Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health technology assessment of a selective BCG vaccination programme

November 2015

Safer Better Care

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The Health Information and Quality Authority (HIQA) is an independent Authority established to drive high quality and safe care for people using our health and social care and support services in Ireland. HIQA's role is to develop standards, inspect and review health and social care and support services, and support informed decisions on how services are delivered. HIQA's ultimate aim is to safeguard people using services and improve the quality and safety of services across its full range of functions.

HIQA's mandate to date extends across a specified range of public, private and voluntary sector services. Reporting to the Minister for Health and the Minister for Children and Youth Affairs, the Health Information and Quality Authority has statutory responsibility for:

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Foreword

Tuberculosis (TB) remains a major health challenge, with an estimated 9.6 million new cases globally in 2014. As with most other Western European states, the incidence of TB in Ireland is low. In line with global trends, TB incidence in Ireland has been in decline over the last 25 years, with over 95% of cases occurring in adults. In 2014, there were eight cases of TB in children aged less than 16 years.

The BCG vaccine provides protection against TB. Universal BCG vaccination of newborns was first introduced in Ireland in the 1950s. Due to declines in TB incidence, many European countries have ceased universal vaccination, mostly switching to selective vaccination of children at higher risk of contracting TB. At present in Western Europe, only Ireland and Portugal have universal vaccination programmes despite neither being considered a high TB incidence country. The purpose of this report was to determine the impact of changing from a universal to a selective national neonatal BCG vaccination programme.

The health technology assessment (HTA) was requested by the Chief Medical Officer of the Department of Health on foot of a recommendation from the National Immunisation Advisory Committee and the National Tuberculosis Advisory Committee. The recommendation was formed based on criteria for discontinuing universal BCG vaccination from the International Union Against Tuberculosis and Lung Disease, epidemiological data on TB incidence, incidence of BCG reactions, and a cost-effectiveness evidence analysis by the National Centre for Pharmacoeconomics (NCPE). This report benefitted from unrestricted access to the work of the NCPE.

The assessment was carried out by an Evaluation Team from the HTA Directorate in the Authority. A multidisciplinary Expert Advisory Group was established to provide advice on the assessment. A public consultation was carried out to get feedback from members of the general public before finalising the report.

The Authority would like to thank the Evaluation Team, the members of the Expert Advisory Group, and all those who contributed to the public consultation and the preparation of this report.

Dr Máirín Ryan

Acting Deputy Chief Executive and Director of Health Technology Assessment

Health Information and Quality Authority

Advice to the Minister for Health

This health technology assessment (HTA) examined proposed changes to the national neonatal BCG vaccination programme. It examined the clinical implications, cost-effectiveness, resource implications, budget impact, organisation and ethical aspects of selective BCG vaccination of high risk infants compared with the existing programme of universal vaccination, and a strategy of no vaccination.

The key findings of this HTA, which inform and precede HIQA's advice, are:

- Universal vaccination of newborns was first introduced in Ireland in the 1950s to protect against tuberculosis (TB). Due to a decline in national TB incidence, many European countries have ceased universal vaccination programmes, mostly switching to a policy of selective vaccination of individuals at high risk. At present in Western Europe, only Ireland and Portugal have universal vaccination programmes despite neither being considered a high TB incidence country.

- In line with global trends, TB incidence in Ireland has been in decline over the last 25 years. The crude national incidence rate per 100,000 has fallen from 18.2 in 1991 to 7.0 in 2014. Between 2005 and 2014 the average annual number of cases in children aged less than 15 years was 20.9 cases, although the incidence has been in decline. The average annual number of cases for 2012 to 2014 was 11.7 cases. In 2007 there were two outbreaks of TB in county Cork linked to two crèches, and in 2010 there were three general outbreaks that occurred in schools.

- The three year notification rate of smear-positive pulmonary TB cases is less than 5 per 100,000 and the notification rate of TB meningitis in children aged less than five years is below one per 10 million general population; two of the IUATLD criteria for stopping or modifying the BCG vaccination programme.

- Treatment for TB is intended to be curative. TB meningitis, which accounts for 4% of childhood TB cases, is associated with a high risk of long-term neurological sequelae including intellectual, behavioural, neurological, and hearing deficits. Between 2002 and 2014 there were no TB deaths in children aged less than 15 years.

- Infants at high risk of developing TB can be defined on the basis of a number of factors, including: born in a high TB incidence country; parents from a high TB incidence country; contact with cases with active respiratory tuberculosis;

member of an at risk group for which there may be difficulty in providing alternative control measures (for example, the Traveller community). The high-risk population in Ireland comprises children born to parents from a high TB incidence country and Irish Traveller children, accounting for approximately 13.4% of births in Ireland annually. High-risk infants were estimated to have a risk of contracting TB three times that of the general population.

- Based on the best available evidence, vaccination is effective at protecting against TB. There is limited evidence on the duration of effect, although it is estimated that it may last for up to 15 years. Disseminated BCG is a rare but very severe adverse reaction to BCG. In Ireland there have been eight confirmed cases of disseminated BCG in 10 years. Although all eight cases survived, based on international data the mortality rate is 29%.

- A policy of no vaccination was estimated to result in the highest mortality (0.44 deaths in the birth cohort), and universal vaccination in the lowest mortality (0.30 deaths in the birth cohort). Selective vaccination was estimated to result in 0.37 deaths. In terms of life years gained, selective vaccination was estimated to be more effective and less costly than universal vaccination. For quality-adjusted life years, universal vaccination was more effective than the alternative but universal vaccination was not cost-effective compared to selective vaccination. Neither universal nor selective vaccination would be considered cost-effective relative to no vaccination under typical willingness-to-pay thresholds.

- It was estimated that TB cases under selective vaccination would reach a maximum of 10.7 cases per annum three years after introduction, compared with 8.0 cases under universal vaccination at the same point in time. In the absence of any other changes to TB control, it was predicted that after 16 years, selective vaccination would, on average, result in an additional 3.6 cases of childhood TB per annum relative to universal vaccination.

- The budget impact of universal vaccination was estimated to be €2,393,335 per annum. The annual budget impact would be €1,339,364 for selective vaccination and €1,125,787 for a programme of no vaccination. In a selective programme, 34% of the budget impact arises from the vaccination programme and 27% is due specifically to the cost of administering the vaccine. The estimated budget savings are unlikely to be realised due to the need to invest in other aspects of TB control.

- TB screening and contact tracing are critical components of a TB control programme. A selective or no vaccination strategy will entail that a large proportion of children will have no protection against TB. An appropriately resourced and consistent approach to screening and contact tracing will be required to contain the spread of TB from index cases to unprotected children. In the interest of public health, a change of vaccination strategy should be supported by a clear commitment to systematic and comprehensive TB control. Consideration should be given to the development of a National Clinical Guideline on the control of TB in line with NCEC Standards for Clinical Practice Guidance.

- To minimise the impact of discontinuing universal vaccination, changes to TB control measures should be in place before changing the BCG vaccination policy. To ensure continued protection against TB, it is important that the uptake of neonatal BCG vaccination in the general population remains high until such time that the BCG vaccination policy is changed.

- A selective vaccination programme should be based on a set of unambiguous and uniformly applied criteria that are clear to both health professionals and the general public. A consistent approach to risk classification should be adopted which will require staff training.

- A change to selective vaccination should be supported by a public awareness campaign that clearly states the rationale for change and ensures that families at high risk understand the need to seek vaccination and to maintain a high uptake in eligible infants. It would be important to consult with high-risk groups to determine the most acceptable and efficient way to identify those eligible for vaccination. The process of seeking relevant information in relation to ethnicity or nationality must be carried out in a way that is non-discriminatory and consistent with the privacy of the infant and the family.

- Although it may be perceived as potentially discriminatory, the targeting of specific population groups for vaccination is justified on the basis of risk assessment and targeting those most likely to benefit. Moving to selective vaccination is therefore justified as a specific protective measure for groups at high risk and avoidance of the burden of vaccination for those for whom it carries little or no benefit.

- The findings and advice contained in this report are independent of supply issues relating to the BCG vaccine. In light of the ongoing issues with the supply of BCG vaccine, it is imperative that the available vaccine is used as efficiently as possible and for maximum benefit. Best use of vaccine points to

the need to minimise wastage and to target those most likely to benefit from vaccination.

As economic models incorporate a number of assumptions and are dependent on the quality of data available, the results are subject to a degree of uncertainty. Bearing in mind the estimates and assumptions that were used in this analysis and arising from the findings above, HIQA's advice to the Minister for Health is as follows:

- Ireland has a childhood TB incidence similar to other Western European countries. With the exception of Ireland and Portugal, no other Western European country has a programme of universal vaccination.
- Based on recent patterns of declining TB incidence, Ireland meets the International Union Against Tuberculosis and Lung Disease criteria for stopping or changing the BCG vaccination policy.
- In terms of the risk:benefit ratio balancing the harms of BCG versus the benefit of TB avoided, selective vaccination was estimated to be more effective and less costly than universal vaccination.
- Selective vaccination will protect children most at risk of contracting TB while avoiding adverse effects of the vaccine in children who are least likely to benefit from vaccination.
- For these reasons, , it is appropriate to change to a programme of selective vaccination.
- Selective vaccination was found to be not cost-effective relative to a programme of no vaccination. As such, if selective vaccination is adopted, the most efficient method of delivering the programme needs to be determined to ensure best use of resources.
- To minimise the impact of discontinuing universal vaccination, which is likely to result in two to four additional cases of TB per annum unless other aspects of TB control are strengthened, steps should be taken to ensure that comprehensive and adequately resourced TB control measures are in place before changes are made to the BCG vaccination policy.

Executive Summary

Background

The Chief Medical Officer of the Department of Health, requested that the Health Information and Quality Authority (HIQA) undertake a health technology assessment (HTA) in relation to proposed changes to the national neonatal BCG vaccination programme.

The request for a formal HTA was on foot of a recommendation from the National Immunisation Advisory Committee and the National Tuberculosis Advisory Committee. The recommendation was formed based on criteria for discontinuing universal BCG vaccination from the International Union Against Tuberculosis and Lung Disease, epidemiological data on tuberculosis (TB) incidence, incidence of BCG reactions, and a cost-effectiveness evidence analysis by the National Centre for Pharmacoeconomics.

Terms of Reference

The Terms of Reference for this health technology assessment were to:

- describe the epidemiology of TB in Ireland
- examine the current evidence of efficacy and safety for BCG vaccination in infants
- review the international cost-effectiveness literature on BCG vaccination strategies in infants
- estimate the clinical implications, cost-effectiveness, resource implications and budget impact of selective BCG vaccination of high-risk infants compared with a programme of universal vaccination, and a strategy of no vaccination
- consider any wider implications that a change in vaccination strategy may have for patients, the general public, or the healthcare system
- use the results of this assessment to advise on the optimal configuration of an Irish BCG vaccination programme for infants.

Technology description

Human tuberculosis (TB) is an infectious disease caused by bacteria of the Mycobacterium tuberculosis complex of which *M. Tuberculosis* is the most common and important agent causing human disease. While it may affect almost any part of the body, pulmonary TB (lungs) is the most common form and accounts for almost

60% of all cases in Ireland. Transmission of the disease is most likely after prolonged close contact with someone whose sputum is smear positive for the bacillus on microscopy. TB is a treatable and curable disease with the majority of non multi-drug resistant cases cured with a standard six-month treatment course. Multidrug-resistant TB can also occur, requiring more complex treatment regimens over periods of more than 18 months.

The BCG vaccine was first administered as an oral vaccine in France in 1921 to prevent TB. Universal vaccination of newborns was first introduced in Ireland in the 1950s. A policy of universal vaccination was consistent with World Health Organization (WHO) recommendations at the time that a single dose of BCG vaccine be given to all infants as soon as possible after birth in countries with a high incidence of TB (greater than or equal to 40 cases per 100,000 population). The benefit of BCG vaccination appears to be that it protects young children against disseminated and severe TB, for example TB meningitis and miliary TB. It is less effective in preventing respiratory disease in children.

The BCG vaccine is considered safe in healthy infants. Localised adverse reactions are usually self-limiting. Allergic reactions and more severe local reactions are rare.

Policies on BCG vaccination differ internationally. This reflects variation in the incidence of TB as well as differences in opinion concerning the relative benefit of the vaccine, particularly where incidence rates are low. As TB incidence declines, the benefit of universal vaccination also declines and the relative importance of adverse events increases. Due to a decline in national TB incidence, many European countries have ceased universal vaccination programmes, mostly switching to a policy of selective vaccination of high-risk individuals. At present in Western Europe, only Ireland and Portugal have universal vaccination programmes despite neither being considered a high TB incidence country.

The International Union Against Tuberculosis and Lung Disease set out criteria that should be met before considering discontinuing universal BCG vaccination. These criteria relate to how well the TB programme functions, the quality of TB reporting, and recent trends in pulmonary TB and TB meningitis. In the context of the current universal BCG vaccination programme, Ireland is considered to have a well-functioning TB programme with high quality reporting of TB notifications.

Among countries that operate a policy of selective vaccination, there is variation in the definition and management of the high-risk population. Criteria include selective vaccination of migrants, or children or grandchildren of migrants who have moved from high incidence countries (≥40/100,000 persons).

Burden of disease

Tuberculosis (TB) remains a global health challenge. An estimated 9.0 million people developed TB in 2013 and there were 1.5 million deaths from the disease in 2013. The incidence of TB in Ireland is similar to that of most other countries in the EU27 States, with the same incidence as Luxembourg, France, Belgium and Austria.

In line with global trends, TB incidence in Ireland has been in decline over the last 25 years. The crude national incidence rate per 100,000 has fallen from 18.2 in 1991 to 7.0 in 2014. The number of cases of TB in Ireland each year has dropped from over 600 in the early 1990s to under 400 since 2012; 324 cases were reported in 2014. Between 2005 and 2014 the average annual number of cases in children aged less than 15 years was 20.9 cases, although the incidence has been in decline; the average annual number of cases for 2012 to 2014 was 11.7 cases.

In 2007 there was an outbreak of TB in County Cork linked to two crèches, and during 2010 there were three general outbreaks that occurred in schools, which impact on figures. Corresponding to the decline in TB cases in the general population, the rate per 100,000 for 0-15 year olds has also been in decline over time.

There is substantial regional variation in incidence rates in Ireland, but no area would be considered high incidence based on the WHO metric of 40 cases per 100,000 persons.

The average annual notification rate of smear-positive pulmonary TB cases has been less than or equal to five per 100,000 during the previous three years. The average annual notification rate of TB meningitis in children aged under five years has been less than one per 10 million general population during the previous five years. Ireland therefore meets the International Union Against TB and Lung Disease TB incidence criteria for discontinuing universal BCG vaccination.

TB may affect different parts of the human body, and different incidence rates apply to each type. In 0 to 15 year olds, pulmonary TB accounts for 59% of TB cases, extrapulmonary TB for 36% of cases, TB meningitis for 4% and miliary TB is associated with 1% of cases.

The recommended treatment schedule for new patients with pulmonary and extrapulmonary TB lasts six months. Treatment is also intended to prevent re-activation of infection, for which a minimum six months treatment is required. Longer schedules of nine months and nine to 12 months have been recommended for TB of bones and joints and TB meningitis, respectively.

As treatment is intended to cure, the main outcome is reduced health-related quality of life in patients being treated for TB. Quality of life is lowest at diagnosis, and improves substantially as symptoms of TB resolve during the initial intensive treatment phase. Due to the lengthy treatment of six to 12 months, patients will experience reductions in quality of life associated with treatment-related restrictions and adverse events.

There is a lack of evidence regarding long-term impairment in those who had pulmonary TB in childhood. TB meningitis is associated with a high-risk of long-term neurological chronic complications including intellectual or behavioural deficits, neurological deficits (including motor deficits, seizures), and hearing deficits.

The case fatality rate for TB in Ireland is approximately 1% to 3% of cases of all ages, similar to Germany and Luxembourg. Between 2002 and 2014 there were no TB deaths in children aged less than 15 years in Ireland.

Infants may be at high-risk of developing TB on the basis of a number of factors, including: born in a high TB incidence country; parents from a high TB incidence country; contact with cases with active respiratory tuberculosis; member of an at risk group for which there may be difficulty in providing alternative control measures.

For this study the high-risk population in Ireland comprises children born to parents from a high TB incidence country and Irish Traveller children. These two groups constitute approximately 13.4% of births in Ireland annually. High-risk infants were estimated to have a risk of contracting TB three times higher than that of the general population.

Clinical effectiveness and safety

A systematic review was carried out to identify relevant studies of the efficacy of neonatal and infant BCG vaccination for the prevention of TB. Four randomised controlled trials and 10 case-control studies were included in the review. Three of the randomised controlled trials were published in the 1940s, and the most recent was published in 1976. The sample sizes of included studies were generally small and may have been underpowered to detect differences for rarer outcomes such as TB meningitis.

The data obtained from the published randomised controlled trials represents the best available evidence and are likely to be broadly accurate for Ireland, given that they were predominantly carried out in North America.

Based on the best available evidence, the following relative risks of TB in vaccinated children were estimated (with a relative risk of less than one indicating a protective effect against TB):

- pulmonary TB: 0.40 (95% CI: 0.26 to 0.60)
- extrapulmonary TB: 0.14 (95% CI: 0.03 to 0.63)
- TB meningitis: 0.15 (95% CI: 0.01 to 2.87)
- miliary TB: 0.08 (95% CI: 0.01 to 0.42)
- TB mortality: 0.16 (95% CI: 0.05 to 0.51).

There is limited evidence available on how long BCG remains effective, although it is estimated that the protective effect may last for up to 15 years.

Almost all BCG vaccinations result in mild ulcers at the injection site and scarring. The rate of severe adverse reactions to BCG in Ireland is approximately one in 1,169 vaccinations. Severe reactions include lymphadenitis and suppuration, and may require medical intervention. In Ireland there has been a relatively high rate of disseminated BCG of approximately one in 83,000 vaccinated infants, compared with one in 230,000 to 640,000 estimated by the WHO. Disseminated BCG is associated with a high-risk of mortality and is more likely to occur in infants with a compromised immune system. Despite the increased mortality risk there have been no deaths from disseminated BCG in Ireland in the last 10 years.

Economic evaluation

A systematic review was carried out to assess the available cost-effectiveness evidence for neonatal BCG vaccination programmes and to inform the economic analysis of BCG vaccination programmes in Ireland. Studies were included if they compared the costs and consequences of selective BCG vaccination to either universal vaccination or a programme of no vaccination. A total of five relevant studies were identified. The identified studies were not considered applicable to the Irish context due to differences in methodology and epidemiological data.

A cost-effectiveness analysis was used to determine the costs and benefits associated with BCG vaccination programmes in Ireland by modelling one years' cohort from birth to life expectancy. Effectiveness was measured in terms of life years gained and quality-adjusted life years. Costs and benefits were assessed from the perspective of the publicly-funded health and social care system. Model parameters were derived from Irish and international datasets, peer-reviewed

literature, and expert opinion. It was assumed that high-risk status would comprise children with a parent from a high TB incidence country and Irish Traveller children.

With selective vaccination there would be an estimated 53,532 fewer vaccinations per annum, with an associated reduction in adverse reactions to BCG. In the absence of any other changes in TB control, the number of cases of TB in the single birth cohort followed to age 15 years was estimated to be higher for strategies of no vaccination (56 cases) and selective vaccination (44 cases) relative to universal vaccination (24 cases). Relative to a policy of no vaccination, the number of vaccinations per case prevented was 638 for selective vaccination and 1,993 for universal vaccination.

Mortality was estimated as the combination of TB-related and disseminated BCG-related mortality in the birth cohort followed to age 15 years. A policy of no vaccination was estimated to result in the highest mortality (0.44 deaths), and universal vaccination in the lowest mortality (0.30 deaths). Selective vaccination was estimated to result in 0.37 deaths. Mortality in universal vaccination is primarily due to very severe reactions to BCG, whereas for selective vaccination it is predominantly due to TB-related mortality.

In terms of life years gained, selective vaccination was estimated to be more effective and less costly than universal vaccination. The incremental cost-effectiveness ratio for selective relative to no vaccination is €340,520 per life year gained. For quality-adjusted life years (QALYs), universal vaccination was more effective than the alternatives. In terms of QALYs, the incremental cost-effectiveness ratio was €2,549,822 per QALY for universal relative to selective vaccination, and €139,557 per QALY for selective relative to no vaccination. Neither universal nor selective vaccination would be considered cost-effective relative to no vaccination under typical willingness-to-pay thresholds.

The model was used to predict the number of cases of childhood TB per annum. It was estimated that, in the absence of any other changes to TB control, TB cases under selective vaccination would reach a maximum of 10.7 cases three years after introduction, compared with 8.0 cases under universal vaccination at the same point in time. It was predicted that after 16 years, selective vaccination would, on average, result in an additional 3.6 cases of childhood TB per annum relative to universal vaccination. At the same point, a programme of no vaccination would, on average, result in an additional 5.7 cases of childhood TB per annum relative to universal vaccination.

The budget impact of universal vaccination was estimated to be €2,393,335 per annum. The annual budget impact would be €1,339,364 for selective vaccination and €1,125,787 for a programme of no vaccination. The annual budget impact of no

vaccination is €213,577 less than for the selective vaccination strategy. In a selective programme, 34% of the budget impact arises from the vaccination programme and 27% is due specifically to the cost of administering the vaccine. The budgetary savings of switching to selective vaccination are unlikely to be realised due to the need to invest in other aspects of TB control.

There was substantial uncertainty regarding a number of the key parameters, all of which were allowed to vary within plausible ranges in the main analysis. Although there was a clear hierarchy in terms of total costs, with universal being the most costly option and no vaccination the least costly, there was greater uncertainty in terms of benefits. The main analysis used a conservative estimate of TB risk based on data from 2005 to 2014. However, if more recent childhood TB incidence rates continue, then selective vaccination would be associated with lower overall mortality than the universal vaccination programme.

To limit the risk of disseminated BCG, consideration should be given to evaluating a national neonatal screening programme to identify infants with severe combined immunodeficiencies.

Organisational and social implications

A change from a universal to a selective programme would have implications for the organisation of services in Ireland. In terms of vaccination, the number of eligible infants would decrease substantially. This would have a consequent impact on the resources required to deliver that service. In light of ongoing shortages of BCG, a selective vaccination policy would ensure that available resources are focused on those who are most likely to benefit from vaccination. A selective vaccination programme should be based on a set of clear and uniformly applied criteria that are understandable to both health professionals and the general public.

Selective vaccination implies the need to identify high-risk infants, a practice which is not currently necessary due to universal eligibility. A consistent approach to risk classification should be adopted which will require staff training. Vaccination uptake rates have been shown to be lower in high-risk populations in some studies.

TB screening and contact tracing are critical components of a TB control programme. A selective vaccination strategy will entail that a large proportion of children will have no protection against TB. An appropriately resourced and consistent approach to screening and contact tracing will be required to reduce the spread of TB from index cases to unprotected children. In the interest of public health, a change of vaccination strategy should be supported by a clear commitment to systematic and comprehensive TB control. The BCG vaccination policy cannot be viewed in isolation from other TB control measures. A change in emphasis from protection to

prevention requires a coherent plan for changes to other TB control measures. That plan must clearly outline the requirements, resources, and steps to ensure that TB control in Ireland is consistent with the requirements for TB elimination. Changes to TB control should be introduced before a change in vaccination policy to minimise the impact of reduced vaccine coverage. Investing in TB control while continuing to provide universal BCG vaccination will result in a temporary net increase in the resources required for TB control, which has implications for planning and budgeting. Consideration should be given to the development of a National Clinical Guideline on the control of TB in line with National Clinical Effectiveness Committee Standards for Clinical Practice Guidance

In the absence of changes to other elements of the current TB control programme, a strategy of selective vaccination has the potential to result in a small number of additional cases of TB in children, placing an additional burden on health services. However, this is counterbalanced by a likely reduction in the numbers of serious adverse reactions to BCG.

From a social perspective, there is widespread acceptance of the existing universal vaccination policy. There may be expectations about the benefits and harms of BCG vaccination that are not supported by the available evidence. A change to a different vaccination strategy should be supported by a public awareness campaign that clearly states the rationale for change. For a selective strategy, awareness is also required to ensure that high-risk families understand the need to seek vaccination and to maintain a high uptake in eligible infants.

For a selective programme, it would be very important to consult with high-risk groups to determine the most acceptable and efficient way to identify those eligible for vaccination.

Ethical considerations

Public health programmes raise a range of ethical issues which require consideration by policy makers. While governments have an obligation to protect the health and wellbeing of citizens, this must be achieved in a way that is equitable, non-discriminatory, transparent and, as far as possible, non-coercive. Refusal by parents and guardians to have their child vaccinated must continue to be respected even in the high-risk groups.

Even though the potential negative side effects of vaccination to low-risk individuals through a universal vaccination programme are relatively minor for the majority of infants, it is still of moral significance that thousands of infants in the low-risk category experience such a burden for comparatively little benefit to themselves.

It is likely that there will be an increase in TB cases as a result of changing from universal to selective vaccination in Ireland. Any decision to proceed with selective vaccination arising from a consideration of the risks and benefits of universal versus selective programmes should be communicated clearly so as to maintain public trust in the vaccination programme.

The targeting of specific population groups for vaccination may be seen as potentially discriminatory. In the context of health policy, selection of particular groups for public health interventions is justified on the basis of risk assessment and targeting of those most likely to benefit. Moving to selective vaccination is therefore justified as a specific protective measure for high-risk groups and an avoidance of the burden of vaccination for those for whom it carries little or no benefit.

The process of seeking relevant information in relation to ethnicity or nationality must be carried out in a way that is non-discriminatory and consistent with the privacy of the infant and the family.

The constituent elements of valid informed consent are capacity, disclosure and understanding of adequate information, and agreement. The giving of clear and comprehensible information is crucial; the use of translation and adult literacy services may be required. Other consent issues include identification of high-risk groups, the perception that a visible scar at the injection site may stigmatise and whether a parent is legally authorised to give consent as in the case of an unmarried father. Appropriate training of staff in managing potentially difficult and sensitive consent issues should be provided.

Conclusions

Health technology assessment supports evidence-based decision making in regard to the optimum use of resources in healthcare services. Measured investment and disinvestment decisions are essential to ensure that overall population health gain is maximised, particularly given constrained healthcare budgets and increasing demands for services provided.

Bearing in mind the estimates and assumptions that were used in this analysis, the following conclusions may be drawn. All European countries with a TB incidence similar to Ireland do not have programmes of universal BCG vaccination. Based on recent patterns of TB incidence, Ireland meets the International Union Against TB and Lung Disease criteria for discontinuing universal BCG vaccination. Selective vaccination will protect children most at risk of contracting TB while avoiding adverse effects of the vaccine in children who are least likely to benefit from vaccination. Selective vaccination delivers a programme that minimises adverse events while a

universal programme maximises benefits but at the expense of increased adverse events.

Universal vaccination is not cost-effective. Selective vaccination was found to be not cost-effective relative to a programme of no vaccination. Should selective vaccination be adopted, the most efficient method of delivering the programme must be determined. A change in emphasis from protection to prevention requires a coherent plan for modifications to TB control measures other than BCG vaccination. Changes to other elements of TB control should be introduced before a change in vaccination policy in order to minimise the impact of reduced BCG coverage.

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The membership of the EAG was as follows:

Dr Roisin Adams	Deputy Head, National Centre for Pharmacoeconomics
Dr Colette Bonner	Deputy Chief Medical Officer and Head of Health Protection Unit, Department of Health
Dr Eleanor Carey	Medical Officer, Health Products Regulatory Authority
Dr Kevin Connolly	Chair, National Immunisation Advisory Committee, Royal College of Physicians of Ireland
Dr Brenda Corcoran	Consultant in Public Health Medicine, National Immunisation Office, Health Service Executive
Dr Patricia Harrington	Head of Assessment, Health Information and Quality Authority
Prof Karina Butler	Consultant Paediatrician, Infectious Diseases Society of Ireland
Dr Ann Hogan	Chair of the Principal Medical Officer Group, Health Service Executive
Dr Kevin Kelleher	Assistant National Director, Health & Wellbeing Division, Health Service Executive
Dr Deirdre Madden	Senior Lecturer in Law, University College Cork
Mr Patrick Moran	Senior HTA Analyst, Health Information and Quality Authority
Ms Mary O'Connor	Chief Executive Officer, Children in Hospital Ireland
Dr Joan O'Donnell	Specialist in Public Health Medicine, Health Protection Surveillance Centre, Health Service Executive
Dr Darina O'Flanagan	Director, Health Protection Surveillance Centre, Health Service Executive
Dr Margaret O'Sullivan	Consultant in Public Health Medicine, Faculty of Public Health Medicine

The membership of the EAG continued:

Dr Máirín Ryan (Chairperson)	Director of HTA, Health Information and Quality Authority
Mr Michael Smith	Assistant Principal Officer, Health Protection Unit, Department of Health
Dr Conor Teljeur	Senior Statistician, Health Information and Quality Authority
Dr Cara Usher	Senior Research Fellow, National Centre for Pharmacoeconomics
Professor Cathal Walsh	Professor of Statistics, University of Limerick
Ms Cora Williams	Director of Public Health Nursing, Institute of Community Health Nursing

Organisations and individuals that assisted the Authority in providing information, in writing or through meetings, included:

Ms Sarah Jackson, Health Protection Surveillance Centre
Dr Mary O'Meara, Specialist in Public Health Medicine, Health Service Executive
Professor Mark Sculpher, Centre for Health Economics, University of York
Healthcare Pricing Office
Health Products Regulatory Authority

Members of the Evaluation Team:

Members of the Authority's Evaluation Team were Dr Conor Teljeur, Dr Patricia Harrington, Patrick Moran, and Dr Máirín Ryan.

Conflicts of Interest

None reported.

List of abbreviations used in this report

BCG	Bacillus Calmette-Guérin
BIA	budget impact analysis
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
EAG	expert advisory group
EVPI	expected value of perfect information
HIQA	Health Information and Quality Authority
HPRA	Health Products Regulatory Authority
HPSC	Health Protection Surveillance Centre
HSE	Health Service Executive
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IGRA	interferon-gamma release assay
IUATLD	International Union Against Tuberculosis and Lung Disease
LYG	life years gained
NCPE	National Centre for Pharmacoeconomics
NIAC	National Immunisation Advisory Committee
NPRS	National Perinatal Reporting System
QALY	quality-adjusted life year
TB	Tuberculosis
TST	tuberculin skin test
WHO	World Health Organisation
WTE	whole time equivalent

1. Introduction

1.1 Background to the request

The Chief Medical Officer of the Department of Health, requested that the Health Information and Quality Authority (HIQA) undertake a health technology assessment (HTA) in relation to proposed changes to the national neonatal BCG vaccination programme.

The request for a formal HTA was on foot of a recommendation from the National Immunisation Advisory Committee and the National Tuberculosis Advisory Committee. The recommendation was formed based on International Union Against TB and Lung Disease criteria for discontinuing universal BCG vaccination, epidemiological data on TB incidence, incidence of TB reactions, and a cost-effectiveness evidence analysis by the National Centre for Pharmacoeconomics.[(1)]

Tuberculosis (TB) is an infection caused by a bacterium called mycobacterium tuberculosis. TB typically affects the lungs, but can also affect other parts of the body such as the bones, joints and kidneys. It can also cause meningitis. Bacille Calmette Guerin (BCG) is the currently licensed TB vaccine, and has been routinely used in Ireland since the 1950s. The BCG vaccine is currently given as part of the routine childhood vaccination schedule.

Policies on BCG vaccination differ both regionally within Ireland and internationally. In countries with a low incidence of TB, often only those with a high risk of contracting TB are given the BCG vaccination. High-risk groups include healthcare workers and infants whose parents are from a country with high TB incidence. A number of European countries, including the UK, France, Germany and Spain, have ceased universal childhood BCG vaccination and now have programmes of selective vaccination for high-risk groups.

The use of selective vaccination may reduce unnecessary vaccination and the numbers of adverse reactions. Selective vaccination will also result in failure to prevent some cases of TB.

1.2 Terms of reference

Based on the available evidence, the Minister for Health will decide on whether there should be a change in policy from a universal to a selective neonatal BCG vaccination programme. In consultation with the Department of Health, questions were developed in relation to the critical information required to inform the decision.

Answers to these questions, which underpinned the Terms of Reference of this HTA, will inform the decision of the Minister.

The Terms of Reference were to:

- describe the epidemiology of TB in Ireland
- examine the current evidence of efficacy and safety for BCG vaccination in infants
- review the international cost-effectiveness literature on BCG vaccination strategies in infants
- estimate the clinical implications, cost-effectiveness, resource implications and budget impact of selective BCG vaccination of high-risk infants compared with a programme of universal vaccination, and a strategy of no vaccination
- consider any wider implications that a change in vaccination strategy may have for patients, the general public, or the healthcare system
- based on this assessment, advise on the optimal configuration of an Irish BCG vaccination programme for infants.

The specific remit of this HTA was to assess the impact of changing from a policy of universal to selective neonatal BCG vaccination. Selective vaccination is directed at those who are at high risk of TB infection. Although there is no universal definition of high-risk, it most commonly includes infants born to parents from countries with a high TB incidence. The World Health Organisation (WHO) defines high incidence as greater than or equal to 40 cases per 100,000 persons per annum. Other potential indicators of high-risk can include: infants from communities or ethnic minorities with high TB incidence or a family history of TB.

1.3 Overall approach

Following an initial scoping of the technology, the Terms of Reference of this assessment were agreed between HIQA and the Department of Health.

HIQA convened an Expert Advisory Group comprising representation from relevant stakeholders including the Department of Health, the Health Protection Surveillance Centre, the National Immunisation Advisory Committee, clinicians with specialist expertise, representatives of patients' organisations, and an ethics expert. The role of the Expert Advisory Group was to inform and guide the process, provide expert advice and information and to provide access to data where appropriate. A full list of the membership of the Expert Advisory Group is available in the acknowledgements section of this report.

The Terms of Reference of the Expert Advisory Group were to:

- Contribute to the provision of high quality and considered advice by the Authority to the Minister for Health.
- Contribute fully to the work, debate and decision making processes of the group by providing expert guidance, as appropriate.
- Be prepared to provide expert advice on relevant issues outside of group meetings, as requested.
- Provide advice to the Authority regarding the scope of the analysis.
- Support the Evaluation Team led by the Authority during the assessment process by providing expert opinion and access to pertinent data, as appropriate.
- Review the project plan outline and advise on priorities, as required.
- Review the draft report from the Evaluation Team and recommend amendments, as appropriate.
- Contribute to the Authority's development of its approach to HTA by participating in an evaluation of the process on the conclusion of the assessment.

HIQA appointed an Evaluation Team comprised of internal staff from the HTA Directorate to carry out the assessment. Dr Deirdre Madden, School of Law, University College Cork was contracted to evaluate the ethical implications of a change in policy.

The Terms of Reference of the HTA were agreed by the Expert Advisory Group at the initial meeting of the group. Draft findings regarding the clinical effectiveness and safety of BCG vaccination programmes were also discussed at the initial meeting. Draft findings from the assessment were discussed at a subsequent meeting. The draft report was reviewed by the Expert Advisory Group on two occasions. HIQA made the draft report available for public consultation between September 9th and October 21st 2015 to provide an opportunity for all potential interested parties and members of the public to give comment and feedback prior to the report being finalised. Amendments were subsequently made, as appropriate, before the final draft was submitted to the Board of HIQA for approval. The feedback and associated responses are described in an accompanying Statement of Outcomes report. The completed assessment was submitted to the Minister for Health as advice and published on HIQA's website.

2. Description of the technology

The purpose of this chapter is to provide a brief description of the clinical course of tuberculosis (TB), to describe vaccination interventions to reduce the risk of acquiring TB, and to provide an overview of the current Irish and international vaccination policies.

2.1 Tuberculosis

Human tuberculosis (TB) is an infectious disease caused by bacteria of the Mycobacterium tuberculosis complex of which *M. Tuberculosis* is the most common and important agent causing human disease. While it may affect almost any part of the body, pulmonary TB (lungs) is the most common form and accounts for almost 60% of all cases in Ireland.[2] TB in Ireland is typically acquired through the respiratory route, due to inhalation of infected respiratory droplets from a person with infectious pulmonary TB. Transmission is most likely after prolonged close contact, such as sharing a home, with someone whose sputum is smear positive for the bacillus on microscopy. The risk of extrapulmonary TB is disproportionately higher in individuals with impaired immunity and in young children from communities with connections to countries with a high TB prevalence.[3] The WHO estimated that approximately 13% of new cases of TB in 2013 were in HIV-positive individuals.[4]

Infection with TB does not always lead to TB disease. Following infection, the bacterium may be eliminated; remain latent (that is, the person has no symptoms, but the TB bacteria remain in the body); or progress to active TB over the following weeks or months. The risk of developing active disease is highest one to two years after a new infection, and decreases as time passes. Latent TB infection may reactivate in later life. Risk factors for reactivation include weakening of the immune system due to disease (for example, HIV) or medical treatment (such as corticosteroids) and old age.[5]

General symptoms of TB may include fever, loss of appetite, shortness of breath, unexplained weight loss, night sweats and fatigue. However, symptoms are varied and depend on the site of infection. Pulmonary TB typically causes a persistent productive cough; this may be accompanied by blood-streaked sputum or, more rarely, frank haemoptysis. If left untreated, TB in otherwise healthy adults is typically a slowly progressive disease that may eventually be fatal. TB is however a treatable and curable disease with the majority of non multi-drug resistant cases cured with a standard six-month treatment course.[3] Multidrug-resistant tuberculosis (MDR-TB) is defined as a form of TB infection caused by a strain of the bacteria that is resistant to treatment with isoniazid and rifampicin, the two most potent anti-TB drugs. Treatment options for MDR-TB are limited and expensive.

Laboratory confirmation of a diagnosis of TB in a person that meets the clinical criteria (for example, signs, symptoms and or radiological findings consistent with active TB in any site) is through isolation of M. tuberculosis complex from a clinical specimen, or detection of *M tuberculosis* nucleic acid in a clinical specimen plus positive microscopy for acid-fast bacillus.[5]

The WHO declared TB a global emergency in 1993 in recognition of its significant and increasing contribution to major causes of morbidity and mortality due to infectious disease. Approximately one-third of the world's population is estimated to be infected with *M. Tuberculosis*. In 2013 there were approximately 1.5 million attributable deaths and 9.0 million new cases of TB disease, although this figure represents a decline since 2000 due to improved access to effective diagnosis and treatment.[4] The disease disproportionately affects the developing world: over 95% of cases occur in low and middle resource countries, with approximately 80% of cases occurring in 22 high-burden countries.[4] In Ireland, improvements in socioeconomic conditions (through better housing and reduced overcrowding) and nutrition as well as introduction of effective treatment in the 1940s led to a rapid decrease in the incidence and mortality rate from TB.[5] BCG vaccination programmes were introduced in Ireland in the 1950s. The burden of TB is discussed in detail in Chapter 3.

TB is a notifiable disease. Suspected and confirmed cases must be notified to the local Medical Officer of Health (in practice the Director of Public Health) by the clinician or the clinical director of the laboratory. Notification should be as soon as possible after diagnosis, ideally within three working days. Detailed surveillance information is subsequently forwarded by the regional Departments of Public Health to the Health Protection Surveillance Centre. Since 2011, TB data has been collated using the Computerised Infectious Disease Reporting, the national infectious disease reporting system used by the Health Protection Surveillance Centre integrating laboratory and clinical data. Left untreated, a patient with infectious TB can infect 10 to 15 other close contacts over the course of a year. Data collected by the regional Departments of Public Health is used to investigate cases in order to prevent the spread of infection and further cases. The information also facilitates the early identification of outbreaks, and is also used to monitor the burden and changing levels of disease.[5]

2.1 Bacillus Calmette Guerin (BCG) vaccine

The BCG vaccine was derived from an isolate of M. Bovis, a closely related organism of *M. Tuberculosis*, and first administered as an oral vaccine in France in 1921 to prevent TB. Percutaneous or intradermal administration began in the 1940s following the completion of trials demonstrating the vaccine's efficacy. The current BCG vaccine contains a live attenuated (modified) strain derived from *M. Bovis*. Daughter strains of BCG have been distributed around the world for vaccine manufacture, leading to the emergence of genetic and antigenic differences between available vaccine strains. This gives rise to concerns about their relative safety and efficacy. There is one licensed product available for immunisation against TB in Ireland, the BCG Vaccine Statens Serum Institut (SSI), which contains the Danish strain 1331. It was authorised for use in Ireland in 2001 and has been used in the immunisation programme since the withdrawal of the Evans BCG vaccine from the Irish market in July 2002.[6]

The BCG vaccine is administered strictly as an intra-dermal injection, normally over the middle of the deltoid muscle of the left arm as recommended by the WHO. To minimise adverse events, the vaccine should be administered by experienced healthcare professionals that are trained in the use of this technique.[7]

BCG is considered a safe vaccine in healthy infants. Localised adverse reactions, including regional adenitis are usually self-limiting: the expected reaction to successful BCG vaccination, seen in 90% to 95% of recipients, is induration (hardening) at the injection site followed by development of a local lesion starting as a papule two or more weeks after vaccination. The papule may ulcerate and then slowly subside over several weeks or months to heal, leaving a small, flat scar. It may also include enlargement of a regional lymph node to less than one centimetre. Contributing factors to severe injection site reactions include excessive dosage, vaccinating individuals who are tuberculin positive, faulty injection technique, and the potency of the vaccine strain used.

Allergic reactions (including anaphylaxis reactions), more severe local reactions such as large local discharging ulcers, abscesses, keloid scarring, lymphadenitits, suppurative lymphadenitis, and disseminated BCG complications are rare. Development of disseminated disease (BCG-osis) is more common in patients with immune systems that are compromised by disease (including some primary immunodeficiency syndromes and chronic granulomatous disease) or treatment. Due to the increased risk of disseminated disease in HIV-infected children, the WHO Global Advisory Committee on Vaccine Safety recommends that BCG should not be administered to HIV-positive individuals, even if asymptomatic at the time of vaccination. Healthcare professionals are requested to report any suspected adverse

reactions associated with BCG vaccines to the Health Products Regulatory Agency. Patients and carers are also encouraged to report any adverse reactions experienced to the Health Products Regulatory Agency. The safety of BCG vaccines is reviewed in detail in Chapter 4.4.2.

Before receiving the BCG vaccination, a tuberculin skin test is necessary for certain patient groups:[8]

- all individuals aged six years or over
- children from three months to six years of age:
    - who have ever lived or stayed more than three months in a country of high endemicity
    - whose parents are from a country of high endemicity (notification rate ≥40 cases of TB per 100,000 population per annum)
    - who are contacts of a pulmonary TB case
- children under three months of age in whom TB disease is suspected.

The tuberculin skin test (Mantoux test) which is based on intra-dermal injection of tuberculin purified protein derivative is used to assess sensitivity to tuberculin protein. A positive reaction likely indicates that an individual is infected or has active TB disease or has been previously vaccinated with BCG. A positive reaction can also be due to infection with non-tuberculous mycobacteria. After BCG vaccination, a child will only reliably return a positive test result for the first one to two years. Those with a positive tuberculin skin test should not be vaccinated as it is unnecessary and may cause a more severe local reaction. Young children and those with strongly positive tests should have specialist paediatric or physician assessment.

The benefit of BCG vaccination appears to be that it protects young children against disseminated and severe TB, for example TB meningitis and miliary TB. It is less effective in preventing respiratory disease, which is the more common form of TB in adults. There is limited data on the protection afforded by the BCG vaccine when it is given to adults (aged 16 years or over), and virtually no data for persons aged 35 years or over. BCG vaccination is not usually recommended for people aged over 16 years, unless the risk of exposure is great (for example, healthcare or laboratory workers at occupational risk).[3] The efficacy of BCG vaccination in infants is assessed in detail in Chapter 4.

2.1.1 Developments in TB vaccination

Due to the limitations of the current BCG vaccine, several new vaccines have been developed and are being trialled. Targeting the infant population are pre-exposure vaccines that could replace BCG, and pre-exposure booster vaccines given in addition to BCG vaccination. Several post-exposure vaccines for administration to adolescents or adults who have been previously vaccinated with BCG as infants have also been developed. Finally, also in development are BCG therapeutic vaccines which are killed mycobacteria preparations that aim to cure active TB as an adjunct to chemotherapy.[9;10] Currently however, only the BCG vaccine is available as a licensed product to prevent TB.

2.2 Irish BCG vaccination policy

Universal vaccination of neonates was first introduced in Ireland in the 1950s. Current national policy is to vaccinate all newborns, with the exception of County Galway where there is a school-age vaccination programme. A policy of universal vaccination was consistent with World Health Organisation (WHO) recommendations that a single dose of BCG vaccine be given to all infants as soon as possible after birth in countries with a high incidence of TB (greater than or equal to 40 cases per 100,000 population). A policy of providing a booster dose of the vaccine to 11 to 12 year olds was discontinued in 1996. This is consistent with the evidence from several studies demonstrating that a booster dose of BCG does not improve protection against TB.[11] The only other significant change to the vaccination policy in recent years has been the switch to use of the Danish 1331 strain by SSI in 2002, due to the withdrawal of the Glaxo-Evans 1077 BCG vaccine from the market.

Given the decline in TB incidence rates in Ireland in the preceding 10 years, in 2013 the National Immunisation Advisory Committee and the National TB Advisory Committee recommended a change from universal BCG vaccination to a selective BCG vaccination programme to the Department of Health. This recommendation took consideration of the International Union Against TB and Lung Disease criteria for discontinuing universal BCG vaccination (Table 2.1) as well as the burden of vaccine-related adverse events in infants at low risk of developing TB.

Table 2.1 International Union Against TB and Lung Disease criteria for discontinuation of universal BCG vaccination[12]

Criteria
▪ There must be a well functioning TB programme. Criteria include having: ○ the structures and processes in place to ensure early detection of cases ○ institution of appropriate treatment in a timely manner ○ early identification of non-compliers, and ○ the capacity and facilities to institute supervised therapy, where appropriate. ▪ There has been a reliable reporting system over the previous five or more years that enables estimation of the annual incidence of active TB by age and risk group and in particular the incidence of TB meningitis and sputum smear-positive pulmonary TB. ▪ Due consideration has been given to the possibility of an increase in the incidence of TB resulting from the burden of HIV in that country With one of the following: ▪ Average annual notification rate of smear-positive pulmonary TB cases ≤ 5 per 100,000 during the previous three years; or ▪ Average annual notification rate of TB meningitis in children aged under five years < 1 per 10 million general population during the previous five years; or ▪ Average annual risk of TB infection ≤ 0.1%

The adequacy of the TB control programme in Ireland is in the context of the existing universal BCG vaccination policy. With regard to the International Union Against TB and Lung Disease criteria, Ireland may be considered as having a well-functioning TB programme and a well-established and reliable reporting system in place. However, concern has been expressed that there may be significant gaps in the existing TB control programme, and that there may be substantial regional variation in the application of TB control measures.[13] Changes to the neonatal BCG vaccination policy may therefore result in the existing TB control programme no longer being considered well-functioning.

An increase in the incidence of TB resulting from the burden of HIV in Ireland is unlikely. The annual average notification rate of smear-positive pulmonary TB cases in Ireland was 2.5 per 100,000 in the period 2012 to 2014, and has been less than five per 100,000 since 2000. Since 2011, the average annual notification rate in Ireland of TB meningitis in children aged less than five years has been less than one per 10 million population during the previous five years. The criterion regarding

average annual risk of TB infection is not applicable to Ireland.[5] It may therefore be considered that Ireland meets the International Union Against TB and Lung Disease criteria for discontinuing the universal BCG vaccination programme.

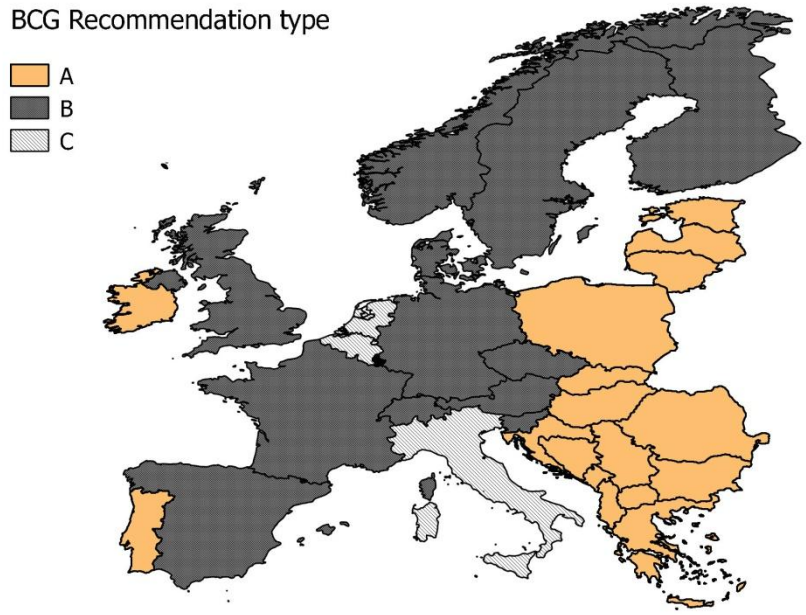
2.3 International BCG vaccination policies

Policies on BCG vaccination differ internationally reflecting differences in the incidence of TB as well as differences in opinion as to the relative benefit of the vaccine, particularly where incidence rates are low. A database of 180 global BCG vaccination policies and practices noted that of the 180 countries for which data is available, 157 currently recommend universal vaccination. The remaining 23 countries operate a policy of selective vaccination of at-risk groups having either stopped universal vaccination (due to a reduction in the incidence of TB) or never recommended it in the first instance. Figure 2.1 illustrates current vaccination policies in European countries.

Due to a decline in national TB incidence, 12 European countries have ceased universal BCG vaccination programmes: Sweden (1975); Spain (1981); Denmark (1986); Austria (1990), Germany (1998), Switzerland (1998), Slovenia (2005), UK (2005), Finland (2006), France (2007), Norway (2009), and the Czech Republic (2010). However, many switched to a policy of selective vaccination of high-risk individuals, comprising those at high risk due to occupation or travel, and infants born into high-risk environments.[14]

In Western Europe, only Ireland and Portugal currently have universal BCG vaccination programmes despite not being considered as high TB incidence countries using the WHO metric (≥40/100,000 persons).[14]

Figure 2.1 BCG vaccination policy by country



Key: A - The country currently has a universal BCG vaccination programme;
B - The country used to recommend BCG vaccination for everyone, but currently does not;
C - The country never had a universal BCG vaccination programme.
Data courtesy of the BCG World Atlas.[14]

Among countries that operate a policy of selective vaccination, there is variation in the definition and management of the high-risk population. Criteria include selective vaccination of migrants or children or grandchildren of migrants who have moved from high incidence countries (≥40/100,000 persons).[4] It is noted that in many low-incidence countries, risk of TB is greatest in migrant populations. In 2014, 40.9% of all TB cases in Ireland, or 134 cases, were born outside the country.[2] This risk persists for many years after migration to the country of low incidence. In the UK, surveillance programmes report that 50% of TB in migrant groups occurs more than five years after entry to the UK. Of those diagnosed with TB whose date of entry to the UK was known, 15% (738) were diagnosed within two years and 44% (2,213) within five years of entering the UK.[15] The aim of the current selective UK vaccination programme is to immunise those who are at increased risk of developing severe disease and, or of, exposure to TB infection. The current UK vaccination programme offers selective neonatal vaccination to:

- all infants (aged 0 to 12 months) living in areas of the UK where the annual incidence of TB is ≥ 40/100,000 or greater.
- all infants (aged 0 to 12 months) with a parent or grandparent who was born in a country where the annual incidence of TB is ≥ 40/100,000.

There are additional criteria for previously unvaccinated children aged between one and 16 years based on the country of birth of the child's parents and grandparents, area of residence, and exposure history.[3]

2.4 Key messages

- Human tuberculosis (TB) is an infectious disease caused by bacteria of the Mycobacterium tuberculosis complex of which *M. Tuberculosis* is the most and important agent causing human disease.
- TB is a treatable and curable disease with the majority of non multi-drug resistant cases cured with a standard six-month treatment course.
- There is one licensed product available for immunisation against TB in Ireland, the BCG Vaccine Statens Serum Institut (SSI), which contains the Danish strain 1331. It has been used in the immunisation programme since July 2002 and is administered by intradermal injection.
- Current national policy is to vaccinate all newborns (universal vaccination), with the exception of County Galway where a programme of school-age vaccination has continued.
- A recommendation to switch to a policy of selective neonatal vaccination has been made based on epidemiological data on TB incidence, International Union Against TB and Lung Disease criteria for discontinuing BCG vaccination, and the incidence of BCG reactions.
- Ireland is one of only two Western European countries that have a policy of universal neonatal vaccination despite not being considered a high TB incidence country using the WHO metric (greater than or equal to 40 cases per 100,000 population).

