

The effects of international migration on the epidemiology of tuberculosis, 2011-2021: a secondary analysis of national surveillance data

**A thesis submitted to Trinity College Dublin, the University of Dublin,
for the Degree of Doctor in Philosophy**



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Summary:

Introduction:

Tuberculosis (TB) remains a global public health threat that was responsible for 1.3 million deaths in 2022 alone. Ireland became a low TB incidence country in 2010 and has experienced a steady decline in crude incidence rates (CIRs) to less than 6 per 100,000 during 2024. While CIRs in the Irish-born have remained below six per 100,000 population since 2011, CIRs in the foreign-born population have been up to 13 times higher. Given the increasing global migration trends, migrants remain a key population for TB prevention and care activities. For this reason, a better and deeper understanding of the epidemiologic patterns among native-born and foreign-born TB patients is required.

Aim:

This thesis aimed to examine the effect of international migration on the epidemiology of TB in low to medium incidence countries by comparing and contrasting the epidemiology of TB among native-born cases and migrant cases, to inform global prevention and control policies. The objectives were met firstly, by conducting a systematic review of the published literature and secondly by analysing Irish TB surveillance data from 2011-2021.

Methods:

A systematic review comparing key epidemiological indicators among migrant and non-migrant TB cases was done to inform the subsequent analysis of the Irish TB surveillance dataset. Differences in the epidemiology of TB in native-born and foreign-born populations were analysed. An in-depth analysis of migrant-TB patient profiles was undertaken. To explore TB prevention, the effect of universal BCG vaccination cessation on the epidemiology of paediatric TB was examined. To explore TB control, factors associated with TB treatment success were analysed using multivariable logistic regression and random forest analyses.

Results:

1) The systematic review identified significant differences among high incidence migrants and non-migrants in the overall proportions of multidrug-resistant TB (MDR-TB) cases, people living with HIV, clustered cases and successfully treated cases. A gap in the evidence base was identified for reporting of TB incidence level among migrant study populations, resulting in 70% of retrieved articles being excluded due to missing data.

2) Of the 3,364 TB cases notified in Ireland between 2011 and 2021, 48% (n=1,605) were migrants, 47% (n=1,593) were Irish-born and 5% (n=166) had no country of birth reported.

Significant differences in the patient profile were observed both between migrants compared to

Irish-born cases, and also between the migrant TB subgroups studied. Compared to Irish-born cases, migrant cases were younger and had higher odds of living with HIV, having an extra-pulmonary site of disease (EPTB), being infected with a drug-resistant strain and residing in a congregate residential setting. They also had lower odds of being detected through contact tracing and of being linked to an outbreak. A significantly declining temporal trend in the CIR was observed for the latter half of the study (2017-2021) in total patients and Irish-born patients, but the declining trend was no longer significant among migrant patients.

Migrant TB patient characteristics differed by the incidence level in the birth-country and by the interval between arrival and notification as a TB case in Ireland. Specifically, migrants from very high incidence countries had the highest proportions of people living with HIV (PLWHIV) and with previous TB screening in Ireland. They also had the lowest proportions with pulmonary TB (PTB) and being linked to outbreaks. Recently arrived migrants were significantly younger and had higher proportions of International Protection Applicants and Refugees, PLWHIV and PTB.

3) In terms of the results relating to the effects of BCG vaccination cessation, the finding of interruption of the previously declining temporal trend in the 0-6 year old age-specific incidence rate during a period of universal vaccination may be an early warning of potential future increases in paediatric TB cases. This finding is particularly important if the selective BCG vaccination programme remains unimplemented. Eight of the 19 children notified since vaccination ceased would have been eligible to receive BCG under the current selective strategy.

4) Consistently lower odds of TB treatment success among cases infected with a drug-resistant strain of *M. tuberculosis* were found across all three populations examined in Ireland; these being total cases, migrant cases and Irish-born cases. Significant predictors of treatment success included both biological (drug resistance, patient age and sex) and social factors (housing and employment status) but differed slightly between migrant and non-migrant populations.

Conclusions:

This study reported key epidemiological and clinical differences between native-born and migrant TB cases in low TB incidence settings, thus informing tailored TB prevention and control strategies, and inclusive TB care services. Coupled with interruptions to previously declining trends in migrant TB cases and in paediatric cases, indications are that TB prevention and care interventions to support migrant health are urgently needed. Furthermore, tackling social determinants of TB will also remain a key focus for future TB control programmes. While surveillance data can be used for monitoring and evaluating aspects of the TB control programme, further attention and investment is critical to strengthen the quality of upstream sources of data utilised by both surveillance systems and health researchers.

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Dedication:

I dedicate this piece of work to my partner Stephen Malone and my child Senan Jackson-Malone.

Table of contents

Contents

Declaration:	2
Summary:	3
Acknowledgements:	5
Dedication:	6
Table of contents.....	7
List of tables:	13
List of figures:	15
List of abbreviations:	17
List of publications from this thesis.....	19
1 Chapter 1: Introduction:.....	20
1.1 Chapter outline.....	20
1.2 TB as a public health issue.....	20
1.1 Rationale for this study:	21
1.2 Study aim.....	23
1.2.1 Study objectives.....	23
1.3 Thesis outline.....	23
1.4 Chapter conclusion.....	24
2 Chapter 2: Literature review	25
2.1 Chapter outline.....	25
2.2 Literature review methods.....	25
2.3 Historical context.....	26
2.4 Pathogen, pathogenesis & clinical features	26
2.5 Laboratory diagnostic methods: TBI and TB disease.....	29
2.6 Treatment regimens.....	29
2.7 Vaccination	30
2.8 Risk factors and social determinants of disease.....	32
2.9 Policy context	34
2.10 Global TB epidemiology.....	35
2.10.1 Paediatric cases	36
2.10.2 Sex differences	36
2.10.3 Drug resistance	37

2.10.4	Treatment success	37
2.11	TB epidemiology in Ireland	38
2.12	Migration and TB epidemiology.....	42
2.13	TB prevention and control continuum.....	45
2.14	Chapter conclusion	45
3	Chapter 3: Theoretical framework, methodology and methods:	46
3.1	Chapter outline	46
3.2	Research paradigm	46
3.3	Research strategy and methodology	46
3.4	Ontological approach.....	47
3.5	Epistemological approach.....	47
3.6	Axiological approach	48
3.7	Conceptual framework and theoretical underpinnings.....	48
3.8	Research design	52
3.8.1	Systematic review and meta-analysis methods.....	52
3.8.2	Secondary data analysis methods.....	58
3.9	Reporting quality:	71
3.10	Ethical considerations	71
3.11	Funding:	72
3.12	Chapter conclusion	72
4	Chapter 4: A systematic review on the effects of migration from high TB incidence countries on the epidemiology of TB in low to medium incidence countries:	73
4.1	Chapter outline	73
4.2	Introduction	73
4.3	Methods.....	75
4.3.1	Population.....	75
4.3.2	Exposure.....	75
4.3.3	Comparator	75
4.3.4	Outcomes.....	75
4.3.5	Inclusion and exclusion criteria.....	76
4.3.6	Search strategy and information sources	76
4.3.7	Data management	78
4.3.8	Study selection and review	78
4.3.9	Data extraction process	78

4.3.10	Quality assessment.....	79
4.3.11	Statistical analysis.....	79
4.4	Results	80
4.4.1	Title and abstract screening	80
4.4.2	Full text review	80
	Figure 10: Flow chart of articles retrieved by the systematic review search strategy.....	81
4.4.3	Quality assessment.....	85
4.4.4	Outcomes:	88
4.5	Discussion:	101
4.5.1	Strengths and limitations:	103
4.5.2	Conclusions.....	104
4.6	Chapter conclusion:.....	105
5	Chapter 5: The comparative epidemiology of tuberculosis among Irish-born TB cases and migrant TB cases in Ireland:	106
5.1	Chapter outline.....	106
5.2	Introduction.....	106
5.3	Methods:	108
5.3.1	Study design and population.....	108
5.3.2	Definitions	108
5.3.3	Statistical analysis.....	108
5.4	Results:	110
5.4.1	Epidemiology of TB among migrants compared to Irish-born:	110
5.4.2	Migrant TB epidemiology:	118
5.5	Discussion:	125
5.5.1	Strengths and limitations	128
5.5.2	Conclusions & recommendations:.....	128
5.6	Chapter conclusion	129
6	Chapter 6: The impact of universal TB vaccination cessation on the epidemiology of paediatric TB in Ireland	130
6.1	Chapter outline.....	130
6.2	Introduction.....	130
6.3	Methods	131
6.3.1	Study design and population.....	131
6.3.2	Statistical analyses.....	131

6.4	Results.....	132
6.4.1	Country of birth and ethnicity:	134
6.4.2	Laboratory confirmation and drug resistance:	134
6.4.3	Case finding and case type:.....	135
6.4.4	Outbreak association:	135
6.4.5	Geographical distribution:	135
6.4.6	Temporal trends:.....	136
6.5	Discussion.....	137
6.5.1	Strengths and limitations:.....	139
6.5.2	Conclusions and recommendations.....	140
6.6	Chapter conclusion:	140
7	Chapter 7: Factors affecting treatment success of tuberculosis cases in Ireland.....	142
7.1	Chapter outline	142
7.2	Introduction	143
7.3	Methods.....	144
7.3.1	Study design and population	144
7.3.2	Definitions	144
7.3.3	Missing data	144
7.3.4	Statistical analyses	145
7.4	Results.....	147
7.4.1	Distribution of the sample for total cases.....	147
7.4.2	Distribution of the sample - Migrant cases.....	155
7.4.3	Distribution of the sample - Irish-born cases.....	159
7.4.4	Predictors of treatment success – total cases	162
7.4.5	Predictors of treatment success - Migrant cases.....	173
7.4.6	Predictors of treatment success - Irish-born cases.....	178
7.5	Discussion.....	184
7.5.1	Strengths and limitations:.....	187
7.5.2	Conclusions and recommendations:.....	188
7.6	Chapter conclusion:	188
8	Chapter 8: General discussion, conclusions and recommendations	189
8.1	Chapter outline	189
8.2	Summary of thesis/ overview	189
8.3	Summary of key findings.....	190

8.4	Discussion of key findings and concepts	194
8.4.1	Drug resistance	194
8.4.2	Social determinants of health:	196
8.4.3	Extrapulmonary disease	198
8.4.4	Diversity within migrant TB sub-populations:	200
8.5	Strengths and limitations of study findings.....	203
8.6	Recommendations for policy, practice and future research.....	204
8.6.1	Policy:	204
8.6.2	Practice:	206
8.6.3	Research:	210
8.7	Unique contribution to the evidence base.....	211
8.8	Overall conclusions of the thesis.....	212
9	References:.....	213
10	Appendices	235
	Appendix 1: Recent trends in TB epidemiology in Ireland (source: HPSC CIDR)	236
	Appendix 2: List of CIDR variables and rationale for inclusion in the study.....	238
	Appendix 3: Systematic review protocol.....	245
	Appendix 4a: Systematic review search strategy supplementary materials	249
	Table A4.1: Inclusion and exclusion criteria	249
	Table A4.2: Terms employed by the search strategy used in EMBASE (Embase.com)	249
	Table A4.3: List of studies excluded on basis of English language inclusion criteria	250
	Appendix 4b: Systematic review data extraction tool	252
	Appendix 4c: Systematic review results supplementary materials.....	255
	Appendix 5: Chapter 5 supplementary materials.....	256
	Appendix 6: Treatment success models supplementary information	259
	Figure A6.1: Model assumptions of treatment success among all cases final model generated through manual method (n=1,074)	259
	Table A6.1: Factors associated with treatment success among migrant TB cases from model produced by multivariable logistic regression algorithm method (complete case sample: N = 478).....	260
	Figure A6.2: Model assumptions of treatment success among migrant TB cases final model generated through manual method (n=477)	261
	Figure A6.3: Model assumptions of treatment success among migrant TB cases final model generated through algorithm method (n=477).....	262

Figure A6.4: ROC AUC for final multivariable logistic regression models for treatment success among generated by algorithm method for migrant cases.....	263
Figure A6.5: Model assumptions for treatment success among Irish-born TB cases for final model generated through manual method (n = 592).....	264

List of tables:

Table 1: National Immunisation Guidelines 2023 Recommendations for BCG.....	32
Table 2: Key differences between narrative reviews and systematic reviews	52
Table 3: Drug resistance patterns for MDR, pre-XDR and XDR-TB.....	63
Table 4: Census of population applied for notification years and specific numerators.....	67
Table 5: Characteristics of included studies.....	82
Table 6: Quality assessment results for included studies (n=32)	86
Table 7: Outcomes reported by included studies (n=32)	89
Table 8: Summary of secondary outcomes reported by included studies.....	95
Table 9: Summary patient characteristics of TB cases by migrant status for full sample (n= 3,198) and results of univariable and multivariable logistic regression analyses (n = 825) for Ireland; 2011-2021.....	114
Table 10: Interval between onset and diagnosis by disease site and migrant status; Ireland 2011-2021.....	116
Table 11: Characteristics of migrant TB cases by WHO TB incidence category, Ireland 2011-2021	119
Table 12: Migrant source countries with top 10 highest percentage of cases or crude incidence rate between 2011-2021, Ireland.....	121
Table 13: Migrant TB patient characteristics by interval between arrival and notification; Ireland	123
Table 14: Patient characteristics of paediatric TB cases aged 0-6 years old by birth cohort.....	133
Table 15: Distribution of patient characteristics for total cases by treatment outcome status (n=3,364)	150
Table 16: Distribution of migrant patient characteristics by treatment outcome status (n=1,605) and by inclusion in model sample (n=950).....	156
Table 17: Distribution of the Irish-born patient characteristics by treatment outcome status (n=1,098) and by inclusion in model sample (n=592)	160
Table 18: Distribution of patient characteristics of total cases by treatment success and crude odds ratios from univariable logistic regression (n=2,084).....	164

Table 19: Factors associated with treatment success among total cases (complete case sample: N = 1,069) for final model (M6b).....	167
Table 20: Distribution of migrant patient characteristics by treatment success and crude odds ratios from binary logistic regression (n=950)	175
Table 21: Factors associated with treatment success among migrant TB cases (complete case sample: N = 477) for final model (M5).....	177
Table 22: Distribution of Irish-born patient characteristics by treatment success and crude odds ratios from binary logistic regression (n=1,098)	180
Table 23: Factors associated with treatment success among Irish-born TB cases (complete case sample: N = 592) for final model (M6).....	182
Table 24: Summary of key findings by concept and results chapter	193

List of figures:

Figure 1: The tuberculosis infection to disease continuum (reproduced from Goletti et al)(Goletti et al., 2022).....	28
Figure 2: The tuberculosis-depression syndemic model (reproduced from Sweetman et al)(Sweetland et al., 2017).....	33
Figure 3: Framework for proximate risk factors and upstream determinants of TB (reproduced from Lönnrot et al) (Lönnroth et al., 2009a)	34
Figure 4: Estimated TB incidence rates per 100,000 population, 2023 (WHO)	35
Figure 5: Annual number of TB cases with resistance to anti-TB drug by geographic origin, Ireland (HSE HPSC).....	39
Figure 6: TB treatment outcomes at 12 months by year, Ireland (HSE HPSC)	39
Figure 7: a) Annual number of incident TB cases compared to End TB Target case number projections; b) Annual TB crude incidence rates compared to End TB Target CIR projections per 100,000 population, Ireland (HSE HPSC)	41
Figure 8: Model of the NICE Conceptual Framework for Public Health, with examples of variables used in quantitative analyses	51
Figure 9: Data flows in infectious disease surveillance systems in Ireland	60
Figure 10: Flow chart of articles retrieved by the systematic review search strategy.....	81
Figure 11: Proportion of TB disease cases in high incidence migrants of total study population with sensitivity analysis by clinical category	91
Figure 12: Meta-analysis of sputum smear positive TB cases with sensitivity analysis	96
Figure 13: Meta-analysis of TB cases with first line anti-TB drug resistance with sensitivity analysis	97
Figure 14: Meta-analysis of MDR-TB cases with subgroup and sensitivity analysis	98
Figure 15: Meta-analysis of clustered TB cases with sub group and sensitivity analysis.....	99
Figure 16: Meta-analysis of HIV co-infected TB cases.....	100
Figure 17: Meta-analysis of successfully treated TB cases with sensitivity analysis.....	100
Figure 18: Cumulative number of TB cases and age-specific incidence rate per 100, 000 population by migrant status in Ireland, 2011-2021.....	111

Figure 19: Interval between onset and diagnosis in months by migrant status for TB cases in Ireland, 2011-2021 (n = 1,955)	112
Figure 20: Annual number of TB cases and crude incidence rate per 100, 000 population by migrant status in Ireland, 2011-2021.....	117
Figure 21: Origin-countries with 10 highest mean crude incidence rates in Ireland compared to WHO incidence estimates, 2011-2021	120
Figure 22: Annual number of TB disease cases and age-specific incidence rate per 100,000 population by birth cohort.....	132
Figure 23: Annual number of TB disease cases and age-specific incidence rate per 100,000 population by country of birth.....	134
Figure 24: Annual age-specific incidence rates per 100,000 population by birth cohort and geographical area of residence.....	136
Figure 25: Visual representation of Chapter 7 results structure	142
Figure 26: a) TB treatment outcome status by reporting year and b) treatment success by reporting year (n= 3,364)	149
Figure 27: Patterns of missing data for selected independent variables and dependent variable (treatment success) within the full sample (n= 3,364)	153
Figure 28: Proportions of missing data for selected independent variables and dependent variable (treatment success) within the full sample (n= 3,364)	154
Figure 29: Forest plots for final multivariable logistic regression models for treatment success among total cases, migrant cases and Irish-born cases.....	169
Figure 30: Variable importance plots calculated by Random Forest algorithm for independent variables included in the full models for a) total cases, b) migrant cases and c) Irish-born cases	170
Figure 31: AUROC curves for final multivariable logistic regression models for treatment success among a) all cases, b) migrant cases and c) Irish-born cases.	171
Figure 32: Calibration plots for final models for treatment success among a) total TB cases, b) migrant TB cases and c) Irish-born TB cases	172

List of abbreviations:

AIC – Akaike Information Criterion
AICc – Akaike Information Criterion corrected for small sample size
aOR – Adjusted Odds Ratio
ASIR – Age-specific incidence rate
AUROC – Area Under the Receiver Operating characteristic Curve
CI – confidence interval
CIDR – Computerised Infectious Disease Reporting system
CIR – Crude incidence rate
cOR – Crude Odds Ratio
CSO – Central Statistics Office
CXR – Chest X-ray
CT scan – Computed Tomography scan
DST - Drug Susceptibility Testing
ECDC – European Centre for Disease Prevention and Control
EPTB – Extrapulmonary TB
HIV - Human Immunodeficiency Virus
HPSC – Health Protection Surveillance Centre
HSE – Health Service Executive
IPA – International Protection Applicant
IPAR – International Protection Applicant or Refugee
IRR – Incidence Rate Ratio
LTBI - Latent TB infection
MCAR – Missing Completely At Random
MDR-TB – Multidrug-resistant Tuberculosis
MTBC – *Mycobacterium tuberculosis* complex
M/XDR – Multi / Extensively drug-resistant TB
NAAT - Nucleic Acid Amplification Testing
NBR - Negative Binomial Regression
NICE – National Institute of Health and Care Excellence
NTM - Non-tuberculous *Mycobacteria* (NTM)
OR – Odds Ratio
PCP - Percentage of Correct Predictions
PLWHIV – People living with Human Immunodeficiency Virus

PTB – Pulmonary TB

Pre-XDR TB – Pre-Extensively Drug-Resistant Tuberculosis

PRISMA – Preferred Reporting Items For Systematic Reviews and Meta-analyses

RF - Random Forest

STROBE – Strengthening the Reporting of Observational Studies in Epidemiology

TB - Tuberculosis

TBI – Tuberculosis infection (previously known as Latent TB infection)

VIF – Variance Inflation Factor

WGS - Whole Genome Sequencing

WHO – World Health Organization

XDR-TB – Extensively drug-resistant Tuberculosis

List of publications from this thesis

Peer-Reviewed Journal Articles

In line with thesis submission guidelines, this thesis includes writings already published by me, which derive from my research work carried out during the period of my registration. These writings have been fully integrated into the body of the thesis.

Jackson S, Kabir Z, Comiskey C. *Effects of migration on tuberculosis epidemiological indicators in low and medium tuberculosis incidence countries: A systematic review*. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2021; 23 (Jackson et al., 2021).

Jackson S, Kabir Z, Comiskey C. *Retrospective cohort study exploring the impact of universal Tuberculosis (TB) vaccination cessation on the epidemiology of paediatric TB in Ireland, 2011–2021*. Vaccine (2024) 42(8) 2099-2105 (Jackson, Kabir, et al., 2024).

Presentation of results from thesis

Jackson S, Kabir Z, Comiskey C. *Divergence in pace of decline in tuberculosis rates among migrants versus non-migrants in Ireland from 2011 to 2020*. The Lancet (2022) 400 S52 (Jackson et al., 2022a)

Jackson S, Kabir Z, Comiskey C. *Impact of universal tuberculosis vaccination cessation on the epidemiology of paediatric tuberculosis cases in Ireland from 2011 to 2021*. The Lancet (2022) 400 S53 (Jackson et al., 2022b)

Jackson S, Kabir Z, Comiskey C. *Social and biological factors associated with unsuccessful TB treatment outcome in Ireland 2011-2021*. European Journal of Public Health (2023) 33(Supplement_2) (Jackson et al., 2023)

1 Chapter 1: Introduction:

1.1 Chapter outline

This chapter aims to provide a brief introduction to the topic of tuberculosis (TB) as a global public health issue, its association with human migration and to outline why this study was required. This chapter will also specify the aims and objectives of the study and provide an outline of the thesis structure.

1.2 TB as a public health issue

For many people today, particularly those living in high income countries, tuberculosis (TB) is perceived as a remnant of the past associated with the Victorian era. Despite this perception, TB is the highest cause of death from any infectious disease and is one of the top ten causes of death from all causes each year globally (World Health Organization, 2024a). During 2023, the World Health Organization (WHO) estimated that the number of incident cases at 10.8 million, an increase compared to 10.6 million in 2022 (World Health Organization, 2024b). WHO also estimated that TB was responsible for 1.3 million deaths in 2022 alone, with 7,000 of those considered excess deaths due to health service disruption association with the Covid-10 emergency response (World Health Organization, 2024b).

TB crude incidence rates (CIRs) in Ireland have dramatically declined since the 1950s when they were over 220 per 100,000 population, to 5.6 per 100,000 during 2024 (HSE Health Protection Surveillance Centre, 2025). Ireland became a low TB incidence country (<10 per 100,000 population) in 2010. Despite this welcome overall decline in TB CIRs, rates among the foreign-born population have been up to 13 times higher (HSE Health Protection Surveillance Centre, 2025). Census data from the Central Statistics Office (CSO) reports that the proportion of the Irish population that was born abroad has steadily increased from 10% in 2002 to 20% in 2022 (Central Statistics Office, 2016b, 2024a). At the same time, the proportion of foreign-born TB cases has increased from 30% to >70% (HSE Health Protection Surveillance Centre, 2025).

While an individual's baseline risk of TB infection and disease is greatly influenced by the level of TB incidence in their country of origin, the process of migration itself can further increase the risk of infection or progression to TB disease through increased risk of exposure along migration routes which may be further compounded by unfavourable social determinants on arrival in the host country (Pareek et al., 2011, 2016; Shete et al., 2018). A large-scale study assessing the

burden of infectious diseases among migrants in the EU/EEA found that migrant populations are disproportionately affected by TB (European Centre for Disease Prevention and Control, 2014). Although migrant TB has been extensively researched, many of these studies have failed to reflect the diversity of this population, often using broad definitions including proxy indicators such as nationality rather than birth country and sometimes using mixed categories of first and second-generation migrants (Hollo et al., 2016, 2017; Ködmön et al., 2016; Odone et al., 2015). International migrants are a diversely heterogenous population group in most countries. This diversity manifests through the migrant's country of origin, mode of migration, socioeconomic grouping, demographic profile and health status. The interaction of these factors leads to differing risks of being already infected with TB prior to arrival in the destination country, differing chances of becoming infected with TB once arrived and differing chances of accessing health services if a person develops infection or disease. An example of this diversity within the European international migrant population was reported by a large study which found that migrants from other European Union (EU) countries did not contribute significantly to the overall incidence of TB in the EU. Instead, most of the migrant TB cases in the study were found to be mainly from high TB incidence countries outside the EU (Hollo et al., 2016).

1.1 Rationale for this study:

Since eliminating human migration is neither feasible nor desirable, it is crucial to improve our understanding of its impact on TB epidemiology to enable progression towards the global goal of TB elimination. This study will approach its aim from a public health perspective and employ epidemiological principles and concepts to investigate patterns of TB disease. This study seeks to fill a gap in the evidence base by conducting a systematic review, the results of which will be used to inform and guide a subsequent in-depth analysis of the Irish TB notification dataset. These analyses will be guided by the National Institute of Health and Care Excellence (NICE) conceptual framework on the determinants of health (National Institute for Health and Care Excellence, 2012).

The systematic review aims to investigate how migration from high TB incidence countries affects the epidemiology of TB in low to medium incidence countries (Jackson et al., 2018). The review will compare the differences in key TB [epidemiological outcomes](#) between cases diagnosed in migrants from high TB endemicity countries who are reported as a case in a low or medium incidence country. Key outcomes analysed in the review will also be analysed in the Irish TB notification dataset.

The quantitative phases of the study, using the Irish notification dataset, aim to inform future global and local TB prevention and control activities by providing a detailed analysis of the comparative epidemiology of TB in native -born and foreign-born populations within the Irish context. These analyses will be stratified by the TB incidence of the migrant countries and by geographical regions of origin, filling an important gap in the literature which has typically analysed migrants simply as “foreign-born”.

In addition, this study will explore two further aspects at either end of the TB prevention and control continuum. At the prevention side of the continuum, the study investigates the impact of universal TB vaccination cessation on the epidemiology of paediatric TB in Ireland. The results of this analysis can be used to tailor the introduction of the planned selective BCG vaccination programme.

At the control end of the continuum, this study aims to identify factors associated with successful and unsuccessful treatment outcomes. This will inform development of targeted interventions to support TB cases to achieve a successful treatment outcome. Supporting cases to achieve a successful treatment outcome is not only beneficial at the patient level but it is also key from a public health perspective to reduce the infectious reservoir and help achieve TB elimination goals.

Although the context of this research will be Ireland, the results of this research will be generalisable across other low TB incidence countries with similar migrant population profiles and can be used to enhance screening programmes and service delivery, as well as inform selective BCG vaccination programmes. This research will illustrate the changing epidemiology of TB and help to direct global prevention and control activities towards the goal of TB elimination.

1.2 Study aim

The overall aim of this study is to examine the effect of international migration on the epidemiology of TB in low to medium incidence countries to inform global prevention and control policies.

1.2.1 Study objectives

1. To conduct a systematic review of the literature on the effect of migration from high TB incidence countries on the epidemiology of TB in low to medium incidence countries
2. To describe and analyse the comparative epidemiology of TB among Irish-born TB cases and migrant TB cases in order to inform future TB prevention and control activities
3. To explore the impact of a national universal BCG vaccination programme cessation on the epidemiology of paediatric TB cases
4. To investigate factors affecting treatment success of TB cases and whether the factors differ between Irish-born and migrant TB cases

1.3 Thesis outline

This thesis comprises eight chapters, four of which are results chapters addressing the specific research question as outlined in the study objectives.

Chapter 1 introduces the study and the rationale for conducting the research, specifies the aims and objectives and outlines the overall thesis structure.

Chapter 2 provides a detailed background to the topic under study synthesised from the published literature and introduces how the topics of human migration and tuberculosis intersect as a public health issue.

Chapter 3 outlines the methodology of the study and introduces the theoretical underpinnings and the conceptual framework used to guide the research design. A summary of the methods used is provided.

Chapter 4 presents the results of the first objective, a systematic review and meta-analysis of the published literature on the effect of migration on the epidemiology of TB in low to medium incidence countries. The results of this systematic review were used to inform the quantitative analyses of the Irish TB notification data that follows in chapters 5, 6 and 7.

Chapter 5 reports the results of the second objective comparing and contrasting the epidemiology of TB among migrants compared to Irish-born within the Irish context. This study contains a descriptive cross-sectional analysis as well as a multivariable analyses of the predictors of TB among migrants compared to TB among Irish-born. This study also presents a detailed analysis of the profile of migrant TB cases according to specific sub-populations.

Chapter 6 presents the results of the third objective, exploring the impact of universal TB vaccination cessation on the epidemiology of paediatric TB in Ireland and contextualises the findings in terms of outcomes reported by other low TB incidence countries after discontinuing universal BCG vaccination.

Chapter 7 reports the results of the fourth objective, exploring factors associated with successful TB treatment outcomes, and whether they differ among migrant TB cases and Irish-born TB cases.

Chapter 8 summarises the findings from all four results chapters and contextualises these in the context of the published literature. Strengths and weaknesses of the study are outlined. Conclusions of the study are presented and recommendations for public health policy and practice, along with directions for future research are made.

1.4 Chapter conclusion

This chapter has introduced the topic of migrant TB epidemiology and how it is linked to TB elimination goals. The aim, objectives and study rationale have been outlined. The following chapter will provide a detailed background to TB as an infection and disease, the policy context, global and Irish epidemiology and how human migration is inextricably linked to the goal of TB elimination.

2 Chapter 2: Literature review

2.1 Chapter outline

This chapter aims to provide a comprehensive overview of TB infection and disease, summarises TB epidemiology globally and within Ireland, and introduces the association between human migration and TB.

2.2 Literature review methods

As the topics covered in this chapter were broad in nature, a structured literature review was not conducted. Instead, a broad search for the combined concepts of TB and epidemiology were carried out on the Embase platform searching both the Embase and Medline bibliographic databases. Title and abstracts were searched for keywords for the two concepts, as well as the relevant Emtree controlled vocabulary, and combined with AND as outlined below.

Concept 1: Tuberculosis

Key words: Tuberculosis OR Tuberculoses OR Tuberculous OR Tuberculoid

EMTREE Controlled vocabulary: "Mycobacterium tuberculosis complex/de" or "Mycobacterium tuberculosis"

AND

Concept 2: Epidemiology

Key words: Epidemiology or

EMTREE Controlled vocabulary: "Epidemiology"

Duplicate records that were present on both Embase and Medline were reduced to a single entry. Snowball searching from key references identified during full text review was also performed. Further sub-searches were conducted on many of the topics such as social determinants, migration, treatment outcomes etc.

2.3 Historical context

While the causative pathogen for TB was identified in 1882 by Robert Koch, it has circulated in human and animal populations for far longer. TB was previously thought to have emerged as a disease during the Neolithic Demographic Transition (NDT) approximately 10,000 years ago, however recent genomic analysis suggest it has been present in humans as far back as 70,000 years ago. It is thought to have evolved the classic features of “crowd” diseases during the expansion of the human population which occurred during the NDT, when humans moved from foraging to farming and began to settle in larger communities (Comas et al., 2013).

In more recent times, TB reached the peak of its epidemic during the 1800s and began a slow but gradual decline (Murray et al., 2015). The exact cause of this decline is not currently known and has been suggested to be the result of multiple wide-ranging factors, as it predated the availability of chemotherapy for TB. Some of the proposed contributing factors include developments that arose from the understanding that it was an infectious disease, such as segregation of infectious cases through the introduction of sanatoria, pasteurization of milk and even natural selection (Davies et al., 1999; Lönnroth et al., 2009a). However, further contributing factors have been proposed from the realm of social determinants; particularly advances in socio-economic conditions due to both economic growth and social reform. Examples include poverty reduction, better housing conditions which were less favourable to the spread of disease as well as improvements in nutrition at the population level (Davies et al., 1999; Lönnroth et al., 2009a; McKeown, 1979; Rasanathan et al., 2011; Wilson, 1990). Treatment for TB was not available until 1952 when an antibiotic regime was introduced and further declines in incidence were observed (Murray et al., 2015). However, this further decline also occurred against a backdrop of intense economic growth and welfare reforms in many industrial countries (Lönnroth et al., 2009a).

2.4 Pathogen, pathogenesis & clinical features

TB is caused by infection with a species of *Mycobacterium*, the sole genus in the family *Mycobacteriaceae*. *Mycobacteria* are categorised as tuberculous and non-tuberculous *Mycobacteria* (NTM) depending on their ability to cause tuberculosis disease or not. There are currently 10 species of *Mycobacteria* known to infect humans, which are referred to as *Mycobacterium tuberculosis* complex (MTBC), in addition to over 170 species of NTM. The most common causes in humans are *M. tuberculosis* (MTB), *M. bovis* and *M. africanum* species (Bespiatykh et al., 2021; Heemskerk et al., 2015). Human tuberculosis cases have been

documented in smaller numbers due to infection with the remainder of species, which are predominantly zoonotic in nature, each of which having a defined host reservoir (Dippenaar et al., 2015; Duffy et al., 2024)

Exposure to MTBC is currently understood to result in four different outcomes depending on both bacterial virulence factors and host factors (Coussens et al., 2024; Migliori et al., 2021; Rotundo et al., 2024). The bacteria are inhaled into the lungs as small droplet nuclei aerosols or can be ingested in contaminated foods, such as unpasteurised milk (Heemskerk et al., 2015). The bacteria may be cleared by the host immune system without infection or disease occurring. Alternatively, exposure may also result in infection which is limited and remains temporarily inert. This was previously referred to as “latent TB infection” (LTBI) but is more recently known as TB infection (TBI) as the infection stage cannot always be considered latent. TBI is asymptomatic and non-infectious. It is not detectable clinically, microbiologically or via imaging and is only detectable by immunological testing. TBI may reactivate as TB disease at a later stage of the hosts life.

Between latent infection and active disease there is a third transitional stage of incipient disease, where the MTBC has become metabolically active. Incipient disease is not usually detectable via imaging or standard microbiological techniques. Finally, the fourth possible outcome of exposure is to progress to TB disease, which may or may not be infectious (Coussens et al., 2024; Heemskerk et al., 2015; Migliori et al., 2021). Both sub-clinical and symptomatic TB disease have macroscopic pathology and are further sub-divided into infectious and non-infectious forms (Coussens et al., 2024). Most forms of TB disease are detectable microbiologically or via imaging techniques. [Figure 1](#) illustrates the potential pathways from exposure to MTBC to disease (Goletti et al., 2022).

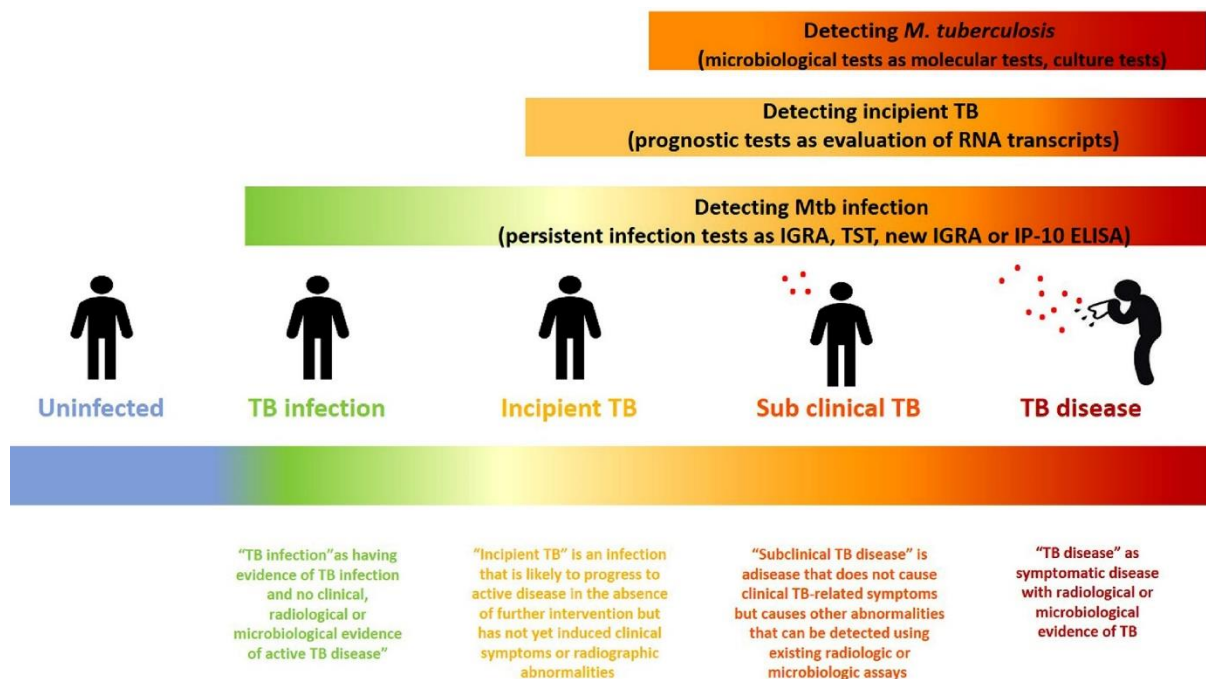


Figure 1: The tuberculosis infection to disease continuum (reproduced from Goletti et al)(Goletti et al., 2022)

Following exposure, if the bacteria reach the alveoli successfully, they begin to proliferate unless prevented by the innate immune system. If the bacteria can infect the alveolar macrophages, they may then be transported to other anatomical sites external to the lungs, where the bacteria can infect any site of the body (Todar, 2015). An effective innate immune response produces a primary granuloma, which may then progress to a solid granuloma associated with TBI, or a granuloma with a liquid centre associated with TB disease. In the case of symptomatic TB disease, this liquid centre allows the bacteria to be discharged into the lung and coughed up as an infectious aerosol (Todar, 2015).

TB disease can affect any organ of the body, and the clinical presentation is mainly dependent on the site of disease. Primary active pulmonary TB usually presents with a persistent cough (>3 weeks), profuse night sweats, shortness of breath, weight loss and fever. Active disease in non-pulmonary sites can present in diverse ways, according to the organ affected (Heemskerk et al., 2015). Miliary or disseminated TB is a severe form of disease resulting from lymphohematogenous dissemination of MTBC causing a characteristic pattern of widespread tiny tubercular lesions throughout numerous organs (Heemskerk et al., 2015).

2.5 Laboratory diagnostic methods: TBI and TB disease

There are two methods of testing for TBI, tuberculin skin testing (TST) and interferon gamma release assays (IGRA). Neither test differentiates between latent infection or TB disease and can only confirm that the person has previously been exposed to and mounted an immune response to TB (World Health Organization, 2024e). TBI tests cannot provide information on the drug sensitivity profile of the infecting strain and so cannot guide the required treatment in the absence of a reliable exposure history.

For many decades, the initial diagnostic test for TB disease was microscopy, using stained specimens to inspect and enumerate the number of acid-fast bacilli (AFB). Microscopy was followed by culture and phenotypic drug susceptibility testing (DST). Phenotypic DST measures the inhibitory effect of the antibiotic on the bacterial isolate in-vitro while genotypic DST detects genes known to be associated with drug resistance. MTBC species are fastidious and slow growing bacteria, with median time to detection of over 2 weeks (Pfyffer & Wittwer, 2012; Tyrrell et al., 2012). Higher numbers of AFB observed during microscopic evaluation and faster time to growth detection in a culture are both indicators of increased infectiousness. Nowadays, genotypic methods can produce both a diagnostic result and DST result for both first line drugs, isoniazid and rifampicin, within two hours (World Health Organization, 2021a). Some genotypic platforms also process whole specimens removing the need for complex laboratory specimen preparations required for a culture. These platforms are now recommended by WHO as first line technology (World Health Organization, 2021a). Most TB diagnostic laboratories in high income countries have augmented traditional culture and phenotypic drug susceptibility testing methods with genotypic drug susceptibility testing methods, such as nucleic acid amplification testing (NAAT) and whole genome sequencing methods (WGS). WGS is able to provide information that is both clinically relevant, such as presence of drug resistance mutations, as well as public health relevance, such as degree of relatedness to isolates derived from other cases.

2.6 Treatment regimens

The required treatment is dependent on whether the person has TBI or TB disease, and the drug susceptibility profile of the mycobacterial isolate.

For TBI preventive treatment (TPT), the most recent WHO strong recommendations have included shorter regimens than the previous standard 6 or 9 months of daily isoniazid, such as 3-

month regimens of either rifapentine plus isoniazid taken weekly, or isoniazid plus rifampicin taken daily (World Health Organization, 2024e). The regimen for TB disease is usually a standard six-month regimen, beginning with two months of isoniazid, rifampicin, ethambutol and pyrazinamide, followed by a further four months of isoniazid and rifampicin. However, WHO also introduced a conditional recommendation for a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide for cases >12 years old (World Health Organization, 2022c).

Treatment regimens are modified appropriately where drug resistance to any of the above is detected. If resistance to both isoniazid and rifampicin is detected, this is referred to as Multidrug-Resistant TB (MDR-TB). Until 2021, if the isolate also had resistance to any fluoroquinolone and any of the injectable second line aminoglycoside drugs, this was referred to as **Extensively** Drug-Resistant TB (XDR-TB). Since 2022, WHO has updated the classification of XDR-TB to those with MDR-TB and resistance to any fluoroquinolone, plus bedaquiline or linezolid (World Health Organization, 2022b). Many treatment regimens required to treat TB cases can have significant side effects and toxicity, including deranged liver function, deafness and nerve sensitivity (Laniado-Laborín, 2015). At the time of writing, there were nine new drugs for the treatment of TB disease undergoing clinical trials (World Health Organization, 2024g).

2.7 Vaccination

The Bacillus Calmette-Guérin (BCG) vaccine remains the only currently licensed vaccine for prevention of Tuberculosis (TB) and has been in use for over 100 years. Vaccination of neonates and school age children with BCG confers up to 70% protection, mainly from severe TB disease, such as meningitis and miliary TB, where previous infection can be ruled out (Lange et al., 2022). BCG is thought to be less effective at preventing disease in older age groups (Nguipdop-Djomo et al., 2016; Rodrigues et al., 1993). The vaccine is less effective at preventing infection and does not prevent progression from TBI to TB disease (Roy et al., 2014). Sixteen new vaccines are at various stages of development and it is currently a WHO priority to develop a fully preventive vaccine for TB (Cho et al., 2021; Scriba et al., 2020; Tuberculosis Vaccine Initiative, 2023; World Health Organization, 2024g).

BCG vaccination programmes are usually operationalised as either universal or selective. Universal vaccination targets all individuals in the population usually by age, such as vaccination of all neonates. Selective vaccination programmes target subgroups of the population who are at higher risk of either infection, disease or resultant sequelae. Between 1949-2015, Ireland had a

policy of universal BCG infant vaccination, with national uptake estimated at 87% in 2014 (Health Information & Quality Authority, 2015; HSE Health Protection Surveillance Centre, 2015). However, there was regional variation in its implementation, with some counties in the south and west of Ireland implementing universal vaccination of 12 year olds, while one district implemented a risk based selective vaccination programme between 1972-2008 (to those with a history of direct TB contact, and upon parental request) (Health Information & Quality Authority, 2015).

According to the International Union Against Tuberculosis and Lung Disease (IUATLD) the quantitative criteria for low TB incidence countries to discontinue BCG are a sputum smear positive crude incidence rate (CIR) of <5 per 100,000 for previous 5 years and a meningitis CIR in the 0–4 year old age group of <1 per 10,000,000 general population (International Union Against Tuberculosis and Lung Disease, 1994). Ireland has met the sputum-smear positive criteria since 2002 and the meningitis criteria in 2011 (Health Information & Quality Authority, 2015). Despite meeting these criteria, Ireland remained an outlier among other low TB incidence European countries in retaining a universal BCG vaccination programme (*The BCG World Atlas, 3rd Edition*, 2023).

Recommendations to move to a selective BCG vaccination programme were made by the National Immunisation Advisory Committee in 2013 and by a Health Technology Assessment (HTA) from the Health Information and Quality Authority (HIQA) in 2015 (Health Information & Quality Authority, 2015). This HTA concluded that an increase in TB cases would be observed in Ireland on moving from universal to a selective vaccination programme. However, before a selective vaccination programme could be implemented, universal BCG vaccination was discontinued in Ireland in April 2015 due to lack of vaccine supply. From April 2015 to the present day, Ireland entered a period of no BCG vaccination. A selective BCG vaccination strategy was published in 2022, but the vaccination programme is not yet operational (National Immunisation Advisory Committee, 2022, 2023). Groups that are recommended BCG vaccination according to the National Immunisation Guidelines are outlined in [Table 1](#).

Table 1: National Immunisation Guidelines 2023 Recommendations for BCG

Groups recommended BCG	Groups who BCG can be considered for after risk-benefit assessment
Neonates who are close contacts of untreated sputum smear-positive pulmonary TB	Unvaccinated TST- or IGRA-negative people >5 years old travelling to high TB, high TB/HIV or high MDR-TB incidence settings
Neonates with household contacts high TB, high TB/HIV or high MDR-TB incidence countries	Unvaccinated TST- or IGRA-negative persons at risk of unprotected occupational exposure (e.g., healthcare workers, laboratory workers, medical students, prison workers and others with occupational exposure).
Unvaccinated children <5 years old who were born in high TB, high TB/HIV or high MDR-TB incidence countries	
Unvaccinated children <5 years old with household contacts who were born in high TB, high TB/HIV or high MDR-TB incidence countries	
Neonates in any locally identified high risk group with TB, TB/HIV or MDR-TB	

2.8 Risk factors and social determinants of disease

Risk factors commonly reported in the international literature include HIV co-infection, diabetes, residence in a high endemicity area (CIR of >40/100,000 population), immunosuppressive therapy, high alcohol intake, tobacco smoking, being a contact of a TB case and under nourishment (Dye et al., 2009; Rasanathan et al., 2011). HIV infection is one of the most important risk factors for TB disease, with a risk 16-27 times higher in people living with HIV compared to non-HIV infected individuals (Peters et al., 2019). The risk of relapse and re-infection is also higher in people living with HIV.

There is also evidence that TB and mental health are bidirectionally linked as illustrated in [Figure 2](#) (Duko et al., 2020; Hayward et al., 2022; Sweetland et al., 2017). Depression is thought to increase risk of disease progression through suppression of cellular and humoral immune responses via the release of pro-inflammatory cytokines, while in the other direction the chronic inflammatory response caused by TB disease can in turn increase the risk of depression through altered enzyme functioning in the central nervous system (Duko et al., 2020).

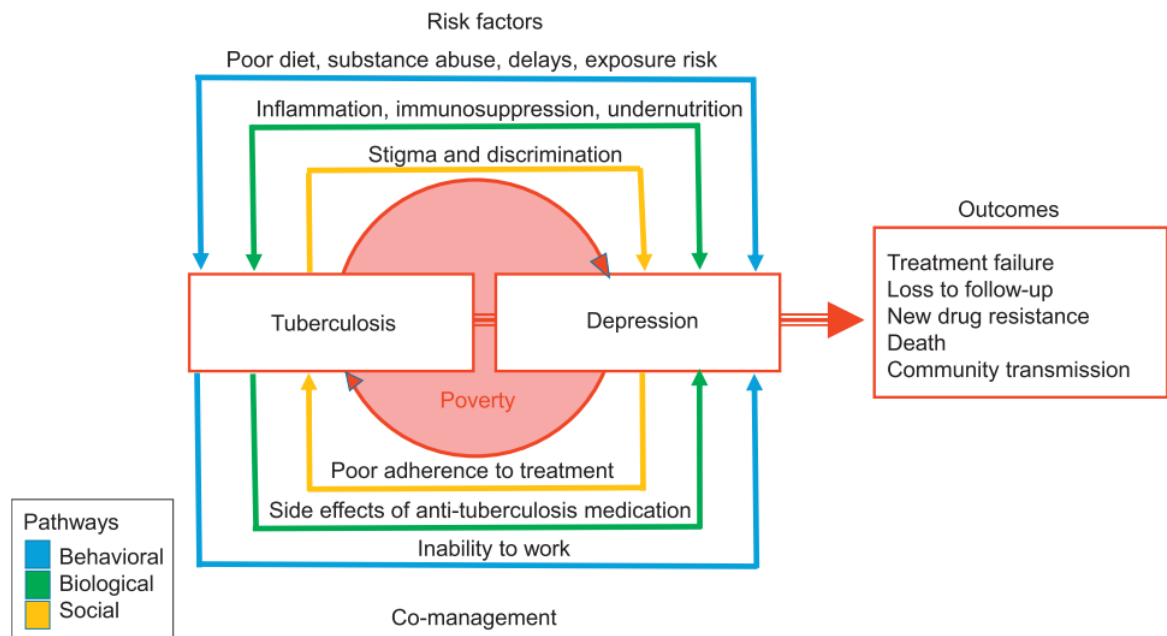


Figure 2: The tuberculosis-depression syndemic model (reproduced from Sweetman et al.)(Sweetland et al., 2017)

There are also multiple social determinants associated with TB and include the side effects of poverty, such as poor housing, poor working conditions, undernutrition and lack of access to health services to name but a few (Duarte et al., 2018; Hargreaves et al., 2011; Lönnroth et al., 2009b; Ploubidis et al., 2012; Rasanathan et al., 2011). [Figure 3](#) depicts a framework devised by Lönnroth et al to describe how these wider social determinants can act on the proximate determinants of TB (Lönnroth et al., 2009a). Ecological studies have shown that TB prevention and control activities alone have not been linked to decreased in TB incidence and instead have shown that higher levels of human development, health spending have been significantly associated with decreasing TB incidence (Dye et al., 2009; Költringer et al., 2023).

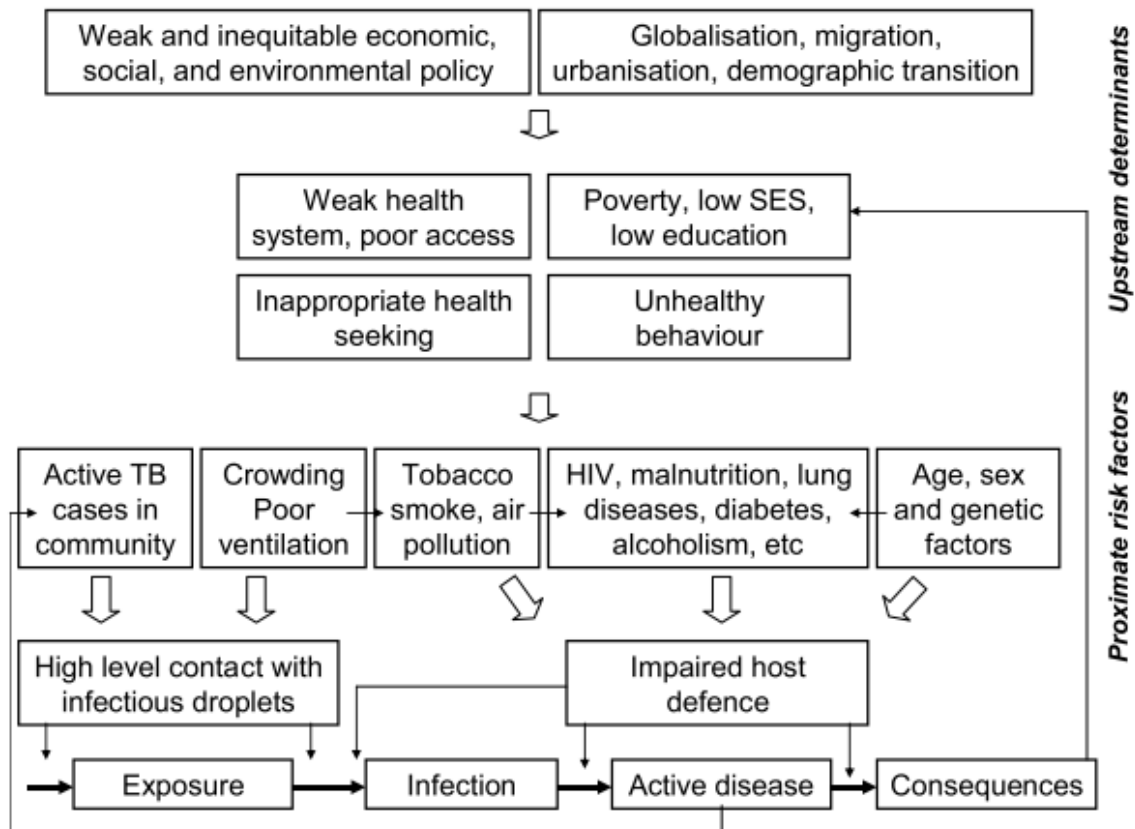


Figure 3: Framework for proximate risk factors and upstream determinants of TB (reproduced from Lönnrot et al) (Lönnroth et al., 2009a)

2.9 Policy context

In 1994, WHO launched its “Framework for effective tuberculosis control”, which focused on interrupting transmission by prioritising treatment of infectious cases with standardised regimens administered via Directly Observed Therapy, Short Course (DOTS) (World Health Organization, 1994). In 2006, the WHO launched the StopTB strategy to work toward the goal of further decreasing the burden of TB (World Health Organization, 2006). Since then, the goal has shifted from TB control to TB elimination. The WHO EndTB strategy encompasses the period 2016-2035 and aims to reduce TB incidence to 1 per million population (or <0.1/100,000 population) by 2030 (World Health Organization, 2022a). The strategy also includes milestones for 2020 (20% reduction in incidence) and 2025 (35% reduction in the number of TB deaths), compared with levels in 2015.

In 2024, the Health Service Executive (HSE) launched Ireland’s first TB strategy “Striving to End Tuberculosis – A Strategy for Ireland 2024 - 2030” to create a roadmap towards the goal of elimination (HSE National Health Protection Office, 2024). This strategy outlines 38 actions for implementation, of which this research supports action number three “Improve the completeness, relevancy and use of surveillance and epidemiological data to inform local and national programmatic activities”.

2.10 Global TB epidemiology

During 2023, the true number of incident cases was estimated at 10.8 million, an increase compared to the estimated figure of 10.6 million in 2023 (World Health Organization, 2024c). WHO also estimated that TB was responsible for 1.3 million deaths in 2023 alone. The same number of deaths was estimated for 2022, with 7,000 of those considered excess deaths due to health service disruption association with the Covid-19 emergency response. The majority of cases in 2023 were reported by the WHO regions of South-East Asia (45%), Africa (24%) and the Western Pacific (17%) (World Health Organization, 2024c). [Figure 4](#) shows the global distribution of TB incidence according to WHO estimates for 2023.

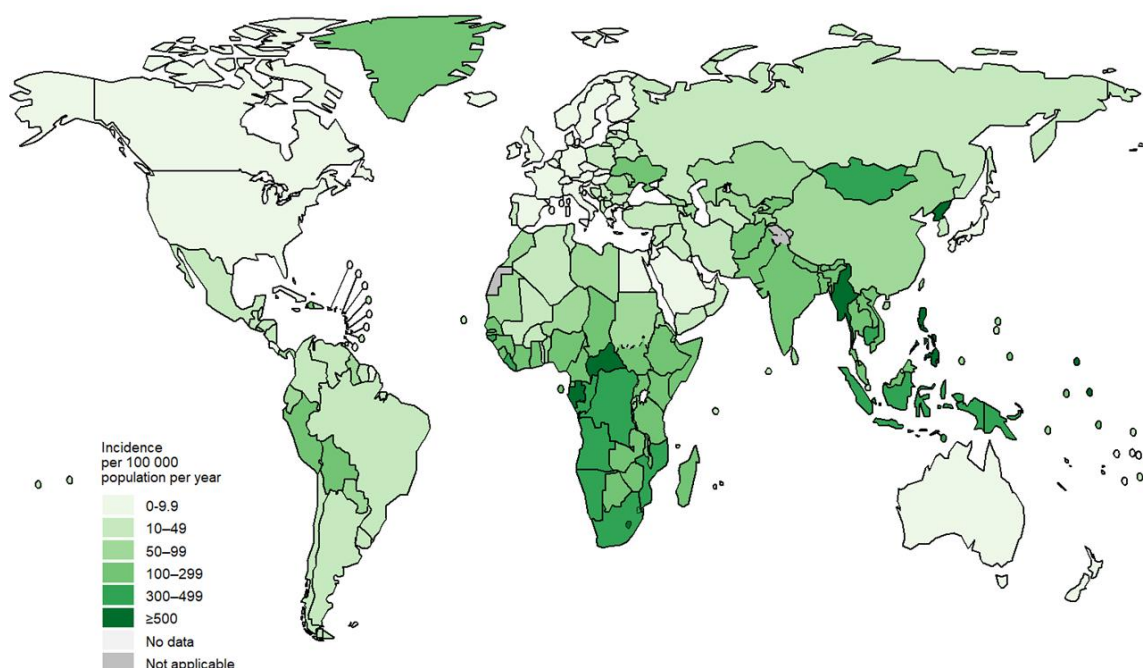


Figure 4: Estimated TB incidence rates per 100,000 population, 2023 (WHO)

Countries are commonly divided into incidence categories based on their annual CIRs. The most commonly used classifications were low (<10), medium (10-39) and high (>39) incidence categories (World Health Organization, 2018). However, in practice many different thresholds were used to define “high” incidence globally. In 2021, WHO introduced updated guidance on high TB burden countries which defined five categories; low (<10), moderate (11-49), upper moderate (50-99), endemic (100-299), highly endemic (300-499) and severely endemic (≥ 500) (World Health Organization, 2021b).

Depending on the incidence category, the epidemiological patterns evident can vary. Low TB incidence countries typically have low rates of transmission and paediatric TB, with higher rates in foreign-born cases and among underserved populations. In comparison, high TB incidence countries usually have the reverse pattern and may also have high rates of drug resistance and previously treated TB (European Centre for Disease Prevention and Control, 2010; Lönnroth et al., 2015; World Health Organization, 2014).

2.10.1 Paediatric cases

Children are more likely to progress from latent TB infection (TBI) to TB disease and do so much faster than adolescents and adults (Marais et al., 2004, 2005). For this reason, the paediatric age group acts as a marker for recent TB transmission in a community. Detection of a paediatric case is usually an indicator of an infectious case among the child’s contacts and one outbreak study reported children became infected after just 15-20 minutes contact with an infectious case (Luzzati et al., 2017). Paediatric cases are less likely than adult cases to be infectious due to the paucibacillary nature of their specimens and non-cavitary nature of their disease (Carvalho et al., 2018).

2.10.2 Sex differences

Globally, TB tends to affect males more than females, with a male to female ratio of almost two to one (World Health Organization, 2024b). This disparity among the sexes manifests after adolescence. The difference in sex ratios has been reported in both research studies and surveillance reports, although the cause is not currently known. Suggested reasons include differences between the sexes immune systems, health seeking behaviours, social mixing patterns and risk factor prevalence (Horton et al., 2016; Nhamoyebonde & Leslie, 2014).

2.10.3 Drug resistance

Resistance to anti-TB drugs is an increasing problem worldwide. In 2023, WHO estimated that 4.1% of cases without a previous diagnosis had MDR-TB. This rose to 20% for cases who were previously treated for TB (World Health Organization, 2024b). ECDC reported similar proportions of MDR-TB cases in the European Union and European Economic Area (EU/EEA) during 2023 (3.9% of new diagnoses and 10.7% of cases with a previous TB diagnosis). For cases with drug susceptibility results, 31.1% were pre-XDR-TB and of these, 10.7% were XDR-TB (European Centre for Disease Prevention and Control / World Health Organization, 2025). Drug resistant TB is considered a serious global public health threat and has recently become a major European concern due to the Russian invasion of Ukraine, which is classified by WHO as a high drug-resistant TB burden country (de Vries et al., 2024; Doležalová et al., 2024; Guthmann et al., 2023; Hauer et al., 2023; World Health Organization, 2021b).

2.10.4 Treatment success

Over 50% of untreated TB disease cases will die (Hermans et al., 2015; Tiemersma et al., 2011). However, successfully treating TB is not only beneficial at the individual patient level but also reduces the infectious reservoir at the population level. For this reason, it is a key element of global TB elimination plans (World Health Organization, 2022a). In keeping with this, WHO sets treatment success targets of >90% (World Health Organization, 2022a). Treatment success is defined as having completed a course of anti-TB treatment as recommended by a country's national policy. The latest WHO reports show that 88% of cases globally were successfully treated in 2021 (World Health Organization, 2024b). However, the European region had the second lowest rate of treatment success at 75%. Treatment success rates are low in many low-incidence countries, for varying reasons including high proportions of cases in older age groups, high prevalence of comorbidities, advanced disease progression due to poor access to health care and migrants transferring between jurisdictions during treatment (Karo et al., 2015, 2016, 2019).

2.11 TB epidemiology in Ireland

TB has been a notifiable disease in Ireland since 1948. Enhanced surveillance was introduced in 1998 using the National TB Surveillance System (HSE Health Protection Surveillance Centre, 2024). In January 2011, enhanced surveillance of TB was migrated to the Computerised Infectious Disease Reporting system (CIDR). CIDR is a web-based system developed to integrate case-based clinical and laboratory data to manage the surveillance and control of notifiable infectious diseases in Ireland. In addition to recording sporadic case-based data, CIDR also facilitates the reporting of clustered cases, according to Irish outbreak case definitions (HSE Health Protection Surveillance Centre, 2010).

Ireland has experienced a steady decline in TB since the 1950s when crude incidence rates (CIRs) were over 220 per 100,000 population, to a CIR of less than 6 per 100,000 during 2024. Ireland became a low TB incidence country in 2010 (HSE Health Protection Surveillance Centre, 2025). In keeping with its profile as a low incidence country, the epidemiology of TB in Ireland is characterised by low rates in the Irish-born population, older age profile in the Irish-born cases, pockets of high incidence associated with urban areas and social deprivation, male sex bias, low rates of clustering, low rates of extra-pulmonary disease, low levels of drug resistance and low mortality rates.

While CIRs in the Irish-born population have remained below six per 100,000 population since 2011, CIRs in the foreign-born population have been up to 13 times higher. Similarly, the proportion of foreign-born cases has increased from 30% to >60% during the same period (HSE Health Protection Surveillance Centre, 2025). Rates of resistance to anti-TB drugs among foreign-born cases have been higher ([Figure 5](#)).

Ireland has failed to meet the WHO treatment success targets and has one of the lowest success rates within the European Union and European Economic Area (EU/EEA) (European Centre for Disease Prevention and Control / World Health Organization, 2025). [Figure 6](#) illustrates that treatment success rates in Ireland have remained below 70% since 2011 and have fallen below 40% in 2023 ([Figure 6](#)) (HSE Health Protection Surveillance Centre, 2025).

