. Enhanced cost-benefit analysis of strategies for LTBI screening and INH chemoprevention in Germany. Respiratory Medicine 2009;103:1838 - 53.
427.Allix-Beguec C, Harmsen D, Weniger T, Supply P, Niemann S. Evaluation and Strategy for Use of MIRU-VNTRplus, a Multifunctional Database for Online Analysis of Genotyping Data and Phylogenetic Identification of Mycobacterium tuberculosis Complex Isolates. J Clin Microbiol 2008;46:2692-9.
428.Office of National Statistics. Ethnic Group Statistics: a guide for the collection and classification of ethnicity data. London: ONS; 2009.
429.Rosenberg NA, Pritchard JK, Weber JL, et al. Genetic Structure of Human Populations. Science 2002;298:2381-5.
430.Cobelens FGJ, van Deutekom H, Draayer-Jansen IWE, et al. Risk of infection with Mycobacterium tuberculosis in travellers to areas of high tuberculosis endemicity. The Lancet 2000;356:461-5.
431.Reed MB, Domenech P, Manca C, et al. A glycolipid of hypervirulent tuberculosis strains that inhibits the innate immune response. Nature 2004;431:84-7.
432.Tsenova L, Ellison E, Harbacheuski R, et al. Virulence of Selected Mycobacterium tuberculosis Clinical Isolates in the Rabbit Model of Meningitis Is Dependent on Phenolic Glycolipid Produced by the Bacilli. Journal of Infectious Diseases 2005;192:98-106.
433.Phyu S, Stavrum R, Lwin T, Svendsen OS, Ti T, Grewal HMS. Predominance of Mycobacterium tuberculosis EAI and Beijing Lineages in Yangon, Myanmar. J Clin Microbiol 2009;47:335-44.
434.Huang H-Y, Tsai Y-S, Lee J-J, et al. Mixed Infection with Beijing and Non-Beijing Strains and Drug Resistance Pattern of Mycobacterium tuberculosis. J Clin Microbiol;48:4474-80.
435.Caws M, Thwaites G, Stepniewska K, et al. Beijing Genotype of Mycobacterium tuberculosis Is Significantly Associated with Human Immunodeficiency Virus Infection and Multidrug Resistance in Cases of Tuberculous Meningitis. J Clin Microbiol 2006;44:3934-9.
436.Dale JW, Bothamley GH, Drobniewski F, Gillespie SH, McHugh TD, Pitman R. Origins and properties of Mycobacterium tuberculosis isolates in London. Journal of Medical Microbiology 2005;54:575-82.
437.Rodger AJ, Story A, Fox Z, Hayward A. HIV prevalence and testing practices among tuberculosis cases in London: a missed opportunity for HIV diagnosis? Thorax 2010;65:63-9.
438.Ahmed AB, Abubakar I, Delpech V, et al. The growing impact of HIV infection on the epidemiology of tuberculosis in England and Wales: 1999-2003. Thorax 2007;62:672-6.

439.Crowle AJ, Elkins N. Relative permissiveness of macrophages from black and white people for virulent tubercle bacilli. Infect Immun 1990;58:632-8.
440.Davies PD. A possible link between vitamin D deficiency and impaired host defence to Mycobacterium tuberculosis. Tubercle 1985;66:301-6.
441.Centres for Disease Control. Online Tuberculosis Information System, National Tuberculosis Surveillance System, United States, 1993 - 2009. In: CDC; 2011.
442.Historical Sunshine and Cloud Data in the United States, CDIAC NDP-021/R1. 2006. (Accessed at http://gcmd.nasa.gov/KeywordSearch/Metadata.do?Portal=GCMD&KeywordPath=&NumericId=1461&MetadataView=Text&MetadataType=0&lbnode=mdlb1.)
443.Mean Sunshine Total Hours (Annual) 2005. (Accessed at http://hurricane.ncdc.noaa.gov/cgi-bin/climaps/climaps.pl?directive=quick_results&subrnum=&pop=YES.)
444.Compston JE. Vitamin D deficiency: time for action. BMJ 1998;317:1466-7.
445.Martineau AR, Wilkinson RJ, Wilkinson KA, et al. A Single Dose of Vitamin D Enhances Immunity to Mycobacteria. Am J Respir Crit Care Med 2007;176:208-13.
446.Martineau AR, Leandro ACCS, Anderson ST, et al. Association between Gc genotype and susceptibility to TB is dependent on vitamin D status. European Respiratory Journal 2010;35:1106-12.