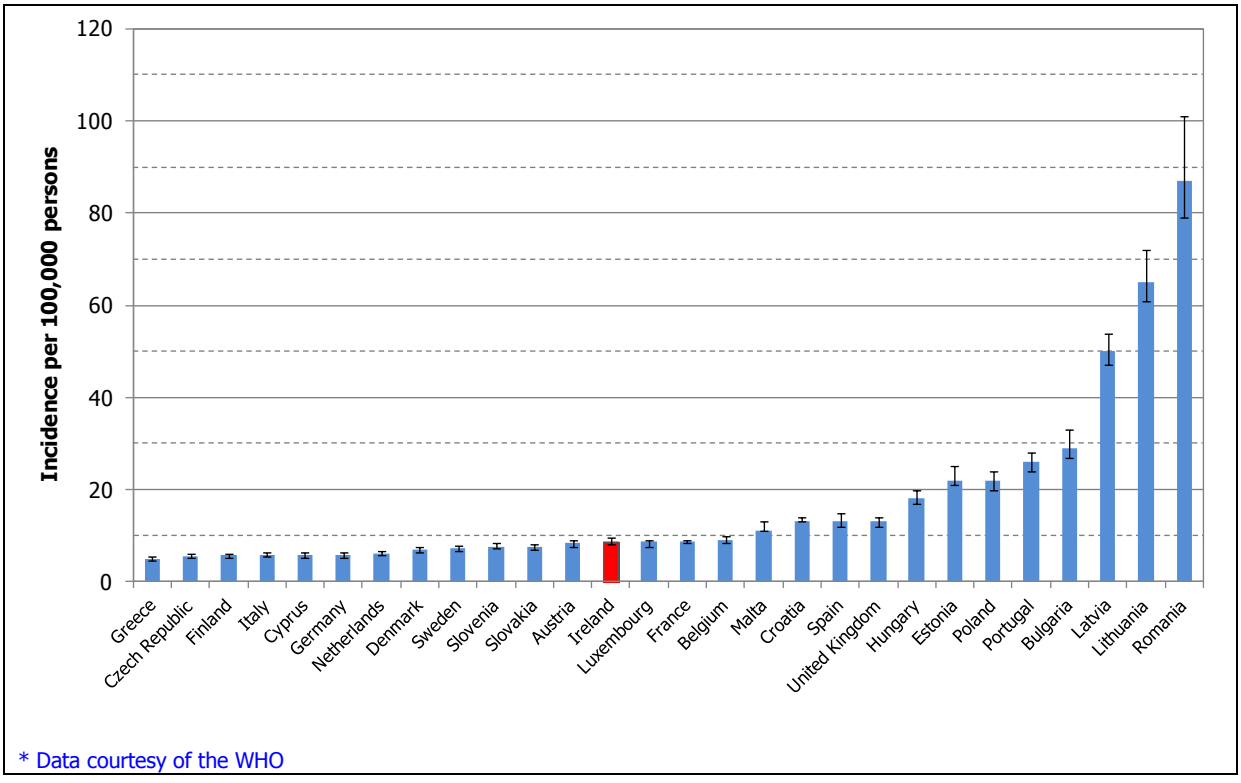
3. Burden of disease

BCG vaccination is used in Ireland for the prevention of tuberculosis (TB). The use of selective rather than universal neonatal vaccination is partly driven by TB incidence rates. When incidence is low, a universal programme may not be justified. This chapter examines the epidemiology of TB in Ireland. Although the current and proposed programmes of BCG vaccination relate to neonates and infants, TB is a communicable disease and the incidence in adolescents and adults is also relevant.

3.1 Incidence of TB in Ireland

Tuberculosis (TB) remains a global health challenge - an estimated 9.0 million people developed TB in 2013 and there were 1.5 million deaths from the disease.[4] The highest burden of disease is in low- and middle-resource countries. Due to the disparities in TB incidence globally, the incidence in Ireland should be viewed in the context of other European countries (Figure 3.1). The incidence in Ireland is similar to most other countries in the EU27 states, with the same incidence as Luxembourg, France, Belgium and Austria.

Figure 3.1 TB incidence rates per 100,000 in the EU27 states, 2013[16]



* Data courtesy of the WHO

It is estimated that a third of the world's population is infected with latent TB, which means they are infected with TB bacteria, but cannot transmit the disease.[17] People with latent TB infection do not feel ill and do not have any symptoms. Without

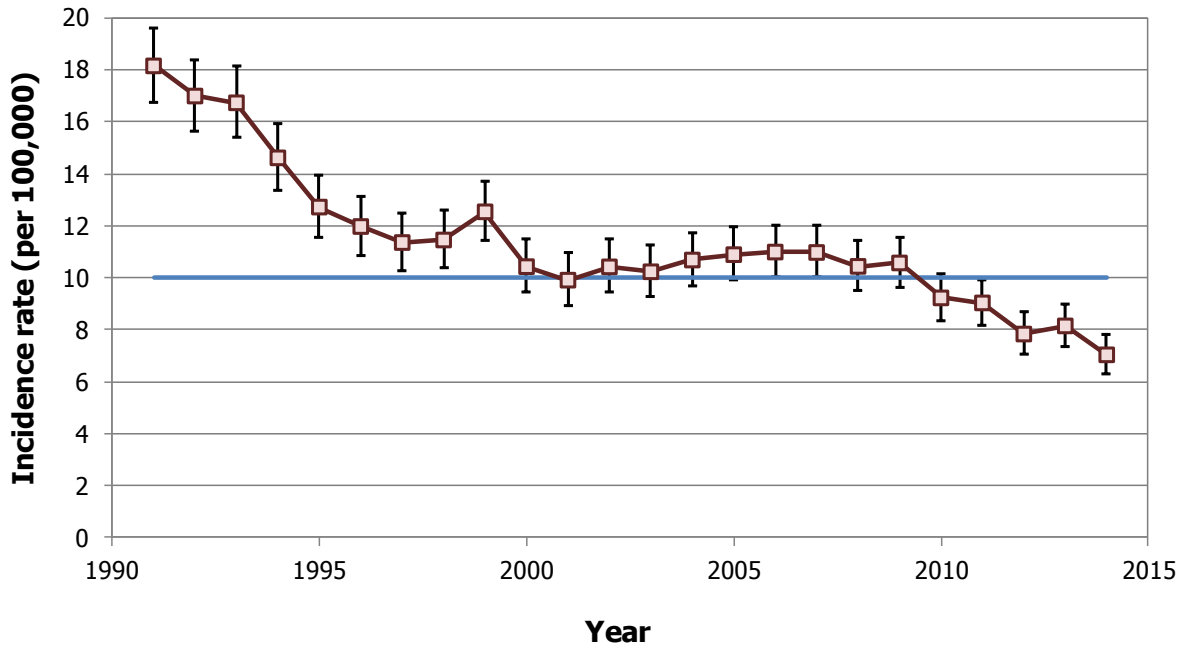
treatment, approximately 5% to 10% of people with latent TB will go on to develop active TB at some point.[18] People with latent TB infection are considered at high risk of developing active TB if they have been recently infected or they have an underlying medical condition, such as HIV, that substantially increases their risk of developing active TB.[5]

The WHO data is age-sex standardised to allow valid cross-country comparisons. The Ireland specific figures in the remainder of this chapter are crude incidence per 100,000 persons.

3.1.1 Trend over time

In line with global trends, TB incidence in Ireland has been in decline over the last 25 years. The crude national incidence rate per 100,000 has fallen from 18.2 in 1991 to 7.0 in 2014 (see Figure 3.2). The number of cases of TB in Ireland each year has dropped from over 600 in the early 1990s to under 400 since 2012; 324 cases were reported in 2014. The rate has consistently remained below 10 per 100,000 since 2010. Between 1991 and 2014, TB incidence fell by 41% globally.[4]

Figure 3.2 Crude national tuberculosis incidence rates, 1991-2014



Data courtesy of the Health Protection Surveillance Centre. Data for 2013 and 2014 are provisional.

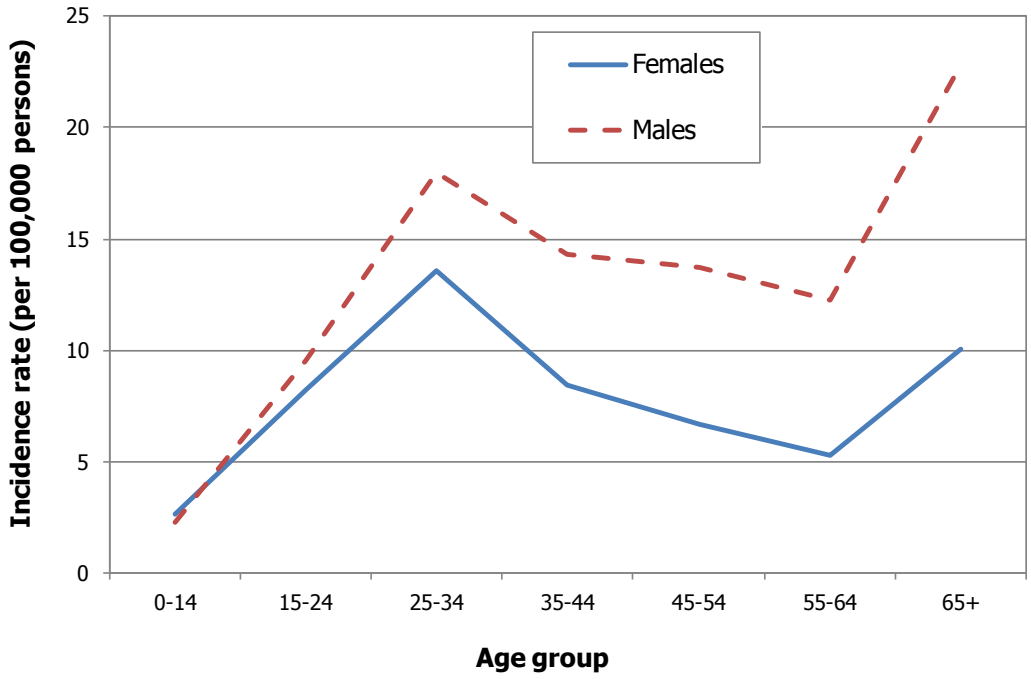
The three year annual average rate of sputum smear positive pulmonary TB cases in Ireland was stable at approximately 3.5 per 100,000 from 2000 to 2008. The rate decreased from 2008 to 2012 and has been approximately 2.5 per 100,000 from 2012 to 2014. The rate has therefore been consistently less than the criterion of 5

per 100,000 suggested by the International Union Against TB and Lung Disease for considering discontinuation of universal BCG vaccination.

3.1.2 Incidence by age and sex

The rate of TB varies by age and sex. In the period 2007 to 2011, incidence rates were higher in men (12.3 per 100,000) than in women (7.8 per 100,000). However, there was no difference in incidence rates for males and females aged 0 to 14 years (see Figure 3.3).

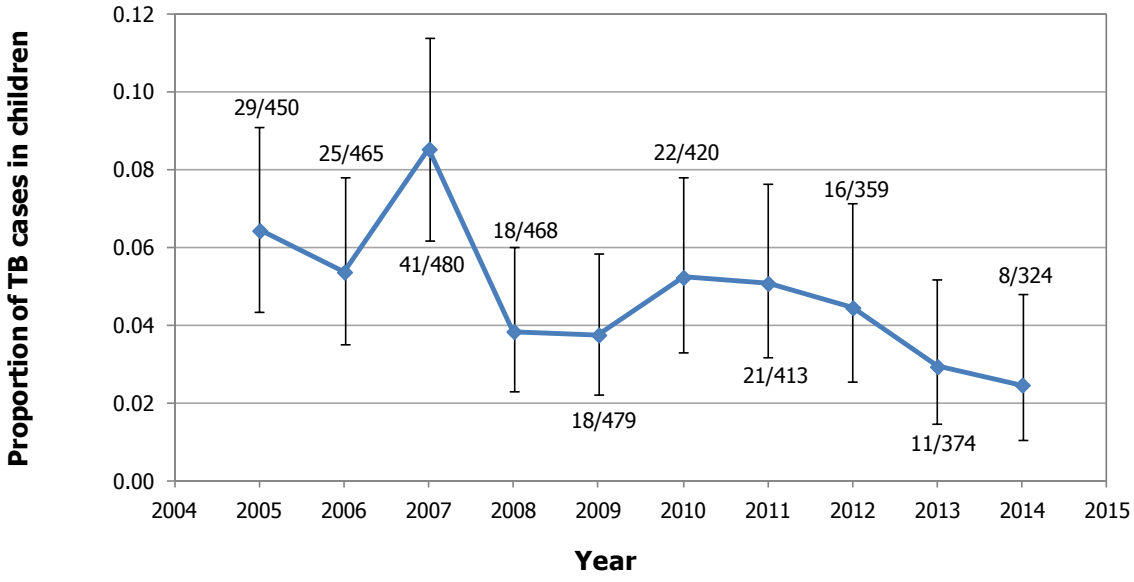
Figure 3.3 Tuberculosis incidence rates per 100,000 by age and sex, 2007-2011



Data courtesy of the Health Protection Surveillance Centre.

In terms of burden of illness, the incidence rate in children aged less than 15 years is relatively low. Based on the proportion of all cases, children aged less than 15 years contributed between 2.2% and 8.5% of all TB cases by year (Figure 3.4). Between 2005 and 2014 the average annual number of cases in children aged less than 15 years was 20.9 cases, although the incidence has been in decline. The average annual number of cases for 2012 to 2014 was 11.7 cases.

Figure 3.4 Proportion of tuberculosis cases occurring in children aged less than 16 years, 2005 to 2014



Data courtesy of the Health Protection Surveillance Centre. Data for 2013 and 2014 are provisional.

3.1.3 Incidence by area

As with any disease, rates can be expected to vary regionally due to demographics, geography, and random variation. TB incidence figures are available by county and local health office area. With the exception of counties Dublin and Cork, local health office areas comprise one or more counties. The finest level of spatial detail was achieved by using local health office data in Dublin and Cork and county data elsewhere.

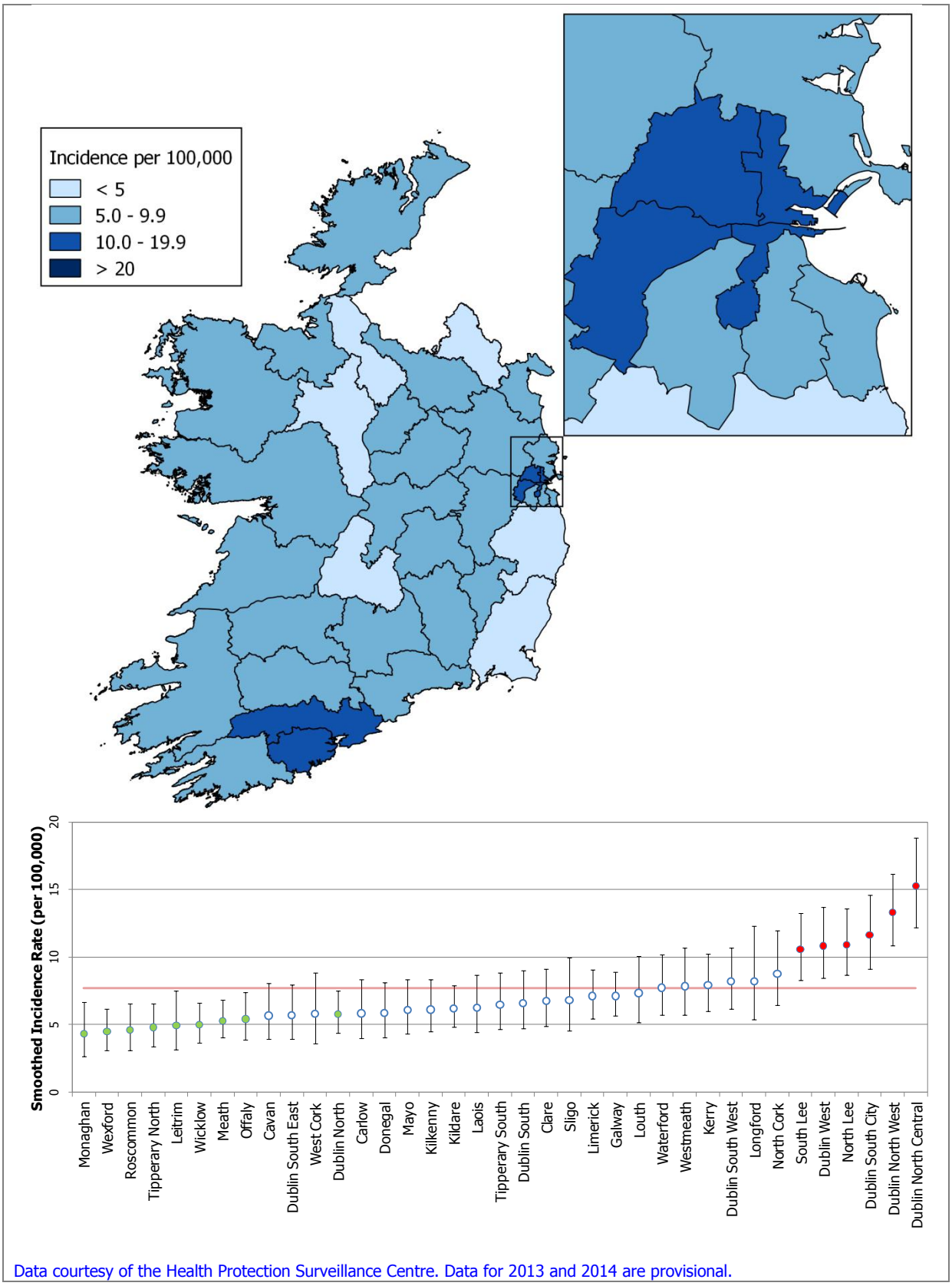
To account for the small numbers of cases, Bayesian methods for estimating disease rates were used. Incidence is expressed as smoothed incidence rates estimated using conditional autoregressive models based on a spatial Poisson model with two random effects.[19] As in any regression model, available area-level covariates may be included. For this analysis, three covariates were considered: proportion total population born in the rest of the world (based on any country outside the EU27); population density (persons per km^2); and material deprivation.[20] Models were fitted using Markov Chain Monte Carlo (MCMC) algorithms with WinBUGS software.[21] Estimates were checked to ensure convergence had been reached. A burn-in of 10,000 iterations was performed for each model and the posterior distributions were derived from the subsequent 80,000 iterations.

The analysis was based on data for the years 2012 to 2014 (see Figure 3.5). Six local health office areas had elevated SIRs for which the difference from the national average was statistically significant: Dublin North Central, Dublin North West, Dublin South City, North Lee, Dublin West, and South Lee. All six areas had smoothed annual incidence rates of between 10 and 20 cases per 100,000. Eight counties and one community care area had low SIRs for which the difference from the national average was statistically significant: Monaghan, Wexford, Roscommon, Tipperary North, Leitrim, Wicklow, Meath, Offaly, and North Dublin.

No area had a smoothed average annual incidence rate in excess of 16 cases per 100,000, and hence all areas were well below the figure of 40 per 100,000 used by the WHO to define high TB incidence areas.

Incidence is positively correlated with the proportion population born outside Europe, population density and material deprivation. When all three covariates are included, only the foreign-born population has a statistically significant coefficient. In this case, foreign-born refers to all countries outside the EU27 and includes countries that would not be considered high TB incidence, such as the US and Australia.

Figure 3.5 Standardised average annual tuberculosis incidence rates by county and community care area 2012-2014



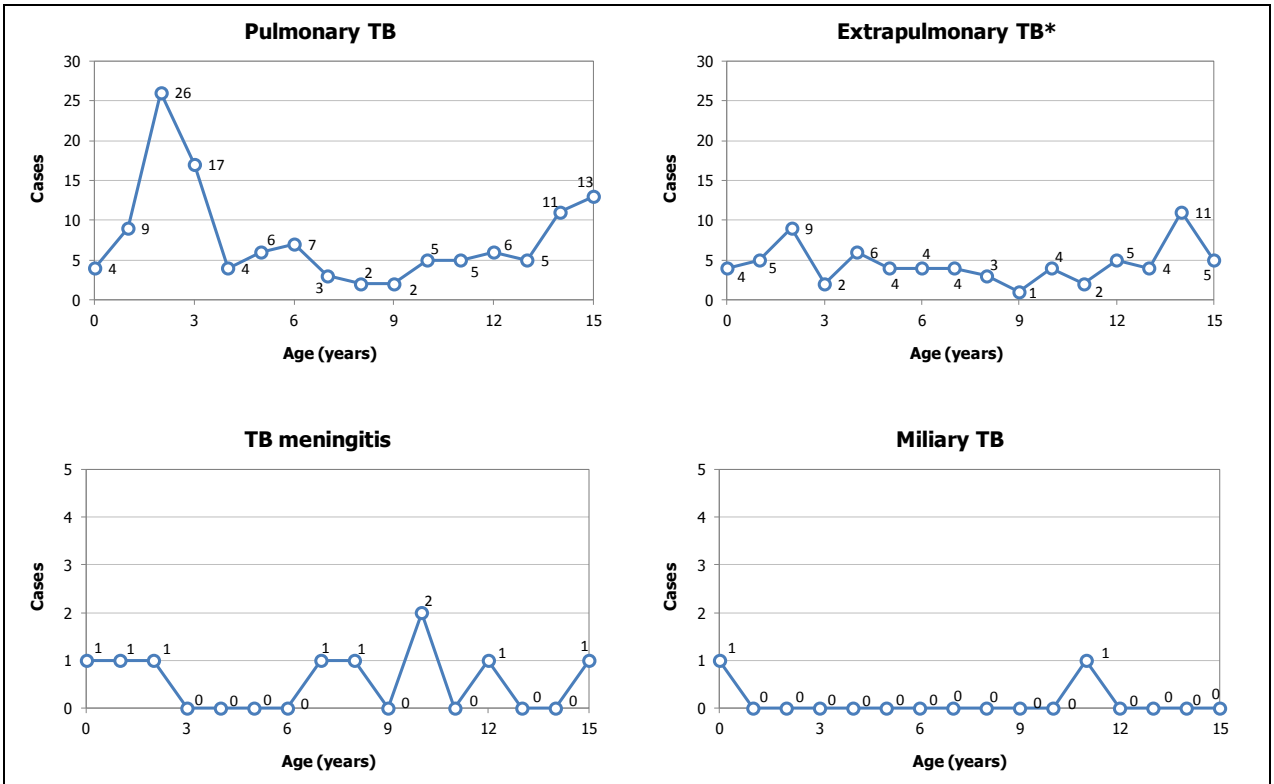
Data courtesy of the Health Protection Surveillance Centre. Data for 2013 and 2014 are provisional.

3.1.4 Incidence by type of TB in children aged less than 15 years

TB may affect different parts of the human body, and different incidence rates apply to each type. Extrapulmonary TB refers to the situation where TB affects organs other than the lungs, and typically accounts for 20% to 25% of TB cases.[22] Individuals may have a dual diagnosis of pulmonary and extrapulmonary TB. TB meningitis and miliary TB are forms of extrapulmonary TB, but are considered more severe forms of TB and will be considered separately for the remainder of this report. Miliary TB is characterised by the small size of lesions and wide dissemination into the body, potentially affecting numerous organs. Although rare, TB meningitis and miliary TB are considered severe forms of TB, particularly for infants.[23]

As previously noted, children represent a small proportion of all TB cases, and peaks in individual ages in children may go unnoticed in national data due to the low incidence in children (Figure 3.6). Pulmonary TB accounts for 59% of cases in 0 to 15 year olds, extrapulmonary TB for 36% of cases, TB meningitis for 4% of cases, and miliary TB for 1% of cases.

Figure 3.6 Tuberculosis cases per 100,000 in 0-15 year olds by single year of age and type of tuberculosis, 2005-2014



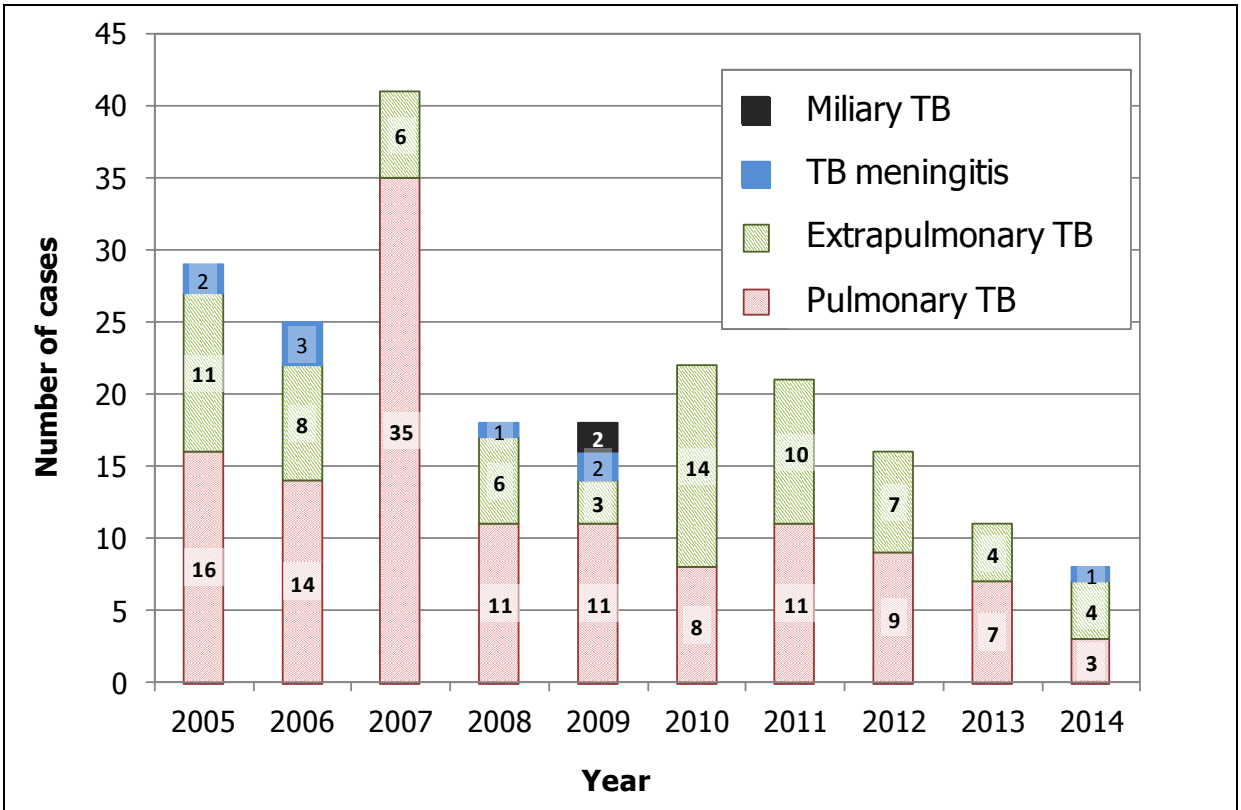
Data courtesy of the Health Protection Surveillance Centre. Data for 2013 and 2014 are provisional.
Cases with both pulmonary and extrapulmonary TB are classified as extrapulmonary.
* TB meningitis and miliary TB are not included in the figures for extrapulmonary TB.

In the period 2005 to 2014 there were three cases of TB meningitis in children aged less than five years. Corresponding to the International Union Against TB and Lung Disease criteria, the five year annual average rate of TB meningitis in children less than five years of age has been less than 1 per 10 million general population since 2011.

In 2007 there was an outbreak of TB in County Cork linked to two crèches.[24] The outbreaks were linked to a single adult index case, and resulted in 20 other TB cases (18 children and two adults). None of the 18 children had been BCG-vaccinated. This outbreak is noticeable as the observed peak in pulmonary TB cases in two and three-year-olds in Figure 3.6. During 2010 there were three general outbreaks that occurred in schools, which also impact on figures.[25]

Corresponding to the decline in TB cases in the general population, the incidence rate and absolute numbers of cases for 0-15 year olds has also been in decline over time. Based on provisional data, the rate in 2014 is an estimated 0.74 cases per 100,000 children. The impact of the crèche-related outbreak in 2007 is evident in Figure 3.7.

Figure 3.7 Tuberculosis cases in 0-15 year olds by year, 2005-2014



Data courtesy of the Health Protection Surveillance Centre. Data for 2013 and 2014 are provisional.

3.2 Treatment

Treatment for TB is intended to be curative, to prevent relapse of TB and transmission of the disease to others.[22] Treatment regimens may be daily or three times per week. Due to the importance of completing the treatment correctly, directly observed therapy (DOT) by a healthcare professional may be required for certain individuals identified as being at risk of non-compliance. DOT treatment is administered daily or on a reduced frequency regimen of three or five times a week using a modified dose regimen, as directed by the treating physician.

Tuberculosis is treated in two phases – an initial phase using four drugs (which is designed to reduce the bacterial population as rapidly as possible and prevent the emergence of drug-resistant bacteria) and a continuation phase that comprises two drugs in fully sensitive cases. The treatment of choice for the initial phase is the daily use of rifampicin, isoniazid, pyrazinamide and ethambutol; the continuation phase typically comprises daily treatment with rifampicin and isoniazid (Table 3.2). Proprietary combination products that combine two or three of these drugs are available for adults, and their use is recommended to maximise adherence.

Based on the WHO TB treatment guidelines, new patients with pulmonary TB should receive a regimen containing six months of rifampicin.[22] Extrapulmonary TB should be treated using the same regimens, although longer schedules of nine months and nine to 12 months have been recommended for TB of bones and joints and TB meningitis, respectively. In TB meningitis, adjuvant corticosteroid treatment is recommended. Modification of these treatment regimens may be required due to resistance or intolerance.

Table 3.2 Treatment options for TB[5]

First line treatment	Second line treatment
Isoniazid Rifampicin Ethambutol Pyrazinamide	Amikacin Capreomycin Ciprofloxacin Ethionamide Kanamycin Moxifloxacin Ofloxacin Para-amino salicylic acid (PAS) Prothionamide Rifabutin Streptomycin

Treatment is also intended to prevent future re-activation of the infection in the treated person. At least six months of treatment is required to prevent future re-

activation. New treatment regimens have not shortened the required treatment duration for preventing re-activation.

Internationally, drug-resistant TB strains are becoming more common. This gives rise to the need for alternative multi-drug treatment regimens. The multi-drug groups recommended by the WHO include: first-line oral agents; injectable agents; fluoroquinolones; and oral bacteriostatic second-line agents (Table 3.2).[22] Multidrug resistant TB remains very uncommon in Ireland, with between one and three cases reported per annum since 2008,[8] and only two reported cases of extensively drug resistant TB. The WHO recommend that treatment for multidrug-resistant TB should continue for a minimum of 18 months after the patient first becomes smear- or culture-negative.[22] Treatment options for MDR-TB are limited and expensive, and should be delivered using DOT. Treatment regimens can be two to three times a day and also require intravenous medication.

3.3 Outcomes

As treatment is intended to be curative, the main outcome should be return to the health status experienced before infection.

Pulmonary TB can give rise to long-term impairment after resolution of the TB infection.[26;27] TB may lead to the formation of anatomical changes that remain after microbiological cure, including bronchovascular distortion, bronchiectasis, emphysematous changes, and fibrotic bands.[26] A study examining pulmonary function tests (including forced vital capacity (FVC) and forced expiratory volume in one second (FEV1)) found lower values for patients recently treated for TB compared with those treated for latent TB infection.[26] However, whether these differences are sustained over the longer-term, and the extent to which they apply to a paediatric population, is not known. Furthermore, where data is derived from developing countries, these differences may reflect inadequate access to appropriate treatment and may increase the potential for long-term sequelae (that is, chronic conditions that are complications of an acute condition and can occur decades after the resolution of the initial acute condition).

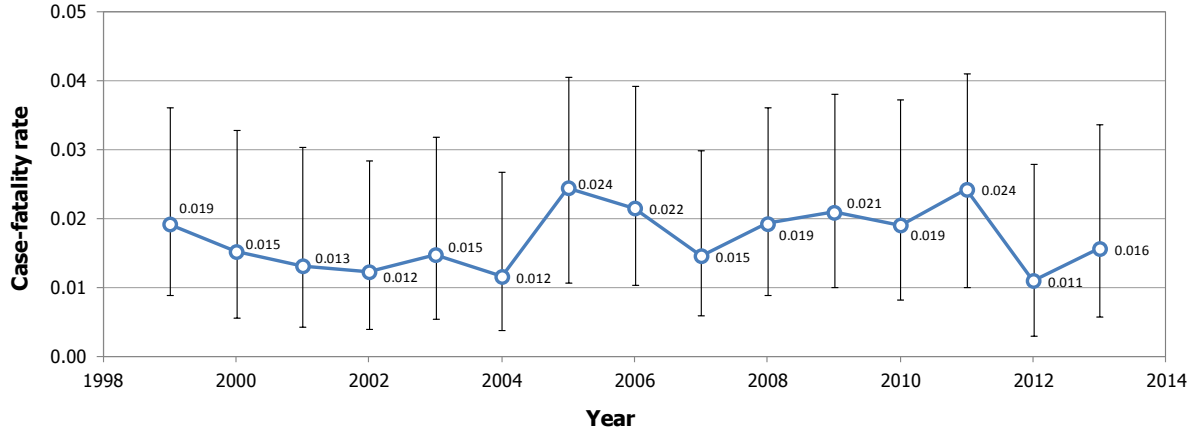
Depending on its form, meningitis is associated with increased mortality and a variety of major long-term chronic conditions.[28;29] A systematic review of treatment outcomes relating specifically to childhood TB meningitis found that risk of death was 19.3%, risk of neurological sequelae was 53.9% and probability of survival with no neurological impairment was 36.7%.[30] The most common sequelae include intellectual or behavioural deficits, neurological deficits (including motor deficits and seizures), and hearing deficits.[29] Although TB meningitis is rare with nine cases observed in 0 to 15 years olds between 2005 and 2014, it has a high potential for

resulting in negative outcomes that may impact on quality of life over a survivor's lifetime.

Health-related quality of life is lower in patients being treated for TB compared with those being treated for latent TB infection.[31] Quality of life is lowest at diagnosis, and improves substantially as symptoms of TB resolve during the initial intensive treatment phase.[32] Improvements in quality of life are seen throughout treatment,[31] although in the absence of high quality information on prior quality of life it is not possible to determine if a full return to pre-TB quality of life is normally achieved. Reductions in quality of life associated with treatment-related restrictions and adverse events will have an impact on patients given the lengthy treatment duration of six to 12 months.

The case fatality rate for TB in Ireland is approximately 0.01 to 0.03 (see Figure 3.8). Mortality is predominantly in older age groups. Between 2002 and 2014 there were no TB deaths in children aged less than 15 years.

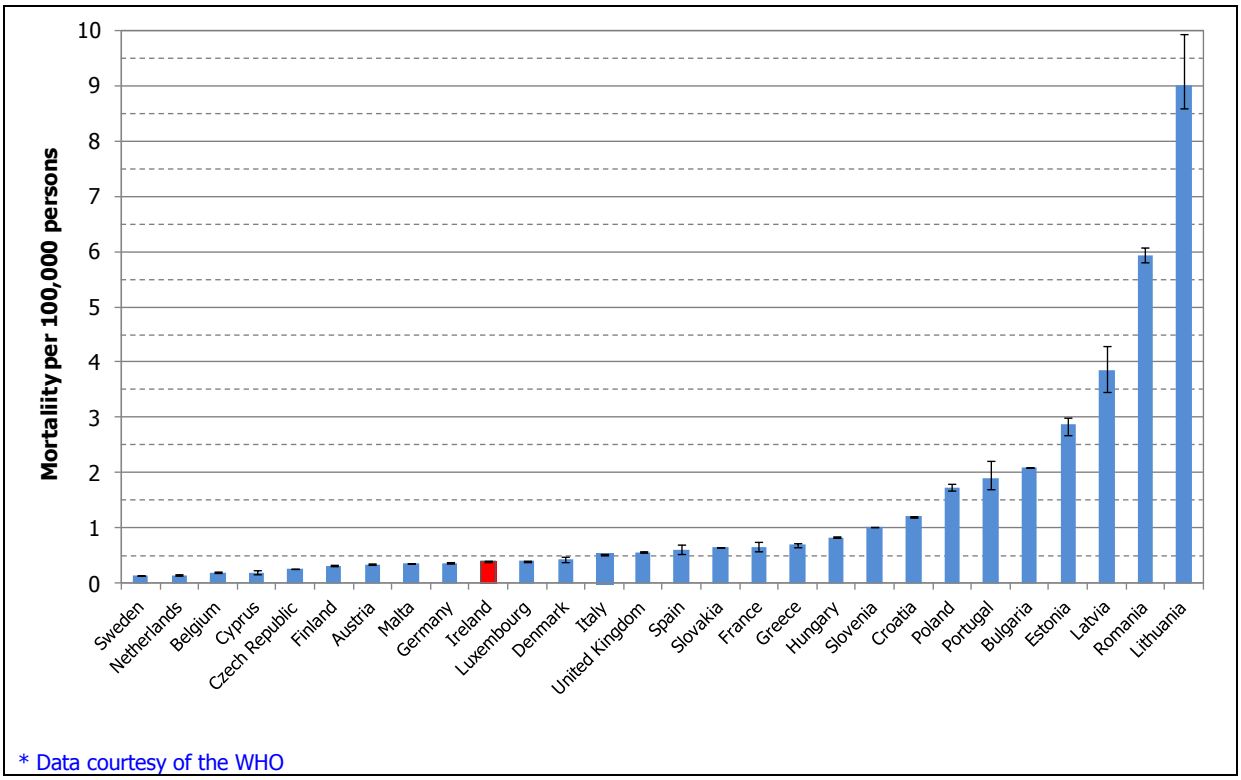
Figure 3.8 Tuberculosis case-fatality rate by year



Data courtesy of the Health Protection Surveillance Centre. Data for 2013 are provisional

The mortality rate in Ireland is 0.39 per 100,000 persons, similar to that of Germany and Luxembourg (see Figure 3.9).

Figure 3.9 Tuberculosis mortality rates per 100,000 in the EU27 states, 2013[16]



* Data courtesy of the WHO

The mortality data described above relates to death associated with the TB infection. However, there is also a burden of mortality associated with sequelae of tuberculosis (recorded as ICD10 code B90). In recent years the mortality burden associated with sequelae of TB is similar or higher than that associated with primary infections. Mortality from sequelae of TB is unusual in those aged less than 70 years. Sequelae could be a reflection of delay in diagnosis, delay in timely initiation of treatment, inadequate treatment, or coming from a high TB incidence country. Increased sequelae may also be a function of relapsed or repeated TB infections.

3.4 High-risk population

Although various population sub-groups may be considered at high risk of exposure to TB (for example, healthcare workers), this study is concerned with neonatal vaccination. As such, high-risk groups are defined for newborns on the basis of a number of factors including: birth in a high TB endemicity country; parents from a high TB endemicity country; contact with cases with active respiratory tuberculosis; member of an at risk group for which there may be difficulty in providing alternative control measures (for example, the Traveller community).[8] Risk status may also be defined by ethnicity or country of birth of grandparents, as has been implemented in the UK.[33]

Regarding ethnicity, the Irish Traveller ethnic minority is an indigenous population group that is considered high-risk. The incidence of TB in Irish Travellers is approximately three times that of the general Irish population, although the small numbers involved mean that estimates are subject to considerable uncertainty.[34] Irish Travellers tend to have a higher occupant density and household size, which increase the risk of TB transmission. Irish Travellers constitute 0.64% of the population and approximately 1.3% of births annually.[35]

In terms of parental nationality, the National Perinatal Reporting System maintained by the Healthcare Pricing Office records the nationality of mothers and, where available, fathers.[36] High incidence countries were identified from the WHO TB incidence data as countries with an incidence of greater than or equal to 40 cases per 100,000 persons. All births where at least one parent came from a high incidence country were labelled as high TB risk births. Based on national births data from 2008 to 2013, 12.0% of births can be classified as high-risk based on parental nationality, although the percentage by county varies from 5.3% in Wexford to 20.1% in Dublin city. Data on the country of birth of grandparents is not captured by the National Perinatal Reporting System.

When the data on Irish Travellers and children born to parents from a high TB incidence country is combined, the proportion of newborns classified as high-risk is 13.4%.

Other population groups may also be considered high-risk, for example those born into a homeless family or to a parent who is, or has recently been in prison. Children of parents that have come from a high incidence area within an otherwise low incidence country (for example, London in the United Kingdom [UK]) may also be considered as high-risk. There are no clear sources of data to determine the likely size of these groups, and identification of these groups in practice could prove challenging.

TB notifications include data on ethnicity and country of birth, allowing for an estimate of the proportion of cases in high-risk individuals. Using data from 2005 to 2014, approximately 40% of cases in 0 to 15 year olds occurred in children who would be classified as high-risk. Based on the assumption that 13.4% of births are considered high-risk, the relative risk of TB in high-risk children is approximately 4.38 times that of children who are not classified as high-risk. However, this may be an overestimate as the figure of 13.4% relates to births that take place in the state, and the proportion of children who are high-risk may be higher when migrants born outside the state are taken into account.

Some countries, such as the UK, also consider births as high-risk if they are resident in a high incidence area (defined as an area with TB incidence ≥40 per 100,000

population). As TB data in Ireland is only available for large areas such as county or local health office areas, classifying an area as high incidence could greatly increase the number of births considered to be high-risk. The TB incidence rates in all Irish local health office areas are well below 40 per 100,000 and none would be considered as high incidence areas.

3.5 Discussion

Although TB poses a significant challenge to health globally, Ireland is considered a low incidence country. Compared with other countries in the EU, Ireland is mid-table in terms of incidence and mortality. There are approximately 400 cases of TB annually in Ireland, of which approximately 10 (2.5%) are in children aged less than 15 years.

Within Ireland there is regional variation in the incidence of TB, with some areas in Cork and Dublin experiencing statistically significant elevated incidence. There are also a number of areas with an incidence rate statistically significantly lower than the national average.

In children aged less than 15 years, almost all cases of TB are pulmonary or extrapulmonary in nature, with cases of miliary TB (two cases from 2005 to 2014) or TB meningitis (nine cases from 2005 to 2014) being very rare. No deaths relating to TB have been recorded in children in Ireland in the last 13 years.

TB disease and TB treatment are associated with reduced quality of life, which improves during treatment as the intensity of the schedule decreases. Quality of life is lower in those being treated for active TB than in those treated for latent TB. TB can give rise to longer-term impairment, although there is limited evidence relating to outcomes in children, particularly for those receiving timely access to adequate treatment in high resource countries. TB meningitis is associated with a high probability of neurological deficits which could lead to significant reductions in quality of life across a survivor's lifetime.

The high-risk population in Ireland comprises children born to parents from a high TB incidence country and Irish Traveller children. These two groups constitute approximately 13.4% of births in Ireland annually.

3.6 Key messages

- TB incidence has been in decline in Ireland over the last 25 years. In 2014 there were 324 cases of TB, equivalent to 7.0 cases per 100,000 persons. Incidence in Ireland is similar to that in most Western European countries.
- TB incidence is lowest in 0-14 year olds and highest in those aged over 65 years. Those aged less than 15 years account for approximately 2% of TB cases in Ireland. Between 2005 and 2014 the average annual number of cases in children aged less than 15 years was 20.9 cases, although the incidence has been in decline. The average annual number of cases for 2012 to 2014 was 11.7 cases.
- There is substantial regional variation in Ireland, but no local health office area would be considered high incidence based on the WHO metric of ≥40 cases per 100,000 persons.
- Treatment for TB is curative and based on antibiotics. Treatment typically lasts six to 12 months for non-multi-drug resistant forms of TB.
- Between 2002 and 2014 there were no recorded TB-related deaths in 0 to 15 year olds in Ireland.
- Between 2005 and 2014 there were nine cases of TB meningitis in 0 to 15 year olds. TB meningitis is associated with a high probability of permanent effects such as hearing or neurological deficits.
- An estimated 13.4% of children born in Ireland each year may be classified as high-risk based on the ethnicity or country of origin of their parents.
- The risk of TB in high-risk children is approximately 4.4 times that of children not at high-risk, and three times that of the general population.

4. Clinical effectiveness and safety

BCG vaccination is used primarily for the prevention of tuberculosis, although it has also been used for the prevention of other conditions, such as leprosy. Vaccination programmes may be directed at specific age groups (for example, neonatal), or may target individuals who have a higher likelihood of exposure to TB, for example health professionals. In line with the agreed scope of the health technology assessment (HTA), this chapter will examine the current evidence of efficacy and safety for BCG vaccination in infants. As the current and proposed programmes of BCG vaccination relate to neonates and infants, evidence regarding older children, adolescents, and revaccinations will not be considered.

4.1 Search strategy

The efficacy of BCG vaccination to prevent TB has been the subject of a number of systematic reviews.[37-42] Some reviews have focussed specifically on vaccination of neonates and infants, while others have included individuals vaccinated at any age. As it is not clear that efficacy estimated based on vaccination of older children or adults is applicable to vaccination programmes involving neonates and infants, we have restricted our review to evidence regarding vaccination of neonates and infants aged less than one year.

This assessment used the recent systematic review of Abubakar *et al.* as a basis for our estimates.[40] Their review was not restricted to neonates and infants, and the search was completed in May 2009. A long list of search terms was used and studies that appeared in previous systematic reviews were all identified. We updated their search to the end of January 2015 using the same search criteria.

A search for studies comparing BCG vaccination with no vaccination was carried out in MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, the Clinical Trials Register and ClinicalTrials.gov. The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and the Health Technology Assessment Database were also searched for relevant secondary studies. Reference lists from reviews were searched to identify primary studies. Full details of the search are provided in Appendix 1 of this document. The PICOS (Population, Intervention, Comparator, Outcomes, Study design) analysis used to formulate the search is presented in Table 4.1 below.

The review is restricted to TB-related outcomes: pulmonary and extrapulmonary TB; TB meningitis; miliary TB; and TB-related mortality. The effect of BCG vaccination on tuberculin reactivity is reported in some trials, but as there is no clear link to the

protective efficacy of the vaccine against the development of active tuberculosis we have excluded the outcome from our analysis.[43]

Table 4.1 PICOS analysis for identification of relevant studies

Population	All children and adults
Intervention	BCG vaccination before the age of one year
Comparator	No BCG vaccination
Outcomes	Pulmonary TB, extrapulmonary TB, TB meningitis, miliary TB, TB mortality
Study design	Randomised controlled trials, case-control studies

By reviewing studies included in previous systematic reviews, it was apparent that adverse events and reactions are not routinely collected or reported. This may be due to inconsistent or incomplete reporting. Due to the high frequency of mild adverse reactions associated with BCG vaccination,[44] and different interventional approaches, any reported data may lack external validity. There is also evidence regarding different adverse reaction rates being associated with different BCG vaccine strains which also impact on the potential applicability to different settings.[45]

The following study types were excluded:

- trials of vaccines other than BCG
- studies of TB prevalence
- investigations of TB control programmes
- reviews of studies
- trials of booster vaccinations or vaccinations in older children or adults
- trials of tuberculin reactions
- case-control studies if controls were from a tuberculin-screened population and cases were not
- case-control studies with non-concurrent controls
- studies in which some or all vaccinated participants were vaccinated more than a year after birth.

Results were reviewed according to the inclusion and exclusion criteria by two researchers independently, and any disagreements were resolved through discussion.

The systematic review of Abubakar *et al.* assessed study bias in randomised controlled trials (RCTs) and quasi-randomised trials using the Cochrane Risk of Bias

Tool.[40] The same review also quality assessed case-control studies based on three criteria: equivalence of vaccination definitions for cases and controls; blinding of BCG assessors regarding disease status; and whether cases were diagnosed independent of vaccination status.[40]

4.2 Results

Four RCTs[46-49] and 10 case-control studies[50-59] included in the systematic review of Abubakar *et al.* met the inclusion criteria for this review. The extension of the systematic review from May 2009 to January 2015 did not identify any additional relevant studies. The characteristics of the included studies are given in Table 4.2.

As all identified studies were included in the review of Abubakar *et al.*,[40] the study quality findings were extracted from that systematic review. One of the four RCTs comprised two sub studies (one based in TB households and one hospital based), [46] giving a total of five RCT datasets. Of the four RCTs included in this review, all were considered at lower risk of bias regarding selective reporting, case ascertainment and diagnosis detection bias. All RCTs were at higher risk of bias regarding generation of allocation sequence and knowledge of allocated intervention. Only the Rosenthal *et al.*[46] sub-study of TB households was at lower risk of bias for treatment allocation concealment. Other than Mehta *et al.*,[49] all studies were at lower risk of bias in terms of addressing incomplete outcome data. All of the case-control studies were at higher risk of bias in at least one of the specified criteria. The studies of Kwong *et al.*[50] and Putrali *et al.*[51] were at highest risk of bias, while the study of Awasthi *et al.*[57] was at lowest risk of bias. In general, more recent studies were at lower risk of bias, possibly reflecting both improved methodology and reporting.

A number of studies identified in previous systematic reviews were excluded because they were not restricted to vaccinations given to infants under one year of age, or because they did not report one of the four specified outcomes. Some studies that were included in a previously published systematic review reported an outcome that amalgamated pulmonary and extra-pulmonary TB data.[37]

Of the included studies, three of the four RCTs were conducted in North America and published in the 1940s.[46-48] The remaining RCT was carried out in India and published in 1976.[49] Length of follow up ranged from 2.5 years[49] to 23 years.[46]

Table 4.2 Characteristics of included studies

Study	Country	Type	Participants		Outcomes reported				
			Vaccinated	Unvaccinated	Pulmonary TB	Extra-pulmonary TB	TB meningitis	Miliary TB	TB mortality
Rosenthal (1945)[46]	USA	RCT	5,737*	4,378*	x		x	x	x
Aronson (1948)[47]	USA	RCT	123	139	x			x	x
Ferguson (1949)[48]	Canada	RCT	306	303	x	x		x	x
Mehta (1976)[49]	India	RCT	396	300	x				
Kwong Chan (1980)[50]	Republic of Korea	CC	76	62			x		
Putrali (1983)[51]	Indonesia	CC	103	412	x	x			
Chavalittamrong (1986)[52]	Thailand	CC	330	1,106	x	x	x		
Miceli (1986)[53]	Argentina	CC	51	256	x	x		x	
Myint (1987)[54]	Myanmar	CC	311	1,536	x	x	x		
Camargos (1988)[55]	Brazil	CC	45	90			x		
Bhattacharjee (1993)[56]	India	CC	21	42			x		
Awasthi (1999)[57]	India	CC	192	70			x		
Martinez-Gonzalez (2002)[58]	Mexico	CC	42	84		x			
Zodpey (2007)[59]	India	CC	877	877	x	x	x		

Notes:
* Study conducted in two settings with outcomes reported separately. Figures reported here correspond to combined participant numbers.

Abbreviations: TB, tuberculosis; RCT, randomised controlled trial; CC, case-control study.

All of the included case-control studies were published after the four RCTs, with three conducted in India,[56;57;59] and one study from each of Indonesia,[51] Thailand,[52] Argentina,[53] Myanmar,[54] Brazil,[55] and Mexico.[58]

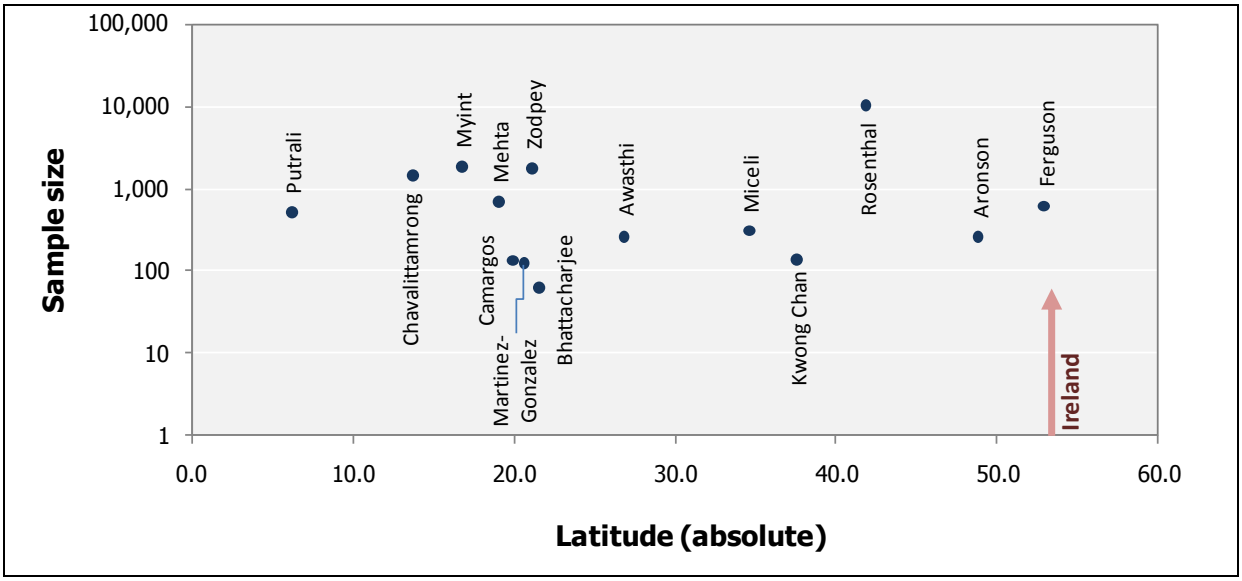
No study recorded all five of the outcomes of interest. The most commonly recorded outcome was pulmonary TB, reported in nine studies. Data on mortality was only provided in three of the RCTs (see Table 4.2).

4.3 Evidence synthesis

For RCTs, relative risks were computed using the outcomes data. As person-years were provided, these were used in the calculations. For case-control studies, the odds ratio was used to summarise study findings. It was assumed that the odds ratio would approximate the relative risk in the general population. Where sufficient studies were available, random-effects meta-analysis was used. RCTs and case-controls studies were pooled separately. When relevant, a continuity correction of 0.5 was added to all cells with 0 cases.

There is evidence to suggest that the efficacy of BCG vaccination differs by distance from the equator.[60] Where sufficient data was available, meta-regression combining RCT and case-control study data was used to estimate the impact of latitude. The results of the meta-regression were used to predict what the efficacy of BCG might be at the latitude of Ireland. All meta-analyses were carried out in the statistical software R[61] using the metaphor package.[62] Latitude data was extracted using the RgoogleMaps package (Figure 4.1).[63] Where sufficient studies were available, funnel plots and Egger's test were used to evaluate the possibility of publication bias.