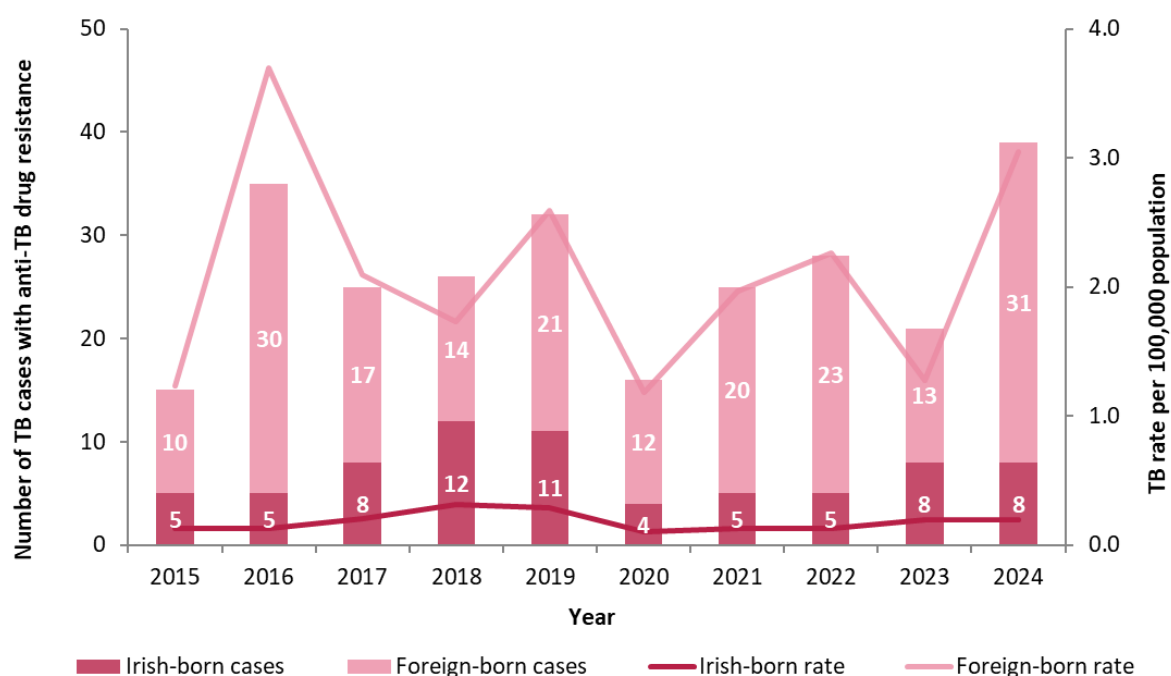


Figure 5: Annual number of TB cases with resistance to anti-TB drug by geographic origin, Ireland (HSE HPSC)

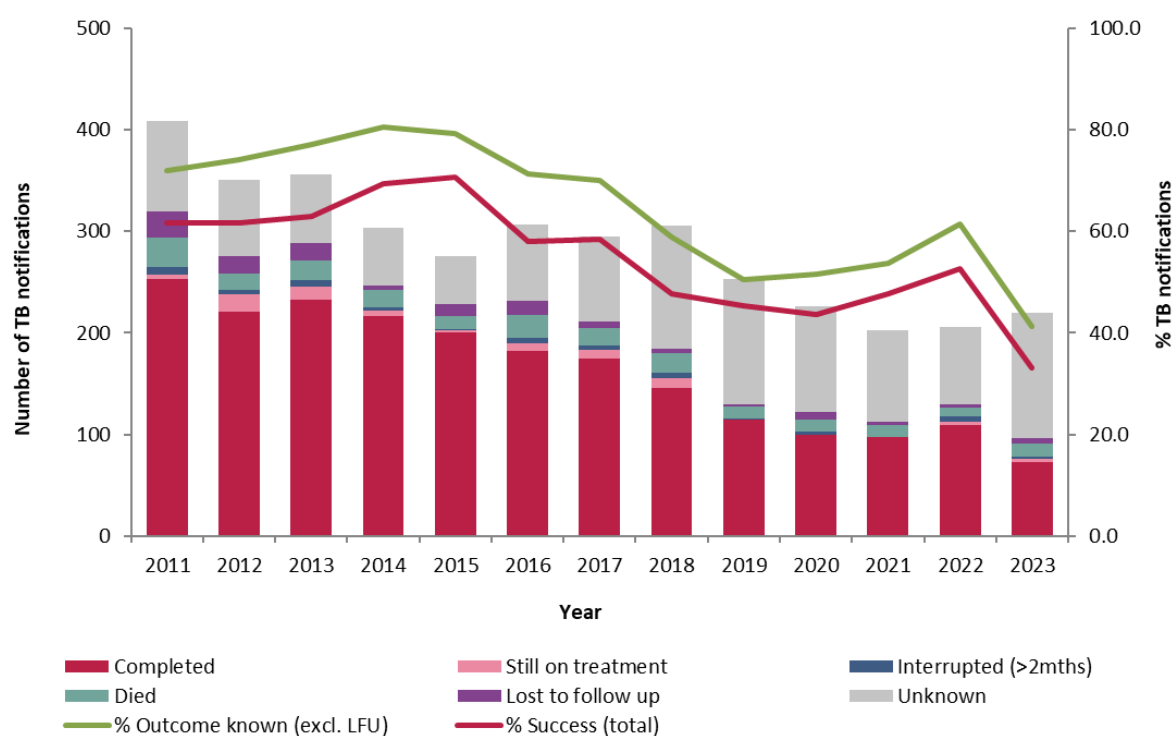


Figure 6: TB treatment outcomes at 12 months by year, Ireland (HSE HPSC)

To reach elimination of TB in Ireland by 2030, the required 80% reduction can be projected as a target of approximately 6% reduction annually for each of the 15 years covered by the strategy, with an end point of <5 cases in the year 2030 to achieve the target CIR of <0.1/100,000 population. This can be translated by a reduction in the annual CIR of 0.4/100,000 population until 2029. [Figure 7](#) illustrates the observed annual CIRs compared to the End TB Target CIR projections population. While Ireland failed to achieve the 2020 milestone of 20% reduction compared to 2015 when viewed in terms of case numbers, the CIR was below the target. As of 2024, Ireland is no longer currently on schedule to meet the 2030 target (HSE Health Protection Surveillance Centre, 2025). To achieve and sustain such a decline requires the disruption of transmission chains both at a national and international level. [Appendix 1](#) illustrates the key features of recent TB epidemiology in Ireland (HSE Health Protection Surveillance Centre, 2025)).

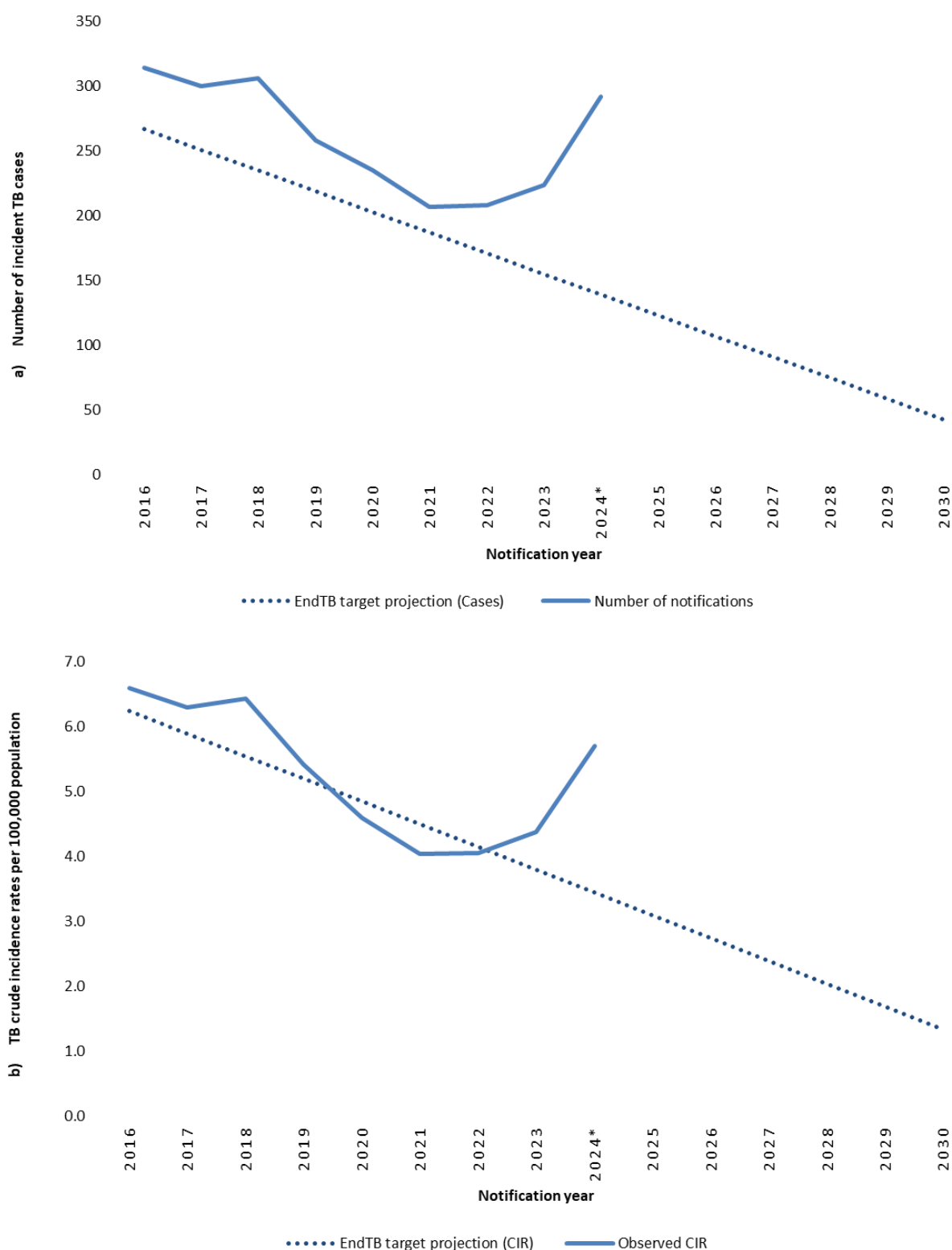


Figure 7: a) Annual number of incident TB cases compared to End TB Target case number projections; **b)** Annual TB crude incidence rates compared to End TB Target CIR projections per 100,000 population, Ireland (HSE HPSC)

2.12 Migration and TB epidemiology

Globally in 2020, 281 million individuals (3.6% of the world's population) were estimated to have migrated across an international border (International Organization for Migration, 2024). Figures from the International Office of Migration also show that the number of refugees reported in 2022 was the highest reported in modern times and was largely due to people fleeing the Russian invasion of Ukraine (International Organization for Migration, 2024). While international migration is increasing globally, the European region has experienced some of the steepest increases in recent years, from 50 million in 1990 to 87 million in 2020. Ireland has also experienced a steady increase in the proportion of the population that was born abroad, from 10% in 2002 to 20% in 2022 (Central Statistics Office, 2016b, 2024a). Since the 2022 Census, the CSO further estimates that inward migration to Ireland has continued to increase from 141,600 in 2023 to 149,200 in 2024 (Central Statistics Office, 2024b). During the 2024, 18,560 individuals applied for international protection during in Ireland, including 957 Palestinian people (International Protection Office, 2025). This represented an increase compared to 13,277 international protection applications received during 2023 (International Protection Office, 2024).

Migrants are a very diverse population group and consequently their TB risk is influenced by many factors. The background risk of TB infection in their country of origin is a key component, however the process of migration itself can alter the risk of acquiring new infection or developing TB disease. Most international migrant populations often comprise individuals who are young, financially stable, healthy enough to travel and who arrive through safe migration pathways for the purpose of employment, education and family re-unification (International Organization for Migration, 2024). Migration through such pathways generally has lesser impact on both the individual migrant and the destination country.

However, a smaller proportion of migrants are compelled to migrate to avoid adverse conditions, such as war or other crises and are often forced to take unsafe migration pathways via hazardous land and sea migration routes to enter the destination country. Such populations are at increased risk of TB, due to the overcrowding, food insecurity and stressful conditions that can occur, which are recognized as risk factors for TB infection (Rendon et al., 2018; Sarivalasis et al., 2012; Walker et al., 2018). After arrival in the destination country the risk of TB may be further influenced by migrant demography and health status, along with structural and social determinants such as presence of screening programmes, health system accessibility and

socioeconomic profile (Hargreaves et al., 2011; Hayward et al., 2018; Pareek et al., 2016). Migrants arriving via unsafe migration pathways can be a vulnerable group that may require greater support from a variety of services within the destination country.

Crises such as natural disasters and violent conflicts have been associated with up to 20 times increased TB risk in populations fleeing those scenarios (Kimbrough et al., 2012). The increased incidence associated with armed conflicts is also thought to increase the risk of drug-resistant forms of TB, possibly due to health system fragmentation in the conflict affected country of origin and fears regarding accessing health systems in the transit and destination countries (S. Hargreaves et al., 2017). Some strains of TB have also been associated with specific peaks in human migration and war (Merker et al., 2015). A marked increase in drug-resistant TB was observed across Europe during 2022 due to the arrival of beneficiaries of temporary protection (BOTPs) who were displaced from Ukraine following the Russian invasion (de Vries et al., 2024; Doležalová et al., 2024; Guthmann et al., 2023; Hauer et al., 2023). In Ireland, 112,189 Personal Public Service Numbers (PPSNs) were issued to Ukrainian BOTPs between March 2022 and February 2025 (Central Statistics Office, 2025). The majority of BOTPs are initially housed in congregate state provided accommodation, with just 32% (n= 36,532) residing in private accommodation.

Although the subject of TB among migrants has been widely studied, the majority of these studies have analysed migrants as a homogenous group, and often mixed migrant definitions, such as birth in a country different to the destination country or possessing nationality different to that of the country under study (Hollo et al., 2017, 2016; Ködmön et al., 2016; Odone et al., 2015). As noted by Hanway et al, the category of “foreign-born” essentially refers to originating in any one of 197 potential other countries (Hanway et al., 2016).

While large-scale European level studies have shown that TB incidence among foreign-born populations is higher and displaying a slower pace of decline compared to native-born populations, studies have also shown that transmission from foreign-born to native-born populations is minimal (Fenner et al., 2012; Sandgren et al., 2014; Stucki et al., 2016a; Stucki, et al., 2016b; Walker et al., 2014). Instead, an ecological study has shown that higher TB incidence in European countries was strongly correlated with higher levels of wealth inequality (Suk et al., 2009). In keeping with this, Gandy and Zumla have asserted that TB disease is not “transported”

across international borders but is instead “activated” by social conditions during the migration process and after arrival in the destination country (Gandy & Zumla, 2003).

2.13 TB prevention and control continuum

Prevention refers to interventions employed to prevent the occurrence of infection or disease. Examples of TB prevention interventions include vaccination, TB infection screening, TB preventive treatment and pasteurisation of milk (World Health Organization, 2024e). Control refers to measures that are applied after the infection or disease has occurred in an individual, to prevent onward transmission to other individuals or populations and includes TB disease screening, contact tracing, TB disease treatment and removal of conditions that are favourable to the spread of infection and development of disease (World Health Organization, 2024e). In practice, prevention interventions can also influence outcomes within the control sphere, and vice versa.

This study will examine two aspects at either end of the TB prevention and control continuum. At the prevention side of the continuum, the study investigates the impact of universal TB vaccination cessation on the epidemiology of paediatric TB in Ireland. While at the control end of the continuum, this study aims to identify factors associated with successful and unsuccessful treatment outcomes. Prevention and control activities are not only beneficial at the patient level but are also key from a public health perspective to reduce the infectious reservoir and help achieve TB elimination goals.

2.14 Chapter conclusion

This chapter has provided a detailed background to TB as both an infection and a disease alongside the policy context of global TB elimination goals. The global and Irish epidemiological backdrops have been summarised, and TB prevention and control concepts were introduced. Furthermore, this chapter has also described how human migration is inextricably linked to the goal of TB elimination.

3 Chapter 3: Theoretical framework, methodology and methods:

3.1 Chapter outline

This chapter outlines the rationale for the selected methodology and how the research process achieves the study aim. Study design, analysis methods and data sources are described. This builds on the background outlined in Chapter 2 by introducing the theoretical foundations and conceptual framework used to design the study and interpret the findings which are presented in Chapters 4, 5, 6 and 7.

3.2 Research paradigm

A research paradigm can be described as the worldview of a particular field of inquiry and covers aspects such as shared assumptions and beliefs as well as practices (McGregor, 2018). A research paradigm can be broken down into four main components; ontology, epistemology, axiology and methodology (Alderson, 2021; Crotty, 1998; Guba & Lincoln, 1994). Ontology is concerned with what can be known about reality (Guba & Lincoln, 1994). Ontological viewpoints span from the positivist belief that reality can be objectively observed to the constructivist belief that reality is perceived differently by all and is constructed through value laden interactions (Guba & Lincoln, 1994). Epistemology sets out how reality can be known while axiology deals with the influence of values on the production of knowledge (Guba & Lincoln, 1994). Methodology is defined as the overall research strategy and study design, including the rationale for selected methods (Crotty, 1998). Methodologies are underpinned by the philosophical components of the research paradigm determined by the world view of the researcher and/or their field of study (McGregor, 2018).

Traditionally, the scientific method has been the dominant research paradigm in medical and life sciences, with observation, hypothesis generation and testing featuring as key principles. In recent years, what constitutes “scientific method” is increasingly subject to debate, particularly with the emergence of machine learning and data driven research (Editorial, 2009; Krauss, 2024).

3.3 Research strategy and methodology

Although some research disciplines use the terms methodology and methods interchangeable, this thesis will reserve the term methods to denote the tools and techniques used to collect and analyse the data (McGregor, 2018). Methodology is concerned with knowledge creation

whereas methods are concerned with data creation and analysis (McGregor, 2018). The results of the analyses are then interpreted through the methodological assumptions. As this study seeks to describe and analyse the effects of migration on the epidemiology of tuberculosis, utilisation of frequentist quantitative methods are appropriate and a post-positivist world view has been adopted. Descriptive epidemiology is particularly suited to the post-positivist view that the context of the research is critical for the interpretation of the results of any study (Fox, 2008). Furthermore, as the study examines correlations rather than causes, the post-positivist worldview that understanding can be an acceptable goal, as distinct from explaining, and that such findings “remain tentative” is appropriate (Fox, 2008; Scotland, 2012). This study has adopted the scientific method of data collection via observation and hypothesis generation and testing.

3.4 Ontological approach

A central tenet of post-positivism is the concept that while an objective reality exists, it cannot be objectively understood in its entirety. Popper proposed an ontology based on three worlds; world 1 where the objective reality exists independent of the observer; world 2 where the perceptions of reality exist including those of the observer; and world 3 where the intersections of world 2 perceptions of world 1 realities produce tangible outputs such theories or technology (Scotland, 2012). As epidemiology is underpinned by process ontology rather than thing-ontology, and is based on non-linear multi-faceted causal pathways, the study has been guided by the National Institute for Health and Care Excellence (NICE) “Conceptual Framework for Public Health” framework (Lee, 2021; National Institute for Health and Care Excellence, 2012).

3.5 Epistemological approach

While post-positivism allows for the existence of an objective reality in world 1, it acknowledges the imperfect way in which we know about it. Post-positivism is also informed by elements of social constructionism which allows that while objects of scientific enquiry may not be products of social practices, the concepts and theories used to describe and investigate them may be influenced by social constructs (Crotty, 1998; Scotland, 2012). This aligns with the study’s approach to comparing and contextualising findings with other similar published studies from other high income low TB incidence countries, and within the Irish epidemiological landscape.

3.6 Axiological approach

While the main focus of the scientific method is observation, notable post-positivists such as Kuhn and Feyerabend have stated that such observation can never be value free and remains influenced by the historical, cultural and socio-political context as well as the prevailing dominant scientific theories of the time (Crotty, 1998). Post-positivist research design aims to detect and minimise sources of bias while acknowledging its effects on the research findings (Scotland, 2012). This axiological viewpoint also recognises the potential influence of the researcher through the development of the research strategy all the way to the interpreting of the study findings (Fox, 2008). In line with this post-positivist axiological stance, the study has sought to minimise bias by using a programmatic data source collected in line with international standards and harmonised with ECDC and WHO reporting requirements. Transparent reporting of methods choices has been implemented along with adherence to best practices for reporting of systematic reviews and meta-analyses, observational studies, studies using routinely collected health data and predictive studies (Benchimol et al., 2015; Brooke et al., 2021; Page et al., 2021).

3.7 Conceptual framework and theoretical underpinnings

A conceptual framework outlines the various components and ideas within a study topic, how they are related and underpinned by relevant theories (van der Walddt, 2020). Use of a conceptual framework can assist the researcher to communicate the various concepts under study to the reader (McGregor, 2018). This study will approach its aim from a Public Health perspective, utilising the NICE “Conceptual Framework for Public Health” to guide the analyses and interpret the findings (National Institute for Health and Care Excellence, 2012).

Public Health is defined as *“the science and art of preventing disease, prolonging life and promoting health through the organised efforts of society”* (Acheson, 1988). According to the NICE *“The unifying factor in topics of public health interest is the linkage of social, psychological and biomedical phenomenon”* (page 137) (National Institute for Health and Care Excellence, 2012).

The NICE framework is particularly suited to epidemiological studies as it employs an ecosystems perspective of the topic under study. It requires the researcher to investigate patterns of disease at the population level while acknowledging that determinants of health are not solely biomedical. The framework asserts that determinants of health function in repetitive patterns, producing causal pathways to cause ill health or to promote good health, which aligns with

epidemiological principles of holism and process ontology (Lee, 2021; National Institute for Health and Care Excellence, 2012). This framework aims to facilitate the linkage of the wider determinants of health and the biological changes they drive. As this study touches on many non-modifiable factors, this framework is particularly appropriate as it does not place the responsibility for health at the individual patient level and instead endorses approaching public health issues with holistic population level solutions

The NICE conceptual framework is underpinned by various theories which approach determinants of health from a holistic and life course viewpoint and include non-medical determinants of health (Cockerham, 2007; Evans & Stoddart, 1990; Krieger, 2008; Starfield, 2006, 2007). In addition, the NICE conceptual framework is further informed by the earlier WHO Conceptual Framework for Social Determinants of Health (SDH) (Solar & Irwin, 2010). While the WHO SDH framework was also based on similar theories, it also contains an explicit acknowledgement of theories of power and how they influence health inequities. In summary, the WHO SDH framework states that *“action on the social determinants of health inequities is a political process that engages both the agency of disadvantaged communities and the responsibility of the state”* (page 23) (Solar & Irwin, 2010).

The NICE conceptual framework makes use of four inter-related vectors to categorise determinants of health; population, environmental, social and organisational, which work through an individual’s life-course and lifeworld. Population determinants include those that affect people as a population group, such as taxation, social protection and legislation imposed by governments, states or supra-national structures. Determinants within the environmental vector include biological threats such as pathogens and toxins; geophysical threats such as radiological, nuclear and chemical hazards; climate-related threats such as droughts or flooding and structural components of determinants such as housing, transport, water sanitation, education systems and workplaces. Many of these determinants traditionally sit within the Public Health domain of Health Protection but are also the responsibility of multiple professional domains such as engineering, urban planners and meteorologists to name a few. The social vector includes determinants which are linked to social, cultural and economic factors and include ethnicity, gender, disability and social class. These determinants are highly influenced by dynamics of power. The organisational vector describes human activities which take place outside of a domestic environment and occurs within a social organisation, such as within health care systems, bureaucracies and religious organisations. The life-course recognises the

cumulative effect of each individual's unique life-story, while the lifeworld acknowledges the effect of the unique subjective core of each human being.

A model of the NICE conceptual framework is illustrated in [Figure 8](#), along with examples of CIDR variables analysed within each domain.

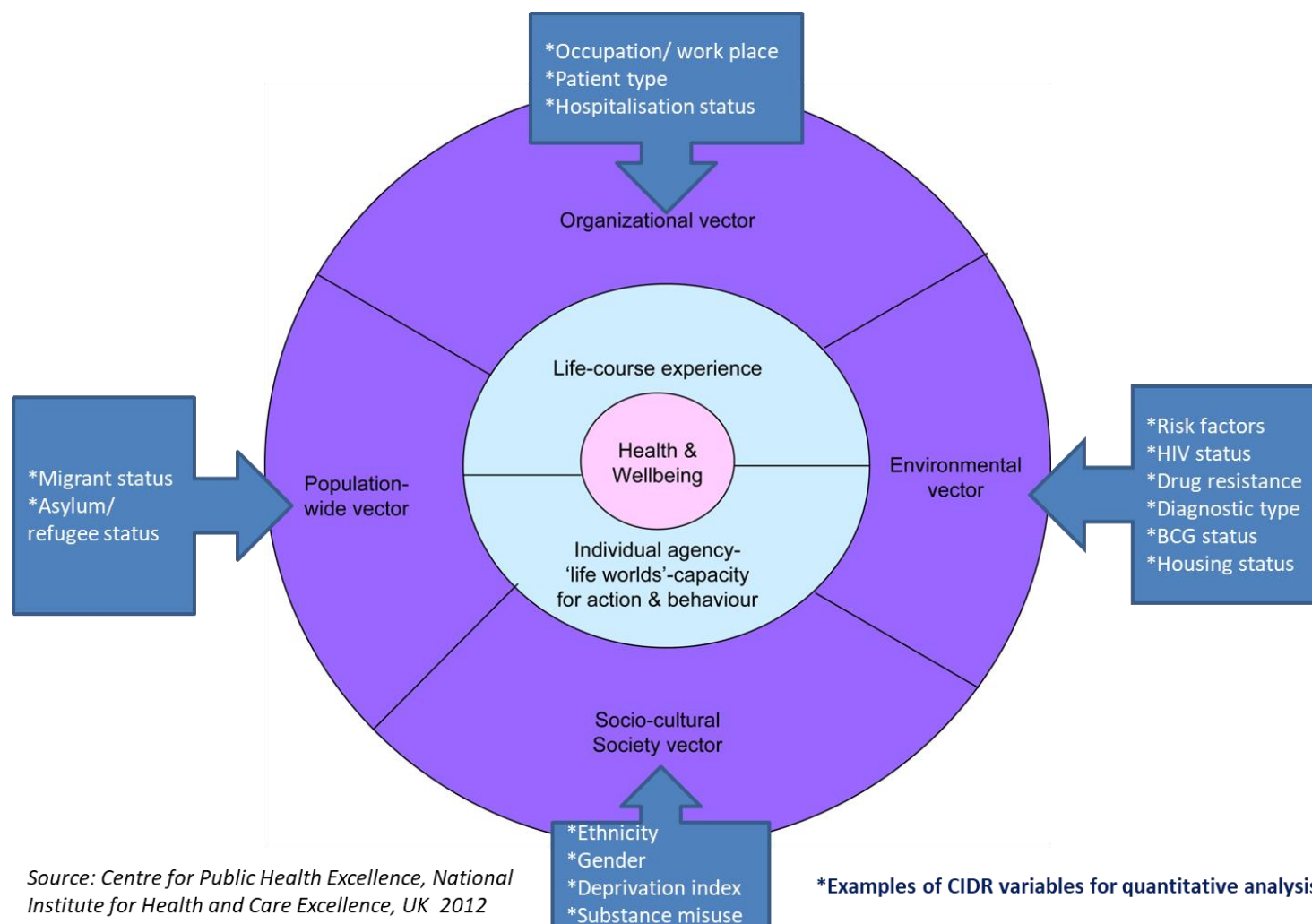


Figure 8: Model of the NICE Conceptual Framework for Public Health, with examples of variables used in quantitative analyses

3.8 Research design

This study employed a quantitative research design using two main types of methods, Chapter 4 utilised systematic review and meta-analysis methods to conduct a systematic review of the published literature, while Chapters 5-7 employed epidemiological principles and concepts to analyse the secondary data source.

3.8.1 Systematic review and meta-analysis methods

Narrative reviews differ from systematic reviews in several ways which are summarised in [Table 2](#). Systematic reviews (SRs) are defined by Cochrane Collaboration as a summary of the results of available relevant studies with the aim of providing a high level of evidence on the effectiveness of healthcare interventions. SRs differ from traditional literature reviews and narrative reviews as they utilise a rigorous and clearly documented methodology which is applied to both the search strategy and the selection criteria applied for inclusion of studies. These additional processes aim to minimise bias of the results. SRs also critically appraise included studies prior to producing a narrative synthesis of the results of available primary research papers. Where the included studies are found to be relatively homogenous, a meta-analysis of the quantitative findings can be produced to provide a pooled estimate of effect for the intervention or exposure of interest as per the SR question. While the type of effect estimates produced will differ according to the research question, common estimates of effect include weighted mean difference, risk ratios/ relative risk and odds ratios. SRs can also be summarised and critically appraised using a review of reviews methodology.

Table 2: Key differences between narrative reviews and systematic reviews

Feature	Narrative review	Systematic review
Question	Broad scope	Focussed question
Search strategy	Not usually specified	Comprehensive and explicit according to predefined published protocol specifications
Appraisal	Variable	Rigorous
Synthesis	Usually qualitative	Qualitative and quantitative
Inferences	Sometimes evidence based	Usually evidence based and assessed using specific methodology

(Source: Centre for Evidence Based Medicine)

Each SR is required to comprehensively document its processes via a pre-defined published protocol ideally adhering to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) standard format. Publication of the SR protocol in advance reduces duplication of effort among researchers investigating the same topic while also allowing the finished review to be reproduced and updated as required. This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Brooke et al., 2021; Page et al., 2021). The protocol for this review was prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO) as CRD42018095038 and is reproduced in [Appendix 3](#) (Jackson et al., 2018).

3.8.1.1 Systematic review framework

This review question utilised a Population Exposure Comparator Outcome (PECO) framework where the population was all TB disease cases diagnosed and resident in countries with low to medium TB incidence (<40/100,000 population) (World Health Organization, 2018, 2024b). The exposure group was TB cases from high TB incidence ($\geq 40/100,000$ population) birth countries who migrated to a low or medium TB incidence country of residence. Migrant status was assigned based on the reported country of birth being different to the country of the study. The comparator group was TB cases born in the low or medium TB incidence country of the study. Studies were included in the review if the primary outcome was diagnosis of TB disease while resident in a country of low or medium TB incidence. The primary outcomes extracted were the number and proportion of TB disease cases in the exposure and comparator categories. Six secondary outcomes were also assessed for the exposure and comparator categories: sputum smear positive cases; cases resistant to any first line anti-TB drug; multi-drug resistant (MDR) cases; cases clustered by genotyping or whole genome sequencing (WGS); HIV co-infected cases; and successfully treated cases.

3.8.1.2 Inclusion and exclusion criteria

Observational studies (including cohort, case control and cross-sectional studies) and publications reporting on routinely collected health data (RCD) using prospective, retrospective or cross-sectional designs published since 2010 were included.

Migrant status was assigned based on reported on country of birth which then allowed determination of TB incidence of the country of origin. Studies which reported geographic regions rather than countries were excluded where such regional groupings included countries with mixed

incidence levels. Studies where country of birth was missing for >5% of foreign-born TB cases were excluded.

Animal studies, cases diagnosed/ resident in countries with high TB incidence, TB infection, internal migration within countries, case studies, case series, studies published prior to 2010, and non-English language abstracts were excluded. Full details of inclusion and exclusion criteria are detailed in Chapter 4, the protocol and Appendix 4a, [Table A4.1](#).

3.8.1.3 Search strategy and information sources

The search strategy utilised three concepts; TB, migrants and active or confirmed status. The search strategy was devised in consultation with an information specialist and peer reviewed by Health Protection experts. The third concept was included to minimise the amount of irrelevant latent / TB infection publications requiring screening.

Five electronic bibliographic databases; Medline (Ebsco), Embase (Embase), CINAHL (Ebsco), Scopus (Elsevier) and the ScieLo (Web of Science) were searched using controlled vocabulary and key words as outlined in the search strategy below. Websites of the WHO, ECDC, Health Protection Scotland (HPS) Public Health Agency, Northern Ireland (PHA NI), Public Health England (PHE), Department of Health Australia, Public Health Surveillance, New Zealand, Public Health Agency Canada (PHAC) and Centers for Disease Control, United States (CDC US) were searched by key words as per the search strategy. Grey literature was searched via OpenGrey (Grey Net). Appendix 4a, [Table A4.2](#) provides the search terms as used in EMBASE as an example of how this was operationalised.

Concept 1: TB

Controlled vocabulary:

Medline: (MH "Tuberculosis+") OR (MH "Lupus Vulgaris")

CINAHL: (MH "Tuberculosis+") OR (MH "Lupus Vulgaris")

Embase: 'tuberculosis'/exp OR 'lupus vulgaris'/exp OR 'pott s disease'/exp

Scopus: Key word search as below of abstract and title

ScieLO: Key word search as below of topic and title

Keywords:

Tuberculosis OR Tuberculoses OR Tuberculous OR Tuberculoid OR "Koch's Disease" OR "Kochs Disease" OR "Koch Disease" OR "potts disease" OR "pott's disease" OR "pott disease" OR scrofula OR phthisis

Concept 2: Migrants

Controlled vocabulary:

Medline: (MH "Transients and Migrants") OR (MH "Refugees") OR (MH "Emigration and Immigration") OR (MH "Human Migration") OR (MH "Relocation")

CINAHL: (MH "Transients and Migrants") OR (MH "Refugees") OR (MH "Emigration and Immigration") OR (MH "Human Migration") OR (MH "Relocation")

Embase: 'migrant'/exp OR 'refugee'/exp OR 'immigration'/exp OR 'migration'/exp

Scopus: Key word search as below of abstract and title

ScieLO: Key word search as below of topic and title

Keywords:

Transient* OR migrant* OR emigrant* OR immigrant* OR refugee* OR "asylum seeker*" OR emigration OR immigration OR relocation OR relocate*

Concept 3: Active or microbiologically confirmed cases

Controlled vocabulary: Not applicable

Keyword: active OR confirm* OR positiv*

3.8.1.4 Data management

Data were exported from online bibliographic databases into EndNote™ as individual libraries and merged into a final library for duplicate screening (The EndNote Team, 2013). Duplicates were automatically discarded by Endnote between individual bibliographic database merges. The deduplication function was run on the merged library within Endnote and duplicates were removed. The deduplicated list was then manually reviewed for further duplicates.

The final deduplicated library was imported into Covidence™ software and a further check for duplicates was run by the software (Veritas Health Innovation, 2020). Covidence was used to screen title and abstracts, extract study data and critically appraise the included studies.

3.8.1.5 Study selection and review

Articles identified by the search strategy were independently evaluated by two reviewers at each stage of the review (title and abstract screening, full text review, data extraction and quality assessment) using Covidence™ software. The researcher screened 100% of citations while the primary and co-supervisors of this study screened 50% each. Full text reports of potentially eligible citations were retrieved and assessed for inclusion in the review based on the inclusion criteria. Any discrepancies between reviewers in the studies selected were resolved by discussion between the two relevant reviewers. Bibliographies of the final list of included studies were hand searched for further relevant citations.

3.8.1.6 Data extraction process

Two reviewers independently reviewed the selected full text articles and used a pre-piloted data extraction form for the listed data items. Variables extracted are detailed in [Appendix 4b](#). The researcher extracted data for 100% of included articles while the primary and co-supervisors of this study extracted data for 50% of included articles each.

3.8.1.7 Quality assessment

Two reviewers independently critically appraised the selected full text articles. The researcher critically appraised 100% of included articles while the primary and co-supervisors of this study critically appraised 50% of included articles each. The National Institute for Health (NIH) quality assessment tool for cohort and cross-sectional studies was used to critically appraise included studies (The National Heart Lung and Blood Institute., 2013). As the exposure was country of birth, multiple assessment of exposure was not evaluated. It was not possible to evaluate the quality of

publications based on routinely collected health data, such as surveillance reports, as no validated tool currently exists for this. Due to the small number of included studies within the meta-analyses, investigation of publication bias via funnels plots was not possible.

3.8.1.8 Statistical methods of analysis

Overall proportions were compared across exposures using Fisher's exact test. Meta-analysis of primary outcome proportions was performed using the Metaprop command which produces weighted sub-group and pooled estimates with inverse-variance weights obtained from a random-effects model in Stata 16™ (Nyaga et al., 2014; StataCorp, 2015). Odds ratios for secondary outcomes were calculated using an inverse variance statistical model with a random effects analysis model in Review Manager 5.4. Meta-analysis results were displayed via Forest plots allowing use of visual inspection, Cochran's Q-tests and I^2 to evaluate heterogeneity (Deeks et al., 2019). Studies whose primary outcome was defined as a secondary outcome of this review were excluded from the meta-analysis for that outcome as the numerator was the same as the denominator.

Subgroup and sensitivity analysis was used to assess methodological heterogeneity via the per protocol subgroups; year of publication, study design, study setting, geographical region and TB incidence level of study country. Due to the clinical heterogeneity observed among included studies, they were further grouped according to clinical categories for sensitivity analysis; all diagnostic types, drug resistant TB, extrapulmonary only TB, pulmonary TB, clustered cases, TB in pregnancy, paediatric cases and deceased donors/ donor recipients. Outcomes were analysed by the total studies that reported the outcome, the clinical categories and per protocol subgroups.

3.8.1.9 Software used for systematic review and meta-analysis:

EndNote™ was used to compile references (The EndNote Team, 2013). Covidence™ software was used for reference screening and data extraction (Veritas Health Innovation, 2020). Stata 16™ and Review Manager 5.4 (StataCorp, 2015; The Cochrane Collaboration, 2020). were used for meta-analysis.

3.8.2 Secondary data analysis methods

3.8.2.1 Data collection:

This study utilised an existing source of routinely collected health data (RCHD) from a national epidemiological surveillance database, Computerised Infectious Disease Reporting (CIDR). RCHD are defined as health data that are collected for non-research purposes and without an a-priori specified research question. Examples of RCHD include drug treatment registries, patient administrative database and epidemiological surveillance databases.

TB is statutorily notifiable in Ireland since 1948 under Health Regulations and under the Infectious Disease Legislation since 1981 (Infectious Diseases Regulations, 1948; Infectious Diseases Regulations, 1981). Under this legislation, all medical practitioners and clinical directors of diagnostic laboratories are required to notify TB cases meeting the EU Commission case definitions to the Medical Officer of Health (MOH) (European Commission, 2018). The MOH role is discharged by Consultants in Public Health Medicine in the eight regional HSE Departments of Public Health*. In addition to individual cases of TB being notifiable, an amendment to the Infectious Disease Regulations introduced in 2004, made “outbreaks, unusual clusters or changing patterns of illness” notifiable by medical practitioners and clinical directors of laboratories to the medical officer of health (Infectious Diseases Regulations (Amendment), 2004).

In practice, diagnostic laboratories upload TB notifications directly to CIDR system as close to real-time as possible. In addition to the basic laboratory notification, further microbiological information is also reported by diagnostic or reference laboratories as they become available, such as drug resistance, molecular typing and Whole Genome Sequencing (WGS) cluster alerts. As TB is a slow growing organism, phenotypic drug resistance and WGS data may not be available for at least 6 weeks after specimens are received by the laboratory. Specimens are submitted by clinical staff to the laboratory at initial diagnosis, at several time points during treatment to monitor the patient's response to treatment and occasionally at the end of treatment to assess the final treatment outcome.

In addition to laboratory notifications, physicians may notify regional Departments of Public Health of cases of TB external to CIDR. This usually occurs for cases lacking microbiological confirmation but

* There were eight Regional Departments of Public Health, aligned to the eight HSE Areas, during this study, which were later re-configured into the current model of six Regional Health Authorities during Slainte Care reforms.

that meet the possible case classification. Department of Public Health staff then enter these notifications on CIDR manually. [Figure 9](#) summarises the data flows within the CIDR system.

TB enhanced surveillance forms are completed by clinical staff in each of the eight regional Departments of Public Health for each TB notification received from laboratories and physicians. These forms summarise all available additional clinical and epidemiological data collected during the public health follow-up and contact tracing of each patient. Data on treatment outcomes are collected by Public Health staff from each patient's treating physician at the end of treatment at the time period indicated by the infecting strain's resistance profile. Treatment outcomes are collected at 12 months after treatment initiation for the majority of cases, at 24 months for MDR-TB cases and at 36 months for XDR-TB cases. These data are then manually entered into the CIDR system by staff in the regional Departments of Public Health.

Outbreak data are also reported on the CIDR system on two levels, at outbreak level and on the case-based level. Outbreak notifications comprise summary information at the outbreak level (location, extent, vulnerable groups involved etc.). Individual outbreak-associated cases can also be linked to the outbreak. In this way it is possible to analyse TB outbreaks through two separate sources, case-based level and outbreak level.

The Irish TB surveillance dataset is harmonised with European Union reporting specifications for key variables. TB surveillance forms displaying the information collected are available on the HPSC website[†].

[†] TB surveillance form: <https://www.hpsc.ie/a-z/vaccinepreventable/tuberculosis/tb/surveillanceforms/>
Outbreak surveillance form: https://www.hpsc.ie/notifiablediseases/notificationforms/File_1836.en.pdf

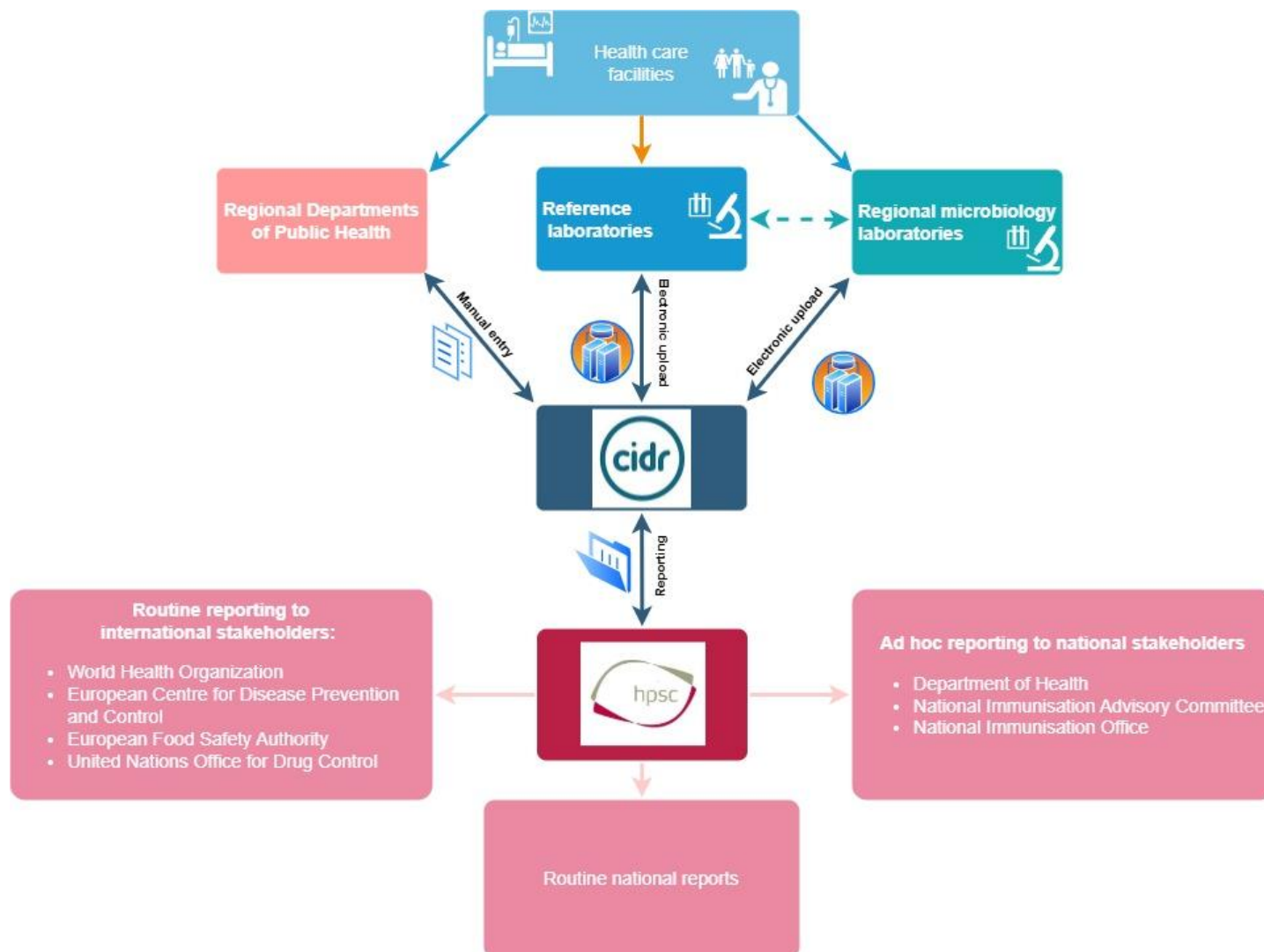


Figure 9: Data flows in infectious disease surveillance systems in Ireland

3.8.2.2 Data access:

The researcher submitted a data access request to the CIDR Data Access Group in 2018 and was granted permission to access anonymised data in 2021. Data quality checks were performed on the raw data and an updated dataset was sent for anonymisation by HPSC CIDR team and release for research purposes on 27/10/2022. A full list of variables and rationale for inclusion in the analysis is included in [Appendix 2](#).

3.8.2.3 Study design

A retrospective cohort study design was utilised to perform a cross-sectional secondary-data analysis of all TB disease notifications reported to the Irish National TB Surveillance System and notified to the CIDR system between 2011 and 2021 (HSE Health Protection Surveillance Centre, 2024).

3.8.2.4 Study population and sampling method

The source population for this study was all cases of TB disease in Ireland diagnosed between 2011-2021. The database population for this study was all TB cases notified to CIDR between 2011-2022. The study population included the database population but restricted to 2011-2021. The start date of 2011 was selected as this was the first year TB data are available on the CIDR system, and the end date of 2021 was selected as this was the most recent complete year at the time of the data request.

3.8.2.5 Chapter specific inclusion criteria

Objective 2 (Chapter 5) will include all notifications with country of birth reported. Objective 3 (Chapter 6) was restricted to cases aged 0-6 years of age at the time of notification. Objective 4 (Chapter 7) will include all cases with a treatment outcome. Cases that were detected via post-mortem diagnoses and who therefore had no opportunity to start treatment were excluded from the models in objective 4.

3.8.2.6 Definitions and outcomes:

Definitions used in this study:

TB cases:

The term “TB disease” will be used to differentiate from TB infection throughout this study where appropriate, in line with WHO recommendations (World Health Organization, 2024e). TB disease (formerly known as “active TB”) was defined as cases meeting the clinical criteria of signs, symptoms and/or radiological findings consistent with TB disease in any site and a clinician’s decision to treat the person with a full course of anti-TB therapy, or a case discovered post-mortem with pathological findings consistent with TB disease that would have indicated anti-tuberculosis antibiotic treatment had the patient been diagnosed before dying, as per the European Union (EU) Commission surveillance case definition (European Commission, 2018; HSE Health Protection Surveillance Centre, 2024). No restrictions on case classification were used; possible, probable and confirmed case classifications were included. Cases were classified as follows:

- Confirmed case – A person meeting the clinical criteria and at least one of the following two:
 - Isolation of *M. tuberculosis* complex* (excluding *M. bovis*-BCG) from a clinical specimen
 - OR**
 - Detection of *M. tuberculosis* nucleic acid in a clinical specimen
 - AND**
 - Positive microscopy for acid-fast bacilli or equivalent fluorescent staining bacilli on light microscopy
- Probable case – A person meeting the clinical criteria and at least one of the following three:
 - Microscopy positive for acid-fast bacilli or equivalent fluorescent staining bacilli on light microscopy OR
 - Detection of *Mycobacterium tuberculosis* nucleic acid in a clinical specimen OR
 - Histological appearance of granulomata
- Possible case: A person meeting the clinical criteria without laboratory confirmation

Previous TB history:

New cases are defined as patients with no previously documented history of TB diagnosis or treatment. Previously diagnosed cases are referred to as “recurrent” cases and are defined as patients who completed TB treatment and were diagnosed with a subsequent episode of TB disease

≥12 months after the first episode. Recurrent cases are further classified as relapse and reinfection. Relapse is defined as recurrent TB due to the original *M. tuberculosis* complex strain while re-infection is subsequent TB disease due to a new strain of *M. tuberculosis*. No restrictions were used in relation to previous TB disease history.

Drug resistance:

- Resistance to TB drugs was defined as resistance to any one or more of the following drugs: isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, any 2nd line injectable (e.g. amikacin, kanamycin) or any fluoroquinolone (e.g. levofloxacin, moxifloxacin).
- Multidrug-resistant TB was defined as resistance to both isoniazid and rifampicin by either phenotypic or genotypic methods.
- Pre-extensively drug-resistant TB (Pre XDR-TB) is defined as a TB strain resistant to all of the following TB drugs: rifampicin and any fluoroquinolone (such as levofloxacin or moxifloxacin).
- Extensively drug-resistant TB was defined according to the pre-2021 definition as resistance to isoniazid and rifampicin and any fluoroquinolone and any second line injectable (e.g. amikacin, kanamycin). The January 2021 updated definition was not applied in this study as the older definition was standard for the majority of the study period (World Health Organization, 2022b).

As the numbers of MDR and XDR were low in this study, they are mainly presented as a combined category of M/XDR-TB.

Table 3: Drug resistance patterns for MDR, pre-XDR and XDR-TB

Drug resistance	MDR-TB	Pre XDR-TB	XDR-TB (pre-2021)
Isoniazid	Yes	Not required	Yes
Rifampicin	Yes	Yes	Yes
Fluoroquinolone	Not required	Yes	Yes
2 nd line injectable	Not required	Not required	Yes

Outcomes used in this study:

Chapter 5: Migrant status:

Migrant TB cases were defined in line with International Organization for Migration (IOM) definition of international migrants as being born in a country other than Ireland but who were resident in Ireland at the time of notification as a TB case. No additional restrictions were placed in terms of legal status or duration of residence in Ireland. Citizenship was not used in this definition. Chapter 5 compared factors associated with the outcome of TB among migrants to the outcome of TB among Irish-born via multivariable logistic regression analysis.

Chapter 7: Treatment outcome:

Each TB case is followed up by staff in regional Departments of Public Health for the period between initial diagnosis and completion of anti-TB treatment. The follow up time for each patient differs as treatment durations can vary from four months to 3 years depending on the resistance profile. At the end of the treatment, the patient is assessed by the treating physician in terms of whether they completed the prescribed course of medications and whether there was any microbiological evidence that the TB infection was cleared. These two pieces of information are combined to classify the treatment outcome of the patient as follows:

Cured – completed course of medication and microbiological evidence of clearance of infection is documented. Only applies to pulmonary cases and those who had microbiological evidence of infection at the initial diagnoses.

Completed: completed course of medication, no microbiological evidence of clearance of infection but patient is clinically well. Applies to all disease sites.

Failed: Treatment completed but patient remains unwell or microbiological evidence of infection persists at the end of prescribed treatment

Interrupted: Treatment interrupted for more than 2 months, due to adverse reaction etc.

Transferred out: patient transferred out to another jurisdiction to complete treatment

Unknown: Includes missing data, cases who are lost to clinical follow up etc.

Treatment success

Treatment success was defined as the combination of cured and completed as outlined above and at the appropriate time point as determined by the resistance profile of TB strain recovered from the patient.

Chapter 7 compared factors associated with the outcome of successful TB treatment with unsuccessful treatment via multivariable logistic regression analysis and Random Forests.

3.8.2.7 Statistical methods of analysis

Descriptive epidemiology methods:

Descriptive epidemiology aims to quantify and describe the distribution of a health state for a population (Lesko et al., 2022). Descriptive analysis of cases by person, place and time characteristics was performed. Although counts are presented, proportions and population adjusted incidence rates are used to describe the data. Use of incidence rates allows the researcher to present the results adjusted for the underlying population denominators. As new TB notifications are only created when a new episode of disease is diagnosed, incidence rates are used rather than prevalence rates.

Incidence rate (IR) calculations:

Crude incidence rates:

Crude incidence rates have been used to describe annual numbers of total TB cases notified with respect to the underlying population.

$$\text{Crude incidence rate} = \frac{\text{Number of cases}}{\text{Number in population}} \times 100,000$$

Age-specific incidence rates (ASIRs):

ASIRs allow for the comparison of counts within age groups in relation to their underlying population denominator. For Chapter 5, ASIRs were calculated for the study population overall and also stratified by migrant origin. For Chapter 6, ASIRs for the 0–6 year old age group were calculated using the 2016 census population denominators. ASIRs in 0-6 year olds were also stratified separately for two categories, by the geographical area of patient residence (using the eight health

administrative regions “HSE Area”[‡]) and by patient birth place (foreign-born or Irish-born, using the patient’s country of birth) (Central Statistics Office, 2016b, 2016c). ASIRs among 0-6 year olds born during a period of universal BCG vaccination (UV) were compared with 0-6 year olds born after BCG vaccination ceased (NV).

$$\text{Age specific incidence rate} = \frac{\text{Number of cases within age group}}{\text{Number in population within age group}} \times 100,000$$

Incidence rates stratified by migrant status:

Due to the increasing migrant population in Ireland, it is more appropriate to describe temporal trends in migrant TB as incidence rates to ensure the fluctuations in the population profile are accounted for. The foreign-born population used included all countries of birth except Ireland. This included where country of birth was not specified beyond foreign-born without the actual migrant country of birth reported.

$$\text{Migrant incidence rate} = \frac{\text{Number of cases born outside Ireland}}{\text{Number in population born outside Ireland}} \times 100,000$$

$$\text{Irish – born incidence rate} = \frac{\text{Number of cases born in Ireland}}{\text{Number in population born in Ireland}} \times 100,000$$

Origin country specific incidence rates:

Each migrant country of birth was mapped to the corresponding population data from the 2016 Census for that country. Where data for a given country was not available in the publicly available Census datasets, the data were requested from the Census Office. As the granularity of the 2022 Census data for countries of birth was poor, the 2016 dataset was used throughout this study.

$$\begin{aligned} \text{Origin country specific incidence rate} \\ = \frac{\text{Number of cases from origin country}}{\text{Number in population from origin country}} \times 100,000 \end{aligned}$$

[‡] There were eight Regional Departments of Public Health, aligned to the eight HSE Areas, during this study, which were later re-configured into the current model of six Regional Health Authorities during Slainte Care reforms.

Population denominator data

Census of Population data from 2011 and 2016 censuses were used as the denominator data for calculation of incidence rates for the different population groups within the study as summarised in Table 3 (Central Statistics Office, 2016c, 2016b). As the granularity of published Census data for countries of birth was insufficient to map to the countries of birth within this study, bespoke tabulation of Census 2016 data was requested from the Central Statistics Office and were used throughout this study for migrant origin country-specific CIRs. At the time of writing Chapter 5 and 6, Census data were not yet available for the 2022 Census disaggregated by age or sex of birth. After the 2022 Census data became publicly available by country of birth, the data were reviewed but did not provide sufficient granularity therefore 2016 data was retained as the denominator data source. As the 2011 Census data were not available by single year of age and country of birth, the 2016 Census was used for the calculation of paediatric ASIRs by migrant status for all years.

Table 4: Census of population applied for notification years and specific numerators

Time period	Census used for CIRs	Census used for age-specific incidence rates (ASIRs)	Census used for Irish-born/ Migrant CIRs	Census used for origin country specific incidence rates
2011-2013	2011	2011 [§]	2011	2016
2014-2019	2016	2016	2016	2016
2020-2021	2016	2016	2016	2016

Incidence rate ratios:

Temporal trends in CIRs and ASIRs were investigated using incidence rate ratios (IRRs) produced by Poisson and Negative Binomial Regression (NBR). While both Poisson and NBR are suitable methods for analysing trends in count data such as annual numbers or rates of notification data, Poisson regression requires the mean and the variance of the count data to be equal. If this assumption is not met and the variance is greater than the mean, overdispersion is said to be present in the dataset and the NBR method is recommended instead (Davis & Wu, 2009). NBR is a parameter-driven generalized linear model with the flexibility to address overdispersion through addition of an extra parameter. As overdispersion was detected within some of the time series examined, results from the negative binomial regressions are reported throughout this thesis.

[§] 2011 Census data were not available for single year of age and country of birth for use in calculation of 0-6 year old ASIRs by migrant status.

Between group comparisons:

Differences between categorical independent variables for categorical outcomes were tested using Pearson's Chi-Square Test or Fisher's Exact Test for differences in proportions and Chi-Square Test for trend in proportions. Associations between numerical independent variables and categorical outcomes were tested using Kruskal Wallis or Wilcoxon rank sum tests. Where numerical variables are compared in tables, median values and their interquartile range (IQR) are presented to enable comparison of the spread of values.

Stratification of patient characteristics analysis

Patient characteristics of two different migrant sub-populations were compared in Chapter 5 and also between two different birth cohorts in Chapter 6 as outlined below.

a) *Categories based on mean WHO incidence estimates*

Each migrant birth country was mapped to the corresponding mean TB incidence estimate per 100,000 population for the same country published by the WHO for the study period (World Health Organization, 2024c). Migrant birth countries were then classified as one of the following incidence categories: low = 0.0-9.9, medium = 10.0-39.9, high = 40.0-99.9 and very high ≥ 100 (World Health Organization, 2024c). WHO incidence estimates were not available for two origin-countries within the study population ($n = 3$ cases). These cases were not possible to include in any analyses of cases according to their WHO incidence levels.

b) *Categories based on interval between arrival and TB notification*

For cases with year of arrival reported, the interval between arrival in Ireland and notification as a TB patient was calculated as the year of notification minus the year of arrival. The interval was categorised within four groups: <2 years, 2-4 years, 5-9 years and ≥ 10 years.

c) *Categories based on birth cohort*

Chapter 6 study compared two birth cohorts; the first cohort consisted of TB cases aged 0-6 years old and born during a period (January 2005 - March 2015) where the universal BCG vaccination policy was operational, while the second cohort of cases were aged 0-6 years old and born during a period (April 2015 - December 2021) where, although universal BCG vaccination was still the official policy, no vaccinations were administered in Ireland due to procurement issues.

Analytical epidemiology methods:

Univariable binary logistic regression analysis was used to explore the unadjusted associations between independent variables (patient characteristics) and the binary dependent variables in Chapters 5 (migrant status) and 7 (treatment success). Variable selection was informed by clinical relevance and those identified a-priori from the published literature and the systematic review results in Chapter 4. Selected independent variables with a p value of ≤ 0.2 in univariable analysis were eligible for investigation in the multivariable model.

Multivariable logistic regression analysis (MVA) was used to explore the adjusted associations of independent variables (patient characteristics) with binary dependent variables in Chapters 5 (migrant status) and 7 (treatment success). Chapter 5 used MVA to produce a descriptive model while Chapter 7 used MVA to identify predictors (Shmueli, 2010). Models were generated by two methods in parallel, a manual stepwise backwards elimination model and an automated algorithm method seeking the lowest Akaike Information Criterion (AIC). For the manual method, variables with the highest Wald p-value and lowest Likelihood Ratio (LR) test statistic were removed one at a time through backwards stepwise elimination until all primary independent variables had a Wald p-value of < 0.05 .

Model assumptions were visually assessed to review residual diagnostics, influential observations and collinearity. The threshold for removing colinear independent variables based on Variable Inflation Factor (VIF) was set at > 9.0 . Apparent model performance was assessed and compared between models. Performance indices reviewed included the Akaike Information Criterion (AIC), Akaike Information Criterion corrected for small sample size (AICc), Bayesian Information Criteria (BIC) and Root Mean Squared Error (RMSE). Apparent performance of models was further evaluated by calculating the Area Under the Receiver Operating Characteristic curve (AUROC) to measure discrimination. Discrimination assesses how well a model can discriminate between those with the outcome (successfully treated cases) and those without the outcome (unsuccessfully treated cases) (Steyerberg, 2019).

Accuracy of model predictions were assessed by examining calibration plots alongside the corresponding Brier scores and Spiegelhalter's Z-scores. Calibration assesses how closely aligned a model's observations are to its predictions, and whether the model fits the data well (Huang et al., 2020; Steyerberg, 2019). A calibration plot with values close to the line of 45 line indicates that the model fits the data well (Yang et al., 2022). Brier scores assess both calibration and sharpness of model predictions while Spiegelhalter's Z-scores assess only the calibration component (Steyerberg,

2019). While no standardised scale exists for Brier scores, a score of 1 indicates complete divergence between observed and predicted while a score of 0 denotes perfect alignment between predicted and observed, so values closer to 0 indicate a better fitting model. A significant result for Spiegelhalter's Z-score indicates poor model calibration (Huang et al., 2020). Model predictive accuracy was examined using Percentage of Correct Predictions (PCP) where 0.7 were considered as good accuracy. Model fit was assessed using Hosmer and Lemeshow's test. Quality assessment of the models including the software packages used are described in detail in Chapter 7.

Final regression models were compared to the results of a Variable Importance plot derived from a Random Forest method run on the independent variables included in the full model from each sample. Random Forest (RF) is an ensemble machine learning method, that generates a model based on pooling the results of several smaller models. RF models are generated from the outputs of multiple decision trees, each run on randomly selected bootstrapped samples of the original dataset (Biau & Scornet, 2016). Individual decision trees provide predictions which are then aggregated to produce the final RF model. This aggregation of predictions reduces overfitting (Biau & Scornet, 2016; Breiman, 2001). Variable Importance attempts to measure the improvement in model fit gained from the inclusion of a predictor variable (Biau & Scornet, 2016).

Multivariable logistic regression and Random Forest analyses were performed on complete case samples. These samples excluded cases with missing data for either the dependent variable variables in Chapters 5 (migrant status) and 7 (treatment success), or any of the candidate independent variables included in the full model. A full assessment of the extent and scope of missing data is provided in Chapter 7.

3.8.2.8 Data quality and information security:

Routine data quality checks are run and resolved by staff in the eight regional Departments in Public Health in response to their own internal validation procedures and in response to quarterly validation requests received from the HPSC. Prior to extracting study data, validation reports were run to identify any events that are missing key laboratory data items and cases were augmented from the laboratory record where applicable. Further internal record consistency reviews were carried out for key variables and missing data were replaced with the information available elsewhere within the case record. For example, if the disease site was missing but the same case had a sputum smear result reported as positive, this information was used to classify the case as a pulmonary case.

Data management and associated information security processes of this study were fully compliant with General Data Protection Regulation (General Data Protection Regulation, 2016). This project fell outside the scope of the Health Research Regulations (HRR) due to the anonymization of the dataset (Data Protection Act (Section 36(2)) (Health Research) Regulations, 2018).

3.8.2.9 Software used for secondary data analyses:

Business Objects software were used to extract data from the CIDR application into MS Excel format. Data were cleaned and recoded in Stata. Statistical analysis was undertaken in Stata and R (R Core Team, 2021; StataCorp, 2015). Details of R packages used for multivariable logistic regression analysis and model diagnostics are provided in Chapter 7.

3.8.2.10 Bias and limitations

The study used a non-randomised sample from TB notification data reported on CIDR based on the specified inclusion criteria. Underreporting may be a limitation of registry-based samples but has not been quantified for TB surveillance. Where low levels of data completeness affected the analyses, this is reported within the individual results chapters. Limitations of the individual studies are discussed in detail within results Chapters 4-7.

3.9 Reporting quality:

To enhance transparency of methods and replicability of this study, the appropriate reporting guidance has been utilised within each chapter. Chapter 4 the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analyses of Observational Studies (MOOSE guidance) (Brooke et al., 2021; Page et al., 2021). Chapters 5-7 utilised the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Reporting of studies conducted using Observational Routinely Collected Health Data (RECORD) guidance (Benchimol et al., 2015; von Elm et al., 2008). Chapter 7 also utilised the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) guidance (Moons et al., 2015).

3.10 Ethical considerations

This project has received ethical approval from the School of Nursing and Midwifery. The potential for negatively labelling of migrants as a source of infection has been given consideration and the focus of this study will remain on how systems can be modified to support migrants to maintain and improve health, rather than on interventions targeted at an individual level.

Informed consent was not sought from the patients in this study as the legal basis for processing surveillance data in Ireland is not consent but based on General Data Protection Regulations, Articles 6(1)(c) and 6(1)(e); Articles 9(2)(i) and 9(2)(j) and the Infectious Disease Regulations (General Data Protection Regulation, 2016; Statutory Instrument No. 258/2022 - Infectious Diseases (Amendment) Regulations 2022, 2022). Furthermore, as this was a secondary data analysis of anonymized data there was no additional requirement for informed consent under the Health Research Regulations Act 2018 (Data Protection Act (Section 36(2)) (Health Research) Regulations, 2018). All data processing was compliant with the General Data Protection Regulations, including the use of data minimisation where possible to meet the principle of proportionality.

3.11 Funding:

This PhD was funded by the HSE. The funders had no role in the study.

3.12 Chapter conclusion

This chapter has outlined the rationale for the selected methodology and how the research process achieves the study aim. An overview of the study designs, analysis methods and data sources for each chapter are described. The theoretical foundations and conceptual framework used to design the study and interpret the findings are described. The following chapter presents the results of a systematic review investigating how migration from high TB incidence countries affects the epidemiology of TB in low to medium incidence countries by comparing key epidemiological outcomes between TB cases diagnosed in migrants from high TB endemicity birth countries and non-migrant cases reported in a low or medium incidence country.

4 Chapter 4: A systematic review on the effects of migration from high TB incidence countries on the epidemiology of TB in low to medium incidence countries:

4.1 Chapter outline

The overall aim of this study was to examine the effect of migration on the epidemiology of TB in low to medium incidence countries in order to inform global prevention and control policies. The study results are presented in four interconnected chapters. This is the first results chapter and focuses on the study objective *“To conduct a systematic review of the literature on the effect of migration on the epidemiology of TB in low to medium incidence countries”*. It details the results of a systematic review investigating how migration from high TB incidence countries affects the epidemiology of TB in low to medium incidence countries by comparing key epidemiological outcomes between TB cases diagnosed in migrants from high TB endemicity birth countries and non-migrant cases reported in a low or medium incidence country.

4.2 Introduction

Despite a background of over two decades of global policy on TB control and several declarations of political support, WHO estimated that during 2023 10.8 million people developed TB disease and 1.3 million people died corresponding to a TB case fatality rate of 12% (World Health Organization, 2024b). TB remains the tenth leading cause of death worldwide and the leading cause of death from any infectious disease (World Health Organization, 2024b, 2024a).

Although TB incidence rates in populations born in low to medium incidence countries have steadily declined in recent years, rates of TB in migrant populations continue to reflect the rates found in their country of origin (Hayward et al., 2018; Pareek et al., 2011). In recent years, TB cases diagnosed in migrants accounted for over half of TB cases reported by two thirds of low TB incidence European countries (European Centre for Disease Prevention and Control / World Health Organization, 2025). In addition to differences in the TB incidence rate between migrants and native-born populations, differences are also observed in the epidemiology of TB in the two populations. Common differences observed include a higher proportion of migrant cases in the younger age groups reflecting the younger age of migrants in general and a higher proportion of extra-pulmonary presentations in migrants (European Centre for Disease Prevention and Control / World Health Organization, 2025). Some studies have also demonstrated a lower rate of clustering in migrant populations (Stucki et al., 2016a). While the reasons for this remain poorly understood, it is thought to indicate that

progression of imported TBI to TB disease is the most significant route of infection for migrants, rather than acquiring infection after arrival in the host country (Hayward et al., 2018).