447.Cole SR, Chu H, Nie L, Schisterman EF. Estimating the odds ratio when exposure has a limit of detection. International Journal of Epidemiology 2009;38:1674-80.
448.Sundquist K, Li X. Coronary heart disease risks in first- and second-generation immigrants in Sweden: a follow-up study. Journal of Internal Medicine 2006;259:418-27.
449. Gale CR, Martyn CN. Migrant studies in multiple sclerosis. Progress in Neurobiology 1995;47:425-48.
450.Rock RB, Sutherland WM, Baker C, Williams DN. Extrapulmonary Tuberculosis among Somalis in Minnesota. Emerg Infect Dis 2006;12:1434-6.
451.Perez-Trallero E, Cilla G, Garcia-Zamalloa A, Idigoras P. Vitamin D and Tuberculosis Incidence in Spain. Am J Respir Crit Care Med 2008;177:798.
452.Holick MF. Vitamin D Deficiency. New England Journal of Medicine 2007;357:266-81.
453.Pearce SH, Cheetham TD. Diagnosis and management of vitamin D deficiency. BMJ 2010;340.
454.DeLuca HF. Overview of general physiologic features and functions of vitamin D. The American Journal of Clinical Nutrition 2004;80:1689S-96S.
455.Holick MF. Resurrection of vitamin D deficiency and rickets. The Journal of clinical investigation 2006;116:2062-72.
456.Cashman KD, Kiely M. Nutrition: New guidelines on vitamin D-ficiency--clear or confusing? Nat Rev Endocrinol 2011;7:566-8.
457.Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. The American Journal of Clinical Nutrition 2007;85:860-8.
458.Webb AR, Kline L, Holick MF. Influence of Season and Latitude on the Cutaneous Synthesis of Vitamin D3: Exposure to Winter Sunlight in Boston and Edmonton Will Not Promote Vitamin D3 Synthesis in Human Skin. Journal of Clinical Endocrinology & Metabolism 1988;67:373-8.
459.Zadshir A, Tareen N, Pan D, Norris K, Martins D. The prevalence of hypovitaminosis D among US adults: data from the NHANES III. Ethn Dis 2005;15:S5-97-101.
460.Ruston D, Hoare J, Henderson L, et al. The National Diet and Nutrition Survey: adults aged 19 to 64 years. Volume 4: Nutritional status (anthropometry and blood analytes), blood pressure and physical activity. . London: The Stationery Office; 2004.
461.Zgaga L, Theodoratou E, Farrington SM, et al. Diet, Environmental Factors, and Lifestyle Underlie the High Prevalence of Vitamin D Deficiency in Healthy Adults in Scotland, and Supplementation Reduces the Proportion That Are Severely Deficient. The Journal of Nutrition 2011;141:1535-42.
462.Parisaei M, Govind A, Clements J, Arora P, Lashkari H, Kapila P. Prevalence of vitamin D deficiency in a North London antenatal population. Obstet Med 2011;4:113-6.
463.Hamson C, Goh L, Sheldon P, Samanta A. Comparative study of bone mineral density, calcium, and vitamin D status in the Gujarati and white populations of Leicester. Postgraduate Medical Journal 2003;79:279-83.
464.Ford L, Graham V, Wall A, Berg J. Vitamin D concentrations in an UK inner-city multicultural outpatient population. Ann Clin Biochem 2006;43:468-73.
465.Garland CF, Garland FC, Gorham ED, et al. The Role of Vitamin D in Cancer Prevention. Am J Public Health 2006;96:252-61.
466.Wang L, Manson JE, Song Y, Sesso HD. Systematic Review: Vitamin D and Calcium Supplementation in Prevention of Cardiovascular Events. Annals of internal medicine 2010;152:315-23.
467.VanAmerongen BM, Dijkstra CD, Lips P, Polman CH. Multiple sclerosis and vitamin D: an update. Eur J Clin Nutr 2004;58:1095-109.
468.Hyppönen E, Läärä E, Reunanen A, Järvelin M-R, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. The Lancet 2001;358:1500-3.

469.Everett D. On the Use of Cod-Liver Oil in Tubercular Disease. Prov Med Surg J 1846;10:538-39.
470.Møller KI, Kongshoj B, Philipsen PA, Thomsen VO, Wulf HC. How Finsen's light cured lupus vulgaris. Photodermatology, Photoimmunology & Photomedicine 2005;21:118-24.
471.Grange JM, Davies PD, Brown RC, Woodhead JS, T K. A study of vitamin D levels in Indonesian patients with untreated pulmonary tuberculosis. Tubercle 1985;66:187-91.