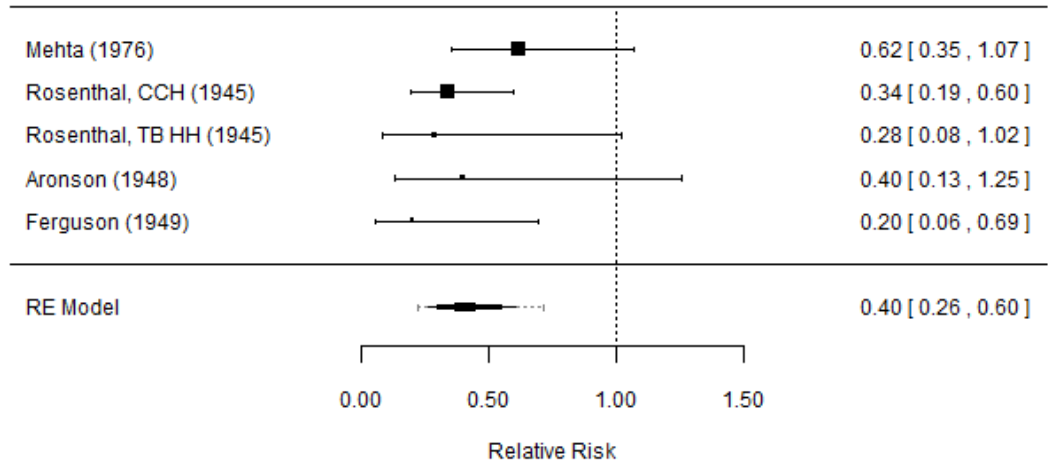
Figure 4.1 Latitude and sample size of included studies



4.3.1 Pulmonary TB

There were five RCT datasets and six case-control study datasets available for inclusion in this analysis. The analysis of RCT studies showed limited heterogeneity (I^2=20.3%), and a pooled relative risk estimate of 0.40 (95% CI: 0.26 to 0.60). The forest plot for the RCT analysis is shown in Figure 4.2.

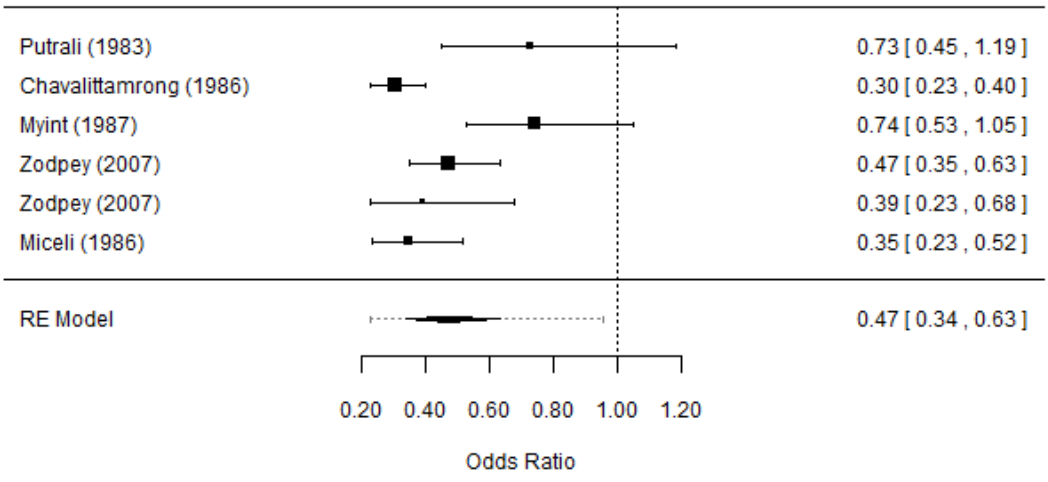
Figure 4.2 Relative risk of pulmonary TB in RCTs (sorted by increasing latitude)



Abbreviations: CCH, Cook County Hospital; TB HH, tuberculosis households; RE, random effects.

The analysis of case-control studies showed substantial heterogeneity (I^2=76.1%). The study of Chavalittamrong *et al.*[52] has an unusually low odds ratio compared with studies at similar latitudes (see Figure 4.3). An analysis of influence metrics, however, suggests that the results of Myint *et al.*[54] have the most impact on the pooled estimate. The summary estimate of odds ratio was 0.47 (95% CI: 0.34 to 0.63).

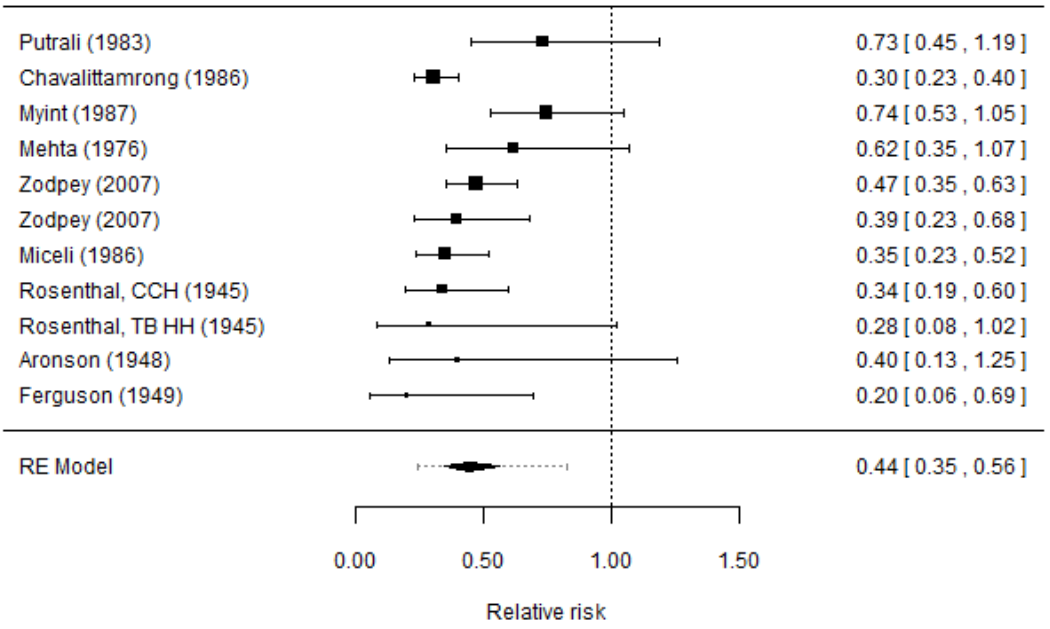
Figure 4.3 Odds ratio of pulmonary TB in case-control studies (sorted by increasing latitude)



Abbreviations: RE, random effects.

When both RCTs and case-control studies are combined, there is substantial heterogeneity (I^2=60.6%). The pooled estimate lies between those estimated for RCTs alone and case-control studies alone (Figure 4.4).

Figure 4.4 Relative risk of pulmonary TB using all studies (sorted by increasing latitude)



Abbreviations: CCH, Cook County Hospital; TB HH, tuberculosis households; RE, random effects.

A meta-regression of all studies was carried out using latitude as a covariate. The relative risk decreased with increasing latitude. Although the association was not statistically significant at the 0.05 level, the confidence bounds for the coefficient

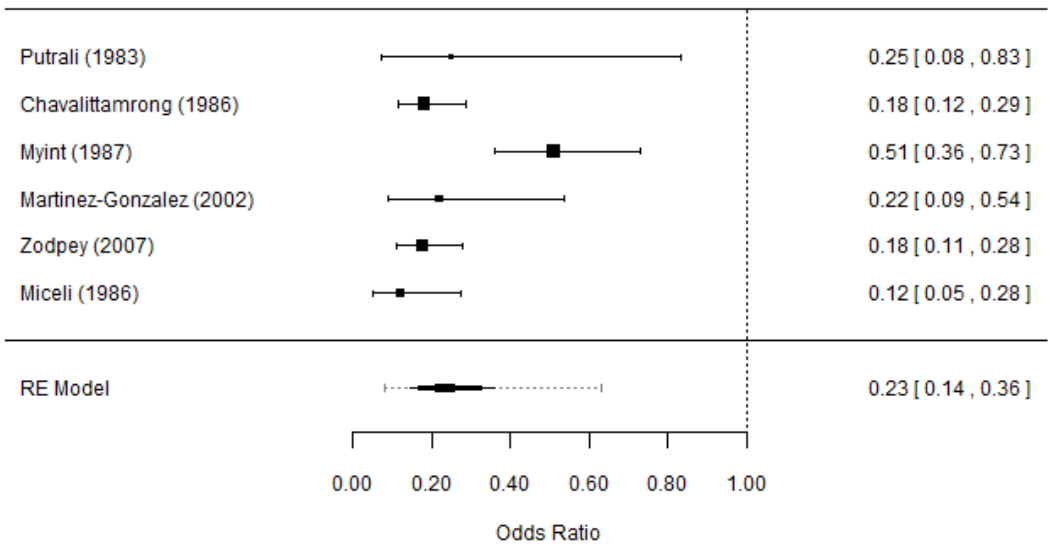
only just embraced 0. Latitude explained only a small amount of between-study variation (τ^2=0.070, compared with τ^2=0.085 without the covariate). However, the between-study variation reduced substantially when the study of Chavalittamrong *et al.* was omitted. Using the meta-regression model including all studies to predict efficacy in Ireland, the estimated relative risk was 0.26 (95% credible interval: 0.12 to 0.58).

4.3.2 Extrapulmonary TB

Only a single RCT reported outcomes for extrapulmonary TB.[48] The relative risk reported in that study was 0.14 (95% CI: 0.03 to 0.63).

Six case-control studies reported data on extrapulmonary TB outcomes. There was substantial heterogeneity (I^2=72.1%). As for the analysis of pulmonary TB, the study of Myint *et al.*[54] was considered influential. Removal of this study from the analysis resulted in I^2=0. Including all case-control studies in the analysis resulted in a pooled odds ratio of 0.23 (95% CI: 0.14 to 0.36) (Figure 4.5).

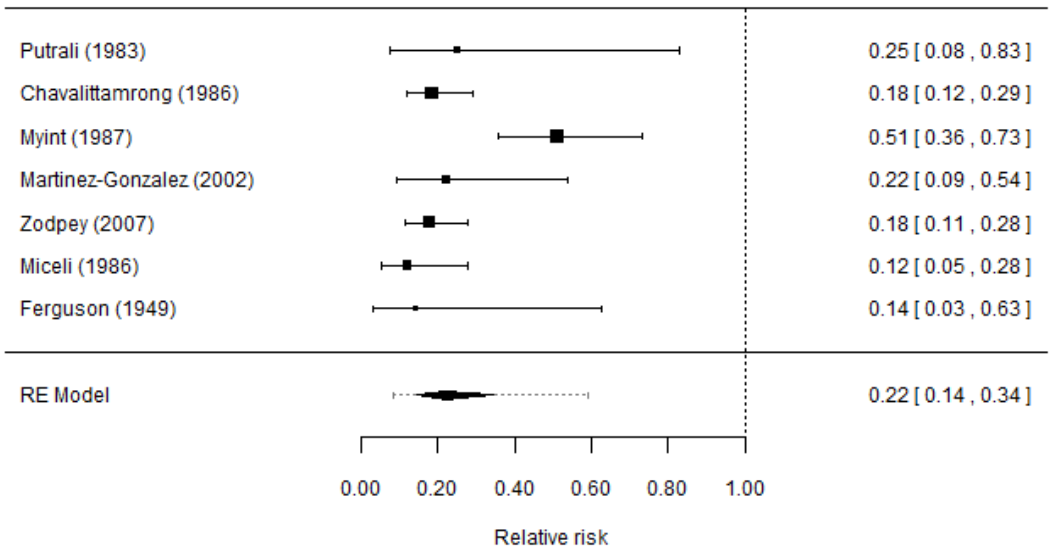
Figure 4.5 Odds ratio of extrapulmonary TB in case-control studies (sorted by increasing latitude)



Abbreviations: RE, random effects.

The addition of the RCT evidence to the case-control study data has a negligible impact on the pooled estimate. The additional data had a minor impact on heterogeneity (I^2=67.8%), and the study of Myint *et al.*[54] was still considered influential, and may represent an outlier. The pooled estimate of relative risk was 0.22 (95% CI: 0.14 to 0.34) (Figure 4.6).

Figure 4.6 Relative risk of extrapulmonary TB using all studies (sorted by increasing latitude)



Abbreviations: RE, random effects.

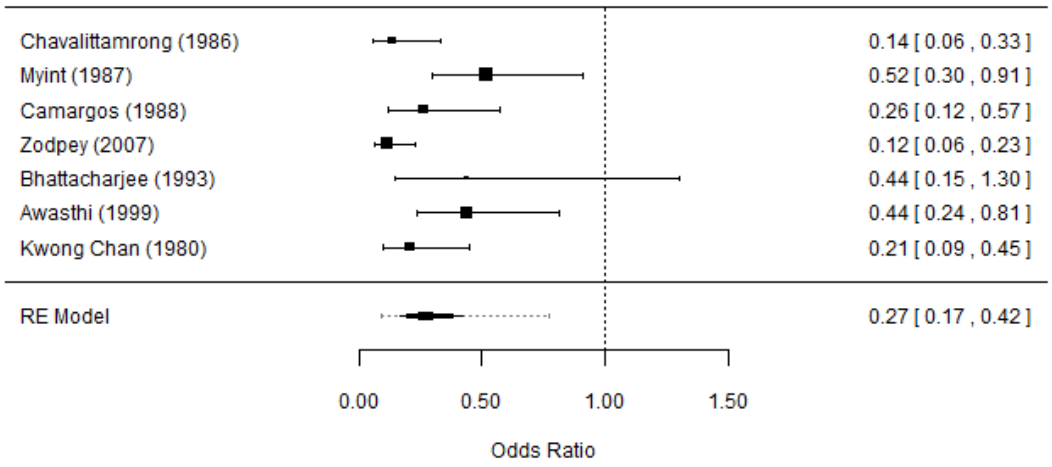
A meta-regression of all studies including latitude as a covariate had a minor impact on between-study variation (τ^2=0.202, compared with τ^2=0.181 without the covariate). The results of the meta-regression were unaffected by the inclusion of the study by Myint *et al.* This analysis does not support the notion of latitude being associated with extrapulmonary TB.

4.3.3 TB meningitis

The sub-study of TB households by Rosenthal *et al.* was the only RCT to report outcomes for TB meningitis.[46] The relative risk reported in that study was 0.15 (95% CI: 0.01 to 2.87).

There were seven case-control studies that reported outcomes for TB meningitis. There was substantial heterogeneity (I^2=63.8%). The pooled odds ratio was 0.27 (95% CI: 0.17 to 0.42) (Figure 4.7). One study, by Zodpey *et al.*,[59] was considered influential. However, this study had a low estimate of the odds ratio, unlike the study by Myint *et al.* which tended to have a high estimate of effectiveness regarding extrapulmonary TB. Removal of the Zodpey *et al.* study increased the estimate of the odds ratio to 0.315, indicating a relatively minor impact.

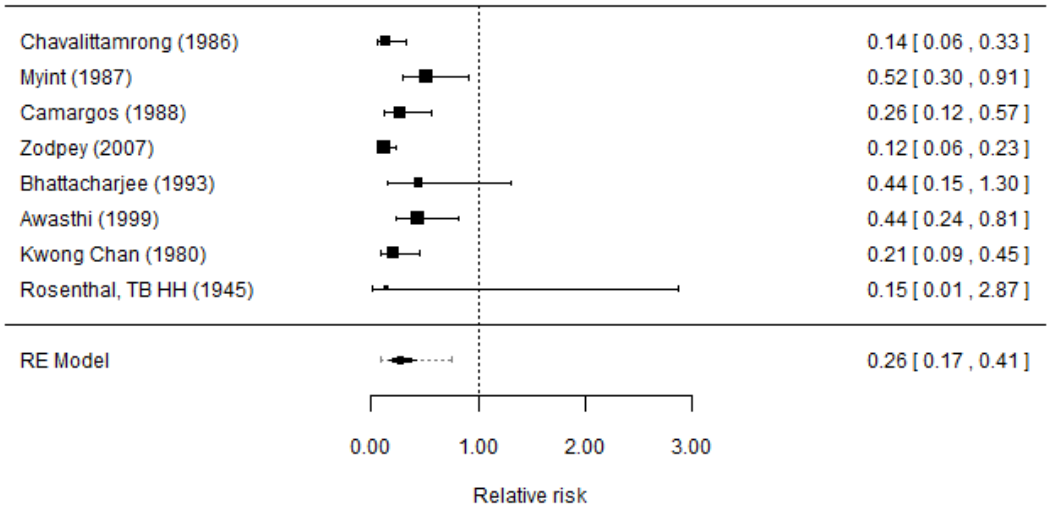
Figure 4.7 Odds ratio of TB meningitis in case-control studies (sorted by increasing latitude)



Abbreviations: RE, random effects.

The addition of the RCT evidence to the analysis has a minor impact on heterogeneity (I^2=59.6%) and the pooled estimate of effectiveness, with a relative risk of 0.26 (95% CI: 0.17 to 0.41) (Figure 4.8). The study by Zodpey *et al.* continued to register as an influential study, although its exclusion had a minor impact on the pooled estimate.

Figure 4.8 Relative risk of TB meningitis in all studies (sorted by increasing latitude)



Abbreviations: TB HH, tuberculosis households; RE, random effects.

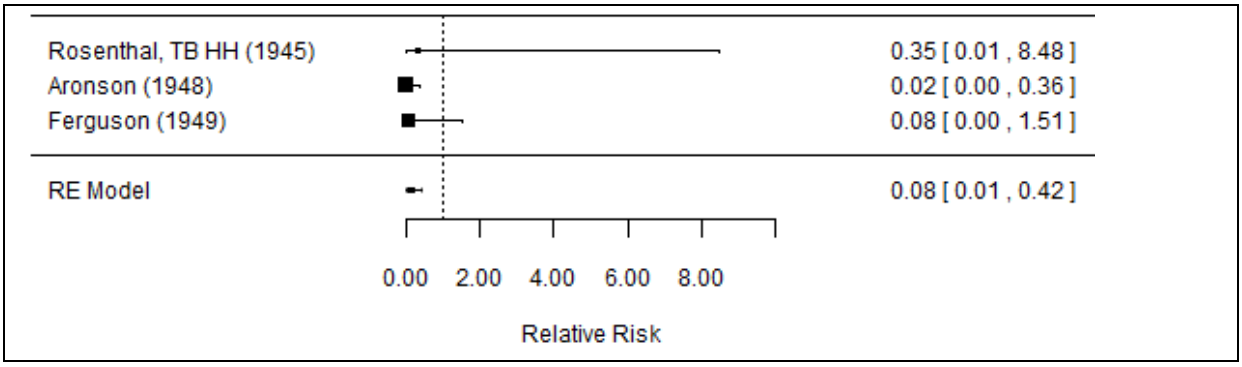
The inclusion of latitude as a covariate increased the between-study variation, and hence the results were not reported here.

4.3.4 Miliary TB

Data on miliary TB was available for three RCTs and one case-control study. A number of studies combined data on miliary TB and TB meningitis, so that the data could not be disaggregated. Miliary TB is relatively rare, so estimates of efficacy were based on small numbers.

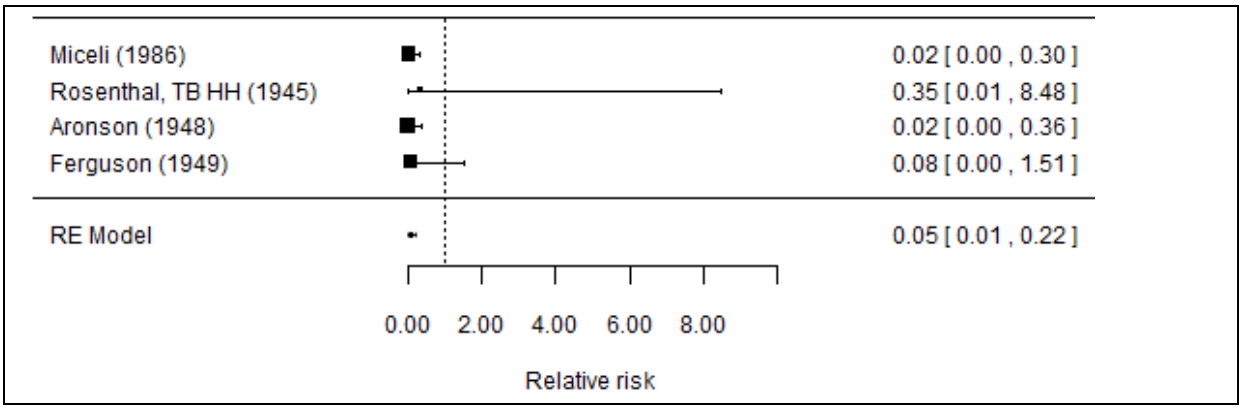
The pooled estimate of relative risk based on RCTs alone was 0.08 (95% CI: 0.01 to 0.42), suggesting that BCG vaccination is highly efficacious in preventing miliary TB (Figure 4.9).

Figure 4.9 Relative risk of miliary TB in RCT studies (sorted by increasing latitude)



The single case-control study available provided an estimated relative risk of 0.02 (95% CI: 0.00 to 0.30). By pooling the RCT and case-control evidence, a summary relative risk of 0.05 (95% CI: 0.01 to 0.22) is obtained (Figure 4.10).

Figure 4.10 Relative risk of miliary TB in all studies (sorted by increasing latitude)

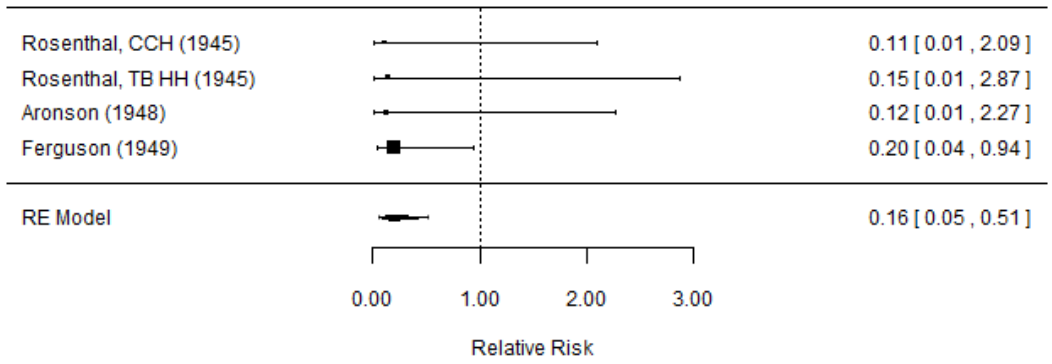


Due to the small number of included studies, a meta-regression including latitude as a covariate was considered inappropriate.

4.3.5 TB mortality

Mortality outcomes were only reported in RCTs, giving four estimates of efficacy. Given the relatively low occurrence of death, individual study estimates were subject to substantial imprecision. The pooled estimate of relative risk was 0.16 (95% CI: 0.05 to 0.50). This result contrasts with the systematic review of Colditz *et al.*[37] The difference arises as the analysis here does not incorporate one study that included children vaccinated up to the age of three. That study estimated the relative risk of TB death as 0.93 (95% CI: 0.35 to 2.48) and clearly impacted on the summary estimate of vaccine efficacy (Figure 4.11).

Figure 4.11 Relative risk of TB mortality in RCT studies (sorted by increasing latitude)



Abbreviations: CCH, Cook County Hospital; TB HH, tuberculosis households; RE, random effects.

Due to the small number of included studies, and the fact that the studies were conducted at similar latitudes, a meta-regression including latitude as a covariate was considered inappropriate.

4.4 Other outcomes

4.4.1 Duration of protective effect

Abubakar *et al.* investigated the duration of the protective effect of BCG vaccination.[40] They found that efficacy declines over time, but some studies have shown a continued protective effect 15 years after vaccination.[40] A faster rate of decline was observed in studies further from the equator and in studies where BCG vaccination was restricted to infants or children after strict tuberculin sensitivity screening.

A study of a TB outbreak in a UK college screened 2,284 students aged over 16 years (mean age 17.8 years) and found no association between TB infection and history of BCG vaccination.[64] The evidence suggested that the protective effect of BCG may no longer be present at age 18.

4.4.2 Protection against latent TB infection

The analysis of clinical effectiveness in Chapter 4.3 evaluated the efficacy of BCG in preventing TB disease. Although not evaluated in the studies included in the evidence synthesis, BCG vaccination may also be effective in preventing latent TB infection. The tuberculin skin test cannot discriminate between responses due to M tuberculosis infection and those due to BCG vaccination or non-tuberculous mycobacterial infection.[42] Interferon ɣ release assays can distinguish between *M tuberculosis* infection and BCG vaccination and other mycobacterial infections, but have only been in use in the last decade.[65]

A systematic review and meta-analysis was used by Roy *et al.* to assess the effect of BCG vaccination against *Mycobacterium tuberculosis* in children aged less than 16 years.[42] They included observational studies in which all children were screened for infection using interferon ɣ release assays. Data from six studies suggested that BCG vaccination was associated with a risk ratio of 0.73, showing a protective effect against latent TB infection. The included data was derived from a mixture of outbreak investigations and studies of individuals with close contact with index cases. Study quality was assessed as generally moderate to high. Age at vaccination and the relevance of the study settings were both unclear.

BCG does not offer protection from reactivation of latent TB infection, and hence the findings here are only relevant to infants vaccinated before exposure to TB.[66]

4.4.3 Non-specific effects of BCG vaccination

It has been suggested that childhood immunisations can lead to non-specific beneficial effects.[67] That is, they may provide beneficial effects beyond those intended. For example, BCG could result in reduced morbidity and mortality from diseases other than TB.

Determining non-specific effects is challenging as infants must be randomised. Effects could also be attributable to one of a number of vaccinations given to each child.[68] Some studies have sought to measure the effect of BCG on infant mortality and hospitalisation. Due to the many possible confounders, it is difficult to attribute benefits directly to BCG vaccination. Due to the low infant mortality rates observed in high resource countries, there is a limited ability to detect the presence of an effect.

As part of a WHO review, a systematic review of studies found limited evidence of non-specific effect on all cause mortality.[69] The report concluded that the available evidence was suggestive of a beneficial effect of BCG in reducing all-cause mortality within the first year of life in countries with high childhood mortality. However, due to the quality of the underlying studies, there was low confidence in the evidence.

More relevant to the Irish setting was a Spanish study investigating the effect of BCG vaccination on hospitalisation due to respiratory infection and sepsis not attributable to TB.[70] They compared events in children from a region of Spain with 100% BCG coverage to non-BCG vaccinated children from the rest of Spain. They found statistically significantly lower hospitalisation rates in the vaccinated cohort. The study design was at risk of bias and as such, the authors concluded that neonatal BCG vaccination may decrease hospitalisation due to respiratory infection and sepsis.

Based on the available evidence, it is not possible to determine whether neonatal BCG vaccination may have measurable non-specific effects in the Irish population.

4.4.4 Safety

BCG is the most widely used vaccine in humans, but also among the most reactogenic vaccines in use.[44] Reactions vary depending on the BCG strain used and on the immune status of the child receiving the vaccine.[44;45] The majority of vaccine recipients develop a papule at the injection site, followed by mild ulceration and a scar. However, other more severe side effects include lymphadenitis and osteitis (Table 4.3). Suppurative lymphadenitis is most commonly associated with the BCG-Pasteur and BCG-Danish strains, while BCG-Russia is associated with osteitis cases.[44]

Among infants and children with a compromised immune system, such as those infected with HIV, the risk of severe adverse events from BCG vaccination occurring is substantially higher than for children with healthy immune systems.[45]

Mild adverse reactions do not require medical intervention. Of the more common severe reactions, antibiotics may be used for suppurative lymphadenitis, although there is little evidence of efficacy.[71] Needle aspiration may prevent discharge and associated complications such as fistulation, and is recommended in some countries.[45] Surgical drainage of suppurative lymphadenitis is also used but there is little evidence supporting its benefit, and it also creates risks in terms of anaesthesia.[45;71]

Table 4.3 Summary of mild and severe adverse events associated with BCG vaccination[45]

Nature of adverse event	Description	Rate
Mild	Injection site papule (onset 2–4 weeks)	Almost all vaccinees
	Mild ulceration (1–2 months)	
	Scar (2–5 months)	
Severe	Local abscess	1 per 1,000–10,000
	Keloid	
	Lymphadenitis	
	Suppuration (onset 2–6 months)	
	Systemic (onset 1–12 months)	Case reports only
	Cutaneous skin lesions	
	Osteitis	1 per 3,333–10^8
	Disseminated BCG	1 per 230,000–640,000
	Immune reconstitution syndrome	1 per 640,000

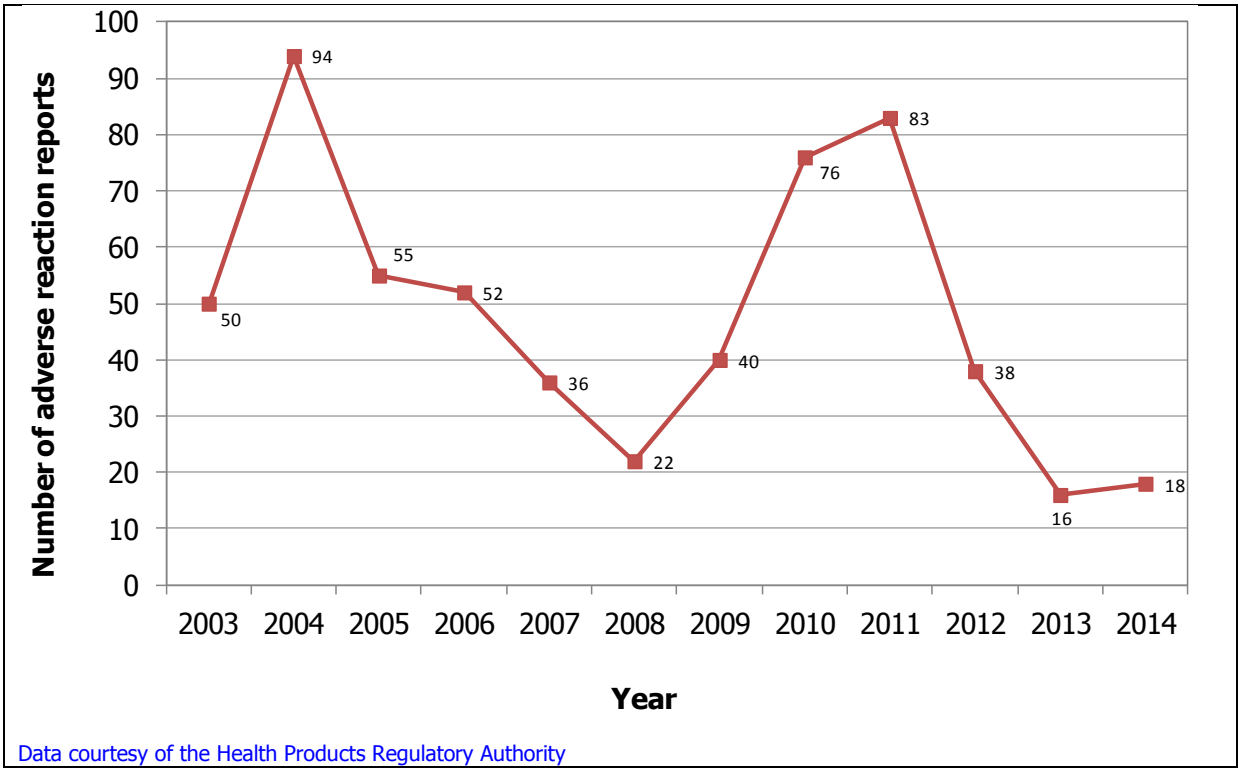
Disseminated BCG is a particularly severe adverse reaction most typically occurring in infants born with immunodeficiency syndromes.[72] There were eight confirmed cases of disseminated BCG in Ireland between 2005 and 2014, which equates to approximately 1 in 83,000 vaccinated infants.[73] This rate is in contrast to the WHO estimate of one in 230,000 to 640,000 given in Table 4.3 previously. The reported mortality rate associated with disseminated BCG varies from 13% to 73%.[74-78] Ireland has a relatively high reported proportion of population affected by primary immunodeficiency syndromes, second only to France in a review of 17 European countries.[79] Based on limited data, a high rate of primary immunodeficiency syndromes has been noted in the Irish Traveller population.[80] One of the eight cases was in an Irish Traveller, representing a risk ratio of approximately 11.4 in Irish Traveller infants. Due to the small numbers of cases, the risk ratio is subject to wide confidence bounds.

Disseminated BCG in Ireland was most commonly seen in infants with severe combined immunodeficiency (SCID). The risk of very severe adverse reactions to BCG may therefore be higher in Ireland than most other European countries, and the associated risk of mortality must also be considered. There were no deaths among the eight confirmed cases of disseminated BCG in Ireland. The mortality rate in Ireland may be lower than some reported estimates due to early recognition and aggressive treatment of BCG-osis and of the underlying primary immunodeficiency syndrome. Although BCG vaccination is contraindicated in infants with a family history of primary immunodeficiency,[8] the presence of a primary immunodeficiency is not always known at the time of vaccination.

The BCG vaccine SSI was authorised for use in Ireland by the Irish Medicines Board in 2001, and has been used in the vaccination programme from July 2002.[81] This vaccine is based on the BCG Danish strain 1331. In the 12 months after its introduction, the vaccine was associated with 41 suspected adverse reactions, all of which involved local reactions. Some cases required surgical intervention, with a suggestion that some of the reactions may have been caused by the vaccine inadvertently being administered subcutaneously or intramuscularly, rather than intradermally.[82] The rate of adverse reactions was seen to be consistent with the frequency expected for the particular strain of BCG.[82]

The adverse reactions reported to the Health Products Regulatory Authority include reactions in adults and children. Details on the age of the vaccine recipient are available in approximately two thirds of reports. Where age is provided, only 1% of reported cases relate to adults. For this analysis, it was assumed that all case reports with no age data related to children.

Figure 4.12 Numbers of annual adverse reaction reports in Ireland relating to BCG-SSI, 2003 to 2014



Data courtesy of the Health Products Regulatory Authority

Based on the estimated number of children vaccinated each year, the rate of reported adverse reactions from 2003 to 2014 was approximately 1 in 1,169 vaccinations. The rate has varied annually between 1 in 502 in 2004 and 1 in 3,766 in 2013 (Figure 4.12).

A study conducted at two Dublin paediatric hospitals between 2002 and 2004 estimated a complication rate of 1 in 931 vaccinees, and 1 in 1,543 developing suppurative lymphadenitis.[83] The rate of suppurative lymphadenitis is consistent with the summary of product characteristics for the vaccine, which suggests a rate of less than 1 in 1,000. Of the 58 cases identified in the study, 12 infants received antibiotic treatment (1 in 4,500) and 26 received surgical intervention (equivalent to 1 in 2,077).

4.5 Applicability of evidence

The meta-analysis of trials showed substantial heterogeneity across studies. Many of the trials have been conducted in high TB incidence countries. As was already noted, distance from the equator is hypothesised as a possible explanation for BCG vaccine efficacy, although a meta-regression showed limited evidence for this. Different BCG strains may also have different efficacy in preventing TB, impacting on the generalisability of study findings.[84] For these reasons, it is difficult to determine the applicability of the data to settings other than those of the trials.

Universal infant BCG vaccination is recommended in Ireland, although there is regional variation. Universal vaccination was discontinued in Cork in 1972. Between 1972 and 2008, BCG vaccination was provided in Cork city and county on parental request and to those with a history of direct TB contact. West Cork also provided BCG vaccination to primary school leavers. Universal BCG vaccination was reintroduced in County Cork in 2008 following the 2007 TB outbreak involving two crèches.[85] Universal neonatal vaccination was also not provided in the Western Health Board, which had a policy of universal vaccination at 12 years of age. Universal vaccination was introduced to Mayo in 2009 and Roscommon in 2012; a policy of vaccination at age 12 years continues in County Galway.

Vaccine uptake rates vary regionally but can be used to determine the approximate vaccinated and non-vaccinated populations. The vaccination status of TB cases is recorded in notification documents and can be used to determine the number of cases in the vaccinated and non-vaccinated cohorts. The risk ratios for four TB outcomes for the Irish vaccinated and unvaccinated cohorts are provided in Table 4.4 below. The effectiveness of vaccination against pulmonary TB (RR=0.25) is better than estimated from the international RCT data (RR=0.40) and similar to that predicted using the meta-regression incorporating latitude (RR=0.26). The risk ratios are similar for the other three outcomes. The risk ratio for any TB cases is 0.26 (95% CI: 0.22 to 0.32).

Table 4.4 Risk ratio of TB in vaccinated versus non-vaccinated 0-15 year olds in Ireland between 2005 and 2014 (Health Protection Surveillance Centre)

Outcome	Non-vaccinated cohort	Vaccinated cohort	Risk ratio
Pulmonary TB	67.2	57.8	0.25 (0.19 – 0.31)
Extrapulmonary TB	37.3	35.7	0.28 (0.20 – 0.38)
TB meningitis	3.6	5.4	0.43 (0.15 – 1.22)
Miliary TB	1	1	0.29 (0.04 – 2.04)
Person years (0-15 year olds)	2,152,543	7,505,253	

Note: cases with unknown BCG vaccination status were allocated to the vaccinated and non-vaccinated cohorts in proportion to the cases with known vaccination status.

An 1997 Irish study used data from the 1991 National Tuberculosis Survey to estimate the efficacy of BCG for preventing TB in Ireland.[86] The data specific to children aged less than 15 years suggests a risk ratio of 0.25, which is very similar to the more recent Irish data shown above. A more recent report based on the Cork outbreak of 2007 found 24% of the exposed children had been previously vaccinated with BCG, and no case of active disease was found in this group.[87] Due to the lack of numerator in the vaccinated group, a risk ratio could not be computed. Similarly, a report of a 1999 cluster of TB cases in secondary school children found no TB cases in the exposed children who had been vaccinated.[88]

The relevance of this data depends on whether they are representative of the population generally. TB cases in non-vaccinated individuals are dominated by Cork cases due to the large number of births and the long period with no universal vaccination programme in that county. An analysis of regional standardised incidence ratios found that the Cork City local health office areas had high rates of TB (see Chapter 3.1.3). This may bias the estimate towards greater vaccine efficacy.

The analysis presented here is intended to show that there is a risk of bias in the Irish data which is difficult to ascertain, and hence it may not provide an accurate estimate of the effectiveness of BCG vaccine.

4.6 Discussion

This chapter reviewed the evidence around the clinical effectiveness and safety of neonatal and infant BCG vaccination. In updating a recent systematic review no additional evidence was found. The review was restricted to randomised controlled

trials (RCTs) and case-control studies in which vaccination was given to infants less than one year old.

BCG vaccination is associated with substantial reductions in the risk of TB and TB mortality. The pooled estimates of RCT and case-control evidence suggest relative risks of 0.44 for pulmonary TB, 0.22 for extrapulmonary TB, 0.26 for TB meningitis, and 0.16 for TB mortality.

Data on the vaccinated and unvaccinated cohorts in Ireland gives indicative figures for vaccine effectiveness in Ireland. With the exception of pulmonary TB, the relative risks are similar to those estimated from the RCT evidence.

The RCT evidence corresponded to greater estimates of efficacy than the case-control studies. There is an association between vaccine efficacy and distance from the equator; three of the four RCTs were conducted in North America, the furthest from the equator of any of the studies. It is possible that this may partially explain the greater estimates of efficacy observed.

In terms of hierarchies of data sources, the highest ranked data on clinical effect should come from an appropriately conducted meta-analysis of RCTs with direct comparison between comparator therapies, measuring final outcomes.[89] Case-control and cohort studies are lower ranked and less preferable due to the greater risk of bias. The context of BCG vaccination is unusual in that the RCT evidence was largely published in the 1940s. Since then, methods for conducting RCTs have become more standardised with a greater recognition of best practice, and reporting has also improved. We cannot exclude the fact that the RCTs included in our study may be subject to a risk of bias. In the absence of clear evidence suggesting a change in vaccine efficacy over time, it is assumed that the efficacy estimated in the trials still holds, subject to the risk of bias. It is likely that the RCT data provides the best evidence regarding the efficacy of BCG in the Irish setting. The data on the vaccinated and unvaccinated cohorts in Ireland provides supplementary information that may inform a sensitivity analysis, but are also subject to a high risk of bias.

Although reactions to BCG vaccination are common, they tend to be mild. More severe reactions do occur and sometimes require surgical intervention. Different BCG vaccine strains may be associated with different rates of adverse reactions. The introduction of BCG-SSI for vaccination in Ireland was associated with an increase in adverse reactions. However, more virulent strains may also confer greater protection.

4.7 Key messages

- A systematic review was carried out to identify relevant studies of the efficacy of neonatal and infant BCG vaccination for the prevention of TB.
- Four randomised controlled trials (RCTs) and 10 case-control studies were included in the review. Three of the RCTs were published in the 1940s, and the most recent was published in 1976.
- The sample sizes of included studies were generally small and may have been underpowered to detect differences for rarer outcomes such as TB meningitis.
- Based on the RCT evidence, the relative risk of pulmonary TB in the vaccinated population is 0.40 (95% CI: 0.26 to 0.60). Inclusion of case-control data increases the relative risk to 0.44 (95% CI: 0.35 to 0.56).
- The relative risk of extrapulmonary TB in the vaccinated population is 0.14 (95% CI: 0.03 to 0.63) based on a single RCT study. The addition of six case-control studies increases the estimated relative risk to 0.22 (95% CI: 0.14 to 0.34).
- A single RCT estimated the relative risk of TB meningitis in the vaccinated population as 0.15 (95% CI: 0.01 to 2.87). The inclusion of data from seven case-control studies results in an increased relative risk estimate of 0.26 (95% CI: 0.17 to 0.41).
- Based on three RCTs, the relative risk of miliary TB in the vaccinated population is 0.08 (95% CI: 0.01 to 0.42). The addition of data from a case-control study resulted in a reduced relative risk estimate of 0.05 (95% CI: 0.01 to 0.22).
- Data on TB mortality was only available from four RCT studies. The estimated relative risk of TB mortality in the vaccinated population was 0.16 (95% CI: 0.05 to 0.51).
- There is limited evidence on the duration of effect, although it is estimated that the protective effect may last for up to 15 years.
- The rate of severe adverse reactions to BCG in Ireland is approximately 1 in 1,169 vaccinations. Severe reactions include lymphadenitis and suppuration, and may require medical intervention. In Ireland there has been a relatively high rate of disseminated BCG, with eight cases between 2005 and 2014. Disseminated BCG is associated with a very high mortality rate, although all eight cases between 2005 and 2014 survived.
- It is difficult to determine the applicability to Ireland of the BCG efficacy estimates. Available Irish data supports the estimates presented here although may point to a greater efficacy against pulmonary TB. The data obtained from the published RCTs represents the best available evidence and are likely to be broadly accurate for Ireland, given that they were predominantly carried out in North America.

5. Economic evaluation

This chapter reviews the existing evidence on the cost-effectiveness of BCG vaccination programmes and describes an economic model assessing the cost-effectiveness of a selective BCG vaccination programme in Ireland.

5.1 Review of published literature

A systematic review was carried out to assess the available evidence on cost-effectiveness for neonatal BCG vaccination programmes and to inform the economic analysis of BCG vaccination programmes in Ireland. Studies were included if they compared the costs and consequences of selective BCG vaccination to either universal vaccination or a programme of no vaccination. The review was carried out in accordance with national guidelines on the retrieval and interpretation of economic evaluations of health technologies.[90]

5.1.1 Search strategy

A search was carried out to identify published economic analyses of BCG vaccination programmes. In tandem with the systematic review of clinical effectiveness, the search for economic evaluations was carried out in MEDLINE, EMBASE, CINAHL, and the health technology assessment (HTA) database maintained by the National Health Service (NHS) Centre for Reviews and Dissemination.

A systematic review of economic evaluations of vaccination against TB was identified.[91] As the methodology used was acceptable it was considered appropriate to conduct an update of this review. The search strategy for more recent studies was therefore applied from August 2011 to the end of March 2015.

Studies were included if they evaluated either universal or selective infant BCG vaccination programmes for the prevention of TB. The BCG programme had to be compared either with another BCG programme or with no vaccination. Studies assessing revaccination, later childhood, adolescent or adult vaccination programmes were excluded. Studies investigating new vaccines were excluded unless they included two BCG programmes or a BCG programme and a no vaccination strategy.

5.1.2 Results

A total of five relevant studies were identified (see Table 5.1), four from the previously published systematic review[39;92-94] and one additional study from 2012.[95] The additional study was separately published as an abstract, in Slovakian and in English. We have used the English language publication in this review along with additional information available in the abstract. In the following section, costs

reflect those quoted in the original studies with 2014 Irish Euro equivalent prices reported in parentheses.

Table 5.1 Economic evaluations of infant BCG vaccination programmes

Author (year)	Country	Technology	Comparator	Evaluation type
Rahman (2001)[92]	Japan	Universal infant vaccination	No vaccination	CEA
Hersch (2003)[93]	Finland	Universal BCG	Selective and no vaccination	CEA
Trunz (2006)[39]	Global	Vaccination	No vaccination	CEA
Altes (2009)[94]	The Netherlands	Selective vaccination of high-risk infants	Vaccination of broader high-risk group	CEA
Marusakova (2012)[95]	Slovakia	Universal infant vaccination	Selective and no vaccination	CEA

Abbreviations: BCG - Bacille Calmette Guerin; CEA, cost-effectiveness analysis.

5.1.3 Overview of studies

The study by Rahman *et al.* evaluated universal infant vaccination compared with no vaccination in Japan.[92] The study estimated the cost and number of vaccinations required to prevent one case of TB. It was assumed that vaccination gave 10 years of protection and a wide range of vaccine efficacy values were used. Incidence of TB was known for vaccinated children and incidence for unvaccinated cases was determined by applying values for vaccine efficacy. Uptake was assumed to be 95%. There was no evidence of TB mortality; hence there was no estimation of life years gained. A discount rate of 5% was applied and the analysis was from the payer perspective. The cost per vaccination was approximately US$15 (€13.07) including both vaccine and administration. Treatment costs were not incorporated into the analysis, as the purpose was to derive a cost per case averted. It was calculated that between 2,125 and 10,399 vaccinations would be required to prevent one child from developing TB. The cost of preventing a case of TB ranged from US$35,950 (€31,317) to US$175,862 (€153,199). Although TB incidence in Japan is relatively high (18 per 100,000 in 2013), the figure is biased by the substantial elderly population; paediatric TB incidence in Japan is similar to other low incidence countries. The authors concluded that universal infant vaccination was not cost-effective. As of 2015, Japan continues to have a programme of universal infant vaccination.

A Finnish study compared universal vaccination with strategies of selective and no vaccination.[93] They developed a three state Markov model (healthy, infected with TB, infected with non-tuberculous mycobacteria), following a birth cohort for 15 years. The model was used to estimate the cost per case prevented. A discount rate of 3% was applied to costs and benefits and the study was undertaken from the perspective of the healthcare system. The cost of a vaccination was $2.45 (€2.73), including the cost of administration. A variety of selective vaccination strategies were evaluated based on subpopulations of increasing risk (ranging from twice to 50 times the risk experienced by the low risk group). BCG vaccination for those with at least twice the risk of the low risk population resulted in a cost of $7,146 (€7,969) per case averted. When BCG vaccination was restricted to those with at least a 25 times higher risk than the low risk population, it was cost saving compared with no vaccination. Selective vaccination was found to be less costly per case averted in all instances. The authors highlighted the challenges in identifying high-risk populations. Finland is considered a low TB incidence country, with 5.7 cases per 100,000 in 2013 and no recorded mortality. In 2006, Finland ceased universal vaccination and switched to a programme of selective vaccination.

Trunz *et al.* carried out an evaluation of BCG vaccination for the prevention of TB meningitis and miliary TB in children.[39] The study used estimated efficacy from meta-analyses and used different estimates for different regions of the world. Cost data was obtained from a small number of countries and then applied to all regions. Vaccine coverage was based on local country-specific data, and hence represented a mix of universal and selective strategies. The outcomes were expressed in terms of number of vaccinations per case prevented, cost per death prevented, and cost per disability-adjusted life years (DALY) gained. Vaccination was found to be most effective in Southeast Asia, Africa and the Western Pacific region. Vaccination was least effective in the established market economies, with 40,605 vaccinations per case of TB meningitis and 110,161 vaccinations per case of miliary TB averted. The costs per case or death prevented were US$101,628 (€103,822) for TB meningitis and US$275,646 (€281,597) for miliary TB averted in the established market economies. However, it was highlighted that the cost per DALY was less than the per-capita gross domestic product (GDP) in all regions, making BCG vaccination cost-effective.

A selective vaccination programme was in place in The Netherlands when Altes *et al.* evaluated the cost-effectiveness of expanding the definition of 'high-risk' to qualify for vaccination.[94] The definition had been based on first- and second-generation immigrant children from non-EU countries with a TB incidence of at least 50 per 100,000. The alternative policy was to extend the definition to include first- and second-generation immigrant children from Turkey, the former Yugoslavia and Surinam. The analysis used a static model to estimate vaccine efficacy and disease

risk, and focussed on severe TB (defined as TB meningitis and miliary TB) in 0 to 5 year old children. The study was conducted from the perspective of the publicly funded healthcare system and a discount rate of 1.5% was used for both costs and outcomes. Vaccination cost €5.86 (€6.81) per dose, including the cost of administration. The numbers needed to vaccinate to prevent one case of severe TB were 8,853 for the existing selective programme and 10,779 for the alternative expanded programme. The cost per case prevented was €69,496 (€80,788) and €84,615 (€98,363) for the existing and alternative programmes, respectively. The cost per DALY averted was €4,477 (€5,204) for the existing programme and €5,527 (€6,425) for the alternative programme. The authors concluded that the alternative programme would be considered cost-effective given a willingness-to-pay threshold of €20,000 per DALY. The Netherlands had a TB incidence of 6.1 per 100,000 in 2013, and an associated mortality rate of 0.03 per 100,000.

Slovakia is a low TB incidence country (7.7 cases per 100,000 in 2013) with a history of universal infant BCG vaccination until 2012, when obligatory vaccination was ceased. The evaluation compared universal vaccination with a policy of no vaccination. The analysis followed that of Rahman *et al.*,[92] but modelled the birth cohort to age 14 years rather than age 10 years. A discount rate of 5% was applied to costs and benefits. The cost of vaccination, €0.30 (€0.54) included only the cost of the vaccine itself with no administration cost. Vaccine efficacy was assumed to be 63.3%. The cost of preventing one case of TB was €784 (€1,403) less for universal vaccination than that for no vaccination. From the published abstract, an analysis of a selective programme was also evaluated, which would cost €440 (€787) less per case prevented than the no vaccination programme.[96] However, the criteria for high-risk were not defined and hence it is not clear what that selective programme described.

5.1.4 Quality of included studies

Modelled cost-effectiveness studies were assessed using the International Society For Pharmacoeconomics and Outcomes Research questionnaire to assess the relevance and credibility of modelling studies.[97] Relevance was assessed on the grounds of the study population, characteristics of the intervention, outcomes measured and the overall study context. The credibility of the results was considered using criteria related to the design, validation and analysis methods, the quality of the data used, as well as how the results were reported and interpreted and whether the authors had any conflicts of interest.

5.1.3 Applicability of the evidence

With the exception of the study by Trunz *et al.*,[39] which sought to determine the cost-effectiveness of BCG vaccination worldwide, the other studies evaluated

national programmes of infant BCG vaccination. Three of the four national studies report outcomes in terms of cost per case averted, with the Dutch study also reporting cost per DALY averted. In presenting the cost per case prevented, it is difficult to compare the cost-effectiveness of the modelled interventions with interventions for other diseases.

In evaluating the applicability of the studies to the Irish context, this document will focus on the four national studies, disregarding the global study as it does not model a tangible programme.

The Japanese study assumed a 10 year duration of vaccine effect, potentially underestimating the length of protective effect and benefits.[92] Results were presented as the cost of preventing one case of TB and the immunisations required to prevent one case of TB, but given for a range of vaccine efficacy estimates. Although treatment costs were not included, they did report an estimated average cost of treatment of €10,500 per case, well below the estimated cost of preventing one case. The absence of a selective programme to compare these figures with makes it difficult to determine if that would have represented a cost-effective alternative.

The study from Finland used a 15 year time horizon and a similar number of annual births to Ireland (60,000 compared with 68,000 in Ireland).[93] The reported incidence of TB in the 0-15 year old population was 0.56 per 100,000, compared with 0.74 per 100,000 in Ireland in 2014, the first time it was less than 1 per 100,000 in the paediatric population. There is no evidence to suggest that the childhood TB burden in Ireland is high in relation to other European countries.

The Dutch study focused on TB meningitis and miliary TB on the grounds that these are the most severe forms of TB.[94] The time horizon of the study was also very restricted, only following the cohort to age five. By excluding the most common forms of TB and ages at which the vaccine may still be efficacious, the study did not capture the full impact of BCG vaccination. However, the study did report a cost per DALY as an outcome and showed selective vaccination to be cost-effective in comparison with no vaccination. Interpretation of the outcome is difficult because of the aforementioned focus on TB meningitis and miliary TB. The costs of treating pulmonary and extrapulmonary TB were excluded from the analysis. Given that these forms of TB account for approximately 95% of cases, this significantly influences total costs. Inclusion of all vaccine costs, but not all of the benefits means that this study may have underestimated the cost-effectiveness of vaccination. Vaccination costs are incurred at the outset and are not affected by the discount rate, whereas benefits can occur many years in the future and so are sensitive to the discount rate. The study used a discount rate of 1.5%, well below the current Irish

rate of 5%. To illustrate the difference, preventing mortality in a newborn would result in 79 life years gained. When discounted at 1.5%, the New Zealand rate, 79 years reduces to 46.1 years. In comparison, a discount of 5%, the current discount rate in Ireland, 79 years reduces to 19.6 years. As such, the study findings will have overestimated the benefits relative to the discount rate that applied in Ireland. However, even if the benefits were halved, the cost per DALY would still be considered cost-effective.

The Slovakian study used a 15 year time horizon and did not include administration costs. It is probable that the study substantially underestimated the cost of delivering a BCG vaccination programme.

The national studies had varying estimates of costs. The Japanese study used costs of $15 (€13.07) for vaccination and $10,500 (€9,147) for treatment. In the Dutch study, vaccination costs were €5.86 (€6.81) and treatment costs were €5,033 (€5,851). The costs in the Finnish study were $2.45 (€2.73) for universal vaccination and $5.71 (€6.37) for selective vaccination, and $3,000 (€3,345) for TB treatment. The Finnish and Dutch studies used lower discount rates, although this is likely to have a greater impact in the Dutch study due to their reporting of benefits as DALYs.

The extent to which the findings are applicable to the Irish setting depends on whether the vaccination costs are similar to Ireland and the impact of using a different discount rate.