Adverse conditions that migrants may face upon arrival to the receiving country can increase their likelihood of reactivating old disease, progressing from TBI to TB disease or becoming newly infected. Such adverse conditions may include poor housing conditions, language and economic barriers to accessing health care and exposure to infection during travel back to their country of origin (Duarte et al., 2018). Migration processes for illegal immigrants can also expose individuals to an increased risk of TB exposure through unsanitary and crowded living and travelling conditions, poor diet and increased stress (International Organization for Migration, 2015). Certain risk factors for reactivation of TBI (such as diabetes mellitus and chronic kidney disease) are also found in higher levels in some migrant populations (Hayward et al., 2018). Many high TB incidence countries are also high HIV incidence countries. HIV infection is one of the most important risk factors for TB disease, with a risk 16-27 times higher in people living with HIV compared to non-HIV infected individuals (Peters et al., 2019). This can lead to an increased risk of TB infection and disease (Peters et al., 2019)".

Understanding the effect of migration from high incidence TB countries on the epidemiology of TB in low to medium incidence countries is vital in order to achieve the WHO EndTB goal of TB elimination in countries with low to medium incidence by 2050 (World Health Organization, 2022c). Although narrative reviews of the effect of migration on the epidemiology of TB exist and a systematic review of the qualitative literature on TB within migrant populations has been conducted, a search of Joanna Briggs Institute (JBI) Database of Systematic Reviews and Implementation Reports, Cochrane Library, Medline (Ebsco) and PROSPERO revealed no quantitative systematic review on this topic has yet been performed (Abarca Tomás et al., 2013; Hayward et al., 2018; Pareek et al., 2016). While both narrative and qualitative reviews can provide valuable insight into the epidemiological situation through the descriptions generated, this systematic review aims to provide an additional quantification of the outcome of interest.

This systematic review aims to investigate how migration from high TB incidence countries affects the epidemiology of TB in low to medium incidence countries by comparing key epidemiological outcomes between TB disease cases diagnosed in migrants from high TB endemicity birth countries and non-migrant cases reported in a low or medium incidence country. The review outcomes

investigated were selected as indicators of potential transmission and case complexity based on clinical evidence.

4.3 Methods

The review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Brooke et al., 2021; Page et al., 2021). The protocol for this review was prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO) as CRD42018095038 and is reproduced in [Appendix 3](#) (Jackson et al., 2018).

4.3.1 Population

The review question utilised a PECO model where the population was all TB disease cases diagnosed and resident in countries with low to medium TB incidence ($<40/100,000$ population) (World Health Organization, 2018, 2024b).

4.3.2 Exposure

The exposure group was TB cases from high TB incidence ($\geq 40/100,000$ population) birth countries who migrated to a low or medium TB incidence country of residence. Migrant status was assigned based on the reported country of birth being different to the country of the study.

4.3.3 Comparator

The comparator group was TB cases born in the low or medium TB incidence country of the study.

4.3.4 Outcomes

Studies were included in the review if the primary outcome was diagnosis of TB disease while resident in a country of low or medium TB incidence. The primary outcomes extracted were the number and proportion of TB disease cases in the exposure and comparator categories. Six secondary outcomes were also assessed for the exposure and comparator categories: sputum smear positive cases; cases resistant to any first line anti-TB drug; multi-drug resistant (MDR) cases; cases clustered by genotyping or whole genome sequencing (WGS); HIV co-infected cases; and successfully treated cases.

4.3.5 Inclusion and exclusion criteria

Observational studies (including cohort, case control and cross-sectional studies) and publications reporting on routinely collected health data (RCD) using prospective, retrospective or cross-sectional designs were included.

A start point of 1980 was originally selected for this review in order to cover the gradual increase observed in both TB incidence and global migration trends, as well as the introduction of the six month four-drug treatment regimen (isoniazid, rifampicin, pyrazinamide and ethambutol) adopted in 1980 along with the emergence of the HIV/AIDS pandemic in early 1980s. However, following peer review of the protocol by Health Protection experts and expert advice from a Systematic Review methods expert, a revised start date of 2010 was later implemented. This change was implemented to avoid cross-over periods where the same country was categorised as both a country with a high TB incidence in earlier publications and a low or medium TB incidence in later publications within the same SR. Such conflict could bias the results and also result in findings that are difficult to interpret and without a clear public health impact. It was also advised that a more recent start year of 2010 would better inform the subsequent analysis of this study, which utilises Irish TB notification data from 2011 to 2021.

Migrant status was assigned based on reported on country of birth which allowed determination of TB incidence of the country of origin. Studies which reported geographic regions rather than countries were excluded where such regional groupings included countries with mixed incidence levels. Studies where country of birth was missing for >5% of foreign-born TB cases were excluded.

Animal studies, cases diagnosed/ resident in countries with high TB incidence, TB infection, internal migration within countries, case studies, case series, studies published prior to 2010, and non-English language abstracts were excluded. Full details of inclusion and exclusion criteria are detailed in the protocol and Appendix 4a [Table A4.1](#).

4.3.6 Search strategy and information sources

The search strategy utilised three concepts; TB, migrants and active or confirmed status. The search strategy was devised in consultation with an information specialist and peer reviewed by Health Protection experts. The third concept was included to minimise the amount of irrelevant latent / TB infection publications requiring screening. This was advised rather than the use of “not latent TB” as a restriction. The keyword “migration” was tested during construction of the search strategy but was

not included in the final version as the search results were greatly inflated by unrelated biochemical and chemical results. The term “migration” was subsequently restricted to inclusions as part of the controlled vocabulary strings (“Human Migration” MESH term and “migration” Emtree term). All databases were searched for keywords listed below and controlled vocabulary where appropriate. [Table A4.2](#) provides the search terms as used in EMBASE as an example of how this was operationalised.

Concept 1: TB

Controlled vocabulary:

Medline: (MH "Tuberculosis+") OR (MH "Lupus Vulgaris")

CINAHL: (MH "Tuberculosis+") OR (MH "Lupus Vulgaris")

Embase: 'tuberculosis'/exp OR 'lupus vulgaris'/exp OR 'pott s disease'/exp

Scopus: Key word search as below of abstract and title

ScieLO: Key word search as below of topic and title

Keywords:

Tuberculosis OR Tuberculoses OR Tuberculous OR Tuberculoid OR “Koch’s Disease” OR “Kochs Disease” OR “Koch Disease” OR “potts disease” OR “pott’s disease” OR “pott disease” OR scrofula OR phthisis

Concept 2: Migrants

Controlled vocabulary:

Medline: (MH “Transients and Migrants”) OR (MH “Refugees”) OR (MH “Emigration and Immigration”) OR (MH “Human Migration”) OR (MH “Relocation”)

CINAHL: (MH “Transients and Migrants”) OR (MH “Refugees”) OR (MH “Emigration and Immigration”) OR (MH “Human Migration”) OR (MH “Relocation”)

Embase: ‘migrant’/exp OR ‘refugee’/exp OR ‘immigration’/exp OR ‘migration’/exp

Scopus: Key word search as below of abstract and title

ScieLO: Key word search as below of topic and title

Keywords:

Transient* OR migrant* OR emigrant* OR immigrant* OR refugee* OR “asylum seeker*” OR emigration OR immigration OR relocation OR relocate*

Concept 3: Active or microbiologically confirmed cases

Controlled vocabulary: Not applicable

Keyword: active OR confirm* OR positiv*

Five electronic bibliographic databases; Medline (Ebsco), Embase (Embase), CINAHL (Ebsco), Scopus (Elsevier) and the ScieLo (Web of Science) were searched using controlled vocabulary and key words as outlined in the search strategy below. Websites of the WHO, ECDC, Health Protection Scotland (HPS) Public Health Agency, Northern Ireland (PHA NI), Public Health England (PHE), Department of Health Australia, Public Health Surveillance, New Zealand, Public Health Agency Canada (PHAC) and Centers for Disease Control, United States (CDC US) were searched by key words as per the search strategy. Grey literature was searched via OpenGrey (Grey Net).

4.3.7 Data management

Data were exported from online bibliographic databases into EndNote™ as individual libraries and merged into a final library for duplicate screening (The EndNote Team, 2013). Duplicates were automatically discarded by Endnote between individual bibliographic database merges. The deduplication function was run on the merged library within Endnote and duplicates were removed. The deduplicated list was then manually reviewed for further duplicates.

The final deduplicated library was imported into Covidence™ software and a further check for duplicates was run by the software (Veritas Health Innovation, 2020). Covidence was used to screen title and abstracts, extract study data and critically appraise the included studies.

4.3.8 Study selection and review

Articles identified by the search strategy were independently evaluated by two reviewers at each stage of the review (title and abstract screening, full text review, data extraction and quality assessment) using Covidence™ software. The researcher screened 100% of citations while the primary and co-supervisors of this study screened 50% each. Full text reports of potentially eligible citations were retrieved and assessed for inclusion in the review based on the inclusion criteria. Any discrepancies between reviewers in the studies selected were resolved by discussion between the two relevant reviewers. Bibliographies of the final list of included studies were hand searched for further relevant citations.

4.3.9 Data extraction process

Two reviewers independently reviewed the selected full text articles and used a pre-piloted data extraction form for the listed data items. Variables extracted are detailed in [Appendix 4b](#). The researcher extracted data for 100% of included articles while the primary and co-supervisors of this study extracted data for 50% of included articles each.

4.3.10 Quality assessment

Two reviewers independently critically appraised the selected full text articles. The researcher critically appraised 100% of included articles while the primary and co-supervisors of this study critically appraised 50% of included articles each. The National Institute for Health (NIH) quality assessment tool for cohort and cross-sectional studies was used to critically appraise included studies (The National Heart Lung and Blood Institute., 2013). As the exposure was country of birth, multiple assessment of exposure was not evaluated. It was not possible to evaluate the quality of publications based on routinely collected health data, such as surveillance reports, as no validated tool currently exists for this. Due to the small number of included studies within the meta-analyses, investigation of publication bias via funnels plots was not possible.

4.3.11 Statistical analysis

Overall proportions were compared across exposures using Fisher's exact test. Meta-analysis of primary outcome proportions was performed using the Metaprop command which produces weighted sub-group and pooled estimates with inverse-variance weights obtained from a random-effects model in Stata 16™ (Nyaga et al., 2014; StataCorp, 2015). Odds ratios for secondary outcomes were calculated using an inverse variance statistical model with a random effects analysis model in Review Manager 5.4. Meta-analysis results were displayed via Forest plots allowing use of visual inspection, Cochran's Q-tests and I^2 to evaluate heterogeneity (Deeks et al., 2019). Studies whose primary outcome was defined as a secondary outcome of this review were excluded from the meta-analysis for that outcome as the numerator was the same as the denominator.

Subgroup and sensitivity analysis

Methodological heterogeneity was explored via the per protocol subgroups; year of publication, study design, study setting, geographical region and TB incidence level of study country. Due to the clinical heterogeneity observed among included studies, they were further grouped according to clinical categories for sensitivity analysis; all diagnostic types, drug resistant TB, extrapulmonary only TB, pulmonary TB, clustered cases, TB in pregnancy, paediatric cases and deceased donors/ donor recipients. Outcomes were analysed by the total studies that reported the outcome, the clinical categories and per protocol subgroups.

4.4 Results

A total of 2,903 references were identified through a combination of bibliographic database searching and a keyword search of the specified grey literature websites. A total of 92 duplicates were removed.

4.4.1 Title and abstract screening

A total of 2,811 references were reviewed by the researcher while 1,406 references were reviewed by the primary supervisor and 1,405 by the co-supervisor of this study respectively. Title and abstract screening resulted in 2,526 records being excluded and 285 references agreed by two votes for inclusion at the full text review stage.

4.4.2 Full text review

Thirty-two studies identified by the search and screening process ([Figure 10](#)) met the inclusion criteria requirements, comprising a total of 93,235 TB cases (median sample size = 98.5; range: 6 - 73,945). Sixteen included studies were conducted in Europe, 12 were set in Middle Eastern / Western Asian countries, two were from Australia and one each were from Guadeloupe and the United States. Twenty-five studies were set in low TB incidence countries while seven were in medium TB incidence countries. The majority of studies were cohort studies, 23 of which were retrospective and one was prospective. The remaining eight included studies were cross sectional design. The most common study setting was hospitals (n=16), followed by studies that utilised routinely collected health data (n=10), such as surveillance or programmatic data. [Table 5](#) outlines the main characteristics of included studies.

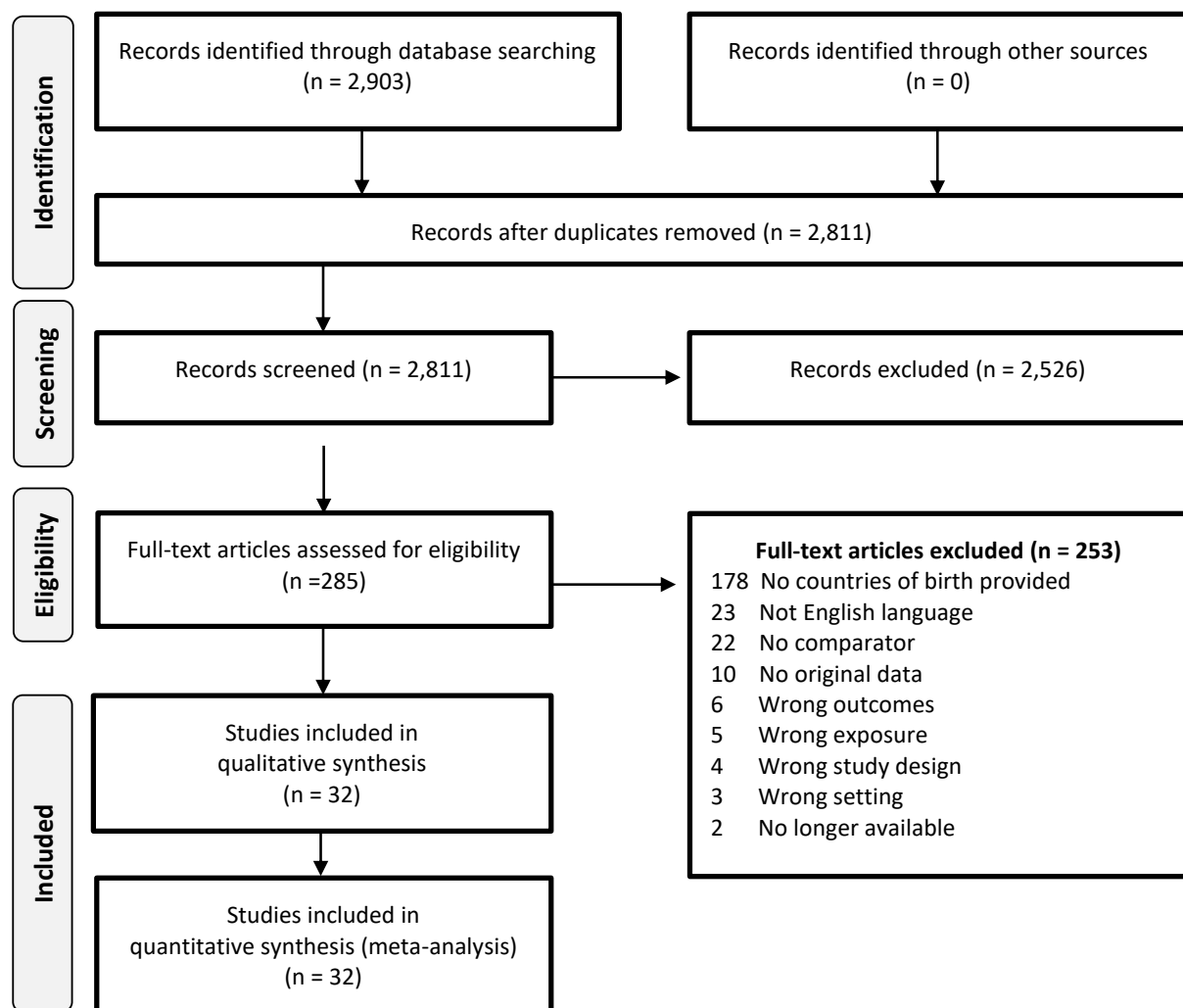


Figure 10: Flow chart of articles retrieved by the systematic review search strategy

Table 5: Characteristics of included studies

Author	Country	TB incidence	Study design	Study setting	Study outcome	Study size	Year of study	Study duration months	Study follow up months	Domains with low RoB**
(Aguayo et al., 2010)	Spain	Low	Cross sectional	Hospital	Extrapulmonary TB	20	1999-2009	132	not reported	n/a
(Al-Hajoj et al., 2015)	Saudi Arabia	Low	Cross sectional	Routinely collected	Extrapulmonary TB - culture confirmed	381	2009-2010	12	not reported	6/13
(Azarkar et al., 2016)	Iran	Medium	Retrospective cohort	TB clinic	Pulmonary TB	85	2010-2011	24	not reported	8/13
(Bartu et al., 2010)	Czechia	Low	Retrospective cohort	Hospital	MDR-TB	50	2001-2009	108	108	10/13
(Bendayan et al., 2011)	Israel	Low	Retrospective cohort	Hospital	MDR-TB - hospitalised new	132	2000-2005	60	24	9/13
(Bishara et al., 2015)	Israel	Low	Retrospective cohort	Routinely collected	TB disease in pregnancy	6	2002-2012	132	not reported	9/13
(Broderick et al., 2018)	United Kingdom	Low	Retrospective cohort	Hospital	Extrapulmonary TB - bone / joint	29	2012-2014	24	not reported	9/13
(Coll et al., 2013)	Spain	Low	Retrospective cohort	Hospital	TB disease in donors and donor recipients	6	1998-2011	162	162	9/13
(Cruz-Ferro et al., 2014)	Spain	Low	Retrospective cohort	TB clinic	TB disease	12,615	1996-2011	192	192	8/13
(Doğru & Döner, 2017)	Turkey	Medium	Retrospective cohort	Hospital	Pulmonary TB - new	211	2010-2013	48	not reported	10/13
(Fallico et al., 2014)	Italy	Low	Retrospective cohort	Hospital	TB disease	339	2006-2009	48	not reported	9/13
(Ferdinand et al., 2013)	Guadeloupe	Low	Prospective cohort	Community setting	TB disease - culture confirmed	129	1999-2005	81	not reported	10/13
(Goblirsch et al., 2014)	Saudi Arabia	Low	Retrospective cohort	Hospital	Extrapulmonary TB & HIV coinfection	39	2008-2012	39	not reported	9/13

** RoB = risk of bias

Author	Country	TB incidence	Study design	Study setting	Study outcome	Study size	Year of study	Study duration months	Study follow up months	Domains with low RoB**
(Helbling et al., 2014)	Switzerland	Low	Retrospective cohort	Routinely collected	MDR-TB	51	2003-2010	115	24	10/13
(Jagielski et al., 2010)	Poland	Medium	Retrospective cohort	TB clinic	MDR-TB	117	2004	12	12	10/13
(Jawad et al., 2014)	Bahrain	Medium	Retrospective cohort	Routinely collected	TB disease	1,584	2000-2006	84	Not reported	9/13
(Jensenius et al., 2016)	Norway	Low	Retrospective cohort	Routinely collected	Drug resistant TB	88	1995-2014	240	not reported	10/13
(B. Jones et al., 2017)	Australia	Low	Retrospective cohort	Routinely collected	TB disease	171	2006-2015	108	Not reported	n/a
(Kentley et al., 2017)	United Kingdom	Low	Retrospective cohort	Hospital	Extrapulmonary intestinal TB	61	2008-2014	84	not reported	8/13
(Krogh et al., 2010)	Norway	Low	Retrospective cohort	Hospital	Paediatric TB	24	1998-2009	124	124	10/13
(Lumb et al., 2013)	Australia	Low	Cross sectional	Laboratory	TB disease - culture confirmed	37	2010	12	Not reported	n/a
(Luzzati et al., 2011)	Italy	Low	Retrospective cohort	Hospital	Pulmonary TB - sputum smear positive	112	2004-2008	60	not reported	11/13
(Mansoori et al., 2016)	Iran	Medium	Cross sectional	Routinely collected	TB disease - culture confirmed new	176	2014-2015	13	not reported	9/13
(Merza et al., 2011)	Iran	Medium	Retrospective cohort	Hospital	TB disease - culture confirmed with DST	1,742	2000-2005	55	not reported	11/13
(Moosazadeh et al., 2014)	Iran	Medium	Cross sectional	Routinely collected	TB disease	73,945	2005-2011	84	not reported	8/13
(Papakala et al., 2017)	Greece	Low	Retrospective cohort	Hospital	TB disease	88	2012-2014	36	not reported	9/13
(Peghin et al., 2017)	Spain	Low	Retrospective cohort	Hospital	Extrapulmonary TB - spinal	54	1993-2014	264	not reported	10/13
(Ravan et al., 2013)	Iran	Medium	Cross sectional	TB clinic	TB disease	258	missing	-	not reported	4/13
(Saavedra et al., 2012)	Spain	Low	Retrospective cohort	Hospital	TB disease	33	2010-2011	13	not reported	n/a

Author	Country	TB incidence	Study design	Study setting	Study outcome	Study size	Year of study	Study duration months	Study follow up months	Domains with low RoB**
(Sanghvi et al., 2011)	United Kingdom	Low	Retrospective cohort	Hospital	Extrapulmonary TB - uveitis	19	1992-2007	184	not reported	10/13
(Vanhomwegen et al., 2011)	United States	Low	Retrospective cohort	Community setting	TB disease - culture confirmed	109	1995-2004	120	not reported	10/13
(Varghese et al., 2013)	Saudi Arabia	Low	Cross sectional	Laboratory	TB disease - culture confirmed	524	2009-2011	24	not reported	9/13

4.4.3 Quality assessment

Twenty-eight studies were assessed for quality and the remaining four studies could not be assessed as they were either an abstract or a surveillance report with no validated tool available. No study achieved a low risk of bias (RoB) score in all domains, with a median of 9 low risk domains out of a total of 13 domains assessed. [Table 6](#) details the quality assessment results for the individual studies appraised.

Table 6: Quality assessment results for included studies (n=32)

Author	1. Research question clearly stated?	2. Study population clearly defined?	3. Participation rate of eligible persons >49%?	4. Subjects selected from similar populations?	5. Sample size justification	6 Exposure of interest measured prior to the outcome(s) being measured	7. Was timeframe sufficient for outcomes to occur?	8. Did the study measure different levels of exposure?	9. Were exposure measures clearly defined?	10. Was the exposure assessed more than once?	11. Were outcome measures clearly defined?	12. Outcome assessors blinded to exposure status of participants?	13. Loss to follow up after baseline <21%	14. Key potential confounders measured and adjusted statistically?
Aguayo	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Al-Hajoj	low	low	unclear	low	high	high	high	low	low	n/a	low	high	unclear	high
Azarkar	low	low	unclear	low	high	high	low	low	low	n/a	low	unclear	unclear	high
Bartu	low	low	low	low	high	low	low	low	low	n/a	low	high	low	high
Bendayan	low	low	low	low	high	high	low	low	low	n/a	low	high	low	high
Bishara	low	low	low	low	high	high	low	low	low	n/a	low	high	low	high
Broderick	low	low	low	low	high	high	low	low	low	n/a	low	high	low	high
Coll	low	low	low	low	high	low	low	low	unclear	n/a	low	high	low	high
Cruz-Ferro	low	low	low	low	high	unclear	low	low	high	n/a	low	high	low	high
Doğru	low	low	low	low	high	low	low	low	low	n/a	low	high	low	high
Fallico	low	low	low	low	high	high	low	low	low	n/a	low	high	low	high
Ferdinand	low	low	low	low	high	low	low	low	low	n/a	low	high	low	high
Goblirsch	low	low	low	low	high	high	low	low	low	n/a	low	high	low	high
Helbling	low	low	low	low	high	low	low	low	low	n/a	low	high	low	high
Jagielski	low	low	low	low	high	low	low	low	low	n/a	low	high	low	high

Author	1. Research question clearly stated?	2. Study population clearly defined?	3. Participation rate of eligible persons >49%?	4. Subjects selected from similar populations?	5. Sample size justification	6 Exposure of interest measured prior to the outcome(s) being measured	7. Was timeframe sufficient for outcomes to occur?	8. Did the study measure different levels of exposure?	9. Were exposure measures clearly defined?	10. Was the exposure assessed more than once?	11. Were outcome measures clearly defined?	12. Outcome assessors blinded to exposure status of participants?	13. Loss to follow up after baseline <21%	14. Key potential confounders measured and adjusted statistically?
Jawad	low	low	low	low	high	high	low	low	low	n/a	low	high	low	high
Jensenius	low	low	low	low	high	low	low	low	low	n/a	low	high	low	high
Jones	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Kentley	low	low	low	low	high	low	low	unclear	low	n/a	unclear	high	low	high
Krogh	low	low	low	low	high	low	low	low	low	n/a	low	high	low	high
Lumb	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Luzzati	low	low	low	low	high	low	low	low	low	n/a	low	high	low	low
Mansoori	low	low	low	low	high	low	low	low	low	n/a	low	high	low	high
Merza	low	low	low	low	high	low	low	low	low	n/a	low	high	low	low
Moosazadeh	low	low	low	low	high	high	low	low	low	n/a	low	high	unclear	high
Papakala	low	low	low	low	high	low	low	low	low	n/a	low	high	high	high
Peghin	low	low	low	low	high	low	low	low	low	n/a	low	high	low	high
Ravan	low	unclear	unclear	low	high	high	high	low	low	n/a	unclear	high	unclear	high
Saavedra	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Sanghvi	low	low	low	low	high	low	low	low	low	n/a	low	high	low	high
Vanhomwegen	low	low	low	low	high	low	low	low	low	n/a	low	high	high	low
Varghese	low	low	low	low	high	high	low	low	low	n/a	low	high	low	high

4.4.4 Outcomes:

Seven review outcome measures were described in the 32 included studies with a total of 93,235 TB cases (median sample size = 98.5; range: 6 - 73,945). Ten studies reported only the primary review outcome and 22 studies described multiple secondary review outcome measures ([Table 7](#)). Of these 22 studies, six studies were not suitable for exploration via meta-analysis as the numerator was the same as the denominator. The remaining 16 studies reported between one and five secondary outcomes that were suitable to explore via meta-analysis. High levels of clinical, methodological and statistical heterogeneity were present among the included studies. [Table 8](#) summarises the results of the analysis of secondary review outcomes while [Figures 12-17](#) display the results of meta-analysis for secondary outcomes.

In addition to data on high incidence migrants and non-migrants, 12 included studies also reported a total of 105 migrants from low to medium TB incidence countries. This corresponds to 0.1% of total TB disease cases within the included studies and a range from 0.2-20.2%.

4.4.4.1 Primary outcome - Proportion high incidence migrant TB cases

The proportion of high incidence migrants among total TB disease cases reported across studies ranged from 0.02 to 0.94. The overall proportion of high incidence migrants was 0.15 but the meta-analysis of this outcome produced a pooled proportion of 0.47. Subgroup and sensitivity analyses were unable to detect the source of the high levels of heterogeneity ($I^2=99\%$) present within the meta-analysis ([Figure 11](#)). Due to such a high level of heterogeneity, the primary outcome is unsuitable for examination via meta-analysis so while it is provided for completeness and transparency, it is not analysed further within this chapter.

Table 7: Outcomes reported by included studies (n=32)

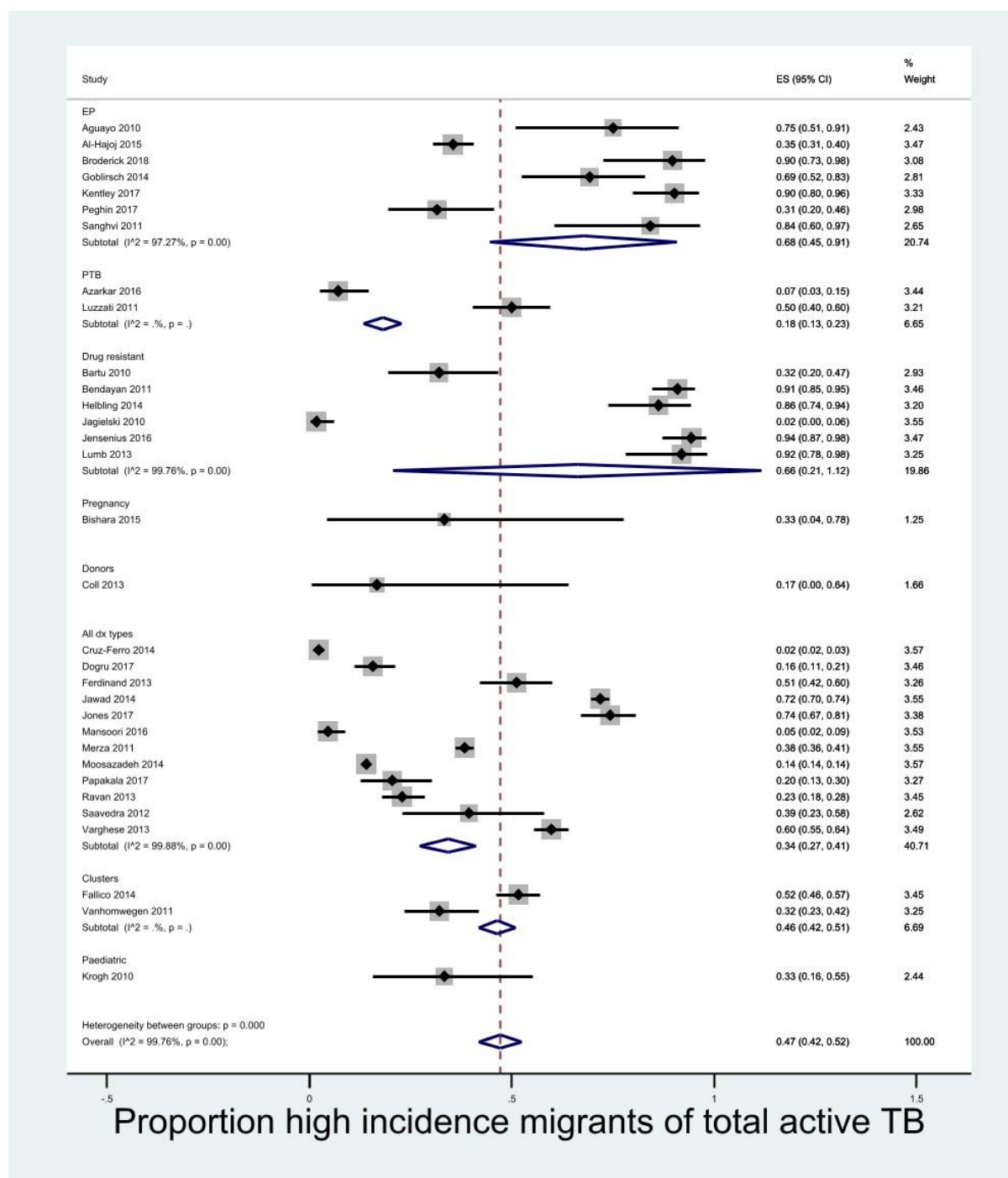
Study name	Clinical group	Primary outcome				Secondary outcomes for consideration via meta-analysis ^{††}
		Total TB cases	Migrants - HI ^{††} n (%)	Migrants – LMI ^{††} n (%)	Non-migrants n (%)	
Aguayo	Extrapulmonary TB	20	15 (75)	0 (0)	5 (25)	None
Al-Hajoj	Extrapulmonary TB	381	135 (35)	22 (5)	224 (58)	None
Azarkar	Pulmonary TB	85	6 (7)	0 (0)	79 (92)	None
Bartu	Drug resistant	50	16 (32)	1 (2)	33 (66)	HIV pos
Bendayan	Drug resistant	132	120 (90)	7 (5)	5 (3)	None
Bishara	Pregnancy TB	6	2 (33)	0 (0)	4 (66)	SS pos, HIV pos, Any Res, MDR, Tx Success
Broderick	Extrapulmonary TB	29	26 (89)	(0)	3 (10)	Any res, MDR
Coll	Donors & recipients	6	1 (16)	0 (0)	5 (83)	None
Cruz-Ferro	All diagnostic types	12,615	287 (2)	0 (0)	12,328 (97)	None
Dogru	All diagnostic types	211	33 (15)	0 (0)	178 (84)	SS pos, Any Res, MDR, Tx Success
Fallico	Clustered cases	339	175 (51)	18 (5)	146 (43)	None
Ferdinand	All diagnostic types	129	66 (51)	0 (0)	63 (48)	SS pos, HIV pos, Any Res, Tx Success
Goblirsch	Extrapulmonary TB	39	27 (69)	0 (0)	12 (30)	None
Helbling	Drug resistant	51	44 (86)	2 (3)	5 (9)	Clustered

^{††} Where Micro conf = microbiologically confirmed cases; SS Pos = sputum smear positive cases; HIV pos = HIV co-infected cases; Any Res = cases with resistance to any 1st line anti-TB drug; MDR – multi-drug resistant TB; Clustered = cases clustered by molecular or whole genome sequencing; Tx Success = successfully treated cases.

^{††} Where HI = high TB incidence migrants; LMI = low to medium TB incidence migrants

Study name	Clinical group	Primary outcome				Secondary outcomes for consideration via meta-analysis ⁺⁺
		Total TB cases	Migrants - HI ⁺⁺ n (%)	Migrants – LMI ⁺⁺ n (%)	Non-migrants n (%)	
Jagielski	Drug resistant	117	2 (1)	0 (0)	115 (98)	MDR
Jawad	All diagnostic types	1584	1138 (71)	(0)	446 (28)	None
Jensenius	Drug resistant	88	83 (94)	3 (3)	2 (2)	Clustered
Jones	All diagnostic types	171	127 (74)	17 (9)	27 (15)	None
Kentley	Extrapulmonary TB	61	55 (90)	2 (3)	4 (6)	None
Krogh	Paediatric TB	24	8 (33)	0 (0)	16 (66)	SS pos, HIV pos, Any Res, MDR
Lumb	Drug resistant	37	34 (91)	0 (0)	3 (8)	None
Luzzati	Pulmonary TB	112	56 (50)	0 (0)	56 (50)	None
Mansoori	All diagnostic types	176	8 (4)	0 (0)	168 (95)	Any res, MDR
Merza	All diagnostic types	1742	668 (38)	0 (0)	1074 (61)	MDR
Moosazadeh	All diagnostic types	73,945	10,377 (14)	0	63,568 (85)	None
Papakala	All diagnostic types	88	18 (20)	9 (10)	61 (69)	Any Res
Peghin	Extrapulmonary TB	54	17 (31)	0 (0)	37 (68)	HIV pos, Any Res, MDR
Ravan	All diagnostic types	258	59 (22)	0 (0)	199 (77)	Clustered
Saavedra	All diagnostic types	33	13 (39)	1 (3)	19 (57)	None
Sanghvi	Extrapulmonary TB	19	16 (84)	0 (0)	3 (15)	SS pos
Vanhomwegen	Clustered cases	109	35 (32)	22 (20)	52 (47)	None
Varghese	All diagnostic types	524	313 (59)	1 (0)	210 (40)	Clustered

Figure 11: Proportion of TB disease cases in high incidence migrants of total study population with sensitivity analysis by clinical category^{§§}



^{§§} ^{§§} Where EP = extrapulmonary, PTB = pulmonary TB and all dx types = all diagnostic types

4.4.4.2 Secondary outcomes

Sputum smear positivity

Data on sputum smear positivity were reported by a total of five included studies ([Figure 12](#)) (Bishara et al., 2015; Doğru & Döner, 2017; Ferdinand et al., 2013; Krogh et al., 2010; Sanghvi et al., 2011). The overall proportion of sputum smear positivity was similar among high incidence migrants (0.71; range: 0.25-1.0) to non-migrants (0.70, range: 0.19-0.74). No difference was detected between the odds for this outcome and the statistical heterogeneity was low ($I^2 = 0\%$). Sensitivity analysis of studies that reported on all diagnostic types of TB found no significant difference between the two groups for this outcome but the statistical heterogeneity increased to moderate ($I^2 = 49\%$).

Resistance to any first line anti-TB drug

Data on drug resistance to any first line drug were reported by eight studies, six of which reported cases of drug resistance ([Figure 13](#)) (Bishara et al., 2015; Broderick et al., 2018; Doğru & Döner, 2017; Ferdinand et al., 2013; Krogh et al., 2010; Mansoori et al., 2016; Papakala et al., 2017; Peghin et al., 2017). No differences were detected in the overall proportions of high incidence migrants versus non-migrants (0.11 versus 0.10) among cases resistant to any first line anti-TB drug. The pooled odds ratio for this outcome was 1.51 [0.81-2.82] but no significant difference was detected between the two groups and the statistical heterogeneity was low ($I^2 = 0\%$). Sensitivity analysis of studies that reported on all diagnostic types of TB found no significant difference between the odds of high incidence migrants versus non-migrants and the statistical heterogeneity remained similar ($I^2 = 0\%$).

MDR-TB

Data on MDR-TB were reported by eight studies but only four studies reported MDR cases, all in medium incidence settings ([Figure 14](#)) (Bishara et al., 2015; Broderick et al., 2018; Doğru & Döner, 2017; Jagielski et al., 2010; Krogh et al., 2010; Mansoori et al., 2016; Merza et al., 2011; Peghin et al., 2017). The proportion of high incidence migrants with MDR-TB was significantly higher than the proportion of non-migrants with MDR in the four studies (0.23 versus 0.09, $P < 0.001$). This was reflected in the results of the meta-analysis with an increased odds of MDR among high incidence migrants compared to non-migrants (OR 3.91 [2.98 - 5.14]) with low levels of statistical heterogeneity found ($I^2=0\%$). The statistical heterogeneity remained similar when a sensitivity

analysis restricting studies to the clinical category of all diagnostic types of TB and subgroup analysis by incidence level was performed.

Clustered cases

Data on clustered cases were reported by four included studies (Helbling et al., 2014; Jensenius et al., 2016; Ravan et al., 2013; Varghese et al., 2013). Two studies were retrospective cohort studies looking at drug resistant TB cases while the remaining two studies were cross sectional studies who analysed all clinical presentations of TB. While the overall proportion of clustered cases was significantly higher among high incidence migrants compared to non-migrants (0.42 versus 0.26, $P < 0.001$), meta-analysis did not detect any significant difference between the odds ratios of exposure categories with moderate levels of heterogeneity detected ([Figure 15](#)). The source of heterogeneity was explored further via subgroup and sensitivity analysis. Heterogeneity was reduced from 49% to 0% when one study was removed (Ravan et al., 2013). Removal of this study from the meta-analysis also resulted in significantly increased odds of the outcome in high incidence migrants. When subgroup analyses by study design was performed, heterogeneity was high for cross sectional study designs and low among cohort studies but the test for subgroup differences was not significant. It was not possible to stratify this subgroup analysis by the sensitivity analysis due to the small numbers of studies included. Neither sensitivity analysis (all diagnostic types and drug resistance only) detected any significant difference between the exposure categories but high levels of heterogeneity were present when only cross-sectional studies were combined.

HIV coinfections

Data on HIV coinfection were reported by five included studies but only two of the studies had HIV coinfecting cases ([Figure 16](#)) (Bartu et al., 2010; Bishara et al., 2015; Ferdinand et al., 2013; Krogh et al., 2010; Peghin et al., 2017). The overall proportion of HIV coinfection was significantly higher among high incidence migrants than non-migrants (0.19 versus 0.05, $P < 0.001$). Meta-analysis of HIV coinfection did not detect any significant difference between exposure categories (OR 1.91 [0.09-41.22]) and high levels of heterogeneity were present. Results from the two included studies were also divergent in direction of effect. It was not possible to explore the source of this heterogeneity via subgroup analysis due to the low number of studies with HIV coinfecting cases ($n=2$) but clinical and methodological heterogeneity were observed in the clinical presentations, settings and geographical regions.

Treatment success

Data on treatment success were reported by three included studies (Bishara et al., 2015; Doğru & Döner, 2017; Ferdinand et al., 2013). Despite the overall proportion of treatment success being significantly lower among high incidence migrants than non-migrants (0.59 versus 0.76, $p < 0.001$) meta-analysis showed a high level of heterogeneity ($I^2 = 93\%$) and no significant difference between exposures or within subgroup analyses. Results from the two studies included in the meta-analysis were also divergent in direction of effect. ([Figure 17](#)).

Table 8: Summary of secondary outcomes reported by included studies

Outcomes	Proportion high incidence migrants	Proportion non-migrants	Chi squared (P value)	Meta-analysis pooled odds ratio	Heterogeneity (I²)	Number of studies reporting outcome
Sputum smear positive TB cases	0.71	0.70	0.010 (0.919)	1.17 (0.49 - 2.80)	0%	4
Case with any first line drug resistance	0.11	0.10	0.594 (0.441)	1.51 (0.81 - 2.82)	0%	8
MDR-TB cases	0.23	0.09	95.292 (< 0.00001)	3.91 (2.98 - 5.14)	0%	7
Clustered cases	0.42	0.26	26.828 (< 0.00001)	1.55 (0.77 - 3.13)	49%	3
HIV co-infected cases	0.19	0.05	14.393 (0.0001)	1.91 (0.09 - 41.22)	73%	5
Successfully treated cases	0.59	0.76	10.578 (0.001)	0.64 (0.08 - 5.05)	93%	3

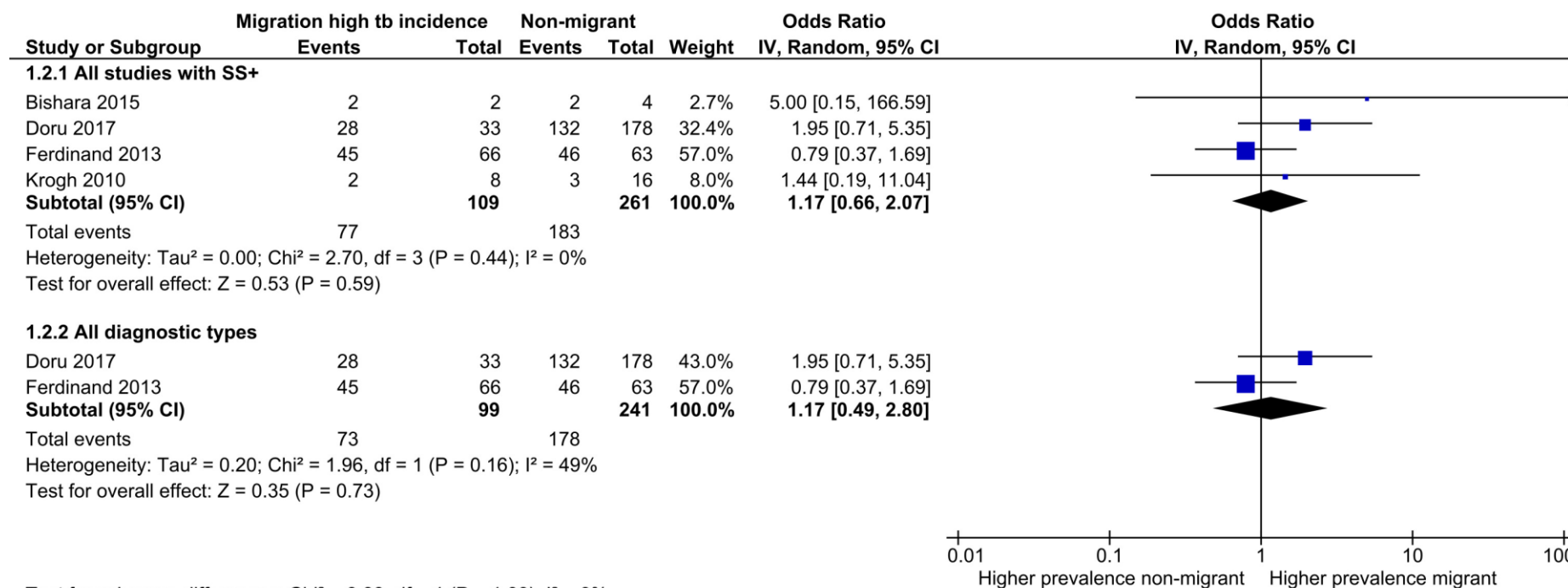


Figure 12: Meta-analysis of sputum smear positive TB cases with sensitivity analysis

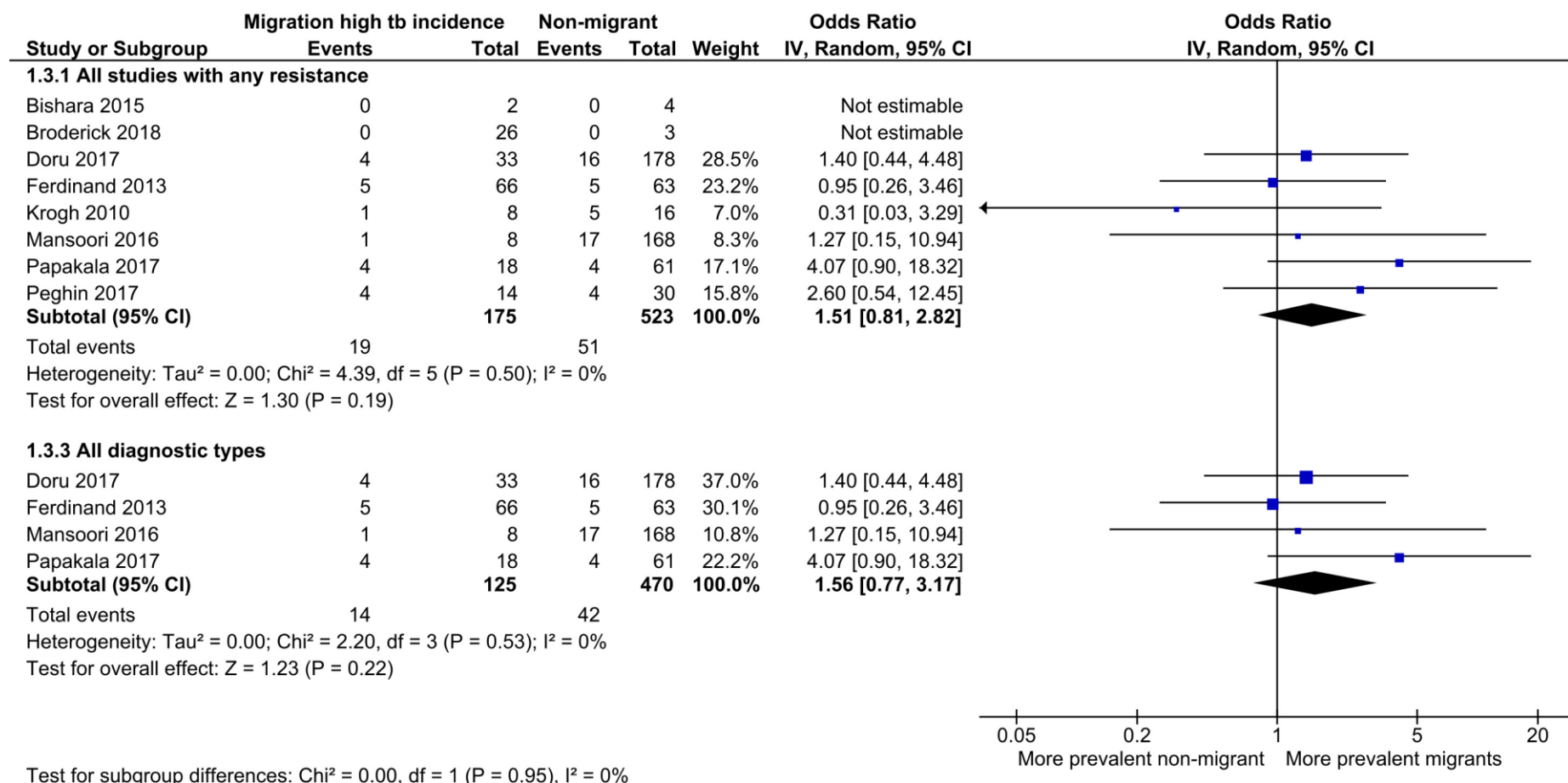


Figure 13: Meta-analysis of TB cases with first line anti-TB drug resistance with sensitivity analysis

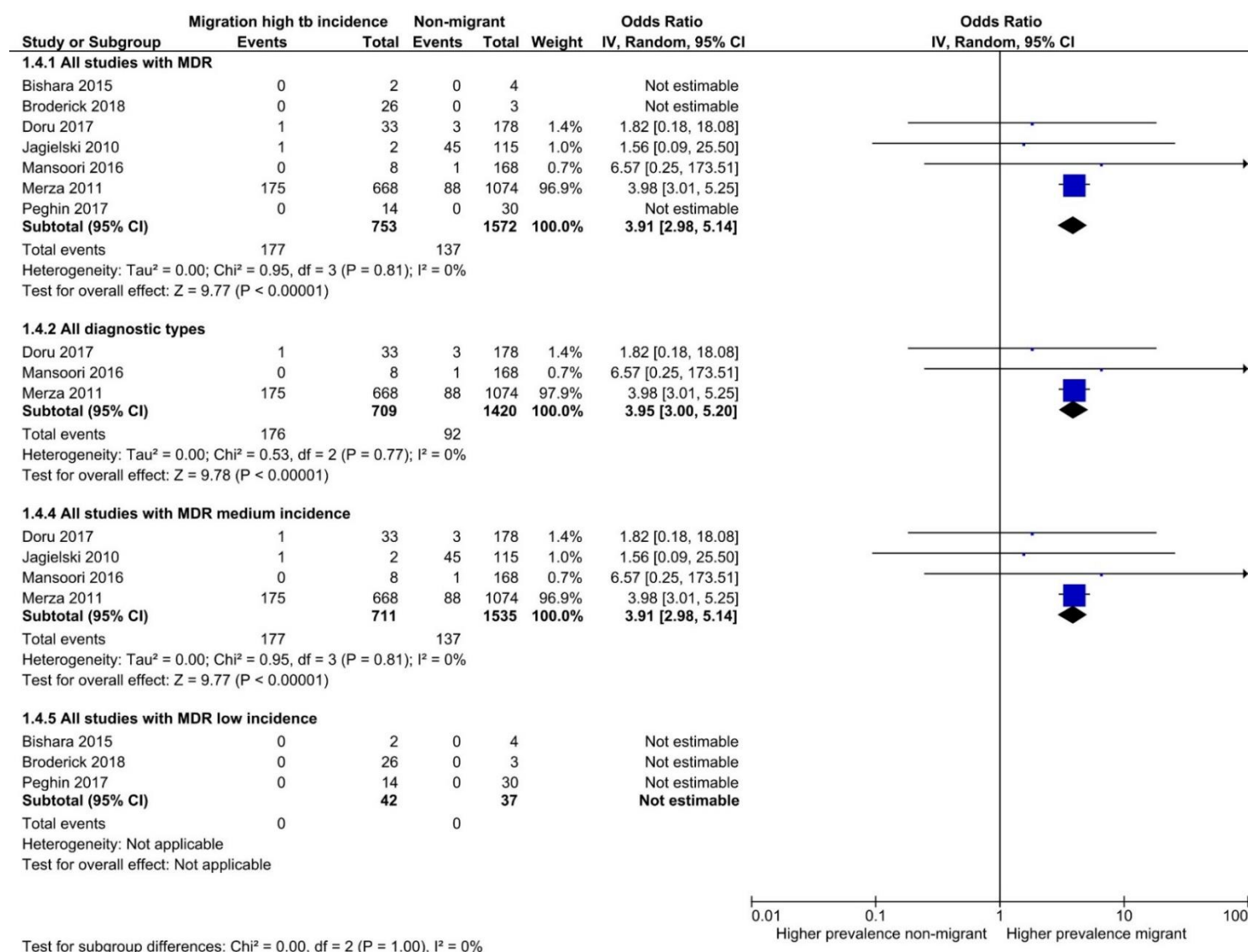


Figure 14: Meta-analysis of MDR-TB cases with subgroup and sensitivity analysis

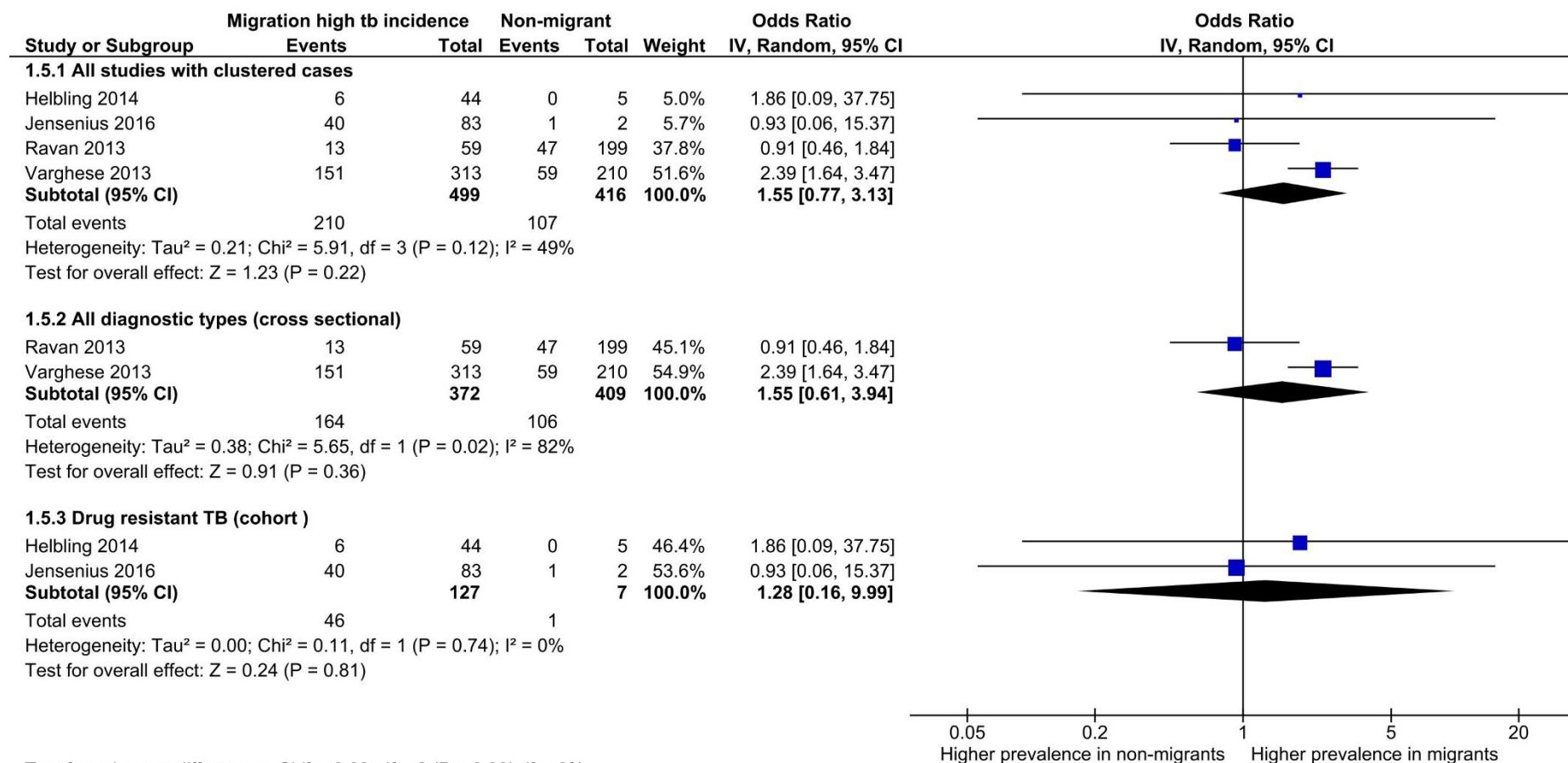


Figure 15: Meta-analysis of clustered TB cases with sub group and sensitivity analysis

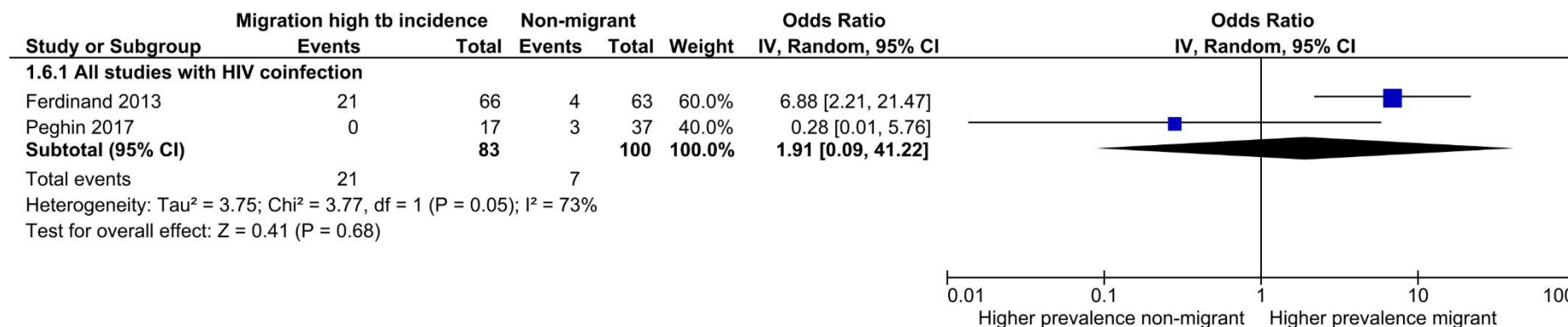


Figure 16: Meta-analysis of HIV co-infected TB cases

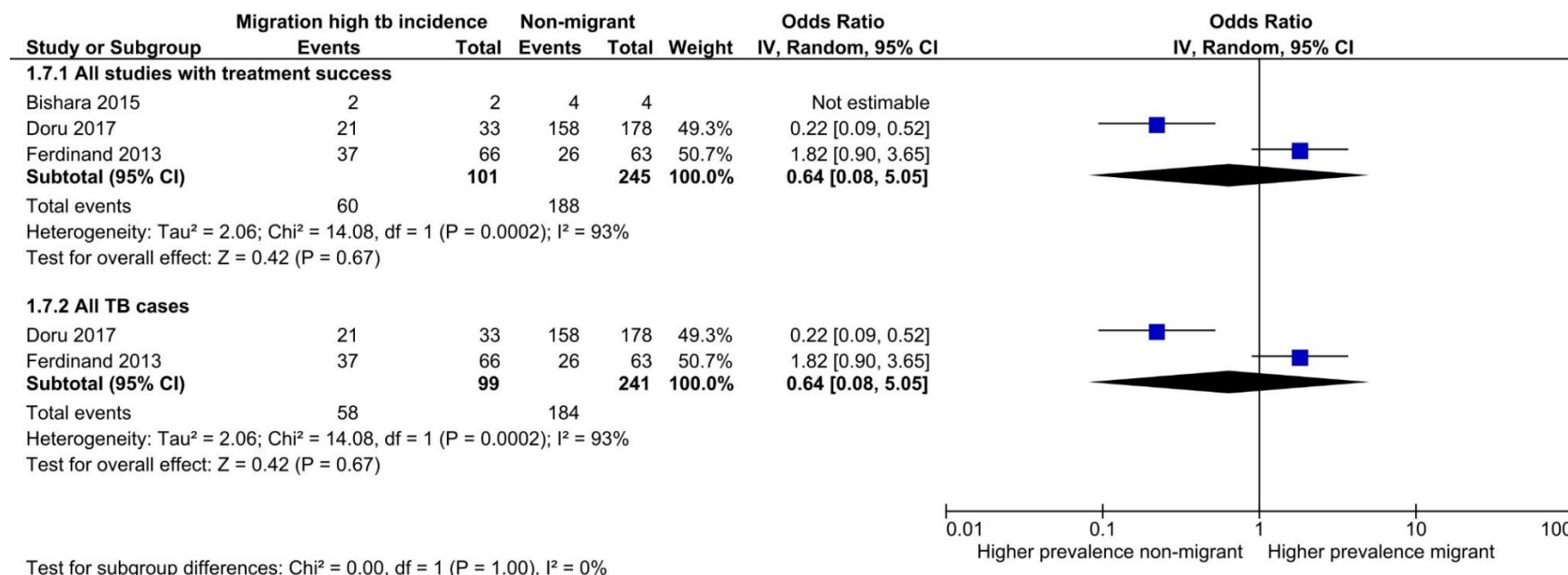


Figure 17: Meta-analysis of successfully treated TB cases with sensitivity analysis

4.5 Discussion:

While significant differences in overall proportions among high incidence migrants and non-migrants were observed in key epidemiological indicators; **MDR-TB, HIV co-infected cases, clustered cases and successfully treated cases**, the results of the meta-analyses only supported this finding for MDR-TB. These findings should be interpreted cautiously due to the high levels of clinical, methodological and statistical heterogeneity present among the included studies.

The high proportion (70%) of articles excluded due to not reporting data which would have allowed for stratification of migrant cases by TB incidence level illustrates a gap in the evidence base. The two most common approaches were to specify the most common countries of origin and report the often-substantial remainder as “other” or else to report by geographical regions of origin. In the latter case, this usually resulted in use of regions that contained different TB incidence levels.

The overall proportion of high incidence migrants among the primary outcome of TB disease cases, appears to have been influenced by the two largest studies which reported lower proportions of high incidence migrants (Cruz-Ferro et al., 2014; Moosazadeh et al., 2014). After excluding these studies, the proportion of high incidence migrants increased from 0.15 to 0.49, which is compatible with the pooled proportion of 0.47 produced by the meta-analysis. These figures are also similar to Pareek 2016 which reported a median proportion of 52% foreign-born TB notifications from all incidence levels for selected Organisation for Economic Co-operation and Development (OECD) countries (Pareek et al., 2016).

This review found a much lower proportion of low to medium incidence migrants (0.1%) among TB disease cases than a previous large scale European study which found that other EU/EEA countries contributed to 2.4% of all migrant TB cases within the EU/ EEA, ranging from 0.05% in Bulgaria to 36.6% in Cyprus (Hollo et al., 2016). In this review, low to medium incidence migrants were mainly reported from US and Australian studies which may reflect their proximity to low and medium incidence migrant source countries.

The higher proportion of MDR-TB detected in high incidence migrants in this review mirrors results in the published literature but this difference in odd ratios disappears if Merza (Iran) is excluded as it has a high weighting due to its study size (Merza et al., 2011). A recent systematic review of MDR-TB prevalence in Iran reported moderate levels (5% in new cases and 23% in retreatment cases) thought to be associated with migration from neighbouring high TB incidence countries, mainly from

Afghanistan (Hargreaves et al., 2017; Nasiri et al., 2014). It should be noted that while it is typical for most studies to report the proportion migrant MDR of the total MDR cases, this review has presented the proportion of high incidence migrant MDR of total high incidence migrant cases.

While equivalence was found between exposure groups for any resistance to first line anti-TB drugs, no data was extracted by this review on whether the cases were newly diagnosed or a mix of new and relapse. The unexpected divergence in the results for any first line resistance and MDR-TB found by this review are thought to be influenced by only two included studies reporting data suitable for inclusion in both meta-analyses (Doğru & Döner, 2017; Mansoori et al., 2016).

The conflicting results for clustered cases appear to be impacted by the inclusion of a poor-quality cross-sectional study (Ravan et al., 2013). Removal of this study from the meta-analysis resulted in significantly increased odds of the outcome in high incidence migrants. All of the studies reporting clustered cases used molecular typing methods, which can overestimate the proportion of clustering in low incidence settings compared to WGS and often reflects lineages that are common in the country of origin but not in the host country (Jajou et al., 2018; Roof et al., 2018; Stucki et al., 2016a).

Large scale representative data on HIV co-infected TB cases remains elusive in many low TB incidence settings (Odone et al., 2015). Although five studies reported data on HIV coinfection, only two studies reported cases of HIV coinfection, with a single study reporting HIV coinfection in both high incidence migrants and non-migrants (Ferdinand et al., 2013). This study was set in Guadeloupe and may reflect the country's proximity to migrant source countries with high TB and HIV prevalence, such as Haiti where the overall HIV adult prevalence rate was estimated at 1.9% in 2019 (UNAIDS, 2021). Although the overall proportion of HIV coinfections were significantly different between the exposure groups, this finding was not supported by the meta-analysis results. The meta-analysis displays divergence in the direction of the odds ratios as Ferdinand reported 32% HIV coinfection among high incidence migrants while Peghin (Spain) reported 0% (Ferdinand et al., 2013; Peghin et al., 2017).

Although treatment success results were inconclusive, migrant status has previously been associated with unsuccessful treatment outcomes, particularly among subpopulations such as undocumented, homeless or incarcerated migrants (Karo et al., 2015; Lin & Melendez-Torres, 2016). Potential explanations include returning to country of origin before treatment completion and language

and/or economic barriers to health service access (Duarte et al., 2018; Figueroa-Munoz, 2008). Some high incidence countries also experience high levels of MDR, which reduce treatment success rates. One study within the treatment success meta-analysis reported levels of MDR that were almost double that of non-migrants (3% versus 1.7%) which may have affected the low proportion of treatment success among migrants (Doğru & Döner, 2017). However, it is not clear why there is a lower rate of treatment success among non-migrants in the remaining study as no cases of MDR were reported by Ferdinand (Ferdinand et al., 2013).