472.Gibney KB, MacGregor L, Leder K, et al. Vitamin D Deficiency Is Associated with Tuberculosis and Latent Tuberculosis Infection in Immigrants from Sub-Saharan Africa. Clinical Infectious Diseases 2008;46:443-6.
473.Talat N, Perry S, Parsonnet J, Dawood G, Hussain R. Vitamin d deficiency and tuberculosis progression. Emerging Infectious Diseases 2010;16:853-5.
474.Davies PD, Brown RC, Woodhead JS. Serum concentrations of vitamin D metabolites in untreated tuberculosis. Thorax 1985;40:187-90.
475.Davies PD, Church HA, Brown RC, Woodhead JS. Raised serum calcium in tuberculosis patients in Africa. Eur J Respir Dis 1987;71:341-4.
476.Davies PD, Church HA, Bovornkitti S, Charumilind A. Altered vitamin D homeostasis in tuberculosis. Int Med Thailand 1988;4:45-7.
477.Chan TY, Poon P, Pang J, et al. A study of calcium and vitamin D metabolism in Chinese patients with pulmonary tuberculosis. J Trop Med Hyg 1994;97:26-30.
478.Sasidharan PK, Rajeev E, Vijayakumari V. Tuberculosis and vitamin D deficiency. J Assoc Physicians India 2002;50:554-8.
479.Nnoaham KE, Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. International Journal of Epidemiology 2008;37:113-9.
480.Williams B, Williams AJ, Anderson ST. Vitamin D Deficiency and Insufficiency in Children With Tuberculosis. The Pediatric Infectious Disease Journal 2008;27:941-2 10.1097/INF.0b013e31817525df.
481.Sita-Lumsden A, Lapthorn G, Swaminathan R, Milburn HJ. Reactivation of Tuberculosis and Vitamin D Deficiency: the contribution of diet and exposure to sunlight. Thorax 2007;62:1003 - 7.
482.Preece MA, Tomlinson S, Ribot CA, et al. Studies of vitamin D deficiency in man. Quarterly Journal of Medicine 1975;176:575-89.
483.Central TB Division Directorate General of Health Services. TB India 2010: RNTCP status report. New Delhi: Ministry of Health and Family Welfare; 2010.
484.Stephens WP, Klimiuk PS, Warrington S, Taylor JL, Berry JL, Mawer EB. Observations on the natural history of vitamin D deficiency amongst Asian immigrants. Quarterly Journal of Medicine 1982;202:171-88.
485.Ginde AA, Liu MC, Camargo CA, Jr. Demographic Differences and Trends of Vitamin D Insufficiency in the US Population, 1988-2004. Arch Intern Med 2009;169:626-32.
486.Health Protection Agency. Tuberculosis in the UK: Annual report on tuberculosis surveillance in the UK 2009. 2009.
487.Wejse C, Gomes VF, Rabna P, et al. Vitamin D as Supplementary Treatment for Tuberculosis: A Double-blind, Randomized, Placebo-controlled Trial. Am J Respir Crit Care Med 2009;179:843-50.
488.Martineau AR, Timms PM, Bothamley GH, et al. High-dose vitamin D3 during intensive-phase antimicrobial treatment of pulmonary tuberculosis: a double-blind randomised controlled trial. The Lancet 2011;377:242-50.
489.Liu PT, Stenger S, Li H, et al. Toll-Like Receptor Triggering of a Vitamin D-Mediated Human Antimicrobial Response. Science 2006;311:1770-3.
490.Liu PT, Stenger S, Tang DH, Modlin RL. Cutting Edge: Vitamin D-Mediated Human Antimicrobial Activity against Mycobacterium tuberculosis Is Dependent on the Induction of Cathelicidin. The Journal of Immunology 2007;179:2060-3.
491.Rook GA, Steele J, Fraher L, et al. Vitamin D3, gamma interferon, and control of proliferation of Mycobacterium tuberculosis by human monocytes. Immunology 1986;57:159-63.
492.McCarty CA. Sunlight exposure assessment: can we accurately assess vitamin D exposure from sunlight questionnaires? The American Journal of Clinical Nutrition 2008;87:1097S-101S.
493.National Institutes for Health Office of Dietary Supplements. Vitamin D: NIH; 2011.
494.Gao L, Tao Y, Zhang L, Jin Q. Vitamin D receptor genetic polymorphisms and tuberculosis: updated systematic review and meta-analysis. The International Journal of Tuberculosis and Lung Disease 2010;14:15-23.