5.1.4 Conclusions

Few economic evaluations of neonatal BCG vaccination strategies have been carried out. The identified economic evaluations are quite heterogeneous in terms of the costs, time horizons, forms of TB included, and discount rates used. The latter is important as discounting can have a large impact on vaccination programmes, particularly those applied in early childhood that are expected to result in morbidity or mortality reductions over a person's lifetime.

The economic evaluations presented results in the form of cost or number of vaccinations per case averted. Treatment costs were not always included and only one presented a cost per disability-adjusted life year.

Given differences in healthcare delivery costs, baseline TB risk and discount rate, it is probable that the identified studies are not readily applicable to the Irish context.

5.2 Economic analysis

In the absence of applicable published cost-effectiveness evidence from another setting, an economic model was developed specific to the Irish setting. The analysis presented here expands on the work originally carried out by the National Centre for Pharmacoeconomics and the National Immunisation Advisory Committee.[1]

5.2.1 Description of the economic model

A decision analysis model was built to compare the costs and benefits associated with a selective BCG vaccination programme with the current universal BCG vaccination programme in Ireland. The objective of the economic evaluation was to aid decision making by estimating the incremental costs and benefits of selective BCG vaccination compared with those of the current situation and an alternative programme of no vaccination.

5.2.2 Study question

The study objective was to determine the cost-effectiveness and budget impact of a programme of selective neonatal BCG vaccination in Ireland, targeting high-risk infants.

5.2.3 Type of economic evaluation

A cost-effectiveness analysis was undertaken in which effectiveness was measured in terms of life years gained (LYG). A secondary cost-utility analysis was also used, with benefits measured as quality-adjusted life years (QALYs) gained for selective vaccination and compared across competing alternatives. A cost-utility analysis was specified as a secondary analysis due to the limited evidence available regarding quality of life in the context of this study.

5.2.4 Study perspective

Costs and benefits were assessed from the perspective of the publicly-funded health and social care system. Only direct costs were included. Indirect costs such as productivity losses associated with mortality and morbidity as a result of a TB infection were excluded.

National guidelines for the economic evaluation of health technologies in Ireland recommend that the perspective of the publicly-funded health and social care system in Ireland should be adopted when assessing costs.[98] For this intervention the majority of costs accrue to the health service, and hence it is appropriate to examine cost-effectiveness from the perspective of the publicly-funded health service only.

5.2.5 Technology

The technology being assessed is a selective neonatal BCG vaccination programme. The aim of the intervention is to reduce unnecessary vaccination of low risk infants who are unlikely to benefit from vaccination. See Chapter 2 for a more detailed description of the technology.

5.2.6 Choice of comparators

Two comparators were included in the evaluation: the current universal vaccination programme, and a programme of no vaccination. The current programme is referred to as universal, although it is acknowledged that there is regional variation in how the programme is implemented. The alternative of no vaccination was modelled to provide information of the relative benefit of selective vaccination. Although included in the analysis, a policy of no BCG vaccination is not considered a viable option as it affords no protection to infants at elevated risk of TB.

5.2.7 Target population

The target population of a universal vaccination strategy is all births in Ireland. For selective vaccination, BCG is only given to infants that are considered high-risk. For this evaluation, an infant is considered high-risk if the nationality of at least one of the parents is that of a high TB incidence country, or if the infant is from the Irish Traveller community. The target population constitutes approximately 13.4% of the annual birth cohort.

5.2.8 Time horizon

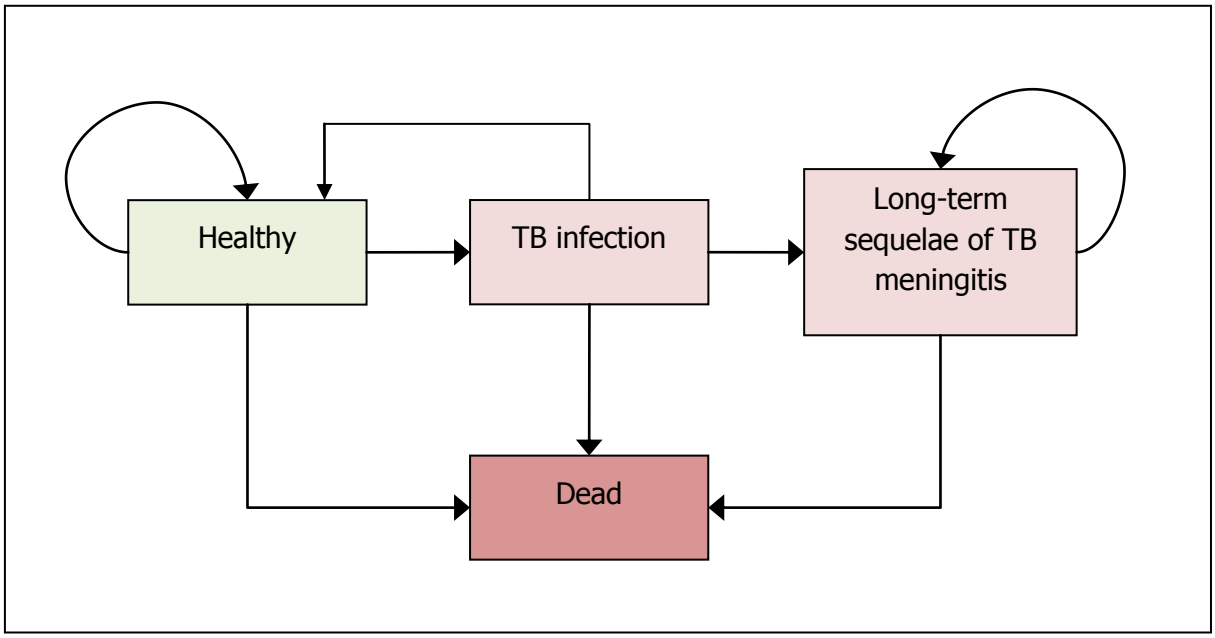
The total cost and clinical benefit for each of the BCG vaccination programmes was estimated by modelling one years' birth cohort from birth to life expectancy. The efficacy of BCG vaccination is assumed to last to age 15, after which there is no protective effect. The risk of TB is modelled to age 15 after which all survivors are assumed to live to life expectancy.

5.2.9 Outline of the model structure

A cost-effectiveness analysis of BCG vaccination strategies in Ireland was carried out previously by the National Centre for Pharmacoeconomics.[(1)] The model simulated a cohort from birth to age 15 and incorporated the risk of pulmonary TB, extrapulmonary TB and TB meningitis. The model structure was replicated and extended to include miliary TB. Parameter values were updated to reflect the latest available data and changes to the discount rate.

A Markov model structure with annual cycles was used with states for healthy individuals, those with TB, those with disability due to TB meningitis, and mortality (including TB deaths and all-cause mortality) (see Figure 5.1).

Figure 5.1 Model structure



The cohort was modelled from birth to life expectancy. TB risk and vaccine efficacy were modelled to age 15 years, after which all those alive were presumed to live to life expectancy. Quality-adjusted life years (QALYs) from age 16 to death were based on age-specific quality of life for a healthy population except for those with long-term sequelae of TB meningitis, who had an additional disutility applied to reflect the impact of disability.

The full model was developed in R 3.1.3[99] and validated using a basic model developed in Microsoft Excel 2010.

5.2.10 Model outputs

The outputs of the model included the number of TB cases, total costs, life years gained and QALYs for each of the three strategies modelled. Summary measures included the incremental cost-effectiveness ratio, and plots of the cost-effectiveness plane, cost-effectiveness acceptability curve, and the expected value of perfect information.

The incremental cost-effectiveness ratio (ICER) presents the additional costs divided by the additional benefits of one intervention relative to another. The ICER is typically considered in the context of a willingness-to-pay threshold, which

represents the maximum a decision maker is willing to pay for a unit benefit, such as a life year gained or a quality-adjusted life year.

Cost-effectiveness acceptability curves (CEACs) are used as a method for summarising information on uncertainty in cost-effectiveness. A CEAC shows the probability that an intervention is cost-effective compared with the modelled alternatives for a range of willingness-to-pay thresholds.[100]

The expected value of perfect information (EVPI) represents the amount a decision maker should be willing to pay to eliminate uncertainty about which intervention is the best option.[101] As with the CEAC, the EVPI is calculated for a range of willingness-to-pay thresholds. The EVPI is an evaluation of how much the decision maker should be prepared to pay for perfect information.

In previous evaluations, willingness-to-pay thresholds of between €20,000 and €45,000 per QALY have typically been used as reference points. Willingness-to-pay thresholds above €250,000 per life year gained were not evaluated in this study.

5.2.11 Sensitivity analysis

A probabilistic model was used that explicitly takes into account the uncertainty in the model parameters. All of the key parameters were varied within plausible ranges of values. Where possible, ranges were derived from published evidence. If published evidence was limited or unavailable, plausible ranges were derived with the support of the Expert Advisory Group. As the structure of the economic model presented here is inherently stochastic, the outputs are equivalent to a multivariate probabilistic sensitivity analysis.

Univariate, or one-way, sensitivity analysis facilitates examination of the impact of each variable in the study by varying it across a plausible range of values while holding all other variables constant at their 'best estimate' or baseline value. The resulting difference provides some indication of how sensitive the results might be to plausible changes in that parameter. Deterministic sensitivity analysis was used to examine this, where each parameter in turn was fixed at its upper and lower confidence bounds while all the other parameters are held at their average value. Any correlations between parameters were taken into account in the sensitivity analysis.

Scenario analyses were also used to look specifically at the impact of a number of key assumptions in relation to parameter values. In each analysis, one or more parameters were set at alternative and potentially justifiable point estimates.

5.2.13 Budget impact analysis

The budget impact analysis was conducted from the perspective of the publicly-funded health and social care system. The analysis reports the annual cost of the modelled BCG vaccination programmes. As with the cost-effectiveness analysis, indirect costs due to productivity losses associated with primary TB cases were not included. Costs used in the budget impact analysis were the same as those used in the economic analysis. A budget impact analysis is inclusive of value-added tax (VAT) where applicable.[102] VAT applies to non-oral medications and to equipment when calculating amortised capital costs. In this study, the standard VAT rate was applied to the BCG vaccine. No other significant costs that would be subject to VAT were identified.

5.3 Model parameters

The economic model required a range of input parameters that describe the cost of BCG vaccination programmes, risk of contracting TB, the efficacy of BCG vaccination, outcomes in terms of survival and disability, treatment costs, and ongoing costs associated with disability.

The overall benefits and costs of competing BCG vaccination programmes were calculated by performing 10,000 model simulations. Randomly sampled individual parameter values were used in each simulation. Summarising across iterations provides an estimate of overall average costs and benefits, as well as the uncertainty associated with these values.

5.3.1 Discount rate

Discounting reflects a societal preference for benefits to be realised in the present and costs to be experienced in the future. Discounting facilitates comparison between costs and benefits that occur at different times. Costs and benefits were discounted at the rate of 5% as set out by the Department of Finance.[98] The discount rate was fixed in the main analysis and varied from 1.5% to 6% in a univariate sensitivity analysis to illustrate the impact of discounting.

5.3.2 Epidemiological measures

A variety of epidemiological parameters were required to model the incidence of TB, efficacy of BCG vaccination, and outcomes for those with TB.

The incidence of TB in the unvaccinated population was determined using TB notification data from 2005 to 2014 (inclusive) for individuals aged less than 16 years. The denominator population was estimated using data on BCG vaccine uptake by region.[103] Three of the 31 local health office areas had not provided BCG uptake

data; in these cases uptake was estimated by expert opinion. TB incidence is highest for pulmonary TB and lowest for miliary TB (see Table 5.2). Given that the incidence of TB has been in decline over the period 2005 to 2014, it is likely that the rates overestimate the current incidence of TB. However, multiple years of data were required due to the rare nature of TB meningitis and miliary TB, and the fact that this data was based on the unvaccinated population only.

Table 5.2 Annual rate of TB per 100,000 in the unvaccinated population (2005 – 2014)

Age	Pulmonary TB	Extrapulmonary TB	TB meningitis	Miliary TB
0	2.3474	0.7825	0.0008	0.0008
1	1.4900	0.7450	0.7425	0.0007
2	14.0714	3.5612	0.0007	0.0007
3	7.7232	1.3780	0.0007	0.0007
4	1.1847	2.0230	0.0007	0.0007
5	0.6650	1.3301	0.0007	0.0007
6	2.0872	1.1516	0.0007	0.0007
7	0.7089	1.5950	0.7065	0.0007
8	0.9125	1.1231	0.0007	0.0007
9	0.7479	0.1870	0.0007	0.0007
10	0.9403	3.0560	0.0008	0.0008
11	1.5363	1.5680	0.0008	0.7722
12	3.4156	1.6382	0.8010	0.0008
13	2.2499	0.4823	0.0008	0.0008
14	4.2147	4.8494	0.0008	0.0008
15	5.6547	2.4654	0.4840	0.0008

Abbreviations: TB - tuberculosis.

TB incidence in the vaccinated population is calculated by applying the relative risk of TB as determined from the meta-analysis of published trials of BCG vaccine efficacy (see Chapter 4.3). The data on TB incidence in unvaccinated children includes a number of outbreaks (as can be seen from the elevated rates for pulmonary and extrapulmonary TB at two years of age). By applying the same relative risk to all ages, elevated rates in certain age bands will be replicated in the vaccinated group, albeit as a reduced rate. An alternative approach to estimate TB incidence, as used in the Japanese economic evaluation, would be to estimate the incidence in the vaccinated population and then apply the relative risk of TB in unvaccinated children.[92] However, that approach may fail to generate the spikes in cases at specific ages that are a feature of the unvaccinated population.

The size of the birth cohort was based on the number of live births in 2013 which presents the best estimate of the eligible population for a universal vaccination

programme.[36] The proportion of births classified as high-risk was estimated in Chapter 3.4, combining data on parental nationality recorded in the National Perinatal Reporting System and data from the 2011 Census on the number of Irish Travellers under the age of one year. It is acknowledged that this is a pragmatic definition and may represent an undercount of the true high-risk population.

National vaccine uptake by local health office was obtained from the Health Protection Surveillance Centre.[103] It was assumed that the uptake in the high-risk population would be lower than in the general population. Although some studies have reported similar or higher uptake after switching from universal to selective vaccination,[104;105] lower uptake figures in the region of 50% have been reported in single institution studies.[106] Data from six studies was combined to generate a summary estimate of uptake of 76% in the high-risk population.[104-109] To acknowledge the uncertainty regarding the evidence, the distribution around the uptake in high-risk infants was wide to allow for the possibility of a low uptake and to explore the impact this would have on cost-effectiveness. To ensure consistency with the overall uptake rate, a lower uptake rate in the high-risk population implies a higher uptake in the low risk population, and vice versa.

The rate of adverse events receiving medical or surgical follow-up was determined using Health Products Regulatory Authority data on reported events as described in Chapter 4.4.2 on vaccine safety. The adverse event rate (excluding disseminated BCG) was estimated at 1 in every 1,363 infants vaccinated. The rate of disseminated BCG was 1 in 82,779 infants vaccinated, reflecting the eight confirmed cases in 10 years. The mortality rate for disseminated BCG was estimated at 28.8% based on a study across 17 countries of BCG vaccination in people with severe combined immunodeficiency disease (SCID).[74] Recorded cases of confirmed disseminated BCG in Ireland have mainly occurred in infants with SCID, and so the mortality rate in those with SCID was assumed to be representative.[73] The mortality rate was estimated from a study that collected data from 17 countries. Thirty four percent of the cases in the study came from high resource nations with similar health care systems to Ireland.

One of the eight confirmed cases of disseminated BCG was in an Irish Traveller. Given that travellers represent approximately 1.3% of births, it was estimated that the risk ratio for disseminated BCG in Irish Travellers was 11.45, possibly reflecting a higher rate of primary immunedeficiency syndromes in Irish Travellers. There have been no deaths among children in Ireland with disseminated BCG in the last 10 years, and hence the figure used in this study may over-estimate mortality due to disseminated BCG.

The high-risk population has an higher risk of TB than the general population. Using TB notification data from 2005 to 2014 it was determined that the high-risk population has a relative risk of 4.38 compared with the low risk population, or 3.02 relative to the population as a whole (95% CI: 2.35 to 3.89). The confidence bounds are relatively narrow which reflects the large size of the denominator data: the figures were estimated using 10 years' of notification data and hence incorporated multiple birth cohorts. Risk status was determined using the reported nationality or ethnicity of cases.

The efficacy of BCG vaccine in reducing the incidence of TB was estimated using a meta-analysis of clinical trials as described in Chapter 4.3. The evidence from the randomised controlled trials was determined to be at least risk of bias, and was used in the model. It was assumed that vaccine efficacy would not extend beyond age 15 years for a cohort vaccinated at birth.[40;64] A meta-regression as part of the meta-analysis that incorporated study latitude predicted that the relative risk of pulmonary TB might be lower than estimated in the unadjusted meta-analysis. The figures reported differ from the meta-analysis results as they reflect the average of the log normal distribution rather than the point estimate. A scenario analysis was used to explore the impact of using an alternative relative risk.

TB incidence data was based on TB notifications from 2005 to 2014. During that period there were no recorded TB-related deaths in children aged less than 16 years in Ireland. Data from the UK suggests a case-fatality rate of 0.8% in children aged less than 15 years.[110] However, based on WHO data the TB mortality rate for all ages in the UK is approximately 1.43 times that in Ireland.[16] In the absence of Irish specific data, the UK data was determined to be applicable. As the UK data may overestimate the case-fatality rate, a scenario analysis was used to evaluate the impact of a reduced rate.

TB meningitis is associated with an increased risk of long-term sequelae, or chronic complications, such as hearing and focal deficits, and learning difficulties. Most studies of meningitis outcomes are not specific to TB meningitis, and may therefore not be representative of outcomes of TB meningitis.[111] Improvements to TB meningitis therapy also mean that the results of older studies may no longer be applicable.[112] A recent systematic review of outcomes of childhood tuberculous meningitis estimated the proportion of survivors with neurological sequelae as 53.9%.[30] Analysis of the studies included in this meta-analysis by Chiang *et al.* made it possible to differentiate between moderate and severe sequelae.[113-115] Moderate sequelae typically included hemiparesis, mild intellectual impairment, impaired vision, and impaired hearing. The term 'moderate' must be understood in the context of a condition with a high probability of mortality. Severe sequelae included quadriparesis, severe intellectual impairment, blindness, and deafness. No

good quality evidence could be found regarding long-term sequelae associated with other forms of TB. The estimates come from a range of countries where case identification and appropriate treatment may be less timely than would be the case in Ireland. The estimate of the proportion of survivors with severe sequelae may therefore be an overestimate.

Life expectancy and all cause mortality rates were derived by single year of age and sex from the Irish life tables.[116] The proportion of cases that were male was estimated from TB notification data. This data was used to weight the life expectancy that was applied to deaths in order to calculate life years lost.

Utilities were estimated for healthy individuals, vaccine-related adverse events, TB treatment, and for long-term sequelae associated with TB meningitis. Utilities by single year of age for a healthy population were derived from the Health Survey for England data.[117] It is assumed that this data is applicable to the Irish population.

It was assumed that vaccination-related adverse events resulting in hospital treatment would incur, on average, a disutility for affected infants. In the absence of direct evidence, it was assumed that for infants with severe adverse events their quality of life would be 0.95 of its normal value. This is equivalent to five weeks with a disutility of 0.5 and the remainder of the year with no disutility. While most reported adverse reactions may be resolved relatively quickly, the estimate takes into account that some reactions may be very severe. The disutility of TB treatment was evaluated in two studies, one of which was a systematic review.[118;119] The disutility is greatest during the initial treatment phase and it is assumed that the patients return to a normal healthy quality of life on completion of treatment. It was assumed that an average disutility of 0.1 would apply for the year during which the patient was in treatment for TB. The disutility was adjusted to account for treatment lasting less than one year on average. The same treatment disutility was applied to all forms of TB.

Due to the heterogeneous nature of long-term sequelae associated with TB meningitis, some studies have determined utilities associated with each outcome.[120] Due to the lack of data on specific sequelae, a simple dichotomy between moderate and severe sequelae was used. The disutility used in a Swiss evaluation of vaccination strategies against meningococcal and pneumococcal diseases were based on expert opinion.[121] Comparison of the mean disutility from the Swiss study[121] with the weighted mean disutility from the Belgian HTA[120] of meningococcal serogroup B childhood vaccination produce similar estimates of disutility. It was therefore assumed that the disutilities for moderate and severe sequelae of meningitis were applicable to TB meningitis.

Full details of the distributions used for the parameter values are provided in Appendix 3.

Table 5.3 Epidemiological parameters

Parameter	Point estimate	95% bounds
Size of birth cohort	68,990	(67,030 to 70,950)
Proportion births classified as high-risk	0.134	(0.131 to 0.136)
Vaccine uptake in all births (proportion)	0.878	(0.875 to 0.880)
Vaccine uptake in high-risk births (proportion)	0.762	(0.591 to 0.897)
Rate of severe vaccination-related adverse events	0.0007	(0.0005 to 0.0010)
Rate of disseminated BCG	$1.2x10^{-5}$	($7.8x10^{-8}$ to $5.2x10^{-5}$)
Mortality rate for disseminated BCG	0.288	(0.220 to 0.360)
Proportion births that are Irish Travellers	0.0134	(0.0126 to 0.0144)
Risk ratio of disseminated BCG in Irish Travellers	11.45	(5.81 to 18.99)
TB risk for high-risk individuals (relative to average risk)	3.04	(2.34 to 3.89)
Efficacy of BCG vaccination		
Pulmonary TB (relative risk)	0.406	(0.263 to 0.600)
Extrapulmonary TB (relative risk)	0.189	(0.032 to 0.626)
TB meningitis (relative risk)	0.465	(0.008 to 2.872)
Miliary TB (relative risk)	0.111	(0.014 to 0.420)
Mortality associated with TB (relative risk)	0.195	(0.053 to 0.512)
Case-fatality rate	0.008	(0.005 to 0.011)
Proportion of TB cases in males	0.48	(0.397 to 0.572)
Proportion meningitis cases with sequelae	0.539	(0.479 to 0.790)
Proportion meningitis sequelae classified as severe	0.394	(0.202 to 0.606)
Disutility for vaccine-related adverse events	0.95	(0.900 to 0.983)
Disutility associated with treatment	0.90	(0.834 to 0.950)
Disutility for moderate sequelae of TB meningitis	0.80	(0.717 to 0.872)
Disutility of severe sequelae of TB meningitis	0.60	(0.503 to 0.693)

Abbreviations: TB, tuberculosis; BCG, Bacille-Calmette Guerin.

5.3.3 Estimates of cost

Costs were associated with delivery of the vaccination programme, treatments costs, and follow-up costs.

The delivery of the vaccination programme includes the cost of both the vaccine and its administration. The vaccine cost for universal neonatal vaccination was taken as a percentage of the total cost of BCG vaccine in Ireland. Based on national data, it was assumed that between 80 and 90% of vaccinations delivered per annum are given

as part of the neonatal vaccination programme.[122] Based on a mean value of 85%, the current cost of BCG vaccine for universal vaccination is approximately €166,000 per annum. BCG vaccine is provided in vials of 20 doses, although in practice there is substantial wastage. Once open, the vial must be used in one session. If only a small number of infants present at a session then most of the vial contents may go unused. Even with large clinics, it is estimated that the rate of use for a 20-dose vial will not exceed 80%.[123] Moving from universal to selective vaccination will reduce the target population for vaccination and could potentially increase vial wastage. This would increase the cost of vaccination per-infant. It was assumed that the vial utilisation would be approximately 35% of the value for universal vaccination. This assumption was based on an analysis of the data published in a US study.[123] Assuming that Irish clinics for selective vaccination would typically have an attendance rate 13.4% of universal vaccination, the vaccine cost per vaccinated infant would increase from an average of €2.74 to €7.77.

Aside from the vaccine cost, there is also the cost associated with the staff required to deliver the vaccination programme. The neonatal BCG vaccination programme is primarily delivered through dedicated BCG clinics, with approximately 30% of vaccinations in 2012 administered in a hospital setting.[122] National data on the staff resources required for delivering the current universal BCG vaccination programme was collected by the Health Protection division of the HSE.[122] Data was collected by staff in local health offices and provided an estimate of whole time equivalents for medical (senior area medical officer), nursing (public health nurse) and administrative staff (clerical officer grade). Two local health offices reported values that were approximately three standard deviations greater than the average. These were considered outliers and were therefore omitted from the analysis. The delivery of 60,919 BCG vaccinations required 7.2, 7.0 and 6.3 whole time equivalents for medical, nursing and administrative staff, respectively. The estimated average staff cost was €26.02 per vaccination. Staff costs included adjustments for pay related social insurance (PRSI), pension contributions and overheads, in accordance with national guidelines.[98]

Although a selective programme would have a target population of only 13.4% of the universal cohort, in order to achieve a similar coverage the new programme would not result in a corresponding reduction in clinics. It was assumed that a selective programme would, on average, incur approximately double the cost due to reduced efficiency.

No costs associated with identification of high-risk infants were included in the analysis. It was assumed that risk status could be determined from existing resources, such as maternity hospital records.

The costs of treatment, contact tracing, and treatment for latent TB infection were all adapted from costs used in the study by the National Centre for Pharmacoeconomics.[1] Where relevant, costs were updated either using the most recent data available or by applying the consumer price index for health to reflect inflation (see Appendix D).

The costs associated with moderate and severe long-term sequelae of TB meningitis were derived from a Canadian economic evaluation.[124] The weighted summary annual cost across all sequelae was similar to the cost across all sequelae in an Italian study.[125] Both studies evaluated the meningococcal serogroup B childhood vaccine MenB. Costs were applied annually and assumed to continue to life expectancy for survivors with long-term sequelae.

All costs were varied by ±20% to reflect uncertainty in the point estimates. Full details of the costs and distributions used are provided in Appendix D.

Table 5.4 Cost parameters

Parameter	Point estimate (€)	(95% bounds)
Vaccination programme:		
Annual vaccine cost (selective programme)	55,060	(28,849 to 101,395)
Annual vaccine cost (universal programme)	164,604	(151,705 to 178,327)
Selective vaccine administration (per child)	52.04	(40.58 to 65.53)
Universal vaccine administration (per child)	26.02	(21.28 to 31.50)
Average treatment cost for vaccination-related adverse events (per case)	2,895	(2,380 to 3,522)
Treatment costs (per case):		
Pulmonary TB	8,354	(6,833 to 10,112)
Extrapulmonary TB	12,606	(10,310 to 15,259)
TB meningitis	18,736	(15,324 to 22,679)
Miliary TB	12,922	(10,569 to 15,642)
Follow-up costs (per case):		
Contact tracing	5,124	(4,192 to 6,203)
Diagnosis and treatment of latent TB	4,691	(3,837 to 5,679)
Annual cost of moderate TB meningitis sequelae	1,881	(1,539 to 2,277)
Annual cost of severe TB meningitis sequelae	12,599	(10,305 to 15,250)

Abbreviations: TB, tuberculosis. Data based on 2015 prices.

5.4 Results of the economic analysis

Stable estimates were obtained within 2,000 simulations, although the results presented here are based on the full 10,000 simulations.

5.4.1 Vaccination programme

Under the current programme of universal vaccination there are an estimated 60,580 vaccinations in a birth cohort of 68,990 infants (Table 5.5). The introduction of a selective vaccination programme would result in 7,048 vaccinations in the birth cohort (95% CI: 5,446 to 8,324). The confidence bounds reflect uncertainty in both the size of the target population and the likely uptake rate for vaccination.

Table 5.5 Number of vaccinations in birth cohort by strategy

Strategy	Number of vaccinations	
	Mean	(95% CI)
No vaccination	-	-
Selective vaccination	7,048	(5,446 – 8,324)
Universal vaccination	60,580	(58,836 – 62,296)

Abbreviations: CI, confidence interval.

5.4.2 Risk of TB disease

Based on the epidemiological data used in the model, the absolute risk of developing TB disease could be estimated (Table 5.6). The risks are expressed as the risk of a child developing TB disease or dying from TB before age 16 years. For example, one in 5,500 vaccinated low-risk children will have had TB by the time they are 16 years old.

Table 5.6 Risk of TB disease and mortality before age 16 years

Population group	Outcome	
	TB disease	TB mortality*
Vaccinated low-risk	1 in 5,500	1 in 300,000
Non-vaccinated low-risk	1 in 1,800	1 in 230,000
Vaccinated high-risk	1 in 1,200	1 in 110,000
Non-vaccinated high-risk	1 in 400	1 in 51,000

Note: the risks tabulated above are based on TB incidence data from 2005 to 2014.
* TB mortality is based on UK data as there were no deaths from TB among 0 to 15 year olds in Ireland in the years 2005 to 2014.

The estimated absolute risk of TB provided in Table 5.6 must be considered in the context of the decline in TB incidence. Based on TB incidence over the most recent

three years of data, the absolute risks are approximately half those reported in Table 5.6. In other words, based on the most recent data the risk of TB disease vaccinated low-risk children by the time they are 16 years old has declined from 1 in 5,500 to 1 in 11,000.

5.4.3 Incidence of TB

In the absence of any other changes to TB control, the number of cases of TB in 0 to 15 year olds was estimated to be higher for strategies of no vaccination and selective vaccination when compared to universal vaccination (Table 5.7). The largest proportionate increase would be in cases of miliary TB, and the lowest increase in pulmonary TB. However, in absolute terms, the largest increase was predicted to occur in cases of pulmonary TB. Strategies of selective and no vaccination would lead to an increase in cases of TB in the birth cohort compared with universal vaccination. A strategy of selective vaccination would see an additional 19.9 cases in the birth cohort and no vaccination an additional 31.5 cases compared with universal vaccination (24.4 cases).

A policy of no vaccination was estimated to result in the highest mortality. Universal vaccination will result in the lowest mortality. Mortality in universal vaccination is primarily due to very severe reactions to BCG, whereas for selective vaccination it is predominantly due to TB-related mortality. There is a probability of 0.58 that universal vaccination results in greater mortality from BCG complications than from TB. The equivalent probability for selective vaccination is 0.016.

Table 5.7 TB cases in single birth cohort by vaccination strategy

Type of TB	No vaccination		Selective		Universal	
	Cases	95% CI	Cases	95% CI	Cases	95% CI
Pulmonary	34.3	(26.4 - 43.2)	28.0	(21.1 - 35.8)	17.2	(11.6 - 24.5)
Extrapulmonary	19.2	(13.4 - 25.9)	14.3	(9.6 – 20.2)	6.0	(2.9 - 13.2)
TB meningitis	1.9	(0.5 - 4.2)	1.6	(0.3 – 3.9)	1.0	(0.1 - 5.1)
Miliary	0.5	(0.0 – 1.9)	0.4	(0.0 - 1.4)	0.1	(0 - 0.5)
Total cases	55.9	(45.8 – 67.1)	44.3	(35.1 – 54.8)	24.4	(16.7 – 35.5)
TB deaths	0.44	(0.28 – 0.64)	0.31	(0.19 – 0.46)	0.09	(0.05 – 0.16)
BCG deaths	-	-	0.05	(0.00 – 0.25)	0.21	(0.00 – 0.91)
Total deaths	0.44	(0.28 – 0.64)	0.37	(0.22 – 0.59)	0.30	(0.07 – 1.01)

Note: discounting not applied. Abbreviations: TB, tuberculosis; CI, confidence interval. Extrapulmonary TB does not include TB meningitis and miliary TB.

The mortality from TB for the vaccination strategies should be viewed in relation to deaths avoided relative to having no vaccination programme. In other words, universal vaccination was estimated to reduce TB mortality by 0.35 but result in 0.21

deaths from BCG-related adverse reactions (Table 5.8). There was a probability of 0.21 that universal vaccination will result in more BCG-related deaths than the number of TB deaths it prevented. Selective vaccination had a smaller impact on reducing TB mortality but also had lower BCG-related mortality than universal vaccination. For selective vaccination, there was a probability of 0.128 that BCG-related mortality exceeds TB-related mortality.

Table 5.8 Mortality differences by vaccination strategy

Vaccination strategy	TB deaths avoided	Deaths associated with BCG	Probability BCG mortality exceeds TB mortality
No vaccination	0	0	0
Selective	0.127	0.055	0.128
Universal	0.345	0.212	0.211

Abbreviations: TB, tuberculosis.

5.4.4 Cases prevented by vaccination

Relative to a policy of no vaccination, the number of vaccinations per case prevented was 638 for selective vaccination and 1,993 for universal vaccination.

The mean cost of the vaccination programmes (including vaccine, administration, and cost of treating adverse reactions) was €437,907 for selective and €1,872,208 for universal vaccination. Relative to no vaccination, the mean number of cases avoided per birth cohort was 11.6 for selective and 31.5 for universal vaccination. The undiscounted cost per case prevented excluding any TB treatment costs was €37,653 for selective vaccination, and €59,379 for universal vaccination.

5.4.5 Life years gained (LYG)

The strategies of selective and no vaccination have lower total costs than universal vaccination, and selective vaccination had a greater number of life years gained. Universal vaccination is therefore dominated by (is more expensive and less effective than) strategies of selective and no vaccination. The incremental cost-effectiveness ratio (ICER) for selective relative to no vaccination is €340,520 per life year gained (LYG). Selective vaccination would not be considered cost-effective relative to no vaccination under willingness-to-pay thresholds in the range of €20,000 to €45,000 per LYG.

Universal vaccination results in fewer LYG than selective vaccination despite generating less overall mortality. This is due to the combination of when mortality

occurs in each strategy and the effect of discounting. Selective vaccination results in less mortality from disseminated BCG which occurs in the first year of life, whereas TB mortality can occur up to age 15 years. Mortality in younger children results in greater life years lost than mortality in older children.

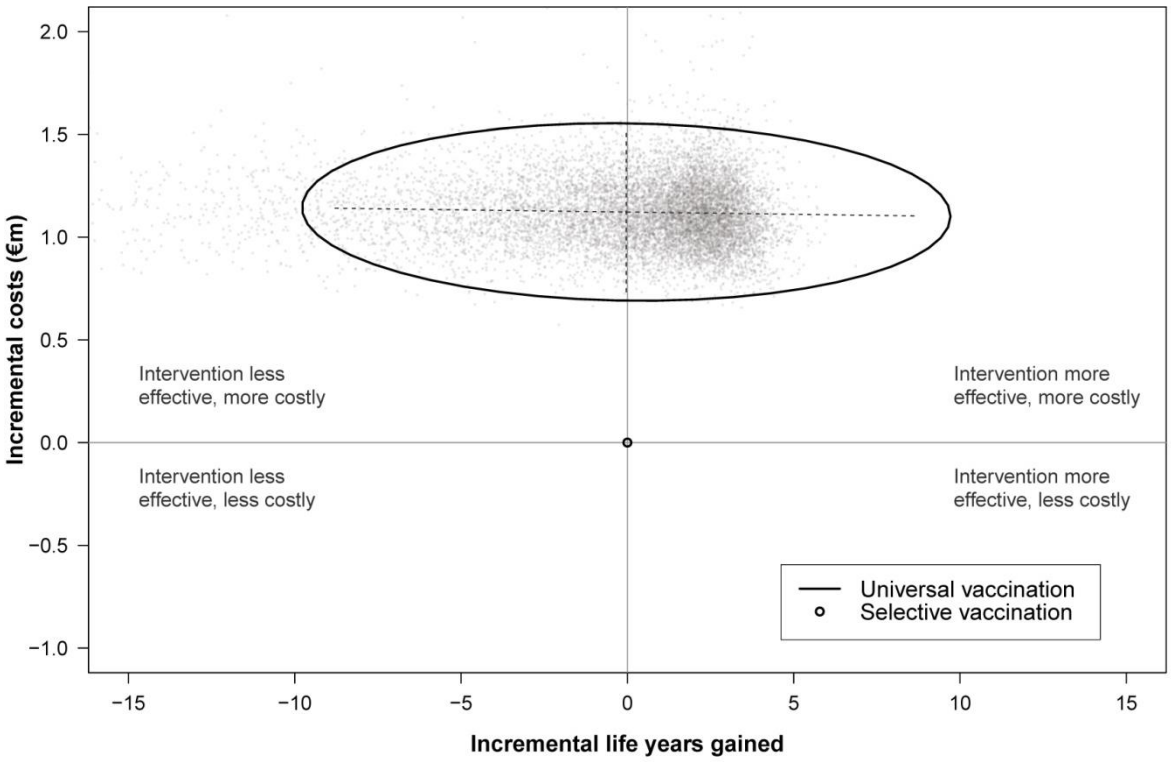
Table 5.9 Cost-effectiveness results based on life years gained

Vaccination strategy	Cost		Life years		ICER (€/LYG)
	Total	Incremental	Total	Incremental	
No vaccination	€890,319		1,418,213.5		
Selective	€1,145,709	€255,390	1,418,214.3	0.75	340,520
Universal	€2,267,631	€1,121,922	1,418,214.3	-0.03	Dominated

Abbreviations: LYG, life years gained; ICER, incremental cost-effectiveness ratio.

Selective vaccination was, on average, estimated to be more effective than universal vaccination. However, due to the skewed distribution of effectiveness, selective vaccination resulted in more life years gained than universal vaccination in only 35% of simulations. The difference in effect between universal and selective vaccination had a strong negative correlation with the rate of disseminated BCG. In other words, if the rate of disseminated BCG was assumed to be less than what was observed between 2005 and 2014, then universal vaccination was highly likely to be more effective than selective vaccination in terms of life years gained. Universal vaccination was the most costly and no vaccination the least costly strategy in all simulations.

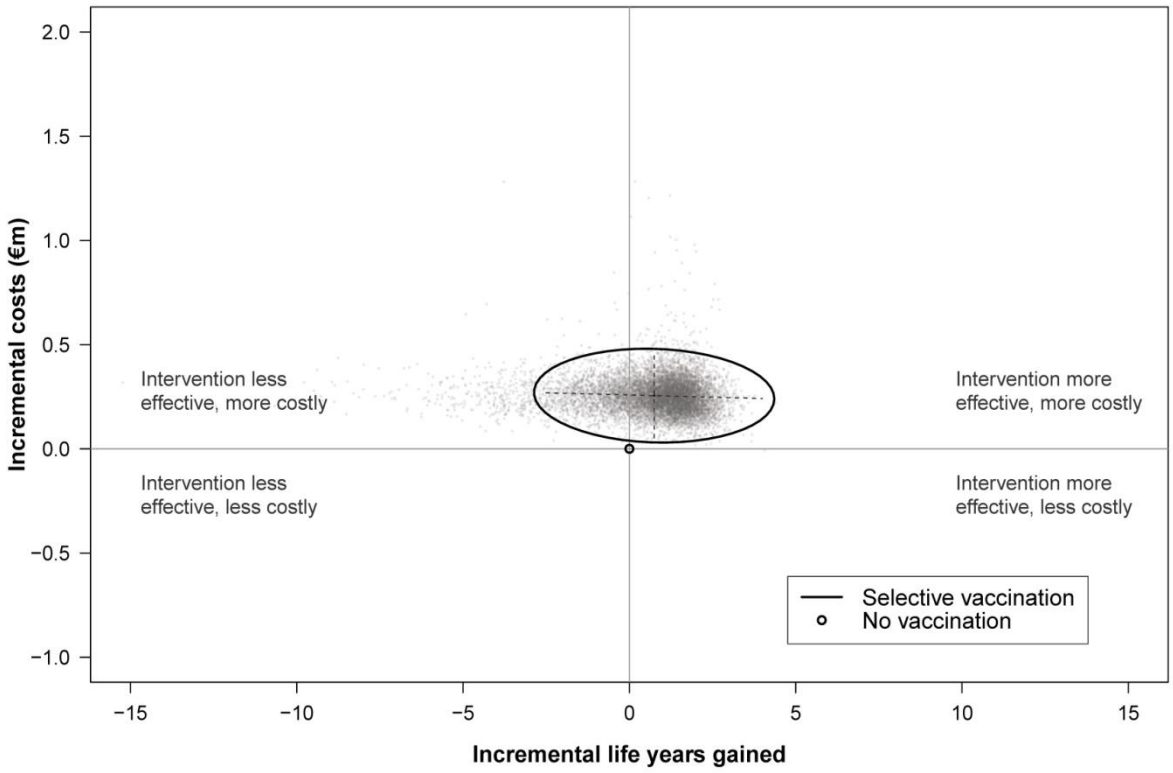
Figure 5.2 Cost-effectiveness plane (life years gained, universal vaccination relative to selective vaccination)



Abbreviation: LYG, life year gained.

Selective vaccination was estimated to result in more life years gained than no vaccination in 79% of simulations (Figure 5.3).

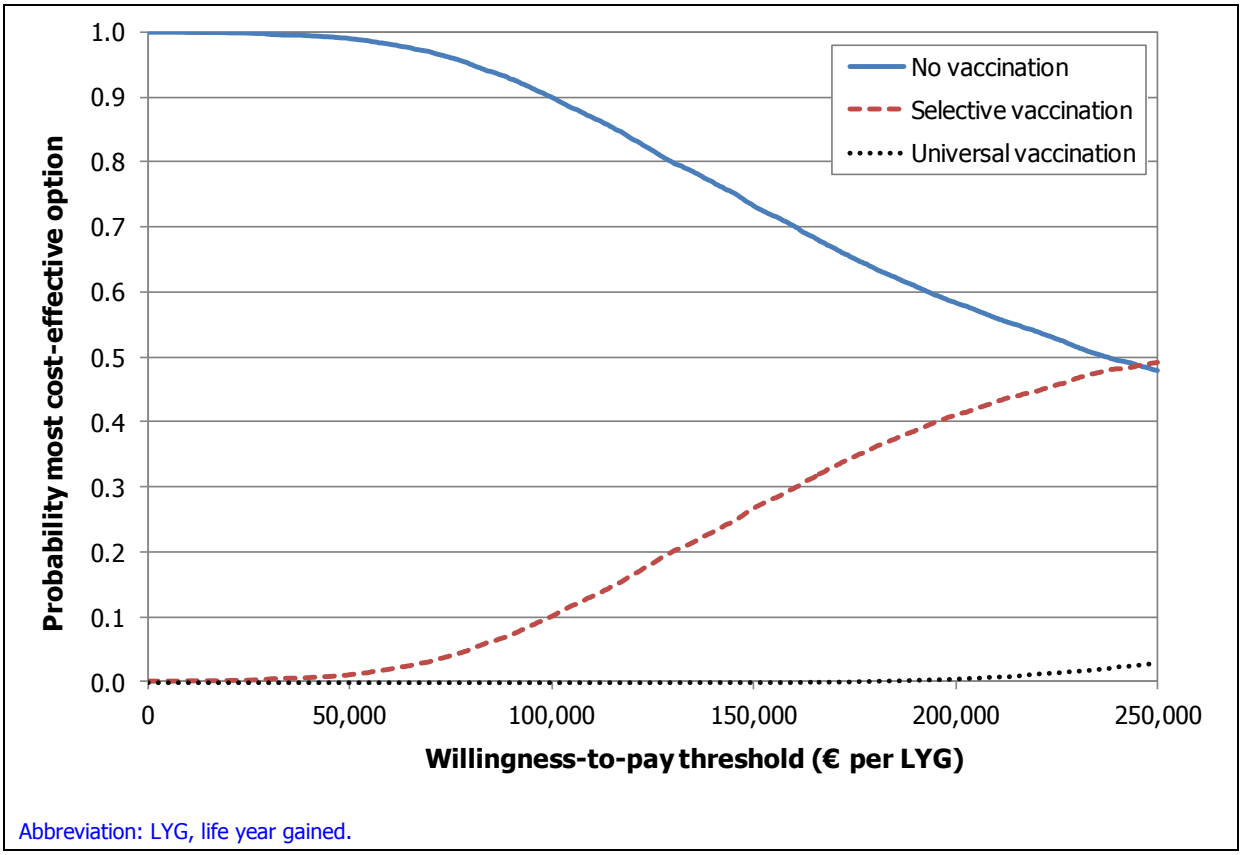
Figure 5.3 Cost-effectiveness plane (life years gained, selective vaccination relative to no vaccination)



Abbreviation: LYG, life year gained.

Up to a willingness-to-pay threshold of €245,000 per life year gained, a strategy of no vaccination has the highest probability of being the most cost-effective option (Figure 5.4). The probability of selective vaccination being the most cost-effective option at thresholds of €20,000 and €45,000 per life year gained was 0.001 and 0.007, respectively. It is highly unlikely that selective vaccination would be considered cost-effective compared with no vaccination. The equivalent probabilities for universal vaccination were both zero.

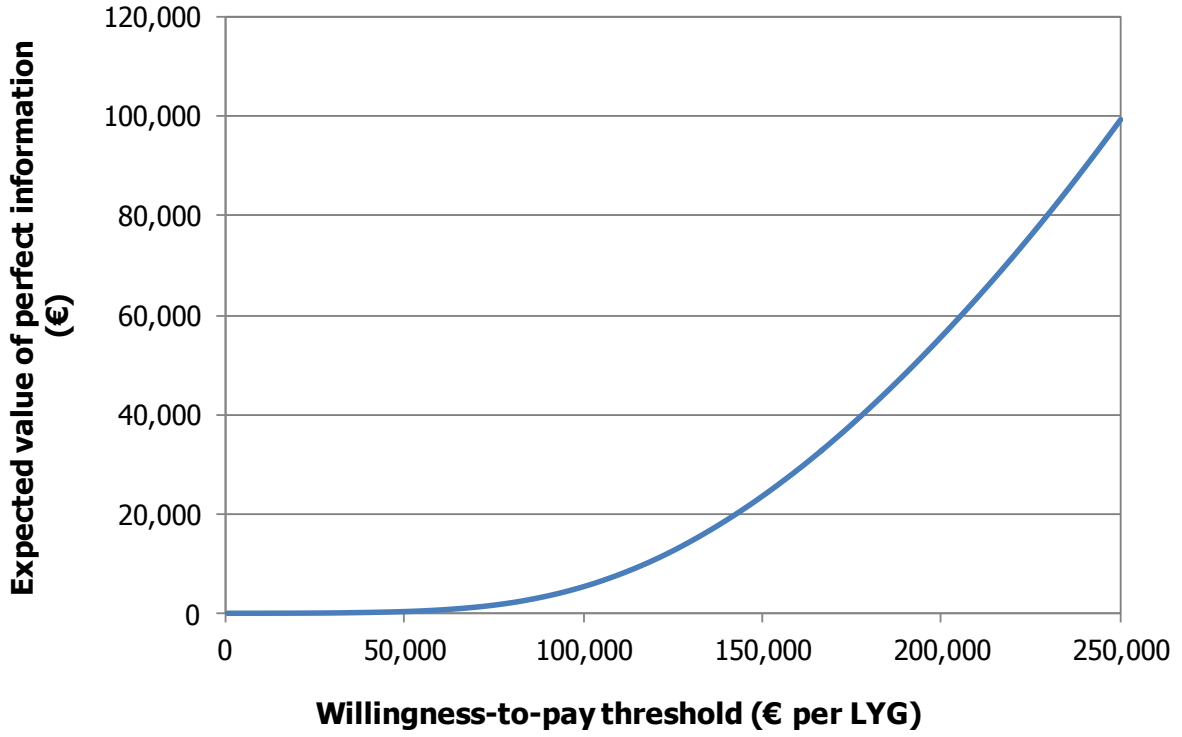
Figure 5.4 Cost-effectiveness acceptability curve (life years gained)



Abbreviation: LYG, life year gained.

Corresponding to the cost-effectiveness acceptability curve, the expected value of perfect information is low for willingness-to-pay thresholds below €100,000 per LYG, and then rises gradually to a value of €99,506 at a willingness-to-pay threshold of €250,000 per LYG (Figure 5.5). At lower willingness-to-pay thresholds, the expected value of perfect information is low because of the very high probability that no vaccination is the most cost-effective strategy.

Figure 5.5 Expected value of perfect information (life years gained)



Abbreviation: LYG, life year gained.

5.4.6 Quality-adjusted life years gained (QALYs)

The strategy of universal vaccination was the most effective and no vaccination the least effective option in terms of QALYs (Table 5.10). The ICER for selective relative to no vaccination was €139,557 per QALY and the ICER for universal relative to selective vaccination was €2,549,822 per QALY. Universal and selective vaccination programmes would therefore not be considered cost-effective.

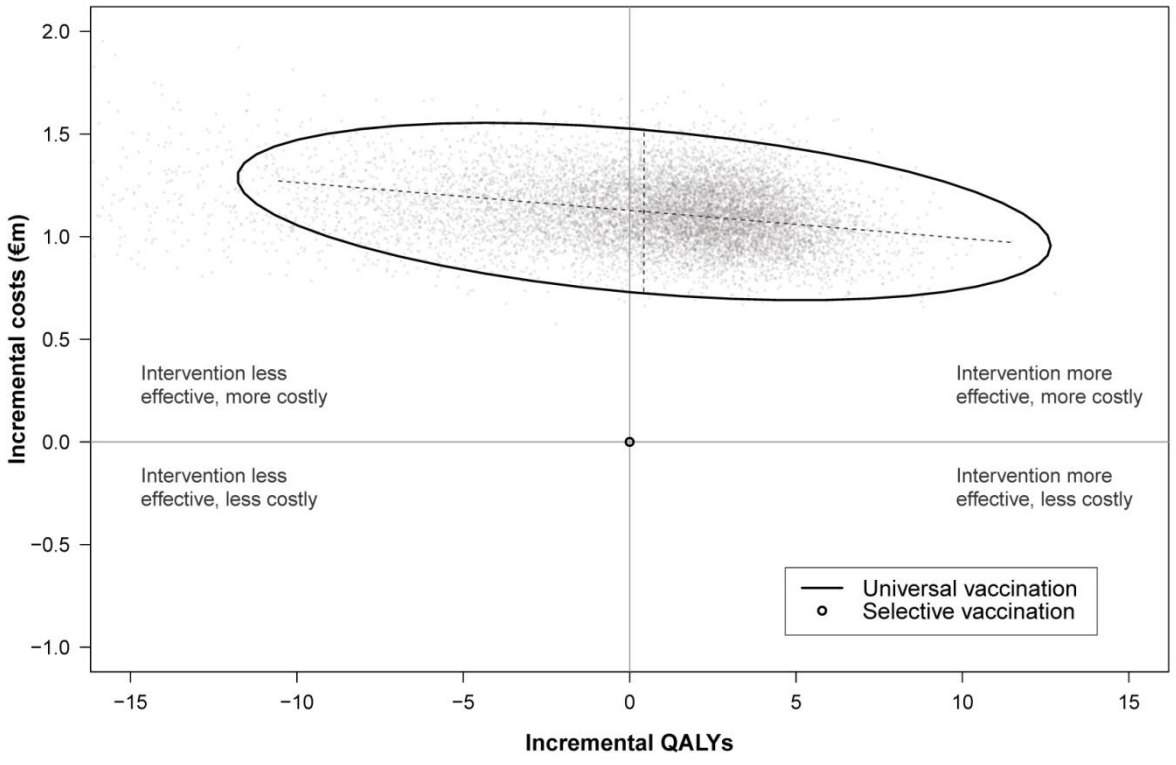
Table 5.10 Cost-effectiveness results based on QALYs

Vaccination strategy	Cost		QALYs		ICER
	Total	Incremental	Total	Incremental	(€/QALY)
No vaccination	€890,319		1,340,381.9		
Selective	€1,145,709	€255,390	1,340,383.7	1.83	139,557
Universal	€2,267,631	€1,121,922	1,340,384.2	0.44	2,549,822

Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.

Based on the model, universal vaccination resulted in more QALYs than selective vaccination in 66% of simulations, although the mean incremental difference was only 0.44 QALYs (Figure 5.6). A programme of no vaccination was more effective than universal vaccination in 25% of simulations.

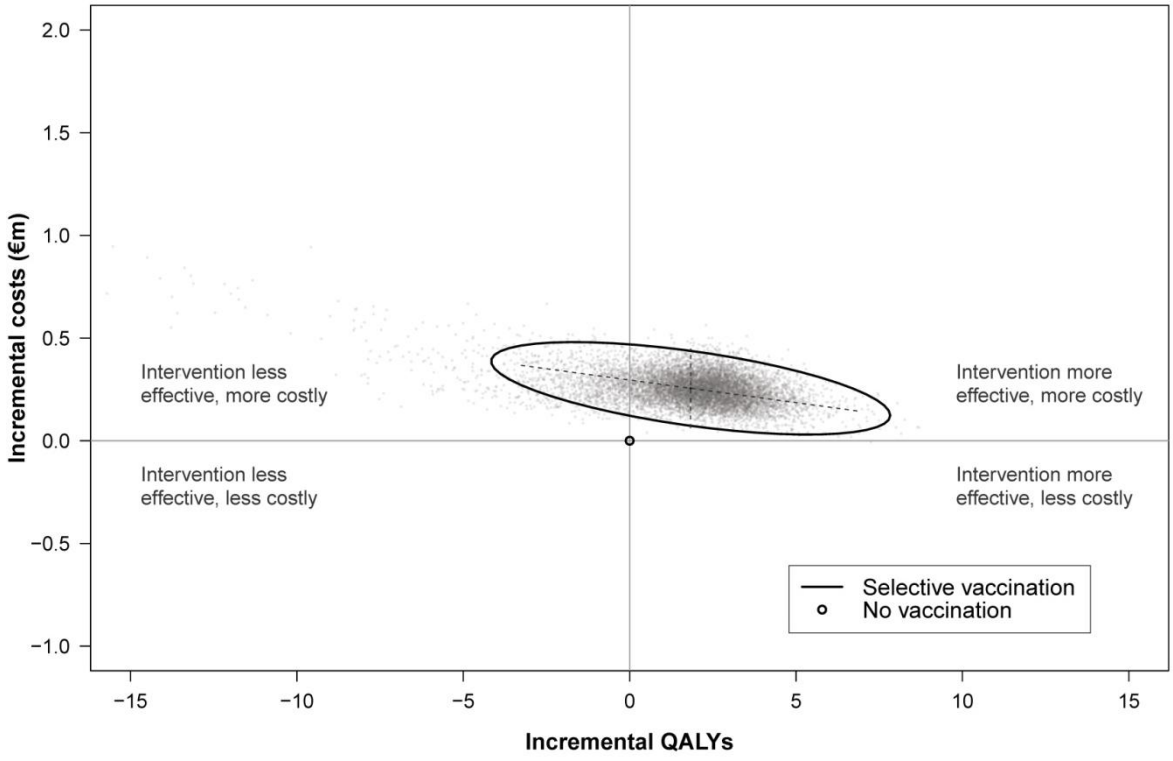
Figure 5.6 Cost-effectiveness plane (quality-adjusted life years, universal vaccination relative to selective vaccination)



Abbreviation: QALY, quality-adjusted life year.