The similar proportions of sputum smear positivity (0.71 versus 0.70) found among the exposure groups may be part of the contributing factors leading to low rates of onward transmission documented from migrants to non-migrants. Previously published studies have found that migrant TB epidemiology continues to reflect the incidence rates in their country of origin (Dahle et al., 2007; Kamper-Jørgensen et al., 2012; Pareek et al., 2016). This finding should also be taken in the context that certain high TB incidence migrant populations may have more paucibacillary disease due to higher HIV prevalence, increased extrapulmonary disease and higher paediatric rates compared to non-migrants in low incidence countries (Carvalho et al., 2018; Odone et al., 2015).

4.5.1 Strengths and limitations:

The strengths of this review comprise the use of robust transparent methods including protocol publication, inclusion of different study designs and grey literature, along with the use of sensitivity and subgroup analysis to investigate sources of clinical and methodological heterogeneity. Multiple outcomes have been examined as key epidemiological indicators relating to potential for transmission (sputum smear positive cases, clustered cases and successfully treated cases) and clinical complexity (HIV co-infected and drug-resistant cases). Although many conflicting recommendations exist regarding systematic review and meta-analysis of observational studies, the applicable sections of the Cochrane Handbook, PRISMA and MOOSE reporting guidelines were followed (Brooke et al., 2021; Deeks et al., 2019; Mueller et al., 2018; Page et al., 2021; Reeves et al., 2019).

The limitations of this review include the lack of denominators within included studies to calculate and compare incidence rates to assess true differences in exposure groups. A pragmatic approach was taken when choosing the time period in order to avoid cross over between incidence levels in the same country over different time periods, however this has necessarily limited the scope of the review. As no translation resources were available to the review team, 23 studies from eight

languages were not reviewed at full text stage, over half of which were Spanish (Appendix 4a, [Table A4.3](#)). Due to the clinical heterogeneity of the included studies, it was not possible to stratify most of the meta-analysis of the secondary outcomes by subgroup analysis as this resulted in too few studies per subgroup for meaningful analysis. Similarly, the small number of studies within meta-analyses, prevented investigation of publication bias via funnels plots.

No randomised controlled trials (RCTs) were included in this review as the exposure of interest cannot be randomly assigned. Despite applying a robust quality assessment process, none of the studies were found to be of high quality. Although many studies had an epidemiological focus, the majority reported the type of analysis performed rather than a defined study design. High risk of bias results were most commonly observed in domains assessing sample size justification, power calculation, confounding and blinding of outcome assessors to exposure status. With the exception of one study, data were retrospectively extracted, so data on outcomes and exposures were extracted at the same time.

4.5.2 Conclusions

This review has demonstrated that significant differences in key epidemiological indicators are present between high incidence migrants and non-migrants. To the researcher's knowledge, this is the first systematic review to compare key epidemiological indicators between high incidence migrants and non-migrant TB cases. Previous studies have focused on migrant TB as a homogenous group, potentially missing key characteristics and failing to inform the tailored prevention and control response required to meet current TB elimination goals (Odone et al., 2015; World Health Organization, 2022a).

Despite an awareness that TB incidence levels within migrant source countries influence TB epidemiology within host countries, this study highlights that an important gap in the literature persists in the form of a lack of detailed data on migrant origin which is required to inform TB elimination programmes. The considerable heterogeneity present in the results indicates that a tailored, migrant inclusive approach should be taken when viewing the issue of TB prevention and control.

4.6 Chapter conclusion:

This chapter has summarised the international evidence base for key TB epidemiological indicators among migrants from high TB incidence countries in low and medium TB incidence countries and comparing those to non-migrant cases from the same countries. This chapter highlights significant differences among high incidence migrants and non-migrants in overall proportions of MDR-TB, People living with HIV and TB co-infection, clustered cases and successfully treated cases. These key differences have relevance for TB prevention and control programmes. In addition, this review highlights an important gap in the literature regarding the reporting of diversity of migrant origin.

The results of this chapter will be used to inform the analysis in Chapter 5, which compares and contrasts the patient characteristics of TB cases among migrants compared to Irish-born cases, and key epidemiological indicators for migrant TB cases. Chapter 5 also provides a detailed analyses of the epidemiology of migrant cases, including migrant country specific incidence rates and analyses of migrant sub-populations.

5 Chapter 5: The comparative epidemiology of tuberculosis among Irish-born TB cases and migrant TB cases in Ireland:

5.1 Chapter outline

The overall aim of this study was to examine the effect of migration on the epidemiology of TB in low to medium incidence countries in order to inform global prevention and control policies. The study results are presented in four interconnected chapters. This second results chapter focuses on the second study objective *“To describe and analyse the comparative epidemiology of TB among Irish-born TB cases and migrant TB cases”*. It details the results of a descriptive analysis comparing the patient characteristics of TB cases among migrants compared to Irish-born cases, and key epidemiological indicators for migrant TB cases. In addition, results of multivariable logistic regression analysis are presented comparing characteristics of migrant cases with TB to Irish-born cases with TB. Finally, a detailed analyses of the epidemiology of migrant cases is provided, including migrant country specific incidence rates and analyses of migrant subpopulations. The results of this chapter inform the statistical models presented in the third results chapter ([Chapter 7](#)).

5.2 Introduction

As already outlined in [Chapter 2](#), CIRs in the foreign-born population have been up to 13 times higher than the CIRs observed among Irish-born cases (HSE Health Protection Surveillance Centre, 2025). However, migrants are a very diverse population group and consequently their TB risk is influenced by many factors. Background risk of TB infection in the country of origin is a key component, however the process of migration itself can alter the risk of acquiring new infection or developing TB disease.

International migration is increasing globally with the European region experiencing some of the steepest increases in recent years, from 50 million in 1990 to 87 million in 2020 (International Organization for Migration, 2024). Similarly, Ireland has also experienced a steady increase in the proportion of the population that was born abroad, from 10% in 2002 to 20% in 2022 (Central Statistics Office, 2016b, 2024a). Given these increasing global migration trends, stimulated by rising environmental and political instability, migrants remain a key population for TB prevention and care activities. For this reason, a better and deeper understanding of the epidemiologic patterns among native-born and foreign-born TB cases is required.

This objective aims to inform future TB prevention and care activities by analysing the differences in the epidemiology of TB in native-born and foreign-born populations within the Irish context, and by

providing an in-depth analysis of migrant-TB patient profiles. The stratification by migrant sub-populations fills an important gap in the evidence base which has typically analysed all migrants simply as “foreign-born”.

5.3 Methods:

5.3.1 Study design and population

A cross-sectional secondary-data analysis of all TB disease notifications reported to the Irish National TB Surveillance System and notified to the CIDR system between 2011 and 2021 was conducted (HSE Health Protection Surveillance Centre, 2024).

5.3.2 Definitions

TB disease was defined as cases with signs, symptoms and/or radiological findings consistent with TB disease in any site and a clinician's decision to treat the person with a full course of anti-TB therapy, or a case discovered post-mortem with pathological findings consistent with TB disease that would have indicated anti-tuberculosis antibiotic treatment had the patient been diagnosed before dying, as per the European Union (EU) Commission surveillance case definition (European Commission, 2018; HSE Health Protection Surveillance Centre, 2024). No restrictions on case classification were used; possible, probable and confirmed case classifications were included. Migrant TB cases were defined in line with International Organization for Migration (IOM) definition of international migrants as being born outside Ireland but notified with TB in Ireland.

Resistance to TB drugs was defined as genotypic or phenotypic resistance to any one or more of the following drugs: isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, bedaquiline, clofazimine, cycloserine, delamanid, ethionamide, linezolid, para-amino salicylic acid, prothionamide, rifabutin, any 2nd line injectable (e.g. amikacin, kanamycin etc.) or any fluoroquinolone (e.g. levofloxacin, moxifloxacin etc.).

Multi-drug resistance (MDR) was defined as resistance to both isoniazid and rifampicin and extensively drug-resistant (XDR) TB was defined using the pre-2021 World Health Organization (WHO) definition of resistance to rifampicin and any fluoroquinolone and a second line injectable. As the numbers of MDR and XDR were low in this study, they are mainly presented as a combined category of M/XDR-TB.

5.3.3 Statistical analysis

Chi squared test for difference in proportions, Kruskal Wallis or Wilcoxon Rank Sum Tests were used as appropriate to test associations between independent variables and categorical outcomes. Crude incidence rates (CIRs) and age-specific incidence rates (ASIRs) per 100,000 population were

calculated using 2016 census population denominators stratified by country of birth and age. Denominator data for countries of birth of TB cases which were not publicly available were sourced from the Central Statistics Office. Temporal trends in CIRs were analysed using Negative-binomial regression and incidence rate ratios (IRRs). Temporal trends were assessed for total cases, migrant cases and Irish-born cases for both the full study period (2011-2021) and the latter half (2017-2021).

Independent variables selected based on clinical relevance and literature review with a p value of ≤ 0.2 in univariable analysis were investigated in a multivariable logistic regression model comparing patient characteristics of TB among migrants compared to TB among Irish-born. Independent variables were assessed for co-linearity using Variable Inflation Factor (VIF) analysis and removed if the VIF was >9.0 . Backwards stepwise elimination was used to reduce the variables, removing the variable with the highest Wald p value one at a time until all variables attained a p value of <0.05 in the final model. Model fit was assessed using Hosmer and Lemeshow's test and models were compared using the Akaike Information Criterion (AIC) and AIC weights. Crude odds ratios (cORs) estimated by univariable logistic regression and adjusted odds ratios (aORs) estimated by multivariable logistic regression are presented.

As complete case analysis was used, the potential effect of excluding cases with missing data from the model was assessed by comparing the distribution of each of the 12 selected independent variables by the dependent variable within the complete cases sample, and within the total sample. The distributions were broadly similar between the two samples. Patterns of missing data were assessed visually and by using Little's test. With the exception of HIV status, variables with missing data for $>25\%$ of cases were not eligible for inclusion in the model.

Each migrant origin-country was mapped to the country-specific mean WHO TB incidence estimate per 100,000 for the study period (World Health Organization, 2023). Origin-countries were classified according to the following incidence categories: low = 0.0-9.9, medium = 10.0-39.9, high = 40.0-99.9 and very high ≥ 100 . WHO estimates were not available for two origin-countries within the study population ($n = 3$ cases). These three cases were excluded from any analyses of cases that involved incidence levels.

Time between arrival in Ireland and notification as a TB patient was estimated by subtracting arrival year from notification year, and categorised as follows: <2 years, 2-4 years, 5-9 years and ≥ 10 years.

5.4 Results:

5.4.1 Epidemiology of TB among migrants compared to Irish-born:

Of the 3,364 cases notified between 2011 and 2021, 48% (n=1,605) were among migrants, 47% (n=1,593) were among Irish-born and 5% (n=166) did not have country of birth reported. Overall, 5% (n=153) of total cases were reported as being an International Protection Applicant or Refugee (IPAR), 9% of migrant cases and 0.3% of Irish-born cases. [Table 9](#) summarises the overall distribution of patient characteristics stratified by migrant status, alongside results of univariable and multivariable logistic regression analysis results comparing patient characteristics of TB among migrants compared to TB among Irish-born.

5.4.1.1 Sex and age

The male to female ratio was 1.3 among migrants and 1.7 among Irish-born. Migrant cases were significantly younger than Irish-born cases, with a median age of 34 years versus 53 year respectively ($p<0.001$). Significantly younger median ages were observed among IPAR migrants (31 years) compared to non-IPAR migrants (34 years) ($p<0.001$). The median age at arrival for migrant cases overall was 29 years; but was slightly younger among females (28 years) for compared to males (30 years).

Cumulative age-specific incidence rates (ASIRs) were higher among migrant cases compared to Irish-born cases in all age groups ([Figure 18](#)). Annual ASIRs were equivalent or higher among migrant cases in all age groups except those aged 0-14 years old and in 2012 for the 65 years and older age group (data not shown). Cumulative ASIRs were higher among males for all age groups except the 0-14 year olds, for both migrant and Irish-born cases. Cumulative age and sex specific incidence rates are shown for Irish-born cases in [Figure A5.1](#) and for migrant cases in [Figure A5.2](#).

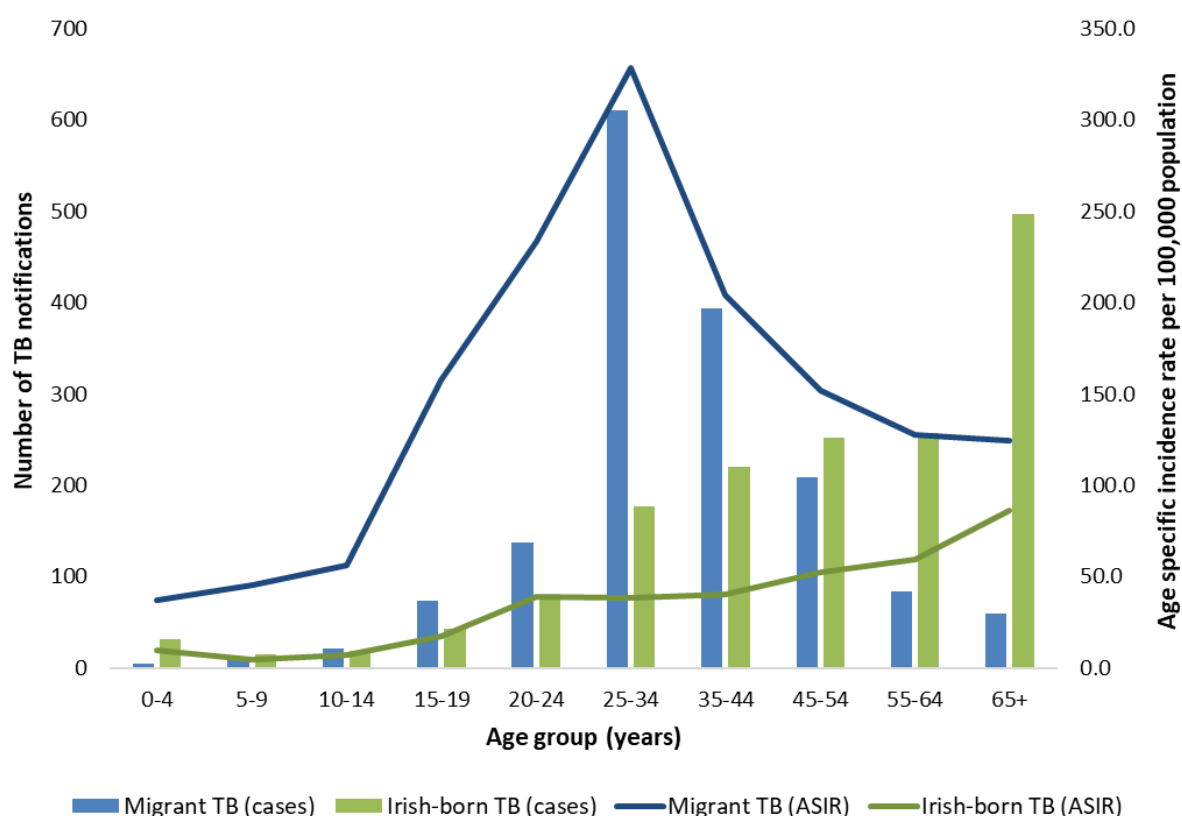


Figure 18: Cumulative number of TB cases and age-specific incidence rate per 100, 000 population by migrant status in Ireland, 2011-2021

5.4.1.2 Clinical features:

Lower proportions of pulmonary TB (PTB) were observed among migrant cases (57.9%) compared to Irish-born cases (77.6%) ([Table 9](#)). Compared to Irish-born cases, migrants also had higher odds of having normal chest X-ray (CXR) result (OR: 3.13, CI: 2.45-4.02) and computed tomography (CT) thorax scan results (OR: 3.62, CI: 1.92-7.26).

For cases with dates of onset and diagnoses reported (n=1,955, 59%), a significantly shorter median interval between onset and diagnosis was observed among migrant cases (63 days, range: 0 – 3,294) compared to Irish-born (75 days, range: 0 – 2,111) (p=0.001). [Figure 19](#) illustrates the interval between onset and diagnosis categorized as months stratified by migrant status. Median intervals were significantly longer among exclusively extrapulmonary TB (EPTB) cases (186 days), compared to PTB cases (66 days). This was also observed within Irish-born EPTB cases and migrant EPTB cases, but the magnitude of divergence in the median interval between PTB and EPTB cases was greater among migrant EPTB cases ([Table 10](#)).

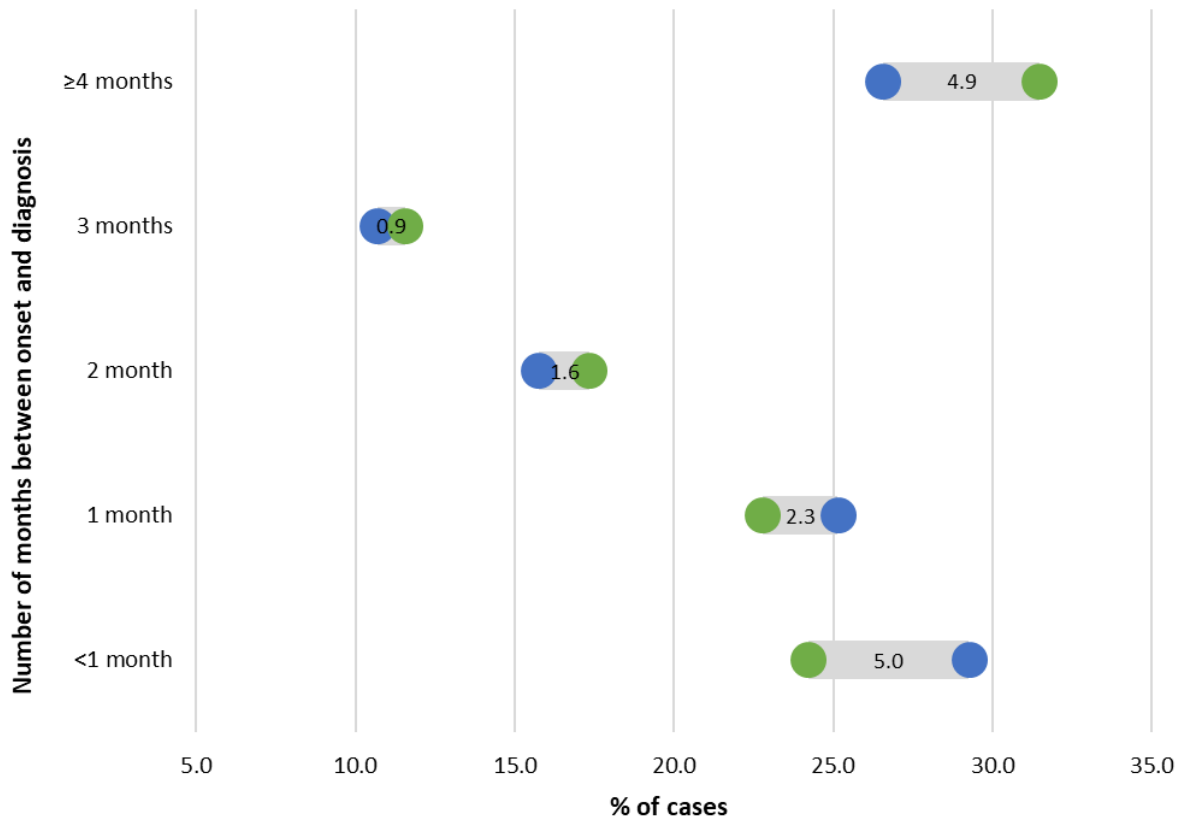


Figure 19: Interval between onset and diagnosis in months by migrant status for TB cases in Ireland, 2011-2021 (n = 1,955)

5.4.1.3 Drug resistance

Drug susceptibility testing (DST) data was available for 73.8 % (n=2,360) of total cases from 86 countries of origin. Infection with a drug-resistant strain was reported in 17.3% of migrant cases and 7.3% of Irish-born cases. Infection with a Multi-Drug Resistant (MDR) or Extensively-Drug Resistant (XDR) strain was reported in 47 cases (1.5% of total, 2.0% of cases with DST results) from 19 countries of origin.

Forty MDR-TB cases were migrants (90.9%), two were Irish-born and no country of birth was reported for the remaining two cases. All three XDR-TB cases occurred among migrants. Of the 47 M/XDR-TB cases, 79.5% (n=35) had PTB. Previous history of TB was known for 36 M/XDR-TB cases and 24% (n=8) were previously diagnosed. Infection with non-MDR poly resistant strains was reported in 40 cases (0.2%) from 17 countries of origin, seven (17.5%) of these were among Irish-born cases.

5.4.1.4 Univariable and multivariable logistic regression analysis results:

The full results of the crude odds ratios produced from univariable logistic regression analysis are detailed in [Table 9](#). Ten candidate variables identified through univariable logistic regression analysis were included in the full model using a complete case sample of 825 cases. Although certain biological risk factor variables were significant at univariable (diabetes, substance use and immunosuppression), data was missing for >50% of these variables so they were not included in the models. HIV status was missing for 56% of cases but this was included in the model given its high clinical significance. A sensitivity analysis was run with a model on a larger complete case dataset without HIV to investigate the effects of its inclusion. Candidate variables examined included patient age (years), sex, geographic area of residence, employment status, disease site, previous TB history, patient type, outbreak association, HIV status and infection with a drug-resistant strain. It was not possible to include housing status in the model due to the small numbers within cells that could not be combined with other categories in a meaningful way. The multivariable logistic regression model building process removed independent variables with the highest Wald p value one at a time, using the backwards stepwise elimination method.

The adjusted odds ratios for the seven independent variables retained in the final model are detailed in [Table 9](#); patient age (years), geographical area of residence, disease site, outbreak association, employment status, HIV status and infection with drug resistant strain. After adjusting for each of the independent variables and compared to TB cases among Irish-born, migrants had a higher adjusted odds of living with HIV (OR: 3.8, CI: 1.99 to 7.73), having an extrapulmonary site of diagnosis (OR: 3.14, CI: 2.09 to 4.79), being infected with a drug resistant strain (OR: 2.30, CI: 1.37 to 4.01), being resident in the Midlands area of Ireland (OR: 3.26, CI: 1.24 to 9.69). Migrant cases had a lower odds of being associated with an outbreak (OR: 0.16, CI: 0.09 to 0.28). Increasing patient age was significantly negatively correlated with the outcome of TB among migrants (OR: 0.97, CI: 0.95 to 0.98). All metrics of the model assumptions were acceptable with 83% of binned residuals within error bounds. VIF analysis indicated that levels of co-linearity were low, with a highest VIF score of 2.2. Hosmer Lemeshow's test found no evidence of poor model fit (statistic: 9.5, p = 0.304).

The sensitivity analysis excluding HIV retained the same variables and exhibited the same magnitude and direction of effects (data not shown).

Table 9: Summary patient characteristics of TB cases by migrant status for full sample (n= 3,198) and results of univariable and multivariable logistic regression analyses (n = 825) for Ireland; 2011-2021

Characteristic	Missing	Overall N = 3,198	Irish-born N = 1,593	Migrant N = 1,605	Univariable		Multivariable (N=825)	
					cOR (95% CI)	p-value	aOR (95% CI)	p-value
Median age (IQR)	4 (0.1%)	40.0 (28.0)	53.0 (33.0)	34.0 (16.0)	0.95 (0.95 to 0.96)	<0.001	0.97 (0.95 to 0.98)	<0.001
Sex	4 (0.1%)					<0.001		
<i>Female</i>		1,276 (40%)	588 (37%)	688 (43%)	—			
<i>Male</i>		1,918 (60%)	1,005 (63%)	913 (57%)	0.78 (0.67 to 0.89)			
Geographical area	0 (0%)					<0.001		0.037
<i>East</i>		1,387 (43%)	563 (35%)	824 (51%)	—		—	
<i>Midlands</i>		155 (4.8%)	69 (4.3%)	86 (5.4%)	0.85 (0.61 to 1.19)		3.26 (1.24 to 9.69)	
<i>Midwest</i>		196 (6.1%)	104 (6.5%)	92 (5.7%)	0.60 (0.45 to 0.82)		1.10 (0.63 to 1.92)	
<i>North East</i>		228 (7.1%)	115 (7.2%)	113 (7.0%)	0.67 (0.51 to 0.89)		1.45 (0.57 to 4.05)	
<i>North West</i>		115 (3.6%)	77 (4.8%)	38 (2.4%)	0.34 (0.22 to 0.50)		0.62 (0.27 to 1.47)	
<i>South</i>		610 (19%)	396 (25%)	214 (13%)	0.37 (0.30 to 0.45)		0.65 (0.41 to 1.03)	
<i>South East</i>		262 (8.2%)	146 (9.2%)	116 (7.2%)	0.54 (0.42 to 0.71)		0.76 (0.46 to 1.28)	
<i>West</i>		245 (7.7%)	123 (7.7%)	122 (7.6%)	0.68 (0.52 to 0.89)		1.16 (0.58 to 2.37)	
Employment status	371 (12%)					<0.001		0.024
<i>Paid employment</i>		1,041 (37%)	399 (28%)	642 (45%)	—		—	
<i>Unemployed</i>		929 (33%)	428 (30%)	501 (35%)	0.73 (0.61 to 0.87)		0.82 (0.56 to 1.19)	
<i>Retired</i>		443 (16%)	403 (29%)	40 (2.8%)	0.06 (0.04 to 0.09)		0.27 (0.12 to 0.60)	
<i>Student/Child</i>		329 (12%)	135 (9.6%)	194 (14%)	0.89 (0.69 to 1.15)		0.86 (0.45 to 1.70)	
<i>Other</i>		85 (3.0%)	46 (3.3%)	39 (2.8%)	0.53 (0.34 to 0.82)		0.81 (0.35 to 1.90)	
Current housing type	343 (11%)					<0.001		
<i>Private house</i>		2,646 (93%)	1,352 (94%)	1,294 (92%)	—			
<i>Congregate residential setting</i>		105 (3.7%)	36 (2.5%)	69 (4.9%)	2.00 (1.34 to 3.05)			
<i>Homeless</i>		27 (0.9%)	16 (1.1%)	11 (0.8%)	0.72 (0.32 to 1.54)			
<i>Prison</i>		22 (0.8%)	9 (0.6%)	13 (0.9%)	1.51 (0.65 to 3.67)			
<i>Residential care facility</i>		20 (0.7%)	18 (1.2%)	2 (0.1%)	0.12 (0.02 to 0.40)			
<i>Other housing</i>		35 (1.2%)	14 (1.0%)	21 (1.5%)	1.57 (0.80 to 3.16)			
Disease site	36 (1.1%)					<0.001		<0.001
<i>Pulmonary</i>		2,140 (68%)	1,223 (78%)	917 (58%)	—		—	
<i>Extrapulmonary</i>		1,022 (32%)	353 (22%)	669 (42%)	2.53 (2.17 to 2.95)		3.14 (2.09 to 4.79)	

Characteristic	Missing	Overall N = 3,198	Irish-born N = 1,593	Migrant N = 1,605	Univariable		Multivariable (N=825)	
					cOR (95% CI)	p-value	aOR (95% CI)	p-value
Outbreak associated	0 (0%)					<0.001		<0.001
<i>Not linked to outbreak</i>		2,875 (90%)	1,345 (84%)	1,530 (95%)	—		—	
<i>Outbreak associated</i>		323 (10%)	248 (16%)	75 (4.7%)	0.27 (0.20 to 0.35)		0.16 (0.09 to 0.28)	
People living with HIV	1,804 (56%)					<0.001		<0.001
<i>Negative</i>		1,266 (91%)	554 (96%)	712 (87%)	—		—	
<i>Positive</i>		128 (9.2%)	22 (3.8%)	106 (13%)	3.75 (2.38 to 6.16)		3.80 (1.99 to 7.73)	
TB drug resistance	838 (26%)					<0.001		0.001
<i>Sensitive</i>		2,065 (88%)	1,046 (93%)	1,019 (83%)	—		—	
<i>Resistant</i>		295 (13%)	82 (7.3%)	213 (17%)	2.67 (2.05 to 3.51)		2.30 (1.37 to 4.01)	
M/XDR-TB	838 (26%)					<0.001		
<i>No</i>		2,315 (98%)	1,126 (100%)	1,189 (97%)	—			
<i>Yes</i>		45 (1.9%)	2 (0.2%)	43 (3.5%)	20.4 (6.26 to 125)			
Previous TB screening in Ireland	887 (28%)					<0.001		
<i>No</i>		1,953 (85%)	908 (80%)	1,045 (89%)	—			
<i>Yes</i>		358 (15%)	224 (20%)	134 (11%)	0.52 (0.41 to 0.65)			
Previous TB diagnosis	801 (25%)					0.086		
<i>No</i>		2,188 (91%)	1,089 (90%)	1,099 (92%)	—			
<i>Yes</i>		209 (8.7%)	117 (9.7%)	92 (7.7%)	0.78 (0.58 to 1.04)			
Patient type	362 (11%)					0.004		
<i>Hospital inpatient</i>		1,658 (58%)	876 (61%)	782 (56%)	—			
<i>Hospital outpatient</i>		914 (32%)	425 (29%)	489 (35%)	1.29 (1.10 to 1.52)			
<i>Other</i>		264 (9.3%)	145 (10%)	119 (8.6%)	0.92 (0.71 to 1.19)			
Diabetes	1,862 (58%)					>0.99		
<i>No</i>		1,204 (90%)	648 (90%)	556 (90%)	—			
<i>Yes</i>		132 (9.9%)	71 (9.9%)	61 (9.9%)	1.00 (0.70 to 1.43)			
Immunosuppression	1,841 (58%)					0.033		
<i>No</i>		1,067 (79%)	569 (76%)	498 (81%)	—			
<i>Yes</i>		290 (21%)	175 (24%)	115 (19%)	0.75 (0.58 to 0.98)			
Substance use	1,881 (59%)					<0.001		
<i>No</i>		945 (72%)	475 (62%)	470 (86%)	—			
<i>Yes</i>		372 (28%)	297 (38%)	75 (14%)	0.26 (0.19 to 0.34)			

cOR = Crude Odds Ratio, aOR: Adjusted Odds Ratio, CI = Confidence Interval

Table 10: Interval between onset and diagnosis by disease site and migrant status; Ireland 2011-2021

Characteristic	Total cases				Irish-born cases				Migrant cases			
	Overall N = 3,272	Pulmonary N = 2,223	Extrapulmonary N = 1,049	p- value ⁱ	Overall N = 1,576	Pulmonary N = 1,223	Extrapulmonary N = 353	p- value	Overall N = 1,586	Pulmonary N = 917	Extrapulmonary N = 669	p- value
Median days between onset and diagnosis (IQR)	70.0 (100.0)	66.0 (98.0)	78.0 (100.3)	0.001	75.0 (102.0)	72.0 (101.0)	87.0 (104.5)	0.024	63.0 (94.0)	60.0 (86.0)	73.0 (97.5)	0.001
<i>(% missing)</i>	41	41	41		41	41	39		38	37	40	

ⁱ Wilcoxon rank sum test

5.4.1.5 Temporal trends:

Between 2011 and 2021, a significantly declining temporal trend was present in the annual crude CIRs per 100,000 population for all three patient cohorts analysed; migrant TB cases, Irish-born TB cases and total TB cases. Between 2011-2021, annual CIRs declined from 9.0 to 4.4 for total cases (IRR: 0.95; CI: 0.94-0.96), from 25.2 to 15.2 among migrants (IRR: 0.96; CI: 0.95-0.98) and from 5.6 to 1.2 among Irish-born (IRR: 0.89; CI: 0.86-0.92). Between 2017 and 2021, a significantly declining temporal trend was still present in Irish-born cases (IRR: 0.76; CI: 0.69 - 0.83) and total cases (IRR: 0.91; CI: 0.88-0.95), but the trend was no longer significant among migrant cases (IRR: 0.96; CI: 0.91-1.01) ([Figure 20](#)).

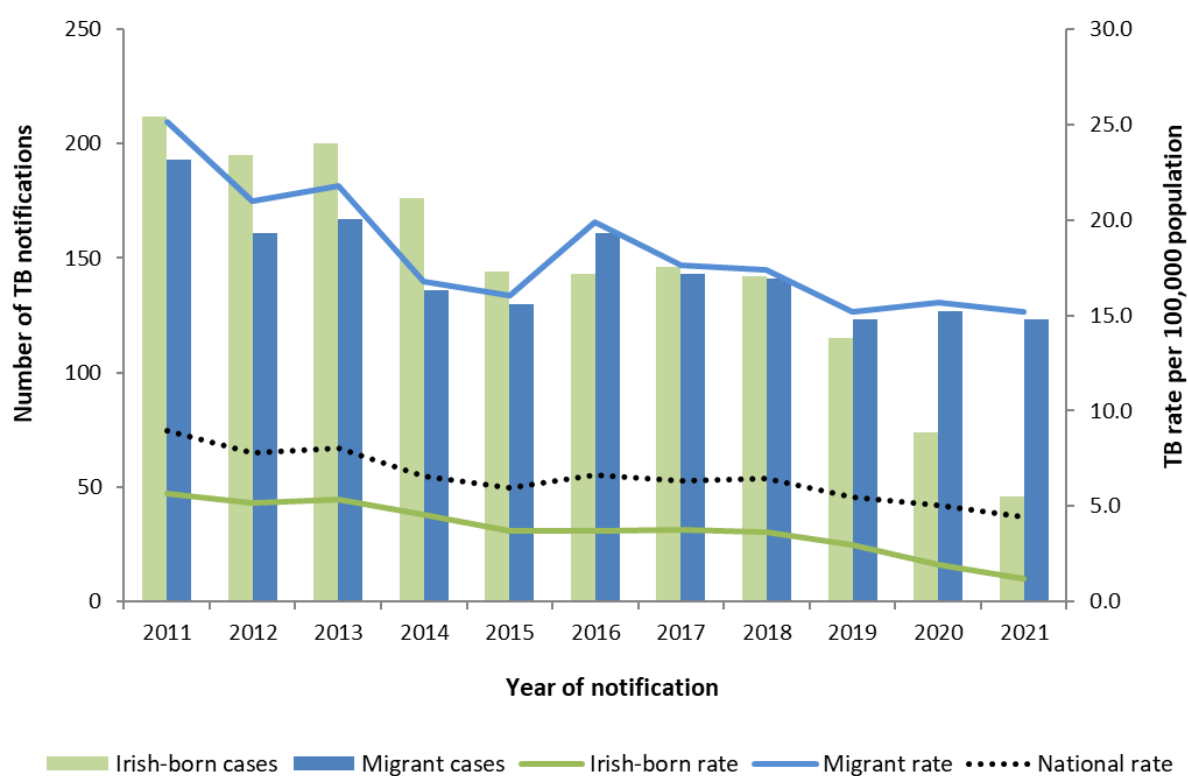


Figure 20: Annual number of TB cases and crude incidence rate per 100, 000 population by migrant status in Ireland, 2011-2021

5.4.2 Migrant TB epidemiology:

Migrant cases originated from 98 countries. The majority of cases (68.5%) originated from countries classified as very high TB incidence (CIR ≥ 100 / 100,000 population) according to the mean WHO CIR estimate for the study period. Annual CIRs for cases from very high birth-countries in Ireland declined from 132.5 per 100, 000 population in 2011 to 84.5 in 2021. Cases originating from countries classified as high and medium incidence accounted for 17.4% and 12.0% of total cases respectively. Fluctuation was observed in annual CIRs for high incidence countries, ranging from 28.3 in 2013 to 11.5 in 2014, while annual CIRs among medium incidence countries declined from 5.9 in 2011 to 2.0 in 2021 ([Figure A5.3](#)). Thirty cases were reported from low incidence countries (1.9%) and annual CIRs remained stable (range: 0.0-6.2).

Migrant TB patient characteristics differed according to the incidence level in the origin-country ([Table 11](#)). Median ages were highest in those originating from low incidence countries. Migrants from very high incidence countries had the highest proportions of PLWHIV and with previous TB screening in Ireland, and the lowest proportions with PTB and being linked to an outbreak. A significant trend in the proportion of international protection applicants was observed in relation to the increasing incidence category.

The top ten migrant origin-countries differed when ranked by patient numbers versus by the mean annual CIR, with the exception of India, Pakistan and Somalia which were ranked by both metrics. Origin-countries with the highest number of TB cases comprised six very high TB incidence countries, two high incidence and two medium incidence countries. Origin-countries with the highest TB CIRs in this study were all classified as very high TB incidence countries according to the mean WHO CIR estimates. [Table 12](#) displays the mean CIR and the percentage of cases originating from each of the origin-countries for the study period in either top ten category. CIRs for migrant TB cases from Eritrea, Botswana, Malawi and Somalia were higher in Ireland than the mean CIR estimates reported by WHO in these countries ([Figure 21](#)). The proportion of IPARs was higher among origin-countries with highest CIRs (9.8%) compared to the remaining countries (5.1%), with highest proportions of IPARs among Eritrea (75.0%), Somalia (27.7%), Uganda (12.5%) and Malawi (12.0%). [Figure A5.4](#) and [Figure A5.5](#) display the annual CIRs for countries of birth with the top 10 highest CIRs in Ireland.

Table 11: Characteristics of migrant TB cases by WHO TB incidence category, Ireland 2011-2021

Characteristic	WHO TB incidence category					p-value ⁺⁺⁺
	Overall N = 1,602	Low N = 30	Medium N = 193	High N = 280	Very high N = 1,099	
Median age (years), (IQR)	34.0 (16.0)	43.5 (25.5)	36.0 (23.3)	35.0 (16.0)	33.0 (15.0)	<0.001
<i>(% missing)</i>	0.1	0	0.5	0	<0.1	
Sex						0.035
Female	687 (43%)	11 (37%)	74 (39%)	104 (37%)	498 (45%)	
Male	911 (57%)	19 (63%)	118 (61%)	176 (63%)	598 (55%)	
<i>(% missing)</i>	0.2	0	0.5	0	0.3	
International Protection Applicant						<0.001
No	1,088 (88%)	24 (100%)	155 (95%)	194 (93%)	715 (85%)	
Yes	148 (12%)	0 (0%)	8 (4.9%)	14 (6.7%)	126 (15%)	
<i>(% missing)</i>	23	20	16	26	23	
People living with HIV						0.20
Negative	711 (87%)	13 (93%)	73 (91%)	129 (91%)	496 (85%)	
Positive	106 (13%)	1 (7.1%)	7 (8.8%)	13 (9.2%)	85 (15%)	
<i>(% missing)</i>	49	53	59	49	47	
Disease site						<0.001
Pulmonary	916 (58%)	24 (80%)	157 (82%)	204 (73%)	531 (49%)	
Extrapulmonary	667 (42%)	6 (20%)	35 (18%)	75 (27%)	551 (51%)	
<i>(% missing)</i>	1.2	0	0.5	0.4	1.5	
Outbreak associated						0.021
Not linked to outbreak	1,527 (95%)	27 (90%)	177 (92%)	266 (95%)	1,057 (96%)	
Outbreak associated	75 (4.7%)	3 (10%)	16 (8.3%)	14 (5.0%)	42 (3.8%)	
<i>(% missing)</i>	0	0	0	0	0	
Previous TB screening in Ireland						0.072
No	1,042 (89%)	22 (100%)	136 (90%)	192 (92%)	692 (87%)	
Yes	134 (11%)	0 (0%)	15 (9.9%)	17 (8.1%)	102 (13%)	
<i>(% missing)</i>	27	27	22	25	28	
Previous TB diagnosis)						0.14
No	1,097 (92%)	22 (96%)	136 (93%)	180 (88%)	759 (93%)	
Yes	92 (7.7%)	1 (4.3%)	11 (7.5%)	24 (12%)	56 (6.9%)	
<i>(% missing)</i>	26	23	24	27	26	
TB drug resistance						0.94
Sensitive	1,017 (83%)	16 (80%)	125 (84%)	192 (82%)	684 (83%)	
Resistant	213 (17%)	4 (20%)	24 (16%)	42 (18%)	143 (17%)	
<i>(% missing)</i>	23	33	23	16	25	
M/XDR-TB						0.038
No	1,187 (97%)	20 (100%)	141 (95%)	220 (94%)	806 (97%)	
Yes	43 (3.5%)	0 (0%)	8 (5.4%)	14 (6.0%)	21 (2.5%)	
<i>(% missing)</i>	23	33	23	16	25	

⁺⁺⁺ Kruskal-Wallis rank sum test; Pearson's Chi-squared test; Fisher's exact test

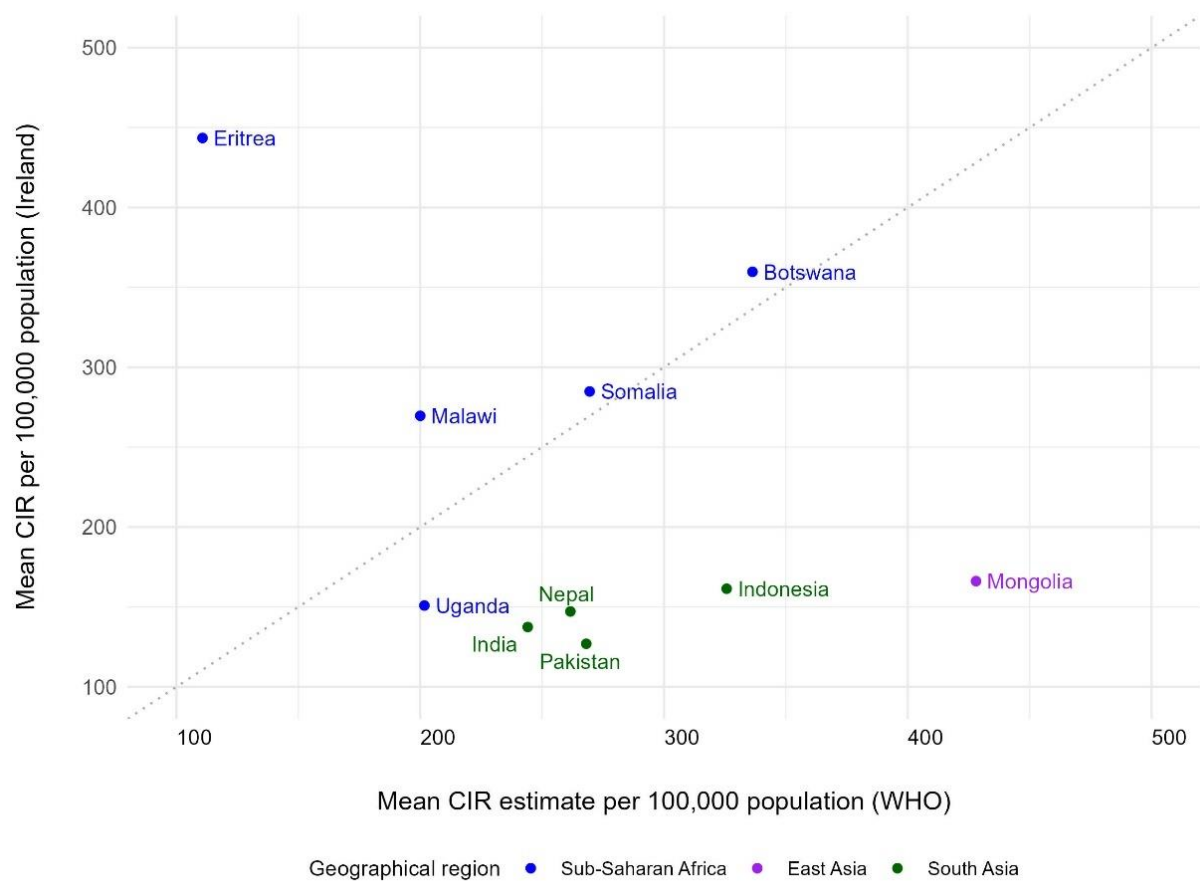


Figure 21: Origin-countries with 10 highest mean crude incidence rates in Ireland compared to WHO incidence estimates, 2011-2021

Table 12: Migrant source countries with top 10 highest percentage of cases or crude incidence rate between 2011-2021, Ireland

Country of birth	Mean CIR in Ireland	Median CIR in Ireland	Mean WHO estimate	Ranking in Ireland	WHO TB CIR category	Years with cases	Total cases	% of migrant cases
Eritrea	443.5	609.8	110.7	Top 10 CIR	Very high	7	8	0.5
Botswana	359.7	359.7	336.3	Top 10 CIR	Very high	6	11	0.7
Somalia	284.8	333.3	269.5	Top 10 CIR & N	Very high	10	47	2.9
Malawi	269.6	237.2	200.0	Top 10 CIR	Very high	8	25	1.6
Mongolia	166.2	261.1	428.0	Top 10 CIR	Very high	6	7	0.4
Indonesia	161.4	0.0	325.7	Top 10 CIR	Very high	5	6	0.4
Uganda	150.9	207.5	201.7	Top 10 CIR	Very high	6	8	0.5
Nepal	147.2	124.5	261.6	Top 10 CIR	Very high	8	13	0.8
India	137.4	133.5	244.1	Top 10 CIR & N	Very high	11	317	19.8
Pakistan	126.9	100.8	268.1	Top 10 CIR & N	Very high	11	180	11.2
Philippines	83.3	81.5	555.6	Top 10 N	Very high	11	135	8.4
South Africa	73.1	61.8	858.0	Top 10 N	Very high	11	65	4.0
Nigeria	36.8	30.2	219.0	Top 10 N	Very high	11	67	4.2
Romania	35.2	41.8	73.8	Top 10 N	High	11	111	6.9
Lithuania	12.3	12.0	48.9	Top 10 N	High	11	45	2.8
Poland	4.7	4.3	17.2	Top 10 N	Medium	11	59	3.7
United Kingdom	1.5	1.1	10.3	Top 10 N	Medium	11	47	2.9

5.4.2.1 Interval between arrival and notification

Year of arrival in Ireland was reported for 1,071 (66.7%) of migrant cases. The median interval between arrival in Ireland and notification as a case was 5 years (mean = 7 years) and ranged from 0-59 years with years of arrival spanning from 1954 to 2021. The median interval was shorter between 2019-2021 (3 years). [Table 13](#) summarises the patient characteristics of migrant TB cases according to the interval between arrival in Ireland and notification as a case.

Cases who were notified less than two years after arrival (recently arrived) were significantly younger and had higher proportions of IPARs, PLWHIV, PTB and unemployed. Recently arrived cases had higher proportions resident in congregate residential /care settings but it was not possible to test if this was significant due to the small values in the cells. The proportions of migrants from very high incidence countries decreased in line with length of stay in Ireland (72% to 65%).

A significant difference in the median interval between onset and diagnosis was observed according to the interval between arrival and notification; 1.7 months among recently arrived migrants compared to 2.6 months for migrants resident in Ireland for ≥ 10 years prior to diagnosis, but the test for trend was not significant here ($p = 0.936$). No significant differences in the median intervals between onset and diagnosis were found by IPAR status overall, or by IPAR status stratified by the arrival interval.

Table 13: Migrant TB patient characteristics by interval between arrival and notification; Ireland

Characteristic N (%)	Overall N = 1,071	Interval between arrival in Ireland and TB diagnosis				p- value ^{***}
		0-1 N = 239	2-4 N = 295	5-9 N = 239	10+ N = 298	
Median age (years), (IQR)	34.0 (15.0)	31.0 (12.0)	30.0 (11.0)	34.0 (12.0)	42.0 (16.0)	<0.001
<i>(% missing)</i>	0.2	0	0	0.4	0.3	
Sex						0.33
<i>Female</i>	473 (44%)	104 (44%)	120 (41%)	116 (49%)	133 (45%)	
<i>Male</i>	596 (56%)	135 (56%)	175 (59%)	123 (51%)	163 (55%)	
<i>(% missing)</i>	0.2	0	0	0	0.7	
International Protection Applicant						<0.001
<i>No</i>	799 (86%)	164 (77%)	223 (85%)	174 (89%)	238 (93%)	
<i>Yes</i>	127 (14%)	49 (23%)	38 (15%)	22 (11%)	18 (7.0%)	
<i>(% missing)</i>	14	11	12	18	14	
Months between onset and diagnosis, Median (IQR)	2.0 (3.2)	1.7 (2.2)	2.1 (3.0)	2.0 (3.7)	2.6 (3.7)	0.014
<i>(% missing)</i>	32	33	30	33	31	
Disease site						0.007
<i>Pulmonary</i>	626 (59%)	163 (68%)	167 (57%)	129 (54%)	167 (56%)	
<i>Extrapulmonary</i>	443 (41%)	76 (32%)	127 (43%)	110 (46%)	130 (44%)	
<i>(% missing)</i>	0.2	0	0.3	0	0.3	
Previous TB screening in Ireland						0.006
<i>No</i>	814 (88%)	202 (94%)	226 (89%)	172 (84%)	214 (85%)	
<i>Yes</i>	113 (12%)	13 (6.0%)	29 (11%)	32 (16%)	39 (15%)	
<i>(% missing)</i>	13	10	14	15	15	
Previous TB diagnosis						0.67
<i>No</i>	839 (93%)	192 (92%)	225 (93%)	192 (95%)	230 (92%)	
<i>Yes</i>	65 (7.2%)	16 (7.7%)	17 (7.0%)	11 (5.4%)	21 (8.4%)	
<i>(% missing)</i>	16	13	18	15	16	
Outbreak associated						0.034
<i>Not linked to outbreak</i>	1,026 (96%)	232 (97%)	274 (93%)	232 (97%)	288 (97%)	
<i>Outbreak associated</i>	45 (4.2%)	7 (2.9%)	21 (7.1%)	7 (2.9%)	10 (3.4%)	
<i>(% missing)</i>	0	0	0	0	0	
People living with HIV						0.004
<i>Negative</i>	542 (89%)	103 (80%)	154 (91%)	120 (92%)	165 (90%)	
<i>Positive</i>	69 (11%)	26 (20%)	15 (8.9%)	10 (7.7%)	18 (9.8%)	
<i>(% missing)</i>	43	46	43	46	39	
TB drug resistance						0.59
<i>Sensitive</i>	697 (81%)	158 (81%)	196 (79%)	165 (84%)	178 (81%)	
<i>Resistant</i>	160 (19%)	36 (19%)	52 (21%)	31 (16%)	41 (19%)	
<i>(% missing)</i>	20	19	16	18	27	
M/XDR-TB						0.39
<i>No</i>	826 (96%)	187 (96%)	235 (95%)	191 (97%)	213 (97%)	
<i>Yes</i>	31 (3.6%)	7 (3.6%)	13 (5.2%)	5 (2.6%)	6 (2.7%)	
<i>(% missing)</i>	20	19	16	18	27	

^{***} Kruskal-Wallis rank sum test; Pearson's Chi-squared test. N/A denotes Fisher's exact could not be run due to the small values in certain cells.

Characteristic N (%)	Overall N = 1,071	Interval between arrival in Ireland and TB diagnosis				p- value ^{***}
		0-1 N = 239	2-4 N = 295	5-9 N = 239	10+ N = 298	
Employment status						<0.001
<i>Paid employment</i>	479 (46%)	76 (33%)	136 (47%)	115 (49%)	152 (52%)	
<i>Unemployed</i>	365 (35%)	92 (40%)	89 (31%)	81 (35%)	103 (35%)	
<i>Retired</i>	26 (2.5%)	9 (3.9%)	4 (1.4%)	2 (0.9%)	11 (3.8%)	
<i>Student/Child</i>	147 (14%)	44 (19%)	50 (17%)	32 (14%)	21 (7.2%)	
<i>Other</i>	29 (2.8%)	10 (4.3%)	10 (3.5%)	4 (1.7%)	5 (1.7%)	
<i>(% missing)</i>	2.3	3.3	2.0	2.1	2.0	
Current housing type						<0.001
<i>Private house</i>	952 (92%)	183 (79%)	271 (93%)	218 (94%)	280 (98%)	
<i>Congregate residential / care setting</i>	60 (5.8%)	35 (15%)	15 (5.2%)	8 (3.4%)	2 (0.7%)	
<i>Prison / Homeless</i>	10 (1.0%)	2 (0.9%)	2 (0.7%)	4 (1.7%)	2 (0.7%)	
<i>Other housing</i>	16 (1.5%)	11 (4.8%)	2 (0.7%)	2 (0.9%)	1 (0.4%)	
<i>(% missing)</i>	3.1	3.3	1.7	2.9	4.4	
WHO TB incidence category						0.016
<i>Low</i>	20 (1.9%)	3 (1.3%)	1 (0.3%)	6 (2.5%)	10 (3.4%)	
<i>Medium</i>	110 (10%)	15 (6.3%)	23 (7.9%)	30 (13%)	42 (14%)	
<i>High</i>	184 (17%)	49 (21%)	50 (17%)	34 (14%)	51 (17%)	
<i>Very high</i>	749 (70%)	172 (72%)	217 (75%)	169 (71%)	191 (65%)	
<i>(% missing)</i>	0.7	0	1.4	0	1.3	

5.5 Discussion:

This chapter provides an in-depth analysis of TB patient characteristics in Ireland, including a detailed profile of TB among migrants which is a key population for consideration when striving for TB elimination in Ireland. Differences were observed in the TB patient profile among migrants compared to Irish-born cases, as well as within the migrant subgroups studied. Compared to Irish-born cases, migrant cases were younger, had higher odds of living with HIV, having EPTB, being infected with a drug-resistant strain and residing in a congregate residential setting; with lower odds of being detected through contact tracing and being linked to an outbreak. While a highly diverse range of migrant origin-countries was observed, the majority of migrant cases (69%) originated from very high TB incidence countries. This contrasts with the Irish migrant population denominator, where 14% of migrants originated from high TB incidence countries (Central Statistics Office, 2016b).

Similar to studies in Europe and the United States, EPTB was more common among migrants in this study, with three times higher odds of EPTB compared to Irish-born after adjusting for other factors (Hayward et al., 2021; Ködmön et al., 2016; Peto et al., 2009). Accordingly, migrant cases were almost twice as likely to have a normal CT thorax scan result and a normal chest X-ray result. While currently there is no systematic TB screening programme in Ireland, thoracic TB symptom screening is offered mainly to international protection applicants (IPAs) and new entrant health-care professionals from high TB incidence countries (HSE Health Protection Surveillance Centre, 2010). Results from this study suggest that restricting screening to PTB could miss over 40% of migrant cases and may need to be supplemented by targeting high-risk migrant groups for TB infection screening to support TB elimination in Ireland (Al Abri et al., 2020). This finding supports the development of a new-entrant immigrant LTBI management programme as one of the key actions in Ireland's Tuberculosis Strategy (HSE National Health Protection Office, 2024). Proportions of EPTB increased in tandem with incidence in the origin-country and similar to European studies, were highest among cases originating from South-Asia (Hayward et al., 2021; Luque et al., 2020). In keeping with the lower levels of PTB, migrant cases had lower odds of being associated with an outbreak, which is supported by findings in the literature that migrants tend to contribute less to transmission (Sandgren et al., 2014; Stucki et al., 2016b; Walker et al., 2014).

This study found migrant cases had almost four times higher adjusted odds of living with HIV than Irish-born cases, which is higher than reported by a large-scale European study which found the proportions of PLWHIV among migrant TB cases were twice as high compared to native-born TB cases (Ködmön et al., 2016). Origin-countries with the highest proportions of PLWHIV in this study were mainly from Sub-Saharan Africa (South Africa 58%, Botswana 62%, Malawi 71%) reflecting the co-epidemic of TB-HIV in this region (World Health Organization, 2021b). Despite a strong recommendation to offer HIV testing to all TB cases (World Health Organization, 2024f), only 42% of cases had HIV status reported. Levels of completeness were further reduced for origin-countries with lower HIV prevalence, possibly reflecting a lower likelihood of clinicians offering testing to those populations. Addressing HIV-associated TB through integrated prevention and care remains a key commitment of the WHO End TB strategy (World Health Organization, 2022a).

Higher levels of anti-TB (17% vs 7%) and multi-drug resistance (3.4% vs 0.2%) were found among migrants compared to Irish-born cases, with the level of MDR broadly similar to that previously reported among migrant TB cases in Europe (Ködmön et al., 2016). The majority of MDR-TB cases in this study originated in Eastern Europe (16% Latvia and 14% Lithuania) reflecting background levels reported in European surveillance data for these origin-countries (European Centre for Disease Prevention and Control / World Health Organization, 2025). Although advances in MDR-TB treatment have been made, it remains a significant obstacle to TB elimination, particularly as 80% of MDR-TB cases in this study had a pulmonary component, which was comparable with findings from other international studies (Eimer et al., 2021).

Two key social determinants, housing type and employment status, were significant at univariable level. Migrant cases had an increased odds of living in congregate residential settings compared to Irish-born cases, which is a key risk factor for transmission (Baker et al., 2008; Hayward et al., 2018). Migrant cases were also more likely to be in paid employment than Irish-born cases after adjusting for other covariates, indicating a potential benefit from directly observed treatment (DOT) via video rather than in-person DOT to facilitate continued attendance in workplace and support treatment success (Mangan et al., 2023).

As previously observed by other European studies of TB among migrants, this study observed differences in the top migrant origin-countries when analysed by CIRs rather than patient numbers, with the exception of India, Pakistan and Somalia which were ranked by both metrics (Domaszewska et al., 2025; Vasiliu et al., 2023). Our study aligned with four of the eight most common origin-

countries reported by Vasiliu et al among migrant TB cases (India, Pakistan, Romania and Somalia) and four of the top five countries reported by Domaszewska et al. Both these studies also reported CIRs that diverged from the published WHO estimates, and similar to this study migrants from Eritrea and Somalia had higher CIRs compared to the WHO estimate while migrants from Mongolia, Nepal and Pakistan migrants had lower CIRs. In contrast to these studies, we observed CIRs that were higher than WHO estimates among migrants from Malawi and Botswana. The divergence in CIRs within origin-countries compared to within Ireland, are likely to be influenced by many factors include type of migrant (economic versus IPARs), mode of migration (transit through hostile conditions such as migrant camps) and conditions upon entry to destination country (accessibility of health systems, screening, accommodation quality). Higher CIRs among Eritreans in Ireland could be influenced by the majority also being IPARs (75%) and possibly experiencing both adverse conditions and increased exposures during hazardous migration pathways, combined with an increased case-detection rate due to being offered TB screening voluntary initial health assessments (IHAs) in IPAR services (HSE Social Inclusion, 2023). Conversely, lower rates observed among migrants from India and Mongolia are likely influenced by the fact that migrants from these countries are not routinely offered screening so may have a lower case-detection rate, as well as often being economic migrants who travel under better conditions. In keeping with this, these countries had the lowest proportion of IPAR TB cases among origin-countries with 10 highest CIRs and employment rates of >64% according to Census data (Central Statistics Office, 2016a). A lower prevalence was estimated for visa applicants from India, Pakistan and Nepal in Australia and was thought to reflect the type of migrant applying for residence (Trauer et al., 2021).

The findings that recently arrived cases had higher proportions of IPARs, PTB and PLWHIV are likely influenced by the practice of offering IHAs, that include pulmonary TB symptom screening and HIV testing, to IPARs upon arrival in Ireland (HSE Social Inclusion, 2023). However, the difference in proportions of PTB and PLHW were also observed in a sensitivity analysis of cases that were reported as not being asylum seekers. A study of migrant TB in low TB incidence European destination countries between 2014-2020 also found higher proportions of PTB among recently arrived migrants which was similarly thought to be linked to the use of chest X-ray based screening for IPARs (Jackson et al., 2025).

While it is commonly accepted that the highest risk of TB among migrants occurs in the first few years after arrival in the destination country due to reactivation of remotely acquired infection in the origin-country or via new infection acquired during hazardous conditions along the migration

pathway (Lonnroth et al., 2017; Pareek et al., 2016; Walker et al., 2018), other studies have found that the increased risk persists for several years after arrival and can be influenced by recurring travel to the origin-country (Dale et al., 2020; Langholz Kristensen et al., 2020; Ronald et al., 2017). This study found that over half of cases presented more than five years after arrival in Ireland, indicating a need to ensure continued access to TB diagnosis and care for this population.

5.5.1 Strengths and limitations

This study utilised a programmatic data source of all cases of TB disease notified in Ireland, helping to reduce selection bias in the sample. Cases were reported according to a standardised European Union (EU) patient definition aiding the generalisability of results to other jurisdictions. This study analysed the data for all countries of birth, rather than pre-selected based on highest numbers to provide an alternate view of TB risk among migrants via CIRs. This study is the first to characterise recent migrants in Ireland and includes several key time periods; before and after the global migration peak in 2015/2016 and the early Covid-19 pandemic period, but prior to recent wars in Ukraine and Palestine which are currently influencing the epidemiology of TB through increased asylum seeking.

This study was mostly limited by issues relating to availability of denominator data and poor completeness of the numerator data. Census data may underestimate the true number of migrants resident in Ireland, particularly among undocumented migrants, causing some rates to be overestimated. Conversely, undocumented migrants may be under diagnosed, possibly due to fears of accessing health services, leading to underestimation of rates presented. The 2016 Census of population was used throughout as the 2022 Census was not available for all countries of birth reported among TB cases. It is possible that population changes during the intervening period have reduced the accuracy of CIRs calculated in this study. Irish population data on recently arrived migrants are not available by country of birth so it was not possible to calculate origin-country specific CIRs for this key population of interest. Key variables such as HIV status and social risk factors had low levels of completeness which may have introduced bias within the results.

5.5.2 Conclusions & recommendations:

While screening for PTB remains a key tool in reducing the infectious reservoir, a heightened awareness of EPTB within health systems is needed and future TBI screening programmes will also need to rule out EPTB prior to offering TBI treatment. The pace of TB decline among migrants is slower than among Irish-born and has plateaued in the final years of this study period, making TB

elimination targets more difficult to achieve. Elevated CIRs observed among migrant subpopulations indicate that factors in addition to incidence in the origin-country need to be considered when evaluating the risk of TB in migrants. Denominator data by country of birth for recently arrived migrants is needed to understand the dynamics and composition of migration in Ireland and how it may be linked to the evolving epidemiology of infectious diseases such as TB. More complete data are needed for key indicators such as HIV status and year of arrival in the country. Differences in the epidemiology of migrant TB cases reported by this study can be used to inform and enhance future service provision.

5.6 Chapter conclusion

Chapter 5 describes the study population in detail, comparing and contrasting patient characteristics and key epidemiological indicators between migrant and Irish-born TB cases. This chapter also details the results of the trend analysis investigating TB CIRs among migrant TB cases and Irish-born TB cases. Finally, a detailed analyses of migrant subpopulations are also provided. These findings also inform the statistical models described in chapter seven. The next chapter presents an investigation of the impact of universal TB vaccination cessation on the epidemiology of paediatric TB in Ireland.

6 Chapter 6: The impact of universal TB vaccination cessation on the epidemiology of paediatric TB in Ireland

6.1 Chapter outline

This is the third results chapter which focuses on a TB prevention intervention, Bacillus Calmette-Guérin (BCG) vaccination and fulfils the third study objective *“To explore the impact of discontinuing a national universal BCG vaccination programme on the epidemiology of paediatric TB cases”*.

6.2 Introduction

Between 1949-2015, Ireland had a policy of universal BCG infant vaccination, with national uptake estimated at 87% in 2014 (HSE Health Protection Surveillance Centre, 2015). However, there was regional variation in its implementation, with some counties in the south and west of Ireland implementing universal vaccination of 12 year olds, while one district implemented a risk based selective vaccination programme between 1972-2008 (Health Information & Quality Authority, 2015). Ireland fully met the International Union Against Tuberculosis and Lung Disease (IUATLD) quantitative criteria (International Union Against Tuberculosis and Lung Disease, 1994) to discontinue BCG in 2011 (Health Information & Quality Authority, 2015). Irish age-specific incidence rates (ASIRs) are lowest in the 0–14 year old age group and have declined from 2.0 per 100,000 population in 2010, to 0.1 in 2021 (HSE Health Protection Surveillance Centre, 2023c, 2025).

Despite this, Ireland remained an outlier among other low TB incidence European countries in retaining a universal vaccination programme (*The BCG World Atlas, 3rd Edition*, 2023). Although recommendations to move to a selective BCG vaccination programme were made as early as 2013, universal BCG vaccination was only discontinued in Ireland in April 2015 due to lack of vaccine supply. A BCG vaccination strategy which recommended a risk-based selective programme was published in 2022, but the vaccination programme is not yet operational at the time of writing (National Immunisation Advisory Committee, 2022).

As the effect of universal BCG vaccination discontinuation has not been retrospectively assessed, this chapter aims to explore the impact of discontinuing a national universal BCG vaccination programme on the epidemiology of paediatric TB cases aged 0–6 years of age, by comparing TB cases notified among 0–6 year olds born during a period of universal vaccination, with TB cases notified among 0–6 year olds born during a period when no vaccination occurred.