Selective vaccination was estimated to result in more QALYs than no vaccination in 88% of simulations (Figure 5.7).

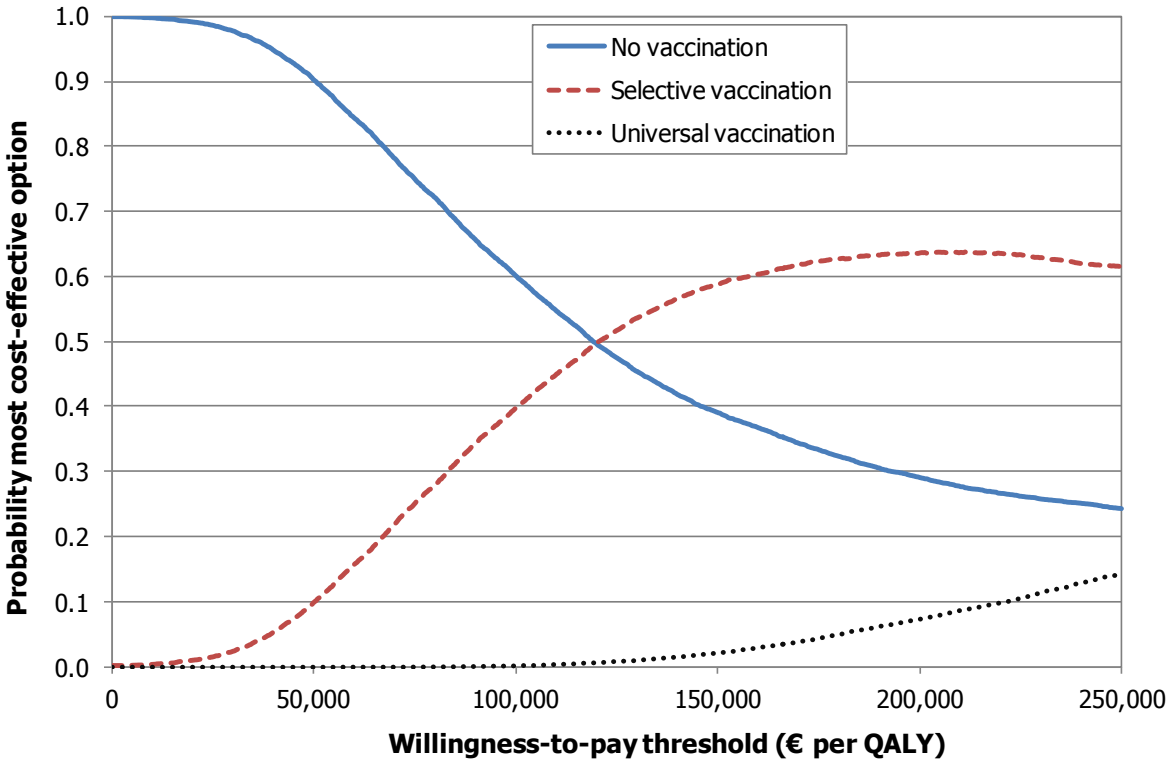
Figure 5.7 Cost-effectiveness plane (quality-adjusted life years, selective relative to no vaccination)



Abbreviation: QALY, quality-adjusted life year.

Up to a willingness-to-pay threshold of €120,000 per QALY, a strategy of no vaccination has the highest probability of being the most cost-effective option (Figure 5.8). The probability of selective vaccination being the most cost-effective option at thresholds of €20,000 and €45,000 per life year gained was 0.008 and 0.07, respectively. At both thresholds the probability of universal vaccination being the most cost-effective option was zero.

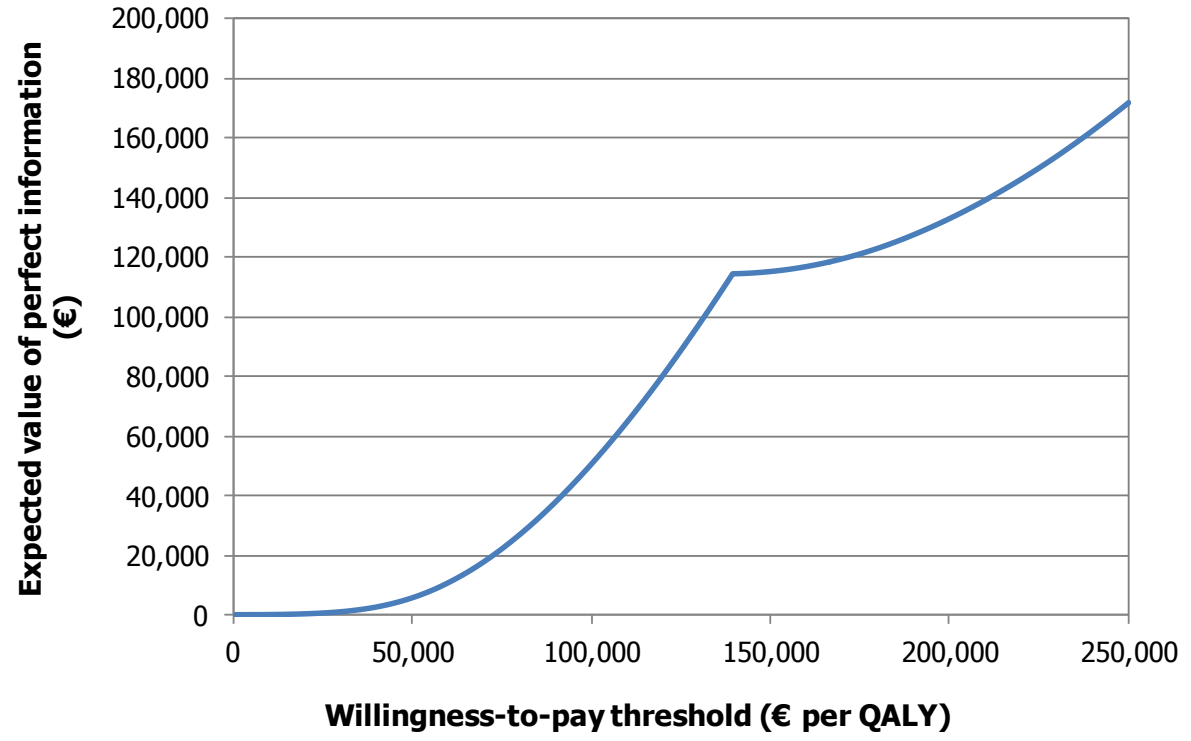
Figure 5.8 Cost-effectiveness acceptability curve (quality-adjusted life years)



Abbreviation: QALY, quality-adjusted life year.

The expected value of perfect information is low for willingness-to-pay thresholds below €50,000 per QALY, and then rises to peak of €114,114 corresponding to a willingness-to-pay threshold of €139,250 per QALY (Figure 5.9). At a willingness-to-pay threshold of €45,000 per QALY, the expected value of perfect information is €3,997.

Figure 5.9 Expected value of perfect information (quality-adjusted life years)



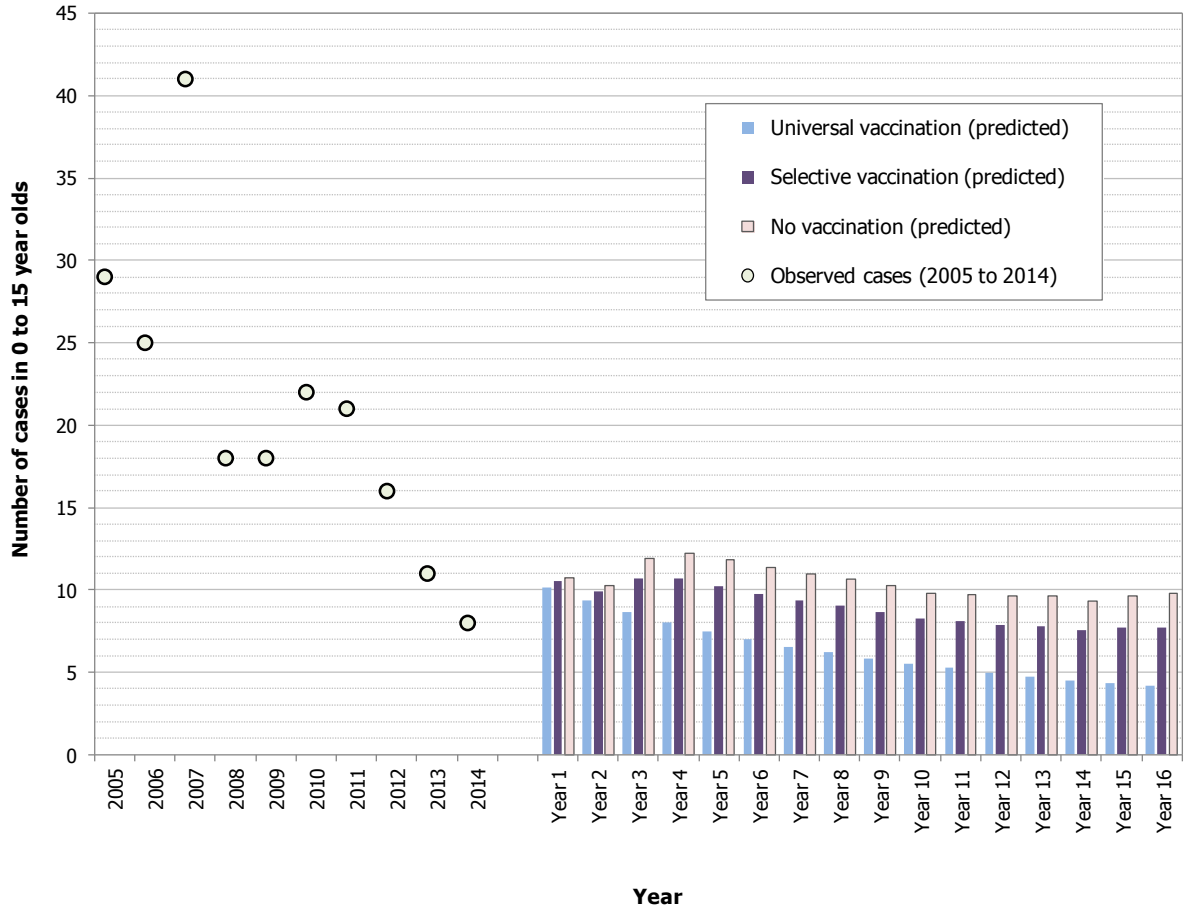
Abbreviation: QALY, quality-adjusted life year.

5.4.7 Prediction of future TB cases and TB mortality in 0 to 15 year olds

The results of the cost-effectiveness analysis estimate the impact of different BCG vaccination strategies on a birth cohort using the average TB risk calculated from 2005 to 2014 data. If the vaccination programme is changed then the impact will be more gradual as the unvaccinated proportion of the child population increases over time. For example, in the first year after discontinuing universal vaccination, reduced vaccine coverage will only affect infants aged less than one year. The number of TB cases per annum was predicted relative to the expected number of cases per annum under universal vaccination. This also took into account the trend for decreasing numbers of childhood TB cases (Figure 5.10).

It was assumed that TB incidence will be similar to 2015 levels when a change in vaccination programme is implemented. It is estimated that TB cases under selective vaccination would reach a maximum of 10.7 cases three years after introduction, relative to 8.0 cases under universal vaccination at the same point in time. It is predicted that after 16 years, selective vaccination would result in an additional 3.6 cases (95% CI: 0.3 to 4.2) of childhood TB per annum relative to universal vaccination. At the same point, a programme of no vaccination would result in an additional 5.7 cases (95% CI: 0.5 to 6.7) of childhood TB per annum.

Figure 5.10 Predicted number of TB cases in 0 to 15 year olds per annum by vaccination strategy



Abbreviations: TB, tuberculosis.

The predicted mortality would be lowest for no vaccination and highest for universal vaccination, as most children would still be protected against TB but vaccinated children would still be exposed to the risk of very severe adverse reactions. Average mortality would be relatively stable for universal (0.25 cases per annum in year one to 0.23 cases in year 16) and selective (0.10 cases per annum in year one to 0.11 cases per annum in year 16). Annual mortality for a policy of no vaccination would increase from 0.04 cases in year one to 0.08 cases by year three, and remain stable thereafter. The analysis is based on estimated cases taking the current rate of TB into account, so the effectiveness (and balance of benefits to harms) of vaccination is lower than estimated in the base-case analysis.

5.4.8 Budget impact analysis

The annual budget impact was estimated based on the cost of vaccination, treatment for TB and costs associated with long-term sequelae of TB meningitis (Table 5.11). The annual budget impact of selective and no vaccination strategies will be €1,053,971 and €1,267,548 less, respectively, than the current policy of universal vaccination. The annual budget impact of no vaccination is €213,577 less than for the selective vaccination strategy.

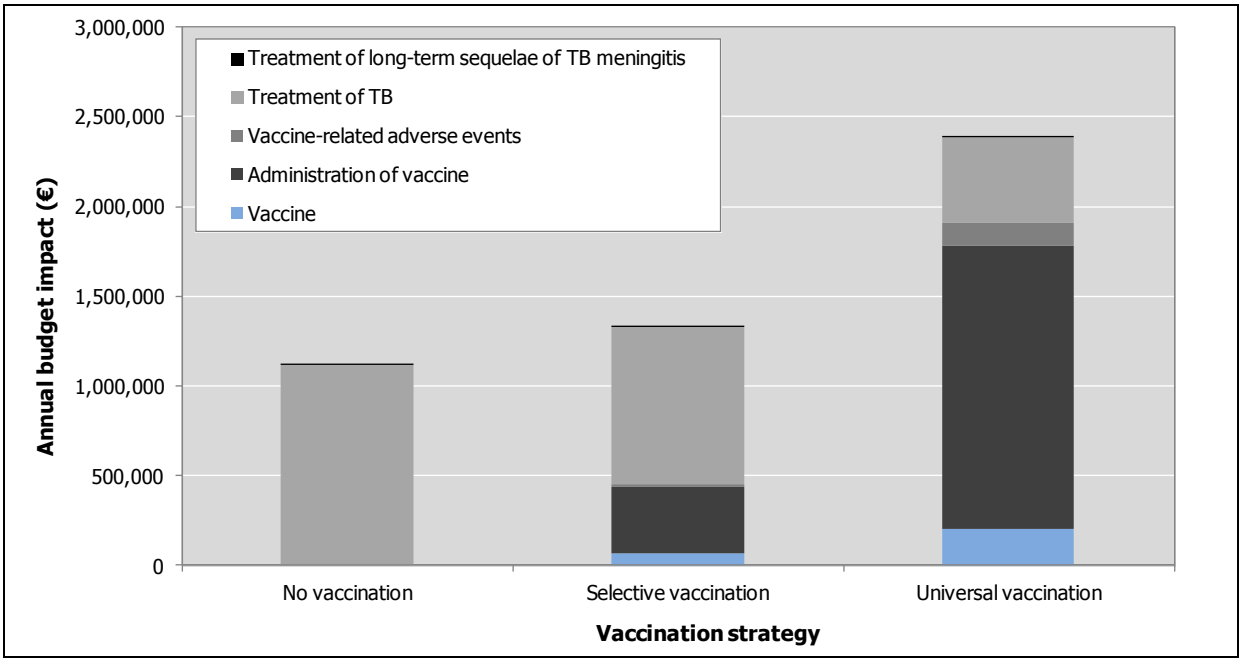
Eighty percent of the cost of universal vaccination is due to the vaccination programme, with the remaining 20% associated with the treatment of TB and long-term sequelae of TB meningitis. More significantly, 66% of the budget impact of the universal programme is the cost of administering the vaccine. In a selective programme, 34% of the budget impact arises from the vaccination programme and 27% is due specifically to the cost of administering the vaccine. In a programme of no vaccination, all of the budget impact is due to the treatment of TB and long-term sequelae. Treatment of TB includes the cost of contact tracing and treatment for latent TB.

Table 5.11 Annual budget impact of vaccination strategies

Item	Vaccination strategy		
	No vaccination	Selective	Universal
Vaccine (€)	0	67,826	202,518
Administering the vaccine* (€)	0	367,820	1,579,129
Vaccine-related adverse events (€)	0	14,941	128,424
Treatment of TB (€)	1,119,638	883,645	479,881
Treatment of long-term sequelae of TB meningitis (€)	6,149	5,132	3,383
Total (€)	1,125,787	1,339,364	2,393,335
Incremental (relative to universal) (€)	-1,267,548	-1,053,971	-

* The cost of administering is based on staff resources and does not include identification of high-risk infants.

Figure 5.11 Predicted annual budget impact of vaccination strategies



The staffing requirements vary by vaccination strategy. Contact tracing is on the basis of an average of 9.4 contacts being screened per index case.

Table 5.12 Staffing requirements (whole time equivalents) for different vaccination strategies

Grade	No vaccination		Selective		Universal	
	Administer vaccine	Contact tracing	Administer vaccine	Contact tracing	Administer vaccine	Contact tracing
Director of Public Health	-	0.07	-	0.06	-	0.03
Specialist in Public Health Medicine	-	0.28	-	0.22	-	0.12
Area medical officer (senior)	-	1.05	1.66	0.83	7.14	0.46
Medical scientist (senior)	-	0.03	-	0.03	-	0.02
Public health nurse	-	0.28	1.62	0.22	6.98	0.12
Clerical officer grade	-	0.56	1.45	0.44	6.25	0.24

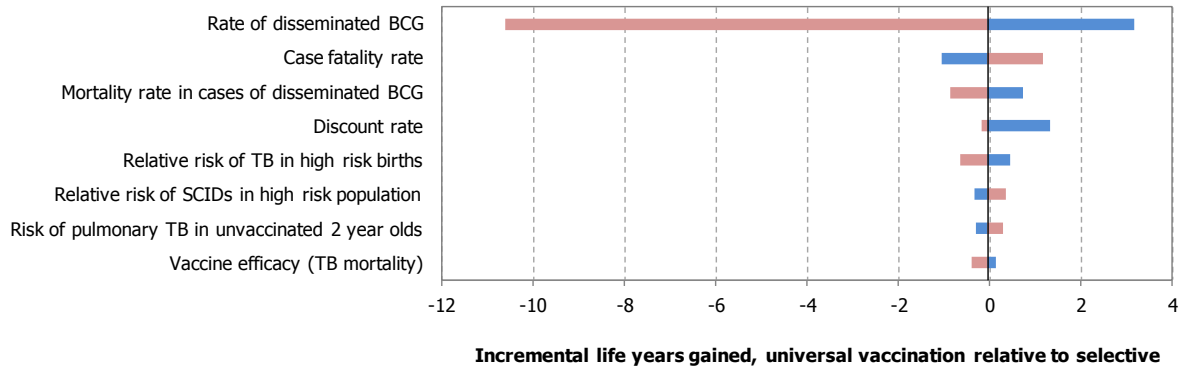
5.5 Sensitivity analysis

A univariate sensitivity analysis was used to assess how sensitive the results were to fluctuations in each parameter. Given the uncertainty around the parameters themselves, the sensitivity analysis shows how that translates into uncertainty about the results.

5.5.1 Life years gained

Universal vaccination was, on average, less effective than selective vaccination in terms of LYG. However, the mean difference in effect was small and varying a number of parameters resulted in universal vaccination being more effective than a selective programme (Figure 5.12). The most marked effect was associated with the rate of disseminated BCG, followed by the case-fatality rate, the mortality rate in disseminated BCG, and the discount rate. The analysis underlines the substantial uncertainty regarding the difference in effect between universal and selective vaccination programmes.

Figure 5.12 Tornado plot of incremental life years gained for universal relative to selective vaccination



Note: All parameters were varied in the analysis. For legibility, only parameters that, when varied, resulted in a fluctuation of at least 0.2 in the incremental life years gained are included in the tornado plot. Red bars correspond to a parameter set at its upper bound, blues bars to the lower bound.

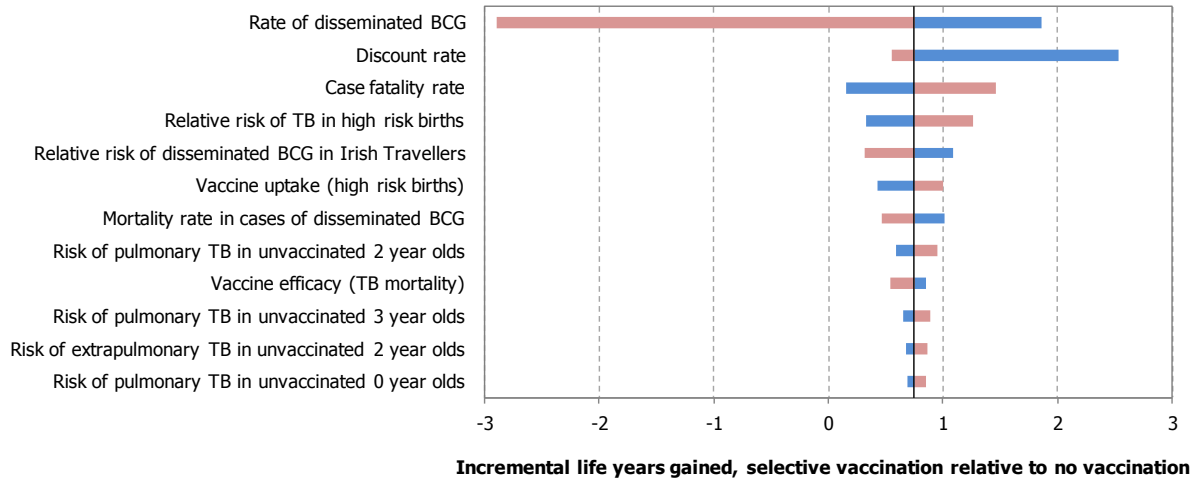
Abbreviations: BCG, Bacillus Calmette-Guérin; TB, tuberculosis.

Varying the rate of disseminated BCG in vaccinated infants had a substantial impact on the estimated life years gained. When the rate was set at its upper bound, selective vaccination generated fewer life years gained than a programme of no vaccination. Although not varied in the main analysis, setting the discount rate at 1.5% and 6% had the largest impact on estimates of the incremental life years gained (Figure 5.13). The next most important parameter was the case-fatality rate, followed by the relative risk of TB in high-risk births. In both cases, an increase in

the parameter value resulted in an increase in the incremental benefit of selective vaccination.

The rate of disseminated BCG was the only parameter for which setting parameter estimates at the bounds resulted in selective vaccination generating fewer life years gained than no vaccination.

Figure 5.13 Tornado plot of incremental life years gained for selective relative to no vaccination



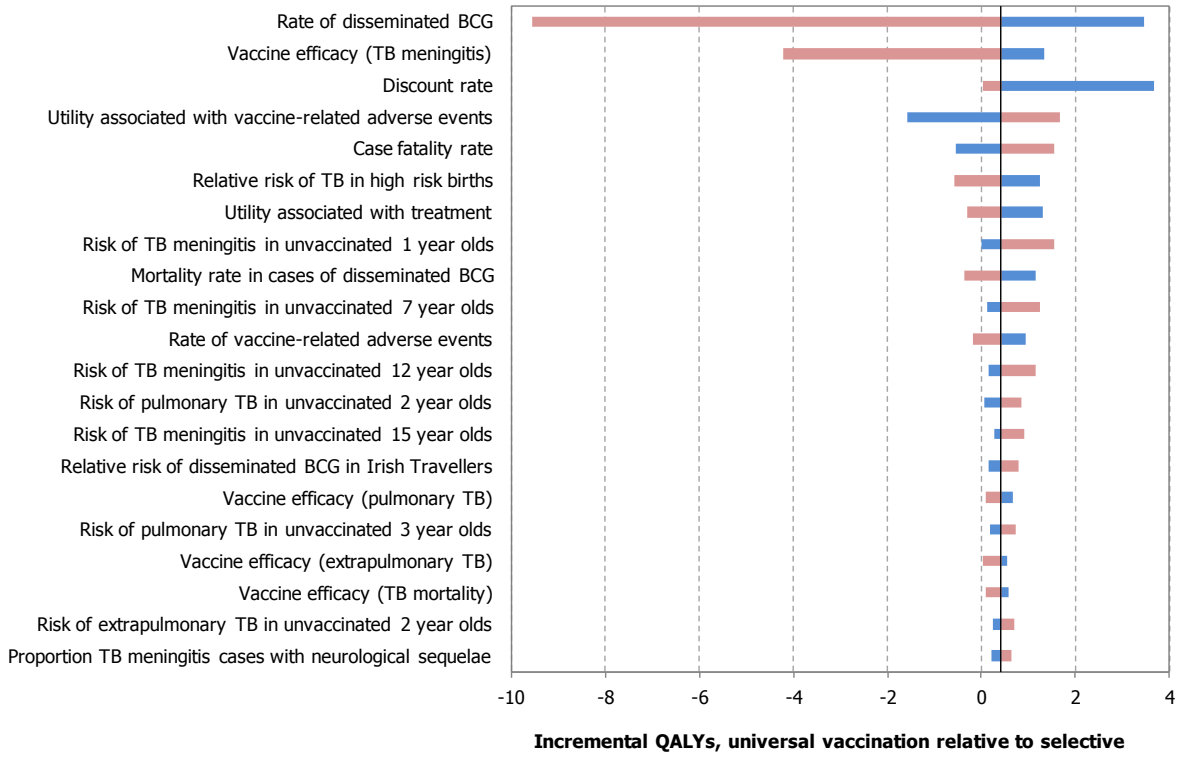
Note: All parameters were varied in the analysis. For legibility, only parameters that, when varied, resulted in a fluctuation of at least 0.1 in the incremental life years gained are included in the tornado plot. Red bars correspond to a parameter set at its upper bound, blues bars to the lower bound.

Abbreviations: BCG, Bacillus Calmette-Guérin; TB, tuberculosis.

5.5.2 Quality-adjusted life years

The incremental QALYs in the comparison of universal and selective vaccination were sensitive to changes in a number of parameters. Eight of the parameters, when set at their bounds, could result in selective vaccination being considered more effective than universal vaccination (Figure 5.14). The most significant parameter was the rate of disseminated BCG which, when set at its upper bound, resulted in a substantial shift in the incremental QALYs. A high rate of disseminated BCG has a greater impact in universal vaccination because of the much larger number of children exposed to BCG. The parameters with most influence were generally estimated based on limited data, resulting in wide distributions which contribute to uncertainty in the estimated benefits of vaccination.

Figure 5.14 Tornado plot of incremental QALYs for universal relative to selective vaccination



Note: All parameters were varied in the analysis. For legibility, only parameters that, when varied, resulted in a fluctuation of greater than ±0.2 QALYs are included in the tornado plot. Red bars correspond to a parameter set at its upper bound, blues bars to the lower bound.

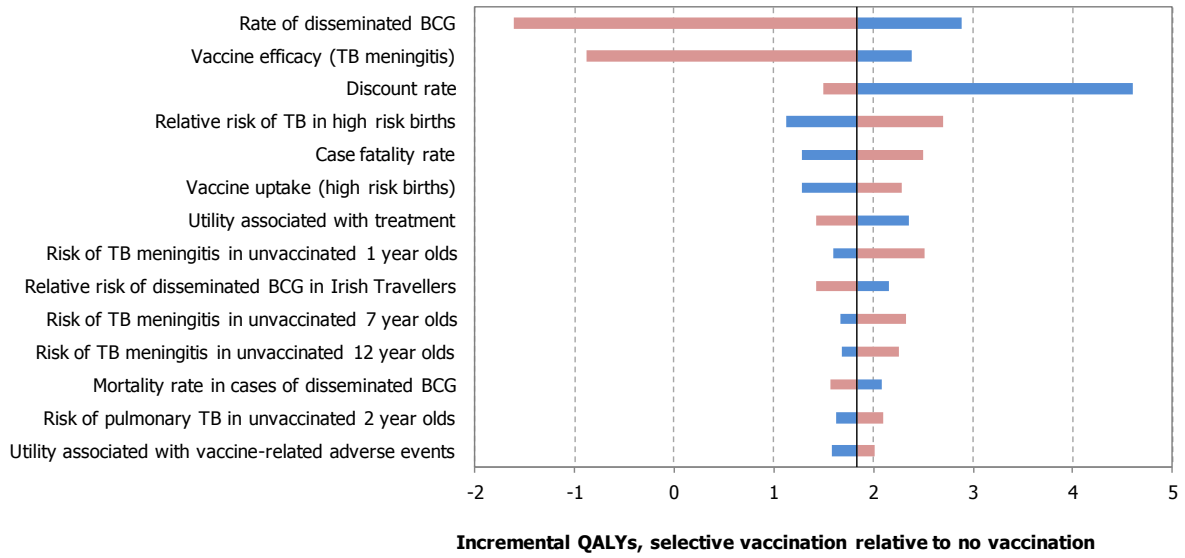
Abbreviations: QALY, quality-adjusted life year; BCG, Bacillus Calmette-Guérin; TB, tuberculosis.

Vaccine efficacy for TB meningitis was also very important, although the credibility of the upper bound is questionable and hence it is of limited relevance. This is due to the very wide confidence bounds for this parameter, which embrace 1.0, as determined by RCT evidence. The wide confidence bounds imply that the reduction in TB meningitis risk is not statistically significant. This parameter impacts on QALYs as the long-term sequelae of TB meningitis have a significant effect on quality of life. In this context, the effect of setting the relative risk of TB meningitis at the upper bound has an artificial effect, as it is unlikely that vaccination will increase the risk of TB meningitis.

Setting the rate of disseminated BCG or vaccine efficacy against TB meningitis at their respective upper bounds resulted in selective vaccination being considered less effective than no vaccination (Figure 5.15). The rate of disseminated BCG was estimated from very limited data and yet has an important impact on the incremental benefits of selective vaccination.

As for incremental life years gained, the discount rate, the relative risk of TB in high-risk births, and the case-fatality rate were the main epidemiological parameters for which parameter uncertainty contributed to substantial uncertainty in the incremental QALYs for selective relative to no vaccination.

Figure 5.15 Tornado plot of incremental QALYs for selective relative to no vaccination



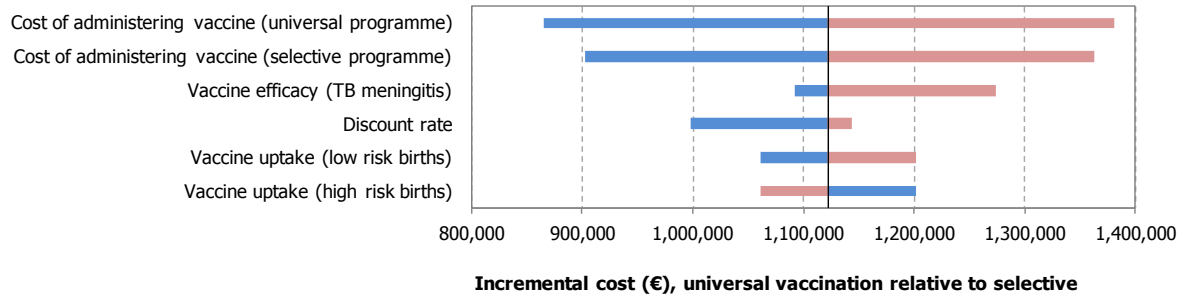
Note: All parameters were varied in the analysis. For legibility, only parameters that, when varied, resulted in a fluctuation of greater than a ±0.2 QALYS are included in the tornado plot. Red bars correspond to a parameter set at its upper bound, blues bars to the lower bound.

Abbreviations: QALY, quality-adjusted life year; BCG, Bacillus Calmette-Guérin; TB, tuberculosis.

5.5.3 Total cost

Two parameters were found to have a major impact on the incremental costs of universal relative to selective vaccination: the cost of administering vaccine in the two strategies (Figure 5.16). As the estimated cost of administering vaccine in the selective programme is correlated with the cost in a universal programme, setting either at a low value results in a lower estimate of incremental cost.

Figure 5.16 Tornado plot of total cost for universal relative to selective vaccination

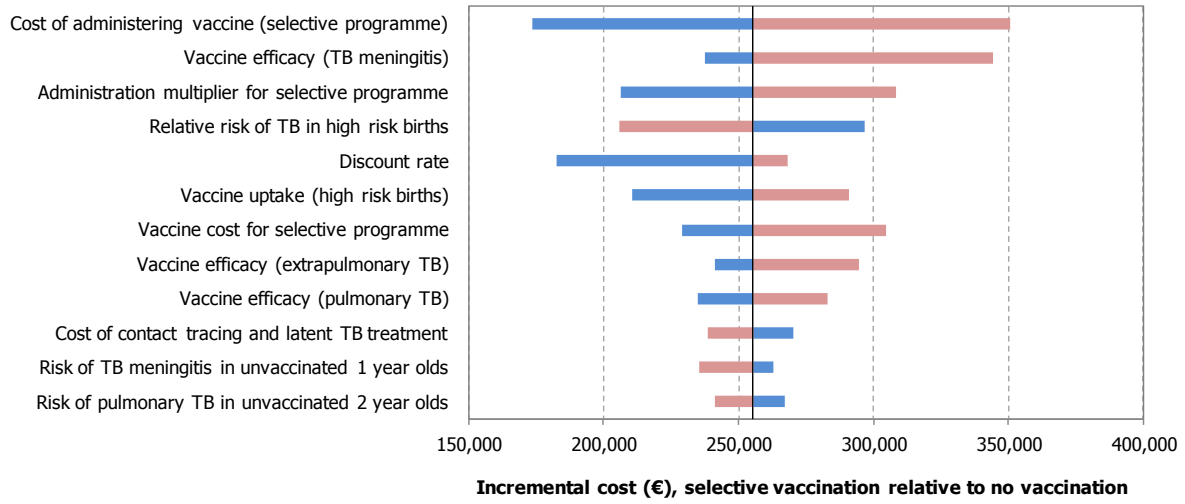


Note: All parameters were varied in the analysis. For legibility, only parameters that, when varied, resulted in greater than a ±5% fluctuation in the incremental cost are included in the tornado plot. Red bars correspond to a parameter set at its upper bound, blues bars to the lower bound.

Abbreviations: TB, tuberculosis.

Varying the cost of administering the BCG vaccine had the largest impact on the incremental costs of selective vaccination relative to no vaccination. As for incremental QALYs, varying the vaccine efficacy against TB meningitis also caused large fluctuations in the incremental cost. Due to the high rate of long-term sequelae of TB meningitis and the lifetime costs associated with those complications, they can have a marked impact on total costs. Varying the relative risk of TB in high-risk births and the discount rate also had substantial impacts on the incremental costs. There was no parameter for which the upper or lower bound resulted in selective vaccination costing less than a programme of no vaccination.

Figure 5.17 Tornado plot of total cost for selective relative to no vaccination



Note: All parameters were varied in the analysis. For legibility, only parameters that, when varied, resulted in greater than a ±5% fluctuation in the incremental cost are included in the tornado plot. Red bars correspond to a parameter set at its upper bound, blues bars to the lower bound.

Abbreviations: TB, tuberculosis.

5.5.1 Incremental cost-effectiveness ratios (ICERs)

The ICERs were calculated on the basis of both life years gained (LYG) and quality-adjusted life years (QALYs). In terms of life years gained, there was no parameter for which the upper or lower bounds resulted in universal vaccination being cost-effective relative to selective vaccination at thresholds of up to €45,000 per LYG. Equally for selective vaccination in comparison with no vaccination, there were no parameters that, when set at their lower or upper bounds, resulted in selective vaccination being considered cost-effective.

For ICERs based on quality-adjusted life years, there was no parameter for which the upper or lower bounds resulted in universal vaccination being cost-effective relative to selective vaccination at thresholds of up to €45,000 per QALY. The only parameter variation that resulted in selective vaccination being considered potentially cost-effective relative to no vaccination was the discount rate. When the discount rate was set at 1.5% and all other parameters were set at their average values, the ICER for selective vaccination compared with no vaccination was €39,661 per QALY.

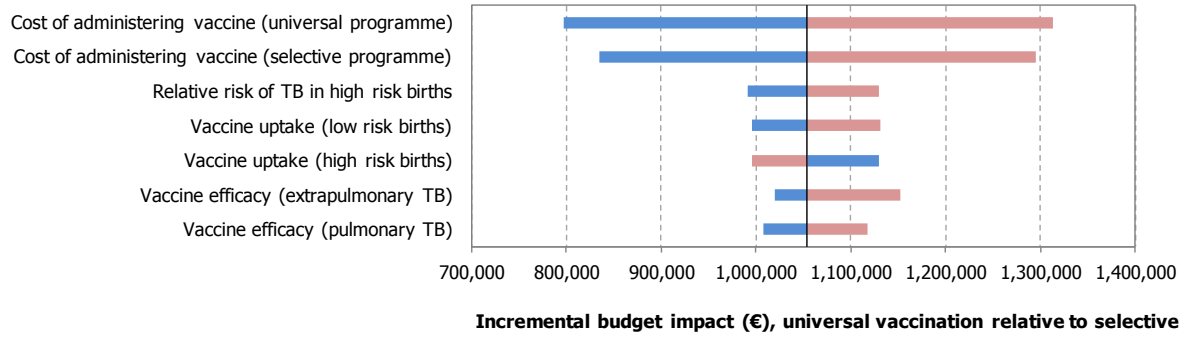
5.5.2 Budget impact

Discounting is not applied in the budget impact analysis, and hence the discount rate is not included in the univariate sensitivity analysis.

The annual budget impact of selective vaccination is €1,053,971 less than for the universal vaccination strategy. Uncertainty in the administration costs of the two programmes was a major contributor to uncertainty in the incremental budget impact (Figure 5.18). Increasing the cost of administering vaccine in the universal programme by €5.57 results in an approximate €259,000 increase in the incremental budget impact.

The administration cost per patient for the selective programme was estimated as the administration cost for the universal programme multiplied by a scaling factor which had an average value of two. The multiplier reflects that administering vaccine in a selective programme is likely to be less efficient than in the current universal BCG vaccination programme. Because of this multiplier, the administration costs for the two programmes are correlated. Due to the correlation, decreases in both costs are associated with a reduction in the incremental budget impact. The next most important parameters were the relative risk of TB in high-risk births and the uptake rates for low- and high-risk births, respectively.

Figure 5.18 Tornado plot of annual budget impact for universal vaccination relative to selective vaccination



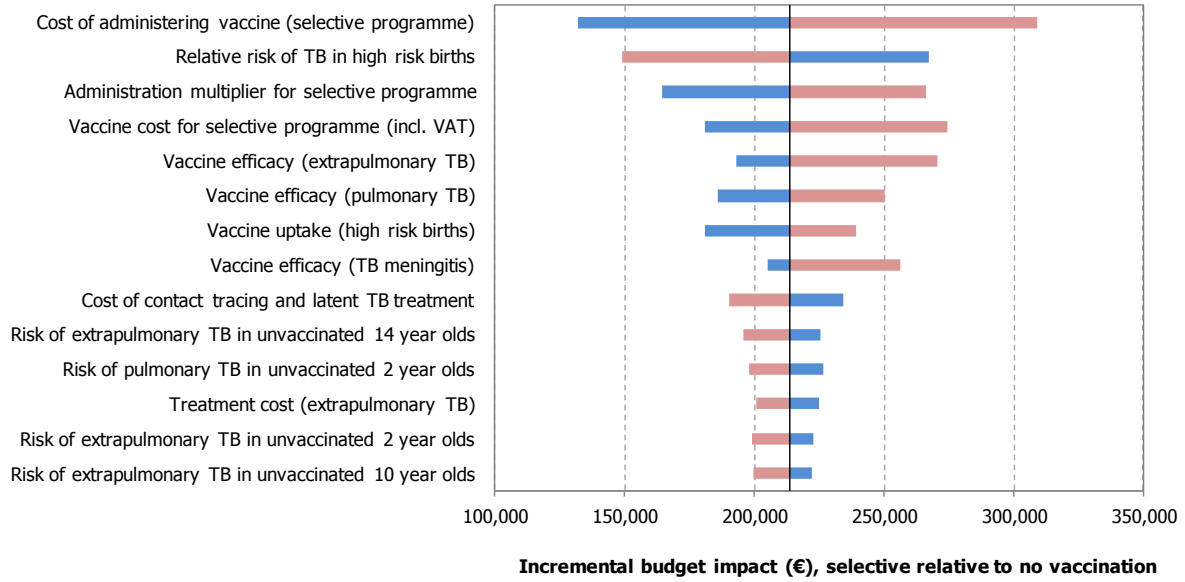
Note: All parameters were varied in the analysis. For legibility, only parameters that, when varied, resulted in greater than a ±5% fluctuation in the incremental budget impact are included in the tornado plot. Red bars correspond to a parameter set at its upper bound, blues bars to the lower bound.

Abbreviations: TB, tuberculosis; VAT, value added tax.

The univariate analysis was also applied to the annual incremental budget impact (Figure 5.19). The annual budget impact of no vaccination is €213,577 less than that for the selective vaccination strategy. Uncertainty in the administration cost of a selective programme is a major contributor to uncertainty in the incremental budget impact. A reduction in the administration cost corresponds to a reduction in the

incremental budget impact. The next most important parameter was the relative risk of TB in high-risk births, followed by the vaccine cost for the selective programme.

Figure 5.19 Tornado plot of annual budget impact for selective relative to no vaccination



Note: All parameters were varied in the analysis. For legibility, only parameters that, when varied, resulted in greater than a ±5% fluctuation in the incremental budget impact are included in the tornado plot. Red bars correspond to a parameter set at its upper bound, blues bars to the lower bound.

Abbreviations: TB, tuberculosis.

5.6 Scenario analyses

Four scenario analyses were defined, three relating to the choice of parameter values and a fourth to explore the relationship between vaccine and administration cost and the ICER.

5.6.1 Vaccine efficacy for pulmonary TB

In the systematic review of clinical effectiveness, the relative risk of pulmonary TB was estimated using data from randomised controlled trials (RCTs) and observational studies. A meta-regression including study latitude found that the distance of the studies from the equator was a potentially useful explanatory variable, as vaccine efficacy increases further from the equator. It was possible to predict the relative risk of pulmonary TB in Ireland by using the latitude of Ireland in the model. Rather than the relative risk of 0.41 that was used in the main model, a value of 0.29 (95% CI: 0.12 to 0.58) was used in a scenario analysis.

Changing the relative risk value increased the estimated effectiveness of vaccination programmes. The improved effectiveness resulted in a modest reduction in the

ICERs (that is, it became more cost-effective) relating to LYG and QALYs (Tables 5.13 and 5.14).

The probability that selective vaccination is the most cost-effective option at willingness-to-pay thresholds of €20,000 and €45,000 per LYG was 0.003 and 0.014, respectively.

Table 5.13 Outcomes (in life years gained) based on increased efficacy for preventing pulmonary TB

Vaccination strategy	Cost		Life years		ICER (€/LYG)
	Total	Incremental	Total	Incremental	
No vaccination	€890,232		1,418,151.7		
Selective	€1,127,240	€237,008	1,418,152.5	0.78	303,857
Universal	€2,219,636	€1,092,396	1,418,152.5	-0.03	Dominated

Abbreviations: LYG, life years gained; ICER, incremental cost-effectiveness ratio.

The probability that selective vaccination is the most cost-effective option at willingness-to-pay thresholds of €20,000 and €45,000 per QALY was 0.014 and 0.113, respectively.

Table 5.14 Outcomes (in quality-adjusted life years) based on increased efficacy for preventing pulmonary TB

Vaccination strategy	Cost		Life years		ICER (€/QALY)
	Total	Incremental	Total	Incremental	
No vaccination	€890,232		1,340,322.1		
Selective	€1,127,240	€237,008	1,340,324.1	1.97	120,309
Universal	€2,219,636	€1,092,396	1,340,324.7	0.61	1,790,813

Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.

This scenario analysis generates estimates similar to what would be found using the Irish observational data on BCG effectiveness (Table 4.4).

5.6.2 Lower case-fatality rate

The case-fatality rate for children aged less than 16 years with TB was derived from UK data. Although there have been no TB-related deaths in children aged less than 16 years in Ireland in the last 15 years, this must be considered in the context of the small numbers available. With a much larger population, from a statistical perspective there is greater power to estimate a reliable case-fatality rate using the UK data. However, a case-fatality rate for Ireland is available for all ages, and the reported value is less than that for all ages in the UK. It is therefore possible that the UK estimate of the case-fatality rate in children may be an over-estimate of the rate in Ireland.

A scenario analysis was used to examine the impact of adjusting the childhood case-fatality rate based on the relative difference in the all-ages case-fatality rates between the UK and Ireland. Rather than the value of 0.0078 used in the main analysis, a mean case-fatality rate of 0.0054 was applied.

The benefits of vaccination in terms of life years gained are dependent on vaccination reducing the risk of mortality. A reduction in the case-fatality rate limits the ability of vaccination to generate benefits and thereby results in increased ICERs with respect to life years gained (Table 5.15). The ICERs for both the selective and universal strategies increase substantially, becoming less cost-effective, relative to the main analysis. The probability that selective vaccination is the most cost-effective option at willingness-to-pay thresholds of €20,000 and €45,000 per LYG was 0.0005 and 0.002, respectively.

Table 5.15 Outcomes (in life years gained) based on a reduced case-fatality rate

Vaccination strategy	Cost		Life years		ICER (€/LYG)
	Total	Incremental	Total	Incremental	
No vaccination	€889,558		1,417,853.8		
Selective	€1,142,883	€253,326	1,417,854.0	0.16	1,583,285
Universal	€2,265,648	€1,122,765	1,417,852.9	-1.08	Dominated

Abbreviations: LYG, life yeard gained; ICER, incremental cost-effectiveness ratio.

A similar situation is noted for benefits of vaccination in terms of QALYs where some of the gain in quality of life can be attributed to reductions in mortality. A lower case-fatality rate results in modest increases in the ICERs based on QALYs (Table 5.16). The probability that selective vaccination is the most cost-effective option at willingness-to-pay thresholds of €20,000 and €45,000 per QALY was 0.005 and 0.044, respectively.

Table 5.16 Outcomes (in quality-adjusted life years) based on a reduced case-fatality rate

Vaccination strategy	Cost		Life years		ICER (€/QALY)
	Total	Incremental	Total	Incremental	
No vaccination	€889,558		1,340,039.6		
Selective	€1,142,883	€253,326	1,340,040.9	1.30	194,886
Universal	€2,265,648	€1,122,765	1,340,040.4	-0.54	Dominated

Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.

Reducing the case-fatality rate has implications for the estimated reductions in TB mortality due to vaccination programmes, and therefore for the ratio of risks to benefits. For universal vaccination, with a reduced case-fatality rate there would be a probability of 0.31 that BCG-related mortality would exceed TB mortality avoided.

In terms of selective vaccination, a reduced case-fatality rate would result in a probability of 0.21 that BCG-related mortality would exceed TB mortality avoided.

5.6.3 Lower risk of TB

The data on risk of TB in unvaccinated children aged 0 to 15 years was obtained from Irish TB notification data from 2005 to 2014. During that time, the rate of TB infection had been in decline. The average annual number of cases in children aged less than 16 years has been 15.6 per annum over the last five years, and 11.7 per annum over the last three years. The model estimated 24.4 cases in the birth cohort to age 15 years based on universal vaccination. Thus the model estimates, when converted into annual figures, are approximately double the average observed over the last three years.

A scenario analysis was carried out with the risk of TB halved for all ages to reflect the more recent observed risk of contracting TB. The risk of TB was halved for the entire cohort, although the high-risk population continued to have a relative risk of 3.02 of developing TB compared with the general population. For the comparison of selective and no vaccination, the use of a lower risk of TB resulted in a substantially increased ICER (that is, became less cost-effective) for both life years gained and quality-adjusted life years (Tables 5.17 and 5.18).

Table 5.17 Outcomes (in life years gained) based on a reduced risk of TB

Vaccination strategy	Cost		Life years		ICER (€/LYG)
	Total	Incremental	Total	Incremental	
No vaccination	€445,717		1,418,089.2		
Selective	€789,793	€344,076	1,418,089.0	-0.17	Dominated
Universal	€2,064,452	€1,274,659	1,418,087.4	-1.59	Dominated

Abbreviations: LYG, life yeard gained; ICER, incremental cost-effectiveness ratio.

There is a probability of zero that selective or universal vaccination are the most cost-effective option at thresholds of €20,000 and €45,000 based either on life years gained or quality-adjusted life years.

Table 5.18 Outcomes (in quality-adjusted life years) based on a reduced risk of TB

Vaccination strategy	Cost		Life years		ICER (€/QALY)
	Total	Incremental	Total	Incremental	
No vaccination	€445,717		1,340,265.0		
Selective	€789,793	€344,076	1,340,265.3	0.31	1,109,921
Universal	€2,064,452	€1,274,659	1,340,263.1	-2.20	Dominated

Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.

Reducing the risk of TB has a marked impact on estimated mortality. The estimated total mortality in the single birth cohort was 0.26 for universal vaccination, 0.21 for selective vaccination, and 0.22 for a programme of no vaccination. Therefore based on recent rates of TB incidence, both selective vaccination and no vaccination would be associated with lower total mortality than universal vaccination.

5.6.4 Varying risk of TB by vaccine strategy

The data used to inform the risk of TB was based on notified cases of TB in unvaccinated children. The majority of counties in Ireland have had programmes of universal vaccination but a small number have not, although some level of vaccination has been in place in those counties (Cork, Mayo and Roscommon). The risk of TB is therefore largely based on unvaccinated children in the context of a universal programme, which may be an underestimate of the risk of TB in programmes of selective or no vaccination. The differences may depend on a variety of factors, such as the extent to which herd immunity applies to childhood TB risk.

A scenario analysis was used where TB risk in a universal vaccination programme was based on data for counties with universal vaccination implemented. The TB risk for selective vaccination was based on data during periods of non-universal vaccination in counties Cork, Mayo and Roscommon. It was assumed that the vaccinated cohort in those counties was similar to the high-risk cohort as identified in this report. For the no vaccination alternative, it was assumed that the data for selective vaccination represented the TB risk for infants not considered at high-risk. The relative risk of TB in high-risk infants was used to adjust the data to account for the increased risk in the 13.4% of the population not represented in the data.

In this scenario analysis, the number of TB cases in a single birth cohort is estimated to be 28.1 for universal, 51.1 for selective and 94.0 for no vaccination. This is compared with 24.4, 44.3 and 55.9 for the equivalent figures in the base-case analysis. In terms of both life years gained and QALYs, selective is more effective and less costly than both of the alternatives (Table 5.20 and Table 5.21). In other words, both universal and no vaccination are dominated by selective vaccination.

Table 5.20 Outcomes (in life years gained) based on a reduced risk of TB

Vaccination strategy	Cost		Life years		ICER (€/LYG)
	Total	Incremental	Total	Incremental	
No vaccination	€1,523,072		1,417,764.1		
Selective	€1,266,550	-€256,522	1,417,768.7	4.68	Dominates
Universal	€2,327,308	€1,060,758	1,417,769.4	0.61	1,738,947

Abbreviations: LYG, life yeard gained; ICER, incremental cost-effectiveness ratio.

There is a probability in excess of 0.92 and 0.95 that selective is the most cost-effective option at thresholds of €20,000 and €45,000 based either on life years gained or quality-adjusted life years.

Table 5.21 Outcomes (in quality-adjusted life years) based on a reduced risk of TB

Vaccination strategy	Cost		Life years		ICER (€/QALY)
	Total	Incremental	Total	Incremental	
No vaccination	€1,523,072		1,339,951.0		
Selective	€1,266,550	-€256,522	1,339,960.3	9.27	Dominates
Universal	€2,327,308	€1,060,758	1,339,961.5	1.26	841,871

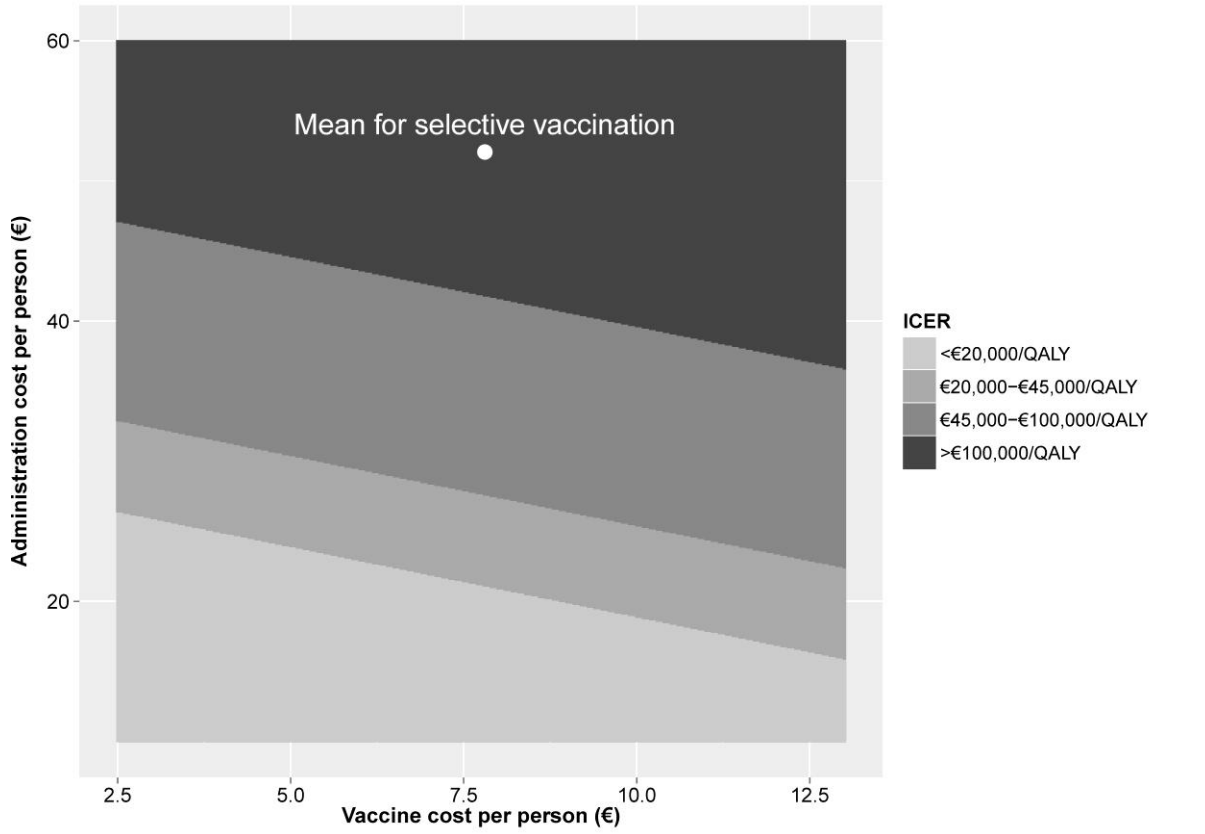
Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.

5.6.5 Varying cost of administration and vaccine

It was shown in the univariate sensitivity analyses that uncertainty in the cost of administering the vaccine has a substantial impact on uncertainty in the ICERs and the budget impact. Unlike the epidemiological parameters, costs can, to a greater or lesser extent, be modified through changes to practice. It is apparent that the estimated cost of vaccine administration in Ireland is far in excess of the values reported in economic evaluations from other countries.

The purpose of this scenario analysis was to determine the extent to which changes to the vaccine administration cost would impact on the ICER for selective vaccination when compared with a policy of no vaccination. Keeping all other parameters fixed at their mean values, the administration and vaccine costs were varied across a range of values. The impact on the ICER (€ per QALY) of varying these costs is shown in Figure 5.20.

Figure 5.20 Impact on ICER (€ per QALY) for selective relative to no vaccination of varying administration and vaccine costs



Abbreviations: ICER, incremental cost-effectiveness ratio.

Changes to the vaccine cost per person have only a modest impact on the ICER. Vaccine cost can be reduced by improving the number of vaccinations achieved per vial. It is apparent that large improvements to efficiency are unlikely to render a programme of vaccination cost-effective.

Reducing the cost of administration however can reduce the ICER. To achieve an ICER of €45,000 per QALY, the administration cost for a selective vaccination programme would have to be reduced to €27.50 per child. To achieve an ICER of €20,000 per QALY, the administration cost would have to be reduced to €21.00 per child. The estimated administration cost for the current programme of universal vaccination is €26 per child and in the main model it was assumed that for a selective vaccination programme the administration cost would double. That assumption was based on the fact that the reduction in BCG clinics required would not be in proportion to the reduction in the target population.

5.7 Discussion

An economic model was presented in this chapter that was used to estimate the cost-effectiveness of three neonatal BCG vaccination strategies: universal, selective, and no vaccination. The parameters used in the model were derived from a wide variety of sources, some of which were used as proxies in the absence of relevant data.

A review of economic evaluations of BCG vaccination programmes from other countries found mixed evidence. Universal vaccination programmes were evaluated for Slovakia and Japan, and found to be cost-effective and not cost-effective, respectively. Selective strategies were modelled for Finland and the Netherlands. The Finnish study found the cost-effectiveness of a selective strategy to be dependent on the increased risk in the vaccinated population. The Dutch study focussed on the extension of an existing selective vaccination programme. The heterogeneity in risk, types of TB considered, costs included, estimated vaccine efficacy, vaccination strategy modelled, and the discount rate used meant that it was difficult to compare results. The applicability of the international studies to Ireland was questionable.

A Markov model that simulated a cohort from birth to age 15 years was used to determine the impact of different vaccination strategies. Benefits were measured in terms of both life years gained and quality-adjusted life years.

5.7.1 Main findings

In the absence of any other changes to TB control measures, a change from universal to selective or no vaccination is likely to lead to increased numbers of childhood TB cases. However, selective vaccination was estimated to lead to lower overall mortality than programmes of universal or no vaccination.

Switching from universal to selective vaccination was estimated to lead to 19.9 additional cases of TB in the modelled birth cohort. When the impact was modelled relative to current and projected incidence of TB, selective vaccination would result in an additional three to four cases per annum, on average, compared with a universal programme. Mortality in the single birth cohort to age 15 years was 0.30 for universal vaccination, 0.37 for selective vaccination, and 0.44 for no vaccination. If recent trends in TB incidence continue, then selective vaccination was estimated to result in lower mortality than universal vaccination.

In terms of life years gained, universal vaccination was more costly and less effective than the alternative of selective vaccination. The ICER for selective vaccination was €340,520 per LYG compared with no vaccination. At traditional

willingness-to-pay thresholds it was almost certain that a programme of no vaccination would be the most cost-effective option. The expected value of perfect information at a willingness-to-pay threshold of €45,000 per LYG was negligible.

Based on quality-adjusted life years, universal vaccination was the most effective option, with an ICER of €2,549,822 per QALY relative to selective vaccination. The ICER was €139,557 per QALY for selective compared with no vaccination. The probability of selective vaccination being the most cost-effective option at thresholds of €20,000 and €45,000 per life year gained was 0.008 and 0.07, respectively. The expected value of perfect information at a willingness-to-pay threshold of €45,000 per QALY was €3,997.

With selective vaccination there would be an estimated 53,532 fewer vaccinations per annum, with an associated reduction in adverse reactions to BCG. The annual budget impact of strategies of universal, selective and no vaccination was estimated at €2,393,335, €1,339,364, and €1,125,787, respectively. Sixty six percent of the budget impact of universal vaccination relates to the cost of administering the vaccine. The equivalent figure for selective vaccination, not including any cost for identifying high-risk infants, is 27%. Policies of selective or no vaccination will result in the need for more resources for contact tracing, but fewer staff resources for administering vaccinations.

5.7.2 Sensitivity and scenario analyses

The univariate sensitivity analyses showed that varying certain parameters had impacts on the estimated incremental costs and benefits of selective vaccination relative to no vaccination. Parameters for which variation led to marked changes in the estimates of costs and benefits included the discount rate, the rate of disseminated BCG, relative risk of TB in high-risk births, the case-fatality rate, and the cost of administering the vaccine.

- Discounting

  Discounting can be expected to have a major impact for a vaccination programme where the cost of vaccination occurs at the outset and is therefore undiscounted whereas the benefits occur over the lifetime of the cohort, and hence are heavily discounted. Some countries apply differential discounting (whereby different discount rates are applied to benefits and costs) or reduce the discount rate for costs and benefits beyond a certain time horizon, for example after 30 years. Both of these approaches are controversial for different reasons,[126] and have not been adopted in Ireland. The discount rate used in the main analysis has been set out by the Department of Finance and must be applied to both costs and benefits.

- Risk of developing TB

  The data on risk of developing TB is based on a ten year period (2005 to 2014) during which there was a substantial decline in TB incidence. This can be seen in the results of the main analysis where the predicted number of cases in the birth cohort was 24.4, approximately double the number of cases expected based on the most recent data. A scenario analysis was used to test the impact of halving the risk of TB to reflect more recent figures. The impact of the reduced risk was to decrease the incremental benefit of selective relative to no vaccination. Universal vaccination was dominated in terms of both life years gained and QALYs, while selective vaccination was dominated in terms of life years gained. However, due to the small numbers of cases per annum, it is possible that the low incidence observed in recent years will not be sustained. As such, the average annual risk from 2005 to 2010 by year of age used in the model (Table 5.2) is considered a pragmatic if conservative estimate.

  The applicability of the TB risk data to the scenario of no vaccination is also questionable. The TB risk data represents unvaccinated children in areas that had universal or selective vaccination policies. The data must therefore be considered in that context. The Irish data represents a situation where the majority of high-risk infants are assumed to be vaccinated. Hence the TB risk data may be more representative of the non-high-risk population rather than the average risk population. For this reason, the model may have underestimated the number of TB cases that would occur in a scenario of no vaccination. A scenario analysis was run using separate risk data for universal, selective and no vaccination. This resulted in considerably higher estimates of total cases under a policy of no vaccination. Selective vaccination was both more effective and less costly than no vaccination in terms of both life years gained and QALYs. Universal vaccination was more effective and more costly than selective vaccination but would not be considered cost-effective. Due to the limited data to support this analysis, the results should not be over-interpreted, although they support the general finding that universal and selective vaccination are similarly effective in terms of life years gained and quality-adjusted life years.

- Relative risk of TB in high-risk births

  The cost-effectiveness of selective vaccination is affected by the level of elevated TB risk in the high-risk population. The Finnish economic evaluation highlighted this by considering a variety of elevated risk levels and demonstrated improved cost-effectiveness with increased risk in the target population.[93] The data used in this evaluation was derived from 10 years of TB notification data. The quality of the coding will impact on the accuracy of the estimate, although a

conservative approach was adopted whereby cases with no recorded nationality or ethnicity were assumed to be high-risk cases.

The denominator population was assumed to be represented by high-risk births, which was estimated at 13.4% of births. However, the TB notifications include cases not born in Ireland. If immigrants were included in the denominator population, the high-risk population might in fact be greater than estimated here. An underestimate of the high-risk population implies an overestimate of the relative risk.

The narrow confidence bounds around the estimate of relative risk of TB reflect the fact that it is derived from 10 years of data on TB cases. For the estimate to be biased, one would have to assume that nationality and ethnicity are poorly recorded or coded, or that case ascertainment in high-risk cases is less than 100%, but there is no evidence for these sources of bias.

- Case-fatality rate

The case-fatality rate was estimated using data from the UK due to an absence of evidence regarding TB deaths in children aged less than 16 years in Ireland. Previous economic evaluations did not include TB mortality as an outcome when there was no evidence of occurrence.[92;93] Due to the rare nature of TB and TB mortality, the fact that no deaths were observed in the Irish data does not imply a case-fatality rate of zero. Due to the much larger population in the UK, there was greater statistical power to detect a low case-fatality rate. However, the UK TB case-fatality rate for all ages is higher than the corresponding figure for Ireland.

A scenario analysis was used to test the impact of a lower case-fatality rate in Ireland. Reduced estimates of TB mortality results in increased ICERs, making it even less cost-effective. The case-fatality rate in the main analysis can be viewed as a conservative figure that is more likely to overestimate rather than underestimate the case-fatality rate. However, the impact on the ICERs of reducing the case-fatality rate was modest.

- The rate of disseminated BCG and associated mortality rate

Disseminated BCG represents what is perhaps the most severe form of adverse reaction to BCG vaccination. The high mortality rate associated with disseminated BCG results in a marked impact on life years gained and the risk:benefit ratio of vaccination. Cases of disseminated BCG are primarily observed in children with primary immunodeficiency syndromes. The estimate of incidence of disseminated BCG used in the model, is based on 10 years of national data combined with data

on the number of BCG vaccinations in that period. Both of these estimates are considered reliable.

The mortality rate associated with disseminated BCG used in the model was based on an international survey and was lower than many of the published estimates, which have included figures as high as 81%. No deaths in cases of confirmed disseminated BCG have been reported in Ireland between 2005 and 2014. However, due to the small number of cases a mortality rate of 29% cannot be ruled out. Due to early recognition and aggressive treatment of BCG-osis and of the underlying primary immunodeficiency syndrome in Ireland, the mortality estimate used in the model may be conservative. However, it is unlikely to substantially over-estimate the risk of mortality.

Due to the reported higher incidence of primary immunodeficiency syndromes in Irish Travellers, it is likely that a selective vaccination programme that includes Irish Travellers may not achieve a reduction in disseminated BCG in proportion to the reduction in exposed infants. The model incorporated an increased risk of disseminated BCG in the Irish Traveller population based on national data.

- Cost of administering the vaccine

The cost of administering the BCG vaccine was an important parameter in all of the sensitivity analyses and makes a very substantial contribution to the overall cost of delivering selective and universal vaccination programmes. The combined per infant cost of vaccine and administering was reported in three international economic evaluations. Two studies reported costs of €13.37 and €2.97 for universal vaccination. Costs of €7.27 and €6.93 were also reported for selective vaccination. The estimated equivalent cost per vaccination in Ireland was €28.76 for the universal programme and €59.81 for the selective programme. This study estimated an approximate doubling of cost of vaccination in moving from a universal to a selective programme. The Finnish study reported a similar relative increase in cost, albeit from a much lower base cost. In the Finnish study, the increase in cost was entirely due to less efficient use of vaccine vials; the cost of administration remained static. It is unclear whether the estimated cost in Ireland is high or whether studies from other countries have under-estimated the true costs of delivering a BCG vaccination programme. The evaluations did not give detailed breakdowns of the included costs and as such the applicability cannot be fully appraised.

The cost of administration in Ireland for the universal programme is more than twice that reported in other studies and has a major impact on the estimate of cost-effectiveness. The extent to which a selective programme may be cost-effective compared with no vaccination is significantly impacted by the ability to

reduce the administration cost. It should be noted that no cost was included for the identification of high-risk infants, which could increase the cost associated with administering the vaccine. However, it may be interpreted that the reduced efficiency of administering vaccine in a selective programme may partly incorporate the resources required for identifying high-risk infants.

A scenario analysis showed that for a selective vaccination programme to be considered cost-effective at willingness-to-pay thresholds of €20,000 and €45,000 per QALY, the cost of administering the vaccine would have to be lowered to €21.00 and €27.50 per infant, respectively. A thorough review of the operational features of the existing programme (which is largely based on delivery of the vaccine in dedicated community care clinics) would be required to determine whether such a reduced cost is feasible. The fact that lower costs have been reported in other countries suggests that it may be achievable in Ireland.

5.7.3 Limitations

The present study was subject to a number of limitations. As with any economic modelling exercise, the applicability of the findings is dependent on the quality of the parameter values used and the assumptions underpinning the model structure.

Some of the key parameters, such as vaccine efficacy and case fatality rate, were not based on Irish data. Vaccine efficacy was derived from a systematic review of the evidence, but there is a lack of consensus on how to interpret the findings. It is understood that efficacy varies by distance from the equator, but there are few high quality studies to support a clear understanding of efficacy in the Irish context. We used sensitivity and scenario analyses to test some of these assumptions, but found a low risk of the ICERs having been overestimated.

Some of the epidemiological parameters, specifically the case-fatality rate and annual risk of developing TB, were possibly overestimates. Both were tested in scenario analyses and it was found that should the values be lower than estimated in the main analysis, the universal and selective vaccination programmes would be considered less effective than reported in the main analysis. The case-fatality rate was uniformly applied to all forms of TB. It is likely that the case-fatality rate would be higher for TB meningitis and miliary TB.[30;94] However, this would have to be associated with a decreased case-fatality rate in pulmonary and extrapulmonary TB. As such, the average mortality would not change. Increased mortality in TB meningitis cases would reduce the number of survivors with long-term sequelae, but given that this represented a very small portion of survivors it is unlikely that such a change would impact on results. The values used for mortality associated with disseminated BCG were also possibly a conservative estimate. However, as was

evident in the univariate sensitivity analysis varying the mortality rate had limited impact on results. Of greater relevance was the rate of disseminated BCG, which was based on observed data of Irish children.

The effect of vaccine on latent TB infection was not directly incorporated into the model. There is very limited data on the potential protective effect of BCG. To explicitly incorporate latent TB infection would require accurate data on the prevalence of latent TB infection in the Irish population aged less then 16 years, which is not available. It was assumed that the TB incidence data incorporates cases where latent TB infection has developed into active disease. Hence the data on vaccine efficacy incorporates some of the protection against latent TB infection.

Data on utilities associated with treatment, adverse reactions and long-term sequelae came from a variety of sources. In some cases the data will have been derived from adults, particularly for treatment. The applicability to children of utility data generated from adults is questionable.[127] However, the values used were pragmatic and the cost-utility analysis is presented as an adjunct to the primary analysis of life years gained.

For this study it was assumed that 13.4% of the population would be considered high-risk and eligible for vaccination in a selective programme. This figure was based only on Irish Travellers and children born to parents from a high TB incidence country. It is recognised that other population groups, such as children who are homeless or children of prisoners, might also be considered high-risk. Unless these population groups have a very different TB risk profile to the already defined high-risk group, then their inclusion is unlikely to impact on the estimate of cost-effectiveness. However, any increase in the eligible population will have implications for estimated budget impact as there would a proportional increase in the number of vaccinations.

The analysis did not directly include a cost associated with identifying high-risk infants in a selective vaccination strategy. It is not clear how this process would work in practice, although it may be possible to capitalise on existing resources to some extent. It could be inferred that the increased cost of administering the vaccine may incorporate the administrative role of identifying eligible infants. The cost of administering the vaccine for a selective programme was on average double the cost of that estimated for a universal vaccination programme. This was despite eligibility being only 13.4% of the population. The cost of administering the vaccine incorporated medical and administrative staff time. It may be reasonable to assume that part of the additional time could be allocated towards the identification of high-risk infants.

As part of a policy to reduce vaccine coverage, additional TB control measures will be advisable to account for the reduced protection against TB in the child population. The cost of contact tracing in relation to TB cases and treatment of latent TB infections were included in the analysis. As the analysis was on the basis of the existing approach to TB control, the cost of a formal TB screening programme was not incorporated into the analysis and, if implemented, would increase the budget impact of the selective and no vaccination strategies. The operational features and likely budget impact should be considered. The various approaches to TB control and how they may be impacted by a change in vaccination policy are discussed in more detail in Chapter 6.1.

The analysis of expected value of perfect information indicated very low values at traditional willingness-to-pay thresholds. This means that there is very little decision uncertainty at thresholds below €45,000 per QALY and therefore little value in doing additional research to reduce uncertainty. However, it does suggest that there may be some value in research which could be directed at determining whether the cost of administering the vaccine is as high as estimated, or if it could be substantially reduced. It is important to appreciate that the decision uncertainty is a function of the specified parameter uncertainty.

5.7.4 Interpretation of findings

A programme of BCG vaccination is effective at reducing the incidence of TB. A selective programme that targets high-risk infants is more effective and less costly than a universal vaccination strategy in terms of life years gained. Based on quality-adjusted life years, universal vaccination is the most effective strategy. However, based on the parameter values used in this evaluation and willingness-to-pay thresholds of up to €45,000 per QALY, strategies of universal and selective vaccination are not cost-effective. In the absence of any other changes to TB control measures, a switch to selective vaccination would reduce the annual budget impact by €1,053,971 per annum relative to the current universal vaccination programme.

The risk of TB used in the primary analysis was based on data from 2005 to 2014 – a period during which there was a large decrease in the incidence of childhood TB. Based on the average risk over that period, the benefits associated with universal vaccination outweigh the harms in terms of mortality. However, when a lower risk of TB was applied, similar to what has been seen in the period 2011 to 2014, it was estimated that selective vaccination would be associated with lower overall mortality than the universal vaccination programme. These findings must be interpreted in the context of existing TB control measures.

There was substantial uncertainty regarding a number of the key parameters, all of which were allowed to vary within plausible ranges in the main analysis. Although

there was a clear hierarchy in terms of total costs, with universal being the most costly option and no vaccination the least costly, there was greater uncertainty in terms of benefits. Regarding life years gained selective vaccination was, on average, the most effective strategy. However, there was also a high probability that universal vaccination could be the most effective, which was almost entirely dependent on a low rate of disseminated BCG in vaccinated infants.

The rate of disseminated BCG was based on eight confirmed cases in Ireland between 2005 and 2014. Disseminated BCG is most common in infants with primary immunodeficiency syndromes. A family history of primary immunodeficiency is a contraindication for BCG vaccination until evaluation of the infant is complete. A formal neonatal screening programme to identify infants with severe combined immunodeficiencies prior to vaccination may be advisable to limit the risk of disseminated BCG. Such a screening programme should be considered for evaluation irrespective of a change to the vaccination policy to ensure the risk of disseminated BCG is minimised.

When interpreting the results it should be noted that among 0 to 15 year olds in Ireland there were no deaths from either TB or severe adverse reactions to BCG vaccination in the years 2005 and 2014. The estimates of mortality presented here are based on international evidence that overestimates what has been observed in Ireland.

Economic evaluations in other jurisdictions have shown policies of selective vaccination to potentially be cost-effective. While a programme of selective vaccination has been shown to be not cost-effective in Ireland relative to no vaccination, it is possible that substantial reductions in the cost of administration could render a selective vaccination programme cost-effective.

5.8 Key messages

- A systematic review of published economic evaluations of neonatal BCG vaccination programmes identified five studies. There was evidence to suggest that a selective vaccination programme may be cost-effective relative to universal or no vaccination, although the relevance to the Irish healthcare setting was questionable.
- A Markov model was developed to simulate a cohort from birth to life expectancy and determine the costs and benefits associated with programmes of universal, selective and no vaccination.
- Mortality in the single birth cohort to age 15 years was 0.30 for universal vaccination, 0.37 for selective vaccination, and 0.44 for no vaccination.
- The strategy of selective vaccination will result in 19.9 additional cases of paediatric TB in the birth cohort while a no vaccination strategy will result in 31.5 additional cases when compared with the current universal vaccination programme.
- Assuming that childhood TB incidence in Ireland is at 10 cases per annum and continuing to decline, a programme of selective vaccination would be likely to result in between three and four additional cases of TB each year relative to universal vaccination.
- In terms of life years gained, universal vaccination is marginally less effective and substantially more costly than an alternative of selective vaccination. Based on quality-adjusted life years, universal vaccination is marginally more effective and substantially more costly than selective vaccination, with an ICER of €2,549,822 per QALY.
- Compared with no vaccination, a strategy of selective vaccination generates ICERs of €340,520/LYG and €139,557/QALY. Compared with no vaccination, selective vaccination is not cost-effective at willingness-to-pay thresholds of up €45,000 per life year gained or per QALY.
- The annual budget impact of the universal vaccination programme is an estimated €2,393,335. The annual budget impact of a selective vaccination programme would be €1,053,971 less than the current universal vaccination strategy. A policy of no vaccination would have an annual budget impact of €1,267,548 less than universal vaccination.
- Among 0 to 15 year olds in Ireland there were no deaths from either TB or severe adverse reactions to BCG vaccination in the years 2005 and 2014. The estimates of mortality presented here are based on international evidence that overestimates what has been observed in Ireland.
- A number of the parameters were specified with values that may overestimate the benefits of a vaccination programme. Sensitivity and scenario analyses

indicate that a selective programme may be less cost-effective (relative to no vaccination) than estimated in the main analysis. The selective vaccination strategy modelled here did not include a specific cost for identifying high-risk infants, which may increase the budget impact of such a programme and reduce the estimated cost-effectiveness.

- The main analysis used a conservative estimate of TB risk based on data from 2005 to 2014. However, if more recent childhood TB incidence rates continue, then selective vaccination would be associated with lower overall mortality than the universal vaccination programme.
- A significant contributor to the cost of the modelled BCG vaccination programmes is the cost of administering the vaccine. The cost in Ireland is far in excess of that reported in other economic evaluations. Substantial reductions in the cost of administration could render a programme of vaccination cost-effective.

6. Organisational and social aspects

This chapter provides a review of the potential implications of changes to the neonatal BCG vaccination programme for the delivery of services within the health system and for society as a whole. The purpose of this review was to identify and discuss any broader issues relevant to the decision-making process, and to highlight potential changes to the organisation or delivery of services required to support changes to the BCG vaccination programme. A change in the vaccination policy will have implications for other elements of the TB control programme. However, it is outside the scope of this report to provide a detailed set of recommendations on TB control generally. This chapter was developed broadly in line with the structure described in the EUnetHTA Core Model.[128]

6.1 Organisational aspects

The analysis of organisational aspects focuses on the implications for patient pathways, staffing, changes to work processes, equipment, and the organisation of activities across different sections of the health services. The neonatal BCG vaccination programme is intended to reduce the risk of infants and children contracting TB. It is therefore a preventive intervention, and a change to a programme of selective vaccination will likely lead to an increase in the number of cases of TB. This section will consider issues relating to the provision of a BCG vaccination programme and also relating to the treatment and management of additional TB cases.

Childhood TB control involves a variety of approaches including active case-finding, contact tracing, treatment for latent TB infection, and BCG vaccination.[129] If offered at a young age, BCG vaccination offers the best protection against TB infection.[41]

6.1.1 Vaccination

Within Western Europe, most countries at one time implemented universal vaccination but subsequently moved to selective vaccination (for example, Austria, France, Germany, Spain, Sweden, Switzerland, UK).[14] Some countries, such as Belgium, Italy, and the Netherlands, never implemented universal vaccination. The World Health Organisation (WHO) recommendation is that a single dose of BCG vaccine should be given to all infants as soon as possible after birth in countries with a high incidence of TB (greater than or equal to 40 cases per 100,000 population).[45] Ireland and Portugal remain as the only Western European countries with universal vaccination programmes despite not being considered as high TB incidence countries using the WHO measure.

A universal vaccination programme has benefits in terms of clarity as all infants are eligible. A selective programme can cause confusion over who is eligible for both parents and clinicians.[130;131] Regional variation in policies and practice can also give rise to misunderstandings, placing an additional burden on service providers to identify, contact and vaccinate eligible infants. In the UK, for example, BCG vaccination policies varied by Primary Care Trust, and areas with high levels of population movement were more likely to adopt universal vaccination given the difficulties in monitoring the high-risk population.[132]

Changes to the BCG vaccination policy will greatly reduce the number of annual vaccinations. There is a concern that a selective vaccination policy may cause issues in the availability of sufficient numbers of medical practitioners who are trained and experienced in administering BCG vaccinations.[13] Inadequate training and poor technique can lead to substantially higher rates of adverse reactions to vaccination.[133]

The BCG vaccination policy in Ireland at present is not consistent, with one county adopting a school-age vaccination policy. Given the relatively small population of Ireland, adoption of the same policy across all areas may be more efficient and, coupled with adequate training of clinicians and increased public awareness, may ensure greater coverage of the eligible population than the current approach.

6.1.2 BCG supply

The BCG vaccine licensed for use in Europe is the BCG Denmark strain, manufactured by Statens Serum Institut (SSI, Denmark). This strain is also used outside Europe in countries such as Libya, Saudi Arabia, South Africa, Tunisia, and Venezuela.[134] Shortages of the BCG vaccine have been noted in Europe and elsewhere affecting not only BCG vaccination programmes, but also other therapies, such as immunotherapy to treat bladder cancer.[132;135;136] On a number of occasions, BCG vaccination has had to be temporarily suspended in Ireland due to an inability to secure sufficient supply of vaccine. Issues with shortages extend to antigens required for tuberculin skin tests, and hence shortages have implications for other aspects of TB control.[137] Compounding the supply difficulties, was the limited shelf-life of the multi-dose vial. The current shelf life of the vaccine is 18 months, having being extended by the Health Products Regulatory Authority from 12 months in March 2015.[7]

In light of the ongoing issues with the supply of BCG vaccine, it is imperative that the available vaccine is used as efficiently as possible and for maximum benefit. Best use of vaccine points to the need to minimise wastage and to target those most likely to benefit from vaccination. A move from universal to selective vaccination would greatly reduce the number of vaccinated infants from approximately 60,559 to

8,110 per annum. Should vaccination continue, selective vaccination would reduce demand for the vaccine and ensure that it is directed at those at highest risk of TB infection. Irrespective of a policy change, it is important that supply issues are clearly communicated to the public along with the implications of delayed vaccination. Delays to BCG vaccination can impact on the timing of other vaccinations in a child's immunisation schedule, with a potential impact on adherence.

6.1.3 Identification of a high-risk cohort

Under the current universal vaccination programme, the target population is all births. This facilitates identification of infants as it can form part of the general vaccination and immunisation programme. A selective vaccination programme requires the identification of a sub-population that may be specific to BCG vaccination. High-risk status is likely to be based on a variety of criteria, including country of birth or ethnicity of an infant's parents and potentially grandparents. This report has used the criteria of at least one parent from a high TB incidence country or being from the Irish Traveller community to identify high-risk status. The criteria used to define 'high-risk' must be clearly set out to facilitate training of healthcare professionals and for informing the public.

A Welsh study described the identification of TB risk in antenatal clinics, using a single tick box in the administrative form.[109] Criteria for high-risk status were clearly stated and provided to all midwifery staff. Referral to a BCG clinic was by midwifery staff and was organised following the birth of the infant.

In Finland, it was proposed that identification of high-risk infants should be through midwife-administered questionnaires at maternity clinics.[138] It was recommended that vaccination would be carried out by paediatricians.

Barriers to the identification of high-risk infants include language, the staff resources required to assess risk status, and difficulties in applying the criteria in some circumstances, for example children of mixed ethnicity.[139] Healthcare professionals must be educated in how to identify high-risk infants.[140] As risk status is tied to countries with high TB incidence; an up to date list of relevant countries as defined by the WHO should be used as part of the criteria.[141]

The NHS has BCG vaccination service specifications that require providers to implement systems for the identification of eligible individuals, and for the assessment of individuals' suitability for immunisation.[142] However, the specifications do not state how individuals might be identified, or in what setting. A review of practice across Primary Care Trusts found the majority of trusts with selective vaccination policies used risk identification primarily carried out by

midwives.[132] Alternatives reported included identification by GPs, health visitors or paediatricians. Close coordination between antenatal services and childhood vaccination services is required to deliver a selective vaccination programme.[107]

The experience in other countries suggests a preference for identification of high-risk infants before birth in antenatal clinics. The extent to which this approach may be a viable option in Ireland should be explored. High-risk status may be more accurately determined in conjunction with the parents of the child, particularly if criteria other than ethnicity or nationality are included in the definition of risk. Although self-selection may facilitate identification of some high-risk infants, it is unlikely to provide a reliable approach in general. Hence, risk status should ordinarily be determined by or in conjunction with a health professional.

A change to a selective vaccination programme will necessitate access to information to identify high-risk infants. A system that is unambiguous and consistent will reduce the burden on health professionals responsible for identifying the high-risk population. There may also be issues in locating or tracking the high-risk population as they may be more transient. This could be problematic if vaccination occurs in a community setting, and families must be contacted or followed up. However, given that vaccination occurs shortly after birth, information given at birth may be reliable for the period immediately after discharge.

6.1.4 Delivery and setting

BCG vaccination in Ireland is, at present, predominantly delivered in a community setting (approximately 70% in 2012).[122] The balance of vaccinations is carried out in a limited number of hospitals providing maternity services and is delivered in postnatal wards by community care staff. It should be noted that although community BCG clinics are explicitly for the purpose of delivering the vaccination programme, they also provide an opportunity for health care professionals to interact with mothers and newborns. Clinics therefore provide an important opportunity to monitor child welfare.

As part of the economic evaluation, the number of staff required to administer the vaccination programme was considered. The current universal vaccination programme was estimated to require 7.1 medical (senior area medical officer), 7.0 nursing (public health nurse), and 6.3 administrative (clerical officer grade) whole time equivalent staff. The equivalent staff requirements for administering vaccine in a selective programme would be 1.7 medical, 1.6 nursing, and 1.5 administrative whole time equivalent staff. These figures do not include time spent identifying high-risk infants.

The introduction of a selective BCG vaccination policy in England has been associated with substantial regional variation in implementation.[132] As criteria include the TB incidence of the area, some areas have continued universal vaccination where appropriate. The most common setting for universal vaccination was in community clinics (69%) followed by postnatal wards (31%). For selective vaccination it was in postnatal wards (50%) followed by community clinics (23%).[132] Other settings included hospital paediatric clinics and chest clinics. A Welsh study reported that the BCG vaccination service was run by TB clinical nurse specialists.[109]

A Scottish maternity hospital successfully implemented a monthly outpatient clinic to administer BCG vaccine to high-risk infants.[141] The clinic involved a staff grade paediatrician, a community nurse trained to administer BCG, and an auxiliary nurse. While a maternity hospital-based approach may be convenient for a local population, this may be less successful for hospitals with larger catchment areas.

In 2006, a multi-puncture device was removed from the market in France and replaced with an intradermal BCG device.[143] Due to a lack of staff training regarding the use of the intradermal technique and a differing safety profile, there was a decrease in BCG uptake. A year later, universal neonatal BCG vaccination ceased in France in favour of a policy of selective vaccination. BCG vaccination is available in both hospital and community settings, with GPs acting as providers of vaccinations.[144]

A selective strategy would target high-risk groups which largely comprise ethnic minorities. There may be language and information barriers to obtaining informed consent. Staff administering the vaccine would require adequate training and access to translation services to ensure informed consent is obtained.

The economic evaluation and associated review of international studies in Chapter 5.1 highlighted the disparity between the cost of administration in Ireland and other countries. From the limited cost data available, the mode of delivery in Ireland appears to be substantially more expensive than reported costs from Finland, Japan and the Netherlands. This may be due to the setting or the number of staff used to deliver the vaccination programme. Although a selective programme is predicted to reduce the absolute cost of administering BCG vaccination relative to a universal programme, the cost per vaccination is likely to increase. Consideration should be given to identifying alternative approaches to delivering the service that enhance the efficiency of service delivery, irrespective of whether the vaccination policy is changed.

The feasibility and costs of a predominantly postnatal ward-based vaccination programme should be considered. There are 19 public hospitals in Ireland providing

maternity care services. For live births, 78.1% have a length of stay of at least two days and 47.5% have a length of stay of at least three days.[36] Vaccination of infants who are discharged within one day may be problematic and would require daily rounds of vaccination. This practice could lead to substantial wastage of vaccine if only small numbers of eligible infants are present. It may not present a practical alternative in all areas, but may be more efficient in high volume maternity hospitals.

6.1.5 Uptake

The uptake of BCG vaccination in the current universal programme is an estimated 87.8%. There is no available data in Ireland for the uptake in the high-risk population. For this study it was assumed that the uptake would be lower in the high-risk population. A number of studies have reported on vaccination uptake after changes from universal to selective vaccination policies.

Vaccine uptake for high-risk infants in France was reported separately for the Île-de-France as 89.8% and outside Île-de-France as 61.7%.[145] Île-de-France has the highest TB incidence in mainland France and has a universal vaccination policy. However, it should be noted that vaccine uptake dropped 54% in the year before the move to selective vaccination after the mode of administration was changed.[146] For this reason, the introduction of selective vaccination coincided with a period of poor uptake in the general population.

A study from a French maternity hospital found increased uptake in the high-risk population after universal vaccination was ceased (increasing from 66% to 81%).[105] This may to some extent have been related to changes in the setting for delivering vaccinations.

A study of neonatal BCG uptake in England reported lower uptake in Primary Care Trusts with selective vaccination (65.6%) compared with those with universal vaccination (71.6%), although the difference was not statistically significant.[107] However, uptake was statistically significantly higher where the primary place of vaccination was the post-natal ward (72.6%) rather than community settings (63.5%). Uptake was also found to be significantly higher in areas with a high TB incidence and where there had been a previous policy of universal BCG vaccination.

An audit of a hospital-based BCG clinic targeting high-risk infants found a low uptake of 51%, with substantial variation in uptake across different ethnic groups.[106] Variation occurred in both the proportion referred for vaccination and the proportion receiving vaccination. Referral was made by midwives who identified risk status by reviewing ethnicity of parents in the maternity records. A review of activity at a Welsh maternity hospital implementing selective BCG vaccination found uptake to

vary between 36.5% and 85.3% across ethnic groups, with an average uptake of 76.0%.[109] As with the above audit, the highest uptake was in infants whose ethnic origin was the Indian subcontinent. Although single-hospital studies may not represent national uptake, they highlight some of the issues encountered in delivering a selective vaccination programme.

It is apparent that high uptake is possible in a selective vaccination programme, but this should be supported by antenatal identification of eligible infants and follow-up to ensure vaccination is completed. The evidence also suggests that uptake may be higher where vaccination is carried out in a postnatal ward rather than in a community setting. Uptake is also reliant on parents consenting to have their children vaccinated. Informed consent requires parents to be provided with suitable information to understand the implications of vaccinating or not vaccinating their child. Uptake rates may therefore be improved by ensuring the provision of adequate information to parents.

Determining uptake in a selective vaccination programme will pose challenges. For example, the denominator population will not be readily identifiable from national datasets, such as the National Perinatal Reporting System. A centralised electronic system would support reliable data collection, but local administrative systems must be in place to ensure accurate reporting. It is noted that there is, at present, regional variation in both the approach to and reporting of vaccination statistics. Such variation creates difficulties for monitoring the degree to which policies are being successfully implemented.

6.1.6 Targeted testing for latent TB infection

In most industrialised nations TB incidence is falling in the native population, but there is an elevated or increasing incidence in foreign-born residents.[147] This is evident in the disproportionate burden of TB in foreign-born residents observed in Ireland, where 40.9% of cases in 2014 were to foreign-born residents.[2] Screening provides a method of identifying those entering the country with active TB or with latent TB infection. Although screening is recommended for the high-risk population in Ireland,[5] there is no organised screening programme at present.[13]

A survey of industrialised countries found that 25 of 29 had systems in place for screening immigrants for active TB, whereas 16 of 29 screened for latent TB infection.[147] Screening was usually targeted on the basis of country of origin, with those from high TB incidence countries screened. Screening was predominantly by clinical examination combined with tuberculin skin test (TST). In most cases, screening is carried out after immigrants have arrived in the destination country. However, pre-arrival and on-arrival screening are also used in some countries.

Pre-entry screening has been shown to be a potentially useful contributor to early diagnosis and treatment of active TB cases.[148] However, screening immigrants before departure from their own country places an undue burden on those countries and immigrants, giving rise to equity and ethical issues.[149]

A systematic review of TB screening approaches found significant heterogeneity across studies.[150] Different costs and assumptions about test accuracy meant that comparison of the included studies was hampered. The evidence suggested that interferon-gamma release-assay based test strategies were more likely to be cost-effective than tuberculin skin test-based strategies.

A multi-centre cohort study in the UK evaluated the cost-effectiveness of screening immigrants for latent TB.[151] The study used interferon-gamma release-assay to detect cases of latent TB infection. A policy based largely on country of origin would identify a large portion (>90%) of infected individuals and would be considered cost-effective by UK standards.

The demand for screening is dependent on migration patterns and the numbers of migrants coming from regions that are considered to have high TB incidence. An effective TB screening programme would have to be cognisant of migration patterns and adapt to meet demand in periods of increased inward migration from high TB incidence countries.

TB screening is an important TB control mechanism, and coupled with timely treatment can reduce the risk of secondary infection. In the context of a universal vaccination programme, TB screening may have less impact on the child population given the protective effect of BCG. However, when considering a selective vaccination programme, TB screening presents a critical element of preventing childhood infection, particularly in relation to adults from high TB incidence countries who intend to work with children.

6.1.7 Treatment

The economic evaluation in Chapter 5.4 estimated that a switch to a policy of selective or no vaccination would lead to an increase in the incidence of TB.

Three studies have investigated changes to rates of childhood TB in relation to changes from universal to selective vaccination. After a switch to selective vaccination, the incidence of childhood TB increased in Sweden.[152] Incidence was linked to BCG coverage and the underlying secular trend for declining incidence that was evident before the policy change continued. An evaluation of the impact of change of policy in France found a moderate increase in childhood TB.[143] No substantial change in the number of cases of TB meningitis and miliary TB were

reported, although the study had limited follow up. A more recent French study with longer follow-up reported no increase in TB meningitis incidence in children after the shift from universal to selective BCG vaccination.[153] Due to the rare nature of TB meningitis, results are sensitive to the coding of suspected cases as distinct from confirmed cases.

Delayed commencement of treatment has implications for worsened disease severity, increased risk of death, and greater risk of disease transmission.[154] Surveillance and active case finding are important for ensuring rapid identification of TB cases. A robust information system that facilitates the tracking of cases across health service regions within Ireland would also offer greater prospects for effective case management.

A change of policy to selective vaccination would benefit from additional resources being directed at other preventive or control measures, such as TB screening, thereby limiting the impact of reduced vaccine coverage. It is also the case that selective strategies are generally adopted in countries that have observed a consistent reduction in TB incidence over time. The low rate of incidence also reduces statistical power to detect differences.

The additional cases that are likely to occur if universal vaccination is discontinued will generate additional demand for treatment. The largest absolute increases in numbers would be observed in cases of pulmonary and extrapulmonary TB. Aside from antibiotic treatment, patients with pulmonary TB require on average nine hospital days and eight paediatrician visits during the course of their treatment. Patients with extrapulmonary TB require on average 14 hospital days. A move from universal to selective vaccination will therefore place an additional burden on paediatric hospital services.

6.1.8 Contact tracing

Contact tracing is a process used to identify individuals who have been in contact with an infected individual. The purpose is to identify those with active TB infection, latent TB infection, and those who may benefit from BCG vaccination.[5] Benefits of early case detection through contact tracing include reductions in the period in which cases are infectious and the risk of secondary infections. Contact tracing is currently recommended as part of standard TB control practice in Ireland.[5]

Contact tracing is carried out for each index case. An increase in TB incidence would therefore translate into an increase in the volume of contact tracing. The staff requirements for the delivery of contact tracing were incorporated into the economic evaluation. The main staff resources used in contact tracing are a senior area medical officer and a clerical officer. The additional whole time equivalent staff

requirements for contact tracing based on a move to selective vaccination would be 0.37 senior area medical officers, 0.20 clerical officers, 0.10 specialists in public health medicine, and 0.10 public health nurses. For a strategy of no vaccination, the additional whole time equivalent requirements would be 0.59 senior area medical officers, 0.32 clerical officers, 0.16 specialists in public health medicine, and 0.16 public health nurses. Some of the additional resources required may be accessible through the reduction in staff requirements for administering vaccinations. However, the additional staff requirements for contact tracing span a variety of staff categories and experiential knowledge in the area of TB control is critical to successful management of contact tracing. Consideration must be given to how changes in resources will be managed to ensure adequate staff for contact tracing.

Contact tracing requires the cooperation and collaboration of a variety of services at national, regional and local levels. The systems required for facilitating effective and rapid communication should be in place to minimise the possibility of delays in identifying active and latent TB cases. Given the high proportion of TB cases that occur in foreign-born residents, resources such as translation services must be available to minimise barriers to successful contact tracing.

Additional childhood cases may give rise to a greater need for contact tracing, but infectivity may be lower. It is sometimes assumed that the majority of childhood TB cases can be considered non-contagious,[155] although the evidence to support this assumption is unclear.[156]

A systematic review of contact tracing investigated the incidence and prevalence of TB and latent TB in contacts of patients.[157] The pooled prevalence of previously undiagnosed active TB among contacts of all ages from high resource countries was 1.4%, although the figure was 4.7% when looking at contacts aged five years or less. The corresponding figures for latent TB infection were 28.1% for all ages and 16.3% for those aged five years or less. The review reported substantial statistical heterogeneity across studies which may reflect differences in approaches to contact tracing and in local incidence of TB. The data may point towards a higher rate of infection in child contacts than in adult contacts.

An Italian study reported on the demographics and TB incidence of a contact tracing programme.[158] Of the primary TB cases, 2.5% were aged less than 16 years. The percentage of identified contacts with primary TB cases that were aged less than 16 years was 11.9%. Thus the child population tends to have a disproportionate exposure to primary cases of TB.

These studies underline the importance of contact tracing in the early detection of childhood cases of secondary TB infection. This is particularly relevant in the context of a selective vaccination policy. The systems in place for contact tracing must be

adequately resourced to ensure that active and latent cases are detected in a timely manner to ensure the rates of secondary infection are minimised.

6.1.9 Latent TB infection

There are no symptoms associated with latent TB infection, and the infected individual cannot transmit the disease to others. Latent TB infection can be detected with immune-based tests such as the TST or interferon-gamma release-assay. There is substantial risk of latent TB developing into active TB – estimated at 5 to 10% over the person's lifetime.[18] For most individuals with latent TB infection it is recommended that they receive treatment to prevent the development of active TB.[5]

Current standard therapy includes isoniazid, which can reduce the risk of active TB by as much as 90% if taken daily for six to nine months.[159] The duration of treatment can give rise to issues with reduced completion rates. An Irish study reported low rates of completion of latent TB treatment.[160] Seventy percent of those recommended to start treatment commenced it, but less than 50% completed treatment. Patients were a mix of healthcare workers, migrants from TB endemic countries, and recent contacts of active TB cases. Few barriers to treatment acceptance were identified, although concern over medication side effects and the duration of treatment were highlighted. A similar completion rate was reported for the US and Canada.[161] Data specific to those aged less than 15 years suggests marginally higher completion rates of 50% to 60%.

Current treatment recommendations in Ireland are for a minimum six months of isoniazid; or rifampicin for four months; or rifampicin and isoniazid in combination for at least three months with an optimum of four months.[5] There is, at present, regional variation in Ireland with regard to the application of chemoprophylaxis in latent TB cases.[13] Consistent application of the guidelines across the country could contribute to greater treatment completion and minimise the risk of latent TB cases developing into active TB.

As TB is a communicable disease, TB medication should be available free of charge. However, it has been noted that some patients with medical cards have been required to pay the prescription co-payment.[13] This presents a potential barrier to treatment completion. The importance of completing treatment and the legislation regarding TB investigations and treatment should be clarified.

A change to a strategy of selective or no vaccination should be supported by a clear commitment of sufficient resources for TB control to ensure comprehensive contact tracing and follow-up of latent TB cases. Failure to adequately resource TB control programmes could have implications for TB incidence in children.

6.1.10 Preparing for a vaccination policy change

A move from universal to selective vaccination implies a change in emphasis from protection to prevention. A reduction in the level of protection must be balanced by an appropriate level of prevention, as provided through a variety of TB control measures.

The national guidelines for the prevention and control of TB in Ireland set out the requirements for TB control.[5] A number of the recommendations in those guidelines, some of which are of particular relevance to a change in BCG vaccination policy, have not as yet been implemented. For example, the guidelines recommend screening of high-risk populations, which is a key component of a prevention-centred TB control policy.

Deficiencies in the implementation of existing TB control measures have been discussed in a recent review of TB control in Ireland.[13] The authors highlighted a lack of consistent provision and inadequate resourcing as common issues. For example, it was noted that there was a loss of surge capacity for contact tracing, which can have serious implications in the context of TB outbreaks. Inadequacies in existing TB control measures can have serious consequences for the successful transition from universal to selective neonatal BCG vaccination.

The existing BCG vaccination policy, as it applies to all infants, does not require the identification of population subgroups. From a logistical and economy of scale perspective, a selective programme adds complexity and creates potential for inefficiencies. The facilities required to identify high-risk infants eligible for vaccination in a selective programme must be clearly described and tested. The criteria that define high-risk status must be clearly stated and unambiguous. An implementation plan should outline who will be responsible for high-risk identification, how it will be done, what administrative support will be provided, and how infants will be followed up. It may be possible that some or all of the information needed for high-risk identification is available in existing administrative databases. However, ensuring that the information is available to the vaccination programme in a timely manner may require additional infrastructure. Data must be managed in accordance with data protection and patient confidentiality.

The existing vaccination programme is delivered predominantly in a community setting, and achieves high uptake rates. Whether this would also be the most appropriate setting for a selective programme must be determined. Both uptake and efficiency must be taken into account when considering where vaccination should take place. If vaccination continues to take place in a community setting, then the frequency and location of clinics will be important to ensure high uptake. It is likely that different approaches may be more suitable in different parts of the country,

depending on the local population density and distribution. Performance indicators should be set in regard to both uptake and what age BCG vaccination should be given by. A move to a selective programme may result in a lower uptake in the eligible population, and hence reliable regional uptake data needs to be routinely available and monitored to determine if uptake rates have fallen below an acceptable level.

As this assessment was solely focussed on a change to the neonatal BCG vaccination policy, it was outside the scope of this project to evaluate the changes required to other elements of the TB control programme. A change to a selective BCG vaccination policy would have to be supported by a number of actions or activities that can be summarised as follows:

- Commitment

  A change in BCG vaccination policy should be underpinned by a clear commitment to ensure a consistent and appropriate level of service across the country. This would include, for example, consideration being given to addressing gaps identified by the review of TB control in Ireland.[13] A failure to address gaps in the existing service could have major implications in the context of reduced protection in the child population. Consideration should be given to the development of a National Clinical Guideline on the control of TB in line with NCEC Standards for Clinical Practice Guidance. Resources would have to be made available to support the development of such a guideline.

- Implementation

  A change to the neonatal BCG vaccination policy should be supported by a detailed implementation plan that outlines how changes to TB control will be operationalised. The processes and procedures for individual elements of the BCG vaccination programme, such as identification of high-risk infants, must be defined. The associated training requirements for healthcare staff must be outlined with a plan for how training will be delivered. If implementation is poorly specified then it is likely that TB control overall will be inadequate or that there may be substantial inefficiencies in the service provided.

- Resourcing

  A change in BCG vaccination policy and TB control generally must be adequately resourced, particularly in terms of staff. Resource requirements vary nationally, as TB incidence is higher in some areas. For a selective BCG vaccination programme, changing patterns of inward migration could impact on local resource requirements. As TB is an infectious disease, demand for resources is to

some extent dynamic and ongoing monitoring is required to ensure adequate coverage to meet local demand.

The requirements for dedicated staff for BCG vaccination, contact tracing, screening and TB treatment should be evaluated. A reliance on non-dedicated staff has implications for interdependencies that could negatively impact on the delivery of TB control.

- Responsibility

  Those responsible for different aspects of the BCG vaccination programme should be clearly identified and appropriately supported. There are issues with integration of services and providers in the existing TB control infrastructure. Clear lines of responsibility have the potential to address some of these gaps for both patients and providers.

  It may be appropriate to consider appointing a national lead for TB control. A national lead would be particularly valuable to provide oversight to a transition from universal to selective vaccination, and to monitor any other changes to TB control deemed necessary.

- Monitoring

  As a selective BCG vaccination programme is likely to result in some increase in the incidence of childhood TB cases, it will be important to monitor incidence and to assess whether fluctuations are within expected bounds. An increase in incidence should be analysed to determine the potential causes and what changes may be required to other TB control measures.

  The neonatal BCG vaccination programme should be periodically evaluated to determine whether it is achieving acceptable uptake rates and that it is being delivered efficiently. Other aspects of TB control should be monitored to ensure that they are delivered in accordance to an acceptable standard and, if not, what changes are required to adhere to the guidelines. In terms of treatment, a defined standard of care could provide clarity for both patients and providers regarding what should be delivered.

A change in the neonatal BCG vaccination policy in Ireland is consistent with the International Union Against TB and Lung Disease criteria and the WHO TB elimination strategy.[17] However, the BCG vaccination policy cannot be viewed in isolation from other TB control measures. A change from protection to prevention requires a coherent plan for any necessary changes to other TB control measures.

That plan must clearly outline the requirements, resources, and steps to ensure that TB control in Ireland is consistent with the requirements for TB elimination.

6.2 Social aspects

It is important to consider the impact of policy changes beyond the immediate clinical setting. An analysis of clinical outcomes and organisational issues identifies implications for the health services and patient outcomes, but may fail to adequately address other implications for patients or society. Some technologies, for example, may require patients to use significant quantities of their own resources (people, support, finances) before, during, and after their use. Use of a technology may have important consequences in terms of ability to work, social relationships, and the attitudes of others towards the technology user. This section considers some of the wider implications of changes to the BCG vaccination policy for individuals and in major life areas.

6.2.1 Individual

A change to the vaccination policy will clearly have an impact on individuals. Should a selective vaccination policy be adopted, those who are not vaccinated will be at increased risk of developing TB and experiencing the associated treatment. There will also be a minimal increased risk of mortality.

A change in policy is unlikely to be phased in gradually, so parents of infants will one week be advised to seek vaccination, and potentially the following week be advised not to. This transition will have to be managed so that there is a widespread understanding of the changes. If a selective programme is adopted, it will also be important that the high-risk population does not perceive that they are also no longer required to seek vaccination. Confusion over policy changes could lead to a drop in vaccination in the high-risk population which would have implications for risk of acquiring TB.

Although the individual being vaccinated is an infant, it is the infant's parents that make decisions regarding vaccination. Informed consent is given by a parent, not the infant. Due to BCG typically being offered in the weeks after birth, it can be difficult to objectively determine the relative risks and harms associated with the vaccination. If a selective vaccination programme is adopted, public awareness must be raised about why universal vaccination is no longer offered and the risks associated with not being vaccinated. Also, the parents of high-risk infants who will continue to be vaccinated must be made aware of the changes. As many of the high-risk infants will be from ethnic minorities, it will be critical to provide the relevant literature and guidance in a variety of languages and formats. While this is currently the case, it will be important that awareness campaigns about policy

changes will also be presented in multiple languages. These issues are further discussed in Chapter 7 on ethical considerations.

There is broad acceptance of BCG vaccination in Ireland, as is evidenced from the high uptake rates. There may be an expectation among parents that BCG vaccination offers complete protection from TB and that the protective effect does not reduce over time. It is also possible that the risk of acquiring TB is poorly understood. Hence, there may be an unrealistic expectation about the benefits of BCG vaccination and the harms of not being vaccinated. Although treatment for TB is generally curative, for those who contract TB meningitis there is a high-risk of long-term neurological sequelae. In a selective or no vaccination strategy, the risk of severe adverse reactions to BCG vaccination will be eliminated for those no longer receiving the vaccination. The risks and benefits must be clearly conveyed to the public in a manner that can be easily understood by all.

Regarding equity of access, a change to selective vaccination clearly targets a sub-population, in this case those from high TB incidence countries or from specific ethnic minorities. TB incidence tends to be higher in socio-economically deprived areas and a focus on the vulnerable population could be seen as a concentration of resources on those at highest need. As such it is unlikely to be perceived as a decision that will increase inequalities. While it can be viewed as positive discrimination, it may be perceived by some in a negative light and as exposing vulnerable groups to the risk of adverse events. It would be important to convey the benefits of vaccination for those at high risk as well as the potential harms. Refer to Chapter 7 for further exploration of these issues.

As the target population are infants, the harms of vaccination and the effect of TB infection impact on both the infected child as well as the parents and family of the child. Serious adverse reactions to the vaccination may require hospitalisation and parents may have to take time off work to care for their child. The treatment associated with TB infection also has major implications for a family as treatment can last for up to 12 months depending on the form of TB. Contact tracing and the risk of latent TB infection for family members also impact on those close to the infected child. The impacts for a family can be longer term if a child develops neurological complications due to TB meningitis. Adoption of a selective or no vaccination policy will have implications for both infected children and their families and will affect the public's view of the benefits or harms of a change in policy.