6.3 Methods

6.3.1 Study design and population

This objective performed a cross-sectional secondary-data analysis of all TB disease notifications aged 0-6 years old reported to the Irish National TB Surveillance System and hosted on the CIDR system between 2011 and 2021 (HSE Health Protection Surveillance Centre, 2024). TB disease was defined as per the European Union (EU) Commission surveillance case definition (European Commission, 2018).

This objective compared two birth cohorts; the first cohort consisted of TB cases born during a period (January 2005 - March 2015) where the universal BCG vaccination policy was operational, while the second cohort of cases were born during a period (April 2015 - December 2021) where although universal BCG vaccination was still the official policy, no vaccinations were administered in Ireland due to procurement issues.

6.3.2 Statistical analyses

Descriptive analysis of cases by person, place and time characteristics was performed. Differences between categorical variables for each birth cohort were tested using Pearson's Chi-Square Test and Fisher's Exact Test.

TB crude incidence rates (CIRs) and age-specific incidence rates (ASIRs) for the 0–6 year old age group were calculated using the most recent census population denominators available at the time. ASIRs were also stratified separately for two categories, by the geographical area of patient residence (using the health administrative region “HSE Area”^{§§§}) and by patient birth place (foreign-born or Irish-born, using the patient's country of birth) (Central Statistics Office, 2016c, 2016b). ASIRs among 0-6 year olds born during a period of universal BCG vaccination (UV) were compared with 0-6 year olds born after BCG vaccination ceased (NV). Temporal trends in CIRs and ASIRs were investigated using incidence rate ratios (IRRs) produced by Poisson and negative binomial regression. As overdispersion was detected within some of the time series examined, results from the negative binomial regressions are reported in this chapter.

^{§§§} There were eight Regional Departments of Public Health, aligned to the eight HSE Areas, during this study, which were later re-configured into the current model of six Regional Health Authorities during Slainte Care reforms.

6.4 Results

A total of 46 TB cases aged 0-6 years old were reported to the national TB surveillance system during the study period of 2011-2021. Twenty-seven cases were born during the period of universal BCG vaccination and 19 were born during the period after BCG vaccination ceased. No cases were notified during 2021 for either birth cohort ([Figure 22](#)).

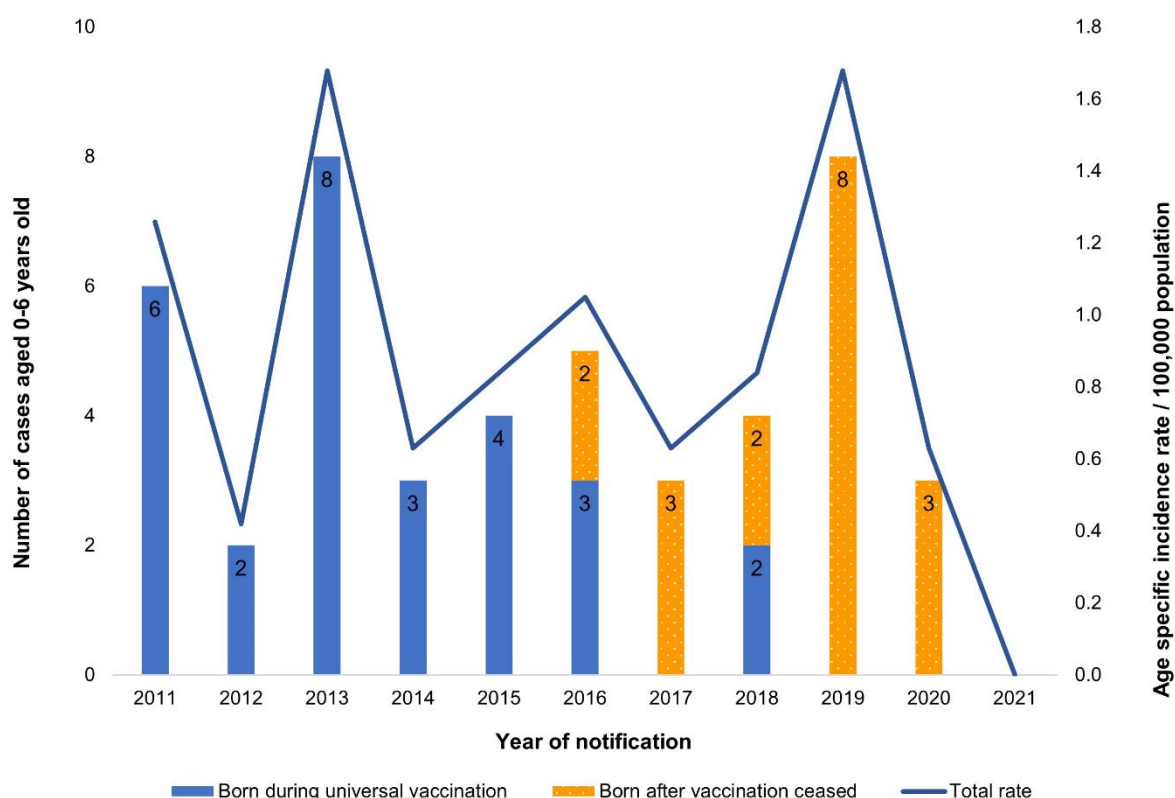


Figure 22: Annual number of TB disease cases and age-specific incidence rate per 100,000 population by birth cohort

Overall, the epidemiology of cases remained similar among those born during universal BCG vaccination and those born after BCG vaccination ceased. Cases born after BCG vaccination ceased were significantly younger than those born during universal BCG vaccination. No TB meningitis cases were reported in 0–6 year olds born during universal vaccination, compared with one TB meningitis case reported in an unvaccinated infant born after BCG vaccination ceased. [Table 14](#) compares key epidemiological characteristics of TB cases born during universal BCG vaccination, with those born after BCG vaccination ceased.

Table 14: Patient characteristics of paediatric TB cases aged 0-6 years old by birth cohort

Characteristic	Overall N = 46	No vaccination N = 19	Universal vaccination N = 27	p-value****
Median age (mean)	2.00 (2.22)	1.00 (1.32)	2.00 (2.85)	0.018
Sex				0.989
<i>Female</i>	29 (63.0%)	12 (63.2%)	17 (63.0%)	
<i>Male</i>	17 (37.0%)	7 (36.8%)	10 (37.0%)	
Migrant status				>0.999
<i>Migrant</i>	8 (17.8%)	3 (16.7%)	5 (18.5%)	
<i>Irish-born</i>	37 (82.2%)	15 (83.3%)	22 (81.5%)	
<i>(Missing)</i>	1	1	0	
Disease site				>0.999
<i>Pulmonary</i>	34 (75.6%)	14 (77.8%)	20 (74.1%)	
<i>Extrapulmonary</i>	11 (24.4%)	4 (22.2%)	7 (25.9%)	
<i>(Missing)</i>	1	1	0	
Culture result				0.405
<i>Positive</i>	16 (69.6%)	8 (80.0%)	8 (61.5%)	
<i>Negative</i>	7 (30.4%)	2 (20.0%)	5 (38.5%)	
<i>(Missing)</i>	23	9	14	
TB drug resistance				0.077
<i>Sensitive</i>	12 (80.0%)	8 (100.0%)	4 (57.1%)	
<i>Resistant</i>	3 (20.0%)	0 (0.0%)	3 (42.9%)	
<i>(Missing)</i>	31	11	20	
Vaccinated with BCG				0.012
<i>Vaccinated</i>	21 (58.3%)	4 (30.8%)	17 (73.9%)	
<i>Unvaccinated</i>	15 (41.7%)	9 (69.2%)	6 (26.1%)	
<i>(Missing)</i>	10	6	4	
Case found by				0.963
<i>Presenting as case</i>	17 (40.5%)	6 (40.0%)	11 (40.7%)	
<i>Contact tracing</i>	25 (59.5%)	9 (60.0%)	16 (59.3%)	
<i>(Missing)</i>	4	4	0	
Case type				0.074
<i>Index case</i>	10 (25.6%)	2 (11.1%)	8 (38.1%)	
<i>Contact</i>	29 (74.4%)	16 (88.9%)	13 (61.9%)	
<i>(Missing)</i>	7	1	6	
Outbreak association				0.655
<i>Outbreak associated</i>	20 (43.5%)	9 (47.4%)	11 (40.7%)	
<i>Not linked to outbreak</i>	26 (56.5%)	10 (52.6%)	16 (59.3%)	

**** ² Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

6.4.1 Country of birth and ethnicity:

Country of birth and ethnicity were reported for 45 cases, eight were born outside Ireland and 37 were born in Ireland. Year of arrival was reported for 4 migrant cases, all which had arrived <2 years before diagnosis. [Figure 23](#) shows the annual number of cases and ASIR by country of birth. A small number of cases were reported in Irish Travellers during universal vaccination, and none were reported after vaccination ceased.

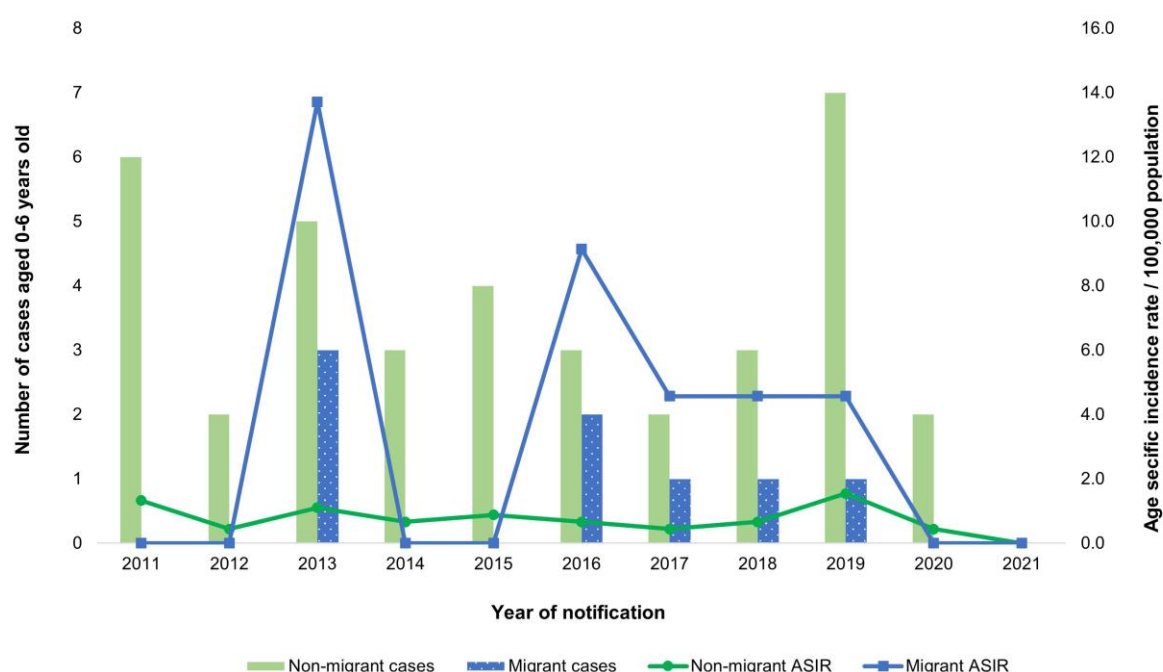


Figure 23: Annual number of TB disease cases and age-specific incidence rate per 100,000 population by country of birth

6.4.2 Laboratory confirmation and drug resistance:

No cases were sputum-smear positive. Culture results were available for 23 cases (50.0%) during the study period. The proportion of cases with culture confirmation increased from 61.5% (n=8) of cases born during universal BCG vaccination to 80% (n=8) after BCG vaccination ceased. Two cases born during universal BCG vaccination reported isoniazid mono-resistance and one pyrazinamide resistance was detected in a case infected with *M. bovis*. No drug resistance was detected in any of the culture positive cases born after vaccination ceased.

6.4.3 Case finding and case type:

During the study period, data on case finding method was reported for 42 cases (91.3%). Case type assigned at the end of public health investigations was available for 39 cases (84.8%) during the study period. A higher proportion of cases born after BCG vaccination ceased were declared contacts of cases (88.9% NV compared to 61.9% UV), but this difference was not significant ($p=0.074$).

6.4.4 Outbreak association:

Of the 46 cases aged 0-6 years, 20 (43.5%) were reported as being associated with outbreaks. These 20 cases were linked to 16 outbreaks reported between 2011 and 2020. A higher proportion of cases born after BCG vaccination ceased were reported as linked to TB outbreaks (47.4% NV compared to 40.7% UV), but this difference was not significant ($p=0.7$).

Data were available for 15 of these outbreaks on the national outbreak surveillance system. Ten of these outbreaks had cases linked who were born during universal BCG vaccination, while five outbreaks had cases linked who were born after BCG vaccination ceased. No outbreak had cases aged 0-6 years from both birth cohorts. Five out of eight regional Departments of Public Health^{††††} reported outbreaks, with eight of the outbreaks reported by the Department of Public Health in the Southern region. Outbreaks were most commonly reported as family outbreaks ($n=8$ UV, $n=3$ NV) and two general outbreaks also occurred in each birth cohort. The most common outbreak locations in both birth cohorts were private houses ($n=4$ UV, $n=2$ NV) and extended families ($n=4$ UV, $n=2$ NV). Two outbreaks were also reported in residential institutions ($n=1$ UV and $n=1$ NV) and one outbreak was reported in a community setting (UV).

6.4.5 Geographical distribution:

Cases were reported by seven of the eight regional Department of Public Health in Ireland. Regional ASIRs increased in two eastern regions after vaccination ceased, while they declined in the remaining six regions ([Figure 24](#)). No significant differences in CIRs within regions before and after vaccination cessation were detected. The highest ASIRs in either birth cohort were observed in the southern region. Rates in the southern region were significantly higher than the national ASIR during universal vaccination but there was no significant difference after vaccination ceased.

^{††††} Data were reported by eight regional Departments of Public, formerly known as HSE Areas. These structures were later reconfigured into six Regional Health Authorities during Sláinte Care reforms.

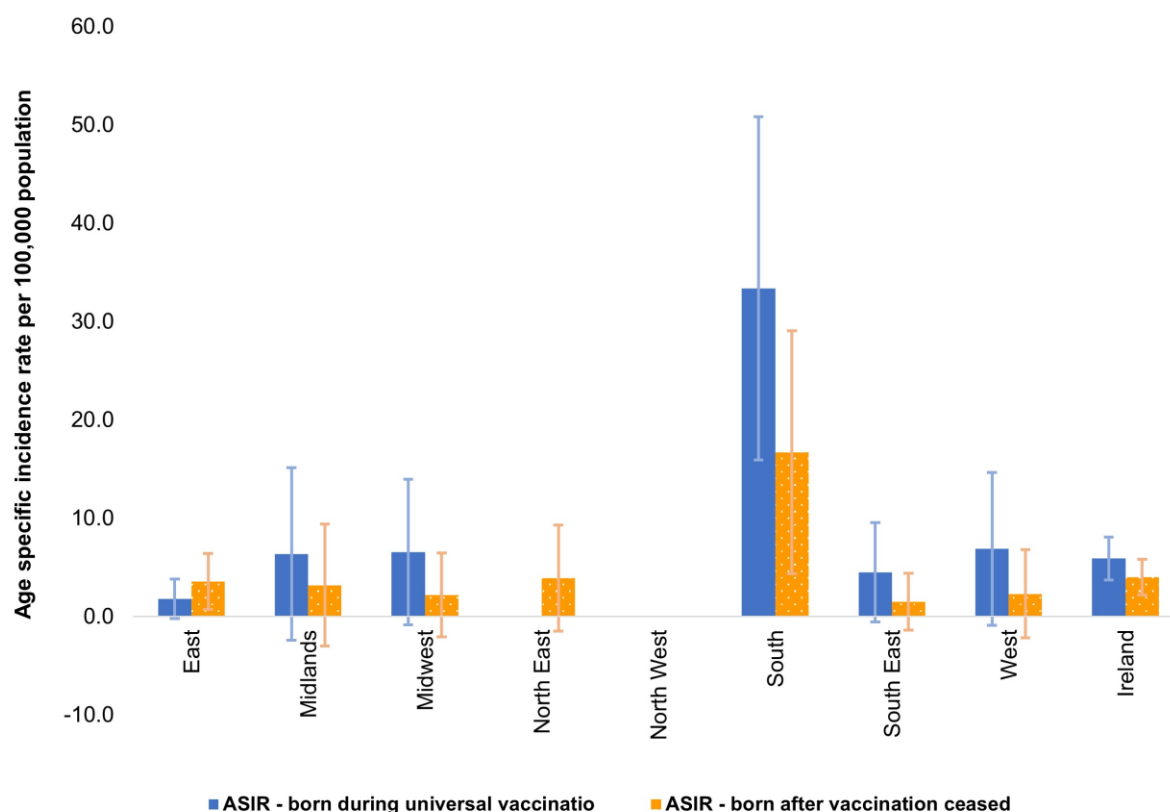


Figure 24: Annual age-specific incidence rates per 100,000 population by birth cohort and geographical area of residence

6.4.6 Temporal trends:

The ASIR for 0–6 year olds ranged from 0.0 in 2021 to 1.7 in 2013 and 2019 ([Figure 21](#)). No significant temporal trend was detected in the overall 0–6 year old ASIR by notification year during 2011-2021 (IRR:0.95; 0.86-1.1). However, the temporal trend for cases born during universal vaccination was significantly declining (0.74; CIR: 0.62-0.89) while cases born after vaccination ceased had a non-significant increase (1.2; CIR: 0.73-1.86). When cases born during universal vaccination were stratified by country of birth (Irish-born versus foreign-born) a significantly declining temporal trend was detected among cases born in Ireland (IRR:0.73; 0.62-0.86), but no significant trend was detected in the cases born outside Ireland (IRR:0.83; 0.53-1.3). No significant trend was detected in cases born after vaccination ceased in either cases born in Ireland (IRR:1.0; 0.60-1.65) or those born outside Ireland (IRR:0.64; 0.29-1.40).

6.5 Discussion

This objective conducted a retrospective analysis of a cohort of 0–6 year old children with TB born between 2007 and 2021 to compare epidemiological trends pre and post cessation of a universal BCG vaccination programme in Ireland. Despite the complete cessation of the BCG vaccination programme in Ireland in 2015 due to the lack of vaccine supply, the annual trends in paediatric TB have remained stable from 2011 to 2021. A consistent pattern was observed at both national and regional levels. ASIRs have reflected typical patterns with no major increase observed during this study in the 0–6 year age group who were most likely to be directly affected by cessation of BCG vaccination.

Although no increase was observed in the CIRs or the ASIRs since vaccination ceased, the declining trend observed in the ASIR among cases who were born during the period of universal vaccination, is no longer evident in cases born after vaccination ceased, in either Irish-born or foreign-born cases. This may be an early-stage indicator of the expected increase predicted by the Health Technology Assessment of a selective BCG vaccination programme but will need further long-term monitoring to verify. Modelling studies conducted in France suggest that increases associated from moving from universal to selective programmes may take up to 15 years to emerge (Guthmann et al., 2011; Lévy-Bruhl, 2005). Increases have been seen in other European countries after moving from a universal to a selective vaccination programme, however many of these studies occurred in times with a different epidemiological profile (Romanus, 1983; Romanus et al., 1992; Trnka et al., 1993). Studies evaluating effects of moving from universal to selective BCG programmes in more recent times, such as Finland, France, Norway and the United Kingdom, detected less impact on the epidemiology of paediatric TB and paediatric TB meningitis or miliary TB (Abbott et al., 2019; Guthmann et al., 2011; Kontturi et al., 2021; Nøkleby & Arnesen, 2018; Van Bui et al., 2015). However, it should be noted that these studies evaluated changing from universal to selective vaccination, rather than a move from universal to no vaccination as was the case in this study.

Although the proportion of cases born outside Ireland remained stable during universal vaccination compared to no vaccination, the proportion of 2nd generation migrants increased from 33% of cases (n=4) born during universal vaccination to 67% (n=8) born during no vaccination (HSE Health Protection Surveillance Centre, 2023a). Similar increases among second generation migrants were also observed in Finland whereas the UK saw an increase in first generation migrants (Abbott et al., 2019; Kontturi et al., 2021).

The current selective BCG strategy for Ireland, which has yet to be implemented, recommends vaccination of children under five years born in a high TB burden country or who have a household contact born in a high TB burden country (National Immunisation Advisory Committee, 2022; World Health Organization, 2021b). Of the 19 cases born after vaccination ceased, at least eight would have been eligible to receive BCG under a selective vaccination programme, based on having a parent from a high TB incidence country or being born in a high TB incidence country (National Immunisation Advisory Committee, 2022). Although the HIQA HTA considered Irish Traveller children as being high risk for TB, they are not recommended to receive BCG vaccination under the current selective strategy, unless meeting additional criteria. No cases among Irish Travellers were reported in those born after vaccination ceased.

While no increase in paediatric TB meningitis was observed during this study period, the sole case of meningitis reported by this study occurred in the unvaccinated birth cohort. Similarly in France, no increase in TB meningitis was observed four years after moving from a universal to selective vaccination programme (Van Bui et al., 2015).

As children are more likely to progress from TB infection (TBI) to TB disease and do so much faster than adolescents and adults, they act as a marker for recent TB transmission in a community (Carvalho et al., 2018; Marais et al., 2004). Detection of a paediatric case is usually an indicator of an infectious case among the child's contacts with one outbreak study reporting children became infected after just 15-20 minutes contact with an infectious case (Luzzati et al., 2017). In keeping with this, the majority of cases (58% overall) in either Irish birth cohort were found through active case finding (via contact tracing) rather than passive case finding (presenting as a case). This is slightly lower than observed in the Netherlands where 66% of 0–4 year olds were found through contact tracing (Erkens et al., 2014). Temporal peaks in the 0–6 year old age group in Ireland were also largely driven by outbreaks, mainly associated with household or extended family settings. While moving to selective BCG vaccination in Norway did not result in an increase in TB cases overall, an increase was observed in those aged 10–39 year olds which was largely due to outbreak in educational facility involving mostly vaccinated individuals (Nøkleby & Arnesen, 2018).

Paediatric cases are less likely than adult cases to be infectious due to the paucibacillary nature of their specimens and typically non-cavitary nature of their disease (Carvalho et al., 2018). Correspondingly, none of the cases in this study were sputum smear positive in either birth cohort,

despite the main disease site being pulmonary disease for the majority of cases, reducing the opportunities for onward transmission.

Despite having a universal vaccination programme operational in the Southern region for both birth cohorts during this study period, the highest ASIRs were observed in this region for both birth cohorts. The majority of outbreaks with cases ages 0-6 years old were also reported from the southern region. This Southern region also had annual CIRs above the national CIR during in nine of the 11 years within this study period (HSE Health Protection Surveillance Centre, 2023a). It is possible that some legacy effect persists from the earlier time periods when universal vaccination was not in place in this region (Sweeney et al., 2019).

6.5.1 Strengths and limitations:

To date, this is the first study in Ireland to examine the direct impact of universal BCG vaccination cessation through focusing on the most likely affected cohort of paediatric TB cases, within a short time frame post-cessation. Access to a well validated population level national surveillance dataset minimized selection and information biases both during design and analysis phase of the study. Use of the EU surveillance case definition enhances the comparability of these results internationally. The inclusion of possible and probable TB cases increased the sensitivity of this study, given difficulties with diagnosis and bacteriological confirmation of paediatric cases (Carvalho et al., 2018; Perez-Velez & Marais, 2012).

Despite these strengths, certain limitations were identified. Information on socioeconomic factors was not available for this age group. The use of the most available population denominator was for 2016, and this may have overestimated rates for the latter years due to potential population growth since 2016.

While the use of a population level surveillance dataset can reduce selection bias, surveillance data could be prone to under-reporting of paediatric TB cases due to difficulties diagnosing TB in children or a potential lack of awareness of paediatric TB within the context of a low TB incidence country. However, the issue of potential under notification applies to both time periods compared so should not overly bias the results. It should be noted that previous cohort studies investigating the risk of infection in unvaccinated children following cessation of universal neonatal BCG vaccination reported that the majority of cases detected in this population were in asymptomatic children who would not have been detected through existing passive case finding methods (Trnka et al., 1993).

Finally, this study may be further limited by the likely but as yet undefined effects of the Covid-19 pandemic on the epidemiology of TB in this age group. Covid-19 restrictions that were in effect during the final two years of the study period likely reduced opportunities for transmission during that period, between both adult to adult, contributing to a reduction in the reservoir of infectious adult cases in the population, and from adults to children. Paradoxically, the converse may also be true due to delayed presentation to services by infectious adult cases, resulting in an increase in transmission. Currently available evidence suggests that these reduced opportunities for transmission were outweighed by service disruption and the resulting increase in untreated infectious cases (Kessel et al., 2023). Furthermore, emerging evidence that Severe Acute Respiratory Syndrome Coronavirus 2 (SARS- CoV-2) infection may increase the risk of TB infection and subsequent progression from TB infection to disease, through suppression of cell mediated immunity, should also be considered when interpreting the observed interruption to the previously declining temporal trend (Shariq et al., 2022).

6.5.2 Conclusions and recommendations

Universal BCG vaccination cessation has not yet directly impacted on new TB cases among 0–6 year olds. However, interruption of the previously declining temporal trend in this age group during a period of universal vaccination may be an early warning of a future increase. This finding emphasises the need for timely and complete enhanced surveillance among paediatric TB cases to monitor for the emergence of any increasing trends or emergent risk groups in this mainly unvaccinated population and to evaluate the longer-term effects of the change in vaccination policy. Robust systems for the identification of, and service delivery to, high-risk populations being targeted by the future selective vaccination programme are needed to ensure sufficient vaccination uptake and ensure a policy of selective vaccination does not result in a practice of no vaccination. Monitoring and evaluation of the future selective vaccination programme will also require robust data collection on the demographic and risk profiles of children vaccinated, including membership of underserved populations, such as minority ethnic groups.

6.6 Chapter conclusion:

Chapter 6 is the third results chapter which explored the impact of cessation of a TB prevention intervention, universal Bacillus Calmette-Guérin (BCG) vaccination. The finding that a previously declining trend has been interrupted since BCG vaccination cessation is of critical concern in the face of continued international migration from high TB incidence countries. Children in the selective vaccination target populations, which are mainly pertaining to links to high TB incidence countries,

are currently not able to avail of the recommended BCG vaccination and remain at risk of TB. The next and final results chapter addresses a TB control intervention and one of the most important indicators of a TB control programme's performance, treatment outcomes.

7 Chapter 7: Factors affecting treatment success of tuberculosis cases in Ireland

7.1 Chapter outline

This fourth and final results chapter addresses a TB control intervention and one of the most important indicators of a TB control programme's performance, treatment outcomes. This chapter aimed to identify factors associated with successful and unsuccessful treatment outcomes among TB cases in Ireland, and whether they differed between migrant and Irish-born cases.

[Figure 25](#) outlines how the results will be sequenced within this chapter. As high levels of missing data were present in the outcome (treatment success), the distributions of missing data are examined in sections 7.4.1 – 7.4.3 to assist with interpretation of the model results. Sections 7.4.4 - 7.4.6 provide tabulations of the sample with known outcomes alongside the crude odds ratios (cORs), as well as the results of the final model on the complete case samples.

The findings presented in this chapter can inform the development of targeted interventions to support TB cases to achieve a successful treatment outcome and hence support TB elimination goals.

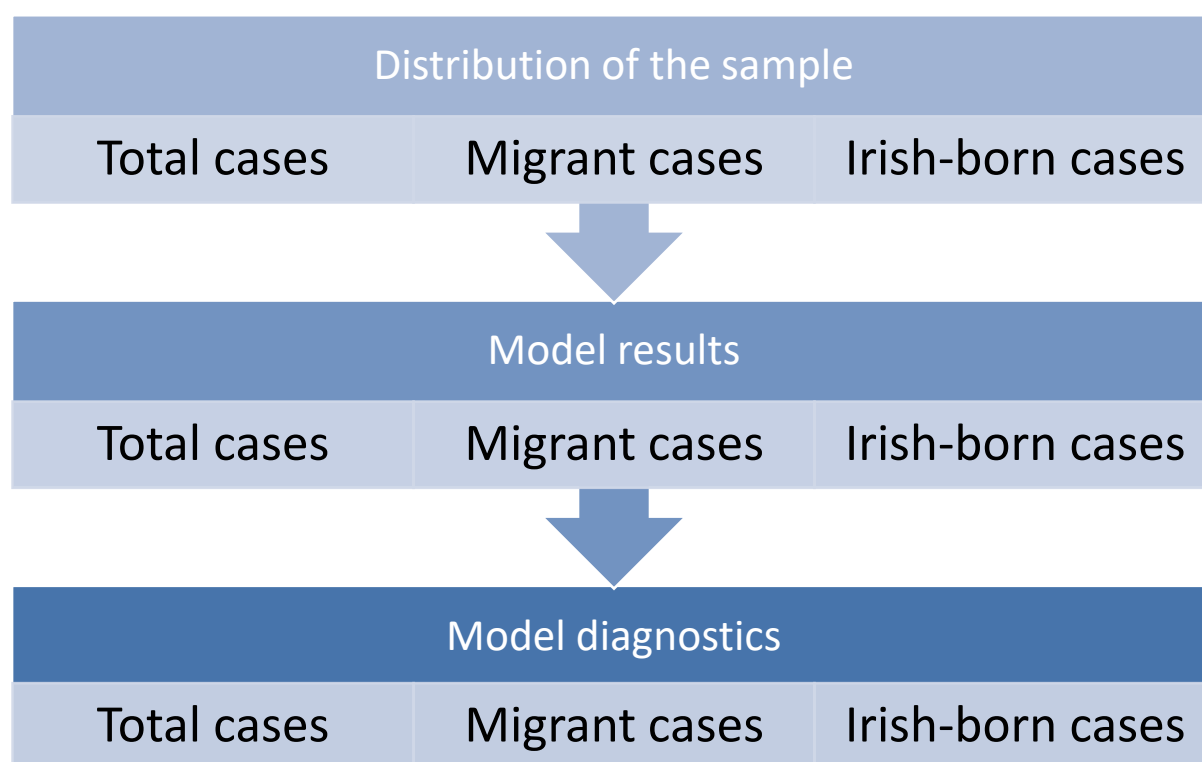


Figure 25: Visual representation of Chapter 7 results structure

7.2 Introduction

Over 50% of untreated TB disease cases will die (Hermans et al., 2015; Tiemersma et al., 2011). However, successfully treating TB is not only beneficial at the individual patient level but it also reduces the infectious reservoir at the population level. For this reason, treatment success is a key element of global TB elimination plans (World Health Organization, 2022a). In keeping with this, the World Health Organisation (WHO) sets treatment success targets of >90% (World Health Organization, 2022a) with latest data showing that 88% of cases globally were successfully treated in 2021 (World Health Organization, 2024b). However, the European region had the lowest rate of treatment success at 68%. Treatment success rates are low in many low-incidence countries, with varying reasons including high proportions of cases in older age groups, high prevalence of comorbidities, advanced disease progression due to poor access to health care and migrants transferring between jurisdictions during treatment (Karo et al., 2015, 2016, 2019).

Ireland has failed to meet the WHO treatment success targets and has one of the lowest success rates within the EU/EEA (European Centre for Disease Prevention and Control / World Health Organization, 2025). According to the latest published reports from the HPSC, treatment success rates remain below 70% since 2011 and have fallen below 50% since 2019 (HSE Health Protection Surveillance Centre, 2025).

In Ireland, over half of TB cases are diagnosed among migrants with a CIR over 10 times higher than among Irish-born (HSE Health Protection Surveillance Centre, 2025). With this epidemiological context, understanding whether predictors associated with treatment success differ between migrant and Irish-born populations is required in order to improve the poor rates of treatment success observed in Ireland.

7.3 Methods

7.3.1 Study design and population

A cross-sectional secondary-data analysis of all TB disease notifications reported to the Irish National TB Surveillance System and notified to the CIDR system between 2011 and 2021 was conducted (HSE Health Protection Surveillance Centre, 2024).

7.3.2 Definitions

The EU Commission TB surveillance [case definition](#) for TB disease was used and all case classifications were included (European Commission, 2018). No restrictions on clinical presentations, drug sensitivity profile or previous history of TB disease were applied.

As the numbers of MDR and XDR (as defined in [Chapter 3](#)) were low in this study, they are mainly presented as a combined category of M/XDR-TB.

The WHO definition of treatment success was used, where the case successfully completed treatment without bacteriological or clinical evidence of treatment failure. Treatment outcomes are recorded at three time periods depending on the duration of their treatment linked to the resistance profiles of the infecting *M. tuberculosis* complex strain. An overall treatment success variable was generated from the combined information in the three outcome variables: treatment success at 12 months for cases on a standard regimens, treatment success for cases on MDR-TB regimens and treatment outcome at 36 months for cases on XDR-TB regimens. Cases with treatment outcome reported as “Died” and who were detected through post-mortem diagnosis and thus had no opportunity to start treatment, were excluded from the analyses.

7.3.3 Missing data

Complete case analysis was used to handle missing data within the sample. The effect of excluding cases with missing data on the representativeness of the sample was assessed in several ways. The distribution of selected independent variables (patient characteristics) stratified by the dependent variable (treatment success) was compared between the full sample (n=3,364) versus the sample with treatment outcomes reported (n=2,121), and between the sample with treatment outcome reported and those without outcome reported (n=1,243). Predictors of missing outcomes were also explored with a multivariable logistic regression model comparing cases with outcomes reported to

those without reported outcomes for independent variables with $\leq 5\%$ missing data; age in years, sex, migrant status, disease site and geographical area of residence.

The distribution of selected independent variables was also compared between the sample of total cases with treatment outcomes reported ($n=2,121$) and the sample with complete case data for all independent variables of interest to be used in the multivariable logistic regression model ($n=1,069$). Distributions were also compared between the complete case sample ($n=1,069$) and those excluded from the complete case sample due to missing data ($n=1,014$).

Variables with missing data for $\geq 25\%$ of cases within the sample with outcomes reported were excluded from multivariable logistic regression models but were examined in the univariable logistic regression analysis of the samples with known treatment outcomes (Tables [18](#), [20](#), [22](#)). Patterns of missing data were assessed visually and the assumption that data were missing completely at random was investigated with Little's test (Little, 1988).

7.3.4 Statistical analyses

Differences between categorical independent variables for binary dependent variables were tested using Pearson's Chi-Square Test or Fisher's Exact Test for differences in proportions or Chi-Square Test for trend in proportions. Associations between numerical independent variables and binary dependent variables were tested using Kruskal Wallis or Wilcoxon rank sum tests. Temporal trends in the proportions of cases successfully treated were investigated using incidence rate ratios (IRRs) estimated by Poisson and negative binomial regressions. As overdispersion was detected within this time series, results from the negative binomial regressions are reported in this chapter.

Sixteen candidate independent variables were selected based on clinical relevance, literature review and aligned with the NICE Conceptual Framework (National Institute for Health and Care Excellence, 2012). Of these, 10 independent variables had a completeness rate of $\geq 75\%$ and were selected for inclusion in a multivariable logistic regression models comparing factors associated with treatment success. These factors were investigated among three complete case samples: all TB cases, TB cases among migrants, and TB cases among Irish-born. Migrant status was included as an eleventh independent variable among the total TB cases sample. All three complete case samples met the criteria of >50 events (successfully treated cases) per independent variable included (Steyerberg, 2019).

Models were generated using two methods in parallel, manual backwards stepwise elimination and an automated backwards elimination algorithm method using the stepAIC function in the {MASS} R package. For the manual method, variables with the highest Wald p-value and lowest Likelihood Ratio (LR) test statistic (generated by the Anova function in {car} R package) were removed one at a time through backwards stepwise elimination until all remaining variables had a Wald p-value of <0.05 . Crude odds ratios (cORs) estimated by univariable logistic regression and adjusted odds ratios (aORs) estimated by multivariable logistic regression are presented.

Model assumptions were visually assessed using the check_model function of the {performance} R package. Residual diagnostics, influential observations and collinearity were reviewed. Independent variables with Variable Inflation Factor (VIF) were removed if the VIF was >9.0 .

Apparent model performance was assessed and compared between models using the model_performance function of the {performance} R package (Lüdtke et al., 2021). Performance indices reviewed included the Akaike Information Criterion (AIC), Akaike Information Criterion corrected for small sample size (AICc) and AICc weight. Apparent performance of models was further evaluated by calculating the Area Under the Receiver Operating Characteristic curve (AUROC) to measure discrimination. Accuracy of model predictions were assessed by examining calibration plots alongside the corresponding Brier scores and Spiegelhalter's Z-scores. Model predictive accuracy was examined using Percentage of Correct Predictions (PCP) where 0.7 were considered as good accuracy. Model fit was assessed using Hosmer and Lemeshow's test from the {glmtoolbox} R package.

Final models were then selected based on apparent performance indicators and subject-matter knowledge. Variables retained in each of the final models were compared to the rankings generated by the Random Forest variable importance plot for candidate independent variables investigated in the full model.

7.4 Results

7.4.1 Distribution of the sample for total cases

Of the 3,364 cases in the full sample, treatment outcome was reported for 2,121 (63%) cases. The proportion of cases with treatment outcome reported remained relatively stable between 2011-2017 (range: 71%-82%). The proportion of cases with outcome known then decreased in 2018 (60%), followed by a further sharp decline in outcome reporting between 2019-2021 (range: 18%-29%) as shown in [Figure 26 a](#). Overall, this represented a significantly declining trend with a 12% decrease for each increase in notification year during the study period (IRR: 0.88, CI: 0.83 to 0.94). Where outcome was reported, a significantly declining trend was also detected in the proportions of cases successfully treated for each increase in year of notification (IRR: 0.87, CI: 0.82 to 0.93). The annual treatment success rates were >80% for most years but decreased to 69% in 2020 and 74% in 2021 ([Figure 26 b](#)). Thirty-six cases were excluded from the treatment success analysis as they were diagnosed post-mortem and therefore had no opportunity to commence treatment.

[Table 15](#) summarises the patient characteristics for the full sample of total cases, stratified by treatment outcome availability and inclusion in complete case sample, and highlights where differences in patient characteristics were statistically significant.

In brief, patient characteristics of cases with outcome data reported were broadly similar to the patient characteristics observed within the full sample of total cases, but differed slightly for migrant status, geographical area of residence and outbreak association. Compared to the full sample, cases with outcomes reported were more often Irish-born (54% vs 50%), detected through contact tracing (8% vs 7%) and outbreak associated (12% vs 10%). The proportion of cases with outcomes reported also differed according to the geographical area of residence for all areas except the North East region. The same differences were also present between the sample with outcomes reported and those without outcomes reported and were statistically significant. In addition, statistically significant differences were observed between the sample of cases with outcomes reported compared to those without outcomes for patient type and employment status. Compared to cases with missing outcomes, cases with outcomes reported had lower proportions of hospital out-patients (31% vs 36%) and people in paid-employment (35% vs 41%) and a higher proportion of retired cases (17% vs 13%).

The strongest predictor of missing outcomes identified by a multivariable logistic regression model comparing cases with outcomes reported to those without reported outcomes, was geographical area of residence ($p < 0.01$), followed by being a migrant (aOR: 0.74; CI: 0.62-0.87). Compared to the reference category of residence in the East, all other geographical areas except the West (aOR: 0.93; CI: 0.70-1.24) had significantly higher odds of reporting treatment outcome. Being identified as a case through contact tracing was associated with higher odds of having treatment outcome reported (aOR: 1.64; CI: 1.2-2.4).

Of the 2,121 cases with outcome reported, 1,069 cases had complete information for the dependent variable (treatment success) plus the 10 independent variables selected for inclusion in the full model; age in years, sex, migrant status, employment status, housing type, disease site, previous history of TB disease, patient type, outbreak association and TB drug resistance. With the exception of geographical region of residence, site of disease and patient type, the distribution of patient characteristics within the complete case sample ($n=1,069$) was broadly similar to that of the full sample ($n=3,364$) ([Table 15](#)). Statistically significant differences were found for five candidate independent variables of interest between the complete case sample and the cases excluded due to missing data ($n=1,015$). The largest absolute differences between proportions of cases included in the complete case sample and excluded cases were observed for patient type and disease site. Compared to excluded cases, cases in the complete case sample had higher proportions of PTB (75.7% vs 60.5%) and a higher proportion of in-patients (64.5% vs 52.6%). No significant differences were found for the outcome (treatment success) or migrant status, age, sex, current housing type and resistance to anti-TB drugs.

Performing Little's test on the full sample restricted to the nine independent variables of interest, detected 145 patterns within the missing data and the chi squared test statistic was significant ($p = < 0.001$) indicating that missing data were not missing completely at random (MCAR). [Figure 27](#) displays patterns of missing data for the full sample for selected independent variables, while [Figure 28](#) displays proportions of missing data for each independent variable.

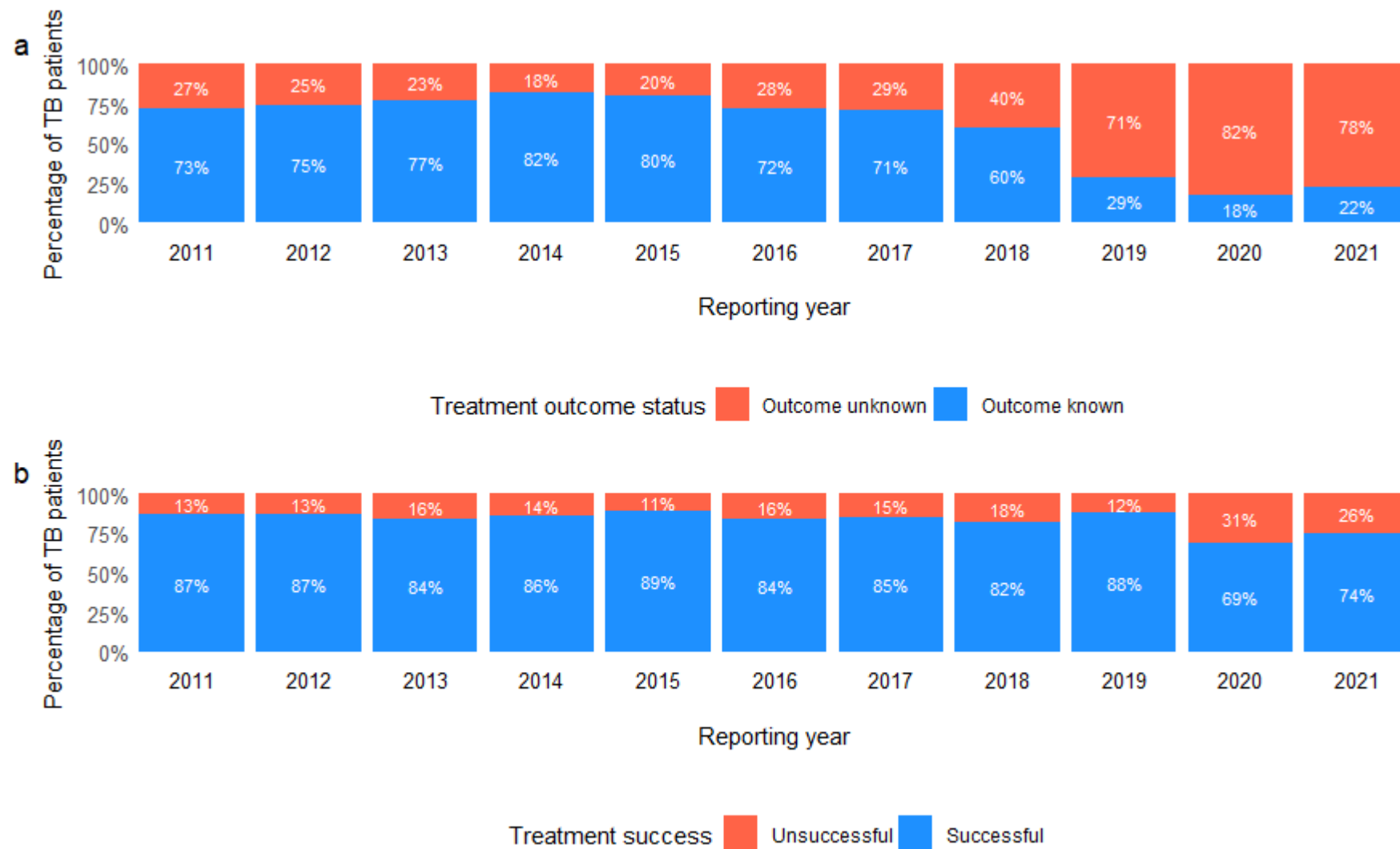


Figure 26: a) TB treatment outcome status by reporting year and b) treatment success by reporting year (n= 3,364)

Table 15: Distribution of patient characteristics for total cases by treatment outcome status (n=3,364)

Characteristic N (%)	Full sample				p-value ^{§§§§}	Treatment success known (N = 2,084 ^{****})			p-value
	Missing %	Overall N = 3,364	Outcome unknown N = 1,243	Outcome known N = 2,121		Missing N (%)	Complete cases N = 1,069	Excluded cases N = 1,015	
Treatment success	38%				>0.99	0%			0.46
Unsuccessful		312 (15.0%)	0 (NA%)	312 (15.0%)			154 (14.4%)	158 (15.6%)	
Successful		1,772 (85.0%)	0 (NA%)	1,772 (85.0%)			915 (85.6%)	857 (84.4%)	
Migrant status	4.9%				<0.001	1.7%			0.094
Irish-born		1,593 (49.8%)	465 (41.7%)	1,128 (54.1%)			592 (55.4%)	506 (51.7%)	
Migrant		1,605 (50.2%)	649 (58.3%)	956 (45.9%)			477 (44.6%)	473 (48.3%)	
Median age (IQR)	0.1%	41.0 (29.0)	39.0 (28.0)	41.0 (29.0)	0.070	0.1%	40.0 (29.0)	41.0 (29.3)	0.56
Sex	0.1%				0.47	<0.1%			0.18
Female		1,346 (40.1%)	487 (39.3%)	859 (40.5%)			422 (39.5%)	429 (42.3%)	
Male		2,013 (59.9%)	753 (60.7%)	1,260 (59.5%)			647 (60.5%)	584 (57.7%)	
Employment status	15%				0.006	9.1%			0.035
Paid employment		1,051 (36.8%)	386 (41.3%)	665 (34.6%)			364 (34.1%)	298 (36.1%)	
Unemployed		935 (32.7%)	290 (31.0%)	645 (33.5%)			376 (35.2%)	259 (31.4%)	
Retired		450 (15.8%)	125 (13.4%)	325 (16.9%)			187 (17.5%)	125 (15.2%)	
Student/Child		334 (11.7%)	104 (11.1%)	230 (12.0%)			111 (10.4%)	119 (14.4%)	
Other		87 (3.0%)	29 (3.1%)	58 (3.0%)			31 (2.9%)	24 (2.9%)	
Current housing type	14%				0.58	7.6%			0.73
Private house		2,677 (92.7%)	865 (92.8%)	1,812 (92.6%)			996 (93.2%)	793 (92.6%)	
Congregate residential setting		106 (3.7%)	33 (3.5%)	73 (3.7%)			35 (3.3%)	34 (4.0%)	
Homeless		27 (0.9%)	10 (1.1%)	17 (0.9%)			11 (1.0%)	5 (0.6%)	
Prison		22 (0.8%)	5 (0.5%)	17 (0.9%)			8 (0.7%)	9 (1.1%)	
Residential care facility		20 (0.7%)	4 (0.4%)	16 (0.8%)			10 (0.9%)	6 (0.7%)	
Other housing		37 (1.3%)	15 (1.6%)	22 (1.1%)			9 (0.8%)	9 (1.1%)	
Patient type	12%				0.007	11%			<0.001
Hospital inpatient		1,717 (58.1%)	599 (56.3%)	1,118 (59.1%)			690 (64.5%)	415 (52.6%)	
Hospital outpatient		957 (32.4%)	379 (35.6%)	578 (30.6%)			274 (25.6%)	302 (38.3%)	
Other		281 (9.5%)	86 (8.1%)	195 (10.3%)			105 (9.8%)	72 (9.1%)	
	2.7%								

**** Excludes cases diagnosed at port-mortem who did not have opportunity to start treatment.

§§§§ Fisher's exact test; Pearson's Chi-squared test; Wilcoxon rank sum test

Characteristic N (%)	Full sample					Treatment success known (N = 2,084****)			
	Missing %	Overall N = 3,364	Outcome unknown N = 1,243	Outcome known N = 2,121	p-value ^{§§§§}	Missing N (%)	Complete cases N = 1,069	Excluded cases N = 1,015	p-value
Disease site					0.27	0.3%			<0.001
Pulmonary		2,223 (67.9%)	772 (66.7%)	1,451 (68.6%)			809 (75.7%)	610 (60.5%)	
Extrapulmonary		1,049 (32.1%)	385 (33.3%)	664 (31.4%)			260 (24.3%)	399 (39.5%)	
Previous TB diagnosis	28%				0.65	21%			0.030
No		2,199 (91.1%)	693 (90.7%)	1,506 (91.3%)			988 (92.4%)	506 (89.2%)	
Yes		215 (8.9%)	71 (9.3%)	144 (8.7%)			81 (7.6%)	61 (10.8%)	
Outbreak associated	0%				<0.001	0%			0.018
Not linked to outbreak		3,037 (90.3%)	1,172 (94.3%)	1,865 (87.9%)			920 (86.1%)	908 (89.5%)	
Outbreak associated		327 (9.7%)	71 (5.7%)	256 (12.1%)			149 (13.9%)	107 (10.5%)	
TB drug resistance	28%				0.032	24%			0.93
Sensitive		2,122 (87.4%)	705 (85.4%)	1,417 (88.4%)			945 (88.4%)	464 (88.5%)	
Resistant		307 (12.6%)	121 (14.6%)	186 (11.6%)			124 (11.6%)	60 (11.5%)	
M/XDR-TB	28%				0.22	48.4%			0.42
No		2,382 (98.1%)	814 (98.5%)	1,568 (97.8%)			1,049 (98.1%)	511 (50.3%)	
Yes		47 (1.9%)	12 (1.5%)	35 (2.2%)			20 (1.9%)	13 (1.3%)	
People living with HIV	58%				0.47	54%			0.50
Negative		1,281 (90.8%)	404 (91.6%)	877 (90.4%)			503 (89.8%)	370 (91.1%)	
Positive		130 (9.2%)	37 (8.4%)	93 (9.6%)			57 (10.2%)	36 (8.9%)	
Diabetes	60%				<0.001	55%			0.45
No		1,208 (89.9%)	334 (84.1%)	874 (92.3%)			564 (92.8%)	297 (91.4%)	
Yes		136 (10.1%)	63 (15.9%)	73 (7.7%)			44 (7.2%)	28 (8.6%)	
Substance use	61%				0.77	55%			0.21
No		948 (71.7%)	256 (71.1%)	692 (71.9%)			443 (71.5%)	241 (75.3%)	
Yes		374 (28.3%)	104 (28.9%)	270 (28.1%)			177 (28.5%)	79 (24.7%)	
Immunosuppression	59%				0.74	54%			0.005
No		1,070 (78.4%)	298 (77.8%)	772 (78.6%)			507 (81.4%)	255 (73.7%)	
Yes		295 (21.6%)	85 (22.2%)	210 (21.4%)			116 (18.6%)	91 (26.3%)	
Geographical area	0%				<0.001	0%			<0.001
East		1,488 (44.2%)	741 (59.6%)	747 (35.2%)			276 (25.8%)	454 (44.7%)	
Midlands		176 (5.2%)	77 (6.2%)	99 (4.7%)			62 (5.8%)	35 (3.4%)	
Midwest		209 (6.2%)	60 (4.8%)	149 (7.0%)			112 (10.5%)	36 (3.5%)	
North East		232 (6.9%)	81 (6.5%)	151 (7.1%)			45 (4.2%)	104 (10.2%)	
North West		116 (3.4%)	23 (1.9%)	93 (4.4%)			71 (6.6%)	21 (2.1%)	

Characteristic N (%)	Full sample					Treatment success known (N = 2,084 ^{****})			
	Missing	Overall	Outcome unknown	Outcome known	p-value ^{§§§§}	Missing	Complete cases	Excluded cases	p-value
	%	N = 3,364	N = 1,243	N = 2,121		N (%)	N = 1,069	N = 1,015	
South		610 (18.1%)	105 (8.4%)	505 (23.8%)			269 (25.2%)	229 (22.6%)	
South East		263 (7.8%)	29 (2.3%)	234 (11.0%)			151 (14.1%)	79 (7.8%)	
West		270 (8.0%)	127 (10.2%)	143 (6.7%)			83 (7.8%)	57 (5.6%)	

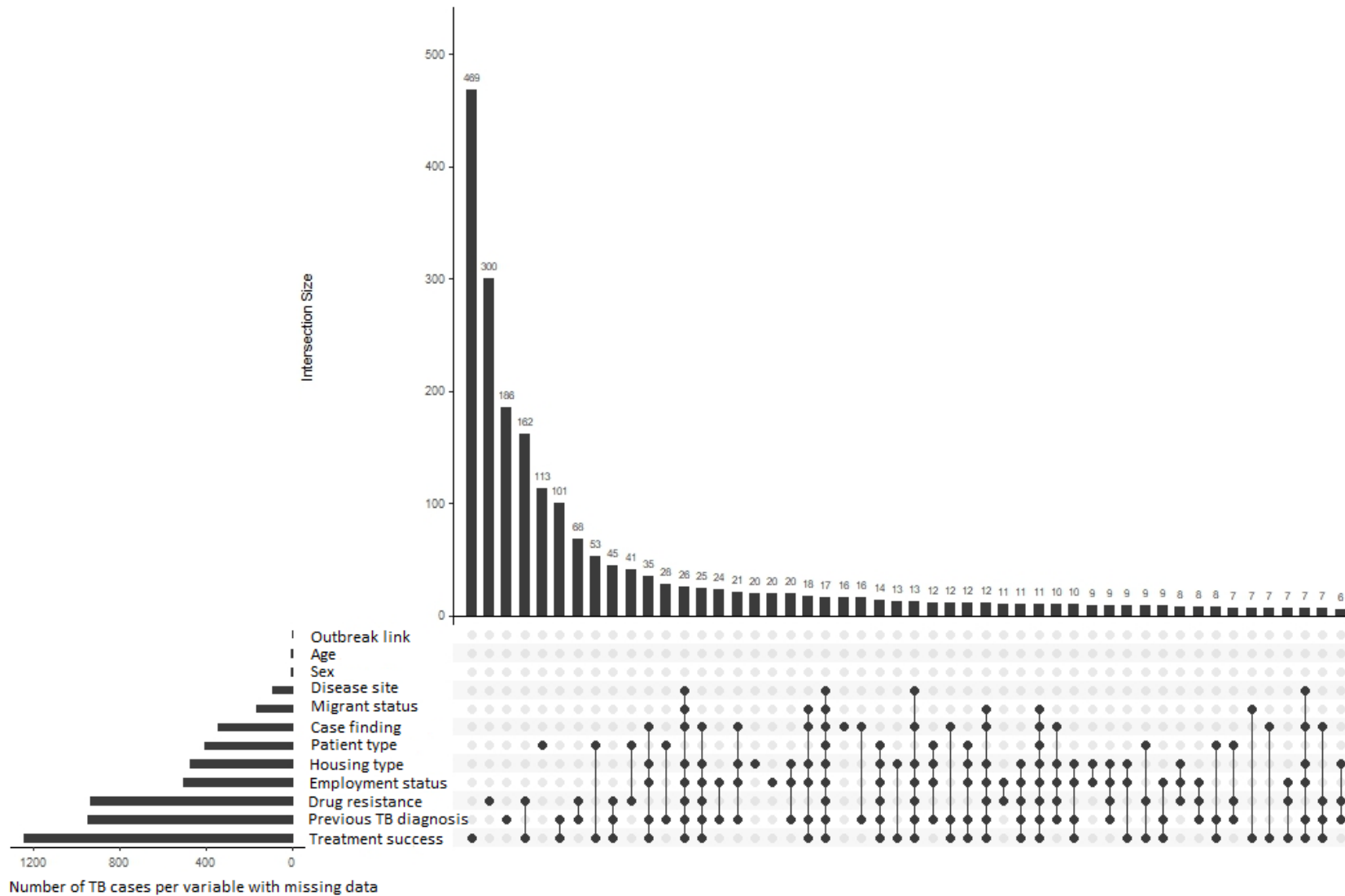


Figure 27: Patterns of missing data for selected independent variables and dependent variable (treatment success) within the full sample (n= 3,364)

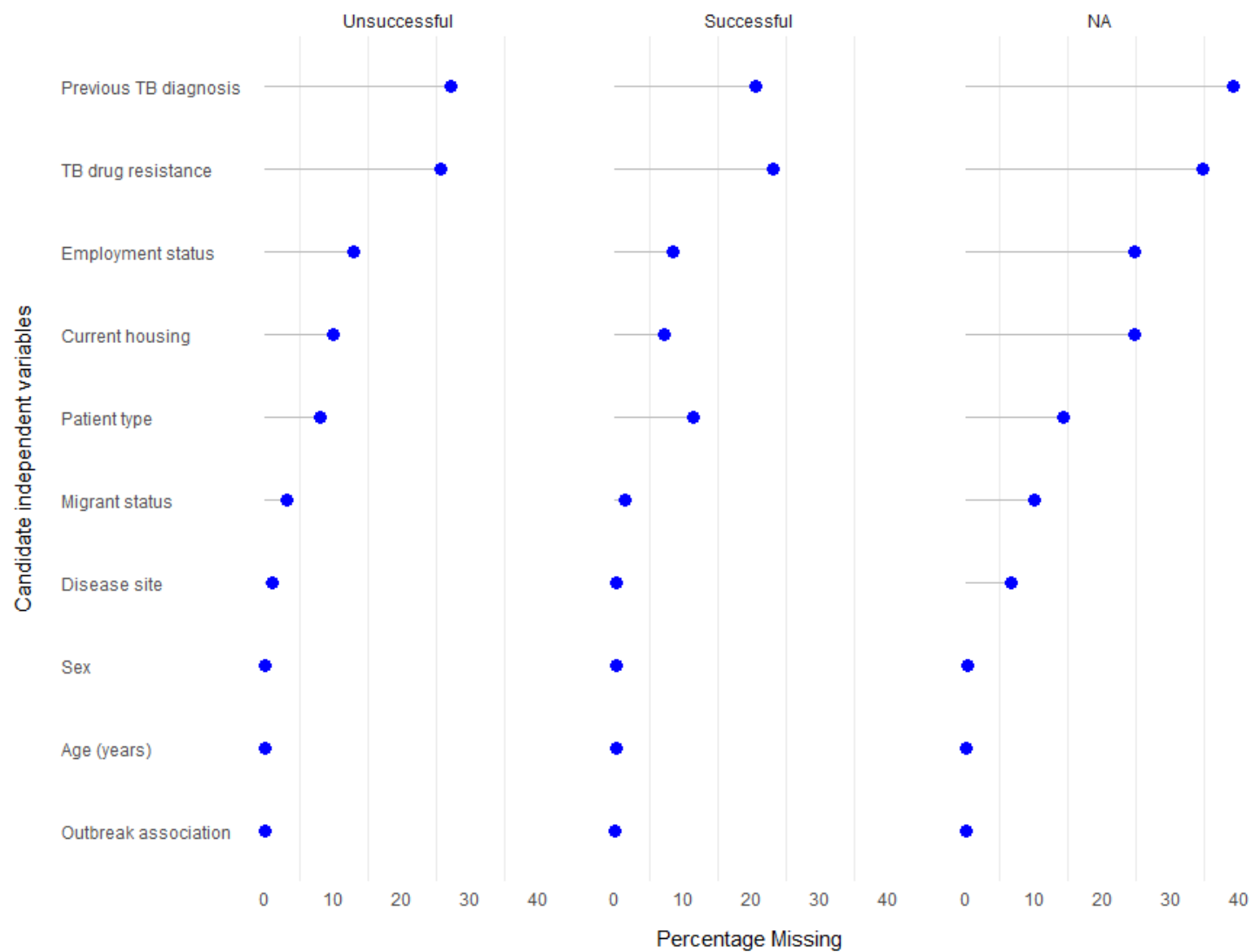


Figure 28: Proportions of missing data for selected independent variables and dependent variable (treatment success) within the full sample (n= 3,364)

7.4.2 Distribution of the sample - Migrant cases

Of the 1,605 migrant cases in the full sample, treatment outcome was reported for 956 (59.6%) migrant cases and six were excluded from the treatment success analysis on the basis of being a post-mortem diagnosis with no opportunity to commence treatment. [Table 16](#) summarises the patient characteristics for the sample of migrant cases, stratified by treatment outcome availability and inclusion in complete case sample, and highlights where differences in patient characteristics were statistically significant. Patient characteristics of cases with treatment outcome reported were broadly similar to the patient characteristics observed within the full sample of 1,605 migrants but differed for geographical area of residence. A lower proportion of cases residing in the East and a higher proportion of cases resident in the South were observed among those with treatment outcome reported. In addition, statistically significant differences were observed between the sample of cases with outcomes reported compared to those without outcomes for sex, M/XDR and interval between arrival and notification as a case of TB.

Of the 950 cases with treatment outcome reported, 477 (50.3%) cases had complete information for the dependent variable (treatment success) plus the eight candidate independent variables selected; age in years, sex, employment status, housing type, disease site, previous history of TB disease, patient type and TB drug resistance. Patient characteristics of cases with complete data for independent and dependent variables were broadly similar to the patient characteristics observed within the full sample of 1,605 migrants with the exception of geographical area of residence. However, statistically significant differences were observed between the complete data sample (n=477) compared to the cases excluded due to missing data (n = 472) for two candidate variables; disease site and patient type. Compared to excluded cases, cases in the complete case sample had higher proportions of PTB (64.4% vs 51.3%) and a higher proportion of in-patients (61.5% vs 50.1%). No significant differences were found for the outcome (treatment success) or age, sex, employment status, current housing type, previous TB diagnosis and resistance to anti-TB drugs.

Performing Little's test on the full sample restricted to the nine independent variables of interest, detected 69 patterns within the missing data and the chi squared test statistic was significant ($p < 0.001$) indicating that missing data were not MCAR.

Table 16: Distribution of migrant patient characteristics by treatment outcome status (n=1,605) and by inclusion in model sample (n=950)

Characteristic N (%)	Total Migrant cases					Migrant cases with outcome known			p-value
	Missing N (%)	Overall N = 1,605	Outcome unknown N = 649	Outcome known N = 956	p- value*****	N	Complete cases++++ N = 477	Excluded cases N = 473	
Treatment success	655 (41%)				>0.99	0 (0%)			0.95
Unsuccessful		103 (10.8%)	0 (NA%)	103 (10.8%)			52 (10.9%)	51 (10.8%)	
Successful		847 (89.2%)	0 (NA%)	847 (89.2%)			425 (89.1%)	422 (89.2%)	
Median age (IQR)	2 (0.1%)	34.0 (16.0)	33.0 (16.0)	34.0 (15.0)	0.57	1 (0.1%)	34.0 (16.0)	34.0 (15.0)	0.69
Sex	4 (0.2%)				0.023	2 (0.2%)			0.99
Female		688 (43.0%)	256 (39.6%)	432 (45.3%)			217 (45.5%)	214 (45.4%)	
Male		913 (57.0%)	391 (60.4%)	522 (54.7%)			260 (54.5%)	257 (54.6%)	
Employment status	189 (12%)				0.30	75 (7.9%)			0.49
Paid employment		642 (45.3%)	262 (48.7%)	380 (43.3%)			199 (41.7%)	181 (45.5%)	
Unemployed		501 (35.4%)	181 (33.6%)	320 (36.4%)			183 (38.4%)	136 (34.2%)	
Retired		40 (2.8%)	14 (2.6%)	26 (3.0%)			16 (3.4%)	9 (2.3%)	
Student/Child		194 (13.7%)	65 (12.1%)	129 (14.7%)			66 (13.8%)	63 (15.8%)	
Other		39 (2.8%)	16 (3.0%)	23 (2.6%)			13 (2.7%)	9 (2.3%)	
Current housing	195 (12%)				0.65	79 (8.3%)			0.76
Private house		1,294 (91.8%)	490 (91.8%)	804 (91.8%)			442 (92.7%)	359 (91.1%)	
Congregate residential / care setting		71 (5.0%)	27 (5.1%)	44 (5.0%)			23 (4.8%)	21 (5.3%)	
Prison/Homeless		24 (1.7%)	7 (1.3%)	17 (1.9%)			8 (1.7%)	8 (2.0%)	
Other housing		21 (1.5%)	10 (1.9%)	11 (1.3%)			4 (0.8%)	6 (1.5%)	
Disease site	19 (1.2%)				0.90	0 (0%)			<0.001
Pulmonary		917 (57.8%)	363 (57.6%)	554 (57.9%)			307 (64.4%)	243 (51.4%)	
Extrapulmonary		669 (42.2%)	267 (42.4%)	402 (42.1%)			170 (35.6%)	230 (48.6%)	
Previous TB diagnosis	414 (26%)				0.52	214 (23%)			0.37
No		1,099 (92.3%)	417 (91.6%)	682 (92.7%)			445 (93.3%)	237 (91.5%)	

***** Fisher's exact test; Pearson's Chi-squared test; Wilcoxon rank sum test

++++ Excludes 6 cases diagnosed at port-mortem who did not have opportunity to start treatment.