6.2.2 Major life areas

A change from universal to selective vaccination will result in a reduction in the protected population. Parents of infants may oppose a policy change on the grounds that they do not believe that it is in the best interests of their children. A selective

vaccination programme offers an opportunity to use resources more effectively and is entirely in line with WHO recommendations. The purpose of the policy change should be clearly outlined to the public. It may be appropriate to consider commencing any information or awareness campaigns in advance of a policy change in conjunction with efforts to ensure uptake remains high in eligible groups.

As noted, parents of infants that are identified as high-risk may perceive discrimination. It may be valuable to consult with representatives of ethnic minority groups to inform them of the rationale for policy changes, the positive impact on them, and to address concerns they may have about the process of high-risk identification. When evaluating risk status, personal details are required that individuals may consider confidential. The setting and manner in which risk status is assessed should be developed in consultation with high risk groups to ensure the appropriateness and acceptability of the process. Refer to Chapter 7 for a discussion of the ethical considerations in these issues.

The technology itself is of limited impact beyond the risk of adverse reactions, and it has widespread acceptance in Ireland. The implications of TB infection, however, are potentially much greater. Hence the technology must be viewed in terms of what may happen if it is scaled back, such as selective vaccination, or withdrawn entirely.

Given the high uptake of BCG vaccination, there is a societal expectation of its availability and benefit. Participation in vaccination may be only partly influenced by the available literature, and mainly guided by a general perception of benefit. A change in policy may take time to gain acceptance if the rationale for change does not concur with societal understanding of the risks and benefits.

6.3 Summary

A change from a universal to a selective or no vaccination programme would have implications for the organisation of services in Ireland. In terms of vaccination, the number of eligible infants would decrease substantially which would have a consequent impact on the resources required to deliver that service. A reduction in vaccine requirements may address some of the issues associated with ongoing shortages of BCG and ensure that available resources are focused on those most likely to benefit from vaccination. A selective vaccination programme should be based on a set of unambiguous and uniformly applied criteria that are clear to both health professionals and the general public.

Selective vaccination involves the need to identify high-risk infants, a practice which is not currently necessary due to universal eligibility. A consistent approach to risk classification should be adopted which will require staff training. There is limited international evidence on risk classification, however it appears that antenatal

identification of risk status in maternity hospitals is effective. Vaccination carried out in postnatal wards may be more efficient than the current practice of mostly community-based BCG clinics. Once eligible infants return to the community, follow-up to ensure high uptake can be challenging. A strategy for public awareness and information dissemination should be planned to ensure high uptake is maintained in a selective programme.

TB screening and contact tracing are critical components of a TB control programme. A selective or no vaccination strategy will mean a large proportion of children will have no protection against TB. An appropriately resourced and consistent approach to screening and contact tracing will be required to contain the spread of TB from index cases to unprotected children. In the interest of public health, a change of vaccination strategy should be supported by a clear commitment to systematic and comprehensive TB control. Changes to TB control should be introduced before a change in vaccination policy in order to minimise the impact of reduced BCG coverage. Investing in TB control while continuing to provide universal BCG vaccination implies that for a period there will be a net increase in the resources required for TB control, and this must be recognised for planning and budgetary purposes.

In the absence of changes to other elements of the current TB control programme, a strategy of selective or no vaccination has the potential to result in additional cases of TB in children, placing an additional burden on health services. However, this must be counterbalanced by a likely reduction in the risk of severe adverse reactions to BCG.

The BCG vaccination policy cannot be viewed in isolation from other TB control measures. A change in emphasis from protection to prevention requires a coherent plan for changes to other TB control measures. That plan must clearly outline the requirements, resources, and steps to ensure that TB control in Ireland is consistent with the requirements for TB elimination.

From a social perspective, there is widespread acceptance of the existing universal vaccination policy. There may be expectations about the benefits and harms of BCG vaccination that are not supported by the available evidence. A change to selective vaccination may not initially have public backing, and should be supported by a public awareness campaign that clearly states the rationale for change. For a selective strategy, awareness is also required to ensure that high-risk families understand the need to seek vaccination and to maintain a high uptake in eligible infants.

For a selective programme, it would be very important to consult with high-risk groups to determine the most acceptable and efficient way to identify those eligible for vaccination, and how best to deliver the programme to ensure a high uptake.

6.4 Key messages

- A selective vaccination programme should be based on a set of unambiguous and uniformly applied criteria that are clear to both health professionals and the general public.
- A consistent approach to risk classification should be adopted which will require staff training. There is international evidence that antenatal identification of risk status in maternity hospitals may be both efficient and effective.
- The efficiency of alternative configurations to the current predominantly community-based programme should be evaluated.
- An appropriately resourced and consistent approach to screening and contact tracing will be required to contain the spread of TB from index cases to unprotected children. Any change of vaccination strategy should be supported by a clear commitment of sufficient resources for TB control. Consideration should be given to the development of a National Clinical Guideline on the control of TB.
- Changes to TB control should be supported by a plan specifying the necessary requirements, resources, and steps. Changes to other elements of TB control should be introduced before a change in vaccination policy in order to minimise the impact of reduced BCG coverage.
- A change to a selective vaccination programme should be supported by a public awareness campaign that clearly states the rationale for change. Awareness is also required to ensure that high-risk families understand the need to seek vaccination and to maintain a high uptake in eligible infants.

7. Ethical analysis

This chapter considers the key ethical issues to reflect on when considering changes to the current policy regarding neonatal BCG vaccination.

7.1 Context

Public health programmes raise a range of ethical issues which require consideration by policy makers. While governments have an obligation to protect the health and wellbeing of citizens, this must be achieved in a way that is equitable, non-discriminatory, transparent and, as far as possible, non-coercive. Vaccination of the population is one means by which governments achieve the objective of preventing infectious disease and although it is reasonable for governments to aim for high vaccination rates, analysis of the risks and benefits to individuals and the population at large must continuously be re-assessed. It must also be recognised that, in keeping with respect for the right to self-determination, individuals have the right to opt-out of such programmes. In this sense, there may be conflict between public and private interests within which a balance must be struck between competing values and principles.

The BCG vaccination programme in existence in Ireland is used primarily for the prevention of tuberculosis. Although traditionally a universal programme here, in many countries in Europe and in North America, the use of selective vaccination is common with many jurisdictions never having introduced universal vaccination.

The purpose of this HTA is to determine the impact of changing from the current policy of universal neonatal BCG vaccination to a selective programme targeting high-risk individuals who will be classified on the basis of risk according to the country of origin of their parents and other factors, or to a policy of no vaccination.

7.2 Ethical principles

Verweij and Dawson[(162)] suggest that there are seven principles that should guide ethical reflection and decision making in relation to collective vaccinations as follows:

1. Collective vaccination programmes should target serious diseases that are a public health problem.

2. Each vaccine, and the programme as a whole, must be effective and safe.

3. The burdens and inconveniences for participants should be as small as possible.

4. The programme's burden/benefits ratio should be favourable in comparison with alternative vaccinations schemes or preventative options.

5. Collective vaccination programmes should involve a just distribution of benefits and burdens.

6. Participation should generally be voluntary unless compulsory vaccination is essential to prevent concrete and serious harm.

7. Public trust in the vaccination programme should be honoured and protected.

7.3 Risk – benefit

The BCG vaccination programme was originally introduced in Ireland to target a serious disease, namely tuberculosis (TB), at a time when the epidemiology of TB was quite different. The vaccination programme has been associated with substantial reductions in TB outcomes and although adverse reactions to this particular vaccine are common, they generally tend to be mild with few infants requiring further intervention. However, the risk of severe adverse reactions is substantially higher among immunocompromised children. Apart from the low incidence of serious adverse reactions for the majority of infants, vaccination can also cause infection at the injection site and is likely to leave a noticeable scar on the upper arm.

The current vaccination programme is based on universal access and therefore the benefits and burdens are intended to be distributed equally and justly throughout the population. The personal benefit to high-risk individuals is the protective effect the vaccine offers, although this declines over time. Vaccination of high-risk individuals also means they will be less likely to infect others and therefore it confers a benefit to those who may not be vaccinated. However, the benefit to low-risk individuals is low and this raises the issue of whether it is ethical to vaccinate low-risk individuals in order to benefit others.

Even though the potential negative side effects of vaccination are relatively small, it is still of moral significance that thousands of infants in the low-risk category experience such small burdens for comparatively little benefit to themselves. The ethical principle of respect for persons means that people should not be used solely as a means to an end and that even small burdens and inconveniences should be avoided or minimised wherever possible. A policy based on respect for persons also contributes to public trust and willingness to participate in public health programmes generally, which is clearly in the public interest.

7.4 International evidence

The indirect population effect of mass vaccination in terms of reducing the number of infectious cases, and hence limiting future transmission to the uninfected population, is considered to be minimal in low prevalence countries. Therefore, internationally, BCG vaccination in populations with a low prevalence of tuberculosis disease is no longer considered necessary.[12] A report from the Department of Health in Australia in 2013[163] states that such an intervention should be directed at well-defined, high-risk groups principally because of its direct effect in reducing the serious consequences from primary infection.[4]

Many European countries have either never had universal vaccination or have changed to selective vaccination programmes. In the United States, BCG was sometimes administered to healthcare workers at risk for tuberculosis (TB) until the middle of the twentieth century but was never adopted for routine childhood immunization. BCG has been recommended in the United States only for immunocompetent children and adults who have high-risk of ongoing exposure that cannot be avoided.

7.5 Potential harm arising from change in policy

It is likely that there will be an increase in TB cases as a result of changing from universal to selective vaccination in Ireland. This may be regarded by some members of the public as a step taken for economic reasons rather than arising from a consideration of the risks and benefits of universal versus selective programmes. Therefore if it is decided to proceed with selective vaccination, it is important to communicate this message clearly so as to reassure the public about the rationale and international scientific basis for this decision in order to maintain public trust in the vaccination programme.

The targeting of specific population groups for vaccination may be seen as potentially discriminatory. Discrimination is regarding or treating others differently on the basis of a particular characteristic such as age, gender, or ethnicity. There is however a difference between positive and negative discrimination – positive discrimination is giving more favourable treatment to those who have a particular characteristic, while negative discrimination is giving less favourable treatment. Not all discrimination is morally or ethically wrong as some forms of positive action in favour of socially disadvantaged groups are justified by sound reasons such as to reduce the effect of health inequities. In the context of health policy, selection of particular groups for public health interventions is justified on the basis of risk assessment (for example, flu vaccine for the elderly) and effective curtailment of the spread of disease. Prioritisation of the use of resources, such as a vaccine, can also

be justified on the same basis by targeting those most likely to benefit. Moving to selective vaccination is therefore justified as a specific protective measure for high-risk groups and avoidance of the burden of vaccination for those for whom it carries no benefit.

It is also important to be clear that although no individual has a legal right to be vaccinated as such, if parents specifically request BCG vaccination of their child, this might be facilitated as long it was not perceived to present undue risk of harm to the child. The cost associated with the vaccination should be borne by the parents or by the State in the case of medical card holders.

7.6 Classification of low and high-risk infants

Another ethical issue arising is in relation to the classification of infants as low and high-risk. The identification of infants as high-risk will be based on the country of origin of their parents or potentially their grandparents, or if they come from a particular ethnic group with high incidence.

Classification of infants will therefore be based on information provided by the infant's parents or guardians in a clinic or hospital setting. The process of seeking relevant information in relation to ethnicity or nationality is one that may raise privacy and sensitivity concerns for many parents and therefore it must be carried out in a way that is non-discriminatory and consistent with the privacy of the infant and the family. In order to ensure trust in the selective vaccination programme, parents must be assured that the information is being sought for an appropriate purpose and will not be used or accessed for other services.

There is a possibility of mistaken classification of infants based on incorrect information provided by parents or guardians. Although every effort should be made to avoid such errors, it is nonetheless possible that some low-risk infants will be vaccinated unnecessarily or some high-risk infants will not receive vaccination. Low-risk infants who receive the vaccination unnecessarily will not generally sustain harm beyond the mild adverse reactions and scar mentioned above.

It is also possible that some parents may seek to dispute the classification of their child as high-risk. A policy should be devised to enable staff to resolve such disputes without undue conflict or intrusion into the family. Given that parents are entitled to refuse permission for vaccination, best practice in situations where the parents dispute the classification of the child as high-risk might be to simply treat this as a refusal and respect the parents' wishes on that basis.

Even where appropriate measures have been taken to ensure privacy, there is still a risk of stigmatisation arising from the presence of a visible scar on the infant's arm.

In 2007 when France changed to selective vaccination, the potential for discrimination linked to the criteria used to define the children for whom BCG vaccination would be recommended was addressed through consultations with the French National Ethics Committee and the French Authority against Discrimination. In addition, the Ministry of Health called for a citizens' conference to discuss this issue which was held by the French Society of Public Health. There are advantages to be gained by public discussion of such topics not only in the context of education and public awareness of the risks and benefits of BCG vaccination but also in relation to prevention of discrimination and stigmatisation of those in high-risk categories. Public consultation gives those in high-risk categories the opportunity to be heard and to voice their concerns about the identification and classification process. This is consistent with ethical principles of transparency and equality.

Communication of risk and raising awareness of the change in policy must be achieved specifically across all potentially affected groups as well as amongst the general population. English language proficiency and literacy issues may be prevalent in all sectors and must be catered for through the provision of accessible information in a range of formats.

7.7 Consent

The constituent elements of valid informed consent are capacity, disclosure and understanding of adequate information, and agreement. Where the proposed intervention involves children who are too young to participate in the consent process themselves, parents and, or legal guardians are invited to give consent on their behalf. Appropriate guidelines and policies should be in place to ensure that all elements of the consent process are present.[164]

The giving of clear and comprehensible information is crucial to obtaining informed consent from parents/legal guardians for vaccination of their children. Such information must be provided in a form, manner and language that are comprehensible to the parents/legal guardians. This may require additional resources to be made available for translation and adult literacy services. Sufficient time must also be afforded to parents and guardians to enable them to reflect on the choices available before making their decision.

Respect for refusal of permission for an intervention is a core element of respect for autonomy and has been recognised in law[165] and in professional guidelines in Ireland.[166] A person who has decision-making capacity is entitled to refuse an intervention on their own behalf even if the consequences may be fatal. Similarly parents and legal guardians are generally entitled to make such decisions for their children although there may be exceptional circumstances in which the courts may intervene to protect the health and well-being of the child.[167] As a general rule

therefore, refusal by parents and guardians of vaccination of their child must continue to be respected even in the high-risk groups. In the event that a child later becomes infectious with TB, protection and detention measures may on rare occasions of non-compliance with treatment regimens be necessary in order to prevent spread of the disease. While such consequences are considered rare, it might be advisable to make parents aware of such a possibility as part of the informed consent process. However, any such information should be provided in a neutral way that is not perceived as a threat to parents to induce them to give their consent.

Other issues relating to consent and vaccination include whether both parents or guardians should give consent, whether non-married fathers who are not guardians of their children can give consent, and whether parents who themselves are under the age of 16 years can give consent.

In the absence of clear legislation on this issue, the HSE National Consent Policy takes the view that the consent of one legal guardian is sufficient unless both have indicated a wish and willingness to participate in decision-making for the child or unless the consequences of the intervention may have profound and irreversible consequences for the child. Under current Irish law, an unmarried father is not an automatic legal guardian of his child unless steps have been taken to apply for guardianship either by statutory declaration or court order.[1] Therefore the informed consent process should seek confirmation from the person giving consent that they are legally authorised to do so. This is a sensitive matter which may cause upset and conflict in some circumstances where parents are not aware of the legal situation and perceive their status as parent to be under suspicion.

In relation to parents who are under the age of 16 years, the HSE National Consent Policy states that all parents, irrespective of age, are presumed to be the best decision-makers for their children. However, if the decision made by the parents is considered not to be in the best interests of the infant, the maternal grandparents might be invited to participate in a discussion regarding the decision. In exceptional circumstances, legal advice should be sought.

These consent issues may be potentially difficult and sensitive matters for staff to deal with and therefore appropriate training should be provided.

[1] Staff should receive training on the changes introduced in the Children and Family Relationships Act 2015 in this regard.

7.8 Key messages

- Public health programmes raise a range of ethical issues which require consideration by policy makers. While governments have an obligation to protect the health and wellbeing of citizens, this must be achieved in a way that is equitable, non-discriminatory, transparent and, as far as possible, non-coercive. Refusal by parents and guardians to have their child vaccinated must continue to be respected even in the high-risk groups.
- Even though the potential negative side effects of vaccination to low-risk individuals through a universal vaccination programme are relatively minor, it is still of moral significance that thousands of infants in the low-risk category experience such a burden for comparatively little benefit to themselves.
- It is likely that there will be an increase in TB cases as a result of changing from universal to selective vaccination in Ireland. Any decision to proceed with selective vaccination arising from a consideration of the risks and benefits of universal versus selective programmes should be communicated clearly so as to maintain public trust in the vaccination programme.
- The targeting of specific population groups for vaccination may be seen as potentially discriminatory. In the context of health policy, selection of particular groups for public health interventions is justified on the basis of risk assessment and targeting of those most likely to benefit. Moving to selective vaccination is therefore justified as a specific protective measure for high-risk groups and avoidance of the burden of vaccination for those for whom it carries little or no benefit.
- The process of seeking relevant information in relation to ethnicity or nationality must be carried out in a way that is non-discriminatory and consistent with the privacy of the infant and the family.
- The constituent elements of valid informed consent are capacity, disclosure and understanding of adequate information, and agreement. The giving of clear and comprehensible information is crucial; translation and adult literacy services may be required. Other consent issues include identification of high-risk groups, the perception that a visible scar at the injection site may stigmatise and whether a parent is legally authorised to give consent as in the case of an unmarried father. Appropriate training of staff in managing potentially difficult and sensitive consent issues should be provided.

8. Summary of findings

A health technology assessment (HTA) is intended to support evidence-based decision making in regard to the optimum use of resources in healthcare services. Measured investment and disinvestment decisions are essential to ensure that overall population health gain is maximised, particularly given finite healthcare budgets and increasing demands for services provided. The purpose of this HTA was to examine potential changes to the existing universal neonatal BCG vaccination programme. Evidence of the safety and effectiveness of BCG vaccination was assessed as well as the cost-effectiveness, budget impact, ethical issues, and organisational and social aspects associated with the alternatives of selective vaccination of high-risk infants and a policy of no vaccination.

8.1 Description of the technology

Human tuberculosis (TB) is an infectious disease caused by bacteria of the Mycobacterium tuberculosis complex of which *M. Tuberculosis* is the most and important agent causing human disease. TB is a treatable and curable disease with the majority of non multi-drug resistant cases cured with a standard six-month treatment course. Multidrug-resistant TB can also occur, requiring more complex treatment regimens over periods of more than 18 months.

There is one licensed product available for immunisation against TB in Ireland, the BCG Vaccine Statens Serum Institut. This strain has been used in the immunisation programme since July 2002 and is administered by intradermal injection.

The current national policy is universal vaccination where all newborns are vaccinated, with the exception of county Galway where a programme of school-age vaccination has continued. A recommendation to switch to a policy of selective neonatal vaccination has been made based on epidemiological data on TB incidence, International Union Against TB and Lung Disease criteria for discontinuing BCG vaccination, and the incidence of BCG reactions.

Ireland and Portugal are the only two Western European countries with a policy of universal neonatal vaccination despite not being considered as a high TB incidence countries using the International Union Against TB and Lung Disease criterion (greater than or equal to 40 cases per 100,000 population).

8.2 Burden of disease

TB incidence has been in decline in Ireland over the last 25 years. In 2014 there were 324 cases of TB, equivalent to 7.0 cases per 100,000 persons. The average

annual number of cases in children aged less than 15 years in Ireland was 20.9 cases per year between 2005 and 2014, and 11.7 cases per year between 2012 and 2014. The incidence rate amongst children in Ireland is similar to that in most Western European countries. There is substantial regional variation in Ireland, but no local health office area would be considered high incidence based on the WHO metric of ≥40 cases per 100,000 persons per annum. The average annual notification rate of smear-positive pulmonary TB cases is less than five and the average annual notification rate of TB meningitis in children aged less than five years is below one per 10 million general population, two of the International Union Against Tuberculosis and Lung Disease criteria for stopping or modifying the BCG vaccination programme.

Treatment for TB is curative and based on antibiotics. Treatment typically lasts 6 to 12 months for non-multi-drug resistant forms of TB. Between 2002 and 2014 there were no recorded TB-related deaths in 0 to 15 year olds in Ireland. Although a rare event, TB meningitis is associated with a high probability of permanent effects such as hearing or neurological deficits. Between 2005 and 2014 there were nine cases of TB meningitis in 0 to 15 year olds.

Children from high TB incidence countries, or born to parents from high TB incidence countries, are at higher risk of developing TB. Irish Travellers are also considered to be at an elevated risk of developing TB. An estimated 13.4% of children born in Ireland each year may be classified as high-risk based on the ethnicity or country of origin of their parents. The risk of TB in high-risk children is approximately 4.4 times that of children not at high risk.

8.3 Clinical effectiveness and safety

A systematic review was carried out to identify relevant studies of the efficacy of neonatal and infant BCG vaccination for the prevention of TB. Four randomised controlled trials (RCTs) and 10 case-control studies were included in the review. The evidence of efficacy was analysed as the relative risk of TB in the vaccinated population, with values of less than one implying a protective effect due to vaccination. The relative risks were estimated as: 0.40 for pulmonary TB; 0.14 for extrapulmonary TB; 0.15 for TB meningitis; 0.08 for miliary TB; and 0.16 for TB mortality.

The RCT evidence was largely derived from North American studies conducted in the 1930s and 40s. The data obtained from the published RCTs represents the best available evidence and are likely to be broadly accurate for Ireland. Despite the substantial uncertainty, BCG vaccination appears to have a significant protective effect against TB and the effect may last for up to 15 years.

BCG may be associated with severe adverse reactions. The rate of reported adverse reactions in Ireland is approximately 1 in 1,169 vaccinations. Severe reactions include lymphadenitis and suppuration, and sometimes require medical or surgical intervention. In Ireland there has been a high rate of disseminated BCG, with one case in every 83,000 vaccinations compared with the international estimate of one in 230,000 to 640,000 vaccinations. Disseminated BCG is associated with a very high risk of mortality and is more likely to occur in infants with a compromised immune system. In Ireland there were eight confirmed cases of disseminated BCG in 10 years and all survived.

8.4 Economic evaluation

A strategy of selective vaccination will result in 19.9 additional cases of paediatric TB in the birth cohort, with a strategy of no vaccination resulting in 31.5 additional cases when compared with the current universal vaccination programme. Taking into account recent trends in childhood TB incidence in Ireland, a programme of selective vaccination would be likely to result in between three and four additional cases of TB each year relative to universal vaccination. Mortality in the single birth cohort followed to to age 15 years was 0.30 for universal vaccination, 0.37 for selective vaccination, and 0.44 for no vaccination.

In terms of life years gained, universal vaccination was found to be marginally less effective and substantially more costly than an alternative of selective vaccination. Compared with no vaccination, a strategy of selective vaccination generated an incremental cost-effectiveness ratio (ICER) of €340,520 per life year gained. Based on quality-adjusted life years, universal vaccination was estimated to be marginally more effective and substantially more costly than an alternative of selective vaccination, with an ICER of €2,549,822 per life year gained. Selective vaccination had an ICER of €139,557 per quality-adjusted life year compared with no vaccination. Neither universal or selective vaccination would be considered cost-effective at willingness-to-pay thresholds of up €45,000 per life year gained or per QALY.

The annual budget impact of a selective vaccination programme would be €1,053,971 less than the current universal vaccination strategy. A policy of no vaccination would have an annual budget impact of €1,267,548 less than universal vaccination. The estimated budget savings may not be realised due to the need to invest in other aspects of TB control.

A significant contributor to the cost of the modelled BCG vaccination programmes is the cost of administering the vaccine. The cost in Ireland is far in excess of that reported in other economic evaluations. Substantial reductions in the cost of administration could render a programme of vaccination cost-effective. The cost of

administering a selective programme did not include resources required to identify high-risk infants or costs associated with extending other TB control measures such as latent TB infection screening.

A number of the parameters were specified with values that may overestimate the benefits of a vaccination programme. Sensitivity and scenario analyses indicate that a selective programme may be less cost-effective (relative to no vaccination) than estimated in the main analysis. The main analysis used a conservative estimate of TB risk based on data from 2005 to 2014. However, if more recent childhood TB incidence rates continue, then selective vaccination would be associated with lower overall mortality than the universal vaccination programme.

8.5 Organisational and social aspects

A selective vaccination programme should be based on a set of unambiguous and uniformly applied criteria that are clear to both health professionals and the general public.

In the event that a policy of selective vaccination be adopted, a consistent approach to risk classification should be implemented which will require staff training. A change in policy that reduces the coverage of vaccination would likely lead to increased incidence of TB in children. An appropriately resourced and consistent approach to screening and contact tracing would be required to contain the spread of TB from index cases to unprotected children.

Any change of vaccination strategy should be supported by a clear commitment of sufficient resources for TB control. A change in emphasis from protection to prevention requires a coherent plan for changes to other TB control measures. That plan must clearly outline the requirements, resources, and steps to ensure that TB control in Ireland is consistent with the requirements for TB elimination. Consideration should be given to the development of a National Clinical Guideline on the control of TB.

Changes to TB control should be introduced before a change in vaccination policy in order to minimise the impact of reduced BCG coverage. Investing in TB control while continuing to provide universal BCG vaccination will result in a temporary net increase in the resources required for TB control, which has implications for planning and budgeting.

A change to selective vaccination should be supported by a public awareness campaign that clearly states the reasons for the change. Awareness is also required to ensure that high-risk families understand the need to seek vaccination and to maintain a high uptake in eligible infants.

8.6 Ethical considerations

Public health programmes raise a range of ethical issues which should be considered by policy makers. While governments have an obligation to protect the health and wellbeing of citizens, this must be achieved in a way that is equitable, non-discriminatory, transparent and, as far as possible, non-coercive. Refusal by parents and guardians to have their child vaccinated must continue to be respected even in the high-risk groups.

The targeting of specific population groups for vaccination may be seen as potentially discriminatory. In the context of health policy, selection of particular groups for public health interventions is justified on the basis of risk assessment and targeting of those most likely to benefit. Moving to selective vaccination is therefore justified as a specific protective measure for high-risk groups and avoidance of the burden of vaccination for those for whom it carries little or no benefit.

In undertaking risk-classification, the process of seeking relevant information in relation to ethnicity or nationality must be carried out in a way that is non-discriminatory and consistent with the privacy of the infant and the family.

The constituent elements of valid informed consent are capacity, disclosure and understanding of adequate information, and agreement. The giving of clear and comprehensible information is crucial; translation and adult literacy services may be required. Other consent issues include identification of high-risk groups, the perception that a visible scar at the injection site may stigmatise and whether a parent is legally authorised to give consent as in the case of an unmarried father. Appropriate training of staff in managing potentially difficult and sensitive consent issues should be provided.

8.7 Conclusions

Health technology assessment supports evidence-based decision making in regard to the optimum use of resources in healthcare services. Measured investment and disinvestment decisions are essential to ensure that overall population health gain is maximised, particularly given constrained healthcare budgets and increasing demands for services provided.

Bearing in mind the estimates and assumptions that were used in this analysis, the following conclusions may be drawn. Ireland has a childhood TB incidence similar to other Western European countries. With the exception of Ireland and Portugal, no other Western European country has a programme of universal BCG vaccination. Based on recent patterns of TB incidence, Ireland meets the International Union Against TB and Lung Disease criteria for stopping or changing the BCG vaccination

policy. Selective vaccination will protect children most at risk of contracting TB while avoiding adverse effects of the vaccine in children who are least likely to benefit from vaccination. Selective vaccination delivers a programme that minimises adverse events while a universal programme maximises benefits, but at the expense of increased adverse events.

Universal vaccination is not cost-effective. Selective vaccination was found to be not cost-effective relative to a programme of no vaccination. Should selective vaccination be adopted, the most efficient method of delivering the programme must be determined. A change in emphasis from protection to prevention requires a coherent plan for modifications to TB control measures other than BCG vaccination. Changes to other elements of TB control should be introduced before a change in vaccination policy in order to minimise the impact of reduced BCG coverage.

Glossary

Adverse event	Any noxious, pathological or unintended change in anatomical, physical or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of a clinical study whether or not considered treatment related. It includes exacerbation of pre-existing conditions or events, intercurrent illnesses, accidents, drug interaction or the significant worsening of disease.
Autonomy	The patient's right of self-determination concerning medical care. It may be used in various senses including freedom of action, effective deliberation and authenticity. It supports such moral and legal principles as respect for persons and informed consent. Making decisions for oneself, in light of a personal system of values and beliefs.
Bias	In general, any factor that distorts the true nature of an event or observation. In clinical investigations, a bias is any systematic factor other than the intervention of interest that affects the magnitude of (that is to say, tends to increase or decrease) an observed difference in the outcomes of a treatment group and a control group.
Budget impact analysis	The financial impact of the introduction of a technology or service on the capital and operating budgets of a government or agency.
Casemix	The mix of patients treated by a hospital in terms of treatment complexity. Reimbursement for the cost of patient care in the Irish public hospital system is based on casemix.
Clinical outcome	An outcome of major clinical importance that is defined on the basis of the disease being studied (for example, fracture in osteoporosis, peptic ulcer healing and relapse rates).

Clinical significance	A conclusion that an intervention has an effect that is of practical meaning to patients and healthcare providers.
Cohort study	An observational study in which outcomes in a group of patients that received an intervention are compared with outcomes in a similar group, that is to say, the cohort, either contemporary or historical, of patients that did not receive the intervention.
Comparator	The technology to which an intervention is compared.
Complication	A secondary disease or condition that develops in the course of a primary disease or condition and arises either as a result of it or from independent causes.
Confidence interval (CI)	Depicts the range of uncertainty about an estimate of a treatment effect.
Contraindication	A clinical symptom or circumstance indicating that the use of an otherwise advisable intervention would be inappropriate.
Cost per QALY	A measure used in cost utility analysis (CUA) to assist in comparisons among programmes; expressed as monetary cost per unit of outcome.
Cost-effectiveness analysis (CEA)	A comparison of alternative interventions in which costs are measured in monetary units and outcomes are measured in non-monetary units, e.g. reduced mortality or morbidity. (See also Cost per QALY).
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis of alternative interventions in which costs are measured in monetary units and outcomes are measured in terms of their utility, usually to the patient, for example, using QALYs.
Discount rate	The interest rate used to discount or calculate future costs and benefits so as to arrive at their present values, for example, 3% or 5%. This is also known as the opportunity cost of capital investment.

Discounting	The process used in cost analyses to reduce mathematically future costs and/or benefits/outcomes to their present value.
Disseminated BCG	A rare life-threatening complication of BCG administration, characterised by miliary pulmonary nodules. Presentation can mimic tuberculosis, both in symptoms and on radiological imaging.
Economic evaluation	The comparative analysis of alternative courses of action, in terms of their costs and consequences.
Economic model	In healthcare, a mathematical model of the patient pathway that describes the essential choices and consequences for the interventions under study and can be used to extrapolate from intermediate outcomes to long-term outcomes of importance to patients.
Effectiveness	The benefit (for example, to health outcomes) of using a technology for a particular problem under general or routine conditions.
Efficacy	The benefit of using a technology for a particular problem under ideal conditions, for example, in a laboratory setting or within the protocol of a carefully managed randomised controlled trial.
Efficiency	The extent to which the maximum possible benefit is achieved out of available resources.
Epidemiology	The study of the distribution and determinants of health-related states or events in specified populations.
Equity	Fairness in the allocation of resources or treatments among different individuals or groups.
Ethics	A general term for what is often described as the science of morality. In philosophy, ethical behaviour is that which is good. The goal of a theory of ethics is to determine what is good, both for the individual and for society as a whole.

EU27	EU-27 is the European Union of 27 Member States: Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the UK.
Evidence-based medicine	The use of current best evidence from scientific and medical research to make decisions about the care of individual patients. It involves formulating questions relevant to the care of particular patients, systematically searching the scientific and medical literature, identifying and critically appraising relevant research results, and applying the findings to patients.
Fistula	A permanent abnormal passageway between two organs in the body or between an organ and the exterior of the body.
Forest plot	A plot showing a series of lines and symbols which represent the results of a meta-analysis.
Funnel plot	A graphical display of sample size plotted against effect size that can be used to investigate publication bias.
Health outcomes	The results or impact on health of any type of intervention (or lack of), for example, a clinical procedure, health policy or programme, and so on.
Health-related quality of life (HRQoL)	A multi-dimensional measure comprising the physical and mental health perceptions of a patient in terms of health status, health risks, functional status, social support, and socioeconomic status.
Health technology	Any intervention that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. This includes the pharmaceuticals, devices, procedures and organisational systems used in healthcare.

Health technology assessment (HTA)	Health technology assessment (HTA): the systematic evaluation of properties, effects, and/or impacts of healthcare technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in healthcare. HTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods.
Heterogeneity	In meta-analysis, heterogeneity refers to variability or differences in the estimates of effects among studies. Statistical tests of heterogeneity are used to assess whether the observed variability in study results (effect sizes) is greater than that expected to occur by chance.
Hierarchy of evidence	Studies are often grouped into a hierarchy according to their validity or the degree to which they are not susceptible to bias. The hierarchy indicates which studies should be given most weight in an evaluation.
HTA	Health technology assessment.
Iatrogenic	An adverse condition in a patient resulting from treatment by a physician or surgeon.
Immune reconstitution syndrome	A condition in which the immune system responds to a previously acquired opportunistic infection with an overwhelming inflammatory response that paradoxically makes the symptoms of infection worse.
Incidence	The rate of occurrence of new cases of a disease or condition in a population at risk during a given period of time, usually one year.
Incremental cost	The additional costs that one intervention imposes over another.
Incremental cost-effectiveness ratio (ICER)	The ratio of incremental costs to incremental benefits (difference in effect of patient outcome) obtained when comparing two technologies, for example, additional

	cost per QALY.
Indication	A clinical symptom, risk factor, or circumstance for which the use of a particular intervention would be appropriate as determined or specified.
Informed consent	The legal and ethical requirement that no significant medical procedure can be performed until the competent patient has been informed of the nature of the procedure, risks and alternatives, as well as the prognosis if the procedure is not done. The patient must freely and voluntarily agree to have the procedure done.
Justice	The principle that states that fairness requires equals to be treated equally.
Keloid	Keloids are an exaggerated connective tissue response of injured skin that extend beyond the edges of the original wound.
Literature review	A summary and interpretation of research findings reported in the literature. May include unstructured qualitative reviews by single authors as well as various systematic and quantitative procedures such as meta-analysis. (Also known as overview.)
Lymphadenitis	An infection of the lymph nodes which leads to swelling of the lymph nodes.
Meta-analysis	Systematic methods that use statistical techniques for combining results from different studies to obtain a quantitative estimate of the overall effect of a particular intervention or variable on a defined outcome.
Osteitis	Inflammation of bone, often with enlargement, tenderness, and a dull, aching pain.
Outcomes	Components of patients' clinical and functional status after an intervention has been applied.
p value	In hypothesis testing, the probability that an observed

	difference between the intervention and control groups is due to chance alone if the null hypothesis is true.
Papule	A papule is a solid raised lesion that has distinct borders and is less than 1 cm in diameter. Papules may have a variety of shapes in profile and may be associated with secondary features such as crusts or scales.
Prevalence	The number of people in a population with a specific disease or condition at a given time, usually expressed as a proportion of the number of affected people to the total population.
Quality of evidence	Degree to which bias has been prevented through the design and conduct of research from which evidence is derived.
Quality of life (QOL)	See Health-related quality of life.
Quality-adjusted life year (QALY)	A unit of healthcare outcomes that adjusts gains (or losses) in years of life subsequent to a healthcare intervention by the quality of life during those years.
Random effects model	A statistical model sometimes used in meta-analysis in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis.
Randomised controlled trial (RCT)	An experiment of two or more interventions in which eligible people are allocated to an intervention by randomisation. The use of randomisation then permits the valid use of a variety of statistical methods to compare outcomes of the interventions.
Relative risk (RR) (risk ratio)	The ratio of (statistical) risk in the intervention group to the risk in the control group. A relative risk of one indicates no difference between comparison groups. For undesirable outcomes an RR that is less than one indicates that the intervention was effective in reducing

	the risk of that outcome.
Risk assessment	The qualitative or quantitative estimation of the likelihood of adverse effects that may result from exposure to specified health hazards or from the absence of beneficial influences.
Risk factor	An aspect of a person's condition, lifestyle or environment that increases the probability of occurrence of a disease. For example, cigarette smoking is a risk factor for lung cancer.
RR	See Relative Risk.
SD	See Standard deviation.
Sensitivity analysis	A means to determine the robustness of a mathematical model or analysis (such as a cost-effectiveness analysis or decision analysis) that tests a plausible range of estimates of key independent variables (for example, costs, outcomes, probabilities of events) to determine if such variations make meaningful changes to the results of the analysis.
Standard deviation (SD)	A measure of the dispersion of a set of data from its mean.
Statistical significance	Statistical significance: a conclusion that an intervention has a true effect, based upon observed differences in outcomes between the treatment and control groups that are sufficiently large so that these differences are unlikely to have occurred due to chance, as determined by a statistical test.
Stochastic	A stochastic process is one that involves random elements so that the outcome varies each time the process is repeated.
Study validity	The degree to which the inferences drawn from the study are warranted when account is taken of the study methods, the representativeness of the study sample, and the nature of the population from which it is drawn

	(internal and external validity, applicability, generalisability).
Suppuration	The formation or discharge of pus.
Systematic review (systematic overview)	A form of structured literature review that addresses a question that is formulated to be answered by analysis of evidence, and involves objective means of searching the literature, applying predetermined inclusion and exclusion criteria to this literature, critically appraising the relevant literature, and extraction and synthesis of data from the evidence base to formulate findings.
Utility	In economic and decision analysis, the desirability of a specific level of health status or health outcome, usually expressed as being between zero and one (e.g. death typically has a utility value of zero and a full healthy life has a value of one).
Validity	The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors). Also, the degree to which a measure or parameter accurately reflects or assesses a concept of interest.
Willingness to pay (WTP)	The maximum amount that a person is willing to pay: (i) to achieve a particular good health state or outcome, or to increase its probability of occurrence; or (ii) to avoid particular bad health state or outcome, or to decrease its probability.

Appendix A – Search details for clinical effectiveness

A search for studies relating to the clinical effectiveness of neonatal BCG vaccination was carried out. The databases searched were:

- PubMed
- EMBASE
- EBSCOhost (CINAHL only)
- Cochrane Central Register of Controlled Trials
- Clinical trials registries (the Clinical Trials Register and ClinicalTrials.gov)

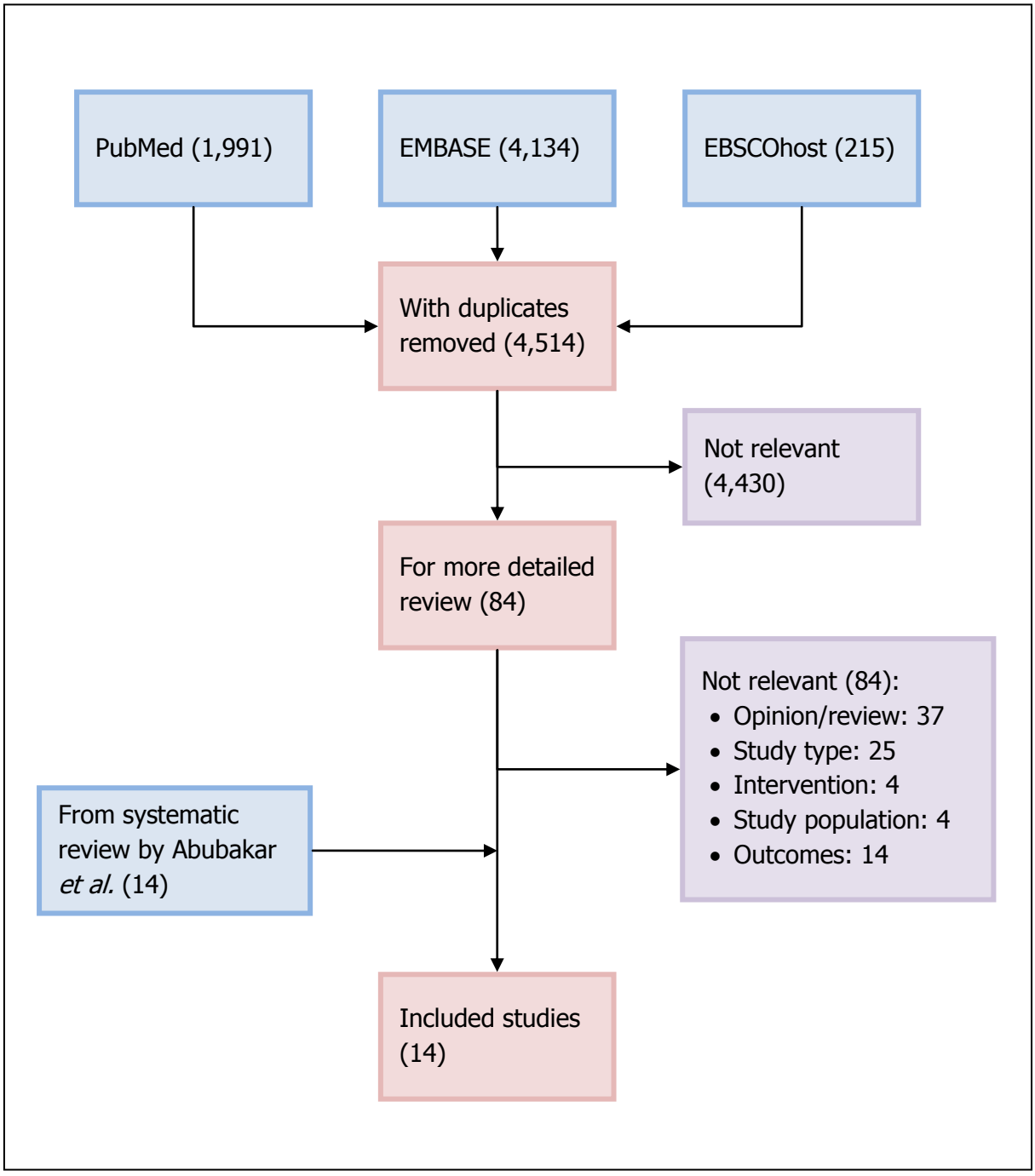
The search was an update of that carried out by Abubakar *et al.*[40] The search string as applied in PubMed is shown in Table A.1 below. The search was restricted to studies published since May 1st 2009.

Table A.1 Search string used in PubMed

Search	Search string	Results
#1	Search ((((((((((((((((((((Tuberculosis) OR tb[Title/Abstract]) OR tuberculous[Title/Abstract]) OR tuberculos*[Title/Abstract]) OR tubercular[Title/Abstract]) OR phthisis[Title/Abstract]) OR tuberculoma*[Title/Abstract]) OR potts disease[Title/Abstract]) OR pott's disease[Title/Abstract]) OR tuberculid*[Title/Abstract]) OR scrofuloderma*[Title/Abstract]) OR scrofula*[Title/Abstract]) OR Mycobacterium bovis) OR Mycobacterium tuberculosis) OR tubercle bacill*[Title/Abstract]) OR mycobacterium africanum[Title/Abstract]) OR mycobacterium microti[Title/Abstract]) OR mycobacterium canetti[Title/Abstract]) OR mycobacterium bovis[Title/Abstract])) AND ((((((BCG Vaccine) OR BCG[Title/Abstract]) OR Calmette Vaccin*[Title/Abstract])) OR ((bacill*[Title/Abstract]) AND Calmette*[Title/Abstract])) OR ((tubercul*[Title/Abstract]) AND vaccin*[Title/Abstract]))	17,947
#2	Search ("2009/05/01"[Date - Publication] : "3000"[Date - Publication]) Filters: Publication date from 2009/05/01 to 2015/01/31; Humans	2,847,836
#3	#1 AND #2	1,991

The bibliographic search returned 6,340 studies from across the three databases, which equated to 4,514 studies following removal of duplicates (Figure 1.1). After removal of studies deemed not relevant based on the titles and abstract, 84 studies were identified for a full-text review. A further 70 studies were excluded (for reasons identified in Figure 1.1) leaving 14 studies for inclusion, all of which had been identified by Abubakar *et al.* As no additional studies were identified in the update to the systematic review, the quality appraisal and risk of bias assessment conducted by Abubakar *et al.* was used in this HTA.[40]

Figure A.1 Flow diagram of included studies



Appendix B – Search details for economic evaluations

The systematic review of economic evaluations used the results of the search for clinical effectiveness data, updated to March 2015. The search terms for clinical effectiveness did not specify a study type or exclude any economic terms. A previous systematic review of economic evaluations was identified as suitable for updating.[91] The earlier systematic review was conducted up until August 2011. For the update in this health technology assessment (HTA), all studies published in 2011 or later were considered.

Studies were included if they evaluated either universal or selective infant BCG vaccination programmes for the prevention of TB. The BCG programme had to be compared either to another BCG programme or to no vaccination. Studies assessing revaccination, later childhood, adolescent or adult vaccination programmes were excluded. Studies investigating novel vaccines were excluded unless they included two BCG programmes or a BCG programme and a no vaccination strategy. Following elimination of duplicates, removal of studies clearly not relevant based on title and abstract review, and exclusion of studies that did not meet the inclusion criteria, a total of five studies were identified for inclusion (Figure B.1).

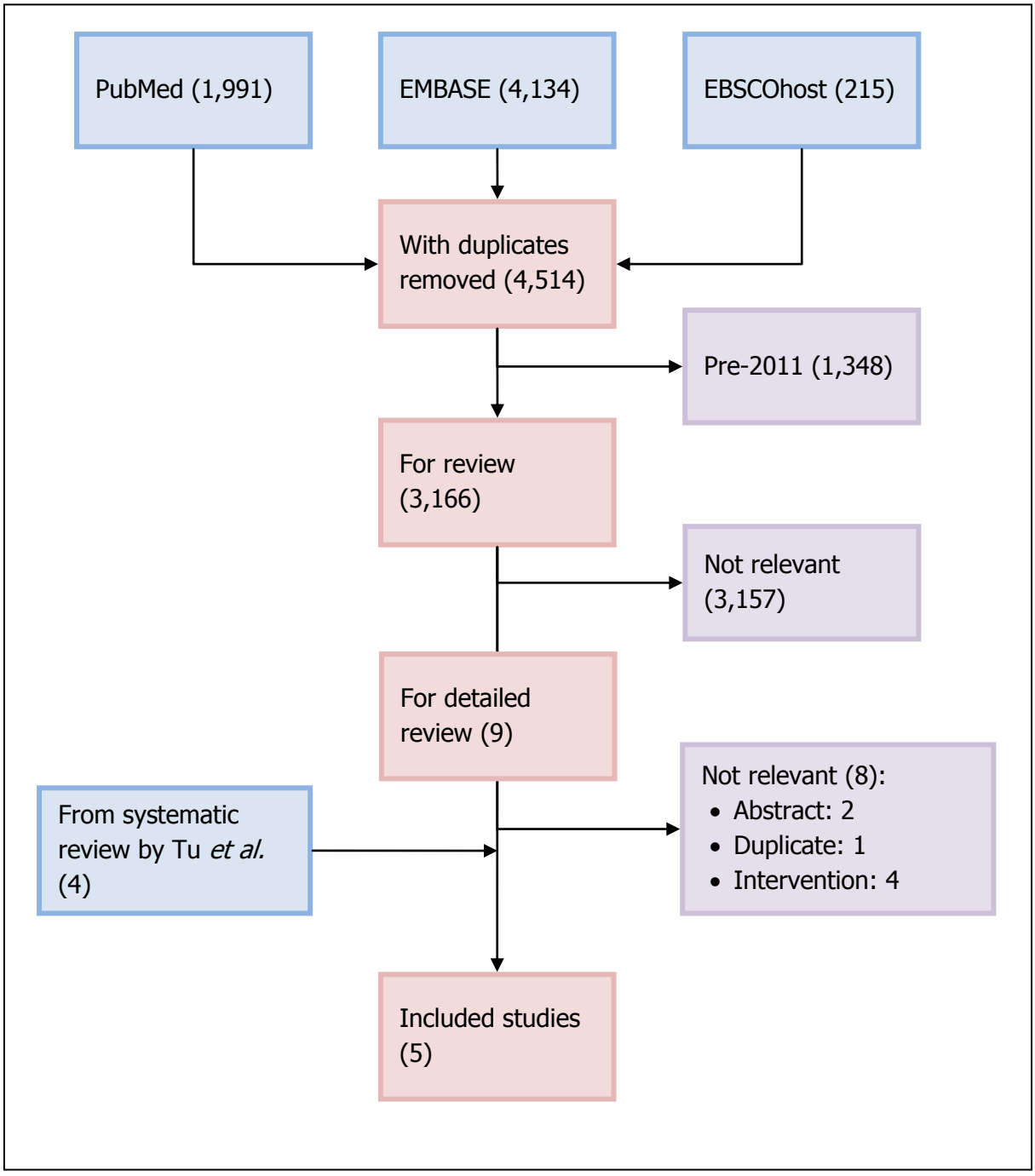
The relevance and credibility of the identified studies was assessed using the appropriate ISPOR questionnaire.[97] In terms of relevance, all five studies assessed neonatal BCG programmes. Three of the five studies did not include mortality, and generally focused on the cost per case of TB avoided.[92;93;95]

The models used generally appeared to be validated, although the details were often limited. Two of the studies were restricted to TB meningitis and miliary TB, giving rise to concerns over the face validity to the Irish context and whether the models were adequate for this HTA[39;94] given that pulmonary and extrapulmonary TB are the most common forms of TB.

As the review was undertaken prior to gathering cost data, it was not possible to determine if the costs used in the studies were applicable to Ireland. Due to various shortcomings (no mortality data, short time horizon, incomplete costs), none of the studies were adequate to inform the decision problem in this HTA. The studies also had inadequate assessment of uncertainty, generally only addressing uncertainty regarding the vaccine efficacy.

Reporting was generally adequate and considered to be fair and balanced. For one study there was a potential conflict of interest, as there was financial support from a pharmaceutical company. It was unclear if this could have given rise to bias in the study results.

Figure B.1 Flow diagram of included studies



Appendix C – Details of model epidemiological parameters

A variety of epidemiological parameters were used in the economic model. The parameters were described in detail in Chapter 5.3.2. This appendix provides information on the statistical distributions used to define the epidemiological parameters in the model.

The incidence of TB in the unvaccinated population was determined using TB notification data from 2005 to 2014 (inclusive) for individuals aged less than 16 years. The denominator population was estimated using data on BCG vaccine uptake by region.[103] This data was then used to define the shape parameters for Dirichlet distributions for each year of age (Table C.1).

Table C.1 Cases of TB in unvaccinated children by age and type of TB

Age	Pulmonary TB	Extrapulmonary TB	TB meningitis	Miliary TB	No TB
0	3.000	1.000	0.001	0.001	127,799.0
1	2.000	1.000	0.997	0.001	134,222.0
2	19.757	5.000	0.001	0.001	140,379.2
3	11.210	2.000	0.001	0.001	145,127.8
4	1.757	3.000	0.001	0.001	148,287.2
5	1.000	2.000	0.001	0.001	150,364.0
6	3.042	1.679	0.001	0.001	145,761.3
7	1.000	2.250	0.997	0.001	141,059.8
8	1.250	1.538	0.001	0.001	136,986.2
9	1.000	0.250	0.001	0.001	133,704.8
10	1.231	4.000	0.001	0.001	130,884.8
11	1.960	2.000	0.001	0.985	127,545.1
12	4.250	2.038	0.997	0.001	124,422.7
13	2.757	0.591	0.001	0.001	122,526.7
14	5.129	5.902	0.001	0.001	121,692.0
15	6.881	3.000	0.589	0.001	121,671.5

The other epidemiological parameters are described in Table C.2. Uptake in the low risk population was computed based on uptake in the high-risk population, and the population size:

$$uptake_{low\ risk} = \frac{population * uptake_{average\ risk} - population_{high\ risk} * uptake_{high\ risk}}{population_{low\ risk}}$$

Table C.2 Statistical distributions for epidemiological parameters

Parameter	Mean	95% CI	Distribution	Value 1	Value 2
Birth cohort	68,990	(67,030 to 70,950)	normal	68990	1000
Efficacy of BCG vaccination against pulmonary TB	0.406	(0.263 to 0.600)	log normal	-0.9229	0.2100
Efficacy of BCG vaccination against extrapulmonary TB	0.189	(0.032 to 0.626)	log normal	-1.9561	0.7589
Efficacy of BCG vaccination against TB meningitis	0.465	(0.008 to 2.872)	log normal	-1.9074	1.5114
Efficacy of BCG vaccination against miliary TB	0.111	(0.014 to 0.420)	log normal	-2.5737	0.8700
Efficacy of BCG vaccination against TB death	0.195	(0.053 to 0.512)	log normal	-1.8044	0.5795
Proportion population high-risk	0.134	(0.131 to 0.136)	beta	9886	63939
Additional risk associated with high-risk individuals	3.044	(2.344 to 3.889)	log normal	1.105	0.1292
Vaccine uptake in all births	0.878	(0.875 to 0.880)	beta	60164	8367
Vaccine uptake in high-risk population	0.762	(0.591 to 0.897)	beta	21.3388	6.6612
Case fatality rate	0.008	(0.005 to 0.011)	beta	31	3920
Proportion meningitis cases with mild or severe sequelae	0.539	(0.427 to 0.649)	beta	40.63	34.75
Proportion sequelae classed as severe	0.394	(0.202 to 0.606)	beta	8.28	12.72
Rate of adverse events (of vaccination)	0.0007	(0.0005 to 0.0010)	beta	42.5	57945.6
Rate of disseminated BCG	1.2×10^{-5}	(7.8×10^{-8} to 5.2×10^{-5})	beta	0.7	57988.1
Case-fatality rate in disseminated BCG	0.288	(0.220 to 0.360)	beta	46	114
Proportion births that are Irish Travellers	0.0134	(0.0126 to 0.0144)	beta	930	68060
Risk ratio of disseminated BCG in Irish Travellers	11.45	(5.81 to 18.99)	gamma	11.447	1
Proportion of cases in males	0.484	(0.397 to 0.572)	beta	60	64
Disutility associated with treatment	0.900	(0.834 to 0.950)	beta	90	10
Disutility associated with adverse event	0.950	(0.900 to 0.983)	beta	95	5
Disutility of meningitis sequelae - moderate	0.800	(0.717 to 0.872)	beta	80	20
Disutility of meningitis sequelae - severe	0.600	(0.503 to 0.693)	beta	60	40

For normal and log normal distributions, value 1 and value 2 refer to the mean and standard deviation parameters, respectively. For beta distributions, values 1 and 2 refer to the shape parameters.