Characteristic N (%)	Total Migrant cases				p-value *****	N	Migrant cases with outcome known		p-value
	Missing N (%)	Overall N = 1,605	Outcome unknown N = 649	Outcome known N = 956			Complete cases ^{****} N = 477	Excluded cases N = 473	
Patient type									
Yes		92 (7.7%)	38 (8.4%)	54 (7.3%)			32 (6.7%)	22 (8.5%)	
Hospital inpatient	215 (13%)	782 (56.3%)	316 (55.6%)	466 (56.7%)	0.21	133 (14%)	294 (61.6%)	170 (50.0%)	<0.001
Hospital outpatient		489 (35.2%)	211 (37.1%)	278 (33.8%)			132 (27.7%)	146 (42.9%)	
Other		119 (8.6%)	41 (7.2%)	78 (9.5%)			51 (10.7%)	24 (7.1%)	
Outbreak associated	0 (0%)				<0.001	0 (0%)			0.57
Not linked to outbreak		1,530 (95.3%)	634 (97.7%)	896 (93.7%)			449 (94.1%)	441 (93.2%)	
Outbreak associated		75 (4.7%)	15 (2.3%)	60 (6.3%)			28 (5.9%)	32 (6.8%)	
TB drug resistance	373 (23%)				0.92	201 (21%)			0.37
Sensitive		1,019 (82.7%)	398 (82.6%)	621 (82.8%)			391 (82.0%)	230 (84.6%)	
Resistant		213 (17.3%)	84 (17.4%)	129 (17.2%)			86 (18.0%)	42 (15.4%)	
M/XDR-TB	373 (23%)				0.030	201 (21%)			0.89
No		1,189 (96.5%)	472 (97.9%)	717 (95.6%)			457 (95.8%)	260 (95.6%)	
Yes		43 (3.5%)	10 (2.1%)	33 (4.4%)			20 (4.2%)	12 (4.4%)	
People living with HIV	787 (49%)				0.074	419 (44%)			0.21
Negative		712 (87.0%)	258 (89.9%)	454 (85.5%)			248 (83.8%)	206 (87.7%)	
Positive		106 (13.0%)	29 (10.1%)	77 (14.5%)			48 (16.2%)	29 (12.3%)	
Geographical area	0 (0%)				<0.001	0 (0%)			<0.001
East		824 (51.3%)	404 (62.2%)	420 (43.9%)			153 (32.1%)	262 (55.4%)	
Midlands		86 (5.4%)	36 (5.5%)	50 (5.2%)			36 (7.5%)	14 (3.0%)	
Midwest		92 (5.7%)	33 (5.1%)	59 (6.2%)			47 (9.9%)	12 (2.5%)	
North East		113 (7.0%)	42 (6.5%)	71 (7.4%)			25 (5.2%)	46 (9.7%)	
North West		38 (2.4%)	8 (1.2%)	30 (3.1%)			22 (4.6%)	8 (1.7%)	
South		214 (13.3%)	52 (8.0%)	162 (16.9%)			92 (19.3%)	69 (14.6%)	
South East		116 (7.2%)	16 (2.5%)	100 (10.5%)			64 (13.4%)	36 (7.6%)	
West		122 (7.6%)	58 (8.9%)	64 (6.7%)			38 (8.0%)	26 (5.5%)	
Years between arrival and notification	543 (34%)				0.006	314 (33%)			0.48
0-1		239 (22.5%)	108 (25.4%)	131 (20.6%)			77 (20.6%)	54 (20.6%)	
2-4		291 (27.4%)	125 (29.4%)	166 (26.1%)			99 (26.5%)	66 (25.2%)	
5-9		238 (22.4%)	73 (17.2%)	165 (25.9%)			103 (27.5%)	62 (23.7%)	
10+		294 (27.7%)	119 (28.0%)	175 (27.5%)			95 (25.4%)	80 (30.5%)	

Characteristic N (%)	Total Migrant cases				N	Migrant cases with outcome known		
	Missing N (%)	Overall N = 1,605	Outcome unknown N = 649	Outcome known N = 956		Complete cases ⁺⁺⁺⁺ N = 477	Excluded cases N = 473	p-value
WHO TB incidence category	3 (0.2%)				0.30	2 (0.2%)		0.030
<i>Low</i>		30 (1.9%)	14 (2.2%)	16 (1.7%)		9 (1.9%)	7 (1.5%)	
<i>Medium</i>		193 (12.0%)	69 (10.6%)	124 (13.0%)		75 (15.8%)	48 (10.2%)	
<i>High</i>		280 (17.5%)	123 (19.0%)	157 (16.5%)		82 (17.2%)	71 (15.0%)	
<i>Very high</i>		1,099 (68.6%)	442 (68.2%)	657 (68.9%)		310 (65.1%)	346 (73.3%)	
Top 10 CIR country of origin	0 (0%)				0.38	0 (0%)		0.035
<i>Top10CIR</i>		622 (38.8%)	260 (40.1%)	362 (37.9%)		166 (34.8%)	196 (41.4%)	
<i>No</i>		983 (61.2%)	389 (59.9%)	594 (62.1%)		311 (65.2%)	277 (58.6%)	

7.4.3 Distribution of the sample - Irish-born cases

Of the 1,593 Irish-born cases in the full sample, treatment outcome was reported for 1,128 (70.8%) cases. Thirty cases were excluded from the treatment success analysis on the basis of being a post-mortem diagnosis with no opportunity to commence treatment. [Table 17](#) summarises the patient characteristics for the Irish-born sample, stratified by treatment outcome availability and inclusion in complete case sample, and highlights where differences in patient characteristics were statistically significantly different.

Patient characteristics of Irish-born cases with outcome data reported were broadly similar to the patient characteristics observed within the full sample (N = 1,593) but differed for geographical area of residence ([Table 17](#)). This difference was also present between the sample with treatment outcomes and those without treatment outcomes and was statistically significant. In addition, statistically significant differences were observed between the sample of cases with treatment outcomes reported compared to those without treatment outcomes for patient type and outbreak association.

Of the 1,128 cases with treatment outcome reported, 592 cases had complete information for the dependent variable (treatment success) plus the nine independent variables selected; age in years, sex, employment status, housing type, disease site, previous history of TB disease, patient type, outbreak association and TB drug resistance. With the exception of geographical region of residence, site of disease and patient type, the distributions of the complete case sample was broadly similar to that of the full sample. Statistically significant differences were found for three independent variables of interest (disease site, patient type and outbreak association) between the complete case sample and the cases excluded due to missing data (n=506). Compared to excluded cases, cases in the complete case sample had higher proportions of PTB (84.8% vs 68.3%), in-patients (66.9% vs 54.6%) and outbreak associated cases (20.4% vs 14.2%). No significant differences were found for the outcome (treatment success) or age, sex, employment status, current housing type, previous TB diagnosis and resistance to anti-TB drugs

Performing Little's test on the full sample restricted to the nine independent variables of interest, detected 58 patterns within the missing data and the chi squared test statistic was significant ($p < 0.001$) indicating that missing data were not MCAR.

Table 17: Distribution of the Irish-born patient characteristics by treatment outcome status (n=1,098) and by inclusion in model sample (n=592)

Characteristic	Treatment outcome status					Complete case sample – Irish-born				p-value
	Missing N (%)	Overall N = 1,593	Outcome unknown N = 465	Outcome known N = 1,128	p- value****	Missing N (%)	Overall N = 1,098	Complete case sample N = 592	Excluded cases N = 506	
Treatment success	495 (31%)				>0.99	0 (0%)				0.41
Unsuccessful		199 (18.1%)	N/A	199 (18.1%)			199 (18.1%)	102 (17.2%)	97 (19.2%)	
Successful		899 (81.9%)	N/A	899 (81.9%)			899 (81.9%)	490 (82.8%)	409 (80.8%)	
Median age (IQR)	2 (0.1%)	53.0 (33.0)	53.0 (32.0)	53.0 (32.8)	0.87	2 (0.2%)	53.0 (32.0)	50.0 (33.0)	54.0 (31.0)	0.30
Sex	0 (0%)				0.54	0 (0%)				0.094
Female		588 (36.9%)	177 (38.1%)	411 (36.4%)			405 (36.9%)	205 (34.6%)	200 (39.5%)	
Male		1,005 (63.1%)	288 (61.9%)	717 (63.6%)			693 (63.1%)	387 (65.4%)	306 (60.5%)	
Employment status	182 (11%)				0.72	93 (8.5%)				0.052
Paid employment		399 (28.3%)	117 (30.8%)	282 (27.4%)			279 (27.8%)	165 (27.9%)	114 (27.6%)	
Unemployed		428 (30.3%)	107 (28.2%)	321 (31.1%)			312 (31.0%)	193 (32.6%)	119 (28.8%)	
Retired		403 (28.6%)	108 (28.4%)	295 (28.6%)			283 (28.2%)	171 (28.9%)	112 (27.1%)	
Student/Child		135 (9.6%)	35 (9.2%)	100 (9.7%)			100 (10.0%)	45 (7.6%)	55 (13.3%)	
Other		46 (3.3%)	13 (3.4%)	33 (3.2%)			31 (3.1%)	18 (3.0%)	13 (3.1%)	
Current housing	148 (9.3%)				0.51	63 (5.7%)				0.92
Private house		1,352 (93.6%)	362 (94.5%)	990 (93.2%)			970 (93.7%)	554 (93.6%)	416 (93.9%)	
Congregate residential / care setting		54 (3.7%)	10 (2.6%)	44 (4.1%)			40 (3.9%)	22 (3.7%)	18 (4.1%)	
Prison/Homeless		25 (1.7%)	8 (2.1%)	17 (1.6%)			17 (1.6%)	11 (1.9%)	6 (1.4%)	
Other housing		14 (1.0%)	3 (0.8%)	11 (1.0%)			8 (0.8%)	5 (0.8%)	3 (0.7%)	
Disease site, n (%)	17 (1.1%)				0.97	4 (0.4%)				<0.001
Pulmonary		1,223 (77.6%)	351 (77.7%)	872 (77.6%)			845 (77.2%)	502 (84.8%)	343 (68.3%)	
Extrapulmonary		353 (22.4%)	101 (22.3%)	252 (22.4%)			249 (22.8%)	90 (15.2%)	159 (31.7%)	
Previous TB diagnosis	387 (24%)				0.86	207 (19%)				0.071
No		1,089 (90.3%)	271 (90.0%)	818 (90.4%)			806 (90.5%)	543 (91.7%)	263 (88.0%)	
Yes		117 (9.7%)	30 (10.0%)	87 (9.6%)			85 (9.5%)	49 (8.3%)	36 (12.0%)	
Patient type	147 (9.2%)				0.033	90 (8.2%)				<0.001
Hospital inpatient		876 (60.6%)	242 (59.0%)	634 (61.2%)			623 (61.8%)	396 (66.9%)	227 (54.6%)	
Hospital outpatient		425 (29.4%)	137 (33.4%)	288 (27.8%)			286 (28.4%)	142 (24.0%)	144 (34.6%)	
Other		145 (10.0%)	31 (7.6%)	114 (11.0%)			99 (9.8%)	54 (9.1%)	45 (10.8%)	

**** Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test

Characteristic	Treatment outcome status					Complete case sample – Irish-born				
	Missing N (%)	Overall N = 1,593	Outcome unknown N = 465	Outcome known N = 1,128	p- value****	Missing N (%)	Overall N = 1,098	Complete case sample N = 592	Excluded cases N = 506	p- value
Outbreak associated	0 (0%)				0.008	0 (0%)				0.007
<i>Not linked to outbreak</i>		1,345 (84.4%)	410 (88.2%)	935 (82.9%)			905 (82.4%)	471 (79.6%)	434 (85.8%)	
<i>Outbreak associated</i>		248 (15.6%)	55 (11.8%)	193 (17.1%)			193 (17.6%)	121 (20.4%)	72 (14.2%)	
Drug resistance	465 (29%)				0.080	272 (25%)				>0.99
<i>Sensitive</i>		1,046 (92.7%)	265 (90.4%)	781 (93.5%)			773 (93.6%)	554 (93.6%)	219 (93.6%)	
<i>Resistant</i>		82 (7.3%)	28 (9.6%)	54 (6.5%)			53 (6.4%)	38 (6.4%)	15 (6.4%)	
Geographical area	0 (0%)				<0.001	0 (0%)				<0.001
<i>East</i>		563 (35.3%)	260 (55.9%)	303 (26.9%)			292 (26.6%)	123 (20.8%)	169 (33.4%)	
<i>Midlands</i>		69 (4.3%)	20 (4.3%)	49 (4.3%)			47 (4.3%)	26 (4.4%)	21 (4.2%)	
<i>Midwest</i>		104 (6.5%)	14 (3.0%)	90 (8.0%)			89 (8.1%)	65 (11.0%)	24 (4.7%)	
<i>North East</i>		115 (7.2%)	38 (8.2%)	77 (6.8%)			75 (6.8%)	20 (3.4%)	55 (10.9%)	
<i>North West</i>		77 (4.8%)	14 (3.0%)	63 (5.6%)			62 (5.6%)	49 (8.3%)	13 (2.6%)	
<i>South</i>		396 (24.9%)	53 (11.4%)	343 (30.4%)			337 (30.7%)	177 (29.9%)	160 (31.6%)	
<i>South East</i>		146 (9.2%)	12 (2.6%)	134 (11.9%)			130 (11.8%)	87 (14.7%)	43 (8.5%)	
<i>West</i>		123 (7.7%)	54 (11.6%)	69 (6.1%)			66 (6.0%)	45 (7.6%)	21 (4.2%)	

7.4.4 Predictors of treatment success – total cases

[Table 18](#) summarises the distribution of 16 candidate independent variables for the full sample of 2,084 cases with treatment success known and their crude odds ratios (cORs) estimated by univariable logistic regression. As the candidate independent variables that were missing data for $\geq 25\%$ of cases were excluded from the multivariable logistic regression analyses, their cORs are presented in Table 18 for completeness. [Figure 29](#) summarises the results of the final models in each of the complete case samples for total cases, migrant cases and Irish-born cases.

[Table 19](#) presents the results of the final model generated by manual backwards stepwise elimination, alongside the distribution of patient characteristics in the complete case sample and the cORs estimated by univariable logistic regression. Variables retained in this model included age (in years), employment status, patient type, previous TB history and infection with a drug-resistant strain of *M. tuberculosis*. With the exception of previous TB diagnosis, the same variables were ranked as the most influential according to a Random Forest variable importance plot of the full model prior to variable removal ([Figure 30](#)). Increasing patient age was significantly negatively correlated with the outcome of treatment success. For each additional year in patient age, the adjusted odds of treatment success decreased by 2% where all other variables remained constant. Compared to the reference group of being in paid employment, cases who were unemployed, retired or with occupational status was reported as “Other” had significantly lower adjusted odds of treatment success. Cases infected with drug-resistant strains had lower adjusted odds of successful treatment. Patient type was the only variable associated with increased treatment success. Compared to the reference category of in-patients, outpatients and cases reported as other patient type had higher adjusted odds of treatment success. Previous TB history was not significant in the final model but removal of this variable decreased both the model fit according to the Hosmer Lemeshaw test and the AICc weight. Cases with a previous TB diagnosis had lower adjusted odds of success compared to the reference group of cases without a previous TB diagnosis. Variables retained in the model generated by the AIC algorithm method (stepAIC) were the same as the manually generated model.

Model assumptions of the full model are displayed in Appendix 6, [Figure A6.1](#). All metrics of the models were acceptable with 76% of binned residuals within error bounds in the final model. The PCP was 78.2% for the final model and also the highest AICc weight of models compared. The Hosmer-Lemeshow goodness-of-fit test results indicated no evidence of poor model fit (statistic = 12.3, $p = 0.14$). The Area Under the Receiver Operating Characteristic Curve (AUROC) was 0.74

(CI:0.70-0.79) indicating an acceptable level of discrimination ([Figure 31](#)). [Figure 32](#) shows the calibration plot for the final model alongside the Brier Score (0.11) and Spiegelhalter's Z score (<0.001 , $p: 0.999$), neither of which indicated that the model was poorly calibrated.

Table 18: Distribution of patient characteristics of total cases by treatment success and crude odds ratios from univariable logistic regression (n=2,084)

Characteristic N (%)	Treatment success				Univariable logistic regression		
	Missing N (%)	Overall N = 2,084	Unsuccessful N = 312	Successful N = 1,772	N	cOR (95% CI) ^{§§§§§}	p-value
Median age (IQR)	3 (0.1%)	41.0 (29.0)	54.0 (39.3)	39.0 (26.0)	2,081	0.97 (0.96 to 0.98)	<0.001
Sex	2 (<0.1%)				2,082		0.051
<i>Female</i>		851 (40.9%)	112 (35.9%)	739 (41.8%)		—	
<i>Male</i>		1,231 (59.1%)	200 (64.1%)	1,031 (58.2%)		0.78 (0.61 to 1.00)	
Migrant status	36 (1.7%)				2,048		<0.001
<i>Irish-born</i>		1,098 (53.6%)	199 (65.9%)	899 (51.5%)		—	
<i>Migrant</i>		950 (46.4%)	103 (34.1%)	847 (48.5%)		1.82 (1.41 to 2.36)	
Employment status	190 (9.1%)				1,894		<0.001
<i>Paid employment</i>		662 (35.0%)	47 (17.3%)	615 (37.9%)		—	
<i>Unemployed</i>		635 (33.5%)	102 (37.5%)	533 (32.9%)		0.40 (0.28 to 0.57)	
<i>Retired</i>		312 (16.5%)	86 (31.6%)	226 (13.9%)		0.20 (0.14 to 0.29)	
<i>Student/Child</i>		230 (12.1%)	22 (8.1%)	208 (12.8%)		0.72 (0.43 to 1.25)	
<i>Other</i>		55 (2.9%)	15 (5.5%)	40 (2.5%)		0.20 (0.11 to 0.40)	
Current housing	159 (7.6%)				1,925		<0.001
<i>Private house</i>		1,789 (92.9%)	242 (86.1%)	1,547 (94.1%)		—	
<i>Congregate residential / care setting</i>		85 (4.4%)	25 (8.9%)	60 (3.6%)		0.38 (0.23 to 0.62)	
<i>Prison/Homeless</i>		33 (1.7%)	8 (2.8%)	25 (1.5%)		0.49 (0.23 to 1.17)	
<i>Other housing</i>		18 (0.9%)	6 (2.1%)	12 (0.7%)		0.31 (0.12 to 0.91)	
Disease site	6 (0.3%)				2,078		0.005
<i>Pulmonary</i>		1,419 (68.3%)	232 (75.1%)	1,187 (67.1%)		—	
<i>Extrapulmonary</i>		659 (31.7%)	77 (24.9%)	582 (32.9%)		1.48 (1.13 to 1.96)	
Previous TB diagnosis	448 (21%)				1,636		<0.001
<i>No</i>		1,494 (91.3%)	192 (84.6%)	1,302 (92.4%)		—	
<i>Yes</i>		142 (8.7%)	35 (15.4%)	107 (7.6%)		0.45 (0.30 to 0.69)	
Patient type	226 (11%)				1,858		<0.001

§§§§§ cOR = Crude Odds Ratio, CI = Confidence Interval

Characteristic N (%)	Treatment success				Univariable logistic regression	
	Missing N (%)	Overall N = 2,084	Unsuccessful N = 312	Successful N = 1,772	N	cOR (95% CI) ^{§§§§§} p-value
<i>Hospital inpatient</i>		1,105 (59.5%)	222 (77.4%)	883 (56.2%)		—
<i>Hospital outpatient</i>		576 (31.0%)	44 (15.3%)	532 (33.9%)		3.04 (2.18 to 4.32)
<i>Other</i>		177 (9.5%)	21 (7.3%)	156 (9.9%)		1.87 (1.18 to 3.09)
Outbreak associated	0 (0%)				2,084	0.005
<i>Not linked to outbreak</i>		1,828 (87.7%)	288 (92.3%)	1,540 (86.9%)		—
<i>Outbreak associated</i>		256 (12.3%)	24 (7.7%)	232 (13.1%)		1.81 (1.19 to 2.87)
TB drug resistance	491 (24%)				1,593	0.049
<i>Sensitive</i>		1,409 (88.4%)	196 (84.5%)	1,213 (89.1%)		—
<i>Resistant</i>		184 (11.6%)	36 (15.5%)	148 (10.9%)		0.66 (0.45 to 1.00)
M/XDR-TB	491 (24%)				1,593	0.056
<i>No</i>		1,560 (97.9%)	223 (96.1%)	1,337 (98.2%)		—
<i>Yes</i>		33 (2.1%)	9 (3.9%)	24 (1.8%)		0.44 (0.21 to 1.02)
People living with HIV	1,118 (54%)				966	0.32
<i>Negative</i>		873 (90.4%)	108 (87.8%)	765 (90.7%)		—
<i>Positive</i>		93 (9.6%)	15 (12.2%)	78 (9.3%)		0.73 (0.42 to 1.37)
Diabetes	1,151 (55%)				933	0.002
<i>No</i>		861 (92.3%)	112 (84.8%)	749 (93.5%)		—
<i>Yes</i>		72 (7.7%)	20 (15.2%)	52 (6.5%)		0.39 (0.23 to 0.69)
Immunosuppression	1,115 (54%)				969	<0.001
<i>No</i>		762 (78.6%)	84 (60.4%)	678 (81.7%)		—
<i>Yes</i>		207 (21.4%)	55 (39.6%)	152 (18.3%)		0.34 (0.23 to 0.50)
Substance use	1,144 (55%)				940	0.005
<i>No</i>		684 (72.8%)	85 (62.5%)	599 (74.5%)		—
<i>Yes</i>		256 (27.2%)	51 (37.5%)	205 (25.5%)		0.57 (0.39 to 0.84)
Geographical area	0 (0%)				2,084	0.089
<i>East</i>		730 (35.0%)	103 (33.0%)	627 (35.4%)		—
<i>Midlands</i>		97 (4.7%)	13 (4.2%)	84 (4.7%)		1.06 (0.59 to 2.06)
<i>Midwest</i>		148 (7.1%)	24 (7.7%)	124 (7.0%)		0.85 (0.53 to 1.40)

Characteristic N (%)	Treatment success			Univariable logistic regression		
	Missing N (%)	Overall N = 2,084	Unsuccessful N = 312	Successful N = 1,772	N	cOR (95% CI) ^{§§§§} p-value
<i>North East</i>		149 (7.1%)	23 (7.4%)	126 (7.1%)		0.90 (0.56 to 1.50)
<i>North West</i>		92 (4.4%)	23 (7.4%)	69 (3.9%)		0.49 (0.30 to 0.84)
<i>South</i>		498 (23.9%)	72 (23.1%)	426 (24.0%)		0.97 (0.70 to 1.35)
<i>South East</i>		230 (11.0%)	26 (8.3%)	204 (11.5%)		1.29 (0.83 to 2.07)
<i>West</i>		140 (6.7%)	28 (9.0%)	112 (6.3%)		0.66 (0.42 to 1.06)

Table 19: Factors associated with treatment success among total cases (complete case sample: N = 1,069) for final model (M6b)

Characteristic N (%)	Treatment success			Univariable logistic regression		Multivariable logistic regression	
	Overall N = 1,069	Unsuccessful N = 154	Successful N = 915	cOR (95% CI) *****	p-value	aOR (95% CI)	p-value
Median age (IQR)	40.0 (29.0)	53.5 (37.8)	39.0 (25.5)	0.97 (0.96 to 0.98)	<0.001	0.98 (0.96 to 0.99)	0.003
Sex					0.034		
<i>Female</i>	422 (39.5%)	49 (31.8%)	373 (40.8%)	—			
<i>Male</i>	647 (60.5%)	105 (68.2%)	542 (59.2%)	0.68 (0.47 to 0.97)			
Migrant status					0.003		
<i>Irish-born</i>	592 (55.4%)	102 (66.2%)	490 (53.6%)	—			
<i>Migrant</i>	477 (44.6%)	52 (33.8%)	425 (46.4%)	1.70 (1.19 to 2.45)			
Employment status					<0.001		
<i>Paid employment</i>	364 (34.1%)	25 (16.2%)	339 (37.0%)	—		—	
<i>Unemployed</i>	376 (35.2%)	58 (37.7%)	318 (34.8%)	0.40 (0.24 to 0.65)		0.48 (0.28 to 0.79)	0.005
<i>Retired</i>	187 (17.5%)	55 (35.7%)	132 (14.4%)	0.18 (0.10 to 0.29)		0.41 (0.19 to 0.84)	0.017
<i>Student/Child</i>	111 (10.4%)	7 (4.5%)	104 (11.4%)	1.10 (0.48 to 2.81)		0.79 (0.33 to 2.14)	0.62
<i>Other</i>	31 (2.9%)	9 (5.8%)	22 (2.4%)	0.18 (0.08 to 0.45)		0.19 (0.08 to 0.50)	<0.001
Current housing					0.031		
<i>Private house</i>	996 (93.2%)	135 (87.7%)	861 (94.1%)	—			
<i>Congregate residential/care setting</i>	45 (4.2%)	12 (7.8%)	33 (3.6%)	0.43 (0.22 to 0.89)			
<i>Prison/Homeless</i>	19 (1.8%)	6 (3.9%)	13 (1.4%)	0.34 (0.13 to 0.98)			
<i>Other housing</i>	9 (0.8%)	1 (0.6%)	8 (0.9%)	1.25 (0.23 to 23.4)			
Disease site					0.079		
<i>Pulmonary</i>	809 (75.7%)	125 (81.2%)	684 (74.8%)	—			
<i>Extrapulmonary</i>	260 (24.3%)	29 (18.8%)	231 (25.2%)	1.46 (0.96 to 2.28)			
Previous TB diagnosis					0.005		
<i>No</i>	988 (92.4%)	133 (86.4%)	855 (93.4%)	—		—	
<i>Yes</i>	81 (7.6%)	21 (13.6%)	60 (6.6%)	0.44 (0.27 to 0.77)		0.61 (0.35 to 1.11)	0.093
Patient type					<0.001		
<i>Hospital inpatient</i>	690 (64.5%)	129 (83.8%)	561 (61.3%)	—		—	
<i>Hospital outpatient</i>	274 (25.6%)	17 (11.0%)	257 (28.1%)	3.48 (2.11 to 6.09)		3.27 (1.95 to 5.82)	<0.001
<i>Other</i>	105 (9.8%)	8 (5.2%)	97 (10.6%)	2.79 (1.40 to 6.36)		2.49 (1.22 to 5.81)	0.020

***** cOR = Crude Odds Ratio, aOR: Adjusted Odds Ratio, CI = Confidence Interval. Note: Age in years was used in the model but median age is also summarised for the sample.

Characteristic N (%)	Treatment success			Univariable logistic regression		Multivariable logistic regression	
	Overall N = 1,069	Unsuccessful N = 154	Successful N = 915	cOR (95% CI)*****	p-value	aOR (95% CI)	p-value
Outbreak associated					0.091		
<i>Not linked to outbreak</i>	920 (86.1%)	139 (90.3%)	781 (85.4%)	—			
<i>Outbreak associated</i>	149 (13.9%)	15 (9.7%)	134 (14.6%)	1.59 (0.93 to 2.90)			
TB drug resistance					0.018		
<i>Sensitive</i>	945 (88.4%)	127 (82.5%)	818 (89.4%)	—		—	
<i>Resistant</i>	124 (11.6%)	27 (17.5%)	97 (10.6%)	0.56 (0.35 to 0.90)		0.36 (0.22 to 0.61)	<0.001

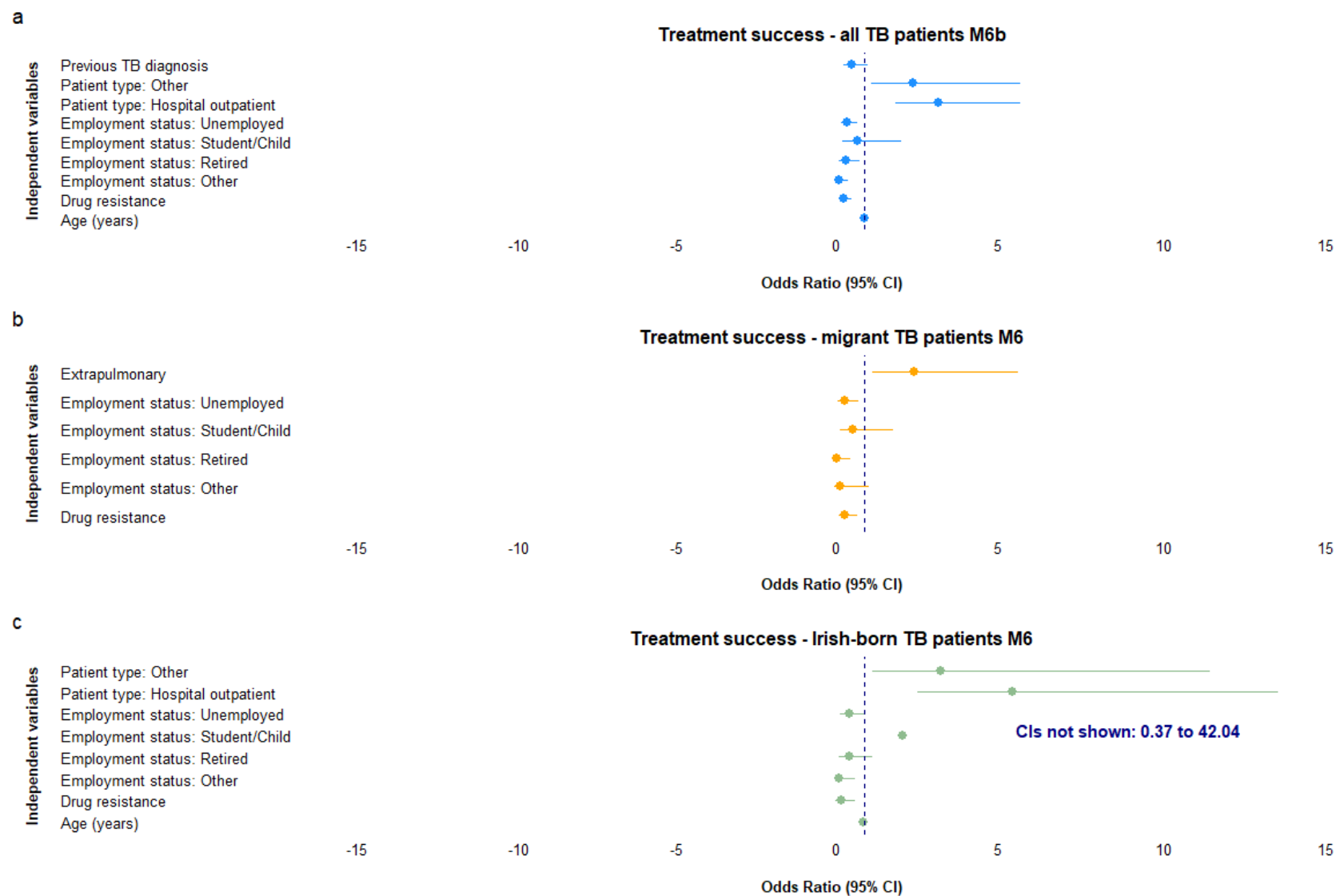


Figure 29: Forest plots for final multivariable logistic regression models for treatment success among total cases, migrant cases and Irish-born cases

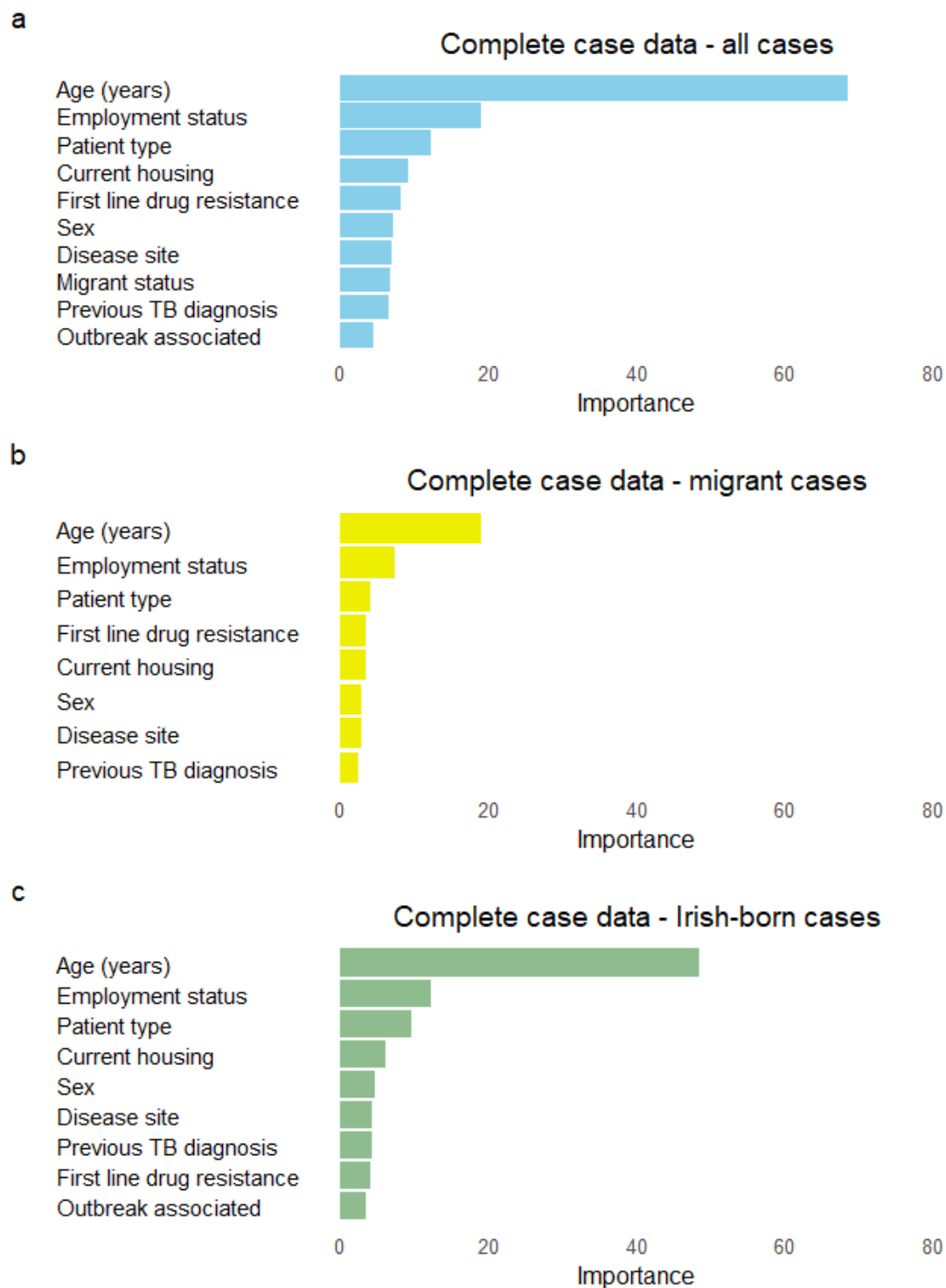


Figure 30: Variable importance plots calculated by Random Forest algorithm for independent variables included in the full models for a) total cases, b) migrant cases and c) Irish-born cases

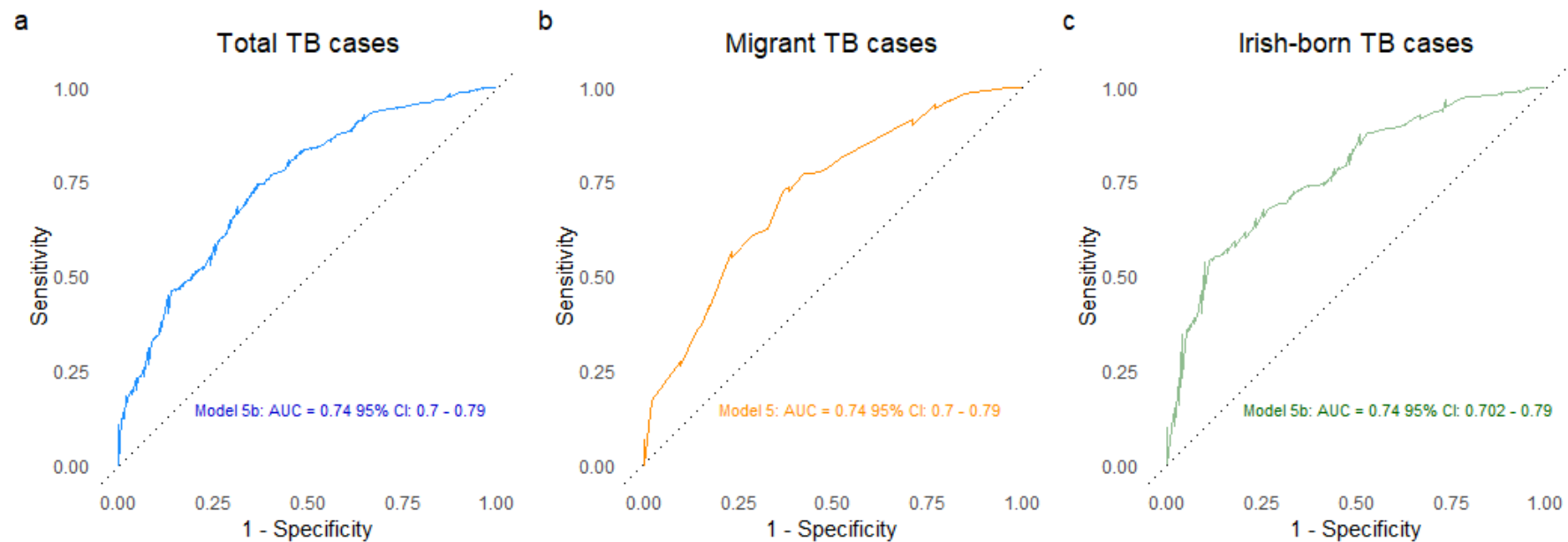


Figure 31: AUROC curves for final multivariable logistic regression models for treatment success among a) all cases, b) migrant cases and c) Irish-born cases.

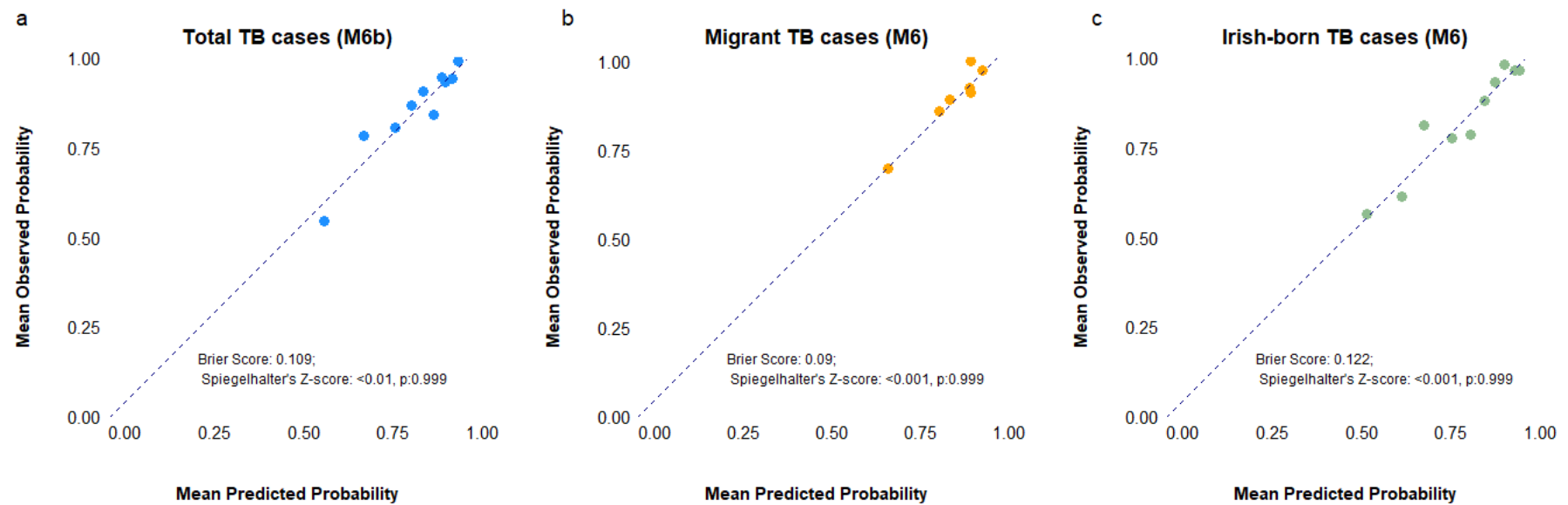


Figure 32: Calibration plots for final models for treatment success among a) total TB cases, b) migrant TB cases and c) Irish-born TB cases

7.4.5 Predictors of treatment success - Migrant cases

[Table 20](#) summarises the distribution of the independent variables for the full sample of 950 migrant cases with treatment success known and the cORs estimated by univariable logistic regression.

Except for years since arrival, no significant differences in treatment success were detected within the migrant subpopulations examined (WHO TB incidence category, Top 10 CIR birth-countries and Top 10 case number birth-countries in Ireland). A significantly increasing trend in the proportion of successfully treated cases was present with increasing interval between arrival in Ireland and notification as a TB case. The high proportion of migrant cases without year of arrival reported (33%) precluded this from being further examined in the model.

[Table 21](#) presents the results of the final model generated by the manual backwards stepwise elimination methods, alongside the distribution of patient characteristics and the cORs estimated by univariable logistic regression for the complete case sample among migrant cases. Variables retained in the final model included employment status, disease site and TB drug resistance. Compared to the reference group of being in paid employment, cases who were unemployed or retired had lower adjusted odds of treatment success. Cases infected with resistant strains of *M. tuberculosis* had lower adjusted odds of successful treatment. Disease site was the only variable associated with increased treatment success. Compared to the reference category of PTB, cases with EPTB had higher adjusted odds of treatment success.

These variables differed slightly compared with those ranked as the most influential according to a Random Forest variable importance plot of the full model prior to variable removal, with patient type ranked higher than disease site ([Figure 30](#)). According to the Random Forest of the full model, age and employment status were the most influential variables in the full model. [Table A6.1](#) displays the results of model generated by algorithm method. In addition to the same variables retained in the manual model, the algorithm model also included sex and previous history of TB disease.

Model assumptions of the final models produced by both algorithm and manual backwards stepwise elimination methods are displayed in Appendix 6 ([Figures A6.2-A6.3](#)). All metrics of the algorithm model were acceptable with 71% of binned residuals within error bounds, whereas only 44% were within error bounds for the model generated by the manual method. Model performance metrics indicated that both models performed similarly with a PCP of 82% for both models. However, the algorithm model (step AIC) had the highest AICc weight of models compared. The Hosmer-Lemeshow goodness-of-fit test results did not indicate any evidence of poor model fit for either the

model generated by the manual method (statistic = 1.96, $p = 0.96$) or the model generated by algorithm method (statistic = 6.66, $p = 0.67$). The AUROC was 0.74 (CI:0.70-0.79) for the manual method and 0.72 (CI:0.65-0.79) for the algorithm method indicating acceptable levels of discrimination ([Figure 31](#)). However, the AUROC curve for the algorithm method exhibited a sharp spike followed by trough pattern ([Figure A6.4](#)) indicating possible issues with model fit, such as overfitting or class imbalance. [Figure 32](#) shows the calibration plot for the final model alongside the Brier Score (0.11) and Spiegelhalter's Z score (<0.001 , $p: 0.999$), neither of which indicated that the model was poorly calibrated.

Table 20: Distribution of migrant patient characteristics by treatment success and crude odds ratios from binary logistic regression (n=950)

Characteristic N (%)	Treatment success				Univariable logistic regression	
	Missing N (%)	Overall N = 950	Unsuccessful N = 103	Successful N = 847	cOR (95% CI) ^{†††††}	p-value
Median age (IQR)	1 (0.1%)	34.0 (15.0)	37.0 (19.0)	33.5 (16.0)	0.98 (0.96 to 0.99)	0.002
Sex	2 (0.2%)					0.15
<i>Female</i>		431 (45.5%)	40 (38.8%)	391 (46.3%)	—	
<i>Male</i>		517 (54.5%)	63 (61.2%)	454 (53.7%)	0.74 (0.48 to 1.12)	
Employment status	75 (7.9%)					<0.001
<i>Paid employment</i>		380 (43.4%)	23 (24.0%)	357 (45.8%)	—	
<i>Unemployed</i>		319 (36.5%)	48 (50.0%)	271 (34.8%)	0.36 (0.21 to 0.61)	
<i>Retired</i>		25 (2.9%)	8 (8.3%)	17 (2.2%)	0.14 (0.05 to 0.37)	
<i>Student/Child</i>		129 (14.7%)	12 (12.5%)	117 (15.0%)	0.63 (0.31 to 1.34)	
<i>Other</i>		22 (2.5%)	5 (5.2%)	17 (2.2%)	0.22 (0.08 to 0.71)	
Current housing	79 (8.3%)					0.090
<i>Private house</i>		801 (92.0%)	77 (84.6%)	724 (92.8%)	—	
<i>Congregate residential/care setting</i>		44 (5.1%)	8 (8.8%)	36 (4.6%)	0.48 (0.23 to 1.14)	
<i>Prison/Homeless</i>		16 (1.8%)	4 (4.4%)	12 (1.5%)	0.32 (0.11 to 1.16)	
<i>Other housing</i>		10 (1.1%)	2 (2.2%)	8 (1.0%)	0.43 (0.10 to 2.85)	
Disease site	0 (0%)					0.004
<i>Pulmonary</i>		550 (57.9%)	73 (70.9%)	477 (56.3%)	—	
<i>Extrapulmonary</i>		400 (42.1%)	30 (29.1%)	370 (43.7%)	1.89 (1.22 to 2.99)	
Previous TB diagnosis	214 (23%)					0.012
<i>No</i>		682 (92.7%)	68 (85.0%)	614 (93.6%)	—	
<i>Yes</i>		54 (7.3%)	12 (15.0%)	42 (6.4%)	0.39 (0.20 to 0.80)	
Patient type	133 (14%)					0.025
<i>Hospital inpatient</i>		464 (56.8%)	64 (69.6%)	400 (55.2%)	—	
<i>Hospital outpatient</i>		278 (34.0%)	21 (22.8%)	257 (35.4%)	1.96 (1.19 to 3.35)	
<i>Other</i>		75 (9.2%)	7 (7.6%)	68 (9.4%)	1.55 (0.73 to 3.85)	
Outbreak associated	0 (0%)					0.50
<i>Not linked to outbreak</i>		890 (93.7%)	98 (95.1%)	792 (93.5%)	—	
<i>Outbreak associated</i>		60 (6.3%)	5 (4.9%)	55 (6.5%)	1.36 (0.58 to 3.98)	

††††† cOR = Crude Odds Ratio, CI = Confidence Interval

Characteristic N (%)	Treatment success				Univariable logistic regression	
	Missing N (%)	Overall N = 950	Unsuccessful N = 103	Successful N = 847	cOR (95% CI) ⁺⁺⁺⁺⁺	p-value
TB drug resistance	201 (21%)					0.011
<i>Sensitive</i>		621 (82.9%)	53 (71.6%)	568 (84.1%)	—	
<i>Resistant</i>		128 (17.1%)	21 (28.4%)	107 (15.9%)	0.48 (0.28 to 0.84)	
M/XDR-TB	201 (21%)					0.011
<i>No</i>		717 (95.7%)	66 (89.2%)	651 (96.4%)	—	
<i>Yes</i>		32 (4.3%)	8 (10.8%)	24 (3.6%)	0.30 (0.14 to 0.75)	
People living with HIV	419 (44%)					0.11
<i>Negative</i>		454 (85.5%)	47 (78.3%)	407 (86.4%)	—	
<i>Positive</i>		77 (14.5%)	13 (21.7%)	64 (13.6%)	0.57 (0.30 to 1.15)	
Diabetes	549 (58%)					0.27
<i>No</i>		372 (92.8%)	38 (88.4%)	334 (93.3%)	—	
<i>Yes</i>		29 (7.2%)	5 (11.6%)	24 (6.7%)	0.55 (0.21 to 1.69)	
Substance use	587 (62%)					<0.001
<i>No</i>		312 (86.0%)	24 (63.2%)	288 (88.6%)	—	
<i>Yes</i>		51 (14.0%)	14 (36.8%)	37 (11.4%)	0.22 (0.11 to 0.47)	
Geographical area	0 (0%)					0.030
<i>East</i>		415 (43.7%)	41 (39.8%)	374 (44.2%)	—	
<i>Midlands</i>		50 (5.3%)	5 (4.9%)	45 (5.3%)	0.99 (0.40 to 2.97)	
<i>Midwest</i>		59 (6.2%)	5 (4.9%)	54 (6.4%)	1.18 (0.49 to 3.54)	
<i>North East</i>		71 (7.5%)	4 (3.9%)	67 (7.9%)	1.84 (0.71 to 6.26)	
<i>North West</i>		30 (3.2%)	2 (1.9%)	28 (3.3%)	1.53 (0.44 to 9.72)	
<i>South</i>		161 (16.9%)	31 (30.1%)	130 (15.3%)	0.46 (0.28 to 0.77)	
<i>South East</i>		100 (10.5%)	7 (6.8%)	93 (11.0%)	1.46 (0.67 to 3.64)	
<i>West</i>		64 (6.7%)	8 (7.8%)	56 (6.6%)	0.77 (0.36 to 1.84)	
Years between arrival and notification	314 (33%)					0.013
<i>0-1</i>		131 (20.6%)	24 (36.9%)	107 (18.7%)	—	
<i>2-4</i>		165 (25.9%)	15 (23.1%)	150 (26.3%)	2.24 (1.13 to 4.56)	
<i>5-9</i>		165 (25.9%)	12 (18.5%)	153 (26.8%)	2.86 (1.40 to 6.15)	
<i>10+</i>		175 (27.5%)	14 (21.5%)	161 (28.2%)	2.58 (1.29 to 5.33)	

Table 21: Factors associated with treatment success among migrant TB cases (complete case sample: N = 477) for final model (M5)

Characteristic n (%)	Treatment success			Univariable logistic regression		Multivariable logistic regression	
	Overall N = 477	Unsuccessful N = 52	Successful N = 425	cOR (95% CI) ^{*****1}	p-value	aOR (95% CI) ¹	p-value
Median age (IQR)	34.0 (16.0)	39.5 (17.5)	33.0 (15.0)	0.98 (0.96 to 1.00)	0.031		
Sex					0.095		
<i>Female</i>	217 (45.5%)	18 (34.6%)	199 (46.8%)	—			
<i>Male</i>	260 (54.5%)	34 (65.4%)	226 (53.2%)	0.60 (0.32 to 1.09)			
Employment status					0.007		0.013
<i>Paid employment</i>	199 (41.7%)	12 (23.1%)	187 (44.0%)	—		—	
<i>Unemployed</i>	183 (38.4%)	26 (50.0%)	157 (36.9%)	0.39 (0.18 to 0.78)		0.40 (0.19 to 0.81)	0.013
<i>Retired</i>	16 (3.4%)	5 (9.6%)	11 (2.6%)	0.14 (0.04 to 0.51)		0.15 (0.05 to 0.56)	0.003
<i>Student/Child</i>	66 (13.8%)	6 (11.5%)	60 (14.1%)	0.64 (0.24 to 1.91)		0.63 (0.23 to 1.89)	0.38
<i>Other</i>	13 (2.7%)	3 (5.8%)	10 (2.4%)	0.21 (0.06 to 1.04)		0.23 (0.06 to 1.15)	0.046
Current housing					0.14		
<i>Private house</i>	442 (92.7%)	46 (88.5%)	396 (93.2%)	—			
<i>Congregate residential / care setting</i>	23 (4.8%)	3 (5.8%)	20 (4.7%)	0.97 (0.32 to 4.18)			
<i>Prison / Homeless</i>	8 (1.7%)	3 (5.8%)	5 (1.2%)	0.19 (0.05 to 0.97)			
<i>Other housing</i>	4 (0.8%)	0 (0.0%)	4 (0.9%)				
Disease site					0.002		0.010
<i>Pulmonary</i>	307 (64.4%)	43 (82.7%)	264 (62.1%)	—		—	
<i>Extrapulmonary</i>	170 (35.6%)	9 (17.3%)	161 (37.9%)	2.90 (1.44 to 6.50)		2.53 (1.23 to 5.74)	
Previous TB diagnosis					0.062		
<i>No</i>	445 (93.3%)	45 (86.5%)	400 (94.1%)	—			
<i>Yes</i>	32 (6.7%)	7 (13.5%)	25 (5.9%)	0.40 (0.17 to 1.05)			
Patient type					0.18		
<i>Hospital inpatient</i>	294 (61.6%)	38 (73.1%)	256 (60.2%)	—			
<i>Hospital outpatient</i>	132 (27.7%)	10 (19.2%)	122 (28.7%)	1.83 (0.91 to 3.98)			
<i>Other</i>	51 (10.7%)	4 (7.7%)	47 (11.1%)	1.74 (0.66 to 6.02)			
TB drug resistance					0.006		0.009
<i>Sensitive</i>	391 (82.0%)	35 (67.3%)	356 (83.8%)	—		—	
<i>Resistant</i>	86 (18.0%)	17 (32.7%)	69 (16.2%)	0.40 (0.21 to 0.76)		0.40 (0.21 to 0.79)	

***** cOR = Crude Odds Ratio, aOR: Adjusted Odds Ratio, CI = Confidence Interval. Note: Age in years was used in the model but median age is also summarised for the sample.

7.4.6 Predictors of treatment success - Irish-born cases

[Table 22](#) summarises the distribution of the independent variables for the full sample of 1,098 Irish-born cases with treatment success known and their cORs estimated by univariable logistic regression.

[Table 23](#) presents the results of the final model generated by the manual backwards stepwise elimination methods, alongside the distribution of patient characteristics and the cORs estimated by univariable logistic regression in the complete case sample for Irish-born cases. Variables retained in the final model generated by manual backwards stepwise elimination included age, infection with a drug-resistant strain, patient type and employment status. Increasing patient age was significantly negatively correlated with the outcome of treatment success. For each additional year in patient age, the adjusted odds of treatment success decreased by 3% where all other variables remained constant. Compared to the reference group of being in paid employment, cases who had occupational status reported as other, had lower adjusted odds of treatment success. Cases infected with resistant strains of *M. tuberculosis* had lower adjusted odds of successful treatment. Patient type was the only variable associated with increased treatment success. Compared to the reference category of in-patients, cases who were reported as being outpatients and other category had higher adjusted odds of treatment success. Housing type was not significant in the final model but all categories had lower adjusted odds of treatment success compared to the reference group of cases residing in private accommodation.

A Random Forest variable importance plot of the full model prior to variable removal ranked the same variables as most influential, except for infection with a drug-resistant strain ([Figure 30](#)). Variables retained in the model generated by the algorithm method (step AIC) were the same as those selected by the manual method.

Model assumptions of the final model are displayed in Appendix 6, [Figure A6.5](#). The proportion of binned residuals within error was 75% for the manual method. Model apparent performance metrics indicated the final model performed adequately with a PCP of 75.7%, highest AICc weight and Log Likelihood of models compared. The Hosmer-Lemeshow goodness-of-fit test results did not indicate any evidence of poor model fit (statistic = 7.21, p-value = 0.51). The AUROC was 0.77 (CI:0.72-0.82) indicating a fair level of discrimination ([Figure 31](#)). [Figure 32](#) shows the calibration plot for the final

model alongside the Brier Score (0.122) and Spiegelhalter's Z score (<0.001 , $p: 0.999$), neither of which indicated that the model was poorly calibrated.

Table 22: Distribution of Irish-born patient characteristics by treatment success and crude odds ratios from binary logistic regression (n=1,098)

Characteristic N (%)	Treatment success: Irish-born cases				Univariable logistic regression	
	Missing N (%)	Overall N = 1,098	Unsuccessful N = 199	Successful N = 899	cOR (95% CI) ^{§§§§§§}	p-value
Median age (IQR)	2 (0.2%)	53.0 (32.0)	67.0 (30.0)	49.0 (31.0)	0.97 (0.96 to 0.98)	<0.001
Sex	0 (0%)					0.38
<i>Female</i>		405 (36.9%)	68 (34.2%)	337 (37.5%)	—	
<i>Male</i>		693 (63.1%)	131 (65.8%)	562 (62.5%)	0.87 (0.62 to 1.19)	
Current housing	63 (5.7%)					<0.001
<i>Private house</i>		970 (93.7%)	161 (86.6%)	809 (95.3%)	—	
<i>Congregate residential / care setting</i>		40 (3.9%)	17 (9.1%)	23 (2.7%)	0.27 (0.14 to 0.52)	
<i>Prison/Homeless</i>		17 (1.6%)	4 (2.2%)	13 (1.5%)	0.65 (0.23 to 2.32)	
<i>Other housing</i>		8 (0.8%)	4 (2.2%)	4 (0.5%)	0.20 (0.05 to 0.85)	
Employment status	93 (8.5%)					<0.001
<i>Paid employment</i>		279 (27.8%)	24 (14.0%)	255 (30.6%)	—	
<i>Unemployed</i>		312 (31.0%)	53 (30.8%)	259 (31.1%)	0.46 (0.27 to 0.76)	
<i>Retired</i>		283 (28.2%)	76 (44.2%)	207 (24.8%)	0.26 (0.15 to 0.41)	
<i>Student/Child</i>		100 (10.0%)	9 (5.2%)	91 (10.9%)	0.95 (0.44 to 2.23)	
<i>Other</i>		31 (3.1%)	10 (5.8%)	21 (2.5%)	0.20 (0.08 to 0.48)	
Disease site	4 (0.4%)					0.73
<i>Pulmonary</i>		845 (77.2%)	154 (78.2%)	691 (77.0%)	—	
<i>Extrapulmonary</i>		249 (22.8%)	43 (21.8%)	206 (23.0%)	1.07 (0.74 to 1.56)	
Previous TB diagnosis	207 (19%)					0.009
<i>No</i>		806 (90.5%)	123 (84.2%)	683 (91.7%)	—	
<i>Yes</i>		85 (9.5%)	23 (15.8%)	62 (8.3%)	0.49 (0.29 to 0.83)	
Patient type	90 (8.2%)					<0.001
<i>Hospital inpatient</i>		623 (61.8%)	152 (82.2%)	471 (57.2%)	—	
<i>Hospital outpatient</i>		286 (28.4%)	20 (10.8%)	266 (32.3%)	4.29 (2.69 to 7.20)	
<i>Other</i>		99 (9.8%)	13 (7.0%)	86 (10.4%)	2.13 (1.20 to 4.11)	
Outbreak associated	0 (0%)					<0.001
<i>Not linked to outbreak</i>		905 (82.4%)	180 (90.5%)	725 (80.6%)	—	
<i>Outbreak associated</i>		193 (17.6%)	19 (9.5%)	174 (19.4%)	2.27 (1.41 to 3.86)	

§§§§§§ cOR = Crude Odds Ratio, aOR: Adjusted Odds Ratio, CI = Confidence Interval

Characteristic N (%)	Treatment success: Irish-born cases				Univariable logistic regression	
	Missing N (%)	Overall N = 1,098	Unsuccessful N = 199	Successful N = 899	cOR (95% CI) ^{§§§§§§}	p-value
TB drug resistance	272 (25%)					0.14
<i>Sensitive</i>		773 (93.6%)	139 (90.8%)	634 (94.2%)	—	
<i>Resistant</i>		53 (6.4%)	14 (9.2%)	39 (5.8%)	0.61 (0.33 to 1.19)	
M/XDR-TB	272 (25%)					
<i>No</i>		826 (100.0%)	153 (100.0%)	673 (100.0%)		
<i>Yes</i>		0 (0.0%)	0 (0.0%)	0 (0.0%)		
People living with HIV	668 (61%)					0.90
<i>Negative</i>		415 (96.5%)	60 (96.8%)	355 (96.5%)	—	
<i>Positive</i>		15 (3.5%)	2 (3.2%)	13 (3.5%)	1.10 (0.29 to 7.14)	
Diabetes	569 (52%)					0.009
<i>No</i>		489 (92.4%)	74 (85.1%)	415 (93.9%)	—	
<i>Yes</i>		40 (7.6%)	13 (14.9%)	27 (6.1%)	0.37 (0.19 to 0.77)	
Substance use	522 (48%)					0.60
<i>No</i>		372 (64.6%)	61 (62.2%)	311 (65.1%)	—	
<i>Yes</i>		204 (35.4%)	37 (37.8%)	167 (34.9%)	0.89 (0.57 to 1.40)	
Immunosuppression	550 (50%)					<0.001
<i>No</i>		426 (77.7%)	53 (60.9%)	373 (80.9%)	—	
<i>Yes</i>		122 (22.3%)	34 (39.1%)	88 (19.1%)	0.37 (0.23 to 0.60)	
Geographical area	0 (0%)					0.002
<i>East</i>		292 (26.6%)	57 (28.6%)	235 (26.1%)	—	
<i>Midlands</i>		47 (4.3%)	8 (4.0%)	39 (4.3%)	1.18 (0.55 to 2.85)	
<i>Midwest</i>		89 (8.1%)	19 (9.5%)	70 (7.8%)	0.89 (0.51 to 1.63)	
<i>North East</i>		75 (6.8%)	19 (9.5%)	56 (6.2%)	0.71 (0.40 to 1.32)	
<i>North West</i>		62 (5.6%)	21 (10.6%)	41 (4.6%)	0.47 (0.26 to 0.87)	
<i>South</i>		337 (30.7%)	41 (20.6%)	296 (32.9%)	1.75 (1.13 to 2.72)	
<i>South East</i>		130 (11.8%)	19 (9.5%)	111 (12.3%)	1.42 (0.82 to 2.55)	
<i>West</i>		66 (6.0%)	15 (7.5%)	51 (5.7%)	0.82 (0.44 to 1.61)	

Table 23: Factors associated with treatment success among Irish-born TB cases (complete case sample: N = 592) for final model (M6)

Characteristic N (%)	Treatment success			Univariable logistic regression		Multivariable logistic regression M6b	
	Overall N = 1,069	Unsuccessful N = 154	Successful N = 915	cOR (95% CI)	p-value ****	aOR (95% CI)	p-value
Median age (IQR)	40.0 (29.0)	53.5 (37.8)	39.0 (25.5)	0.97 (0.96 to 0.98)	<0.001	0.98 (0.96 to 0.99)	0.003
Sex					0.034		
<i>Female</i>	422 (39.5%)	49 (31.8%)	373 (40.8%)	—			
<i>Male</i>	647 (60.5%)	105 (68.2%)	542 (59.2%)	0.68 (0.47 to 0.97)			
Migrant status					0.003		
<i>Irish-born</i>	592 (55.4%)	102 (66.2%)	490 (53.6%)	—			
<i>Migrant</i>	477 (44.6%)	52 (33.8%)	425 (46.4%)	1.70 (1.19 to 2.45)			
Employment status					<0.001		
<i>Paid employment</i>	364 (34.1%)	25 (16.2%)	339 (37.0%)	—		—	
<i>Unemployed</i>	376 (35.2%)	58 (37.7%)	318 (34.8%)	0.40 (0.24 to 0.65)		0.48 (0.28 to 0.79)	0.005
<i>Retired</i>	187 (17.5%)	55 (35.7%)	132 (14.4%)	0.18 (0.10 to 0.29)		0.41 (0.19 to 0.84)	0.017
<i>Student/Child</i>	111 (10.4%)	7 (4.5%)	104 (11.4%)	1.10 (0.48 to 2.81)		0.79 (0.33 to 2.14)	0.62
<i>Other</i>	31 (2.9%)	9 (5.8%)	22 (2.4%)	0.18 (0.08 to 0.45)		0.19 (0.08 to 0.50)	<0.001
Current housing					0.031		
<i>Private house</i>	996 (93.2%)	135 (87.7%)	861 (94.1%)	—			
<i>Congregate residential / care setting</i>	45 (4.2%)	12 (7.8%)	33 (3.6%)	0.43 (0.22 to 0.89)			
<i>Prison/Homeless</i>	19 (1.8%)	6 (3.9%)	13 (1.4%)	0.34 (0.13 to 0.98)			
<i>Other housing</i>	9 (0.8%)	1 (0.6%)	8 (0.9%)	1.25 (0.23 to 23.4)			
Disease site					0.079		
<i>Pulmonary</i>	809 (75.7%)	125 (81.2%)	684 (74.8%)	—			
<i>Extrapulmonary</i>	260 (24.3%)	29 (18.8%)	231 (25.2%)	1.46 (0.96 to 2.28)			
Previous TB diagnosis					0.005		
<i>No</i>	988 (92.4%)	133 (86.4%)	855 (93.4%)	—		—	
<i>Yes</i>	81 (7.6%)	21 (13.6%)	60 (6.6%)	0.44 (0.27 to 0.77)		0.61 (0.35 to 1.11)	0.093
Patient type					<0.001		
<i>Hospital inpatient</i>	690 (64.5%)	129 (83.8%)	561 (61.3%)	—		—	
<i>Hospital outpatient</i>	274 (25.6%)	17 (11.0%)	257 (28.1%)	3.48 (2.11 to 6.09)		3.27 (1.95 to 5.82)	<0.001
<i>Other</i>	105 (9.8%)	8 (5.2%)	97 (10.6%)	2.79 (1.40 to 6.36)		2.49 (1.22 to 5.81)	0.020

***** cOR = Crude Odds Ratio, aOR: Adjusted Odds Ratio, CI = Confidence Interval. Note: Age in years was used in the model but median age is also summarised for the sample.