Appendix D – Details of model cost parameters

The cost of the vaccine incorporates the cost of a vial of vaccine and the average proportion of doses used per vial. As the cost per vial is commercially sensitive, it cannot be reported here. The proportion doses used per vial can also not be reported, as in combination with the mean cost of vaccine for the programme (as reported in Chapter 5.3.3), it would be possible to determine the cost of a vial.

The cost of administering the vaccine for the selective programme is calculated as the product of the cost of administering in the universal programme and a multiplier to reflect the reduced efficiency of a selective programme.

The costs of treatment, contact tracing and treating latent TB infection were all derived from the National Centre for Pharmacoeconomics report on BCG vaccination.[1] Where available, costs were updated based on the latest available information. Other costs were inflated from 2013 to 2015 prices using the consumer price index for health.[98] In accordance with guidelines, all pay-related costs were adjusted for non-pay costs associated with hiring additional staff including employers' PRSI, superannuation, and general overheads.[98]

The cost of treatment for miliary TB was adapted from the costs associated with the treatment of extrapulmonary TB. The treatment regimens were defined in accordance with WHO treatment guidelines.[22]

For the estimates of antibiotic doses, it was assumed that a child aged between 0 and 15 years would, on average, weigh 25kg. Where multiple brands were available for a particular drug, the price was based on a simple average of the available brands. It was presumed that all prescriptions were dispensed on a monthly basis with oral medications dispensed as liquid formulations. Licensed proprietary medications were used if available, otherwise either the cost of extemporaneous dispensing of a liquid formation or the cost of an unlicensed proprietary brand was used according to the existing dispensing practices of a tertiary-level paediatric hospital.

In the following tables some items are reported to apply to a percentage of patients rather than all patients. In these cases the reported cost reflects the average contribution of the item to the cost of treatment. For example, in Table D.6 the cost of an MRI (10% of cases) is listed as €19.30. The cost of an individual MRI is €193 but as it only applies to 10% of cases, it contributes on average €19.30 to cost of treatment.

Table D.1 Cost parameters for the economic model

Parameter	Mean	95% CI	Distribution	Value 1	Value 2
Cost of treating pulmonary TB	8,354	(6,833 to 10,112)	log normal	9.026	0.10
Cost of treating extrapulmonary TB	12,606	(10,310 to 15,259)	log normal	9.437	0.10
Cost of treating TB meningitis	18,736	(15,324 to 22,679)	log normal	9.833	0.10
Cost of treating miliary TB	12,922	(10,569 to 15,642)	log normal	9.462	0.10
Cost of contact tracing & diagnosis and treatment of LTBi	9,814	(8,031 to 11,885)	log normal	9.187	0.10
Costs Adverse Events	2,895	(2,380 to 3,522)	log normal	7.971	0.10
Costs of long term disability - moderate	1,881	(1,539 to 2,277)	log normal	7.535	0.10
Costs of long term disability - severe	12,599	(10,305 to 15,250)	log normal	9.436	0.10
Cost of administering vaccine - universal (per child)	26.02	(21.28 to 31.50)	log normal	3.254	0.10
Multiplier for cost of administering vaccine - selective	2.0000	(1.73 to 2.29)	gamma	200	100

Abbreviations: LBTi, latent TB infection.

D.1 Treatment of pulmonary TB

Table D.2 Cost of diagnosis and initial hospital treatment of pulmonary TB

Item	Cost
Diagnostic tests	
Tuberculin skin test	€20.85
Chest x-ray	€29.85
Sputum smear microscopy (x3)	€174.35
Polymerase chain reaction test	€34.75
Physician visits/Hospital days	
Paediatrician visit (x2)	€278.00
Ophthalmology prior to starting ethambutol	€139.00
Hospital days (paediatric ward) (x9)	€5,166.00
Total	€5,842.80

Table D.3 Cost of initial treatment success in pulmonary TB

Item	Cost
Oral antibiotics	
Isoniazid (125mg x 168 days)	€531.48
Rifampicin (250mg x 168 days)	€105.07
Pyrazinamide (625mg x 56 days)	€37.76
Ethambutol (500mg x 56 days)	€152.36
Physician visits/Hospital days	
Follow-up paediatrician visits (x6)	€834.00
Liver function tests (x6)	€76.42
Sputum smears and cultures (x3)	€174.35
Full blood count (x6)	€95.52
Follow-up	
Follow-up chest x-ray after 1 month	€29.85
Repeat chest x-ray	€29.85
Eye review ophthalmology	€139.00
Management of therapy	
Clinical nurse specialist (5 hours per week for 24 weeks, 5% of cases)	€228.43
Total	€2,434.10

Table D.4 Cost of initial treatment failure in pulmonary TB

Item	Cost
Oral antibiotics	
Isoniazid (125mg x 56 days)	€177.16
Rifampicin (250mg x 56 days)	€35.02
Pyrazinamide (625mg x 56 days)	€37.76
Ethambutol (500mg x 56 days)	€152.36
Physician visits/Hospital days	
Sputum smears and cultures	€58.12
Follow-up paediatrician visits	€139.00
Total	€599.43

Table D.5 Cost of revised treatment in pulmonary TB

Item	Cost
Oral antibiotics	
Isoniazid (125mg x 196 days)	€620.06
Rifampicin (250mg x 196 days)	€122.58
Physician visits/Hospital days	
Follow-up paediatrician visits (x6)	€834.00
Liver function tests (x6)	€76.42
Sputum smears and cultures (x3)	€174.35
Full blood count (x6)	€95.52
Follow-up	
Follow-up chest x-ray after 1 month	€29.85
Repeat chest x-ray	€29.85
Eye review ophthalmology	€139.00
Management of therapy	
Clinical nurse specialist (5 hours per week for 24 weeks, 5% of cases)	€228.43
Total	€2,350.07

Following the NCPE report, it was assumed that 85% of cases would achieve treatment success and 15% would require revised treatment following failure.

The average cost of treatment was calculated as:

$$D.2 + (0.85 \times D.3) + (0.15 \times (D.4 + D.5)) = €8,354.21$$

D.2 Treatment of extrapulmonary TB

Table D.6 Cost of diagnosis and initial hospital treatment of extrapulmonary TB

Item	Cost
Diagnostic tests	
Tuberculin skin test	€20.85
Chest x-ray	€29.85
Sputum smear microscopy (x3)	€174.35
Interferon-Gamma Release Assay (50% of cases)	€32.34
CT scan (69% of cases)	€75.41
MRI scan (10% of cases)	€19.30
Ultrasound scan (37% of cases)	€42.11
Peritoneal biopsy (5% of cases)	€22.21
Lymph node biopsy (intra-thoracic) (10% of cases)	€414.89
Lymph node biopsy (extra-thoracic) (27% of cases)	€198.88
Liver biopsy (needle) (4% of cases)	€34.90
Bone biopsy (3% of cases)	€9.27
Pleural biopsy (24% of cases)	€217.42
Other (bronchoscopy) (16% of cases)	€75.15
Genitourinary (dilation and curettage) (1% of cases)	€1.99
Lumbar puncture/cerebrospinal fluid (including culture and sensitivity) (11% of cases)	€17.33
Polymerase chain reaction test	€34.75
Other (1% of cases)	€3.45
Physician visits/Hospital days	
Paediatrician	€139.00
Ophthalmology prior to starting ethambutol	€139.00
Hospital days (paediatric ward) (x14)	€8,036.00
Total	€9,738.44

Table D.7 Cost of initial treatment success in extrapulmonary TB

Item	Cost
Oral antibiotics	
Isoniazid (125mg x 168 days)	€531.48
Rifampicin (250mg x 168 days)	€105.07
Pyrazinamide (625mg x 56 days)	€37.76
Ethambutol (500mg x 56 days)	€152.36
Surgical	
Anterior spinal fusion (3% of cases)	€94.66
Physician visits/Hospital days	
Follow-up paediatrician visits (x6)	€834.00
Liver function tests (x6)	€76.42
CT scan (x2; 69% of cases)	€150.82
MRI scan (x2; 10% of cases)	€38.61
Ultrasound scan (x2; 37% of cases)	€84.22
Full blood count (x9)	€143.28
Follow-up	
Ophthalmology	€139.00
Management of therapy	
Clinical nurse specialist (5 hours per week for 24 weeks, 5% of cases)	€228.43
Total	€2,616.11

Table D.8 Cost of initial treatment failure in extrapulmonary TB

Item	Cost
Oral antibiotics	
Isoniazid (125mg x 168 days)	€531.48
Rifampicin (250mg x 168 days)	€105.07
Pyrazinamide (625mg x 56 days)	€37.76
Ethambutol (500mg x 56 days)	€152.36
Physician visits/Hospital days	
Sputum smears and cultures	€58.12
Follow-up paediatrician visits	€139.00
Total	€1,023.79

Table D.9 Cost of revised treatment in extrapulmonary TB

Item	Cost
Oral antibiotics	
Isoniazid (125mg x 196 days)	€620.06
Rifampicin (250mg x 196 days)	€94.08
Surgical	
Anterior spinal fusion (3% of cases)	€94.66
Physician visits/Hospital days	
Follow-up paediatrician visits (x10)	€1,390.00
Liver function tests (x10)	€127.36
CT scan (x2; 69% of cases)	€150.82
MRI scan (x2; 10% of cases)	€38.61
Ultrasound scan (x2; 37% of cases)	€84.22
Full blood count (x9)	€143.28
Follow-up	
Ophthalmology	€139.00
Management of therapy	
Clinical nurse specialist (5 hours per week for 24 weeks, 5% of cases)	€380.72
Total	€3,262.81

Following the NCPE report, it was assumed that 85% of cases would achieve treatment success and 15% would require revised treatment following failure.

The average cost of treatment was calculated as:

$$D.6 + (0.85 \times D.7) + (0.15 \times (D.8 + D.9)) = €12,605.12$$

D.3 Treatment of TB meningitis

Table D.10 Cost of diagnosis and initial hospital treatment of TB meningitis

Item	Cost
Diagnostic tests	
Lumbar puncture/cerebrospinal fluid (including culture and sensitivity)	€157.21
Blood (culture and sensitivity)	€28.95
Urine (culture and sensitivity)	€28.95
Full blood count	€15.92
Interferon-Gamma Release Assay	€64.68
Chest x-ray (65% of cases)	€19.40
CT scan (head) (30% of cases)	€28.66
Electroencephalogram	€17.37
Polymerase chain reaction test	€34.75
Physician visits/Hospital days	
Paediatric consult	€139.00
Infectious disease/micro consult	€139.00
Oral antibiotics	
Isoniazid (125mg x 365 days)	€1,062.96
Rifampicin (250g x 365 days)	€218.57
Pyrazinamide (625g x 56 days)	€37.76
Ethambutol (500g x 56 days)	€117.60
Prednisolone (25g x 365 days)	€152.36
Management of therapy	
Clinical nurse specialist (5 hours per week for 52 weeks, 5% of cases)	€494.94
Total	€2,758.08

Table D.11 Cost of treatment of stable patient in TB meningitis

Item	Cost
Physician visits/Hospital days	
Paediatric ward day (x14 days)	€8,036.00
Total	€8,036.00

Table D.12 Cost of treatment success in TB meningitis

Item	Cost
Physician visits/Hospital days	
Follow-up paediatrician visits (x3)	€417.00
Total	€417.00

Table D.13 Cost of treating persistent fever in TB meningitis

Item	Cost
Diagnostic tests	
Lumbar puncture/cerebrospinal fluid (including culture and sensitivity) (50% of cases)	€78.61
Blood (culture and sensitivity)	€28.95
Full blood count	€15.92
Chest x-ray (60% of cases)	€17.91
CT scan (head) (70% of cases)	€66.86
MRI scan (head) (10% of cases)	€18.91
Electroencephalogram (10% of cases)	€17.37
Physician visits/Hospital days	
Paediatric ward stay (x14 days)	€4,592.00
Total	€4,836.53

Table D.14 Cost of patient that responds to treatment in TB meningitis

Item	Cost
Physician visits/Hospital days	
Paediatric neurosurgical consultation	€139.00
Total	€139.00

Table D.15 Cost of septic patient in TB meningitis

Item	Cost
Diagnostic tests	
Coagulation test	€60.23
Lumbar puncture/cerebrospinal fluid (including culture and sensitivity) (75% of cases)	€117.91
Full blood count (x4)	€63.68
Renal profile	€9.95
Liver function test	€12.74
MRI scan	€193.03
Physician visits/Hospital days	
ICU day (x5 days)	€11,782.98
Hospital days (x10)	€5,740.00
Total	€17,980.51

Table D.16 Cost of neurosurgical drainage in TB meningitis

Item	Cost
Physician visits/Hospital days	
Neurosurgical drainage of subdural empyema	€3,413.50
Hospital days (x7)	€4,018.00
Total	€7,431.50

Table D.17 Cost of successful neurosurgical drainage in TB meningitis

Item	Cost
Physician visits/Hospital days	
Follow-up paediatrician visits (x9)	€1,251.00
Follow-up paediatric neurosurgeon (x3)	€417.00
Total	€1,668.00

Table D.18 Cost of unsuccessful neurosurgical drainage in TB meningitis

Item	Cost
Physician visits/Hospital days	
Hospital day (paediatrics ward) (x6)	€3,444.00
Total	€3,444.00

Table D.19 Cost of spontaneous resolution of unstable patient in TB meningitis

Item	Cost
Physician visits/Hospital days	
Follow-up paediatrician visits (x9)	€1,251.00
Follow-up paediatric neurosurgeon	€139.00
Total	€1,390.00

The computation of treatment pathways followed the decision tree approach used by the NCPE.

A = stable patient with successful treatment

= (D.10 + D.11 + D.12) x (1 x 0.6 x 0.8)

B = stable patient with persistent fever that responds to treatment

= (D.10 + D.11 + D.13 + D.14) x (1 x 0.6 x 0.2 x 0.3)

C = unstable patient with successful neurosurgical drainage

= (D.10 + D.15 + D.16 + D.17) x (1 x 0.4 x 0.2 x 0.9)

D = unstable patient with unsuccessful neurosurgical drainage

= (D.10 + D.15 + D.16 + D.18) x (1 x 0.4 x 0.2 x 0.1)

E = unstable patient with spontaneous resolution

= (D.10 + D.15 + D.19) x (1 x 0.4 x 0.8)

F = stable patient with persistent fever that does not respond to treatment

= (D.10 + D.11 + D.13 + (C + D + E)/0.4) x (1 x 0.6 x 0.2 x 0.7)

The average cost of treatment was calculated as:

A + B + C + D + E + F = €18,735.71

D.4 Treatment of miliary TB

Table D.20 Cost of diagnosis and initial hospital treatment of miliary TB

Item	Cost
Diagnostic tests	
Tuberculin skin test	€20.85
Chest x-ray	€29.85
Sputum smear microscopy (x3)	€174.35
Interferon-Gamma Release Assay (50% of cases)	€32.34
CT scan (69% of cases)	€75.41
MRI scan (10% of cases)	€19.30
Ultrasound scan (37% of cases)	€42.11
Peritoneal biopsy (5% of cases)	€22.21
Lymph node biopsy (intra-thoracic) (10% of cases)	€414.89
Lymph node biopsy (extra-thoracic) (27% of cases)	€198.88
Liver biopsy (needle) (4% of cases)	€34.90
Bone biopsy (3% of cases)	€9.27
Pleural biopsy (24% of cases)	€217.42
Other (bronchoscopy) (16% of cases)	€75.15
Genitourinary (dilation and curettage) (1% of cases)	€1.99
Lumbar puncture/cerebrospinal fluid (including culture and sensitivity) (11% of cases)	€17.33
Polymerase chain reaction test	€34.75
Other (1% of cases)	€3.45
Physician visits/Hospital days	
Paediatrician	€139.00
Ophthalmology prior to starting ethambutol	€139.00
Hospital days (paediatric ward) (x14)	€8,036.00
Total	€9,738.44

Table D.21 Cost of initial treatment success in miliary TB

Item	Cost
Oral antibiotics	
Isoniazid (125mg x 365 days)	€1,062.96
Rifampicin (250mg x 365 days)	€218.57
Pyrazinamide (625mg x 56 days)	€37.76
Ethambutol (500mg x 56 days)	€152.36
Surgical	
Anterior spinal fusion (3% of cases)	€94.66
Physician visits/Hospital days	
Follow-up paediatrician visits (x6)	€834.00
Liver function tests (x6)	€76.42
CT scan (x2; 69% of cases)	€150.82
MRI scan (x2; 10% of cases)	€38.61
Ultrasound scan (x2; 37% of cases)	€84.22
Full blood count (x9)	€143.28
Follow-up	
Ophthalmology	€139.00
Management of therapy	
Clinical nurse specialist (5 hours per week for 24 weeks, 5% of cases)	€228.43
Total	€3,261.09

Table D.22 Cost of initial treatment failure in miliary TB

Item	Cost
Physician visits/Hospital days	
Sputum smears and cultures	€58.12
Follow-up paediatrician visits	€139.00
Total	€197.12

Table D.23 Cost of revised treatment in miliary TB

Item	Cost
Surgical	
Anterior spinal fusion (3% of cases)	€94.66
Physician visits/Hospital days	
Follow-up paediatrician visits (x10)	€1,390.00
Liver function tests (x10)	€127.36
CT scan (x2; 69% of cases)	€150.82
MRI scan (x2; 10% of cases)	€38.61
Ultrasound scan (x2; 37% of cases)	€84.22
Full blood count (x9)	€143.28
Follow-up	
Ophthalmology	€139.00
Management of therapy	
Clinical nurse specialist (5 hours per week for 24 weeks, 5% of cases)	€380.72
Total	€2,548.67

In line with treatment for miliary TB, it was assumed that 85% of cases would achieve treatment success and 15% would require revised treatment following failure.

The average cost of treatment was calculated as:

$$D.20 + (0.85 \times D.21) + (0.15 \times (D.22 + D.23)) = €12,922.24$$

D.5 Cost of contact tracing

The cost of contact tracing was estimated based on resource use in the HSE East region in 2012. Costs include staff, diagnostic equipment, chemoprophylaxis, and other equipment. The data reflects resource use relative to 160 index cases. It was assumed that the costs in the HSE East region would be broadly representative of the costs incurred in other regions.

Table D.24 Cost of contact tracing (HSE East)

Item	Cost
Staff	
Director of Public Health (0.2 WTE)	€35,718.70
Specialist in Public Health Medicine (0.8 WTE)	€122,532.80
Area medical officer (senior) (3 WTE)	€358,576.14
Medical scientist (senior) (0.1 WTE)	€7,287.96
Public health nurse (0.8 WTE)	€55,390.19
Clerical officer grade (1.6 WTE)	€61,583.91
Consumables	
Tuberculin skin test (x50)	€1,492.51
Interferon-Gamma Release Assay (x50)	€3,250.00
Chest x-ray (x1000)	€74,625.30
Medication*	€52,374.00
Liver function test (x400)	€5,094.42
Patient care	
Complex paediatric cases	€10,000.00
Miscellaneous	
Travel costs - nurse	€4,000.00
Travel costs – Senior Medical Officer	€8,000.00
Stationery and postage	€20,000.00
Total for HSE East (2012, 160 index cases)	€819,925.94
Cost per index TB case	€5,124.54

* Medication costs based on 200 adults and 100 children completing chemoprophylaxis.

D.6 Cost of treatment for latent TB infection

The cost of latent TB infection includes diagnosis, medical care and antibiotics. The dose and duration of antibiotics are as for pulmonary TB. The antibiotic doses are based on a child weighing 25kg. It was assumed prescriptions are dispensed on a monthly basis and in a liquid form. Some cases of latent TB infection could occur in adults. However, isoniazid is available in tablet form for adults and costs less per patient than the unlicensed proprietary liquid form used for children.

Table D.24 Cost per case of treatment for latent TB infection

Item	Cost
Diagnostic tests	
Tuberculin skin test	€20.85
Chest x-ray	€29.85
Physician visits/Hospital days	
Paediatrician visit	€139.00
Liver function test	€12.74
Oral antibiotics	
Isoniazid (125mg x 168 days)	€265.74
Rifampicin (250mg x 168 days)	€52.54
Follow-up visits	
Follow-up paediatrician visits	€69.50
Out-patient follow-up	€69.50
GP consult (x2)	€110.00
Management of therapy	
Clinical nurse specialist (5 hours per week for 24 weeks, 5% of cases)	€228.43
Total	€998.14

It was assumed that for each index TB case there would be an average of 4.7 individuals identified with latent TB infection requiring diagnosis and treatment.

References

(1) National Centre for Pharmacoeconomics. *Economic evaluation of BCG vaccination strategies in Ireland*. Dublin: NCPE; 2013.

(2) Health Protection Surveillance Centre. *National TB Surveillance: Quarter 1 - 4 2014 TB Report*. Dublin, Ireland: Health Service Executive; 2015.

(3) Public Health England. *Immunisation against infectious disease*. London: Public Health England; 2013.

(4) World Health Organization. *Global Tuberculosis Report 2014*. Geneva: WHO; 2014.

(5) Health Protection Surveillance Centre. *Guidelines on the prevention and control of tuberculosis in Ireland 2010*. Dublin: HPSC; 2014.

(6) Irish Medicines Board. *BCG Vaccine SSI and Severe Local Reactions.* [Pamphlet]. Dublin, Ireland: Irish Medicines Board; 2010. Available online from: https://www.hpra.ie/docs/default-source/Safety-Notices/bcg-vaccine-ssi-and-severe-local-reactions.pdf.

(7) Health Products Regulatory Authority. *BCG Vaccine SSI - Summary of Product Characteristics.* [Pamphlet]. Dublin, Ireland: HPRA; 2015. Available online from: http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0798-002-001_10032015102039.pdf.

(8) National Immunisation Advisory Committee. *Immunisation guidelines for Ireland - 2013 edition*. Dublin, Ireland: National Immunisation Advisory Committee; 2013.

(9) Montagnani C, Chiappini E, Galli L, de MM. Vaccine against tuberculosis: what's new? *BMC Infect Dis.* 2014; 14 Suppl 1 p.S2.

(10) Weiner J, Kaufmann SH. Recent advances towards tuberculosis control: vaccines and biomarkers. *J Intern Med.* 2014; 275(5): pp.467-80.

(11) Rodrigues LC, Pereira SM, Cunha SS, Genser B, Ichihara MY, de Brito SC, et al. Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG-REVAC cluster-randomised trial. *Lancet.* 2005; 366(9493): pp.1290-5.

(12) Criteria for discontinuation of vaccination programmes using Bacille Calmette-Guerin (BCG) in countries with a low prevalence of tuberculosis. A statement of the International Union Against Tuberculosis and Lung Disease. *Tuber Lung Dis.* 1994; 75(3): pp.179-80.

(13) HSE TB Control Subcommittee. *TB Control Review*. Dublin, Ireland: Health Service Executive; 2015.

(14) Zwerling A, Behr MA, Verma A, Brewer TF, Menzies D, Pai M. The BCG World Atlas: a database of global BCG vaccination policies and practices. *PLoS Med.* 2011; 8(3): p.e1001012.

(15) Public Health England. *Tuberculosis in the UK, 2014 report*. London: Public Health England; 2014.

(16) World Health Organisation. *TB Burden Estimates* [Online]. Available from: http://www.who.int/tb/country/data/download/en/. Accessed on: 31 March 2015.

(17) World Health Organisation. *Towards TB elimination - an action framework for low-incidence countries*. Geneva: WHO; 2014.

(18) Centers for Disease Control and Prevention. *TB elimination - the difference between latent TB infection and TB disease*. Atlanta, USA: CDC; 2011.

(19) Mollié A. Bayesian mapping of disease. Gilks WR, Richardson S, Spiegelhalter DJ, (Eds) In: *Markov Chain Monte Carlo in Practice.* London. Chapman & Hall; 1996. pp.359-79.

(20) Kelly A, Teljeur C. *The national deprivation Index for health & health services research - update 2013*. Dublin: Small Area Health Research Unit; 2013.

(21) Lunn D, Jackson C, Best N, Thomas A, Spiegelhalter D. *The BUGS book: a practical introduction to Bayesian analysis.* Boca Raton: CRC Press; 2013.

(22) World Health Organisation. *Treatment of tuberculosis guidelines - fourth edition*. Geneva: WHO; 2010.

(23) Powell DA, Hunt WG. Tuberculosis in children: an update. *Adv Pediatr.* 2006; 53 pp.279-322.

(24) O'Sullivan M, Keane E. TB Outbreak Linked to Two Crèches. *Epi-Insight.* 2007; 8(6): p.1.

(25) Health Protection Surveillance Centre. *Report on the epidemiology of tuberculosis in Ireland 2010*. Dublin, Ireland: Health Service Executive; 2013.

(26) Pasipanodya JG, Miller TL, Vecino M, Munguia G, Garmon R, Bae S, et al. Pulmonary impairment after tuberculosis. *Chest.* 2007; 131(6): pp.1817-24.

(27) Hnizdo E, Singh T, Churchyard G. Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment. *Thorax.* 2000; 55(1): pp.32-8.

(28) Saez-Llorens X, Cracken Jr GH. Bacterial meningitis in children. *Lancet.* 2003; 361(9375): pp.2139-48.

(29) Chandran A, Herbert H, Misurski D, Santosham M. Long-term sequelae of childhood bacterial meningitis: an underappreciated problem. *Pediatr Infect Dis J.* 2011; 30(1): pp.3-6.

(30) Chiang SS, Khan FA, Milstein MB, Tolman AW, Benedetti A, Starke JR, et al. Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis. *The Lancet Infectious Diseases.* 2014; 14(10): pp.947-57.

(31) Bauer M, Leavens A, Schwartzman K. A systematic review and meta-analysis of the impact of tuberculosis on health-related quality of life. *Qual Life Res.* 2013; 22(8): pp.2213-35.

(32) Atif M, Sulaiman SA, Shafie AA, Asif M, Sarfraz MK, Low HC, et al. Impact of tuberculosis treatment on health-related quality of life of pulmonary tuberculosis patients: a follow-up study. *Health Qual Life Outcomes.* 2014; 12 p.19.

(33) Department of Health. *Public health functions to be exercised by the NHS Commissioning Board, Service specification No.2, Neonatal BCG immunisation programme.* London: Department of Health; 2012.

(34) O'Toole RF, Jackson S, Hanway A, O'Donnell J, Comiskey CM, Rogers TR, et al. Tuberculosis incidence in the Irish Traveller population in Ireland from 2002 to 2013. *Epidemiol Infect.* 2015; pp.1-7.

(35) Central Statistics Office. *Profile 7 - Religion, ethnicity and Irish Travellers*. Dublin: Stationery Office; 2012.

(36) Healthcare Pricing Office. *Perinatal Statistics Report, 2013*. Dublin, Ireland: Health Service Executive; 2014.

(37) Colditz GA, Brewer TF, Berkey CS, Wilson ME, Burdick E, Fineberg HV, et al. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *JAMA.* 1994; 271(9): pp.698-702.

(38) Brewer TF. Preventing Tuberculosis with Bacillus Calmette-Gu,rin Vaccine: A Meta-Analysis of the Literature. *Clinical Infectious Diseases.* 2000; 31(Supplement 3): p.S64-S67.

(39) Trunz BB, Fine PEM, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet.* 2006; 367(9517): pp.1173-80.

(40) Abubakar I, Pimpin L, Ariti C, Beynon R, Mangtani P, Sterne JA, et al. Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guerin vaccination against tuberculosis. *Health Technol Assess.* 2013; 17(37): p.1-vi.

(41) Mangtani P, Abubakar I, Ariti C, Beynon R, Pimpin L, Fine PEM, et al. Protection by BCG against tuberculosis: a systematic review of randomised controlled trials. *Clinical Infectious Diseases.* 2014; 58(4): pp.470-80.

(42) Roy A, Eisenhut M, Harris RJ, Rodrigues LC, Sridhar S, Habermann S, et al. Effect of BCG vaccination against Mycobacterium tuberculosis infection in children: systematic review and meta-analysis. *BMJ.* 2014; 349

(43) Menzies D. What Does Tuberculin Reactivity after Bacille Calmette-Gu,rin Vaccination Tell Us? *Clinical Infectious Diseases.* 2000; 31(Supplement 3): p.S71-S74.

(44) Liu J, Tran V, Leung AS, Alexander DC, Zhu B. BCG vaccines: their mechanisms of attenuation and impact on safety and protective efficacy. *Hum Vaccin.* 2009; 5(2): pp.70-8.

(45) Dara M, Acosta CD, Rusovich V, Zellweger JP, Centis R, Migliori GB. Bacille Calmette-Guerin vaccination: The current situation in Europe. *Eur Respir J.* 2014; 43(1): pp.24-35.

(46) Rosenthal SR, Blahd M, Leslif EI. Ten years' experience with BCG (experimental and clinical). *The Journal of Pediatrics.* 1945; 26(5): pp.470-80.

(47) Aronson JD. Protective vaccination against tuberculosis with special reference to BCG vaccination. *Am Rev Tuberc.* 1948; 58(3): pp.255-81.

(48) Ferguson RG, Simes AB. BCG vaccination of Indian infants in Saskatchewan. *Tubercle.* 1949; 30(1): pp.5-11.

(49) Mehta KP, Merchant SM, Korde U. Environmental influence on immunity due to B.C.G. vaccination. *Indian Pediatr.* 1976; 13(7): pp.525-32.

(50) Kwong Chan D, Yong C, Ki Sub C. A clinical observation on tuberculous meningitis in childhood. *Tuberc Respir Dis.* 1980; 27 pp.9-18.

(51) Putrali J, Sutrisna B, Rahayoe N, Gunardi AS. *A case-control study of the effectiveness of vaccination in children in Jakarta, Indonesia.* 20 November 1983. 1983. pp. 194-200.

(52) Chavalittamrong B, Chearskul S, Tuchinda M. Protective value of BCG vaccination in children in Bangkok, Thailand. *Pediatr Pulmonol.* 1986; 2(4): pp.202-5.

(53) Miceli I, Colaiacovo D, Kantor IN, Peluffo G. Evaluation of the effectiveness of BCG vaccination using the case control method. *Dev Biol Stand.* 1986; 58 (Pt A) pp.293-6.

(54) Myint TT, Win H, Aye HH, Kyaw-Mint TO. Case-control study on evaluation of BCG vaccination of newborn in Rangoon, Burma. *Ann Trop Paediatr.* 1987; 7(3): pp.159-66.

(55) Camargos PA, Guimaraes MD, Antunes CM. Risk assessment for acquiring meningitis tuberculosis among children not vaccinated with BCG: a case-control study. *Int J Epidemiol.* 1988; 17(1): pp.193-7.

(56) Bhattacharjee J, Sharma RS, Singh J, Datta KK, Verghese T. Case series evaluation of BCG vaccine efficacy against tubercular meningitis in children in Delhi. *J Commun Dis.* 1993; 25(2): pp.71-4.

(57) Awasthi S, Moin S. Effectiveness of BCG vaccination against tuberculous meningitis. *Indian Pediatr.* 1999; 36(5): pp.455-60.

(58) Martinez-Gonzalez MTG, Vazquez Castellanos JL, Gallardo Meza FA. Effectiveness of the BCG vaccine to prevent severe extrapulmonary tuberculosis in children. *Int Pediatr.* 2002; 17 pp.110-4.

(59) Zodpey SP, Shrikhande SN, Kulkarni SW, Maldhure BR. Scar size and effectiveness of Bacillus Calmette Guerin (BCG) vaccination in the prevention of tuberculosis and leprosy: a case-control study. *Indian J Public Health.* 2007; 51(3): pp.184-9.

(60) Wilson ME, Fineberg HV, Colditz GA. Geographic Latitude and the Efficacy of Bacillus Calmette-Gu,rin Vaccine. *Clinical Infectious Diseases.* 1995; 20(4): pp.982-91.

(61) R Core Team. *R: A Language and Environment for Statistical Computing* [Online]. Available from: http://www.R-project.org/.

(62) Viechtbauer W. Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software.* 2010; 36(3): pp.1-48.

(63) Loecher M, Ropkins K. RgoogleMaps and loa: Unleashing R Graphics Power on Map Tiles. *Journal of Statistical Software.* 2015; 63(4): pp.1-18.

(64) Abubakar I, Matthews T, Harmer D, Okereke E, Crawford K, Hall T, et al. Assessing the effect of foreign travel and protection by BCG vaccination on the spread of tuberculosis in a low incidence country, United Kingdom, October 2008 to December 2009. *Euro Surveill.* 2011; 16(12): pp.1-7.

(65) Herrera V, Perry S, Parsonnet J, Banaei N. Clinical Application and Limitations of Interferon-+¦ Release Assays for the Diagnosis of Latent Tuberculosis Infection. *Clinical Infectious Diseases.* 2011; 52(8): pp.1031-7.

(66) Lin MY, Geluk A, Smith SG, Stewart AL, Friggen AH, Franken KLMC, et al. Lack of Immune Responses to Mycobacterium tuberculosis DosR Regulon Proteins following Mycobacterium bovis BCG Vaccination. *Infection and Immunity.* 2007; 75(7): pp.3523-30.

(67) Aaby P, Kollmann TR, Benn CS. Nonspecific effects of neonatal and infant vaccination: public-health, immunological and conceptual challenges. *Nat Immunol.* 2014; 15(10): pp.895-9.

(68) Shann F. The non-specific effects of vaccines. *Archives of Disease in Childhood.* 2010; 95(9): pp.662-7.

(69) SAGE non-specific effects of vaccines Working Group. *Evidence based recommendations on non-specific effects of BCG, DTP-containing and measles-containing vaccines on mortality in children under 5 years of age*. Geneva: WHO; 2014.

(70) de Castro MJ, Pardo-Seco J, Martinón-Torres F. Nonspecific (Heterologous) Protection of Neonatal BCG Vaccination Against Hospitalization Due to Respiratory Infection and Sepsis. *Clinical Infectious Diseases.* 2015; 60(11): pp.1611-9.

(71) FitzGerald JM. Management of Adverse Reactions to Bacille Calmette-Gu,rin Vaccine. *Clinical Infectious Diseases.* 2000; 31(Supplement 3): p.S75-S76.

(72) Clark M, Cameron DW. The benefits and risks of bacille Calmette-Guerin vaccination among infants at high risk for both tuberculosis and severe combined immunodeficiency: assessment by Markov model. *BMC Pediatr.* 2006; 6 p.5.

(73) Butler, Karina. Personal communication. 16 June 2015. Date received: 16 June 2015.

(74) Marciano BE, Huang CY, Joshi G, Rezaei N, Carvalho BC, Allwood Z, et al. BCG vaccination in patients with severe combined immunodeficiency: complications, risks, and vaccination policies. *J Allergy Clin Immunol.* 2014; 133(4): pp.1134-41.

(75) Rezai MS, Khotaei G, Mamishi S, Kheirkhah M, Parvaneh N. Disseminated Bacillus Calmette-Guerin infection after BCG vaccination. *J Trop Pediatr.* 2008; 54(6): pp.413-6.

(76) Sadeghi-Shanbestari M, Ansarin K, Maljaei SH, Rafeey M, Pezeshki Z, Kousha A, et al. Immunologic aspects of patients with disseminated bacille Calmette-Guerin disease in north-west of Iran. *Ital J Pediatr.* 2009; 35 p.42.

(77) Talbot EA, Perkins MD, Silva SF, Frothingham R. Disseminated bacille Calmette-Guerin disease after vaccination: case report and review. *Clin Infect Dis.* 1997; 24(6): pp.1139-46.

(78) Ying W, Sun J, Liu D, Hui X, Yu Y, Wang J, et al. Clinical characteristics and immunogenetics of BCGosis/BCGitis in Chinese children: a 6 year follow-up study. *PLoS One.* 2014; 9(4): p.e94485.

(79) Gathmann B, Grimbacher B, Beaute J, Dudoit Y, Mahlaoui N, Fischer A, et al. The European internet-based patient and research database for primary immunodeficiencies: results 2006-2008. *Clin Exp Immunol.* 2009; 157 Suppl 1 pp.3-11.

(80) Abuzakouk M, Feighery C. Primary Immunodeficiency Disorders in the Republic of Ireland: First Report of the National Registry in Children and Adults. *J Clin Immunol.* 2005; 25(1): pp.73-7.

(81) Irish Medicines Board. BCG Vaccine SSI - Update on Experience. *Drug Safety Newsletter.* 2003;(17): pp.4-5.

(82) Irish Medicines Board. BCG vaccine - update. *Drug Safety Newsletter.* 2007;(24): p.2.

(83) Bolger T, O'Connell M, Menon A, Butler K. Complications associated with the bacille Calmette-Gu,rin vaccination in Ireland. *Archives of Disease in Childhood.* 2006; 91(7): pp.594-7.

(84) Favorov M, Ali M, Tursunbayeva A, Aitmagambetova I, Kilgore P, Ismailov S, et al. Comparative tuberculosis (TB) Prevention effectiveness in children of bacillus calmette-guerin (BCG) vaccines from different sources, Kazakhstan. *PLoS One.* 2012; 7(3):

(85) Braima O, Rigney A, Ryan CA, Murphy C. Uptake of newly introduced universal BCG vaccination in newborns. *Ir Med J.* 2010; 103(6): pp.187-8.

(86) Kelly P, McKeown D, Clancy L. Neonatal BCG vaccination in Ireland: evidence of its efficacy in the prevention of childhood tuberculosis. *Eur Respir J.* 1997; 10(3): pp.619-23.

(87) Gaensbauer JT, Vandaleur M, OΓÇÖNeil M, Altaf A, N+i Chr+¦in+in M. BCG protects toddlers during a tuberculosis outbreak. *Archives of Disease in Childhood.* 2009; 94(5): pp.392-3.

(88) O'Sullivan M, Burke M. A teenage tuberculosis cluster. *Epi-Insight - Disease Surveillance Report of NDSC, Ireland.* 2001; 2(3): pp.2-3.

(89) Welton NJ, Sutton AJ, Cooper NJ, Abrams KR, Ades AE. *Evidence synthesis for decision making in healthcare.* Chichester, UK: John Wiley & Sons; 2012.

(90) Health Information and Quality Authority. *Guidelines for the Retrieval and Interpretation of Economic Evaluations of Health Technologies in Ireland*. Dublin, Ireland: HIQA; 2014.

(91) Tu HA, Vu HD, Rozenbaum MH, Woerdenbag HJ, Postma MJ. A review of the literature on the economics of vaccination against TB. *Expert Rev Vaccines.* 2012; 11(3): pp.303-17.

(92) Rahman M, Sekimoto M, Takamatsu I, Hira K, Shimbo T, Toyoshima K, et al. Economic evaluation of universal BCG vaccination of Japanese infants. *Int J Epidemiol.* 2001; 30(2): pp.380-5.

(93) Hersh AL, Tala-Heikkila M, Tala E, Tosteson AN, Fordham von RC. A cost-effectiveness analysis of universal versus selective immunization with Mycobacterium bovis bacille Calmette-Guerin in Finland. *Int J Tuberc Lung Dis.* 2003; 7(1): pp.22-9.

(94) Altes HK, Dijkstra F, Lugner A, Cobelens F, Wallinga J. Targeted BCG vaccination against severe tuberculosis in low-prevalence settings: epidemiologic and economic assessment. *Epidemiology.* 2009; 20(4): pp.562-8.

(95) Marusakova E, Bielik J, Frecerova K, Nevicka E, Sedlakova D. Cancelling obligatory mass vaccination of newborns against TB in Slovakia: predicted development. *University Review.* 2012; 6(1): pp.2-11.

(96) Marusakova E, Bielik J, Frecerova K, Nevicka E, Sedlakova D. Cost-effectiveness analysis of the primovaccination of newborns against tuberculosis in slovakia. *Value Health.* 2012; 15(7): p.A393.

(97) Jaime Caro J, Eddy DM, Kan H, Kaltz C, Patel B, Eldessouki R, et al. Questionnaire to Assess Relevance and Credibility of Modeling Studies for Informing Health Care Decision Making: An ISPOR-AMCP-NPC Good Practice Task Force Report. *Value Health.* 2014; 17(2): pp.174-82.

(98) Health Information and Quality Authority. *Guidelines for the Economic Evaluation of Health Technologies in Ireland*. Dublin, Ireland: HIQA; 2014.

(99) R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2014.

(100) Fenwick E, Byford S. A guide to cost-effectiveness acceptability curves. *The British Journal of Psychiatry.* 2005; 187(2): pp.106-8.

(101) Barton GR, Briggs AH, Fenwick EA. Optimal cost-effectiveness decisions: the role of the cost-effectiveness acceptability curve (CEAC), the cost-effectiveness acceptability frontier (CEAF), and the expected value of perfection information (EVPI). *Value Health.* 2008; 11(5): pp.886-97.

(102) Health Information and Quality Authority. *Guidelines for the Budget Impact Analysis of Health Technologies in Ireland*. Dublin, Ireland: HIQA; 2014.

(103) Health Protection Surveillance Centre. *Early Childhood Immunisation Uptake Statistics Q1 1999-Q3 2014 Summary*. Dublin, Ireland: Health Service Executive; 2014.

(104) Bakshi D, Sharief N. Selective neonatal BCG vaccination. *Acta Paediatr.* 2004; 93(9): pp.1207-9.

(105) Parache C, Carcopino X, Gossot S, Retornaz K, Uters M, Mancini J, et al. Bacillus Calmette-Guerin (BCG) vaccine coverage in newborns and infants at risk before and after a change in BCG policy. *Arch Pediatr.* 2010; 17(4): pp.359-65.

(106) Deshpande SA. Ethnic differences in the rates of BCG vaccination. *Arch Dis Child.* 2004; 89(1): pp.48-9.

(107) Nguipdop-Djomo P, Mangtani P, Pedrazzoli D, Rodrigues LC, Abubakar I. Uptake of neonatal BCG vaccination in England: performance of the current policy recommendations. *Thorax.* 2014; 69(1): pp.87-9.

(108) Romanus V. Selective BCG vaccination in a country with low incidence of tuberculosis. *Euro Surveill.* 2006; 11(3): pp.14-7.

(109) Srinivasan R, Menon L, Stevens P, Campbell I, Alfaham M. Ethnic differences in selective neonatal BCG immunisation: white British children miss out. *Thorax.* 2006; 61(3): pp.247-9.

(110) Health Protection Agency. *Tuberculosis update*. London: The Stationery Office: HPA; 2013.

(111) Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. *Lancet Infect Dis.* 2010; 10(5): pp.317-28.

(112) Schoeman J, Wait J, Burger M, van ZF, Fertig G, van Rensburg AJ, et al. Long-term follow up of childhood tuberculous meningitis. *Dev Med Child Neurol.* 2002; 44(8): pp.522-6.

(113) Paganini H, Gonzalez F, Santander C, Casimir L, Berberian G, Rosanova MT. Tuberculous meningitis in children: clinical features and outcome in 40 cases. *Scand J Infect Dis.* 2000; 32(1): pp.41-5.

(114) Kumar R, Dwivedi A, Kumar P, Kohli N. Tuberculous meningitis in BCG vaccinated and unvaccinated children. *J Neurol Neurosurg Psychiatry.* 2005; 76(11): pp.1550-4.

(115) van Well GT, Paes BF, Terwee CB, Springer P, Roord JJ, Donald PR, et al. Twenty years of pediatric tuberculous meningitis: a retrospective cohort study in the western cape of South Africa. *Pediatrics.* 2009; 123(1): p.e1-e8.

(116) Central Statistics Office. *Irish Life Tables No. 15: 2005-2007*. Dublin, Ireland: Central Statistics Office; 2009.

(117) Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. *Value Health.* 2011; 14(4): pp.539-45.

(118) Balgude A, Sontakke S. Study of impact of antitubercular therapy on quality of life. *Indian J Med Sci.* 2012; 66(3-4): pp.71-7.

(119) Bauer M, Leavens A, Schwartzman K. A systematic review and meta-analysis of the impact of tuberculosis on health-related quality of life. *Qual Life Res.* 2013; 22(8): pp.2213-35.

(120) Hanquet G, Christensen H, Agnew E, Trotter C, Robays J, Dubois C, et al. *A quadrivalent vaccine against serogroup B meningococcal disease: a cost-effectiveness study*. Brussels: elgian Health Care Knowledge Centre (KCE); Report No.: KCE Reports 231. 2014.

(121) Ruedin HJ, Ess S, Zimmermann HP, Szucs T. Invasive meningococcal and pneumococcal disease in Switzerland: cost-utility analysis of different vaccine strategies. *Vaccine.* 2003; 21(27-30): pp.4145-52.

(122) Kelleher, Kevin. Personal communication. 11 May 2015. Date received: 26 February 2013.

(123) Lee BY, Norman BA, Assi TM, Chen SI, Bailey RR, Rajgopal J, et al. Single versus Multi-Dose Vaccine Vials: An Economic Computational Model. *Vaccine.* 2010; 28(32): pp.5292-300.

(124) Tu HA, Deeks SL, Morris SK, Strifler L, Crowcroft N, Jamieson FB, et al. Economic evaluation of meningococcal serogroup B childhood vaccination in Ontario, Canada. *Vaccine.* 2014; 32(42): pp.5436-46.

(125) Tirani M, Meregaglia M, Melegaro A. Health and Economic Outcomes of Introducing the New MenB Vaccine (Bexsero) into the Italian Routine Infant Immunisation Programme. *PLoS One.* 2015; 10(4): p.e0123383.

(126) Westra TA, Parouty M, Brouwer WB, Beutels PH, Rogoza RM, Rozenbaum MH, et al. On Discounting of Health Gains from Human Papillomavirus Vaccination: Effects of Different Approaches. *Value Health.* 2012; 15(3): pp.562-7.

(127) Noyes J, Edwards RT. EQ-5D for the Assessment of Health-Related Quality of Life and Resource Allocation in Children: A Systematic Methodological Review. *Value Health.* 2011; 14(8): pp.1117-29.

(128) EUnetHTA Joint Action 2 Work Package 8. *HTA Core Model version 2.1 (Pdf)* [Online]. Available from: http://www.corehta.info/BrowseModel.aspx.

(129) Erkens CG, de VG, Keizer ST, Slump E, van den HS. The epidemiology of childhood tuberculosis in the Netherlands: still room for prevention. *BMC Infect Dis.* 2014; 14 p.295.

(130) Gordon M, Roberts H, Odeka E. Knowledge and attitudes of parents and professionals to neonatal BCG vaccination in light of recent UK policy changes: a questionnaire study. *BMC Infect Dis.* 2007; 7 p.82.

(131) Rossignol L, Guthmann JP, Kerneis S, ubin-Auger I, Lasserre A, Chauvin P, et al. Barriers to implementation of the new targeted BCG vaccination in France: a cross sectional study. *Vaccine.* 2011; 29(32): pp.5232-7.

(132) Pilger D, Nguipdop-Djomo P, Abubakar I, Elliman D, Rodrigues LC, Watson JM, et al. BCG vaccination in England since 2005: a survey of policy and practice. *BMJ Open.* 2012; 2(5):

(133) Daoud W. Control of an outbreak of BCG complications in Gaza. *Respirology.* 2003; 8(3): pp.376-8.

(134) Ritz N, Curtis N. Mapping the global use of different BCG vaccine strains. *Tuberculosis.* 2009; 89(4): pp.248-51.

(135) Dal Moro F. BCG shortage in Europe. *Prev Med.* 2013; 57(2): p.146.

(136) European Parliament. *E-004181-13* [Online]. Available from: http://www.europarl.europa.eu/sides/getAllAnswers.do?reference=E-2013-004181&language=EN.

(137) Health Protection Surveillance Centre. *Advisory notice: Current Shortage of Tuberculin PPD RT 23 SSI (2TU)*. Health Service Executive; 2015.

(138) Salo EP. BCG in Finland: changing from a universal to a selected programme. *Euro Surveill.* 2006; 11(3): pp.18-20.

(139) Teo SSS, Shingadia DV. Does BCG have a role in tuberculosis control and prevention in the United Kingdom? *Arch Dis Child.* 2006; 91(6): pp.529-31.

(140) Venkatesan P, Jayakumar S, Sharief N. Selective neonatal BCG vaccination - a re-audit. *Acta Paediatr.* 2007; 96(1): pp.145-6.

(141) Athavale D, McCullough S, Mactier H. Implementing the new BCG vaccination guidelines--a maternity hospital-based clinic approach. *J Public Health (Oxf).* 2006; 28(2): pp.133-6.

(142) National Health Service. *Public health functions to be exercised by the NHS Commissioning Board, Service specification No.2, Neonatal BCG immunisation programme*. London: Department of Health; 2012.

(143) Guthmann JP, Antoine D, Fonteneau L, Che D, Levy-Bruhl D. Assessing BCG vaccination coverage and incidence of paediatric tuberculosis following two major changes in BCG vaccination policy in France. *Euro Surveill.* 2011; 16(12):

(144) Wattrelot P, Brion JP, Labarere J, Billette d, V, Girard-Blanc MF, Stahl JP, et al. [Vaccination practices following the end of compulsory BCG vaccination. A cross-sectional survey of general practitioners and pediatricians]. *Arch Pediatr.* 2010; 17(2): pp.118-24.

(145) Guthmann JP, Fonteneau L, Desplanques L, Levy-Bruhl D. BCG vaccination coverage in children born after the end of compulsory BCG vaccination and followed in maternal and child health clinics in France: a national survey 2009. *Arch Pediatr.* 2010; 17(9): pp.1281-7.

(146) Bruhl DL, Paty MC, Antoine D, Bessette D. Recent changes in tuberculosis control and BCG vaccination policy in France. *Euro Surveill.* 2007; 12(9): p.E070913.

(147) Pareek M, Baussano I, Abubakar I, Dye C, Lalvani A. Evaluation of immigrant tuberculosis screening in industrialized countries. *Emerg Infect Dis.* 2012; 18(9): pp.1422-9.

(148) Aldridge RW, Yates TA, Zenner D, White PJ, Abubakar I, Hayward AC. Pre-entry screening programmes for tuberculosis in migrants to low-incidence countries: a systematic review and meta-analysis. *The Lancet Infectious Diseases.* 2014; 14(12): pp.1240-9.

(149) van der Werf MJ, Lönnroth K. Pre-entry, post-entry, or no tuberculosis screening? *The Lancet Infectious Diseases.* 2014; 14(12): pp.1171-2.

(150) Nienhaus A, Schablon A, Costa JT, Diel R. Systematic review of cost and cost-effectiveness of different TB-screening strategies. *BMC Health Serv Res.* 2011; 11 p.247.

(151) Pareek M, Watson JP, Ormerod LP, Kon OM, Woltmann G, White PJ, et al. Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis. *Lancet Infect Dis.* 2011; 11(6): pp.435-44.

(152) Romanus V, Svensson A, Hallander HO. The impact of changing BCG coverage on tuberculosis incidence in Swedish-born children between 1969 and 1989. *Tuber Lung Dis.* 1992; 73(3): pp.150-61.

(153) Van Bui T, Levy-Bruhl D, Che D, Antoine D, Jarlier V, Robert J. Impact of the BCG vaccination policy on tuberculous meningitis in children under 6 years in metropolitan France between 2000 and 2011. *Euro Surveill.* 2015; 20(11):

(154) Gosoniu GD, Ganapathy S, Kemp J, Auer C, Somma D, Karim F, et al. Gender and socio-cultural determinants of delay to diagnosis of TB in Bangladesh, India and Malawi. *Int J Tuberc Lung Dis.* 2008; 12(7): pp.848-55.

(155) Hamzaoui A, Yaalaoui S, Tritar Cherif F, Slim Saidi L, Berraies A. Childhood tuberculosis: a concern of the modern world. *European Respiratory Review.* 2014; 23(133): pp.278-91.

(156) Piccini P, Chiappini E, Tortoli E, de Martino M, Galli L. Clinical peculiarities of tuberculosis. *BMC Infectious Diseases.* 2014; 14(Suppl 1): p.S4.

(157) Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Respir J.* 2013; 41(1): pp.140-56.

(158) Borraccino A, Migliore E, Piccioni P, Baussano I, Carosso A, Bugiani M. Yield of tuberculosis contact investigation in a low-incidence country. *J Infect.* 2014; 68(5): pp.448-54.

(159) World Health Organisation. *Guidelines on the management of latent tuberculosis infection*. Geneva: WHO; 2015.

(160) Kane M, Korn B, Saukkonen J, McDonald C, Walsh C, Waters R, et al. Barriers to accepting and completing latent tuberculosis infection treatment. *Ir Med J.* 2013; 106(7): pp.200-4.

(161) Horsburgh CR, Jr., Goldberg S, Bethel J, Chen S, Colson PW, Hirsch-Moverman Y, et al. Latent TB infection treatment acceptance and completion in the United States and Canada. *Chest.* 2010; 137(2): pp.401-9.

(162) Verweij M, Dawson A. Ethical principles for collective immunisation programmes. *Vaccine.* 2004; 22(23-24): pp.3122-6.

(163) National Tuberculosis Advisory Committee. The BCG vaccine: information and recommendations for use in Australia. *Communicable Diseases Intelligence.* 2013; 37(1): p.E65-E72.

(164) National Consent Advisory Group. *National Consent Policy*. Dublin, Ireland: Health Service Executive; 2013.

(165) *Fitzpatrick & Anor -v- K. & Anor*. IEHC 104 . 2008.

(166) Medical Council. *Guide to professional conduct and ethics for registered medical practitioners*. Dublin, Ireland: Medical Council; 2009.

(167) *North Western Health Board -v- H.W. & C.W.* IESC 90 (2001) . 2001.

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