Characteristic N (%)	Treatment success			Univariable logistic regression		Multivariable logistic regression M6b	
	Overall N = 1,069	Unsuccessful N = 154	Successful N = 915	cOR (95% CI)	p-value*****	aOR (95% CI)	p-value
Outbreak associated					0.091		
<i>Not linked to outbreak</i>	920 (86.1%)	139 (90.3%)	781 (85.4%)	—			
<i>Outbreak associated</i>	149 (13.9%)	15 (9.7%)	134 (14.6%)	1.59 (0.93 to 2.90)			
TB drug resistance					0.018		
<i>Sensitive</i>	945 (88.4%)	127 (82.5%)	818 (89.4%)	—		—	
<i>Resistant</i>	124 (11.6%)	27 (17.5%)	97 (10.6%)	0.56 (0.35 to 0.90)		0.36 (0.22 to 0.61)	<0.001

7.5 Discussion

This study presents the first analysis of factors associated with TB treatment success in Ireland, finding consistently lower adjusted odds of treatment success among cases infected with a drug-resistant strain of *M. tuberculosis* across all three populations examined. The remaining predictors of treatment success differed slightly according to the population group examined, with predictors of treatment success being more similar between total cases and Irish-born cases than for migrant TB cases.

Rates of treatment success among MDR-TB cases derived from both programmatic data sources and individual studies are markedly lower than cases with pansensitive TB (Chaves Torres et al., 2019; Faustini et al., 2005; Karo et al., 2015; World Health Organization, 2024b). In keeping with this, the current study found that having any form of TB drug resistance was associated with lower adjusted odds of treatment success among total cases (OR:0.4), Irish-born cases (OR:0.3), and migrant cases (OR:0.4). This finding is particularly of note given the low proportion of MDR-TB cases in the complete case sample (2%) and the adjustment for previous TB diagnoses.

As has been commonly reported in the literature elsewhere, lower odds of success were observed with increasing age among total cases and Irish-born cases (Chaves Torres et al., 2019; Guthmann et al., 2020; Karo et al., 2015; Nguyen & Graviss, 2018). This finding is commonly attributed to the increased complexity of case management due to increased comorbidities among older age groups as well as delayed diagnoses among older TB cases who may present with less specific symptoms than observed among younger TB cases (Abbara et al., 2019; Kwon et al., 2013). Although age was not a significant predictor among migrant cases in this study, possibly due to the younger age distribution observed among these cases, it was the most influential variable according to the Random Forest. In the upper end of older age, increasing mortality may also contribute to unsuccessful treatment outcomes (Pradipta et al., 2019).

The finding of lower odds of success among total cases and migrant cases who were unemployed, retired or with other employment status aligns with findings reported by Sauer et al (Sauer et al., 2018). Although levels of co-linearity between age and employment status were low, the finding of lower success among retired TB cases may potentially be influenced by the older median age of retired cases compared to the overall median age among both total cases (74 vs 40 years) and migrant cases (69 vs 34 years). While the finding of lower success among cases with other employment status is difficult to interpret with certainty it should be noted that where additional

details were reported for these cases the majority were actually unemployed but for a specific reason such as due to disability, incarceration, being a carer, or not having legal right to work due to their international protection applicant status. It is therefore plausible that at least part of the observed effect is due to these types of unemployment also having a similar mechanism that contributes to a lower treatment success, similar to the overall category of unemployment.

Although it was not possible to include housing type in the model due to the small numbers of cases in certain mixed categories, compared to the reference groups of private housing, the crude odds of treatment success were significantly lower among total cases and Irish-born resident in congregate or residential care settings and among those experiencing homelessness or incarceration. The type of patient accommodation has been shown to influence treatment success elsewhere in the international literature, with studies reporting lower odds of success among cases who did not reside in private housing. Cases experiencing homelessness, residing in long-term care facilities or prisons were shown to have lower treatment success rates and higher rates of TB mortality were also shown for cases resident in residential care or prison (Baussano et al., 2008; Guthmann et al., 2020; Pradipta et al., 2019).

Two factors were associated with increased odds of treatment success but differed across patient groups. Among total cases and Irish-born cases, the patient type was associated with increased odds of treatment success. Compared to in-patients, outpatients and other patient types had an increased odds of treatment success but this was not a significant predictor among migrant cases. This finding is likely a reflection of the reasons that cases are admitted as in-patients, such as having severe or complex disease, or infection with drug resistant strain all of which can have a negative effect on treatment outcomes. Current national guidelines recommend in-patient management in circumstances such as severe forms of TB, complex co-morbidities, adverse drug reactions, M/XDR-TB or challenging social conditions such as residing in a congregate setting, experiencing homelessness, substance use or poor treatment adherence (HSE Health Protection Surveillance Centre, 2014). A similar finding was reported by Baussano et al with a lower success rate among cases whose treatment was initiated in an in-patient setting, who also attributed this result to national guidelines recommending inpatient treatment of difficult to treat or severe cases (Baussano et al., 2008).

The only factor associated with increased odds of treatment success among migrants was the disease site, with exclusive extrapulmonary disease having increased odds of treatment success

compared to cases with exclusively PTB. This finding is difficult to contextualise within the evidence base from low TB incidence and high-income countries where EPTB is often excluded from treatment outcome analyses. Although treatment success rates among EPTB cases are not published by WHO or ECDC, a previous study examining over half a million TB cases reported to ECDC found a higher rate of treatment success for EPTB compared to PTB (81.4% vs 73.5% respectively) (Sandgren et al., 2013). However, individual studies have reported lower rates of treatment success for EPTB cases (Luque et al., 2020; Vasankari et al., 2010). Our finding may be partially supported by other studies finding smear positive PTB is associated with reduced odds of treatment success (Guthmann et al., 2020). It may also be explained by the fact that, similar to Sandgren et al, rates of MDR-TB in this study were significantly lower among migrant cases with EPTB than among migrant cases with PTB (1.8% vs 4.5% respectively) (Sandgren et al., 2013). MDR-TB is a stronger determinant of treatment success than disease site. Patient characteristics of EPTB compared to PTB cases included in the complete case sample were similar for most relevant predictors of treatment success. However, proportions of EPTB cases reported as having substance use issues were lower than observed among PTB cases in this sample (6.3% vs 21% respectively) which could partly explain the finding of higher treatment success among EPTB. Finally, this result could also be influenced by the significantly higher proportion of EPTB among cases who were excluded from the complete case analyses (45% vs 36%).

Although this study only retained sex in the algorithm model for migrants, male sex is well established in the literature as a risk factor for unsuccessful treatment outcomes (Chidambaram et al., 2021; Guthmann et al., 2020; Karo et al., 2015). Both social and biological factors have been suggested as reasons why treatment success is lower in males. Treatment adherence is also reported to be lower among males than females and has been linked to underlying behaviours which are more common among men than women, such as higher substance use among males in European countries (European Monitoring Centre for Drugs and Drug Addiction, 2006; Van Den Hoff et al., 2010). Other social determinants linked to poor treatments outcomes such as being incarcerated or experiencing homelessness are also more common in males (Jones et al., 2021; O'Sullivan et al., 2021). Poorer outcomes in males also occur against a backdrop of being diagnosed and treated earlier than females, which is thought to be due to initially presenting to services with more severe disease (Chidambaram et al., 2021; Dale et al., 2017). A recent systematic review of sex disparities among TB treatment outcomes found this effect persisted across multiple subgroups analysed and was most evident in high income countries where health system access inequities were lower between sexes (Chidambaram et al., 2021).

7.5.1 Strengths and limitations:

This is the first study to undertake comprehensive analysis of TB treatment success predictors in Ireland using a comprehensive programmatic national level dataset. The use of standardised EU definitions will enhance international comparability and replication. The models are based on information that is readily available to both clinical and public health practitioners, allowing the use of this information as part of early-stage risk assessments to enable the provision of enhanced treatment supports for cases. This study attempted to reflect the diversity within migrant populations by examining differences between treatment outcomes for migrant sub-populations. However, the final model analysed migrants as a whole as no significant differences were detected between subgroups analysed except for years since arrival, but poor data completeness for this variable (33% missing) prevented its inclusion in the model.

This study has several limitations and was heavily impacted by the poor completeness of the study data available for these models. Firstly, treatment outcome data were missing for almost a third of cases while data on several key predictors (e.g. HIV status, diabetes) were too incomplete to be examined in the models. Data completeness further declined sharply in the latter years of the study, mainly due to the effects of the Covid-19 pandemic emergency response. TB treatment outcomes for these years were scheduled for collection at a time when Public Health staff were redeployed away from routine TB activities. Accordingly, these models may be more representative of cases diagnosed in the earlier years of this study.

Geographical bias was also evident with high levels of missing data from the region containing the Dublin metropolitan area. Use of complete case analysis in this context may have increased selection bias. The significant differences observed between cases with outcome reported and for cases with missing outcomes for employment status and patient type could also have biased the model estimates. These models will need to be validated on an external data source with higher completeness rate to further test the model performance.

The calibration plot shows that although the model was well calibrated for the data, there are indications that the lower frequency of unsuccessful treatment outcomes (c.15%) in the dataset used to develop this model may have affected the model's performance and overall calibration. Future validation on external datasets will be needed to refine this model as it was not possible to conduct validation within the scope of this project.

7.5.2 Conclusions and recommendations:

Ireland fails to meet WHO target of >90% treatment success with poor completeness of surveillance data. Data quality improvement initiatives are needed to allow accurate monitoring of this key indicator of TB control and so that the model can be validated externally on a more robust dataset. Predictors of TB treatment success include both biological and social factors but differed slightly between migrant and Irish-born populations. Additional supports should be considered for cases who are of older age, or infected with drug resistant TB strains, or unemployed. Achieving the goal of End TB Strategy remains dependent on addressing social determinants of TB so TB control programmes should address these as a priority.

7.6 Chapter conclusion:

This fourth and final results chapter identified factors associated with successful and unsuccessful treatment outcomes among TB cases in Ireland, finding that there were both similarities and differences in these factors between migrant cases and Irish-born cases. The findings presented in this chapter can inform development of targeted interventions to support TB cases to achieve a successful treatment outcome and support TB elimination goals globally and in line with the HSE TB strategic actions (HSE National Health Protection Office, 2024). The following Chapter 8 is the final chapter in this thesis, which will summarise the findings of this study as a whole and outline the key concepts that emerged as important consistently throughout each chapter. Chapter 8 will also outline their implications for future research, policy and practice.

8 Chapter 8: General discussion, conclusions and recommendations

8.1 Chapter outline

This final chapter presents a review of the thesis, followed by an overall discussion and conclusion of the findings. While the individual study findings from Chapters 4, 5, 6 and 7 have already been discussed within the context of the international literature, this chapter will re-examine the overall study and present key concepts that were found to be consistently important across the range of research questions explored along with the overall conclusions. Strengths and limitations of the overall study will be presented, alongside recommendations for policy, practice and future research directions. [Table 24](#) summarises the findings within these concepts for the four results chapters.

8.2 Summary of thesis/ overview

As evidenced by the international literature and global policy context, migrant populations are a key group requiring enhanced public health interventions and service provision in order to achieve TB elimination goals in low incidence settings (European Centre for Disease Prevention and Control, 2018). Despite this, the international literature was unclear on how to adequately describe the diversity present among international migrant TB patient populations. Studies have mainly described migrants as a homogenous group or according to their legal status (Hollo et al., 2016, 2017; Ködmön et al., 2016; Langholz Kristensen et al., 2019; Odone et al., 2015; van den Boogaard et al., 2020). As such the evidence base is lacking regarding the influence of the migrant patient's country of origin, mode of migration, social risk factors and health status; all of which interact to produce differing risks of importing TB into a host country, of becoming infected with TB once arrived and of accessing health services if they develop TB infection or disease.

The rationale for conducting this study was to provide a better understanding of the effects of migration on the epidemiology of TB to inform tailored TB prevention and control activities working towards the global goal of TB elimination. This study approached its aim from a public health perspective guided by the NICE conceptual framework on the determinants of health (National Institute for Health and Care Excellence, 2012). Epidemiological principles and concepts were employed to investigate patterns of TB disease by examining environmental, sociocultural, population and organisational level factors. The study explored its aim firstly through a systematic review investigating how migration from high TB incidence countries affects the epidemiology of TB in low to medium incidence countries. Secondly, the aim was addressed through three additional objectives which were assessed through a secondary-data analysis of the national TB surveillance

dataset. A detailed cross-sectional analysis of the comparative epidemiology of TB notifications in Irish-born and foreign-born populations within the Irish context was conducted. At the prevention side of the continuum, the impact of universal TB vaccination cessation on the epidemiology of paediatric TB in Ireland was explored. While at the control end of the continuum, factors associated with successful treatment outcomes were investigated.

8.3 Summary of key findings

The systematic review findings reported in [Chapter 4](#) describe significant differences in key epidemiological indicators between high incidence migrants and non-migrants (Jackson et al., 2021). Significant differences among high incidence migrants and non-migrants were observed in the overall proportions of key epidemiological indicators; MDR-TB, HIV co-infected cases, clustered cases and successfully treated cases. However, only the MDR-TB findings were significant according within the meta-analysis results. This chapter also identified a gap in the evidence base in relation to reporting information on TB incidence level of migrant populations under study, which resulted in 70% of retrieved articles being excluded due to missing data. The two most common analytical approaches were to specify the most common countries of origin and report the often substantial remainder as “other”, or else to report by geographical regions of origin, resulting in mixed categories that were impossible to interpret.

[Chapter 5](#) used the Irish TB notification dataset to conduct a detailed cross-sectional analysis of the comparative epidemiology of TB in Irish-born and foreign-born populations. The key finding from this study was that differences in the TB patient profile were observed not only among migrants compared to Irish-born cases, but also between the migrant subgroups studied. Compared to Irish-born cases, migrant cases were younger and had higher odds of:

- living with HIV,
- having an EPTB,
- being infected with a drug-resistant strain and
- residing in a congregate residential setting

and lower odds of

- being detected through contact tracing and
- being linked to an outbreak.

Although a significantly declining temporal trend was still present for the latter period of the study (2017-2021) in total cases and Irish-born cases, the trend was no longer significant among migrant cases.

Migrant TB patient characteristics differed according to the incidence level in the origin-country and according to the interval between arrival and notification as a TB case. Specifically, migrants from very high incidence countries were younger and had the highest proportions of PLWHIV and with previous TB screening in Ireland, and the lowest proportions with PTB and being linked to an outbreak, while migrants originating from low incidence countries were older. A significant trend in the proportion of IPARs was observed in relation to the increasing TB incidence category of the migrant origin country. Recently arrived migrants were significantly younger and had higher proportions of IPARs, PLWHIV and PTB. The proportions of migrants from very high incidence countries decreased in line with duration of residence in Ireland. This chapter filled an important gap in the literature which has typically analysed international migrants simply as “foreign-born”.

[Chapter 6](#) reported that despite the complete cessation of the BCG vaccination programme in Ireland in 2015 due to the lack of vaccine supply, the annual trends in paediatric TB cases aged 0-6 years old remained stable from 2011 to 2021, with consistent patterns observed at both national and regional levels. ASIRs continued to reflect typical patterns with no major increase observed during this study in this age group who were most likely to be directly affected by cessation of BCG vaccination. However, it was highlighted that interruption of the previously declining temporal trend in this age group during a period of universal vaccination may be an early warning of a future increase. Eight of the 19 children notified since vaccination ceased would have been eligible to receive BCG under the current selective strategy highlighting an important gap in health service delivery currently and supporting the planned introduction of a selective BCG vaccination programme. This chapter emphasised the need to continue timely and complete enhanced surveillance among paediatric TB cases to monitor for the emergence of any increasing trends, or emergent risk groups in this mainly unvaccinated population and to evaluate the longer-term effects of the change in vaccination policy, which is a key TB prevention activity.

[Chapter 7](#) addressed TB treatment which is a critical TB control activity and found consistently lower odds of treatment success among cases infected with a drug-resistant strain of *M. tuberculosis* across all three populations examined in Ireland; total cases, migrant cases and Irish-born cases. The remaining predictors of treatment success differed slightly according to the three population groups

examined, with predictors of treatment success being more similar between total cases and Irish-born cases than for migrant TB cases. Predictors of TB treatment success included both biological (patient age and infection with a drug-resistant strain) and social factors (employment status) but differed slightly between migrant and Irish-born populations, highlighting the continued need for TB control programmes to address social determinants of TB as a priority in order to achieve the End TB Strategy goals.

Table 24: Summary of key findings by concept and results chapter

Concept	Chapter 4 Systematic Review	Chapter 5 TB Epidemiology in Ireland	Chapter 6 Effects of universal BCG cessation	Chapter 7 Factors associated with treatment success
Drug resistance	Higher among migrants	Higher % among migrants	All resistant cases among Irish-born and low TB incidence migrants	Reduced treatment success associated with drug resistance
Employment	Not investigated	Higher % employed among migrants	n/a	Reduced treatment success associated with unemployment
Housing	Not investigated	Higher % in congregate housing among migrants	Not investigated	Reduced treatment success associated with being in prison/ experiencing homeless
Site of disease	No difference in odds of sputum smear positivity detected	Higher % of EPTB, normal CXR results and CT thorax scan results among migrants	No meningitis during universal vaccination, 1 meningitis after cessation	Increased treatment success associated with extrapulmonary disease among migrants
TB incidence level in country of birth	Only high and very high incidence migrants included	Migrants from very high incidence countries had the highest % PLWHIV, previous TB screening in Ireland, and the lowest % with PTB and outbreak linkage	At least 8/19 cases born after vaccination ceased would have been eligible to receive BCG based on high incidence birth country or parental birth country	Not significantly associated with treatment success
Interval between arrival and diagnosis	Not investigated	Higher % PTB, PLWHIV & IPARs	Where reported, cases were notified 0-1 years after arrival	Lower treatment success among recently arrived migrants

8.4 Discussion of key findings and concepts

Although this thesis examined a very broad range of areas related to migrant TB epidemiology, from prevention through to control interventions, several key concepts were found to be consistently important across the range of questions examined; drug resistance, social determinants (housing and employment status) and EPTB. Concepts that emerged as important among the migrant cases included TB incidence level of the country of birth and the duration of residence in Ireland prior to notification with TB.

8.4.1 Drug resistance

Drug resistance is a major public health threat and potential obstacle to TB elimination. The finding of significantly higher proportions of anti-TB drug resistance among migrants compared to non-migrants was reported in both the systematic review presented in [Chapter 4](#), and within the Irish notification dataset examined in [Chapter 5](#). The odds of infection with a drug-resistant strain were three times higher among migrant cases, while the odds of infection with a M/XDR strain was 19 times higher among migrant cases compared to Irish-born cases and occurred almost exclusively among migrant cases. Furthermore, [Chapter 7](#) found that infection with a drug-resistant strain of *M. tuberculosis* was the only significant predictor consistently associated with reduced treatment success across the three population groups examined in Ireland, even after adjusting for other factors such as age, patient type, employment status and housing category.

While the level of M/XDR was low overall in this study, it is important to note that the majority of these cases (80%) were diagnosed with PTB, which increases the risk of onward transmission. These high levels of PTB found among M/XDR cases are particularly notable against the backdrop of a much lower overall proportion of PTB among migrants (58%) in this study.

The combined finding of high levels of drug resistance, coupled with high proportions of potentially infectious PTB and reduced treatment success is particularly important given the continued increasing trend in global migration that has occurred since the study period. Since the study period, international migration has continued to increase driven in part by further wars in Ukraine and Palestine. In Ireland, the proportion of rifampicin-resistant TB increased to 6.8% in 2022, more than double the previous 5-year mean value (HSE Health Protection Surveillance Centre, 2025). Across Europe, many countries experienced similar steep rises in levels of drug resistance following the accommodation of BOTPs fleeing war in Ukraine (de Vries et al., 2024; Dohál et al., 2023; Doležalová et al., 2024; Guthmann et al., 2023; Hauer et al., 2023). As no systematic screening of Ukrainian

BOTPs was recommended by ECDC, it may take several years for these cases to be detected through passive case presentation. Perhaps unsurprisingly, European countries that conducted screening of BOTPs found higher rates of TB than countries that did not screen. In Norway where screening of all BOTPs was mandatory, TB incidence levels in this population exceeded those estimated by WHO (de Vries et al., 2024). In France, active screening detected cases that were sputum positive and MDR-TB which may otherwise not have been found for several more years (Guthmann et al., 2023).

The cost of drugs required to treat TB increase in line with increasing level of drug resistance (Günther et al., 2023). Drug regimens for treatment of M/XDR TB are expensive in low incidence countries as market demands have historically been low. Currently, WHO recommend a six-month, all-oral treatment regimen for drug-resistant TB, utilising bedaquiline, pretomanid, linezolid and moxifloxacin (BPALM) which can cost over €40,000 per patient in many EU/EEA countries (Günther et al., 2023). A recent survey of drug availability and access in 18 European countries found Ireland was the only country reporting limited availability for all drugs surveyed (Otto-Knapp et al., 2024). The majority of other European countries that responded reported better availability for a minimum of bedaquiline, linezolid and fluoroquinolones. Ireland was also the only country to report a pricing obstacle for all component drugs in the BPALM regimen. Issues of access and availability to medications required to treat these higher levels of M/XDR TB have resulted in ongoing discussions between WHO and Ministries of Health in the WHO European region regarding how pharmaceutical companies might be incentivized to stay in the market (World Health Organization, 2024d). At the time of writing, the minimum cost of treating a single MDR-TB patient in Ireland with BPALM in 2025 is approximately €40,500 but may extend upwards to €60,000 (St. James' Hospital pharmacy, personal communication, 17/01/2025).

Significant health costs are also incurred by the patient as many of the drugs required to treat drug resistant forms of TB cause significant side effects, affecting both physical (joint or muscle pains, hearing loss, gastrointestinal disturbance and hallucinations) and mental health (depression, anxiety and suicidal ideation) (Massud et al., 2022; Naran et al., 2023). Such side effects can complicate and prolong the required treatment. However, failing to treat drug resistant cases successfully can increase the level of drug resistance in circulating strains and allow further transmission among those at increased risk of TB. Consequently, successful patient outcomes are further reduced, and significant societal costs are incurred.

8.4.2 Social determinants of health:

Although earlier TB control strategies utilized a biomedical model that focused on removal of infectious cases through successful treatment, later strategies have come to acknowledge this will be insufficient to achieve TB elimination without a strong political commitment to address the broader determinants of TB, including social determinants (World Health Organization, 1994, 2022a). The 2022 update to the WHO End TB Strategy endorses biomedical, public health and socioeconomic interventions along with research and innovation, delivered through engagement with government departments (such as social protection, labour, justice, education, transport to name a few) in addition to engagement with technical and scientific institutions; financial partners and development agencies; civil society; and the private sector (World Health Organization, 2022a). In line with this Ireland published a TB elimination strategy in 2024, addressing the social determinants as the first priority (HSE National Health Protection Office, 2024). This study provides key findings that can potentially contribute to the HSE strategy's objective of improving *"the understanding of the social determinants of TB across sectors"*.

Employment

[Chapter 5](#) found that migrant TB cases were significantly less likely to be unemployed or retired compared to Irish-born TB cases, which is likely influenced by the younger age profile of migrant TB cases overall. Almost half of the migrant population resident in Ireland in 2016 was aged 25-44 years old, in contrast just over a quarter of the Irish-born population (Central Statistics Office, 2016b). The proportion of the population that was aged 65 years and older was over twice as high among Irish-born (15%) compared to the population born outside Ireland (6%) (Central Statistics Office, 2016b). This has important implications for the design of health service delivery and treatment support interventions (such as Directly Observed Therapy) which may not have originally been designed for such a young population with high rates of employment. [Chapter 7](#) also uncovered key findings in relation to employment with significantly lower treatment success among total and migrant cases who were unemployed, retired or of other employment status. While lower levels of treatment success among retired cases might be influenced by an interaction with increasing age, the lower success among cases who were unemployed is more likely associated with socioeconomic deprivation. For cases with other employment status, while this finding must be interpreted with caution due to the non-specific nature of this category, it should be noted as an angle for future research to investigate as the available information indicated many of these cases were in some way precluded from employment due to having a disability or caring responsibilities, being incarcerated, or not having legal right to work due to International Protection Applicant status.

In Ireland, universal Directly Observed Therapy (DOT) is currently recommended for all TB cases either in-person or facilitated through Video Observed Therapy (VOT) (Health Service Executive, 2024). In practice, selective DOT is more commonly implemented. Following clinical assessment of the patient, selective DOT is recommended for cases where either the assessment indicates that they may have difficulties with treatment adherence, or for those who are infected with drug resistant strains or have a previous history of unsuccessful TB treatment. In-person DOT requires the patient to be supervised by a health care professional while taking their daily medication. Patients are observed either in their home, in a clinic or at a community location. This requires financial, healthcare and human resources as well as psychosocial and financial impositions on the patient (McLaren et al., 2016). VOT involves the patient recording themselves taking the medication at a time that suits their schedule. The video can be viewed by the health care worker live or later using a time-stamped video stored on a secure server. VOT has been shown to improve medication adherence and treatment success (Truong et al., 2022).

Implementation of a national VOT programme has been identified as a high priority action within the Irish TB Strategy but is so far unfunded despite regional pilot programmes being highly successful. A recent case study of 34 participants attending the National TB Treatment Centre in St. James Hospital, showed that VOT participants had higher levels of treatment observation in the first two months of treatment which remained consistently high throughout treatment compared to DOT. In this pilot study, seven participants were transferred from DOT to VOT due to an inability to comply with DOT, citing work hours or the stress caused by in-person DOT. Delivering a VOT programme as the standard of care in Ireland will be a key intervention in the package of patient supports to help increase treatment success rates.

Housing

Housing emerged as a key concept within both Chapter 5 and 7. In [Chapter 5](#), this study observed that migrants are almost twice as likely to reside in a congregate residential setting, compared to Irish-born TB cases. This finding is influenced by the type of accommodation provided to IPAs and BOTPs. Residence in congregate settings is a well-established risk factor for transmission of infectious diseases which is amplified by the fact that many residents in IPA congregate settings also originate from, or transit through, high TB incidence areas (Castelli & Sulis, 2017; Walker et al., 2018).

In acknowledgement of the importance of housing as a determinant of TB and the potential effects of unstable housing on treatment adherence, [Chapter 7](#) examined housing status in the univariable logistic regression analyses of factors associated with treatment success. Unfortunately, it was not possible to examine housing within the multivariable logistic regression analyses due to the small numbers of cases in certain mixed categories. Compared to the reference group of cases residing in private housing, reduced odds of treatment success were observed among total cases and Irish-born resident in congregate / residential care settings and those incarcerated or experiencing homelessness. Of note, the lowest odds of treatment success among total cases were observed for the combined group of cases who were either resident in a prison or were experiencing homelessness at the time of diagnoses.

8.4.3 Extrapulmonary disease

[Chapter 5](#) showed that migrant cases were over two and half times more likely to be diagnosed with EPTB, this rose to over three times as likely after adjusting for other factors, including HIV co-infection. Compared to Irish-born cases, migrants were also three times more likely to have a normal CXR result and over three and half times more likely to have a normal CT thorax scan result. [Chapter 7](#) observed an increased odds of treatment success among migrant cases with EPTB, a finding that was not replicated among total cases or Irish-born cases.

The findings of elevated levels of exclusive EPTB among migrant cases coupled with high levels of normal CXR and CT scan results are important on several levels. Firstly, systematic screening of migrants is not implemented in Ireland, but CXR is the mainstay of screening that is offered to symptomatic IPAs during Individual Health Assessments and to new entrant health-care professionals from high TB incidence countries (HSE Health Protection Surveillance Centre, 2010). However, CXR is more suited to detections of thoracic forms of TB and may not detect forms of exclusive ETB occurring outside the thorax. As reported in Chapter 5, restricting screening to PTB could miss up to 40% of migrant cases and may need to be supplemented by targeting high-risk migrant groups for TB infection screening to support TB elimination in Ireland (Al Abri et al., 2020). This finding supports the development of a new-entrant immigrant TBI management programme as one of the key actions in Ireland's Tuberculosis Strategy (HSE National Health Protection Office, 2024).

Secondly, diagnosing EPTB can be difficult given the wide-ranging clinical presentations and similarity of symptoms to other illnesses, which leads to a wide differential diagnosis. Even where EPTB is suspected, it can be difficult to confirm microbiologically due to the often paucibacillary nature of extrapulmonary specimens and reduced sensitivity of nucleic acid amplification tests (NAAT) on non-respiratory samples (Solovic et al., 2013). These combined challenges may contribute to underdiagnosis of EPTB. Such operational difficulties can also delay diagnosis and appropriate treatment of a patient, which has been suggested to contribute to the poor treatment outcomes often observed among EPTB cases. In this study, a significantly longer median interval between onset and diagnoses was observed among EPTB (78 days) compared to PTB cases overall (66 days). The interval between onset and diagnosis was shorter among migrants compared to Irish-born cases, and remained shorter when stratified by disease site (Irish-born EPTB = 87 days vs migrant EPTB cases = 73 days).

The above features raise important points for consideration within Ireland's planned screening activities listed as actions under the TB Strategy, as well as for clinical practice. These include introduction of new entrant migrant TBI management programme; improving screening among those at-risk of TB due to social risk factors (e.g., people in prisons), medical risk factors (e.g., people living HIV, and occupational exposures (e.g., abattoir workers); and improving the targeted pre-employment screening for those entering high-risk occupations (e.g., health care workers, prison officers). In particular, TBI screening programmes will need to stringently rule out EPTB before offering TBI treatment to populations being screened, especially where the target populations are likely to have significant numbers of migrants (e.g. health care worker screening programmes). For clinical practice, high levels of awareness of EPTB are necessary to ensure detection and appropriate treatment. This is particularly important in the current Irish context as international migration can reasonably be expected to continue increasing with several wars currently ongoing and the resultant populations seeking international protection, alongside the current levels of full employment recorded among the Irish population overall resulting in a need to recruit from the international labour (Department of Enterprise, 2024).

8.4.4 Diversity within migrant TB sub-populations:

This study provided an in-depth examination of the epidemiological diversity of migrant TB cases which are seldom reported within the published literature. Several key characteristics emerged as important features of the migrant TB cases in this study, most notably the TB incidence level in the country of birth and the time since arrival in Ireland before being notified as a case.

Incidence level in origin country

In [Chapter 5](#), significant differences were found in the patient profiles of migrant TB cases according to the TB incidence level in their countries of birth. Background TB incidence is one of the most commonly used criteria in screening algorithms for TBI or TBD. Cases originating from very high incidence birth countries had the lowest median ages and lowest proportion of cases linked to outbreaks, and the highest proportions of PLWHIV, EPTB, female cases and IPARs.

A significant trend was observed in the proportion of IPARs in relation to the increasing TB incidence category of the migrant origin country, with cases originating from very high TB incidence countries accounting for 85% of TB cases reported among IPAR overall. While this provides support for the continued practice of offering TB screening in IPA reception centres, it also provides supporting evidence for augmenting current TB screening services in IPA settings with targeted TBI screening as recommended by the HSE TB strategy action to introduce a new entrant migrant TBI management programme (HSE National Health Protection Office, 2024).

The combined findings in relation to TB cases born in very high incidence countries are particularly important given that they represent 69% of the migrant TB cases overall, but also as they describe a complex patient profile with additional challenging clinical and social contexts.

Time since arrival

A key challenge for both TB clinical services and control programmes is ensuring service delivery remains relevant to the populations being served. In Chapter 5, the unavailability of country of birth denominator data for recently arrived migrants in Ireland was highlighted, preventing the calculation of CIRs for this key population. Understanding the fluctuating dynamics of the underlying population remains key for interpreting trends in TB epidemiology. A recent study of over 100,000 migrant TB cases in 20 low TB-incidence European countries between 2014 and 2020 found CIRs were higher among recently arrived migrants compared to the overall migrant TB incidence rate (Domaszewska et al., 2025). In addition, nine of the 20 origin countries with the highest CIRs among recently arrived

migrants were higher than the WHO estimates for their origin country, underlining the need for TB control programmes to be informed by local epidemiological analysis in addition to using WHO TB estimates when assessing background TB levels in countries of origin (Domaszewska et al., 2025).

The underlying patient characteristics of the recently arrived migrant TB patient cohort analysed by Domaszewska et al were also different to migrants who had arrived >2 years prior to being notified as a TB case (Jackson et al., 2025). Similar to their findings, [Chapter 5](#) of this study reported that migrant TB cases who had arrived in Ireland <2 years before being notified as a case were significantly younger and had higher proportions of IPARs, PLWHIV and PTB, compared to cases who had been resident in Ireland for longer prior to their diagnosis. These characteristics again describe a population with heightened clinical and social complexity, as well as a higher risk of onwards transmission due to the higher levels of PTB present and residence in congregate settings.

In addition to the distinctive patient characteristics of recently arrived migrant TB cases, [Chapter 7](#) also found a lower treatment success rate among the recently arrived migrants in the univariable analysis. This was the only migrant specific patient characteristic significantly associated with treatment success rates. The lower treatment success rates may be influenced by the higher levels of PLWHIV observed among recently arrived migrants in this study, which is known to reduce treatment success. However, it may also be influenced by social factors such as the challenges involved in navigating the very complex Irish healthcare system and due to the precarious housing conditions that recently arrived migrants may face upon arrive in Ireland due to the current housing crisis. The higher levels of IPARs within this category, may also be at risk of poorer health outcomes overall due to multiple pre-departure factors in their countries of origin as well as their uncertain circumstances once in Ireland.

The higher proportion of PTB among recently arrived migrants is possibly influenced by the targeting of newly arrived IPAs with Individual Health Assessments (IHAs) and chest x-rays (CXR) where appropriate. However, IPARs remain a small proportion of migrants in this study overall (n=127 cases; 12% of migrant cases) and include longer term refugees as well as International Protection Applicants (IPAs). However, IPARs accounted for a higher proportion of recently arrived migrants (23%) and the majority of TB cases among IPARs were diagnosed <2 years after arrival in Ireland (39%). In addition, if the high proportion of PTB among recently arrived migrants was mainly due to increased active case finding among IPAs, it might reasonably be expected that the interval between onset and diagnosis would be shorter in IPARs than among non-IPAR migrants which was not found in this study. The higher prevalence of PTB among recently arrived migrants compared to those resident in Ireland for longer periods may be influenced by other factors. These factors might include pre-departure factors such increased risk of exposure to TB infection due to higher incidence level in the country of birth or precarious travelling conditions for IPAs, including time spent in over-crowded camps for displaced people.

This study found significant differences in the intervals between onset and diagnosis according to the interval between arrival and notification; with shorter intervals among recently arrived migrant TB cases compared to migrant cases resident for longer in Ireland. This may be a reflection of the shorter interval between onset and diagnosis generally observed among PTB cases, which was more common among recently arrived migrants.

Recently arrived migrants are likely to have a higher background risk of TB than those residing in Ireland for longer periods due to the more recent history of exposure to high incidence of TB in the country of origin. In addition, the international literature has reported further biological and social determinants that increase the risk of progression from TBI to TB disease post-migration (Duarte et al., 2018; Hargreaves et al., 2011; Lönnroth et al., 2009a; Ploubidis et al., 2012; Rasanathan et al., 2011). These determinants include but are not limited to immunosuppression due to the stress of relocation and poor housing conditions upon arrival. It is also likely that a heightened suspicion of TB among clinicians could exist with regard to recently arrived migrants due to this increased risk.

These insights into the nuances of migrant TB epidemiology are particularly useful given the interruption of a previously declining trend among migrants described in Chapter 5 indicating that TB incidence is no longer consistently declining in Ireland during the latter years of the study period. Latest data from HPSC shows that migrant TB incidence rates have since increased during 2023 and

2024 (HSE Health Protection Surveillance Centre, 2025). It is currently expected that international migration trends will continue to increase. This has important implications for both TB service delivery and the TB control programme. In order to support and enhance the health of the migrant population in Ireland, the National TB Strategy actions will need to be fully resourced for implementation.

8.5 Strengths and limitations of study findings

The strengths of this study include use of a programmatic data source derived from a mandatory notification framework, which ensured a high sampling coverage of the target population of TB cases in Ireland and also reduced selection bias within the sample. Use of the EU case definition and internationally applicable WHO definitions enhances the generalisability of the study's results to other high income, low TB incidence jurisdictions using the same reporting conventions.

The methods used in this study have been transparently reported and in line with international best practice for systematic reviews, observational studies and prediction studies. Where possible, metrics without internationally accepted definitions were aligned with other European studies to enhance comparability (e.g. TB incidence categories, intervals between arrival and diagnoses).

This study has also analysed data for all countries of birth, rather than pre-selected countries based on highest numbers to provide an alternate view of TB risk among migrants via CIRs, rather than relying solely on the simplified view of case numbers. Diversity of the migrant population has also been examined, rather than simply reporting on migrant TB as though it were a homogenous entity.

This study also has certain limitations, one of the most important being the suboptimal completeness of many key variables analysed within Chapter 5 and 7. Despite recommendations by WHO that 100% of TB cases have a HIV status reported, only 42% of cases in this study had a known HIV status reported. Completeness levels for most biological risk factors such as diabetes, substance use and immunosuppressive medications were <50%. However, the data were not MCAR. Similarly, treatment outcome data was missing for 38% of cases, despite this information being critical to estimate treatment success rates which need to be measured against the 85% targets set by WHO. This study was unable to explore the effect of geographical region of residence due to low levels of treatment outcome completeness in a particular health region which accounted for 36% of the 2016 population. Learnings from practice indicate that in general, regional Departments of Public Health with higher staff to population ratios had more complete and higher quality data.

8.6 Recommendations for policy, practice and future research

8.6.1 Policy:

Several internal reports have been commissioned by the Department of Health and the HSE in the last decade on the topic of evaluating the TB Control Programme in Ireland and assessing current and future requirements to enhance it. These reports were commissioned as part of efforts to define the path towards the global goal of TB elimination, and also to facilitate the move from a national universal BCG vaccination programme to a selective programme targeting only individuals at higher TB risk. The most recent review of TB control structures in Ireland during 2016 concluded that a robust national TB control programme does not currently exist and that the majority of the recommendations endorsed by the National TB Guidelines could not be implemented (HSE Health Protection Surveillance Centre, 2010).

The majority of recommendations from these reports have not been implemented despite remaining relevant to current challenges. A 2022 audit of TB control activities in Departments of Public Health reported little change to the structure and staffing levels allocated to TB control activities despite increasing levels of drug-resistant TB, increasing migration trends and case complexity (C. Carroll, personal communication, 2022). Although a HSE Strategy for TB elimination was launched in 2024, no dedicated funding was released to implement the 38 actions, many of which represent new work packages for the TB Service (HSE National Health Protection Office, 2024).

General Recommendation 1:

Current and future TB control policies, strategies and commissioned evaluations should be accompanied by implementation plans with clear sources of funding mapped for each recommendation or action.

General Recommendation 2:

In order to provide the infrastructure for the following recommendations for [practice](#) and [research](#) derived from findings of this study, the following HSE Strategic Actions should be implemented.

- *Update the 2016 Report on the Resources Required for TB Control to account for the resources and associated funding needed to meet the strategic objectives.*
- *Agree, nationally, a model of service and care delivery for TB Control to be implemented regionally (from prevention to post care delivery).*
- *Determine skills mix and capabilities required to provide TB services, undertake a gap analysis and develop a workforce implementation plan*

General Recommendation 3:

High income low TB incidence countries with a high proportion of TB among migrants should explore the possibility of collaborating with and investing in the TB prevention and control programmes of high TB incidence countries of origin, in addition to their own domestic TB prevention and control activities. This approach has been shown to be cost-effective elsewhere and could help to reduce TB incidence globally as well as health inequalities, as this practice would help deliver more treatment to a wider population rather than the current practice which only targets people leaving high TB incidence countries (Campbell & Schwartzman, 2022; Schwartzman et al., 2005). Further research could be commissioned by the TB control programme to assess the cost-effectiveness of this intervention in an Irish setting.

General Recommendation 4:

Health should be seen as a global public good. In working towards that, minimising restrictions on social protections and ensuring universal health care access is available to all patients, especially for IPARs and BOTPs, are important enablers of health.

8.6.2 Practice:

Data quality:

Completeness of key variables in the national TB surveillance dataset needs to be improved in order to be useful for monitoring and evaluating the performance of the TB control programme in Ireland, and to contribute to global monitoring and evaluation of progress towards TB elimination. To enable this, regional Departments of Public Health need to be adequately resourced to collect the required data and ensure its transfer to CIDR. In addition to the intense public health follow up each TB case requires, the TB enhanced surveillance dataset is the third largest among mandatory notifiable infectious diseases in Ireland, after Covid-19 and influenza, with 129 enhanced variables collected in addition to the core dataset. Knowledge from the practice of the researcher indicates that regional Departments of Public Health with lower surveillance staff ratios to the population being served, had lower quality data captured on CIDR.

During the course of the researcher's 20+ years practice, it has commonly been reported by respiratory consultants and infectious disease consultants treating TB patients that they definitely test TB patients for HIV co-infection. They often also state that they are disappointed by the low treatment outcomes reported within surveillance reports. However, staff in Departments of Public Health maintain it is extremely difficult to collect either HIV status or treatment outcomes from clinical staff that are responsible for treatment of TB patients. Yet, in a recent Quality Improvement collaboration between HPSC, Public Health and clinical staff in one region, HIV status was collected for >97% of cases and treatment outcomes were collected for >90% of cases from two hospitals where key workers were identified. In the other two hospitals where no key workers were available to participate, between 20-50% of outcomes were retrieved and no additional information on HIV was available. This project demonstrated that although these data were missing after public health follow up had concluded, it was available in the clinical site but retrieval was only possible if a key worker could be identified as the treating physicians did not have personal capacity to retrieve it.

Recommendation 5:

- The HSE TB Strategy recommendation “*Improve the completeness, relevancy and use of surveillance and epidemiological data to inform local and national programmatic activities*” should be prioritised for implementation.
- To do so will require resources for an evaluation of the TB surveillance system to ensure all data collected remains relevant. As part of this, variables with both low completeness and low relevancy can be retired so that resources can be directed towards achieving higher completeness for data items with higher priority.
- Collaborative quality improvement initiatives need to be undertaken to identify barriers to data collection and enablers of improved data quality.
- Quality Improvement collaborations should have multi-disciplinary participation from clinical sites and public health to enable identification of the appropriate key workers for each site.

TB as an anti-microbial resistance (AMR) threat:

Drug-resistant forms of TB are one of the leading causes of death associated with Antimicrobial Resistant (AMR) organisms (Stop TB Partnership, 2024). While all patients are entitled to free TB investigation and care, access to drugs is usually through local hospital procurement structures and reimbursement from the HSE can be problematic. Given increasing levels of drug-resistant forms of TB in Ireland, measures are needed to ensure TB services are equipped to deal with this public health threat.

Recommendation 6:

- Access to drugs required to treat drug resistant TB should be centralised through a publicly funded system with clear governance structures, rather than procured through individual hospital budgets
- Access to rifapentine for TBI treatment in Ireland should be secured. This will reduce the frequency and volume of medications required to treat TB, improving patient experience and adherence to reduce reservoir of TBI.

Vaccination:

Given the interruption of a previously declining temporal trend among the 0-6 years olds reported in Chapter 6, the National Immunisation Advisory Committee recommendations for a selective BCG vaccination programme should be implemented without further delay.

Recommendation 7:

- The HSE TB Strategy recommendation “*Agree and implement a comprehensive, adequately funded and resourced, inter-stakeholder selective BCG programme*” should be prioritised for implementation without further delay.

Recommendation 8:

- In addition to the current BCG target groups for vaccination, consideration should be given to whether infants and children <5 years of age and residing in congregate settings (IPA accommodation or temporary accommodation for people experiencing homelessness) should also be offered BCG vaccination in scenarios where they do not qualify based on their other circumstances.

Tailoring TB services to current patient profiles:

As international migration is expected to continue increasing, it should be explicitly acknowledged as a driver of TB service demand. TB services, including both clinical services and public health sectors, need to be appropriately funded and configured to reflect this changing demography to support and enhance migrant health. New entrant migrant screening was recommended as part of the 2010 National TB Guidelines and by the previously mentioned evaluations of TB control in Ireland in 2014 and 2016 but has yet to be implemented systematically.

Recommendation 9:

- Any health screening programmes should be designed with a human rights focus, delivered in a non-exclusionary way and linked to continuous and high-quality care for all patients

Recommendation 10:

- The HSE TB Strategy recommendation “*Agree a comprehensive, adequately funded and resourced, inter-stakeholder implementation plan for the new entrant immigrant TBI management programme.*” should be funded and implemented
- Such TBI screening programmes will need to stringently rule out exclusively EPTB before offering TBI treatment to populations being screened, especially where the target populations are likely to have significant numbers of migrants (e.g. health care worker screening programmes).

Recommendation 11:

- Consideration of how opportunities for diagnosis and care can be enhanced among the migrant population is needed given the high proportion of EPTB observed which may be missed if TB screening remains focused on thoracic forms of TB.
- A heightened awareness of the elevated levels of EPTB among migrant TB patients must be maintained and enhanced among clinical and public health staff.
- There is also a need to promote awareness of the continued risk of TB for long-term migrant residents, due to elevated baseline risk of reactivation and return travel to their country of origin.

Recommendation 12:

- The HSE TB Strategy recommendation “*Implement a national VOT programme.*” should be funded and implemented. This will enable a flexible service responsive to the needs of the patients described in this study (e.g. high levels of drug resistance, younger age and with high levels in paid employment)

8.6.3 Research:

A challenge for researchers working towards the goal of TB elimination within low TB incidence settings, where in-migration is more common, can be producing robust research to support underserved target populations but without reinforcing existing stigma or legitimizing discriminatory worldviews (Craig et al., 2017). Several findings of this thesis would benefit from further research through rigorously designed studies with an emphasis on promoting migrant health in low TB incidence settings, such as Ireland.

Recommendation 13:

- Research into the cascade of care in the Irish context is needed. A robust knowledge of the cascade is required to minimize attrition at the intersections. This is particularly important given increasing levels of drug resistance, more difficult to diagnose EPTB and a backdrop of globally mobile populations. It is also required to support the most effective design of new entrant screening programmes and programmatic management of TBI. Such studies should be appropriately designed with sufficient power and good quality data to detect real effects.

Recommendation 14:

- Studies investigating the timeline between arrival and diagnoses, and onset and diagnosis among migrants are needed to identify if there are periods of increased risk of TB among migrants that can be targeted with interventions to support access to diagnoses and treatment.

Recommendation 14:

- Further investigation of the factors associated with treatment success are needed on a dataset with higher completeness, including internal and external validation of the models developed within this study.
- Future studies should use robust causal inference epidemiological study designs.

8.7 Unique contribution to the evidence base

This study broadened the scope of the evidence base on migrant TB epidemiology in several areas:

1. The systematic review provides a rigorous synthesis of the reported differences among high TB incidence migrants and non-migrants. Not only are significant differences observed in the overall proportions of key epidemiological indicators but also an important gap in the evidence is highlighted regarding reporting information on TB incidence level of migrant populations under study, with 70% of retrieved articles being excluded due to missing data.
2. This is the first in-depth study to examine the differences in the epidemiology of migrant TB cases and Irish-born TB cases in Ireland. Although migrant TB epidemiology has been explored at the European level, the ECDC dataset covers a subset of the variables examined within this thesis and lacks completeness on many of the key national epidemiological indicators that were examined in this study.
3. This study captures the effects of significant time periods; before and after the global migration peak in 2015/2016 as well as the early Covid-19 pandemic. It also provides an epidemiological baseline of the period prior to recent wars in Palestine and Ukraine which are influencing the present-day epidemiology of TB through increased asylum seeking and increased levels of drug resistance.
4. This study is also the first to comprehensively characterise TB epidemiology among recent migrants to Ireland and to decipher distinctive epidemiological features within the recently arrived migrant TB patient population.
5. This study was the first to investigate the effects of universal BCG vaccination cessation on paediatric TB epidemiology in Ireland. Interruption of the previously declining temporal trend among 0-6 year olds during a period of universal vaccination may be an early warning of a future increase and supports the planned introduction of a selective BCG vaccination programme.
6. Significant predictors of successful treatment outcomes have been elucidated for three population groups in this study. This study has identified that these predictors differ for migrant TB cases and Irish-born cases.

7. This study has both national and international relevance, given that migration is global and we are all striving towards the global goal of TB elimination.

8.8 Overall conclusions of the thesis

This study identified key epidemiological and clinical differences between Irish-born and migrant TB cases in Ireland which can be used to inform tailored TB prevention and control strategies, as well as inform reconfiguration of TB care services. Coupled with interruptions to previously declining trends among migrant TB cases and among paediatric cases, indications are that TB prevention and care interventions are urgently needed to support migrant health. Furthermore, tackling social determinants of TB will also remain a key focus for future TB control programmes. While surveillance data can be used for monitoring and evaluating aspects of the TB control programme, further attention and investment is needed to strengthen the quality of upstream sources of data utilized by surveillance systems. Many of these observations are in alignment with the actions recommended in the recent HSE National TB Strategy Report 2024 (HSE National Health Protection Office, 2024).

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Appendix 1: Recent trends in TB epidemiology in Ireland (source: HPSC CIDR)

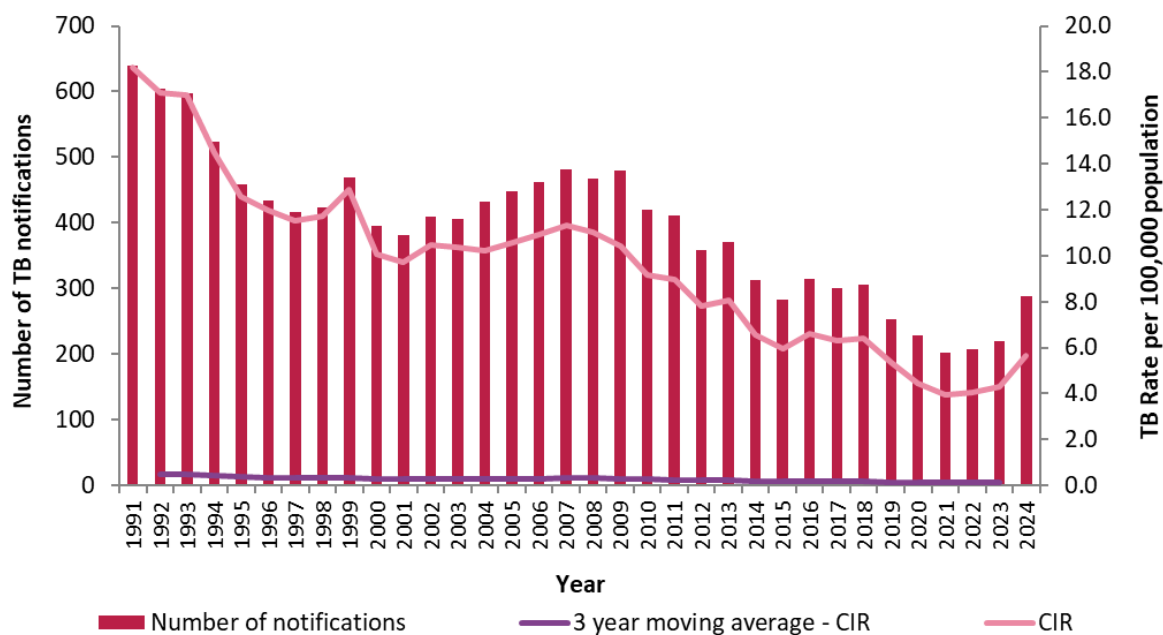


Figure A1: Annual number of TB notifications, CIRs and 3 year moving average, Ireland (HSE HPSC)

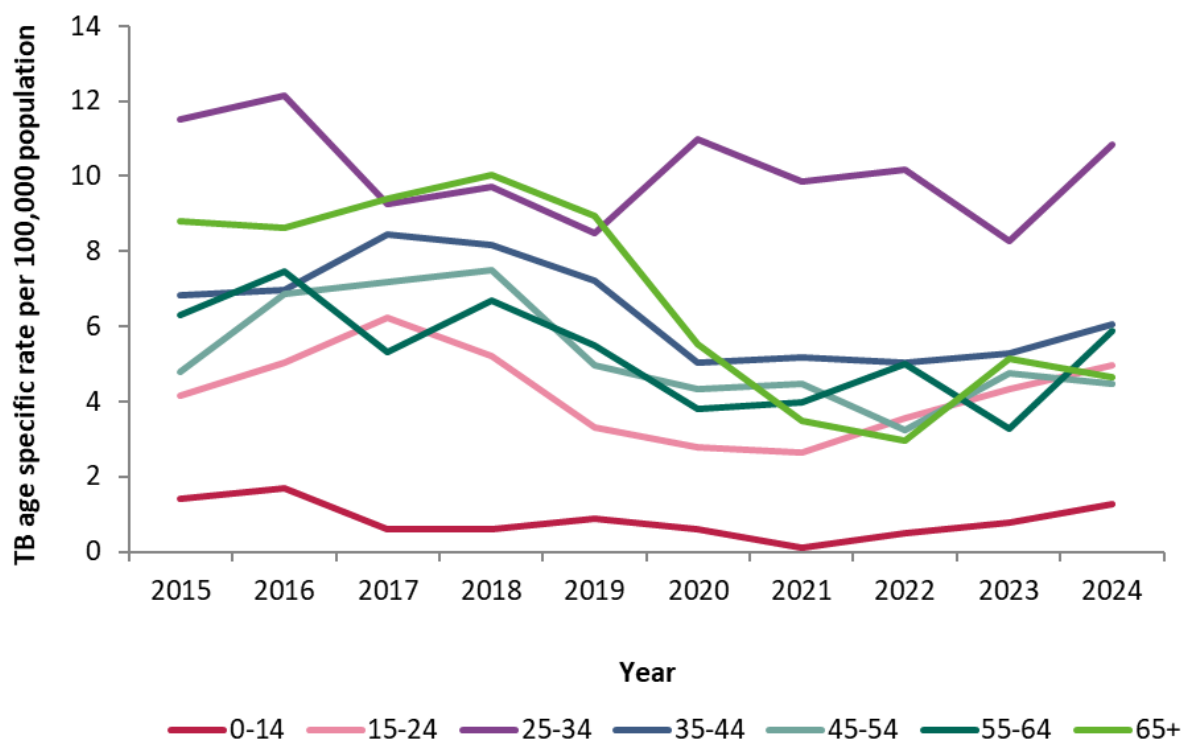


Figure A2: Annual TB age-specific incidence rate, Ireland (HSE HPSC)

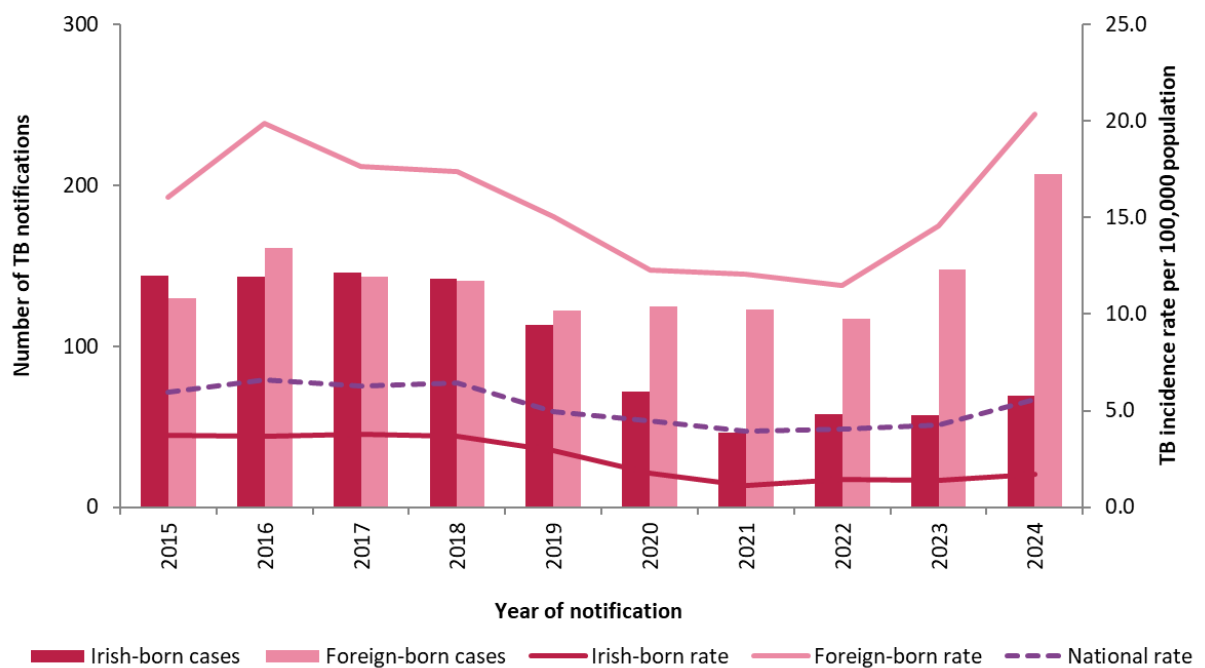


Figure A3: Annual number of TB notifications and CIR by geographic origin, Ireland (HSE HPSC)

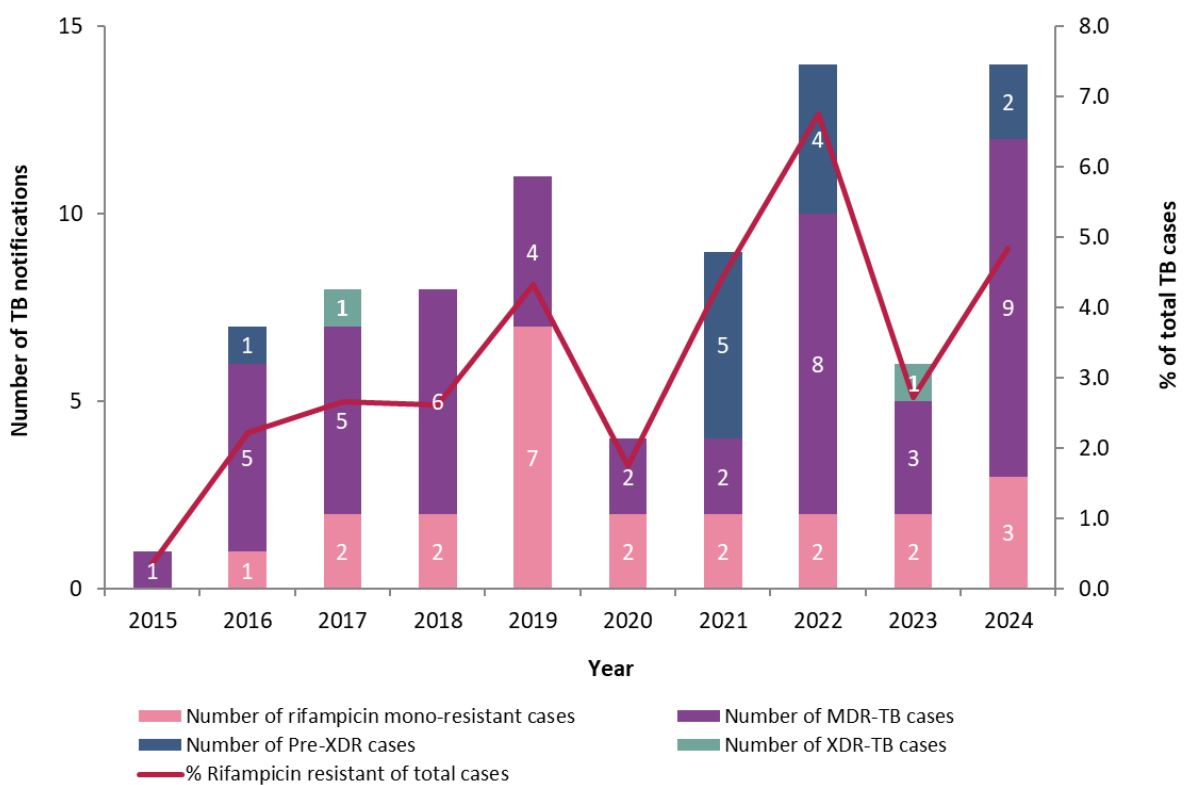


Figure A5: Annual number and percentage of MDR and XDR TB notifications, Ireland (HSE HPSC)

Appendix 2: List of CIDR variables and rationale for inclusion in the study

CIDR variable name	Data type ⁺⁺⁺⁺⁺	Rationale
Event ID	Numeric	Unique pseudonymised identifier for episodes of TB. Not possible to link back to named patient data.
HB	Dropdown	To enable regional analysis.
County	Dropdown	To enable regional analysis.
CCA	Dropdown	To enable regional analysis.
Organism Name	Dropdown	To describe the different species circulating in Ireland.
Patient Type	Dropdown	Proxy indicator to describe disease severity.
Hospital of Admission (current)*	Dropdown	To augment missing "Patient type" for hospitalised cases.
Sex	Dropdown	Basic epidemiological descriptor.
Ages	Numeric	Basic epidemiological descriptor.
Age Type	Dropdown	Basic epidemiological descriptor.
Current employment status	Dropdown	To investigate whether occupation is a risk .
Current / most recent occupation (within last 2 years)	Free text	To enable analysis by employed/unemployed for factors associated with treatment success.
Current living status	Dropdown	To investigate factors associated with treatment success (e.g. homeless might be associated with poor treatment outcomes).
If other living status, please specify*	Free text	To investigate factors associated with treatment success (e.g. homeless might be associated with poor treatment outcomes).
Country of Birth (core)	Dropdown	To assign migrant status to cases.
Race or ethnic group	Dropdown	To investigate factors associated with treatment success (e.g. minority ethnicity might be associated with poor treatment outcomes).
If other race or ethnic group, please specify*	Free text	To augment race or ethnic group. "Other" category is frequently assigned to existing ethnic groups overestimating proportion of "other" ethnicities.

⁺⁺⁺⁺⁺ All free text variables were deleted from the data prior to its release for research purposes.

CIDR variable name	Data type ⁺⁺⁺⁺⁺	Rationale
Refugee / Asylum seeker	Y/N/UNK	To investigate factors associated with treatment success (underserved population group).
If born outside Ireland, year of entry into Ireland	Numeric	To enable analysis of migrant TB cases by interval between arrival and diagnosis.
Comments (Event)*	Free text	Free text field which may contain identifiers so will be reviewed for validation and completeness purposes but will be deleted prior to release for research purposes
Onset Date	DD/MM/YYYY	To enable analysis of the interval between onset of symptoms and diagnosis an whether they differ between migrant and indigenous cases.
Date of Diagnosis	DD/MM/YYYY	To enable analysis of the interval between onset of symptoms and diagnosis an whether they differ between migrant and indigenous cases.
Event Creation Date	DD/MM/YYYY	Date used for reporting.
Date treatment commenced	DD/MM/YYYY	To enable analysis of the interval between onset of symptoms and treatment and whether they differ between migrant and indigenous cases.
Diagnosis	Dropdown	To enable analysis of site of infection and act as indicator of infectiousness.
Extrapulmonary or P+E site 1	Dropdown	To enable analysis of site of infection.
Extrapulmonary or P+E site 2	Dropdown	To enable analysis of site of infection.
Chest X-Ray result	Dropdown	To enable analysis of site of infection and act as indicator of infectiousness.
Was this case hospitalised due to TB?	Y/N/UNK	Proxy indicator to describe disease severity.
CT Thorax scan result	Dropdown	To enable analysis of site of infection and act as indicator of infectiousness.
Case found by	Dropdown	To investigate factors associated with treatment success
Did this case previously undergo TB screening in Ireland?	Dropdown	To enable analysis by previous screening history for factors associated with treatment success.
Previous history of TB disease	Y/N/UNK	To enable analysis of new, relapse or recurrent TB
Previous year of diagnosis	Numeric	To enable analysis of new, relapse or recurrent TB
Previous treatment (>1 month)	Y/N/UNK	To enable analysis of new, relapse or recurrent TB

CIDR variable name	Data type⁺⁺⁺⁺⁺	Rationale
Previous treatment completed	Y/N/UNK	To enable analysis of new, relapse or recurrent TB
History of BCG vaccination	Y/N/UNK	Basic epidemiological descriptor
Risk factors present	Y/N/UNK	To enable risk factor analysis and investigate whether differences are present between migrant and indigenous cases and whether any are associated with treatment success.
Anti-TNF treatment	Y/N/UNK	To enable risk factor analysis and investigate whether differences are present between migrant and indigenous cases and whether any are associated with treatment success.
Other immunosuppressive medication	Y/N/UNK	To enable risk factor analysis and investigate whether differences are present between migrant and indigenous cases and whether any are associated with treatment success.
Immunosuppressive illness	Y/N/UNK	To enable risk factor analysis and investigate whether differences are present between migrant and indigenous cases and whether any are associated with treatment success.
Diabetes	Y/N/UNK	To enable risk factor analysis and investigate whether differences are present between migrant and indigenous cases and whether any are associated with treatment success.
HighEndem Origin	Y/N/UNK	To enable risk factor analysis and investigate whether differences are present between migrant and indigenous cases and whether any are associated with treatment success.
Residence in country of high endemicity	Y/N/UNK	To enable risk factor analysis and investigate whether differences are present between migrant and indigenous cases and whether any are associated with treatment success.
Contact of case	Y/N/UNK	To enable risk factor analysis and investigate whether differences are present between migrant and indigenous cases and whether any are associated with treatment success.

CIDR variable name	Data type ⁺⁺⁺⁺⁺	Rationale
Alcohol misuse	Y/N/UNK	To enable risk factor analysis and investigate whether differences are present between migrant and indigenous cases and whether any are associated with treatment success.
Drug misuse	Y/N/UNK	To enable risk factor analysis and investigate whether differences are present between migrant and indigenous cases and whether any are associated with treatment success.
Please specify other / additional risk factors*	Free text	To enable risk factor analysis and investigate whether differences are present between migrant and indigenous cases and whether any are associated with treatment success.
HIV status	Dropdown	To enable risk factor analysis and investigate whether differences are present between migrant and indigenous cases and whether any are associated with treatment success.
Is patient currently on ARV treatment?	Y/N/UNK	To investigate factors associated with treatment success.
Is this case linked to an outbreak?	Y/N/UNK	Basic epidemiological descriptor
Outbreak Identifier	Alphanumeric	Unique identifier for analysing outbreak associated cases. Unique identifier per outbreak, not possible to link back to personally identifiable data.
First DSM result	Dropdown	To enable analysis of site of infection and act as indicator of infectiousness.
Second DSM result	Dropdown	To enable analysis of site of infection and act as indicator of infectiousness.
First microscopy result of other specimens (e.g. BAL, gastric washings etc.)	Dropdown	To enable analysis of site of infection and act as indicator of infectiousness.
First microscopy specimen type*	Free text	To augment missing diagnostic types
Second microscopy result of other specimens (e.g. BAL, gastric washings etc.)	Dropdown	To enable analysis of site of infection and act as indicator of infectiousness.
Second microscopy specimen type*	Free text	To augment missing diagnostic types
Histology	Dropdown	To enable analysis of site of infection and act as indicator of infectiousness.
Histology specimen site*	Free text	To augment missing diagnostic types

CIDR variable name	Data type⁺⁺⁺⁺⁺	Rationale
First culture result	Dropdown	To augment missing diagnostic types
First culture specimen type*	Free text	To augment missing diagnostic types
First culture specimen site*	Free text	To augment missing diagnostic types
Second culture result	Dropdown	To augment missing diagnostic types
Second culture specimen type*	Free text	To augment missing diagnostic types
Second culture specimen site*	Free text	To augment missing diagnostic types
Isoniazid sensitivity	Dropdown	To enable analysis by drug-resistance profile
Rifampicin sensitivity	Dropdown	To enable analysis by drug-resistance profile
Ethambutol sensitivity	Dropdown	To enable analysis by drug-resistance profile
Pyrazinamide sensitivity	Dropdown	To enable analysis by drug-resistance profile
Streptomycin sensitivity	Dropdown	To enable analysis by drug-resistance profile
Amikacin sensitivity	Dropdown	To enable analysis by drug-resistance profile
Capreomycin sensitivity	Dropdown	To enable analysis by drug-resistance profile
Kanamycin sensitivity	Dropdown	To enable analysis by drug-resistance profile
Ciprofloxacin sensitivity	Dropdown	To enable analysis by drug-resistance profile
Gatifloxacin sensitivity	Dropdown	To enable analysis by drug-resistance profile
Levofloxacin sensitivity	Dropdown	To enable analysis by drug-resistance profile
Moxifloxacin sensitivity	Dropdown	To enable analysis by drug-resistance profile
Ofloxacin sensitivity	Dropdown	To enable analysis by drug-resistance profile
Para-amino salicylic acid (PAS) sensitivity	Dropdown	To enable analysis by drug-resistance profile
Ethionamide sensitivity	Dropdown	To enable analysis by drug-resistance profile
Prothionamide sensitivity	Dropdown	To enable analysis by drug-resistance profile
Rifabutin sensitivity	Dropdown	To enable analysis by drug-resistance profile
Nucleic acid amplification test (e.g. PCR)	Dropdown	To enable analysis by case classification
If PCR positive, were genetic resistance determinants to Isoniazid detected	Dropdown	To enable analysis by drug-resistance profile

CIDR variable name	Data type⁺⁺⁺⁺⁺	Rationale
If PCR positive, were genetic resistance determinants to Rifampicin detected	Dropdown	To enable analysis by drug-resistance profile
MIRU-VNTR Type	Numeric	To enable analysis by molecular typing results
MTC Lineage	Dropdown	To enable analysis by molecular typing results
DSM during treatment (at least 2 months)	Dropdown	To investigate factors associated with treatment success
Culture result during treatment (at least 2 months)	Dropdown	To investigate factors associated with treatment success
DSM at end of treatment	Dropdown	To investigate factors associated with treatment success
Culture result at end of treatment	Dropdown	To investigate factors associated with treatment success
Treatment outcome (at 12 months)	Dropdown	To investigate factors associated with treatment success
Treatment outcome for MDR TB (at 24 months)	Dropdown	To investigate factors associated with treatment success
Treatment outcome for XDR TB (at 36 months)	Dropdown	To investigate factors associated with treatment success
Did drug resistance develop during treatment?	Y/N/UNK	To investigate factors associated with treatment success
If drug resistance developed during treatment, specify type	Dropdown	To investigate factors associated with treatment success
DOTS recommended?	Y/N/UNK	To investigate factors associated with treatment success
DOTS commenced?	Y/N/UNK	To investigate factors associated with treatment success
DOTS successful?	Y/N/UNK	To investigate factors associated with treatment success

CIDR variable name	Data type⁺⁺⁺⁺⁺	Rationale
Date of Death	DD/MM/YYYY	To calculate interval between diagnosis and death
Cause of Death	Dropdown	To exclude deaths diagnosed post-mortem from treatment outcome analysis
Case type	Dropdown	To investigate factors associated with treatment success
If contact case, nature of contact	Free text	To investigate factors associated with treatment success
If other nature of contact, please specify*	Free text	To investigate factors associated with treatment success
Comments (Enhanced)*	Free text	Free text field which may contain identifiers so will be reviewed for validation and completeness purposes but will be deleted prior to release for research purposes.
Patient ID	Numeric	Unique pseudonymised identifier for patients of TB to enable analysis of re-activation/re-infection. Not possible to link back to named patient data

Appendix 3: Systematic review protocol

A systematic review on the recent effects of migration from high TB incidence countries on the epidemiology of tuberculosis in low to medium incidence countries

Sarah Jackson, Catherine Comiskey, Zubair Kabir

Citation

Sarah Jackson, Catherine Comiskey, Zubair Kabir. A systematic review on the recent effects of migration from high TB incidence countries on the epidemiology of tuberculosis in low to medium incidence countries. PROSPERO 2018 CRD42018095038 Available from:

https://www.crd.york.ac.uk/prospERO/display_record.php?ID=CRD42018095038

Review question

How does migration from high TB incidence countries affect the epidemiology of tuberculosis in low to medium incidence countries?

Population:

Cases of active TB, resident in countries with low to medium TB incidence

Exposure:

Migration from a high TB incidence country to a low or medium TB incidence country

Comparator: TB cases born in and resident in low or medium TB incidence countries.

Outcomes:

Studies were included in the review if the primary outcome was diagnosis of microbiologically confirmed active TB while resident in a country of low or medium tuberculosis incidence. Secondary outcomes were sputum smear positive cases, cases clustered by genotyping or WGS, MDR-TB cases, and successfully treated cases.

Study characteristics:

Observational studies (including cohort, case control and cross-sectional studies) and publications reporting on routinely collected health data (RCD) using prospective, retrospective, cross-sectional or longitudinal designs where information on migrant status was also reported. Migrant status was defined as information reported on country of birth which allowed determination of TB incidence of the country of origin.

Exclusion criteria:

Animal studies, cases diagnosed/ resident in countries with high TB incidence, latent TB, migration from rural to urban within countries, studies that did not report country of birth, studies published prior to 1980 and non-English language abstracts (a list of untranslated references retrieved by the search strategy are documented in an appendix).

Searches

Information sources:

- Five electronic databases; MEDLINE(EBSCO), Embase (Embase), CINAHL (EBSCO), Scopus (Elsevier) and the SciELO (Web of Science) were searched. Reference lists of relevant publications were hand searched for additional articles.
- Websites of the World Health Organization (WHO), European Centre for Disease Prevention and Control (ECDC), Health Protection Scotland (HPS) Public Health Agency, Northern Ireland (PHA NI), Public Health England (PHE), Department of Health Australia, Public Health Surveillance, New Zealand, Public Health Agency Canada (PHAC) and Centers for Disease Control, United States (CDC US) were searched by key words as per the search strategy. Most recent relevant reports were selected for trend data.
- Grey literature was searched via OpenGrey, Grey Net and ERIC.

Types of study to be included

Study characteristics:

Observational studies (including cohort, case control and cross-sectional studies) and publications reporting on routinely collected health data (RCD) using prospective, retrospective, cross-sectional or longitudinal designs where information on migrant status was also reported. Migrant status was defined as information

reported on country of birth which allowed determination of TB incidence of the country of origin.

Inclusion criteria:

Studies were included in the review if the primary outcome was diagnosis of microbiologically confirmed active TB while resident in a country of low or medium tuberculosis incidence where data on country of birth was also reported.

Exclusion criteria:

Animal studies, cases diagnosed/ resident in countries with high TB incidence, latent TB, migration from rural to urban within countries, studies that did not report country of birth, studies published prior to 1980 and non-English language abstracts (a list of untranslated references retrieved by the search strategy are documented in Appendix X).

Condition or domain being studied

Effects of migration from high TB incidence countries on the epidemiology of tuberculosis in low to medium incidence countries.

Participants/population

Cases of active TB, resident in countries with low to medium TB incidence.

Intervention(s), exposure(s)

Migration from a high TB incidence country to a low or medium TB incidence country.

Comparator(s)/control

TB cases born in and resident in low or medium TB incidence countries.

Context

Main outcome(s)

Studies were included in the review if the primary outcome was diagnosis of microbiologically confirmed active TB while resident in a country of low or medium tuberculosis incidence.

Additional outcome(s)

Secondary outcomes were sputum smear positive cases, cases clustered by genotyping or WGS, MDR-TB cases and successfully treated cases.

Data extraction (selection and coding)

Data management:

Data were exported from online bibliographic databases into EndNote and screened for duplicates.

Covidence software was used to screen title and abstracts. RevMan software was used to record the characteristics of studies and study data, conduct critical appraisal and meta-analysis.

Data selection process:

Two reviewers independently screened the title and abstract of all citations returned by the search strategy after deduplication. SJ screened 100% of citations while CC and ZK screened 50% of citations each. Full text reports of potentially eligible citations were retrieved and assessed for inclusion in the review based on the inclusion criteria. Any discrepancies between reviewers in the studies selected were resolved by discussion between the two relevant reviewers initially and the third reviewer was consulted for final arbitration where required. Excluded studies were detailed in a table. The study selection process is detailed in a PRISMA flowchart.

Data extraction process:

Two reviewers independently reviewed the selected full text articles and used a pre-piloted data extraction form for the listed data items. The Population, Exposure, Comparator, Outcomes, Study characteristics (PECOS) framework was used to systematise data extraction.

Data items:

All relevant study characteristics were extracted and are detailed in an appendix. Studies that reported the total number of cases of active TB stratified by migrant status were included in the meta-analysis. Variables selected for meta-analysis stratified by migrant status were number of sputum smear positive cases, number of clustered cases/ isolates, number of multi-drug resistant (MDR) cases and number of successfully treated cases.

Risk of bias (quality) assessment

Quality assessment/ Risk of bias:

Relevant articles were critically appraised using CASP checklists for cohort and case control studies and the Newcastle Ottawa Scale (NOS) was used to assess the quality of other non-randomised studies. Risk of bias was assessed using the RevMan Risk of Bias tool. The strength of the body of evidence was assessed using GRADE methodology. Evidence of publication bias was investigated using a funnel plot.

Strategy for data synthesis

A narrative synthesis of the results was produced, with a tabulation of characteristics of included studies. Where data was available in studies that met the selection criteria, numerator and denominator were extracted and effect estimates for both the individual studies and the pooled results were calculated and displayed in a Forest Plot using RevMan software.

Analysis of subgroups or subsets

Subgroup analyses were carried out by year of study, study setting, study region and TB incidence of study (low or medium).

Contact details for further information

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Review team members and their organisational affiliations

Ms Sarah Jackson. Health Protection Surveillance Centre, Health Service Executive
Professor Catherine Comiskey. Trinity College Dublin, Ireland
Mr Zubair Kabir. University College Cork, Ireland

Type and method of review

Epidemiologic, Meta-analysis, Systematic review

Anticipated or actual start date

01 May 2018

Anticipated completion date

30 April 2019

Funding sources/sponsors

This review was undertaken as part of Ms Sarah Jackson's doctoral project in the School of Nursing and Midwifery, Trinity College Dublin, University of Ireland and is funded by the Health Service Executive, Ireland.

Conflicts of interest

Language

(there is not an English language summary)

Country

Ireland

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Emigration and Immigration; Environment; Humans; Incidence; Tuberculosis

Date of registration in PROSPERO

17 May 2018

Date of publication of this version

17 May 2018

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions

17 May 2018

PROSPERO

This information has been provided by the named contact for this review. CRD has accepted this information in good faith and registered the review in PROSPERO. The registrant confirms that the information supplied for this submission is accurate and complete. CRD bears no responsibility or liability for the content of this registration record, any associated files or external websites.

Appendix 4a: Systematic review search strategy supplementary materials

Table A4.1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Human studies	Animal studies
Case control, cohort or cross-sectional studies	Case studies, case series
Cases diagnosed/ resident in countries with low/medium TB incidence (<40/100,000)	Cases diagnosed/ resident in countries with high TB incidence (≥40/100,000)
Active TB	Latent TB
Migration from high TB incidence country (>39/100,000) to low or medium TB incidence country (<21/100,000)	Internal migration within national boundaries
English language publications	Non-English language publications
Studies published after 2009	Studies published prior to 2010
Studies reporting country birth for >94% of foreign-born TB cases	Studies reporting country of birth for <95% of foreign-born TB cases
Studies reporting data on migrants and non-migrants	Studies reporting migrants only or non-migrant only

Table A4.2: Terms employed by the search strategy used in EMBASE (Embase.com)

No.	Terms employed by the search strategy in EMBASE
#9	#8 AND [embase]/lim
#8	#5 AND #6 AND #7
#7	#3 OR #4
#6	#1 OR #2
#5	active OR confirm* OR positiv*
#4	migrant'/exp OR 'migrant' OR 'refugee'/exp OR 'refugee' OR 'immigration'/exp OR 'immigration' OR 'migration'/exp OR 'migration' OR 'population migration'/exp OR 'population migration'
#3	transient*:ab,ti OR migrant*:ab,ti OR emigrant*:ab,ti OR immigrant*:ab,ti OR refugee*:ab,ti OR 'asylum seeker':ab,ti OR emigration*:ab,ti OR migration*:ab,ti OR immigration*:ab,ti OR relocation*:ab,ti OR relocate*:ab,ti
#2	'tuberculosis'/exp OR 'tuberculosis' OR 'lupus vulgaris'/exp OR 'lupus vulgaris' OR 'pott s disease'/exp OR 'pott s disease' OR 'pott disease'
#1	tuberculosis:ab,ti OR tuberculoses:ab,ti OR tuberculous:ab,ti OR tuberculoid:ab,ti OR 'koch s disease':ab,ti OR 'kochs disease':ab,ti OR 'koch disease':ab,ti OR 'potts disease':ab,ti OR 'pott s disease':ab,ti OR 'pott disease':ab,ti OR scrofula:ab,ti OR phthisis:ab,ti

Table A4.3: List of studies excluded on basis of English language inclusion criteria

1. [Tuberculosis Annual Report 2012. (1). Summary of tuberculosis notification statistics and foreign-born tuberculosis patients]. Kekkaku: [Tuberculosis]. 2014;89(6):619-25.
2. Ayerra MG, Gorostidi AM, Aguirre MH, Setas AG. Tuberculous disease in pediatrics: Ten years' experience. *Pediatría de Atención Primaria*. 2019;21(82):e61-e6.
3. Berzosa Sánchez A, Illán Ramos M, Prados M, Calderón Gallego C, Francisco González L, Callejas Caballero I, et al. Tuberculosis in the paediatric population of Madrid in the last 26 years. *Enfermedades Infecciosas Y Microbiología Clínica*. 2019.
4. Chalela R, Sánchez-Font A, Domínguez-Álvarez M, Badenes-Bonet D, Pijuan L, Curull V. [Role of endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of mediastinal tuberculosis]. *Medicina Clínica*. 2016;146(12):532-5.
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6. Fica A, Herrera T, Aguilera X. [Worsening situation of tuberculosis in Chile]. *Revista Medica De Chile*. 2019;147(8):1042-52.
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10. García-Zamalloa AM, Arrizabalaga J. [Tuberculosis in the Bajo Deba area (Guipúzcoa, Spain) from 1995 to 2006]. *Enfermedades Infecciosas Y Microbiología Clínica*. 2008;26(4):187-93.
11. Gil M, Moreno R, Marín M, Romeu MÁ, Gomila B, González F. [Influence of immigration on tuberculosis transmission patterns in Castellón, Spain (2004-2007)]. *Gaceta Sanitaria*. 2011;25(2):122-6.
12. Ikeda K, Nishikiori H, Kondo S, Kobayashi T, Taya T, Mori Y, et al. [THE CURRENT SITUATION OF FOREIGN TUBERCULOSIS PATIENTS AND THEIR CONCURRENT HIV INFECTION IN HOKKAIDO]. *Kekkaku: [Tuberculosis]*. 2016;91(2):33-9.
13. Kubín M, Malý M, Jágrová Z. Contribution of homeless people to the incidence of tuberculosis in Prague. *Studia Pneumologica et Phthiseologica*. 2016;76(2):67-72.
14. Margarit A, Simó S, Rozas L, Deyà-Martínez À, Barrabeig I, Gené A, et al. [Adolescent tuberculosis; a challenge and opportunity to prevent community transmission]. *Anales De Pediatría (Barcelona, Spain: 2003)*. 2017;86(3):110-4.
15. Masvidal Aliberch RM, Gil BM, Vall Mayans M, Zabaleta Del Olmo E, Carnero Olmedo E, Rodríguez De La Rubia Rodríguez-Manzanique CR. Tuberculous infection from an area of high incidence of tuberculosis and with a high proportion of immigrants. *Anales de Pediatría*. 2004;60(1):22-7.

16. Morales-García C, Parra-Ruiz J, Valero-Aguilera B, Sanbonmatsu-Gámez S, Sánchez-Martínez JA, Hernández-Quero J. [Characteristics of tuberculosis in the immigrant population in South Granada Health Area]. *Enfermedades Infecciosas Y Microbiología Clínica*. 2015;33(3):166-72.
17. Morgado A, Köhnenkamp R, Navarrete P, García P, Balcells ME. [Clinical and epidemiological profile of tuberculosis in a university hospital in Santiago, Chile]. *Revista Medica De Chile*. 2012;140(7):853-8.
18. Pape S, Groß F, Ulrichs T. [The tuberculosis situation in the Berlin prison system from 2011-2016-a follow-up study]. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz*. 2019;62(7):893-903.
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21. Rodrigo T, García-García J-M, Caminero JA, Ruiz-Manzano J, Anibarro L, García-Clemente MM, et al. Evaluation of the Integrated Tuberculosis Research Program Sponsored by the Spanish Society of Pulmonology and Thoracic Surgery: 11 Years on. *Archivos De Bronconeumologia*. 2019.
22. Ruffini E, Compagnoni L, Tubaldi L, Infriccioli G, Vianelli P, Genga R, et al. [Congenital and perinatal infections in the Marche region (Italy): an epidemiological study and differences between ethnic groups]. *Le Infezioni In Medicina: Rivista Periodica Di Eziologia, Epidemiologia, Diagnostica, Clinica E Terapia Delle Patologie Infettive*. 2014;22(3):213-21.
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Appendix 4b: Systematic review data extraction tool

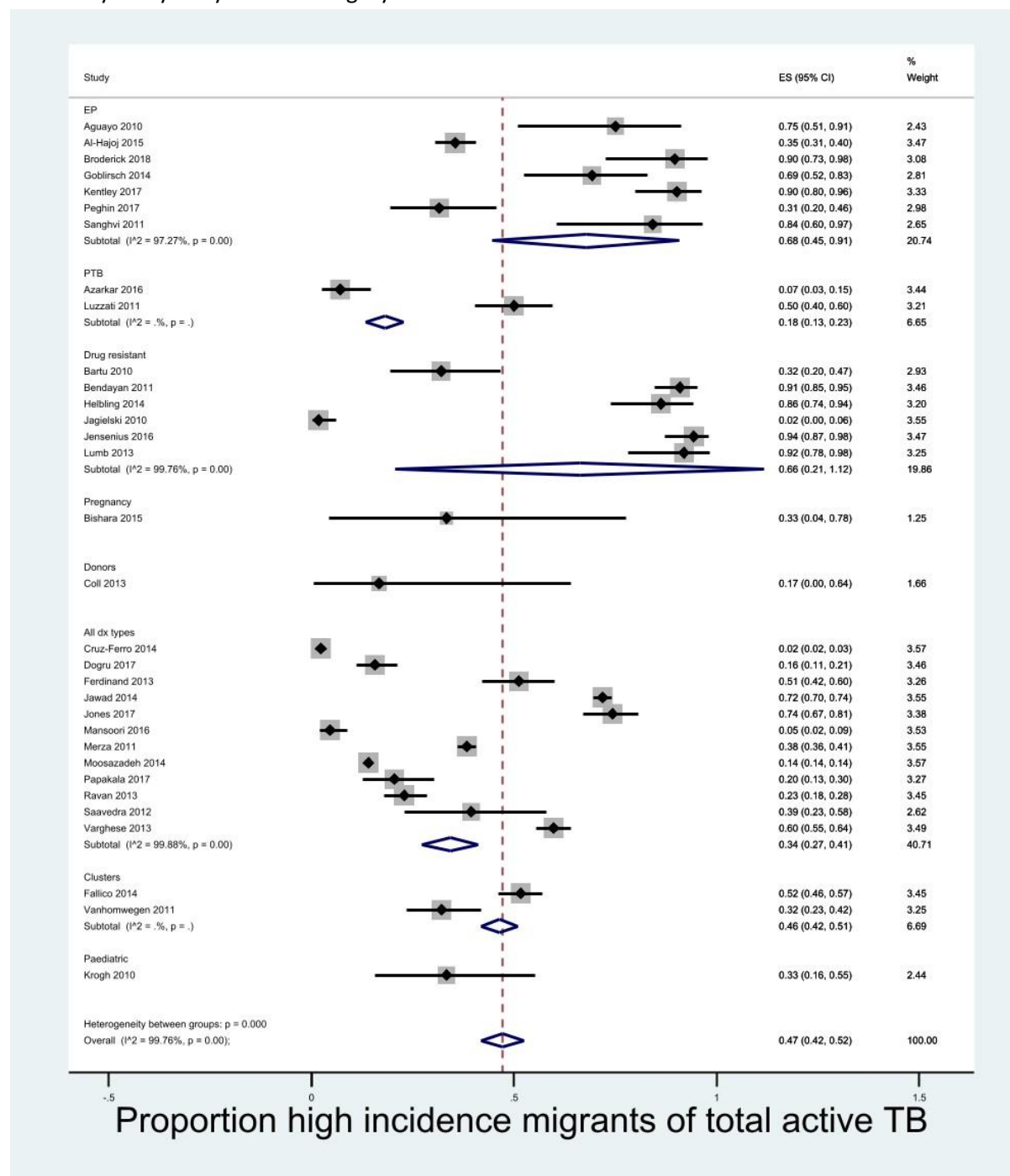
Section	Variable name	Variable description	Data type
Study details	Study ID	Generated by Covidence	Numeric
	Reviewer details	CC or SJ or ZK	Drop down
	Citation	Citation & DOI of report	Free text
	Author contact	Corresponding author & institution	Free text
	Author	First author	Free text
	Year Report	Year study was published	Numeric
	Year Study*	Year study was conducted	Numeric
	Study Setting*	Description of setting in which study was conducted	Free text
	Study Design*	Case control, cohort pro, cohort retro, cross-sectional, RCHD	Drop down
	Study Duration Mo	Duration of study in months	Numeric
	StudyFU Mo	Duration of follow up in months	Numeric
	Funding	Source of funding for study	Free text
	Study Aims	Description of aims and objectives of study	Free text
Study population	Inclusion/ exclusion criteria	Inclusion/ exclusion criteria of the study	Free text
	Pop Age	Age range of study population or restrictions on age.	Free text
	Pop Female	Number females reported in the study	Numeric
	Pop Male	Number of males reported in study	Numeric
	Pop Country	Name of country study conducted in, option for multiple	Drop down
	Pop Region*	Euro/SSEAsia/E Asia/ Africa/LatAm/Oceania	Drop down
	Pop Migrant source	Details of the main source countries of incoming migrants	Free text
	Pop CoMorbidity	Details of any co-morbidities in population	Free text
	Pop SocioDemo	Details of any socio-demographics in population	Free text
	Pop Ethnicity	Details of any ethnicities mentioned in population	Free text
	Pop TB incidence*	TB incidence of country study conducted in (per 100,000 pop)	Numeric
	Total Active TB cases	Total number of active TB cases reported by study	

Section	Variable name	Variable description	Data type
Primary outcome N	Total Active TB cases Migrant HI	Total number of active TB cases in high incidence migrants reported by study	
	Total Active TB cases Migrant LMI	Total number active TB cases in high incidence migrants reported by study	
	Total Active TB cases Indig	Total number of active TB cases in non-migrants reported by study	
Primary outcome rates	Active TB incidence rate	Active TB incidence rate reported by study	Numeric
	Active TB incidence rate Migrant HI	Active TB incidence rate in high incidence migrants reported by study	Numeric
	Active TB incidence rate Migrant LMI	Active TB incidence rate in low/medium incidence migrants reported by study	Numeric
	Active TB incidence rate Indig	Active TB incidence rate in in non-migrants reported by study	Numeric
2° outcome: Sputum smear positive cases	SSPos Total	Total number of sputum smear positive cases reported by study	Numeric
	SSPos Mig HI	Total number of sputum smear positive cases in high incidence migrants reported by study	Numeric
	SSPos Mig LMI	Total number of sputum smear positive cases in low/med incidence migrants reported by study	Numeric
	SSPos Indig	Total number of sputum smear positive cases in non-migrants reported by study	Numeric
2° outcome: Clustered cases	Clustered Total	Total number of clustered cases reported by study	Numeric
	Clustered Mig HI	Total number of clustered cases in high incidence migrants reported by study	Numeric
	Clustered Mig LMI	Total number of clustered cases in low/med incidence migrants reported by study	Numeric
	Clustered Indig	Total number of clustered cases in non-migrants reported by study	Numeric
2° outcome: Successfully treated cases	TxSuccess Total	Total number of successfully treated cases reported by study	Numeric
	TxSuccess Mig HI	Total number of successfully treated cases in high incidence migrants reported by study	Numeric
	TxSuccess Mig LMI	Total number of successfully treated cases in low/med incidence migrants reported by study	Numeric
	TxSuccess Indig	Total number of successfully treated cases in non-migrants reported by study	Numeric
2° outcome: HIV co-infections	TB HIV total	Total number of TB HIV coinfections reported by study	Numeric
	TB HIV total	Total number TB HIV coinfections in high incidence migrants reported by study	Numeric
	TB HIV total	Total number of TB HIV coinfections in low/med incidence migrants reported by study	Numeric
	TB HIV total	Total number of TB HIV coinfections in non-migrants reported by study	Numeric

Section	Variable name	Variable description	Data type
2° outcome: Cases resistant to any first to anti-TB drug	AnyRes Total	Total number of MDR cases reported by study	Numeric
	AnyRes Mig HI	Total number of MDR cases in high incidence migrants reported by study	Numeric
	AnyRes Mig LMI	Total number of MDR cases in low/med incidence migrants reported by study	Numeric
	AnyRes Indig	Total number of MDR cases in non-migrants reported by study	Numeric
2° outcome: MDR cases	MDR Total	Total number of MDR cases reported by study	Numeric
	MDR Mig HI	Total number of MDR cases in high incidence migrants reported by study	Numeric
	MDR Mig LMI	Total number of MDR cases in low/med incidence migrants reported by study	Numeric
	MDR Indig	Total number of MDR cases in non-migrants reported by study	Numeric
Comments	Comments	General comments and relevant references identified from bibliography	Free text

Appendix 4c: Systematic review results supplementary materials

Figure A4: Proportion of active TB cases in high incidence migrants of total study population with sensitivity analysis by clinical category



Appendix 5: Chapter 5 supplementary materials

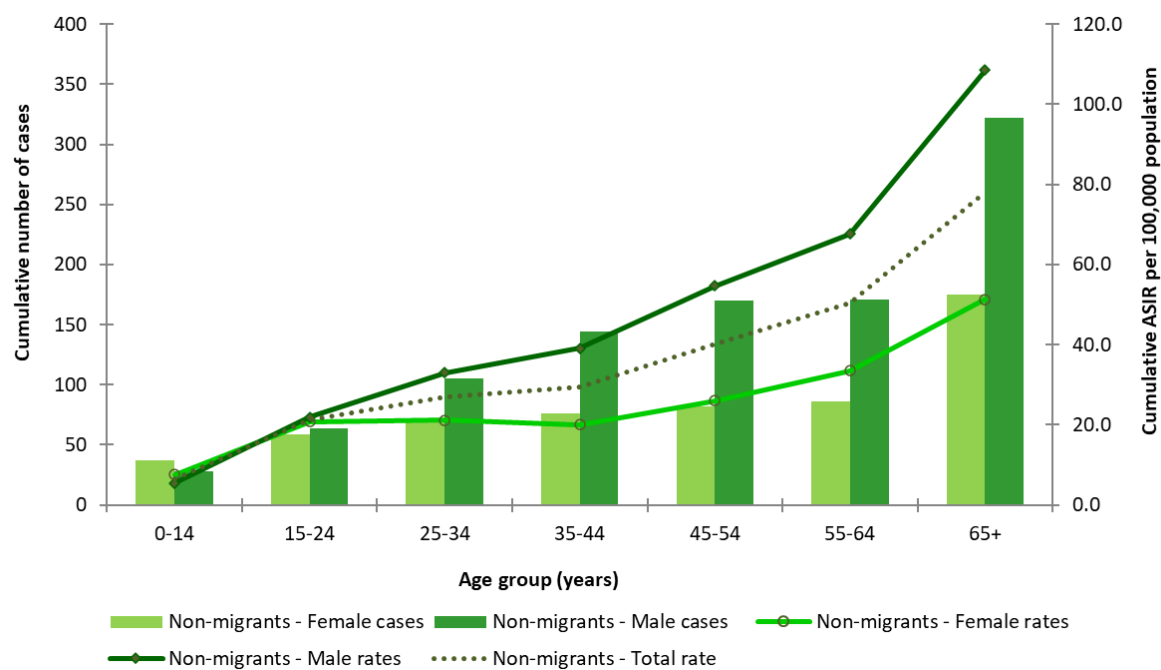


Figure A5.1: Cumulative Irish-born TB age-specific incidence rates by sex in Ireland

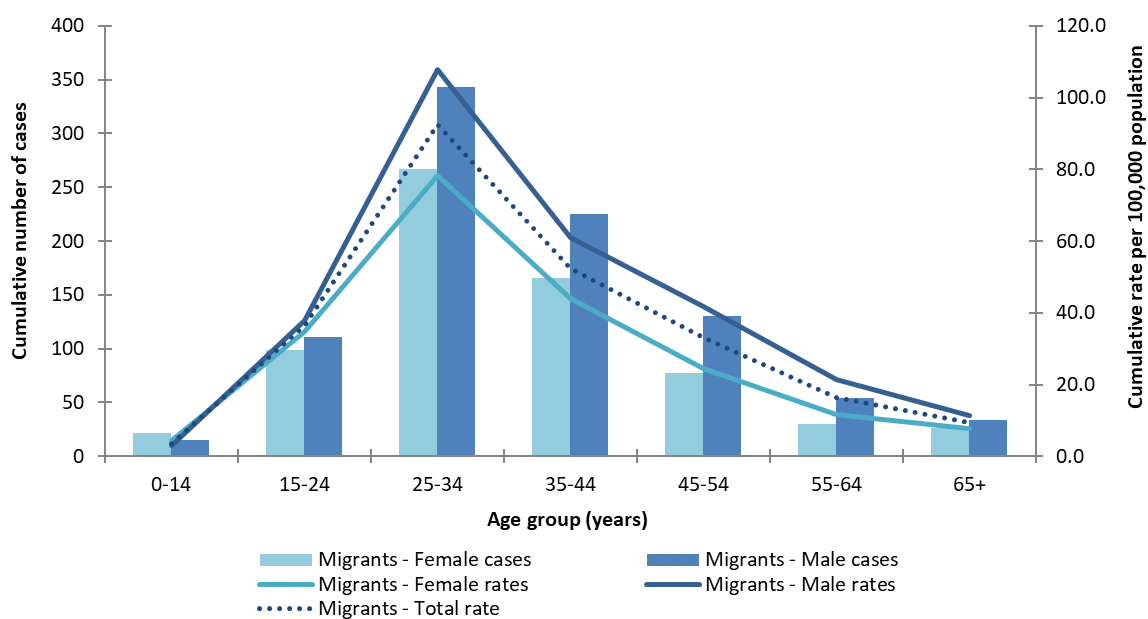


Figure A5.2: Cumulative migrant TB age-specific incidence rates by sex in Ireland

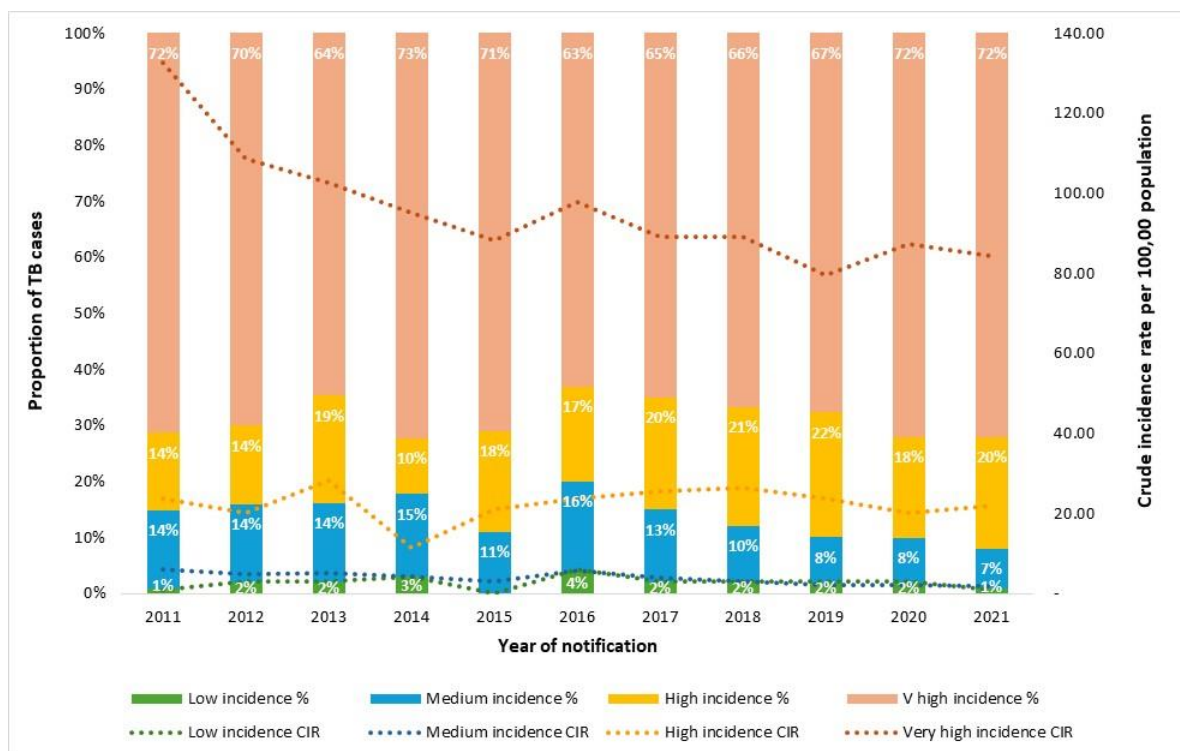


Figure A5.3: Annual proportion and crude incidence rates by WHO incidence categories for migrant TB patients in Ireland

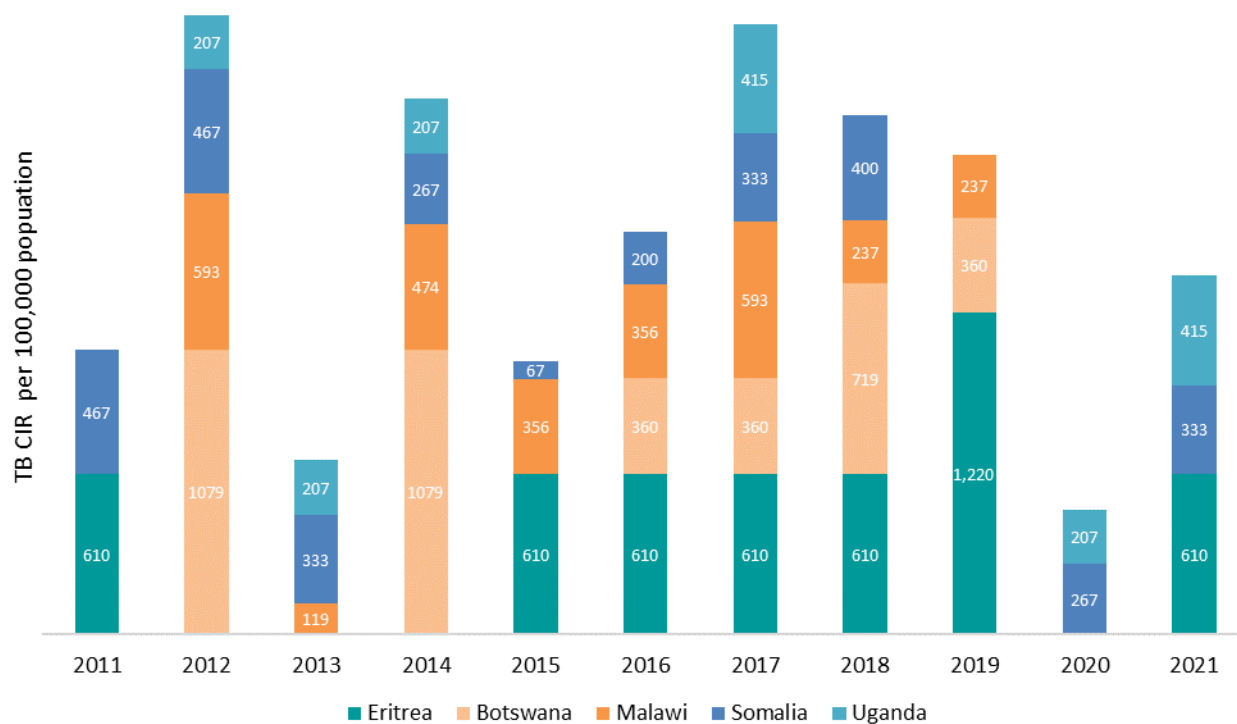


Figure A5.4: Annual TB incidence rates for birth countries with Top 10 highest CIRs in Ireland: Sub Saharan African countries

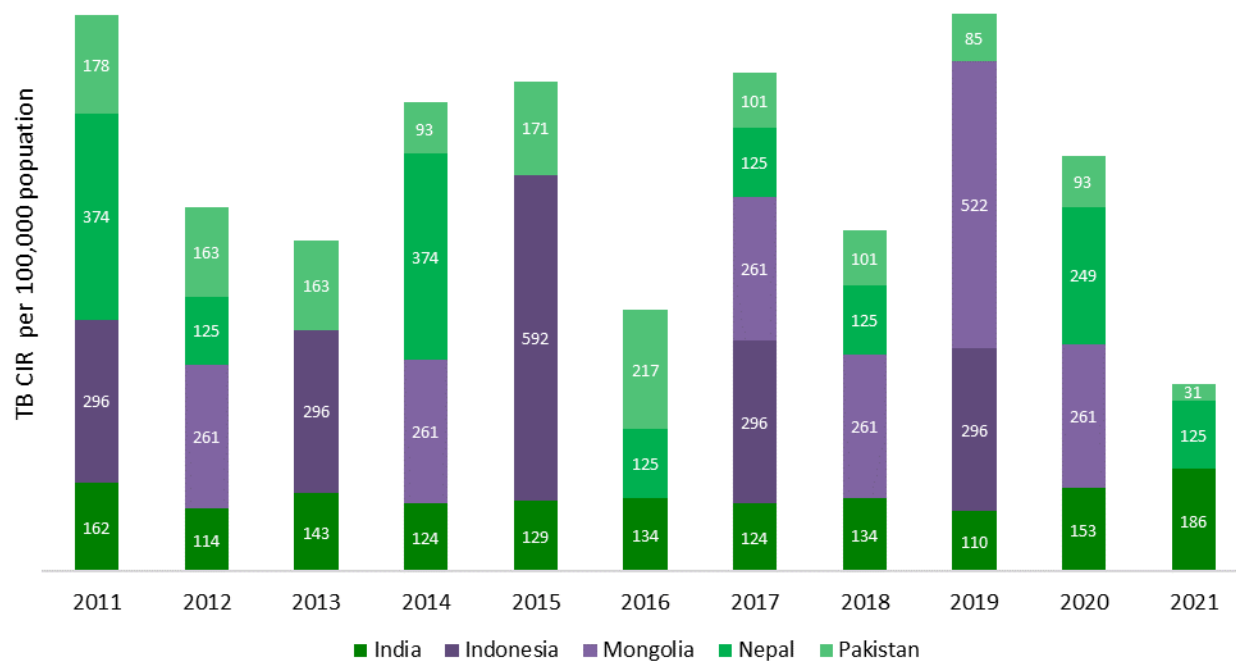


Figure A5.5: Annual TB incidence rates for birth countries with Top 10 highest CIRs: South / South East Asian countries

Appendix 6: Treatment success models supplementary information

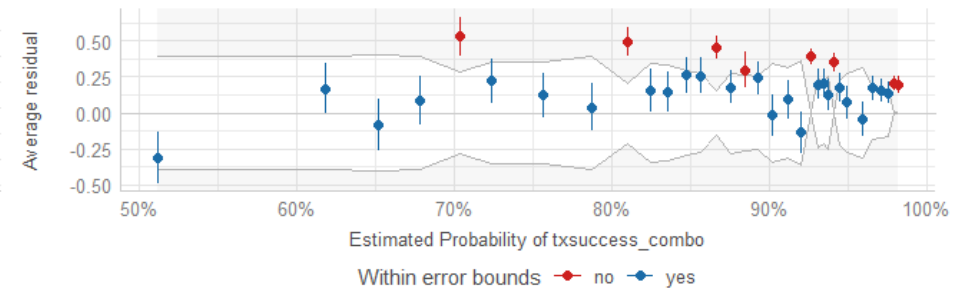
Posterior Predictive Check

Model-predicted intervals should include observed data points



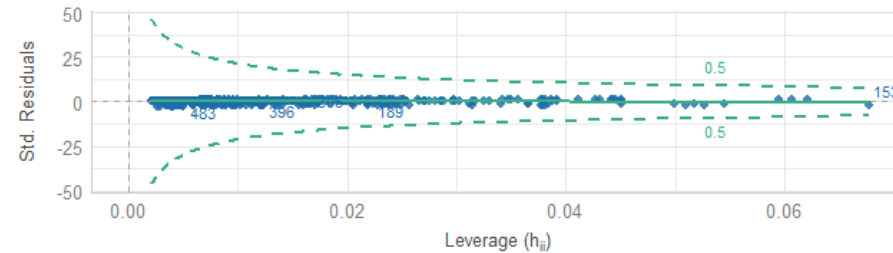
Binned Residuals

Points should be within error bounds



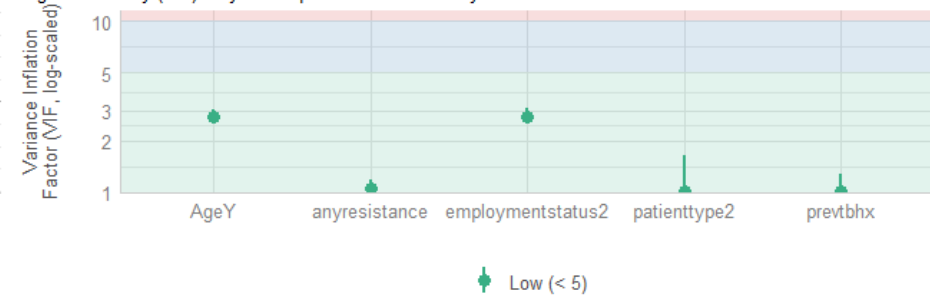
Influential Observations

Points should be inside the contour lines



Collinearity

High collinearity (VIF) may inflate parameter uncertainty



Uniformity of Residuals

Dots should fall along the line

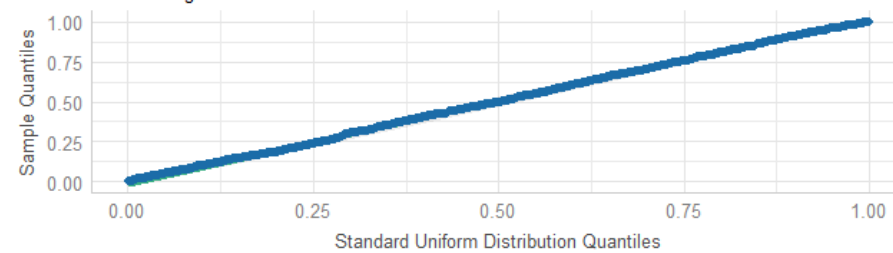


Figure A6.1: Model assumptions of treatment success among all cases final model generated through manual method (n=1,074)

Table A6.1: Factors associated with treatment success among migrant TB cases from model produced by multivariable logistic regression algorithm method (complete case sample: N = 478)

Characteristic	Adjusted Odds Ratio (95% Confidence Intervals)	p-value
Sex		
<i>Female</i>	—	
<i>Male</i>	0.56 (0.29 to 1.05)	0.074
Disease site		
<i>Pulmonary</i>	—	
<i>Extrapulmonary</i>	2.42 (1.17 to 5.51)	0.024
Previous TB diagnosis		
<i>No</i>	—	
<i>Yes</i>	0.48 (0.19 to 1.34)	0.13
TB drug resistance		
<i>Sensitive</i>	—	
<i>Resistant</i>	0.41 (0.21 to 0.81)	0.008
Employment status		0.010
<i>Paid employment</i>	—	
<i>Unemployed</i>	0.37 (0.17 to 0.76)	0.008
<i>Retired</i>	0.16 (0.05 to 0.59)	0.004
<i>Student/Child</i>	0.59 (0.21 to 1.78)	0.32
<i>Other</i>	0.20 (0.05 to 1.02)	0.031

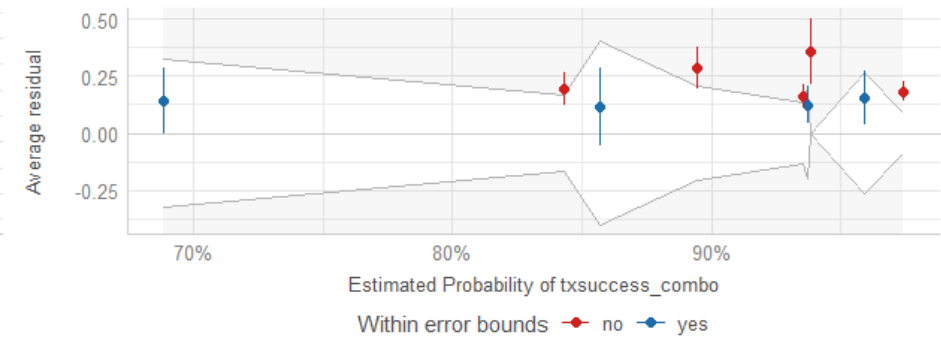
Posterior Predictive Check

Model-predicted intervals should include observed data points



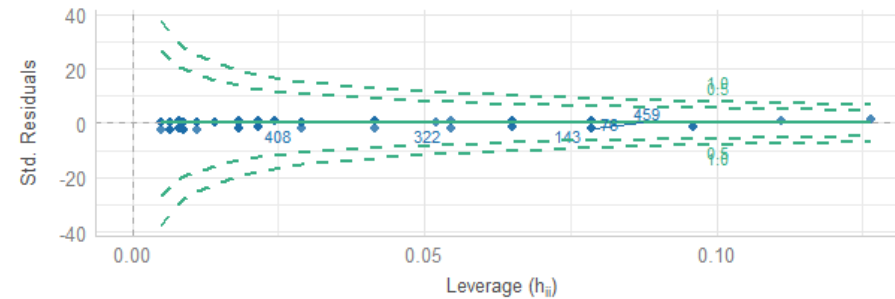
Binned Residuals

Points should be within error bounds



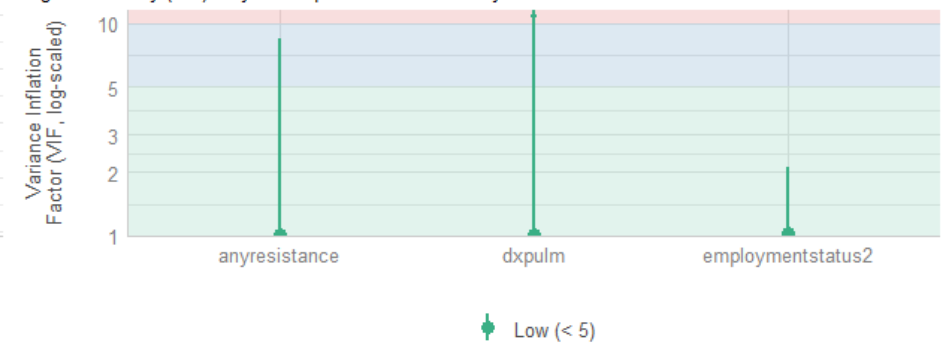
Influential Observations

Points should be inside the contour lines



Collinearity

High collinearity (VIF) may inflate parameter uncertainty



Uniformity of Residuals

Dots should fall along the line

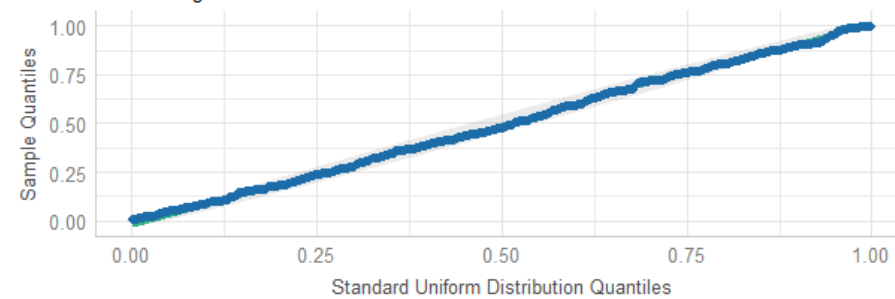


Figure A6.2: Model assumptions of treatment success among migrant TB cases final model generated through manual method (n=477)

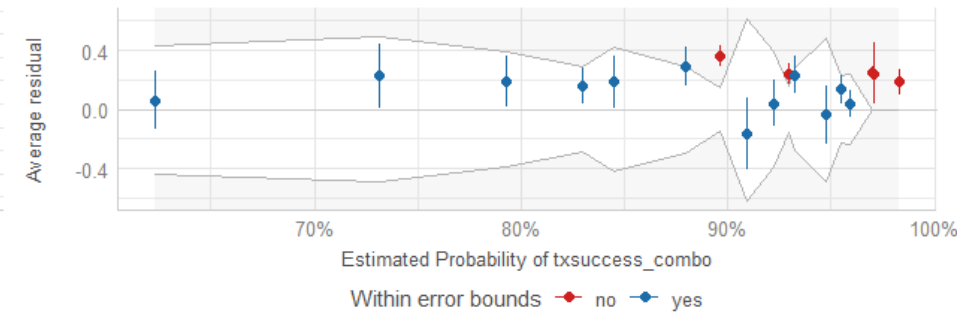
Posterior Predictive Check

Model-predicted intervals should include observed data points



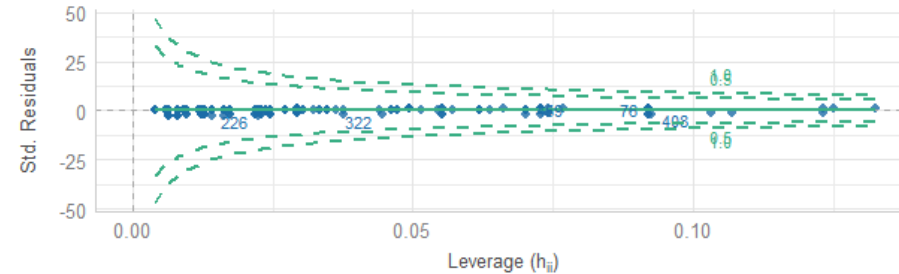
Binned Residuals

Points should be within error bounds



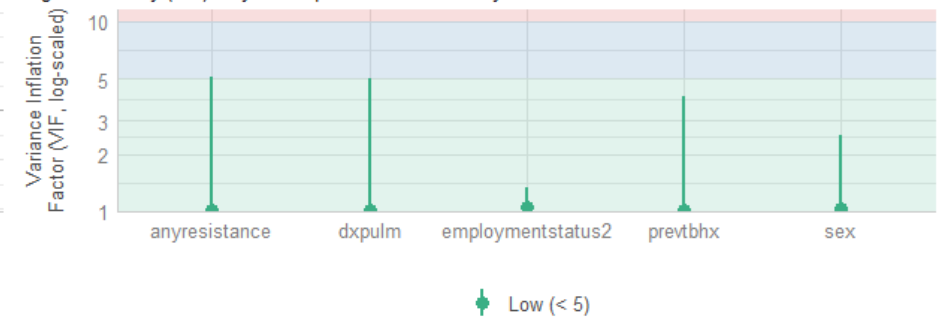
Influential Observations

Points should be inside the contour lines



Collinearity

High collinearity (VIF) may inflate parameter uncertainty



Uniformity of Residuals

Dots should fall along the line

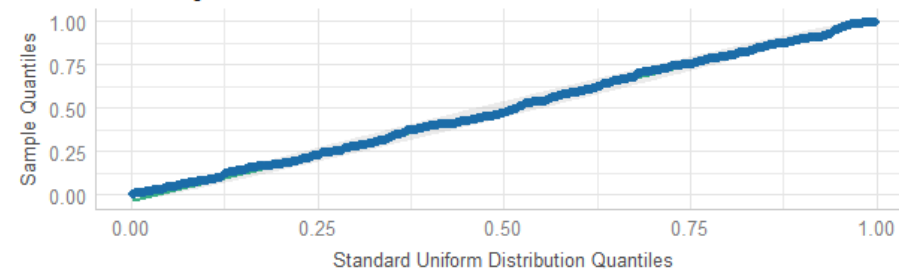


Figure A6.3: Model assumptions of treatment success among migrant TB cases final model generated through algorithm method (n=477)

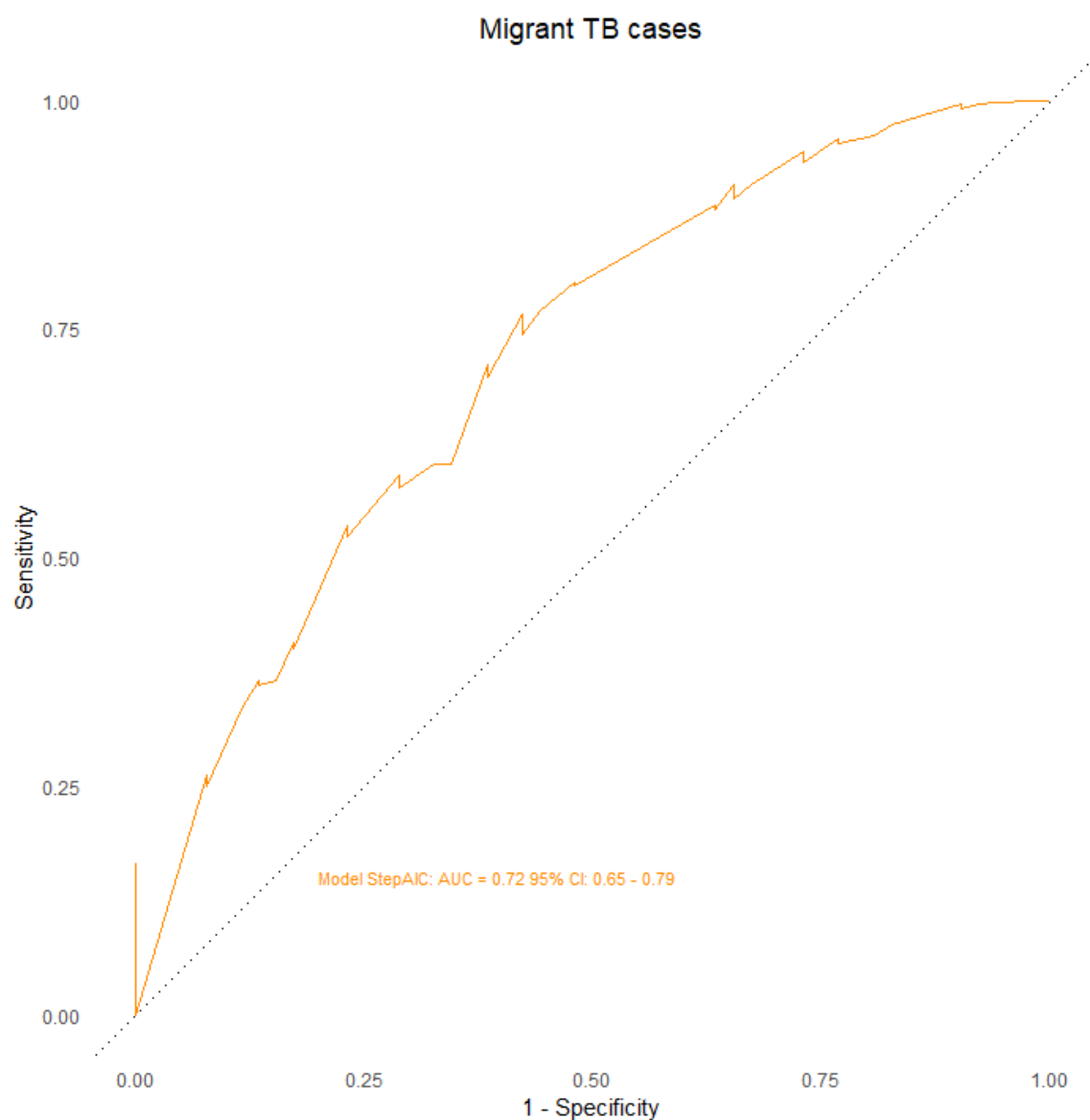
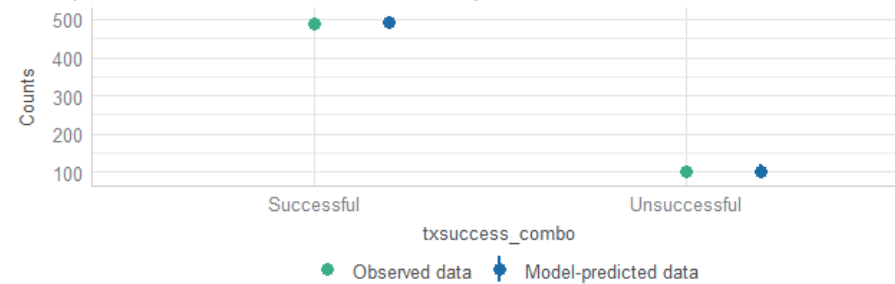


Figure A6.4: ROC AUC for final multivariable logistic regression models for treatment success among generated by algorithm method for migrant cases

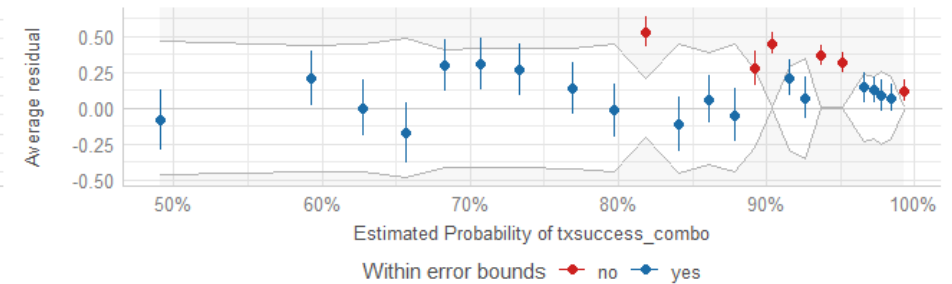
Posterior Predictive Check

Model-predicted intervals should include observed data points



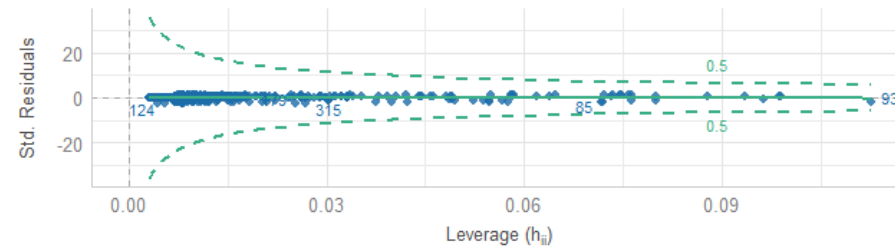
Binned Residuals

Points should be within error bounds



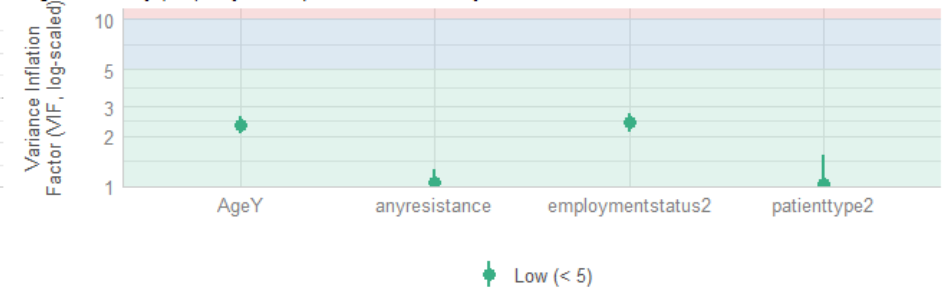
Influential Observations

Points should be inside the contour lines



Collinearity

High collinearity (VIF) may inflate parameter uncertainty



Uniformity of Residuals

Dots should fall along the line

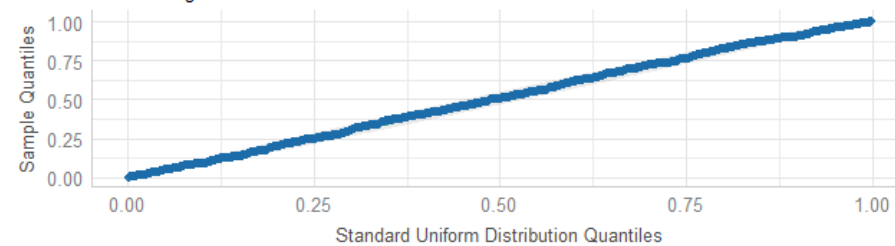


Figure A6.5: Model assumptions for treatment success among Irish-born TB cases for final model generated through manual method (n = 592)